Strahlenschutzkommission

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# Dose and dose-rate effectiveness factor (DDREF)

Recommendation by German
Commission on Radiological Protection

with scientific grounds

Adopted at the 268th meeting of the German Commission on Radiological Protection on 13 and 14 February 2014

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**Dosis- und Dosisleistungs-Effektivitätsfaktor (DDREF)**

Empfehlung der Strahlenschutzkommission mit wissenschaftlicher Begründung

# Introduction

The somewhat cumbersome term “dose and dose-rate effectiveness factor (DDREF)” is a remarkably subtle factor with a considerable conceptual and quantitative influence when it comes to radiation protection. Justification for retaining/modifying/abolishing such a “factor” is therefore not only based on radiobiological or radioepidemiological findings, it also gives rise to questions relating to radiation protection requirements for operational implementation.

For practical radiation protection purposes, it is assumed that stochastic radiation effects are proportional to the dose. This assumption forms what is known as the linear no-threshold (LNT) model, which is one of the basic concepts with major consequences for the entire field of radiation protection. However, radiobiological and radioepidemiological studies indicate deviations from “pure” linearity at low doses and the possibility of dependencies on the dose rate. Such influences would lead to an overestimate of the radiation risk determined on the basis of the LNT model, which is why in previous recommendations the International Commission on Radiological Protection (ICRP) developed a concept summarising all of these influences into a common factor, the DDREF. The risk coefficients for low loses and low dose rates calculated by linear extrapolation are divided by the DDREF. In recommendation ICRP 103, the ICRP confirmed the previously introduced DDREF of 2.

Prior to discussions surrounding ICRP 103, the German Commission on Radiological Protection (Strahlenschutzkommission, SSK) adopted a critical stance to the DDREF concept, not in the least due to its design, and called for the DDREF to be abolished, i.e. a DDREF of 1. Due to the ongoing and somewhat controversial debates surrounding DDREF and its major significance in terms of radiation protection, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asked the SSK to provide a comprehensive assessment of the situation. In order to handle this advisory mandate, the SSK formed a task group consisting of the following people:

- Prof. Dr. Michael Atkinson, Helmholtz Zentrum München (German Research Centre for Environmental Health in Munich)
- Prof. Dr. Joachim Breckow, Technische Hochschule Mittelhessen (University of Applied Sciences), Giessen
- Dr. Günther Dietze, formerly of the Physikalisch-Technische Bundesanstalt (Germany’s national metrology institute), Braunschweig
- Prof. Dr. Jürgen Kiefer, formerly of the Justus Liebig University Giessen
- Prof. Dr. Werner Rühm, Helmholtz Zentrum München (German Research Centre for Environmental Health in Munich).

Bonn, June 2014

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| Prof. Dr. Wolfgang-U. Müller | Prof. Dr. Joachim Breckow |
| Chairman of the German Commission on Radiological Protection | Chairman of the task group |

# Contents

**Dose and dose-rate effectiveness factor (DDREF)
Recommendation of the German Commission on Radiological Protection .....1**

**Dose and dose-rate effectiveness factor (DDREF)
Scientific grounds of the recommendation
of the German Commission on Radiological Protection .....17**

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# Contents

**1 Introduction ..... 5**
**2 Basic information about DDREF ..... 5**
**3 Radiobiological studies ..... 7**
**4 Radioepidemiological studies ..... 8**
**5 Basic scientific principles and other criteria relevant to radiation protection used to assess the DDREF ..... 9**
**6 Summary assessment ..... 12**
**Literature ..... 14**

# 1 Introduction

One of the main aims and duties of radiation research is to quantify the relationship between radiation exposure and the resulting potential human damage. The International Commission on Radiological Protection (ICRP) defined the "detriment" concept (ICRP 2007) to quantify damage by expressing above all the risk of carcinogenesis or cancer mortality as a result of exposure. Quantitative risk estimates are generally based on epidemiological studies involving relatively high doses[1] and high dose rates[2]. In order to make statements involving low doses[3] and low dose rates[4], extrapolations for low doses and low dose rates are required for which there is still not enough data available to reliably express risk.

Dose-response relationships from epidemiological studies alwaysrefer to a given exposure scenario with certain dose rates by observing the effect of a given dose. The stated dose is often only the temporally limited additional dose arising in this exposure situation excluding any doses from other sources such as natural ambient radiation. On the other hand, other studies compare various different exposure situations with differing levels of ambient radiation, e.g. radon studies. In general, the dose rate here is very low, while the dose accumulated over prolonged periods also involves values well in excess of 100 mSv.

A linear no-threshold relationship (LNT model) was adopted by the radiation protection community many years ago. It is also assumed that at low doses, the risk is not dependent upon radiation exposure over time, i.e. that it is not contingent upon the dose rate. Another assumption is that at low doses and low dose rates, the actual risk is overestimated by a certain factor if the risk values of high doses and high dose rates are extrapolated in linear fashion to low doses and low dose rates. The ICRP therefore adopted a dose and dose-rate effectiveness factor (DDREF) to adjust for this perceived overrepresentation. Risk values largely determined using epidemiological studies on the survivors of the Hiroshima and Nagasaki atomic bombings are divided by this DDREF for low-dose and low-dose-rate radiation protection applications. In recommendation 103 (ICRP 2007), the ICRP confirmed its previous argumentation and recommends retaining a DDREF of 2 for solid tumours in the case of photon and electron exposures (sparsely ionising radiation).

In recent times, the scientific basis for justifying DDREF has increasingly become the subject of controversial debate all the way up to expert committees. In 2006, the German Commission on Radiological Protection (SSK) recommended a DDREF of 1 (SSK 2006). UNSCEAR (2010) and the WHO (2013) did not apply DDREF in recent publications. Given these circumstances, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) commissioned the German Commission on Radiological Protection (SSK) with reviewing the current state of science and preparing a recommendation regarding DDREF.

# 2 Basic information about DDREF

A dose-proportionate relationship based on radioepidemiological studies is relatively well established for doses of several 100 mSv in solid tumours. This applies both to acute radiation exposures involving large dose rates (mainly studies involving atomic bomb survivors (Preston

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1 Unless otherwise stated, the doses used in this recommendation refer to the effective dose.

2 Dose rate = dose / time (according to DIN 6814, part 3).

3 Effective dose <100 mSv

4 Effective dose rate <0.1 mSv/min (according to UNSCEAR 2010)

et al. 2003, 2004, 2007)) as well as to chronic radiation exposures of up to around 1 Sv with a low dose rate. However, the progression of this dose-response relationship at low doses (below several 10 mSv) remains a controversial topic. At this level, the major statistical uncertainties of epidemiological studies make it impossible to provide reliable statements hence the need for radiobiological in vitro and in vivo studies. Based on biological considerations, it appears plausible that there may be a non-linear relationship between the dose and radiation risk at low doses. Epidemiological and biological results are also unable to fully negate the existence of a dose threshold below which there is no radiation risk.

After an acute exposure (high dose rate), in a lot of cellular studies the dose-response relationship is followed by a linear-quadratic relationship. This indicates that dose and dose-rate dependencies could be linked to one another.

In conventional models describing for example the effects of high doses in radiation therapy, this can be understood such that in the case of fractionated exposure, the total dose-response relationship can be determined by sequencing dose-response relationships from single fractions. This is justified by the fact that regeneration and repair processes during irradiation breaks return the cells to an "initial state" from which they again follow a "new" (non-linear) dose-response relationship. In the case of fractionated exposure, this means the effect of a certain dose will be lower than when receiving the same dose during a single exposure. If such a fractionation is subdivided into further fractions (while maintaining the same length of time between exposures) with diminishing single doses, the limit will result in chronic exposure at a low dose rate. This explains why, when maintaining the same dose, chronic exposures involving low dose rates will have less of an effect than acute exposures involving high dose rates. The dependency of the response on the dose rate is known as the dose-rate effect and has been proven many times for cell survival.

In the conventional model mentioned above, the extent of the dose-rate effect depends on the level of non-linearity of the dose-response relationship. Here, a purely linear dose-response relationship would mean that the temporal distribution of an exposure has no impact on the effect and thus no dose-rate dependency exists.

The above argumentation is not binding, however, and the cellular mechanism on which it is based does not apply to every effect, i.e. is limited to a certain set of effects. Mechanisms are possible whose response follow a non-linear (or linear-quadratic) dose relationship as a result of damage and with which the affected cells are not reset to an initial state after a certain recuperation phase. In such cases there is no dose-rate dependency, irrespective of the non-linear dose-response relationship. On the other hand, it is possible that repair mechanisms and other processes could at least partly repair molecular or cellular damage, even in the case of a linear underlying dose-response relationship. In this case, a linear relationship could well give rise to a dose-rate dependency.

If high doses give rise to higher risks per dose than low doses, a linear extrapolation from high to low doses would lead to an overrepresentation of the actual risk ("dose effect"). The same also applies when extrapolating from high dose rates to low dose rates ("dose-rate effect"). For radiation protection purposes, this potential risk overrepresentation is compensated for by a common factor, DDREF, by which the risk coefficients measured at high doses and high dose rates are divided. The method used to determine the DDREF does not involve a single "factor" in the sense of an inherently constant parameter for estimating risk coefficients. Instead the DDREF value depends on the respective dose and dose rate used to extrapolate low doses and low dose rates. Other influences may also occur, such as dependencies on radiation energy (Trabalka and Kocher 2007). However, there is not enough information available about the type and magnitude of all these dependencies, hence why DDREF – irrespective of the value

assigned to it – is of rather general relevance in radiation protection and it adresses less to certain specific aspects. In fact, the effects of all these dependencies are summarised by a single constant "factor", namely the DDREF.

In 2007, the ICRP concluded "*that the adoption of the LNT model combined with a judged value of DDREF provides a prudent basis for practical purposes of radiological protection*" (ICRP 2007). In 2013, the ICRP set up a task group to again take up the discussion on DDREF.

# 3 Radiobiological studies

At molecular and cellular level (in vitro studies), a range of linear and non-linear effects can be observed in various cell systems and in relation to the investigated end points. Nowadays, when observing a large dose range, it is generally assumed that other biological mechanisms have an impact at low doses (< 100 mGy) when compared with high doses. It is however unclear what health effects these mechanisms may have at low doses.

This in turn makes it difficult to determine the relevance of these effects for evaluating a DDREF. While the number of double-strand breaks and other radiation-induced DNA damage have a linear relationship with dose, chromosome aberrations and repair processes also reveal, at least in part, non-linear dose-response components. Dependencies on dose rate may be observed in a range of different effects while, in spite of previous assumptions, the dose and dose rate effects appear to be largely "independent".

As there are only limited epidemiological options at low doses and low dose rates, it was often argued that a response to open issues could be provided by performing in vitro studies to clarify basic mechanisms. The current state of research renders in vitro studies ambivalent such that they can barely be used to justify DDREF. For a long time it was assumed that dose-response relationships for chromosome aberrations, mutation induction and the loss of colony forming ability after sparsely ionising radiation could be well described by a linear-quadratic function. This model was mainly based on microdosimetric considerations and on theoretical justifications for non-linearities and thus also on dose-rate effects. Recently discovered effects now call this assumption into question.

Even if non-linear effects could generally be assumed at in vitro level, it is still largely unclear whether and how they interact during complex biological processes and whether and how non-linearities are "passed on" in vivo to carcinogenesis.

A critical examination of the in vivo evidence on rodents suggests that there is no good cause to introduce a low-dose effectiveness factor (LDEF) or a dose-rate effectiveness factor (DREF).

Studies used to support the DDREF often investigate end points such as tumours of the Harderian gland (a tumour type with no human counterpart) or tumours such as ovarian tumours with a different metabolism in rodents to that seen in humans. Initial studies used very large numbers of animals in an attempt to provide results of adequate statistical power. At the same time, however, these methods were flawed as causes of death other than the investigated radiation-induced tumours or non-standardised animal husbandry and/or various different irradiation scenarios were not sufficiently taken into account. These early studies fail to meet current standards for comparative studies and their validity is therefore highly limited.

In contrast, most of the more recent animal studies on solid tumours performed under more careful conditions only indicate non-linearity of tumour incidence dose dependency at levels above 1 Gy to 2 Gy.

# 4 Radioepidemiological studies

Epidemiological studies have an important part to play when it comes to DDREF. If dose effects and dose rate effects are investigated independently of one another, a distinction is usually made between the low-dose effectiveness factor (LDEF) and the dose-rate effectiveness factor (DREF). The influence of any potentially present non-linear dose dependency on the LDEF can, for example, be investigated by performing tests on atomic bomb survivors. Influences of a potential dose rate effect on the DREF may, however, be investigated by comparing groups of people exposed to a small dose rate (nuclear industry employees, residents of areas with higher levels of background radiation, people who live near the Techa river, people who helped in the wake of the Chernobyl accident) with groups of people exposed to a high dose rate (atomic bomb survivors).

The Radiation Effects Research Foundation (RERF) in Japan publishes regular reports on the latest findings of its Life Span Study (LSS) which investigates the life-long health effects based on epidemiological data of survivors of the Hiroshima and Nagasaki atomic bombings. The LSS investigations are by far the most important source of radioepidemiological risk estimates, and are also of key importance to DDREF discussions. As the LSS is based on exposures with a high dose rate, only the dose effects (LDEF) and not the dose-rate effects (DREF) can be investigated. In the latest report (Ozasa et al. 2012), consideration of the total available dose range (colon dose < 3 Gy) indicated a linear dose-response relationship which provides the best adjustment for solid tumours in the mortality data. On the other hand, the authors observed a significant curvature of the dose-response relationship at a limited dose range of 0 to 2 Gy which was adjusted using a linear-quadratic curve. There was no indication of a dose threshold. If the authors limited their analysis to a dose range of 0 to 0.5 Gy or 0 to 1 Gy, they observed lower values than the ERR[1] per dose for the entire dose range. When the analysis was limited to even smaller dose ranges (0 to 0.1 Gy or lower), the resulting ERR values per dose were in fact higher. This would imply a steep dose-response relationship at doses of under 0.1 Gy, which is significantly relativised by the extremely broad associated confidence intervals. Overall, in terms of solid tumours, these analyses do not indicate a certain type of dose-response relationship among atomic bomb survivors.

Most studies on people employed in the nuclear industry returned a positive ERR value per dose for solid tumour mortality that was, however, non-significant from a statistical perspective. By way of contrast, a study from 2005 summarising data from 15 countries showed a statistically significant positive estimator for the ERR value per dose which reduced to a positive, non-significant value of 0.58 (95% CI[2]: -0.22 – 1.55) $Sv^{-1}$ if the data from Canada were excluded (Cardis et al. 2007). A recently published meta-analysis from Japan, which to some extent involved more recent results, also provided a positive yet non-significant estimator for the ERR value per dose of 0.14 (95% CI: -0.12 – 0.41) $Sv^{-1}$ (Akiba et al. 2012).

Analyses involving the incidence of solid tumours in areas with elevated levels of natural terrestrial radiation in Kerala in India indicate a non-significant negative ERR value per dose of -0.13 (95% CI: -0.58 – 0.46) $Gy^{-1}$ (Nair et al. 2009) despite the mean cumulated dose of 170 mGy observed in the study participants being far higher than the dose values generally seen in studies involving people who work in the nuclear industry. In contrast, the results of a study involving residents of Guangdong, an area with elevated terrestrial radiation in China, shows a

1 ERR: Excess relative risk

2 95% CI: 95% confidence interval

slightly positive, non-significant point estimate of 0.19 $Gy^{-1}$ but with a high confidence interval (95% CI: -1.87 – 3.04 $Gy^{-1}$) (Tao et al. 2012).

The latest mortality study involving people who live near the Techa river in the Southern Urals in Russia provided a significantly positive ERR value per dose of 0.92 (95% CI: 0.2 – 1.7) $Gy^{-1}$ (Krestinina et al. 2005, Schonfeld et al. 2013). A similarly significantly positive ERR value per dose of 1.52 (95% CI: 0.20 – 2.85) $Gy^{-1}$ was observed as a result of the latest mortality study involving people who helped in the wake of the Chernobyl accident (Ivanov et al. 2006). This result was confirmed by analysing the tumour incidence data of both cohorts (people who live near the Techa river: 1.0 (95% CI: 0.3 – 1.9) $Gy^{-1}$ (Krestinina et al. 2007); people who helped in the wake of the Chernobyl accident: 0.96 (95% CI: 0.28 – 1.72) $Gy^{-1}$ (Ivanov et al. 2009)).

In 2009, Jacob et al. published a study based on systematic literature research available at that time which looked into all of the individual studies into mortality or incidence following exposure to low dose rates and low/moderate cumulated doses (Jacob et al. 2009). They took the individual estimators of the excess relative risk per dose derived by assuming a linear dose-response relationship and compared them with the corresponding excess relative risk per dose derived from the data resulting from the study on atomic bomb survivors. The authors compared results from cohorts involving low dose rates with results from a cohort involving a high dose rate to gain DREF information. The result of this meta-study indicates that exposures involving a low dose rate do not lead to a lower cancer risk than exposures involving high dose rates. The authors therefore concluded that their studies did not indicate a DREF of greater than 1.

The analysis performed by Jacob et al. (2009) also showed that the results of individual studies have to be compared and discussed with caution as the statistical data analyses carried out were often based on differing assumptions. Against this backdrop, Jacob et al. systematically excluded each of the identified studies in turn during their meta-analysis in order to investigate the extent to which the meta-study's ERR value per dose varied as a result of doing so. They were able to show that this led to changes of at most 30% (Jacob et al. 2009).

To sum up, the previously published results of epidemiological studies on the effect of exposures to a low dose rate do not generally indicate tumour risk to be dependent upon dose rate, hence promoting a DREF of 1. Most of these studies involving a dose-response relationship analysis do not allow conclusions to be drawn in terms of a LDEF value. The study on atomic bomb survivors involving exposure with a high dose rate does not allow a LDEF value to be derived due to the given uncertainties, particularly those present at low doses below 100 mGy. This therefore prevents the confirmation of a specific LDEF value of 1 to 2, which is currently being discussed.

# 5 Basic scientific principles and other criteria relevant to radiation protection used to assess the DDREF

## Scientific principles

The DDREF was introduced to determine radiation risks due to exposure by low dose and low dose rates based on studies involving high doses and high dose rates. An assessment of the extent to which the use of a DDREF is justified and the value that should be assigned to is based on scientific findings pertaining to the radiation risk at various different doses and at various different dose rates. These findings are based on a range of different areas of research and require considerations as to which research results and which criteria should be used for the assessment and with which priority they should be used. The findings are set out below:

– **Radiobiological studies on molecular and cellular systems**

For the last 50 years, the results of radiobiological studies formed the main basis for stipulating a DDREF, despite most – but not all – of them being based on studies involving doses of several Gy. Here, studies were performed involving single cells or cell cultures in order to determine dose and dose-rate dependencies. These studies are still considered the most important source for justifying a DDREF of higher than 1, even though they refer to high doses. It remains to be seen whether and/or how these results can be extrapolated to the human tumour induction situation. This applies, in particular, with regard to more recent findings such as the bystander effect, genomic instability, adaptive response and their relevance regarding radiation effects at low doses and low dose rates. One aspect of these studies is the question of whether dose effects (deviation from a linear dose-response relationship) and dose rate effects are linked or whether they need to be observed independently of one another.

– **Radiobiological studies on animals**

Studies on animals form part of discussions on determining a DDREF and generally involve observing a series of different end points (life shortening, tumour incidence, tumour mortality, etc.) in mice or rats. Although the extent to which the results of these studies can be extrapolated to human tumour induction remains to be seen, irradiation of an entire organism is more indicative of the human situation than irradiation of single cells. It should be noted, however, that the design of studies on animals (end points) and various influencing parameters when conducting the studies have a major impact on the results, therefore making it difficult to make a general statement about DDREF.

– **Epidemiological studies**

Epidemiological data are also an important source for determining a DDREF, in particular as they directly refer to human cancer. Epidemiological studies also allow dose effects (LDEF) and dose-rate effects (DREF) to be investigated along with the question of whether they are independent of one another. While dose-response relationships can in principle be determined by studying a single exposed cohort (e.g. survivors of the Hiroshima and Nagasaki atomic bombings who received differing doses) (LDEF), studies into the dose-rate effect (DREF) generally require comparable studies on various different populations exposed to differing dose rates. In contrast to doses above 100 mSv, current epidemiological studies into the risk of radiation-induced cancers are of little significance with doses of several 10 mSv. Studies involving low dose rates generally require long exposure and/or observation periods. This makes it difficult to obtain substantiated results on the effect of low dose rates. In the last few years, however, a series of studies involving medium doses and dose rates have been conducted that enable a more precise assessment. The combined investigation of individual studies in meta-analyses may help to improve the situation further.

– **Mechanistic radiobiological models**

Extrapolations from high doses to low doses are required in order to make statements involving low doses and low dose rates which are of importance to radiation protection. Such extrapolations are often based on mathematically formulated mechanistic models which play a major role in interpreting experimental and epidemiological data. This includes, for example, the assumption of a purely linear or linear-quadratic dose-response relationship. In addition, the use of a multiplicative, additive, or mixed risk model is also important when evaluating epidemiological data that also include the background risk. The

extent to which age and gender dependencies (including even individual characteristics) of radiation risk need to be taken into consideration also needs to be considered when estimating risk coefficients. Data uncertainty is also vital for the question of which model best describes present experimental and/or epidemiological data where data for the lowest observed doses and lowest dose rates generally exhibit the largest uncertainties. This greatly restricts the choice of model for best describing the data and leads to major uncertainties in determining a DDREF based on modelling.

## Operational implementation criteria relevant to radiation protection requirements

As was the case several times in the past, an assessment to determine whether or not the DDREF value currently generally used in radiation protection to estimate radiation risk should be changed is not solely based on specified scientific findings in a narrow sense as it also includes other criteria pertaining to other key aspects of radiation protection and practical implementation. Assessment solely on the basis of scientific principles and criteria is not commensurate to the importance and function of DDREF, which is why the following criteria are used in the assessment along with scientific findings:

- **Influence of uncertainties**

  There are major uncertainties in terms of the determined risk values and DDREF derived therefrom, thus only allowing for the stipulation of a range of DDREF values (between 1 and 2, currently the subject of discussion) compatible with experimental and epidemiological data. Considerations as to whether to change the DDREF of 2 used to date therefore also have to take account of uncertainties. A decision is required to determine whether today's improved data situation (and reduced uncertainty) would give cause to introduce a DDREF (if there hadn't already been one) or whether the uncertainties are still as significant to be unable to clearly support the abolition of an existing DDREF.

- **Implementation in real-life radiation protection**

  Continuity, consensus, comprehensibility and acceptance are very important to radiation protection. Frequent changes of concepts and regulations/guidelines can lead to unsettledness, particularly during implementation in real-life scenarios, that are counterproductive to radiation protection and should therefore be avoided whenever possible. Changes should only be pursued if there is sufficient scientific justification for doing so and if they are expected to lead to a major improvement in radiation protection, e.g. an improved protective effect and/or risk-benefit ratio.

- **International involvement**

  The current radiation protection concept is the result of an ongoing worldwide process. International agreement on radiation protection regulations has always been remarkably high, which is also the result of continuous efforts to achieve maximum international consensus. This far-reaching consensus also include estimates pertaining to the scientific basis of radiation protection such as radiobiology and radiation effect findings as well as questions relating to radiation protection conservatism. Active involvement in gaining international consensus is therefore a key aspect.

– **Consequences for stipulating limits**

  With its three "basic conceptional pillars", i.e. justification, optimisation and limitation, radiation protection has such a robust framework in place that quantitative fluctuations of one of the implemented factors (e.g. DDREF or weighting factors) do not necessarily require changes to limits, but could form the subject of discussion. Here, the problem of stipulating limits for occupationally exposed persons would inevitably be based on arguments where the radiation risk value and DDREF play a far greater part than the limit that applies to the general public. Justification for stipulating a limit for the public is largely based on the fact that it is within the fluctuation range of natural radiation exposure and that no risk statements can be made at levels of 1 mSv.

– **Risk communication**

  The general public is highly sensitive when it comes to radiation risk, but public debate regarding the effects of radiation and radiation risk levels are often governed by misconceptions. This is why careful and comprehensive communication is required every time a reassessment takes place.

  Public trust in the credibility of scientific bodies is a fundamental part of successful communication. Credibility can only be achieved by extensively discussing issues pertaining to higher risks. Such discussions and communication must take place within a context and in such a way that the general public is able to assess the relevance and value of new scientific findings[1].

# 6 Summary assessment

A statement on DDREF based on radiobiological studies involving cell cultures does not provide a clear picture. At molecular and cellular level (in vitro studies), a range of linear and non-linear effects can be observed. While effects at an "early" effect level, e.g. energy deposition, double-strand breaks and other radiation-induced DNA damage, have a linear relationship with dose, more complex "late" effects such as chromosome aberrations, repair processes and other effects on a subsequent effect level also reveal, at least in part, non-linear dose-response components. In addition to that, other biological mechanisms have an impact at low doses when compared with high doses. Dependencies on dose rate may be observed in a range of different effects, and there are no clear indications of a relationship between dose and dose-rate effects. This means that they can largely be observed "independently" of one another.

The effects of studies on animals indicate a large variability, meaning that it is not possible to determine clear dose-response relationships at low doses, nor is it possible to determine dose-rate dependencies. Overall, studies on animals provide little indication of a general deviation from a linear dose-response relationship or of a general dose rate dependency.

To date, radiobiological studies were the main argument in favour of a DDREF higher than 1. Non-linearities in terms of dose-response relationships and dose rate dependencies are still being observed in current studies. A large spectrum of differing dose-effect dependencies can be seen depending on the biological end point.

[1] The German Commission on Radiological Protection (SSK) has already dealt with this topic on several occasions: see SSK vol. 56 "Estimating, evaluating and managing risks" and SSK vol. 66 "Risks involving ionising and non-ionising radiation"

A comparison of the latest results of epidemiological studies involving low and high dose rates does not currently provide any indication that tumour risk is dependent on dose rate, i.e. on a DREF higher than 1. Most of the studies involving low dose rates use a linear dose-response relationship for analysis, which is why the dose-response relationship curve and a certain LDEF value cannot be determined. The latest study on atomic bomb survivors involving the effect of large dose rates does not provide any clear distinction between various types of dose-response relationship, e.g. linear or linear-quadratic, meaning that it is not currently possible to derive a LDEF value.

Theoretically, mechanistic models can provide a way of deriving a functional relationship between dose and effect, which is why they play a major part in extrapolating from high to low doses. The linear-quadratic dose-response relationship was originally designed as a mechanistic model, thus making it a strong indicator of a DDREF > 1. Even if this model now barely claims to realistically describe a response mechanism, it has still retained some of its validity.

However, mechanistic models generally only map a segment of the highly complex yet largely unknown response curve between the primary event (ionisation) and the end point (cancer). It is unlikely that the entire carcinogenesis process can be described by one of these models if it is to extend beyond simple data fitting. This is why models only have a limited part to play in deciding on an appropriate DDREF value.

Uncertainties have a major impact on justifying a DDREF. No single scientific criterion is sufficient to provide a clear DDREF value. Instead, the many variabilities of the various study approaches as well as their results and uncertainties only allow a DDREF to be limited to a value of less than 2. However, an assessment of the scientific findings does not permit any specification of the DDREF with more precision.

As described in Chapter 2, the DDREF is a very subtle design factor in terms of influence and function. In light of the current level of scientific knowledge and major radiation risk uncertainty, various scientific criteria indicate that such a factor would not be introduced if it were not already in place. Ensuring maximum continuity in terms of radiation protection gives rise to the question of whether weaker evidence based on current scientific assessment provides sufficient justification for abolishing a DDREF and any potentially resulting consequences, or whether the uncertainties permit a value between 1 and 2 that cannot be decided upon, therefore rendering it debatable. It should also be noted that the conceptional construct of radiation protection is based on the three fundamental principles, i.e. “justification”, “optimisation” and “limitation”, and therefore not largely based on knowing the exact radiation risk at low doses.

In view of the continuity criterion described above, implementation within practical radiation protection requires meticulous considerations as to whether the DDREF value should be changed. Such considerations should only take place with international consensus.

Based on current scientific findings, the German Commission on Radiological Protection (SSK) no longer considers there to be sufficient justification for the DDREF used in radiation protection. If a reduction or abolition of the DDREF is the subject of consideration for scientific reasons, however, it must be justified such that this scientific motive is sufficient, especially if the purported radiation protection improvement cannot be clearly stated. On the other hand, consideration should be given in terms of the extent to which a potential underestimate of the risk of cancer at low doses and low dose rates could be in line with the precautionary principle customary to radiation protection.

The German Commission on Radiological Protection (Strahlenschutzkommission, SSK) sets great store on the scientific basis of its statements and recommendations. The SSK considers maximum scientific objectivity and constant efforts to incorporate all current research results

paramount to gaining and building the necessary trust of the general public in its assessments. The SSK also takes this view when it comes to changing the DDREF on the basis of new scientific findings. Beyond its commitment to scientific objectivity, the SSK considers its mission to observe issues regarding public perception and take account of them in frequent ongoing communication.

For radiation protection, the most important factors are damage associated with exposure (carcinogenesis and genetic mutation) and their likelihood of occurrence. These factors are quantified by the "detriment" (damage to health), which is a weighted probability of damage including, among others, risk coefficients (including a DDREF) (see Chapter 1). However, the detriment also includes a number of other parameters, such as probability of survival, quality of life and loss of life expectancy. These parameters are subject to development over time. Improved living conditions and medical progress could, for example, lead to an increase in probability of survival in the case of developing cancer, an improvement in quality of life and a reduction in loss of life expectancy. All of these parameters need to be taken into account when further assessing the health effects of a certain exposure. An isolated view of the risk coefficient and/or DDREF is not sufficient to take account of the overall situation.

This aspect is important when deciding whether or not to change the DDREF as both effects may have a complex interactive effect that could lead to a compensatory tendency: The abolition of the DDREF would in itself lead to an increase in radiation-induced detriment, whereas adjusting the above parameters to meet current statistics could lead to a reduction of the detriment.

### Recommendation of the German Commission on Radiological Protection

Based on current scientific findings, the German Commission on Radiological Protection (Strahlenschutzkommission, SSK) no longer considers justifications for the DDREF used in radiation protection as being sufficient.

In view of the assessments set out in this report, 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 radiation protection, 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.

The SSK means that an international agreement in these issues is urgently necessary and recommends that its assessment be used as a basis for international discussions on these issues.

## Literature


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

Cardis et al. 2007 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. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res. 2007;167:396-416

ICRP 2007 International Commission on Radiological Protection (ICRP). The 2007 Recommendations of the International Commission on Radiological Protection. Publication 103, Annals of the ICRP 37 (2-4), Pergamon Press, Oxford. 2007

Ivanov et al. 2009 Ivanov VK, Gorsky AI, Kashcheev VV, Maksioutov MA, Tumanov KA. Latent period in induction of radiogenic solid tumors in the cohort of emergency workers. Radiat Environ Biophys. 2009;48(3):247-252

Jacob et al. 2009 Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H. Cancer risk of radiation workers larger than expected? Occup Environ Med. 2009 Dec 66;(12):789-796. doi: 10.1136/oem.2008.043265. Epub 2009 Jun 30

Krestinina et al. 2005 Krestinina LYu, Preston DL, Ostroumova EV, Degteva MO, Ron E, Vyushkova OV, Startsev NV, Kossenko MM, Akleyev AV. Protracted radiation exposure and cancer mortality in the Techa River Cohort. Radiat Res. 2005;164:602-611

Krestinina et al. 2007 Krestinina LY, Davis F, Osroumova EV, Epifanova SB, Degteva MO, Preston DL, Akleyev AV. Solid cancer incidence and low-dose-rate radiation exposure in the Techa River cohort: 1956-2002. Int J Epid. 2007;36:1038-1046

Nair et al. 2009 Nair RRK, Rajan B, Akiba S, Jayalekshmi P, Nair MK, Gangadharan P, Koga T, Morishima H, Nakamura S, Sugahara T. Background radiation and cancer incidence in Kerala, India – Karunagaplpally cohort study. Health Phys. 2009;96:55-66

Ozasa et al. 2012 Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. Radiat Res. 2012;177:229-243

Schonfeld et al. 2013 Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL. Solid Cancer Mortality in the Techa River Cohort (1950-2007). Radiat Res. 2013;179:183-189

SSK 2006 — Strahlenschutzkommission (SSK). Comments on the 2006 Draft of the ICRP Recommendations. Stellungnahme der Strahlenschutzkommission. Verabschiedet in der 209. Sitzung der Strahlenschutzkommission am 5. September 2006

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

Trabalka and Kocher 2007 — Trabalka JR and Kocher DC. Energy dependence of dose and dose-rate effectiveness factor for low-LET radiations: Potential importance to estimate of cancer risks and relationship to biological effectiveness. Health Phys. 2007;93(1):17-27

UNSCEAR 2010 — United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2010. Report to the General Assembly, includes Scientific Report: Summary of low-dose radiation effects on health. 2011

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

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# Dose and dose-rate effectiveness factor (DDREF)

## Scientific grounds of the recommendation by the German Commission on Radiological Protection

Adopted at the 268th meeting of the German Commission on Radiological Protection on 13 and 14 February 2014

# CONTENTS

**1 Introduction ..... 21**

1.1 Question ..... 21
1.2 Background ..... 22
Literature ..... 24

**2 Basic information about DDREF ..... 26**

2.1 Link with dose-response relationships ..... 26
2.2 Relationship between dose and dose-rate effects ..... 27
2.3 Relationship between LET and energy ..... 29
2.4 Conclusion ..... 31
Literature ..... 32

**3 Radiobiological studies ..... 33**

3.1 In vitro studies ..... 33

3.1.1 Dose dependencies ..... 33
3.1.2 Dose-rate dependencies ..... 37
3.1.3 Conclusion ..... 39
Literature ..... 39

3.2 In vivo studies ..... 43

3.2.1 Animal studies used to assess DDREF ..... 43
3.2.2 Influence of non-targeted processes on the shape of the dose-response relationship and hence on DDREF ..... 44
3.2.3 Types of study ..... 44

3.2.3.1 Influence of study design on tumour incidence, latency and mortality ..... 44
3.2.3.2 Effect of changes in age at exposure for studies using chronic exposures ..... 45
3.2.3.3 Differences in exposure regimes ..... 45
3.2.3.4 Data handling ..... 45
3.2.3.5 Sporadic vs. induced tumours ..... 46
3.2.3.6 Reliance upon a mixture of life-shortening and cancer cause of death as end points ..... 46

3.2.4 Pitfalls in long-term animal studies ..... 46

3.2.4.1 Assume dosimetry accurate and unbiased ..... 46
3.2.4.2 Background rate fluctuations ..... 46
3.2.4.3 Strain drift ..... 47
3.2.4.4 Gender ..... 47
3.2.4.5 Seasons ..... 47
3.2.4.6 Environment ..... 47
3.2.4.7 Hygiene ..... 47
3.2.4.8 Competing causes of death ..... 48
3.2.4.9 Histopathological evaluation and relevance of the tumour type to human situation ..... 48

3.2.5 Conclusion ..... 49
Literature ..... 49

**4 Radioepidemiological studies ..... 51**

4.1 Conclusion ..... 54
Literature ..... 54

**5 Basic scientific principles and other criteria relevant to radiation protection used to assess the DDREF ..... 56**

**6 Summary assessment ..... 59**

**List of figures ..... 62**

# 1 Introduction

## 1.1 Issue

One of the main objectives of radiation research is to quantify the relationship between radiation exposure and the resulting potential human detrimental health effects. The International Commission on Radiological Protection (ICRP) developed the "detriment" concept (ICRP 103) to quantify damage by expressing above all the risk of carcinogenesis or cancer mortality as a result of exposure. More recent findings give rise to the need to include also cardiovascular disease (SSK 2012). This is not, however, the subject of this recommendation; instead it focuses on another important aspect, the dose and dose-rate effectiveness factor (DDREF). Quantitative risk estimates are generally based on epidemiological studies involving relatively high doses[1] and high dose rates[2]. In order to make statements involving low doses[3] and low dose rates[4], extrapolations to low doses and low dose rates are required for which there are still not enough data available to reliably express risk.

Dose-response relationships from epidemiological studies each refer to a given exposure scenario with certain dose rates by observing the effect of a given dose. The stated dose is often only the temporally limited additional dose arising in this exposure situation excluding any doses from other sources such as natural ambient radiation. On the other hand, other studies compare various different exposure situations with differing levels of ambient radiation, e.g. radon studies. In general, the dose rate here is very low, while the dose accumulated over prolonged periods also involves values well in excess of 100 mSv.

A linear no-threshold relationship (LNT model) was adopted by the radiation protection community many years ago. It is also assumed that at low doses, the risk is not dependent upon radiation exposure over time, i.e. that it is not contingent upon the dose rate. Another assumption is that at low doses and low dose rates, the actual risk is overestimated by a certain factor if the risk values of high doses and high dose rates are extrapolated in linear fashion to low doses and low dose rates. The ICRP therefore adopted a dose and dose-rate effectiveness factor (DDREF) to adjust for this perceived overestimation. Risk values largely determined using epidemiological studies on people who survived the Hiroshima and Nagasaki atomic bombings are divided by this DDREF for low-dose and low-dose-rate radiation protection applications. In recommendation 103 (ICRP 2007), the ICRP confirmed its previous argumentation and recommends retaining a DDREF of 2 for solid tumours in the case of photon and electron exposures (low-LET[5] radiation). In its statements regarding ICRP 103, the German Commission on Radiological Protection (Strahlenschutzkommission, SSK) rejected this argumentation and called for a DDREF of 1, i.e. for the use of the "pure" LNT model. The SSK largely based its opinion on a lack of evidence regarding risk reduction at low doses and on reasons pertaining to design (SSK 2006).

With its many facets, the DDREF is an extremely subtle concept and should not strictly be seen as a single "factor" since it contains several influencing factors that have only been bundled into a single factor for practical radiation protection purposes.

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[1] Unless otherwise stated, the doses used in this recommendation refer to the effective dose.

[2] Dose rate = dose / time (according to DIN 6814, part 3).

[3] Effective dose <100 mSv

[4] Effective dose rate <0.1 mSv/min (according to UNSCEAR 2010)

[5] Linear energy transfer

In recent times, the scientific basis for justifying DDREF has increasingly become the subject of controversial debate all the way up to expert committees. Given these circumstances, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) commissioned the SSK with reviewing the current state of science and preparing a recommendation on DDREF. Due to the complexity of the problem, the BMU intentionally dispensed with stating more specific areas or aspects in its advisory mandate and instead chose to request a "statement and assessment of the general situation regarding the effect of radiation resulting from occupational exposure".

## 1.2 Background

Within the scope of the three basic radiation protection principles (*justification* of applications associated with ionising radiation, *optimisation* of radiation protection measures and *limitation* of exposure), knowledge of the relationship between radiation risk and dose is imperative, particularly when stipulating dose limits. For this reason, the development of limits over time is directly associated with corresponding knowledge of human health damage following exposure to ionising radiation. The low to medium doses (< 1 Gy) covered here largely involve stochastic damage (incidence and/or mortality due to tumours and hereditary damage) where the probability of an effect occurring correlates with the level of the exposure, i.e. the applied dose. This is quantified by a risk coefficient, i.e. the quotient of the probability of damage to the observed person's health and the dose causing the health damage. This report focuses on the dependency of this risk coefficient on the applied dose and dose rate, and the risk coefficient for low-dose and low-dose-rate exposures derived therefrom.

In the 1940s and 1950s, studies involving high doses to cell cultures, plants and animals showed that with a large number of observed post-exposure stochastic effects, the effect (and hence the rsik) of ionising radiation demonstrates a non-linear correlation with the applied dose and also depends on the dose rate.

Various publications by the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) document how research into the effect of ionising radiation is developing, including statements on the issue of dose and dose-rate dependency of the risk coefficient and its value at low doses and low dose rates.

The first UNSCEAR report (UNSCEAR 1958) only includes a few statements regarding the dose and dose-rate dependency of a risk coefficient for carcinogenic effects. Chapter VII (Summary and Conclusions) contains the following:

*"(36)… Our knowledge of the biological effects of low radiation levels is meagre because of experimental difficulties and the lengthy observations necessary to obtain results in this field. At present, opinions as to the possible effects of low radiation levels must be based only on extrapolations from experience with high doses and dose rates."*

The second UNSCEAR report (UNSCEAR 1962) used the two-hit theory (Lea 1955) and available data from very different experimental studies on cells and animals to hypothesise an exponential and/or linear-quadratic dose response relationship:

$$I = \alpha \cdot D + \beta \cdot D^2. \tag{2.1}$$

Low doses ($D \ll \alpha/\beta$) are dominated by a linear dose-response relationship without a threshold on which the quadratic term has no impact.

Annex B (Radiation Carcinogenesis in Man) of the third UNSCEAR report (UNSCEAR 1964) contains the following paragraph, which does not provide any quantitative data on the perceived overestimate of risk at low doses:

*"(17) In most cases in which extrapolation to low doses has been attempted a linear relationship between dose and effect has been assumed. A discussion of the use of the linear hypothesis can be found in the 1962 report. It should be noted that the assumption of linearity is the only one which allows the use of mean doses in estimating risks. 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."*

For a long time this statement on overestimation at low doses formed the prevailing opinion on the subject, although animal studies also showed that the stochastic effect is dependent upon the dose rate. This is also expressed in the NCRP, ICRP and UNSCEAR reports published in the 1970s.

An assessment of animal studies (somatic effects, cancer induction, life shortening) produced a DREF (**D**ose **R**ate **E**ffectiveness **F**actor) estimate of 2 to 10 (UNSCEAR 1977). Nevertheless, the following statement was made:

*"Because of the complexity and wide spectrum of the tumorigenic responses to radiation in the experimental animal, however, there appears to be no rigorously-defensible approach to deriving satisfactory DREFs for the human being, for either single tumour types or for all tumours collectively. Thus, the NCRP is reluctant at this time to go beyond providing a range of factors within which a single factor for the total yield of tumours in man after exposure of the whole body probably would lie. The DREF range is 2 to 10, when the actual absorbed dose is 20 rad (0.2 Gy) or less, or the dose rate is 5 rad per year (0.05 Gy/y) or less."*

In the 1980s, the linear-quadratic model was preferred when observing mutations, chromosome damage and the induction of certain tumours, and the 1986 UNSCEAR report (UNSCEAR 1986) described a factor of 1.5 to 3 between the risk coefficient at a range of 0.5 Gy to 1.5 Gy and that at 10 mGy for sparsely ionising radiation. A similar factor is also estimated for the high and low dose rate ratio. On the other hand, a linear dose-response relationship is also reported for other tumours, and in the end no generally valid reduction factor is specified. As with the NCRP report published in 1980, the following UNSCEAR report (UNSCEAR 1988) stated a DREF range of 2 to 10.

Annex B, B53 et seqq. of ICRP 60 (ICRP 1991) describe the reduction factor situation at length and specify a "**D**ose and **D**ose **R**ate **E**ffectiveness **F**actor" (DDREF) as it is still currently defined. Based on theoretical models, numerous animal studies on cancer incidence and life shortening, various clinical data, limited epidemiological information from Hiroshima and Nagasaki (Life Span Study, LSS), and by taking account of other available reports and assessments (UNSCEAR, BEIR, NUREG, US NIH), the ICRP recommended a DDREF of 2 for low doses and low dose rates involving low-LET radiation to convert risk coefficients determined at high doses and high dose rates. This value was seen to be relatively conservative and it was noted that this recommended value could change in future in the case of improved information levels.

ICRP 99 was published in 2005 and again confirmed a DDREF of 2 for questions relating to extrapolation of the risk coefficient at low doses (ICRP 2005). However it was emphasised that a value > 2 would no longer be consistent based on the latest LSS studies (Pierce and Preston 2000).

The UNSCEAR 2006 and UNSCEAR 2010 reports include extensive risk calculations involving various different dose-response relationships. The majority of the tabulated results

indicated the cancer risk per dose to be similar at doses of 10 mSv and 1 Sv. The results of epidemiological studies do not provide a clear distinction between a linear and linear-quadratic dose-response relationship (UNSCEAR 2006: *"... are consistent with a linear or linear-quadratic dose-response relationship*", UNSCEAR 2010: "*The dose-response relationship for mortality at low doses ... may be described by both a linear and a curvilinear function."*). There is however no clear evidence to support the need for a linear-quadratic function to describe data.

The BEIR VII Committee (BEIR 2006) also reanalysed the experimental data pertaining to DDREF and performed a Bayesian analysis to derive a range of 1.1 to 2.3. The committee considered the derived range to be implausibly narrow, which is why a larger uncertainty range was used in the calculations. Based on the statistical distribution of this data, the committee proposed a DDREF of 1.5.

In its general radiation protection recommendations published in 2007 (ICRP 103), the ICRP did not revise its DDREF recommendation from 1991 and continued to recommend a DDREF of 2 for solid tumours given the substantial uncertainties. Annex A states the following:

*"A dose and dose-rate effectiveness factor (DDREF) of 2 recommended in Publication 60 (ICRP 1991) should be retained for radiological protection purposes; the effect of introducing the possibility of a low-dose threshold for cancer risk is judged to be equivalent to that of an uncertain increase in the value of DDREF."*

In its statements regarding ICRP 103, the German Commission on Radiological Protection (SSK) rejected this argumentation and called for a DDREF of 1, i.e. for the use of the pure LNT model to extrapolate from high to low doses and low dose rates (SSK 2006).

By observing the historical development of determining general radiation risk coefficients, it must also be taken into account that the term "detriment" and therefore radiation risk have changed over time. In the past, the mortality risk was largely used to express risk coefficients. Nowadays, the probability of cancer incidence is mainly used, although the mortality risk and detriment to quality of life and life shortening are also included. Other illnesses involving, e.g. the cardiovascular system, are currently being discussed and may also have to be taken into account if future findings give rise to the need to include them. Risk coefficients therefore do not just include the DDREF, they also involve a number of other factors resulting from new medical developments and scientific findings, thus also rendering them subject to change.

## Literature


| | |
|---|---|
| BEIR 2006 | Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation. BEIR VII – Phase 2. United States National Academy of Sciences. National Academy Press, Washington DC. 2006 |
| ICRP 1991 | International Commission on Radiological Protection (ICRP). The 1990 Recommendations of the International Commission on Radiological Protection. Publication 60, Annals of the ICRP 21 (1-3). Pergamon Press, Oxford. 1991 |

| | |
|---|---|
| ICRP 2005 | International Commission on Radiological Protection (ICRP). Low-dose Extrapolation of Radiation-related Cancer Risk. Publication 99, Annals of the ICRP 35 (4). Pergamon Press, Oxford. 2005 |
| ICRP 2007 | International Commission on Radiological Protection (ICRP). The 2007 Recommendations of the International Commission on Radiological Protection. Publication 103, Annals of the ICRP 37 (2-4). Pergamon Press, Oxford. 2007 |
| Lea 1955 | Lea DE. Actions of Radiations on Living Cells. 2nd. Ed. University Press, Cambridge. 1955 |
| NCRP 1980 | National Council on Radiological Protection (NCRP). Influence of dose and its distribution in time on dose-response relationships for low-LET radiations. NCRP Report 64, NCRP, Washington DC. 1980 |
| Pierce and Preston 2000 | Pierce DA and Preston DL. Radiation-related cancer risk at low doses among atomic bomb survivors. Radiat Res. 2000;154:178-186 |
| SSK 2006 | Strahlenschutzkommission (SSK). Comments on the 2006 Draft of the ICRP Recommendations. Stellungnahme der Strahlenschutzkommission. Verabschiedet in der 209. Sitzung der Strahlenschutzkommission am 5. September 2006 |
| SSK 2012 | Strahlenschutzkommission (SSK). Herz-Kreislauferkrankungen nach zulässigen beruflichen Strahlenexpositionen. Stellungnahme der Strahlenschutzkommission. Verabschiedet in der 256. Sitzung der Strahlenschutzkommission am 19./20. April 2012 |
| UNSCEAR 1958 | United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation. General Assembly Official Records, 13th Session, Chapter VII. United Nations, New York, NY. 1958 |
| UNSCEAR 1962 | United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation. General Assembly Official Records, 17th Session, Chapter VII. United Nations, New York, NY. 1962 |
| UNSCEAR 1964 | United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation. General Assembly Official Records, 19th Session, Chapter III. United Nations, New York, NY. 1964 |
| UNSCEAR 1977 | United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation. Report to the General Assembly with Annexes, Annex G. United Nations, New York, NY. 1977 |

UNSCEAR 1986 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Genetic and Somatic Effects of Ionizing Radiation. Report to the General Assembly with Annexes, Annex B. United Nations, New York, NY. 1986

UNSCEAR 1988 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources, Effects and Risks of Ionizing Radiation. Report to the General Assembly with Annexes. United Nations, New York, NY. 1988

UNSCEAR 2006 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): 2006. Report to the General Assembly, with scientific annexes, Volume I: Report to the General Assembly, Scientific Annex A: Epidemiological studies of radiation and cancer. 2006 http://www.unscear.org/docs/reports/2006/07-82087_Report_Annex_A_2006_Web_corr.pdf (7637 kB) with corrections

UNSCEAR 2010 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): 2010. Report to the General Assembly, includes Scientific Report: Summary of low-dose radiation effects on health. 2011

# 2 Basic information about DDREF

One of the main objectives of radiation protection is to limit the risk of health damage due to exposure by ionising radiation. At low doses, such damage involves the stochastic effects (cause of cancer and hereditary damage). Individual and collective risks cannot be directly measured or monitored, which is why current radiation protection practices limit the risk by limiting the (measurable or calculable) dose and by stipulating dose limits. Here it is assumed that the various dose definitions (e.g. organ dose or effective dose) represent a meaningful measure of radiation risk for specific applications, i.e. that there is a clear link between dose and risk, which is why clarification of such dose-response relationships is a key aspect of radiation research.

## 2.1 Link with dose-response relationships

Dose-response estimates are generally based on evaluations of epidemiological studies into exposures involving doses above 50 mSv to 100 mSv. This enables risks close to the limit for occupational lifetime dose (400 mSv) to be directly estimated for both low and high dose-rate exposures. Extrapolations from high to low doses are needed to arrive at statements pertaining to a range of several 10 mSv, which is of importance to radiation protection. This extrapolation includes radiobiological results, mechanistic studies, and biophysical models that are used to reveal effect mechanisms and are included in the description of the (qualitative) form of a dose-response relationship at low doses. The linear-quadratic model is often used as an extrapolation model (see Chapters 2.2 and 2.3). In the past, this was largely justified by microdosimetric considerations that can no longer be fully maintained, so nowadays it is used as a simple mathematical description of non-linear dependencies. The extrapolated dose-response relationships provide the risk coefficients for low doses (e.g. ICRP 2007).

In the last few decades, various different approaches were made to obtain dose-response relationships for the various stochastic effects, in particular for cancer. An extrapolation to low

doses purely on the basis of epidemiological data does not provide a clear decision as to the type of dose-response relationship. The majority of controversial discussions about the risk of low doses of ionising radiation can be attributed to this fact. However, the inclusion of animal studies and mechanistic studies at a biophysical, molecular, and cellular level still fails to provide sufficiently substantiated statements about the risk of radiation at low doses (see Chapter 4).

In spite of this, the ICRP – along with almost every other radiation protection committee in the world – uses the LNT model to arrive at quantitative statements for radiation protection purposes, e.g. to stipulate dose limits. The LNT model assumes that the effect of ionising radiation at low doses increases in a linear manner with the dose and does not exhibit a dose threshold (ICRP 2007, Tubiana et al. 2006, Brenner and Sachs 2006, Breckow 2006, Shore 2009). The key radiation protection concepts (ALARA principle, justification principle, effective dose concept, etc.) are based on the LNT model, as currently implemented almost everywhere in the world.

The key point of discussion is the relationship between dose and effect with regard to radiation-induced human carcinogenesis. A dose-proportionate relationship based on radioepidemiological studies is comparably well established for doses of several 100 mSv in solid tumours. This applies both to acute radiation exposures involving large dose rates (mainly studies involving atomic bomb survivors (Preston et al. 2003, 2004, 2007)) and to chronic radiation exposures up to around 1 Sv with a low dose rate. However, the progression of this dose-response relationship at low doses (below several 10 mSv) remains a controversial topic. Due to the major statistical uncertainties with epidemiological data, it is practically impossible to determine the curve accurately enough at this dose level. Based on biological considerations, it appears plausible that there may be a non-linear relationship between the dose and radiation risk at low doses. Epidemiological and biological results are also unable to fully negate the existence of a dose threshold below which there is no radiation risk.

## 2.2 Relationship between dose and dose-rate effects

A lot of cellular studies show that after an acute exposure (high dose rate), the dose-response relationship is non-linear and often follows a linear-quadratic relationship. In principle, dose and dose-rate dependencies can be linked to one another.

In conventional models describing for example the effect of high doses in radiation therapy, this can be understood such that in the case of fractionated exposure, the total dose-response relationship can be determined by sequencing dose-response relationships from single fractions (Fig. 2.1). This is justified by the fact that regeneration and repair processes during irradiation breaks return the cells to an “initial state” from which they again follow a “new” (linear-quadratic) dose-response relationship. In the case of fractionated exposure, the effect of a certain dose will be lower than when receiving the same dose during a single exposure. If such a fractionation is subdivided into further fractions (including breaks between exposures) with diminishing single doses, the limit will result in chronic exposure at a low dose rate (Fig. 2.1). This explains why, when maintaining the same dose, chronic exposures involving low dose rates will have less of an effect than acute exposures involving high dose rates. The dependency of the response on the dose rate is known as the dose-rate effect and has been proven many times for cell survival.

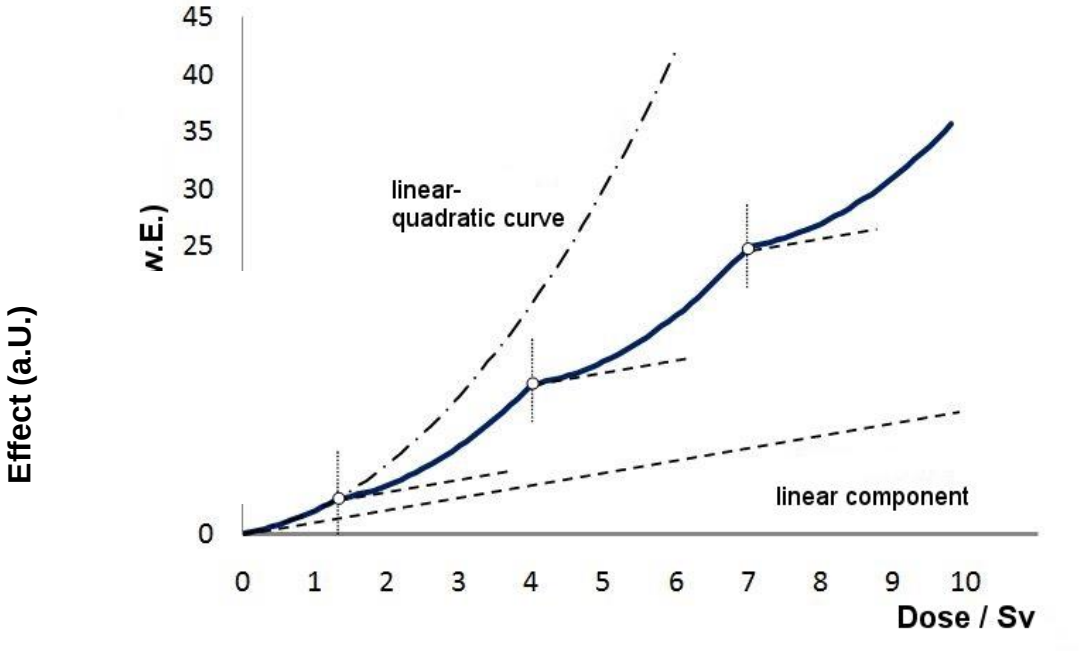


*Fig. 2.1: Dose-rate effect: Based on a linear-quadratic dose-response relationship (equations (2.1) and (2.2)), here: $\alpha/\beta$ = 1 Sv), fractionation, i.e. exposure involving several single doses, has less of an effect (solid line) than that caused by a single exposure with the same dose (dotted and dashed line). At the limit to very many fractions, the effect (in arbitrary units, a.U.) follows the linear component (dashed line) of the linear-quadratic curve.*

In the conventional model mentioned above, the extent of the dose-rate effect depends on the level of non-linearity or, as is the case with the linear-quadratic model, on the extent of the quadratic component. Here, a purely linear dose-response relationship would assume that the temporal distribution of an exposure has no impact on the effect and thus no dose-rate dependency exists.

With the linear-quadratic model, the increase in dose-response relationship at low doses is determined by the linear term (often represented by $\alpha \cdot D$, see equation (2.1) (Fig. 2.2). Based on the above statement (cf. Fig. 2.1), the effect of chronic exposures (low dose rates) is determined by this term. The quadratic term ($\beta \cdot D^2$) gains importance at higher doses. The dose at which the linear and the quadratic term have the same value is known as the $\alpha/\beta$ value and is a measure of the non-linearity of a dose-response relationship. The higher this value, the more linear is the dose-response relationship and the smaller the difference between the effect of acute and chronic exposure in the model illustrated in Figure 2.1. At the limit to very high $\alpha/\beta$ values, a linear-quadratic relationship will become a linear relationship and the dose-rate effect disappears (see above). Given these considerations, the LNT model at low doses also inherently means that the effect is independent of the dose rate at this dose level.

However, the above argumentation is not binding and the cellular mechanism on which it is based does not apply to every effect, i.e. it is limited to a certain set of effects. Mechanisms are possible whose response follow a non-linear (including linear-quadratic) dose relationship as a result of damage which accumulates such that the affected cells are not reset to an initial state after a certain recuperation phase. In such cases there is no dose-rate dependency, irrespective of the non-linear dose-response relationship. On the other hand, it is possible that repair mechanisms and other processes could at least partly repair molecular or cellular damage, even

in the case of an underlying linear dose-response relationship. In this case, a linear relationship could indeed give rise to a dose-rate dependency.

The dose-response relationships of many molecular and cellular radiation effects are known, partially up to doses of 1 mSv (see Chapter 3.1). In connection with this there are effects with linear dependencies (e.g. double-strand breaks), with linear-quadratic dependencies (e.g. chromosome aberrations), and with other non-linear dependencies (e.g. adaptive response, bystander effect, apoptosis). However, knowledge of their interaction within a highly complex carcinogenic process is still too poor to be able to make substantiated statements about their total dose response curve at low doses and derive any occurring dose-rate dependencies therefrom. Statements regarding potential relationships between dose and dose rate are also vague, which is one of the reasons why the ICRP and other committees introduced a *single* factor (DDREF) to account for dose and dose-rate effects rather than trying to view and quantify the various effects separately (ICRP 2007, BEIR 2006).

Based on epidemiological studies the dependency of radiation risk upon the dose rate was investigated (Jacob et al. 2009). A meta-analysis of 12 studies was performed in which the risk coefficients derived from studies involving medium doses and low dose rates were compared with studies involving survivors of the Hiroshima and Nagasaki atomic bombings (Life Span Study, LSS) who were exposed to high dose rates (see Chapter 4). The study by Jacob et al. investigated the influence of various dose rates on risk estimates, based on the LNT model. This approach therefore permits a separate discussion regarding a "*dose* effectiveness factor" on the one hand, and a "*dose-rate* effectiveness factor" on the other hand (Jacob et al. 2009).

Various different terms are often inconsistently used to describe the various dose and dose-rate dependencies. Pertinent literature uses terms such as "low-dose extrapolation factor", "linear risk overestimation factor", "linear extrapolation overestimation factor", etc. The terms "**L**ow-**D**ose **E**ffectiveness **F**actor" (LDEF) and "**D**ose-**R**ate **E**ffectiveness **F**actor" (DREF) are often used to individually describe the influence of dose dependencies and dose-rate dependencies. The curvature of the dose-response relationship for single (acute) exposures at various different doses is analysed in order to determine the LDEF. Such analyses can be performed using a single dose-response relationship. The increases or curvature of various different exposures at high and low dose rates are compared in order to determine the DREF. Such comparisons therefore require results from at least two populations (one exposed with a high dose rate and one exposed with a low dose rate).

## 2.3 Relationship between LET and energy

Models used to extrapolate to low doses are largely based on considerations involving the linear-quadratic model (Fig. 2). A lot of cellular and animal studies can be clearly described by a linear-quadratic dose-response model. This model was originally ascribed to mechanistic response relationships based on microdosimetric approaches (theory of dual radiation action) (Kellerer and Rossi 1972). This model is in particular able to express LET dependencies of various different types of radiation. Following exposure, an observed response *W(D)* results in the following relationship:

$$W(D) = \alpha \cdot D + \beta \cdot D^2 . \qquad (2.1)$$

Here, the $\alpha/\beta$ ratio is a factor specific to the type of radiation that is closely correlated to the LET and corresponds to the dose at which the linear and the quadratic term are of equal size. With high $\alpha/\beta$ values (high LET, densely ionising radiation), the linear term dominates throughout the entire dose range, while with low $\alpha/\beta$ values (low LET, sparsely ionising

radiation), the quadratic component dominates increasingly as the dose increases. With low doses, the linear-quadratic model always evolves into the LNT model (cf. Fig. 2.2).

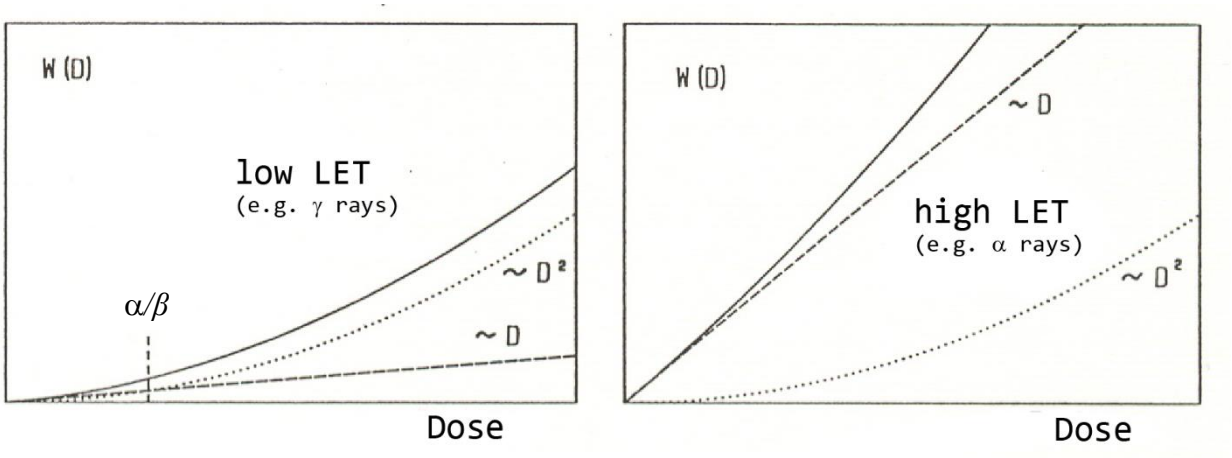


*Fig. 2.2: Linear-quadratic dose-response relationships for radiation types with a low and a high LET. The quotient α/β depends on the LET and describes the dose at which the linear and the quadratic term have the same size. N.B.: The quadratic component (dotted line) is the same on both charts. The dose-response relationship is calculated based on*

$$W(D) = c \cdot (\frac{\alpha}{\beta} \cdot D + D^2) \quad with \quad \frac{\alpha}{\beta} \sim LET \quad .$$

In epidemiological studies, risk coefficients are generally determined at doses ranging from 100 mSv to several Sv. By using the LNT model to extrapolate from this dose range to low doses, and if the actual risk follows a linear-quadratic relationship, an overestimate of the risk depending on the α/β ratio (proportional to LET) and the dose will occur (see Chapter 2.2). A DDREF or LDEF (see equation (2.2)), which should compensate this overestimate, is therefore also dependent on the α/β ratio (LET) and the dose (Trabalka and Kocher 2007):

$$LDEF = \frac{\alpha \cdot D + \beta \cdot D^2}{\alpha \cdot D} = 1 + \frac{D}{\alpha / \beta} \quad . \qquad (2.2)$$

Figure 2.3 illustrates the LDEF's dependency on the α/β ratio. By performing a linear extrapolation from a dose of 1 Sv to lower doses, a value of α/β = 1 Sv leads to an LDEF of 2 (marked in the figure). Extrapolating from 600 mSv results in a LDEF of 1.6. Extrapolating from 600 mSv with α/β = 3 Sv results in a LDEF of 1.2.

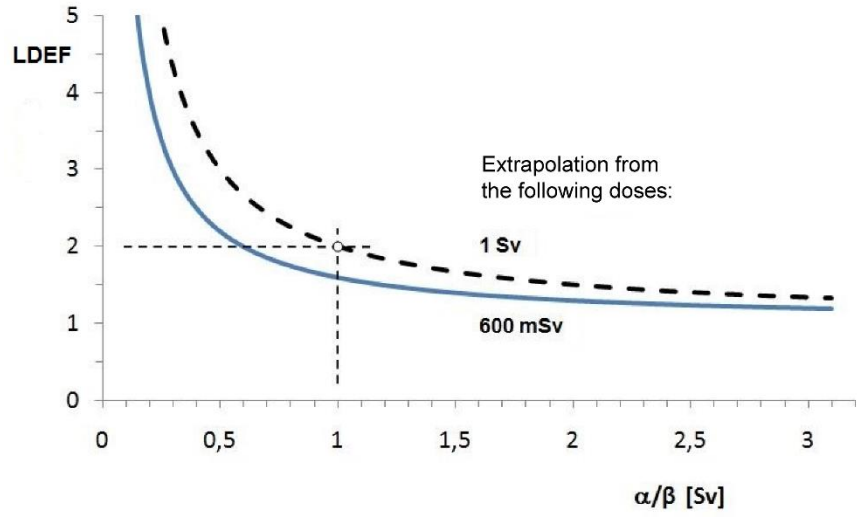


*Fig. 2.3*: *Dependence of the LDEF on the α/β ratio of a linear-quadratic dose-response relationship (equation (2.2)) when extrapolating from a dose of 1 Sv (dashed line) or 600 mSv (solid line).*

In radiation protection the radiation quality is accounted for by the LET-dependent quality factor used to calculate the dose equivalent or by the radiation weighting factor used to determine the equivalent dose. With low-LET radiation, the quality factor and radiation weighting factor have a value of 1, meaning that low-LET radiation (photon radiation) is the reference radiation used to determine risk coefficients. Therefore, considerations to the DDREF are relevant particularily for this radiation type. According to the above-described model for radiation types with a high LET, i.e. a high α/β ratio, the LDEF (or DDREF) is smaller, which means that the DDREF problem is limited to low-LET radiation.

## 2.4 Conclusion

By assuming that higher risks per dose occur at high doses when compared to low doses, a linear extrapolation from high to low doses will lead to an overestimation of the actual risk (dose effect). The same also applies when extrapolating from high dose rates to low dose rates (dose-rate effect). For radiation protection purposes, this potential risk overestimate is compensated for by a common factor by which the risk coefficients measured at high doses and high dose rates are divided. In terms of the method used, the DDREF is not a "factor" in the sense of an inherently constant parameter for estimating risk coefficients. Instead the DDREF value depends on the respective dose and dose rate used to extrapolate low doses and low dose rates. It may also depend on the quality of the observed radiation and, therefore, on the radiation energy (Trabalka and Kocher 2007). However, there is not enough information available about the type and magnitude of all these dependencies. Hence the DDREF – irrespective of the value assigned to it – is of rather general relevance in radiation protection and adresses to any specific aspect. In fact, the effects of all these dependencies are summarised by a single constant "factor", namely the DDREF. In 2007, the ICRP concluded "*that the adoption of the LNT model combined with a judged value of DDREF provides a prudent basis for practical purposes of radiological protection (i.e. the management of risks from low-dose radiation exposure in prospective situations)*" (ICRP 2007). In 2013, the ICRP set up a task group to again take up the discussion on DDREF.

In its statements regarding ICRP 103, the Strahlenschutzkommission (SSK) rejected this argumentation and called for a DDREF of 1, i.e. for the use of a "pure" LNT model (SSK 2006).

## Literature


BEIR 2006 — Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation. BEIR VII – Phase 2. United States National Academy of Sciences. National Academy Press, Washington DC. 2006

Breckow 2006 — Breckow J. Linear-no-threshold is a radiation-protection standard rather than a mechanistic effect model. Radiat Environ Biophys. 2006;44:257-260

Brenner and Sachs 2006 — Brenner DJ and Sachs RK. Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach. Radiat Environ Biophys. 2006;44:253-256

ICRP 2007 — International Commission on Radiological Protection (ICRP). The 2007 Recommendations of the International Commission on Radiological Protection. Publication 103, Annals of the ICRP 37 (2-4). Pergamon Press, Oxford. 2007

Jacob et al. 2009 — Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H. Cancer risk of radiation workers larger than expected? Occup. Environ. Med. published online 2009 Jun 30; doi:10.1136/oem.2008.043265

Kellerer and Rossi 1972 — Kellerer AM and Rossi HH. The theory of dual radiation action. Curr Top Radiat Res. 1972;Q8:85-158

Preston et al. 2003 — Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. Radiat Res. 2003;160:381-407

Preston et al. 2004 — Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res. 2004;162:377-389

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

Shore 2009 — Shore RE. Low-dose radiation epidemiology studies: Status and issues. Health Phys. 2009;97(5):481-486

SSK 2006 — Strahlenschutzkommission (SSK). Comments on the 2006 Draft of the ICRP Recommendations. Stellungnahme der Strahlenschutzkommission. Verabschiedet in der 209. Sitzung der Strahlenschutzkommission am 5. September 2006

Trabalka and Kocher 2007 — Trabalka JR and Kocher DC. Energy dependence of dose and dose-rate effectiveness factor for low-LET radiations: Potential importance to estimate of cancer risks and relationship to biological effectiveness. Health Phys. 2007;93(1):17-27

Tubiana et al. 2006 — Tubiana M, Aurengo A, Averbeck D, Masse R. Recent reports on the effect of low doses of ionizing radiation and its dose-effect relationship. Radiat Environ Biophys. 2006;44:245-251

# 3 Radiobiological studies

## 3.1 In vitro studies

### 3.1.1 Dose dependencies

In vitro studies were and still are often used to justify a DDREF > 1, with particular emphasis on chromosome aberrations. It is still not clear, however, what role they play when it comes to tumour induction. The particular emphasis placed on chromosome aberrations is due to the fact that the "Theory of dual radiation action" (Kellerer and Rossi 1972) was believed to be able to quantitatively substantiate their occurrence, which in turn allowed dose-response relationships to also be extrapolated to low dose ranges for which there were no experimental results. Nowadays, when observing a large dose range, it is generally assumed that other biological mechanisms may play a role at low doses (several 100 mGy) when compared to high doses. It is however unclear what health effects these mechanisms may have at low doses.

Apart from chromosome aberrations, other investigated effects include the induction of mutations, the loss of colony-forming ability and in vitro transformation. Epigenetic approaches have also recently become a focus of interest. The path from initial energy deposition to tumour manifestation is both long and extremely complex (e.g. the role of the immune system), which raises serious doubts about the transferability of in vitro results to the human body. This is compounded by the fact that cellular end points seldom give rise to reliable results at low doses.

The quantum structure of energy transfer during the interaction of ionising radiation with matter implies that there cannot be any arbitrarily small energy deposition during a single interaction event. The lowest deposited amount of energy during a single event depends on the dimensions of the observed region and LET of the radiation. When reducing the dose, only the number of randomly distributed events in an observed volume decreases, while the mean amount of energy deposited per event remains the same. If the observed effects are linearly dependent on the dose, there cannot be any thresholds, i.e. thresholds are only ever possible if there is a non-linear dose-response relationship.

Non-linearities can be attributed to a number of different causes: The simple scenario involves a direct interaction between (dose-proportionately induced) primary lesions, e.g. DNA double-strand breaks (DBS), such as the one postulated in the "two-hit theory" to explain the origin of chromosome aberrations. Another scenario is where the probability of errors that occur when repairing primary damage increases along with their number in a cell. A threshold value may

occur for end points based on repair of primary lesions in a cell if cellular process activation only occurs above a certain amount of damage. Conversely, saturation mechanisms could lead to a levelling-out of the dose-response relationship curve. Non-linear dependencies may also be caused by the fact that cells not directly affected by radiation exhibit response reactions (bystander effect) or if effects only occur at a later stage in irradiated cell descendants.

The extent to which such processes are relevant to tumour induction is still unknown. This means that in vitro studies can provide not more than important points of reference, but are not suited to justifying dose and dose-rate dependencies for tumour induction.

### *DNA damage*

DNA double-strand breaks (DSB) are induced in linear dependence on the dose by sparsely ionising radiation across a range of 5 orders off magnitude (1 mGy to 100 Gy) (Rothkamm and Löbrich 2003, Löbrich and Kiefer 2006)[1]. Depending on the genetic characteristics of the investigated system, the DSB can be repaired but the process is not error-free and may therefore lead to the induction of chromosome aberrations or mutations. The probability of repair depends on the dose. At exposures < 10 mGy, in vitro and in vivo, DSB are retained for prolonged periods (Grudzenski et al. 2010). In this case, DSB repair could be promoted by $H_2O_2$ in concentrations that are too low to induce DSB itself. This phenomenon can be interpreted by the assumption that oxygen radicals, single-strand breaks or base changes can stimulate repair processes. This is also supported by the fact that a series of repair-relevant genes that are inactive at very low doses are upregulated when treated with $H_2O_2$ (Grudzenski et al. 2010). Gene regulation issues are covered in more detail below. Deliberations should therefore continue as to whether the described results generally indicate an increased level of sensitivity at very low doses, particularly as full DSB repair was also observed (Asaithamby and Chen (2009)) at very low doses (around 1 mGy) in other cell types and populations exhibiting exponential growth.

The importance of repair processes when it comes to determining DSB by means of experiment and the possible formation of cellular radiation damage are substantiated by a more recent study performed by Neumaier et al. (2012). Similar to other authors, they used special cytological techniques on proteins that are proven to bind to DSB, but also pursued the temporal progression of the formation of these bonds. They found that the number of x-ray-induced DSB (foci) estimated by this method did not uniformly rise in proportion to the dose at doses above the investigated range (50 mGy to 4 Gy). At low doses, far more foci were measured per dose unit than at higher doses. This is interpreted by the assumption that neighbouring DSB aggregate to form "repair centres" that appear as foci at microscopic level, thus feigning a single DSB. If, as the authors assume, one postulates that these aggregated DSB could primarily be the starting point for defective repair processes and thus for mutations and transformations, this would lead to a disproportionate rise for such end points at higher doses which could in turn lend plausibility to a non-liner dose dependency. However, it should be noted that the described assumptions have already been made in the past, e.g. to explain the incidence of chromosome aberrations, meaning that results from new experiments – important though they are for quantifying primary radiation damage – do not provide any new arguments to help understand tumour induction.

[1] DSB were determined by γH2X foci at low doses and by gel electrophoresis at high doses.

### *Chromosome aberrations*

With x-rays and gamma rays, chromosome aberrations usually exhibit a linear-quadratic dependency. This applies both to dicentric (unstable) aberrations and (stable) translocations (UNSCEAR 2000, Sasaki 2009). Detection of chromosome aberrations is of limited sensitivity. In mammalian cells, considerable experiment work only produces statistically significant results at doses well in excess of 20 mGy (UNSCEAR 2000 and other literature referenced there).

A number of other studies were conducted where radiation-induced simple and complex chromosome exchange aberrations (involving more than two breakpoints) were investigated in terms of their dose and dose-rate dependency (Loucas et al. 2004, Cornforth 2006). At high dose rates a linear-quadratic dose dependency occurs for the entirety of all aberrations, although closer analysis shows that non-linearity is solely due to complex aberrations. A clearly linear dose dependency was observed with very low dose rates (see below, Fig. 3.1.). Only a weak dose effect is seen (slight deviation from linearity), which is contrasted by a strong dose-rate effect (approximately a factor of five in slope of the linear component). It could therefore be concluded that complex aberrations are not formed in this case, but in fact this is not true. Its level is much lower, but it still remains significant.

### *Cell survival, mutations, in vitro transformation*

The survival curves for mammalian cells after exposure to sparsely ionising radiation generally indicate a non-linear dose dependency often described by a linear-quadratic function where the lowest doses that can be applied in experiments are however around 0.5 Gy. Nowadays, special techniques are available that allow experiments to be performed at lower doses. Such experiments provided surprising results: At doses of approx. 300 mGy to 600 mGy, there were major deviations from the "standard survival curves" as the cells were far more sensitive than expected. Although not found in every cell type, this phenomenon is known as "low-dose radiation hypersensitivity" (HRS). Survival at low doses can therefore not be determined by extrapolating down from high doses. The described behaviour can be explained by the assumption that repair processes induced at higher doses remain inactive at lower doses (Marples and Joiner 1993). The transition is apparently brought about by activating the ATM (ataxia telangiectasia mutated) gene which plays a major part in triggering radiation-induced delays to the cell cycle. It has long been known that G2 phase progress in the cell cycle slows down following exposure, which provides time for damage repair. This "conventional G2 checkpoint" comes relatively late during the G2 phase. However, an "earlier" G2 checkpoint was recently identified for whose function the ATM gene plays a key role (Xu et al. 2002), which is characterised by a clear dose threshold of less than 400 mGy (Krueger et al. 2007a) and where the cell cycle is not halted at low doses. In contrast to the "conventional" G2 block whose length increases with the dose, the length of the delay at the "early" G2 delay point does not depend on the dose. High sensitivity at very low doses is due to the fact that early cell cycle control with a threshold of around 10 DSB to 20 DSB (Löbrich and Jeggo 2007) is not activated, thus providing no time for DSB repair. The cells with unrepaired DSB are probably eliminated due to apoptosis (Krueger et al. 2007b). To date, the HRS phenomenon has only been proven with regard to survival (see Marples and Collis 2008 for an overview), meaning that it can be interpreted as a safeguard mechanism against the proliferation of cells with hereditary damage but cannot be drawn on as proof of enhanced sensitivity in terms of stochastic effects. Corresponding studies on mutation induction or in vitro transformation would be required to justify such effects, but such studies are not available.

Mutation induced by low-LET radiation in mammalian cells usually exhibits a linear-quadratic dependency on dose. However, the methods available do not permit studies at very low doses.

The lower limit in human lymphoblastoid cells ($TK_6$), which are very sensitive, is around 250 mGy (König and Kiefer 1988). An increase in sensitivity at low doses has not been observed to date.

Of all the cellular parameters, in vitro transformation represents the closest relationship with risk estimation for stochastic effects and can be investigated in special cell systems. Representative data were collected within the scope of a European Community study involving six laboratories (Mill et al. 1998). $C3H10T_{1/2}$ cells were used most frequently and exhibited a linear dose-response dependency at doses of 250 mGy to 5 Gy when adjusted for the number of killed cells. There are no studies available for the behaviour at low doses.

### *Bystander effect, delayed effects, genomic instability[1], adaptive response*

Radiation effects may also be exhibited in cells that were not directly irradiated. This phenomenon, commonly known as the "bystander effect", is either exhibited by targeting exposure at single cells using microbeam facilities (MBF) or as a result of the influence of culture media of irradiated populations on non-irradiated cells. This contradicts the conventional notion that only direct energy depositions trigger radiobiological effects. The underlying mechanism still remains controversial, but it appears to be without question that irradiated cells emit chemical signals that trigger effects in recipients similar to those seen in directly irradiated cells such as loss of capacity to divide, chromosome aberrations (Lorimore et al. 1998), sister chromatid exchanges (Lehnert et al. 1997), micronuclei (Belyakov et al. 2001), mutations (Nagasawa and Little 1999) and neoplastic transformations (Sawant et al. 2001). The bystander effect plays a role at low doses where a significant proportion of the cell population is not directly affected as it leads to a (virtual) enlargement of the target and, with it, to a greater radiation effect than would be expected on the basis of conventional dosimetry.

Cells that survived radiation often exhibit delayed effects such as a significant reduction in cell-forming ability several generations later (depending on the primary dose) and delayed onset of mutations. Their spectrum differs from that of directly induced effects, which indicates that radiation exposure causes a certain genomic labilisation usually known as genomic instability (Smith et al. 2003, Streffer 2010). This phenomenon was first found in irradiated two-cell zygotes of mouse embryos (Pampfer and Streffer 1989) and later in human bone marrow cells (Kadhim et al. 1995). Current estimates indicate that genomic instability could play a key role in carcinogenesis, but there are indications that it only occurs in transformed in vitro cells (Dugan and Bedford 2003), which would therefore call this interesting hypothesis into question. Previously described phenomena tend to lead to higher sensitivity at low doses than would be expected by extrapolating from higher doses.

Adaptive response is a different effect with a protective impact at low doses. Pre-irradiation with a dose of 10 mGy to 200 mGy (priming dose) can significantly reduce the level of damage caused by a subsequent exposure at far higher doses (challenging dose). This was initially observed with chromosome aberrations (Olivieri et al. 1984) and subsequently demonstrated with other end points, namely mutations, colony-forming ability (Zhou et al. 2003, Cai and Liu 1990) and neoplastic transformations (Elmore et al. 2008). Adaptive response is characterised by a high level of variability and is not always found in every system (Preston 2005, Schwartz 2007, Tapio and Jacob 2007).

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[1] Genomic instability is a collective term for all hereditary chromosome mutations. This includes simple events such as stable chromosome translocation as well as progressive chromosome disruptions such as those seen in the breakage-fusion-bridge (BFB) cycle or single major disruptions of several chromosomes, e.g. chromothripsis.

### *Influence of gene activity and epigenetic effects*

Cells exposed to radiation exhibit a change in the activity of a large number of genes (Criswell et al. 2003, Ljungman 2010), including those involved in repair processes and cell-cycle regulation. However, the pattern seen in sets of affected genes and the extent of induced changes differ at high and low doses (Amundson et al. 2003, Ding et al. 2005). Models were developed on the basis of these findings that should be able to explain the bystander effect and adaptive response phenomena at molecular level (see e.g. Matsumoto et al. 2009), but are still awaiting confirmation. Alongside these non-targeted or delayed effects, the last few years have seen epigenetic effects gain in importance when it comes to understanding regulatory cell processes. Epigenetic effects impact gene expression regulation without the information having to be saved in the DNA. However, the roles played by non-targeted, delayed and epigenetic effects on radiation-induced molecular and cellular effects and their repair still largely remain unexplained (Little 2010). This applies in particular to their potentially modifying influences on dose and dose-rate dependencies.

## 3.1.2 Dose-rate dependencies

At low dose rates there is a vastly reduced number of chromosome aberrations (see Fig. 3.1.). When compared to acute exposure, the dose-response relationship is purely linear and exhibits a slope that is five times lower. Similar behaviour can generally be observed in terms of cell survival. In the case of a loss of colony-forming ability, a reduction in dose rate generally leads to a reduced effect (Amdur and Bedford 1994). However, with some cell lines an inverse dose-rate effect was observed, i.e. enhanced radiation sensitivity, at a dose rate below 300 mGy/h (Mitchell et al. 2002), which can be linked to low-dose hypersensitivity (HRS) (see below). Such behaviour appears to be dependent upon genetic factors and is not universally observed (Williams et al. 2008). A more recent study into the effect of different dose rates on the formation of micronuclei showed that a reduction in dose rate leads to an increase in micronuclei (Brehwens et al. 2010).

With in vitro transformations, a protective irradiation effect was found at low dose rates (Elmore et al. 2006, Elmore et al. 2008) and attributed to an adaptive-response effect (Ko et al. 2006). The authors concluded that a reduced cancer risk can be assumed under these conditions.

A considerable inverse dose-rate effect was found by various working groups and in various different cell lines for mutation induction where the mutant yield per dose rises when the dose rate drops (Vilenchik and Knudson 2000), which is a surprising result observed with gamma rays back in 1990 (Crompton et al. 1990) but given little attention. Closer analysis shows that this phenomenon only occurs in exponentially growing cell populations, but not in stationary ones (Brehwens et al. 2010, Kiefer et al. 2002).

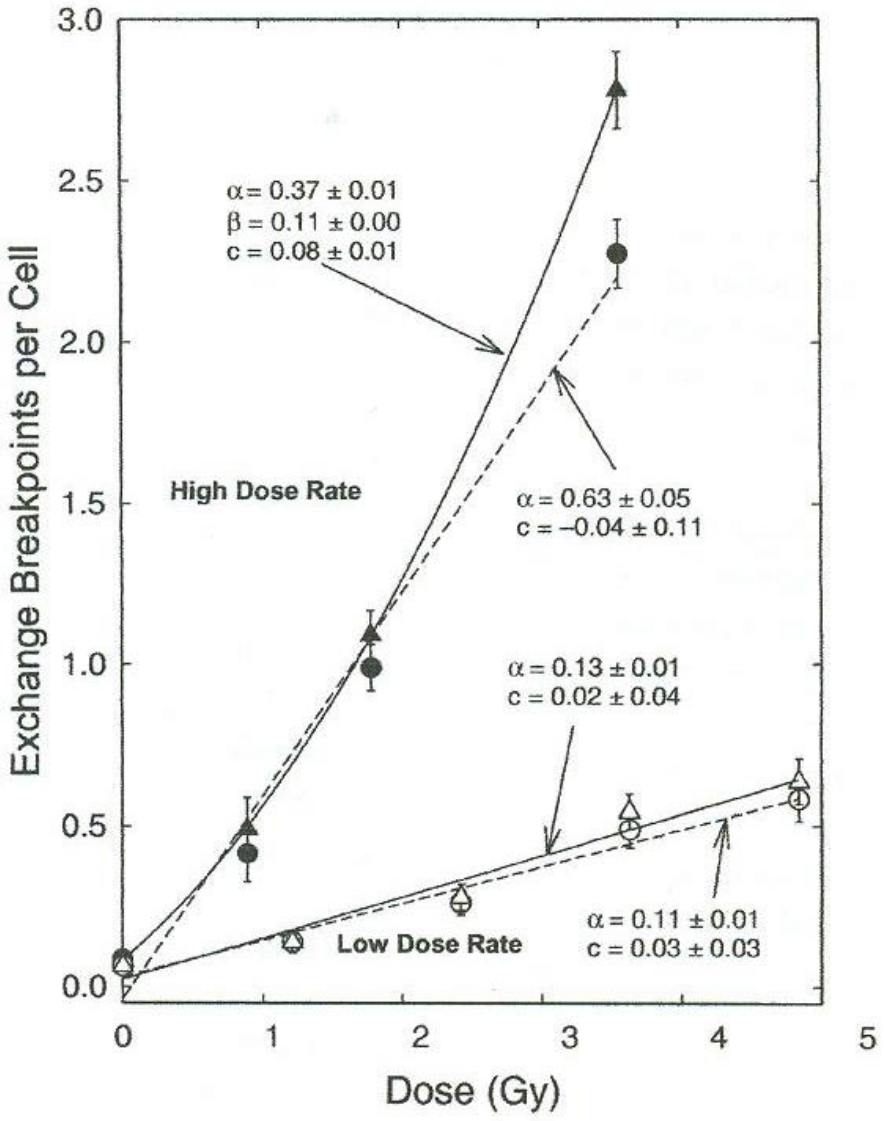


*Fig. 3.1:* *Number of breakpoints per cell in chromosome exchange aberrations depending on the dose at various different dose rates. The parameters α and β represent the linear and quadratic terms in the linear-quadratic relationship (see equation 2.1), while c is the polynomial axis intercept. Triangles represent "complex" aberrations (several breakpoints per exchange), while circles indicate "simple" aberrations (one or a few breakpoints per exchange).*

*(Source: Loucas et al. 2004, Fig. 4, p. 343. This figure is republished with the permission of the journal "Radiation Research". The original title is: Exchange breakpoints as a function of acute and chronic dose. Triangular symbols represent the dose response for total exchanges (simple plus complex). Circular symbols show the response for simple exchanges alone. For both high and low dose rates, the induction of simple exchanges is fitted well by a linear model. At high dose rates virtually all of the curvature in the shape of the dose response is due to breakpoints from complex exchanges, whose contribution to total damage becomes significant above 2 Gy. At limiting low dose rates all evidence of upward curvature is gone, and the dose responses for total and simple exchanges are almost superimposable, demonstrating that the relative contribution of complex aberrations is small. Nevertheless, complex aberrations are formed under these conditions, accounting for roughly 10 to 15% of the total exchange breakpoints.*

### 3.1.3 Conclusion

At molecular and cellular level (in vitro studies), a range of linear and non-linear effects can be observed in various cell systems depending on the investigated end points. Nowadays, when observing a large dose range, it is generally assumed that other biological mechanisms have an impact at low doses (< 100 mGy) when compared with high doses. It is however unclear what health effects these mechanisms may have at low doses.

This in turn makes it difficult to determine relevance when evaluating a DDREF. While the number of double-strand breaks and level of other radiation-induced DNA damage increase linearly to the dose, chromosome aberrations and repair processes reveal, at least in part, non-linear dose-response components. Dependencies on dose rate may be observed in a range of different effects, although a reduction in effectiveness is not always seen at low dose rates. There are however no clear indications of a relationship between dose and dose-rate effects as they appear to be largely "independent" of one another.

As there are only a limited number of epidemiological options available at low doses and low dose rates, it was often argued that a response to open issues could be provided by performing in vitro studies to clarify basic mechanisms. The current state of research renders in vitro studies ambivalent such that they can barely be used to justify a DDREF. For a long time it was assumed that dose-response relationships for chromosome aberrations, mutation induction and the loss of colony-forming ability after exposure to sparsely ionising radiation are generally described by a linear-quadratic function. Recent studies and the demonstration of "unconventional" effects (bystander effect, low-dose hypersensitivity (HRS), genomic instability) now call this assumption into question as it is based on microdosimetric considerations as a theoretical justification for non-linearities, and thus also for dose-rate effects.

Even if non-linear effects might generally be assumed at in vitro level, it is still largely unclear whether and how they interact during complex biological processes and whether and how non-linearities are "passed on"to the in vivo situation for carcinogenesis.

## Literature


| | |
|---|---|
| Amdur and Bedford 1994 | Amdur RJ and Bedford JS. Dose-rate effects between 0.3 and 30 Gy/h in a normal and a malignant human cell line. Int J Radiat Oncol Biol Phys. 1994;30(1):83-90 |
| Amundson et al. 2003 | Amundson SA, Lee RA, Koch-Paiz CA, Bittner ML, Meltzer P, Trent JM, Fornace J. Differential responses of stress genes to low dose-rate γ irradiation. Mol. Cancer Res. 2003;1:445-452 |
| Asaithamby and Chen 2009 | Asaithamby A and Chen DJ. Cellular responses to DNA double-strand breaks after low-dose gamma-irradiation. Nucleic Acids Res. 2009;37(12):3912-3923 |
| Belyakov et al. 2001 | Belyakov OV, Malcolmson AM, Folkard M, Prise KM, Michael BD. Direct evidence for a bystander effect of ionizing radiation in primary human fibroblasts. Br J Cancer. 2001;84(5):674-679 |

Brehwens et al. 2010 — Brehwens K, Staaf E, Haghdoost S, González AJ, Wojcik A. Cytogenetic damage in cells exposed to ionizing radiation under conditions of a changing dose rate. Radiat Res. 2010;173(3):283-289

Cai and Liu 1990 — Cai L and Liu SZ. Induction of cytogenetic adaptive responses of somatic and germ cells in vivo and in vitro by low dose X-irradiation. Int. J. Radiat. Biol. 1990;58:187-194

Cornforth 2006 — Cornforth MN. Perspectives on the formation of radiation-induced exchange aberrations. 2006 Sep 8;5(9-10):1182-1191. Epub 2006 Jun 27

Criswell et al. 2003 — Criswell T, Leskov K, Miyamoto S, Luo G, Boothman DA. Transcription factors activated in mammalian cells after clinically relevant doses of ionizing radiation. Oncogene. 2003;22(37):5813-5827

Crompton et al. 1990 — Crompton NE, Barth B, Kiefer J. Inverse dose-rate effect for the induction of 6-thioguanine-resistant mutants in Chinese hamster V79-S cells by 60Co gamma rays. Radiat Res. 1990;124(3):300-308

Ding et al. 2005 — Ding L-H, Shingyoji M, Chen F, Hwang J-J, Burma S, Lee C, Cheng J-F, Chen DJ. Gene expression profiles of normal human fibroblasts after exposure to ionizing radiation: a comparative study of low and high doses. Radiat Res. 2005;164:17-26

Dugan and Bedford 2003 — Dugan LC and Bedford J.S. Are chromosomal instabilities induced by exposure of cultured normal human cells to low- or high-LET radiation? Radiat Res. 2003;159:301-311

Elmore et al. 2006 — Elmore E, Lao XY, Kapadia R, Redpath JL. The effect of dose rate on radiation-induced neoplastic transformation in vitro by low doses of low-LET radiation. Radiat Res. 2006;166(6):832-838

Elmore et al. 2008 — Elmore E, Lao XY, Kapadia R, Giedzinski E, Limoli C, Redpath JL. Low doses of very low-dose-rate low-LET radiation suppress radiation-induced neoplastic transformation in vitro and induce an adaptive response. Radiat Res. 2008;169(3):311-318

Grudzenski et al. 2010 — Grudzenski S, Raths A, Conrad S, Rübe CE, Löbrich M. Inducible response required for repair of low-dose radiation damage in human fibroblasts. Proc Natl Acad Sci U S A. 2010;107(32):14205-14210

Kellerer and Rossi 1972 — Kellerer AM and Rossi HH. The theory of dual radiation action. Current topics radiation research quarterly. 1972;8:85-158

Kadhim et al. 1995 — Kadhim MA, Lorimore SA, Townsend KM, Goodhead DT, Buckle VJ, Wright EG. Radiation-induced genomic instability: delayed cytogenetic aberrations and apoptosis in primary human bone marrow cells. Int J Radiat Biol. 1995;67:287-93

Kiefer et al. 2002 — Kiefer J, Kohlpoth M, Kuntze M. Mutation induction by continuous low dose rate gamma irradiation in human cells. International Congress Series, Radiation and homeostasis. 2002 Jul;Vol 1236:255-263

Ko et al. 2006 — Ko M, Lao XY, Kapadia R, Elmore E, Redpath JL. Neoplastic transformation in vitro by low doses of ionizing radiation: role of adaptive response and bystander effects. Mutat Res. 2006;597(1-2):11-17

König and Kiefer 1988 — König F and Kiefer J. Lack of dose-rate effect for mutation induction by gamma-rays in human TK6 cells. Int J Radiat Biol. 1988;54(6):891-7

Krueger et al. 2007a — Krueger SA, Collis SJ, Joiner MC, Wilson GD, Marples B. The transition in survival from low-dose hyper-radiosensitivity to increased radioresistance is independent of activation of ATM SER1981 activity. Int J Radiat Oncol Biol Phys. 2007;69:1262-1271

Krueger et al. 2007b — Krueger SA, Joiner MC, Weinfeld M, Piasentin E, Marples B. Role of apoptosis in low-dose hyper-radiosensitivity. Radiat Res. 2007;167(3):260-267

Lehnert et al. 1997 — Lehnert BE, Goodwin EH, Deshpande A. Extracellular factor(s) following exposure to alpha particles can cause sister chromatid exchanges in normal human cells. Cancer Res. 1997;57(11):2164-2171; Erratum in: Cancer Res. 2003;63(6):1439

Little 2010 — Little, MP. Do non-targeted effects increase or decrease low dose risk in relation to the linear-non-threshold (LNT) model? Mutat Res. 2010;687:17-27

Ljungman 2010 — Ljungman M. The DNA damage response − repair or despair? Environ Mol Mutagen. 2010;51(8-9):879-889

Löbrich and Kiefer 2006 — Löbrich M and Kiefer J. Assessing the likelihood of severe side effects in radiotherapy. Int J Cancer. 2006;118(11):2652-2656

Löbrich and Jeggo 2007 — Löbrich M and Jeggo PA. The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. Nat Rev Cancer. 2007;7(11):861-869

Lorimore et al. 1998 — Lorimore SA, Kadhim MA, Pocock DA, Papworth D, Stevens DL, Goodhead DT, Wright EG. Chromosomal instability in the descendants of unirradiated surviving cells after alpha-particle irradiation. Proc Natl Acad Sci U S A. 1998;95(10):5730-5733

Loucas et al. 2004 — Loucas BD, Eberle R, Bailey SM, Cornforth MN. Influence of dose rate on the induction of simple and complex chromosome exchanges by gamma rays. Radiat Res. 2004;162:339-349

Marples and Collis 2008 — Marples B and Collis SJ. Low-dose hyper-radiosensitivity: past, present, and future. Int J Radiat Oncol Biol Phys. 2008;70(5):1310-1318

Marples and Joiner 1993 — Marples B and Joiner MC. The response of Chinese hamster V79 cells to low radiation doses: Evidence of enhanced sensitivity of the whole cell population. Radiat Res. 1993;133:41-51

Matsumoto et al. 2009 — Matsumoto H, Tomita M, Otsuka K, Hatashita M. A new paradigm in radioadaptive response developing from microbeam research. J Radiat Res. (Tokyo). 2009;50 Suppl A:A67-79

Mill et al. 1998 — Mill AJ, Frankenberg D, Bettega D, Hieber L, Saran A, Allen LA, Calzolari P, Frankenberg-Schwager M, Lehane MM, Morgan GR, Pariset L, Pazzaglia S, Roberts CJ, Tallone L. Transformation of C3H 10T1/2 cells by low doses of ionising radiation: A collaborative study by six European laboratories strongly supporting a linear dose-response relationship. J Radiol Prot. 1998;18(2):79-100

Mitchell et al. 2002 — Mitchell CR, Folkard M, Joiner MC. Effects of exposure to low-dose-rate $^{60}$Co gamma rays on human tumor cells in vitro. Radiat Res. 2002;158(3):311-318

Nagasawa and Little 1999 — Nagasawa H and Little JB. Unexpected sensitivity to the induction of mutations by very low doses of alpha-particle radiation: evidence for a bystander effect. Radiat Res. 1999;152(5):552-557

Neumaier et al. 2012 — Neumaier T, Swenson J, Pham C, Polyzos A, Lo AT, Yang P, Dyball J, Asaithamby A, Chen DJ, Bissell MJ, Thalhammer S, Costes SV. Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells: Proc Natl Acad Sci U S A. 2012;109(2):443-8

Olivieri et al. 1984 — Olivieri G, Bodycote J, Wolff S. Adaptive response of human lymphocytes to low concentrations of radioactive thymidine. Science. 1984;223:594-597

Pampfer and Streffer 1989 — Pampfer S and Streffer C. Increased chromosome aberration levels in cells from mouse fetuses after zygote X-irradiation. Int J Radiat Biol. 1989;55:85-92

Preston 2005 — Preston RJ. Bystander effects, genomic instability, adaptive response, and cancer risk assessment for radiation and chemical exposures. Toxicol Appl Pharmacol. 2005;207(2 Suppl):550-556

Rothkamm and Löbrich 2003 — Rothkamm K and Löbrich M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. Proc Natl Acad Sci U S A. 2003;100(9):5057-5062

Sasaki 2009 — Sasaki MS. Advances in the biophysical and molecular bases of radiation cytogenetics. Int J Radiat Biol. 2009;85(1):26-47

Sawant et al. 2001 — Sawant SG, Randers-Pehrson G, Geard CR, Brenner DJ, Hall EJ. The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T1/2 cells in vitro can be initiated in the unirradiated neighbors of irradiated cells. Radiat Res. 2001;155(3):397-401

Schwartz 2007 — Schwartz JL. Variability: the common factor linking low dose-induced genomic instability, adaptation and bystander effects. Mutat Res. 2007;616(1-2):196-200

Smith et al. 2003 — Smith LE, Nagar S, Kim GJ, Morgan WF. Radiation-induced genomic instability: radiation quality and dose response. Health Phys. 2003;85(1):23-29

Streffer 2010 — Streffer C. Strong association between cancer and genomic instability. Radiat Environ Biophys. 2010;49(2):125-131

Tapio and Jacob 2007 — Tapio S and Jacob V. Radioadaptive response revisited. Radiat Environ Biophys. 2007;46(1):1-12, Epub 2006 Nov 28

UNSCEAR 2000 — United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Report 2000: Sources and Effects of Ionizing Radiation, Biological effects of low radiation doses. 2000; Vol. II:177-296

Vilenchik and Knudson 2000 — Vilenchik MM and Knudson AG Jr. Inverse radiation dose-rate effects on somatic and germ-line mutations and DNA damage rates. Proc Natl Acad Sci U S A. 2000;97(10):5381-5386

Williams et al. 2008 — Williams JR, Zhang Y, Zhou H, Gridley DS, Koch CJ, Slater JM, Little JB. Overview of radiosensitivity of human tumor cells to low-dose-rate irradiation. Int J Radiat Oncol Biol Phys. 2008;72(3):909-917

Xu et al. 2002 — Xu B, Kim ST, Lim DS, Kastan MB. Two molecularly distinct G(2)/M checkpoints are induced by ionizing irradiation. Mol Cell Biol. 2002;22:1049-1059

Zhou et al. 2003 — Zhou H, Randers-Pehrson G, Geard CR, Brenner DJ., Hall EJ, Hei TK. Interaction between radiation-induced adaptive response and bystander mutagenesis in mammalian cells. Radiat Res. 2003;160:512-516

## 3.2 In vivo studies

### 3.2.1 Animal studies used to assess DDREF

Evidence from animal studies has had a considerable influence on the decisions to apply or to continue to apply DDREF. For example, BEIR VII (2006) concluded that "…*animal data relating to protracted radiation exposures provide a convincing argument for the inclusion of*

*DDREF in judgments about cancer risk at low doses and low dose rates. The animal data showing reduction in carcinogenic effectiveness, including life shortening, following protracted exposure constitute the strongest element in this argument…"*

Initial evaluations on the use of animal studies to address DDREF concluded that the shape of dose response is widely variable across different species and tumour types. Nevertheless the preponderance of available "relevant" data was considered to suggest a linear quadratic (and hence DDREF) relationship. (BEIR VII).

It is the reliance upon selective use of available "relevant data" that is a major weakness of interpretations of animal studies. The decision as to the inclusion of a specific study as being relevant appears to be somewhat arbitrary, with decisions being based upon non-transparent arguments. For example, ovarian tumours and thymic lymphoma were excluded by BEIR VII, but tumours of the Harderian gland, for which there is no human equivalent, were included (see BEIR VII Chapter 3). Moreover, the translation of data from a mouse study to human situation must be made with caution, principally because the different genetic constitutions of different inbred mouse strains determine to a large extent which tumour type is prevalent. The histological type of common radiation-induced mouse tumours, for example of the thyroid and breast, do not correspond to the radiation-associated tumours seen for example in the LSS study or after the Chernobyl accident.

For the sake of expediency and constancy of evaluation criteria this review focuses on studies using mouse models. The main conclusions nevertheless apply to studies using other species (particularly rat and beagle dog).

The importance of studies on mouse inbred lines in radiobiology is not without controversy. Inbred strains were originally bred to answer a number of biological questions with the aim of excluding the phenotypical selection of desired characteristics as well as less desired characteristics. These strains' sensitivity to radiation is generally much higher than that of other wild type mice with shorter lifespans. Most lines also exhibit an unusually high sporadic incidence of one or more cancers.

### 3.2.2 Influence of non-targeted processes on the shape of the dose-response relationship and hence on DDREF

A number of experimental observations show that biological responses of cells and tissues may deviate from linearity, in particular in the low dose range. Processes such as the adaptive response, enhanced cell killing of non-targeted cells, as well as the induced genomic instability of both targeted and bystander cells, may all result in non-linear in vitro biological responses to radiation (cf. Chapter 3.1). The dose range at which these processes act in vitro is in the range of doses where animal studies lack sufficient sensitivity to demonstrate an increase (or decrease) above the spontaneous rate of cancer incidence. Consequently, there is no experimental evidence for or against these processes contributing to a non-linearity of cancer induction at low doses.

### 3.2.3 Types of study

#### 3.2.3.1 Influence of study design on tumour incidence, latency and mortality

Considerable variation exists in the growth rates, metastatic spread and mortality of different tumour types. These parameters can all be influenced by strain, gender, age, housing environment as discussed elsewhere, but are also highly dependent upon the degree of animal care. Thus, some life-span studies are done under conditions where animals are sacrificed upon the first outward appearance of tumour growth. This may mean that externally visible slow growing low malignancy radiation-induced tumours (such as osteosarcoma or squamous cell

carcinoma of the skin) result in the early sacrifice of animals in some laboratories, whereas in other institutes these animals may eventually succumb to a second, rapidly growing tumour with a longer latency. This is most important when the second tumour arises spontaneously, such as late age onset lymphoma.

In many publications the diagnostic criteria used are unclear. Assigning mortality to a particular tumour is often done by untrained observers, who in cases with multiple tumours preferentially nominate the most obvious (largest) tumour as the cause of death. Only after careful pathological evaluation can the relevance of each tumour be evaluated and the cause of death correctly assigned.

The alternative strategy proposed by Fry (Fry 1992) for assessing carcinogenesis is to ignore the tumour type and to evaluate only life shortening as the sum of all radiation-induced cancers. Here the most malignant tumour may cause death when developing in a critical organ such as the lung. Consequently mouse strains sensitive to tumours metastasising to the lung may show greater life shortening than strains with no lung propensity. It is discussed elsewhere how complex regulatory systems determine life span in animal models, and how this parameter (as well as cancer incidence) is confounded by numerous other variables.

#### 3.2.3.2 Effect of changes in age at exposure for studies using chronic exposures

One particular problem of comparing acute exposure with doses protracted over a long period is that the effect of age at exposure comes into play. As observed by Heidenreich et al. (2006), application of the two-stage clonal expansion model (LNT assumed) to gamma-irradiated mice from the JANUS[1]-Study confirmed that protraction (acute exposure at 110 days age versus fractionated exposure over 24 or 60 weeks) delivered evidence for a DDREF of 2 for lung tumours. However, as the authors point out, the same phenomenon can be explained by the lower incidence that would be expected in the protracted exposure cohort due to the majority of the dose being delivered to mice at higher age. The exposure of aged mice to the acute dose would have been a more appropriate control for possible dose rate effects.

A second criticism of the failure to consider age at exposure can be readily seen in studies comparing an acute dose with a protracted one. Often the acute dose is given in the youngest animals, whilst the time required for protraction ensures that these animals are irradiated at a greater age. The application of the acute dose to animals of the same age as those competing the protracted exposure is not usually done.

#### 3.2.3.3 Differences in exposure regimes

The studies using mouse models include a range of different exposure modalities, ranging from a single dose delivered acutely to chronic lifetime exposure at very low dose rates. In between these two extremes are a range of fractionation and protraction procedures that are almost limitless in their imaginative design.

#### 3.2.3.4 Data handling

A number of different strategies have been developed to normalise and correct animal study datasets. Amongst these the correction for competing causes of death is most important, as animals sacrificed after developing one tumour are automatically no longer included in the analysis of the incidence of other later tumour types. The importance of correcting for competing causes is best illustrated by the studies of radiation-induced osteosarcoma reviewed by Goessner (1999). At lowest doses the numbers of osteosarcoma detected consistently

[1] Name of the research reactor at the Argonne National Laboratory (USA)

outweigh those of malignant fibrous histiosarcoma (MFH). As doses are increased osteosarcoma begin to disappear, but the incidence of MFH rises. Goessner interpreted this shift in tumour spectrum to represent a balance between different sensitivities to cell killing and malignant transformation of the different cellular targets. This is important for reviewing studies by Ullrich and Storer (see below). Here the authors observe a decrease in the incidence of reticulum cell sarcoma (Follicular B-cell lymphoma) with increasing radiation dose, but at the same time the incidence of other hematopoietic malignancies increases with dose. It is probable that the incidence of this common sporadic lymphoma decreases due to competition from the radiation-induced tumours.

#### 3.2.3.5 Spontaneous vs. induced tumours

It is almost impossible to assign a definite radiation aetiology to any individual tumour. Exceptions may be the presentation at an abnormally early or late incidence (such as the peak of lymphoma arising many months before the peak of spontaneuous lymphoma in $^{227}$Th-treated mice) or presenting with a histological type usually absent from the strain under investigation (e.g. acute myeloid leukaemia (AML) which only appears after irradiation in the CBA strain and osteosarcoma which is not seen as a sponteneous tumour in any common inbred strain).

#### 3.2.3.6 Reliance upon a mixture of life-shortening and cancer cause of death as end points

Note that the ability of animal studies to describe the dose-response relationship for cancer at low (<100 mGy) doses is limited by the endogenous "spontaneous" incidence of cancer, resulting in appreciable cancer incidences even in non-exposed (0 Gy) animals.

Inbred strains exhibit major strain-specific differences in terms of the incidence of various types of tumour. One such example is where C3H mice demonstrate high liver tumour incidences, while BALB/C mice exhibit higher incidences of reticulum cell and breast tumours (Jackson Laboratories inbred strain data 2012).

Therefore, even though a linear dose-response relationship may be applied, the power of animal studies to resolve questions on DDREF in the low dose range is very limited.

### 3.2.4 Pitfalls in long-term animal studies

Study of radiation carcinogenesis using animal models are unique in that there is an absolute requirement for constant experimental conditions, and these must be maintained over long periods of time, even years.

#### 3.2.4.1 Quality of dosimetry

The exposure scenarios in chronic, protracted or fractionated dose studies require considerable care to ensure that cages are rotated with respect to the source, and that all animals in a cage receive comparable doses. Otherwise differences in geometry may influence the received dose and hence the result. Changes in the source itself are unlikely. Some studies report the strategy used to ensure even exposures, others use measurements to validate uniformity of fields, but a number of studies do not provide details.

#### 3.2.4.2 Background rate fluctuations

Changes to the natural background radiation exposure are not expected to be a critical issue in carcinogenesis studies using acute exposures. Even for situations where very low doses are applied the contribution of a background exposure will be minimal. For chronic exposures at low dose rates it is possible that changes in background may influence both the cumulative dose and the dose rate. Such changes could be encountered following unintentional radiation releases into the environment.

#### 3.2.4.3 Strain drift

A serious complication in large-scale animal studies is the need for phased enrolment of animals into the study, sometimes lasting years. A number of inbred strains show evidence for past contamination with genetic material from other inbred strains, and incorrect matings are documented, even from reputable animal supply companies. Monitoring of strain purity during long-term animal studies is not commonly reported, although intelligent study planning will ensure such occurrences will be distributed across all experimental and control arms.

#### 3.2.4.4 Gender

All of the studies reported here have distinguished between male and female cancer incidences and lifespans, as sex-specific incidences of most tumours are recognised. One additional contribution of gender is the aggressive behaviour seen in males of some strains. Animal numbers and cage size play a major role, as does moving animals from cage to cage to consolidate space. Fighting and the resultant injuries can have a dramatic influence on the number of animals lost to follow-up in long-term studies.

#### 3.2.4.5 Seasons

Mice exhibit strong circannual variation in their endocrine functions, and tumour incidence and lifespan are influenced by season. Indeed, the study of AML incidence by Mole et al. (1983) found an 8-month difference in the lifespan of mice dependent upon season. Such seasonal differences are not always recognised or protocolled and if control and test cohorts are entered into the studies at different times abnormal values may be obtained.

#### 3.2.4.6 Environment

The original report of the lifespan study of the National Cancer Institute study into dose rate and dose effects on mouse survival purport to show evidence for increased survival of the lowest dose exposure cohort compared to their non-irradiated controls. As reported by Grahn (Grahn 1994) the experimental design was seriously flawed due to housing experimental and control mice in different buildings. Control mice contacted dermatitis and were replaced mid-way through the study by a new set of control animals. The observed differences in survival may be related to radiation exposure, but many other variables may have been included by the change in the control cohort. Other environmental variables may differentially affect individual mouse strains, such as sensitivity to crowding, change in bedding or localised humidity. These can all influence long-term survival and can lead to unexpected experimental observations. An example is the apparent 36% decrease in lifespan of the hitherto radioresistant C3H strain seen at the Argonne National Laboratory when animal housing was changed to smaller cages (Grahn 1994).

#### 3.2.4.7 Hygiene

It is understood that the hygiene status of mice determines the type and incidence rate of spontaneous cancer, in particular haematological cancers. Animals maintained in an SPF (specific pathogen free) environment have quite different cancer incidences, living longer with lower incidence of malignant disease, in particular haematological cancers. The phenomenon itself is strain independent, with all of the common inbred strains exhibiting altered survival rates in pathogen-free versus uncontrolled habitat. The variation in the scale of the SPF influence between strains may be due to variation in immune competence.

That this effect can be relevant to radiation studies was convincingly demonstrated by the studies of Ina and Sakai (2004, 2005), of Ullrich and Storer (1979a, b, c) and of Maisin et al. (1996). The former investigation used an immune compromised mouse strain with homozygous

inactivation of the Fas gene resulting in an aggressive autoimmune disease and significant life shortening. Mice exposed to short-term (5 week) and lifetime chronic low dose rate gamma irradiation show significant life-span extension, probably due to activation of regulatory T cells leading to an amelioration of the autoimmune activity (Ina and Sakai 2004, 2005). In the studies of Ullrich and Storer in 1979, the changeover from standard animal facility to a SPF facility resulted in changes in the radiation-induced incidences of both myeloid (reduced) and thymic leukaemia (increased) (Ullrich and Storer 1979a, b, c and Upton 1970). Similarly, during the early Manhattan studies into radiation effects animal husbandry issues led to large variation in animal survival due to infection (Grahn 1994). Maisin et al. (1996) provides a direct comparison of survival rates of SPF mice with the laboratories own historical studies, showing life-prolonging effects of SPF conditions.

#### 3.2.4.8 Competing causes of death

In any lifespan study animals may be lost to follow-up due to the appearance of both spontaneous cancers and radiation-induced cancers. Clearly an animal succumbing to a spontaneous tumour at an early age can no longer continue to develop a radiation-induced malignancy at a later age. This is best illustrated by the experience of the Oak Ridge National Laboratory (ORNL) studies, where the risk of death from spontaneous cancers and radiation-induced cancers show a reciprocal relationship over the dose response range. Correcting survival data for animals lost to any cause of death (competing causes of death) is now conventionally used to adjust survival data to reflect the loss of animals to follow up. The induction of mammary cancer presents a rather unique situation in evaluating competing causes as the incidence of mammary tumours is linked to endocrine function and can thus be influenced by the appearance of slow growing cancers of the uterus and pituitary. Here the animals are not lost due to competing deaths, but the existence of one tumour type can influence the incidence of the other.

#### 3.2.4.9 Histopathological evaluation and relevance of the tumour type to human situation

Tumours for which there is mechanistic knowledge that they are unlikely to be applicable to radiation carcinogenesis in human populations should not be considered. On this basis, quantitative data on dose-rate effects for thymic lymphomas and for ovarian tumours, which have been shown to be highly sensitive to dose-rate effects, should not be used. (Covelli et al. 1998).

Likewise, caution should also be exercised when considering data for the induction of pituitary tumours in RFM female mice because of potential effects associated with the sensitivity of the mouse ovary and the subsequent disruption of pituitary and ovarian hormone functions. Other difficulties arise from studies on mice ovary tumours. As mice have an ovarial cycle length of 4 days and produce multiple eggs, their ovaries and therefore their tumour induction cannot be compared with human ovaries. This leaves a limited data set upon which to base DDREF calculations, which includes data for myeloid leukaemia and a few solid tumours including Harderian gland (although there is no comparable tissue in humans), lung adenocarcinomas, and mammary tumours. Data for myeloid leukaemia are available for two mouse strains and from at least three independent studies. Despite all of the data supporting a reduced effect when comparing high- and low-dose-rate exposures over the 0-3 Gy dose range, there are some contradictions. Calculation of DDREF values using the procedures described above yields estimates on the order of 2 to 6, with most values in the range of 4-5. For lung adenocarcinomas and Harderian gland tumours, DDREF values of approximately 3 have been calculated over the 0-2 Gy dose range. For mammary tumours, all of the data suggest a DDREF value of less than 2 and closer to a value of 1 when effects of high-dose-rate and low-dose-rate exposures are

compared in this 0-2 Gy dose range. Thus, it appears that myeloid leukaemia is probably more sensitive to dose-rate effects than are solid tumours.

### 3.2.5 Conclusion

A critical retrospective investigation into the in vivo evidence on rodents suggests that there is no good cause to introduce a LDEF or DREF. As recently published by Morgan and Bair, the main benefit of animal studies for mechanistic questions is a disadvantage when applied in practical radiation protection since controlled uniformity in experimental studies does not represent the various radiation exposure options and genetic diversity among the general public (Morgan and Blair 2013).

Studies used to support the DDREF often investigate end points such as tumours of the Harderian gland (a tumour type with no human counterpart) or tumours such as ovarian tumours with a different metabolism to that seen in humans. Initial studies used very large numbers of animals in an attempt to provide results of adequate statistical value. At the same time, however, these methods were flawed as causes of death other than the investigated radiation-induced tumours or non-standardised animal husbandry and/or various different irradiation scenarios were not sufficiently taken into account. These early studies fail to meet current standards for comparative studies and their validity is therefore highly limited.

Finally, it should be noted that the authors of some of the cited works state a linear-quadratic dose relationship, although the LNT model could represent the data just as well.

## Literature


BEIR 2006 — Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation. BEIR VII – Phase 2. United States National Academy of Sciences. National Academy Press, Washington DC. 2006

Covelli et al. 1988 — Covelli V, Coppola M, Di Majo V, Rebessi S, Bassani B. Tumor induction and life shortening in BC3F1 female mice at low doses of fast neutrons and x rays. Radiat Res. 1988;113:362-374

Fry 1992 — Fry RJM. The role of animal experiments in estimates of radiation risks. In: Lett JT, Sinclair WK (eds). Advances in Radiation Research. Academic Press, New York. 1992;181-197

Goessner 1999 — Gössner W. Pathology of radium-induced bone tumours: new aspects of histopathology and histogenesis. Radiat Res. 1999;152(Suppl):12-15

Grahn 1994 — Grahn D. Report ANL-94/26: Studies of Acute and Chronic Radiation Injury at the Biological and Medical Research Division, Argonne National Laboratory, 1953-1970: Description of individual studies, data files, codes, and summaries of significant findings, 1994

Heidenreich et al. 2006 — Heidenreich WF, Carnes BA, Paretzke HG. Lung Cancer Risk in Mice: Analysis of Fractionation Effects and Neutron RBE with a Biologically Motivated Model. Radiat Res. 2006;166:794-801

Ina and Sakai 2004 — Ina Y and Sakai K. Prolongation of life span associated with immunological modification by chronic low dose rate irradiation in MRL-lpr/lpr mice. Radiat Res. 2004;161:168-173

Ina and Sakai 2005 — Ina Y and Sakai K. Further Study of Prolongation of Life Span Associated with Immunological Modification by Chronic Low-Dose-Rate Irradiation in MRL-lpr/lpr Mice: Effects of Whole-Life Irradiation. Radiat Res. 2005;163(4):418-423. doi: http://dx.doi.org/10.1667/RR3316

Maisin et al. 1996 — Maisin JR, Gerber GB, Vankerkom J, Wambersie A. Survival and diseases of C57BL mice exposed to X rays or 3.1 MeV neutrons at an age of 7 or 21 days. Radiat Res. 1996;146:453-460

Mole et al. 1983 — Mole RH, Papworth DG, Corp MJ. The dose-response for x-ray induction of myeloid leukaemia in male CBA/H mice. Br J Cancer. 1983;247:285-291

Morgan and Bair — Morgan WF and Bair WJ. Issues in low dose radiation biology-The controversy continues. A Perspective Radiat Res. 2013;179:501-510

Spalding et al. 1970 — Spalding JF. Popp DM, Popp R.. A genetic effect on radiation sensitivity consistent with a single gene locus hypothesis. Radiat Res. 1970;44:670-673

Ullrich and Storer 1979a — Ullrich RL and Storer JB. Influence of gamma irradiation on the development of neoplastic disease in mice. I. Reticuloendothelial tumours. Radiat Res. 1979;80:303-316

Ullrich and Storer 1979b — Ullrich RL and Storer JB. Influence of gamma irradiation on the development of neoplastic disease in mice. II. Solid tumours. Radiat Res. 1979;80:317-324

Ullrich and Storer 1979c — Ullrich RL and Storer JB. Influence of gamma irradiation on the development of neoplastic disease in mice. III. Dose-rate effects. Radiat Res. 1979;80:325-342

Upton et al. 1970 — Upton AC, Randolph ML, Conklin JW, Kastenbaum MA, Slater M, Melville GS Jr, Conte FP, Sproul JA Jr. Late effects of fast neutrons and gamma rays in mice as influenced by the dose rate of irradiation: Induction of neoplasia. Radiat Res. 1970;41:467-491

# 4 Radioepidemiological studies

Radiobiological and epidemiological studies both play a major part in determining whether a DDREF is necessary and justified. The influences of a potentially non-linear dose relationship on the LDEF and a potentially present dose-rate effect on the DREF can also in epidemiological studies be taken into account and investigated independently of one another.

In 2009, Jacob et al. published a study based on systematic literature research which looked at all of the individual studies into mortality or incidence following exposure to low dose rates and low/moderate cumulated doses in order to derive estimates of the excess risk per dose (Jacob et al. 2009). They used the individual estimates of the excess risk per dose derived by assuming a linear dose-response relationship and compared them with the corresponding excess relative risk per dose derived from the data resulting from the study on atomic bomb survivors. This entailed a comparison of results from cohorts involving low dose rates with results from a cohort involving a high dose rate to gain information about the DREF. In contrast to previous assumptions among the international radiation protection community, the result of this meta-analysis indicated that exposures involving a low dose rate do not lead to a lower cancer risk than exposures involving high dose rates such as those afflicted upon atomic bomb survivors. The authors therefore concluded that their studies did not indicate a DREF of greater than 1.

The individual studies often encountered major difficulties in stipulating the dose. Studies involving nuclear facility employees are useful here as they can draw upon regular radiation protection monitoring data, while other studies have to painstakingly reconstruct the dose (people who live near the Techa river, Russia, people who helped in the wake of the Chernobyl accident, people who live in Kerala, India, and Guangdong, China), which would lead to major dose stipulation uncertainties. In addition, some studies included internal exposure (e.g. to Tritium, $^{137}$Cs, $^{90}$Sr, etc.), while others saw no evidence of incorporation or it was not taken into account during dose calculations. Some studies on nuclear industry employees included neutron doses, while others did not.

The results of individual studies therefore have to be compared and discussed with caution as the statistical data analyses carried out are often based on differing assumptions. Several studies (Ivanov et al. 2009, Cardis et al. 2007) showed that the choice of latency period for the incidence of solid tumours can have a major influence on the derived ERR values per dose. However, this was not taken into consideration in most studies and a latency period of 10 years was assumed. The study into Japan's nuclear industry employees provided major indications that alcohol consumption can have a substantial effect on the result (Akiba and Mizuno 2012). This parameter was not, however, taken into account in most of the studies discussed here. Age at exposure also appears to play a part in some studies (Cardis et al. 2007, Wing and Richardson 2005, Krestinina et al. 2005), but not in others. This is also the case with socioeconomic status, which was not always considered.

Against the backdrop of these difficulties, the method adopted by Jacob et al. appears to make sense as they systematically excluded each of the identified studies in turn during their meta-analysis in order to investigate the extent to which the ERR value per dose varied as a result of doing so. They were able to show that this led to a change of at most 30% (Jacob et al. 2009). The meta-analysis performed by Akiba et al. that was also discussed here adopted this method as well, but they were not quite as systematic in their approach (Akiba and Mizuno 2012).

Below is a description of some of the studies used by Jacob et al. along with other and mostly more recent studies. In general, four groups of people are investigated to establish the risk of solid tumour incidence or mortality following exposure to ionising radiation at low or moderate doses and low dose rates: a) Nuclear industry employees from various different countries,

b) people who live near the Techa river in the Southern Urals who were contaminated by the former Soviet Union's nuclear weapons programme, c) People who live in Kerala, India, and Guangdong, China, who are exposed due to higher dose rates of terrestrial radiation, and d) People who worked within a 30 km radius in the wake of the Chernobyl accident. In addition, the latest evaluation on mortality among survivors of the Hiroshima and Nagasaki atomic bombs is the only study to be considered that involves exposure with a high dose rate.

In general, most studies on people employed in the nuclear industry returned a positive ERR value per dose for solid tumour mortality that was, however, non-significant from a statistical perspective. Exceptions to this are the individual studies involving people who work in the UK's nuclear industry (Muirhead et al. 2009) (0.275 (90% CI[1]: 0.02 – 0.56) $Sv^{-1}$) and in Oak Ridge (Stayner et al. 2007) (4.82 (90% CI: 0.41 – 13.31) $Sv^{-1}$) for which a statistically significant ERR per dose was derived, albeit at the 90% level. A positive significant ERR value per dose was observed at this level for solid tumour incidence among people who work in the UK's nuclear industry (0.266 (90% CI: 0.04 – 0.51) $Sv^{-1}$) (Muirhead et al. 2009). Only two individual studies provided RR values of less than 1 at 100 mSv (Boice et al. 2011, Laurent et al. 2010). Correspondingly, a study into nuclear industry employees from 2005 summarised data from 15 countries which showed a statistically significant positive estimate for the ERR value per dose (Cardis et al. 2005). Another analysis excluding the data from Canada, whose validity were called into question, provided a reduced, non-significant value of 0.58 (95% CI: -0.22 – 1.55) $Sv^{-1}$ (Cardis et al. 2005, 2007). A recently published meta-analysis from Japan, to some extent involving more recent results, also provided a positive yet non-significant estimate for the ERR value per dose of 0.14 (95% CI: -0.12 – 0.41) $Sv^{-1}$.

The latest mortality study involving people who live near the Techa river in the Southern Urals in Russia provided a significantly positive ERR value per dose of 0.92 (95% CI: 0.2 – 1.7) $Gy^{-1}$(Krestinina et al. 2005, Schonfeld et al. 2013). A similarly significantly positive ERR value per dose of 1.52 (95% CI: 0.20 – 2.85) $Gy^{-1}$ was observed as a result of the latest mortality study involving people who helped in the wake of the Chernobyl accident by (Ivanov et al. 2006). These results were confirmed by analysing the tumour incidence data of both cohorts (people who live near the Techa river: 1.0 (95% CI: 0.3 – 1.9) $Gy^{-1}$ (Krestinina et al. 2007); people who helped in the wake of the Chernobyl accident: 0.96 (95% CI: 0.28 – 1.72) $Gy^{-1}$ (Ivanov et al. 2009)).

However, analyses involving the incidence of solid tumours in areas with elevated levels of natural terrestrial radiation in Kerala in India indicate a non-significant negative ERR value per dose of -0.13 (95% CI: -0.58 – 0.46) $Gy^{-1}$ (Nair et al. 2009) despite the mean cumulated dose of 170 mGy observed in the study participants being far higher than the dose values generally seen in studies involving people who work in the nuclear industry. In contrast, the results of a study involving residents of Guangdong, an area with elevated terrestrial radiation in China, shows a slightly positive point estimate but with a high confidence interval (0.19 (95% CI: -1.87 – 3.04) $Gy^{-1}$).

The Radiation Effects Research Foundation (RERF) in Japan publishes regular reports on the latest findings of its Life Span Study (LSS) which investigates the life-long health effects based on epidemiological studies involving survivors of the Hiroshima and Nagasaki atomic bombings. The LSS studies are by far the most important source of radioepidemiological risk estimates, and are also of key importance to DDREF discussions. As the LSS is based on exposures involving a high dose rate, it can only be used to investigate the dose effects (LDEF) and not the dose-rate effects (DREF). The publication discussed here represents the 14th and

[1] Confidence interval

latest report in this series with a follow-up period (1950 to 2003) that is six years longer than the previous analysis.

By taking the entire dose range into account during data analysis, a linear dose-response relationship provided the best data fit for solid tumours (Fig. 4.1). On the other hand, the authors observed a significant curvature at a limited dose range of 0 Gy to 2 Gy which they were able to adjust using a linear-quadratic curve. This curvature proved to be more prominent the longer the observation period starting from 1950. There was no indication of a dose threshold.

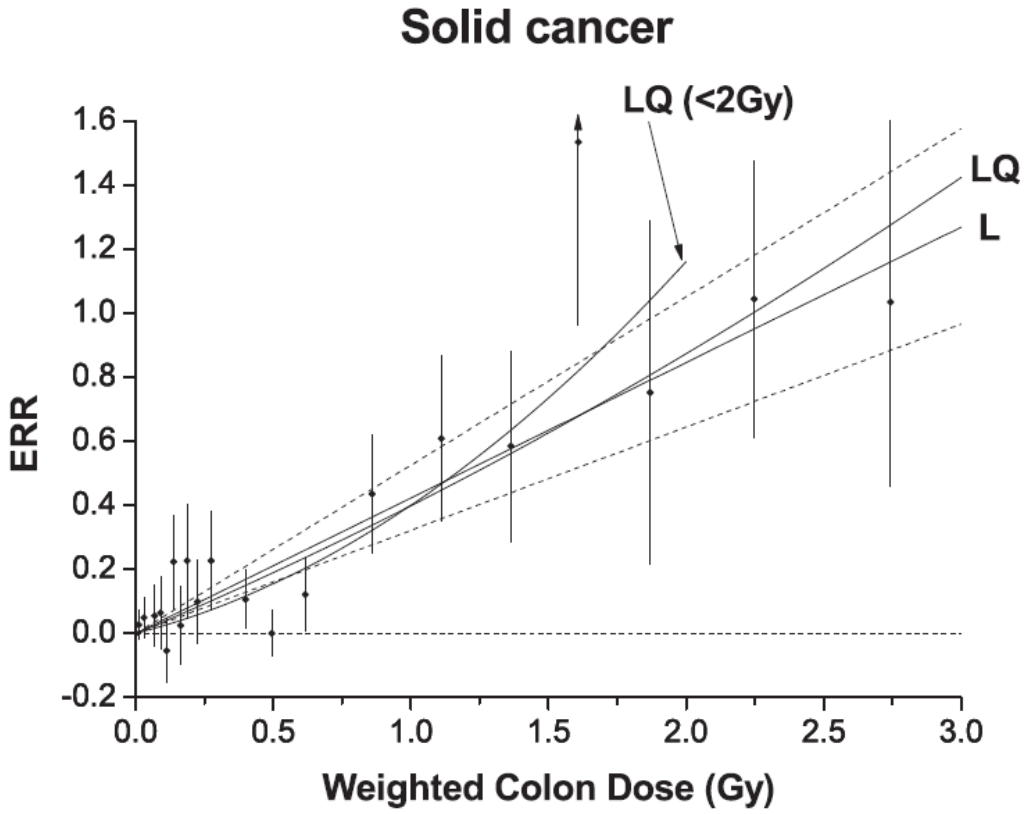


*Fig. 4.1:* *Excess relative risk (ERR) for all tumours as a function of the colon dose (gamma absorbed dose plus the neutron absorbed dose weighted by a factor of 10). The black dots correspond to ERR values with the corresponding 95% confidence intervals (CI) for the selected dose groups. Solid lines: Linear model (L) (incl. 95% CI, represented as dashed lines) and linear-quadratic (LQ) model, each for the total dose range, and the linear-quadratic (LQ(< 2 Gy)) model for doses between 0 Gy and 2 Gy.*

*(Source: Ozasa et al. 2012, Fig. 4, p. 237. This figure is republished with the permission of the journal "Radiation Research". The original title is: Excess relative risk (ERR) for all solid cancer in relation to radiation exposure. The black circles represent ERR and 95% CI for the dose categories, together with trend estimates based on linear (L) with 95% CI (dotted lines) and linear-quadratic (LQ) models using the full dose range, and LQ model for the data restricted to dose <2 Gy.)*

An earlier study into the consequences of revising the dose values from DS86 to DS02 showed an ERR value per dose of 0.42 $Gy^{-1}$ (Preston et al. 2004) based on DS02 for all solid tumours combined and an observation period from 1950 to 2000, which concurs with the results of the present study. At first glance the significant curvature found at doses of 0 Gy to 2 Gy appeared

to favour a DDREF greater than 0 *("...so that this upward curvature may imply a DDREF greater than one*"). The authors emphasise, however, that this curvature came about due to inexplicably low values for the ERR per dose between 0.3 Gy and 0.7 Gy, and that inexplicably high values occurred at even lower doses.

The results of other studies into the effect of low dose and low dose-rate values were often compared with those from the Life Span Study on atomic bomb survivors, and the value of 0.47 $Gy^{-1}$ was used without taking account of the fact that this value only applies to survivors aged 70 who were 30 years old at the time of exposure and averaged for both genders. This fact was accounted for in the meta-analysis by Jacob et al. and an ERR value per dose was calculated for the comparison based on atomic bomb survivors and adjusted to the age and gender ratios of the respective comparative study.

## 4.1 Conclusion

The results of epidemiological studies published to date on the effect of exposures involving a low dose rate do not generally indicate tumour risk to be dependent upon dose rate. In particular they do not provide any arguments in favour of a DREF greater than 1 (cf. Chapter 2.2). Most of these studies involving a dose-response relationship analysis do not, however, allow conclusions to be drawn about a LDEF value. Depending on the dose range, the study on atomic bomb survivors which, as mentioned above, represents an exposure with a high dose rate, can be described by a linear and linear-quadratic dependency. Given the observed dose range in this study, it is not possible to derive a specific LDEF value of 1 to 2, which is currently the subject of discussion.

## Literature


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

Boice et al. 2011 — Boice JD, Jr., Cohen SS, Mumma MT, Ellis ED, Eckerman KF, Leggett RW, Boecker BB, Brill AB, Henderson BE. Updated Mortality Analysis of Radiation Workers at Rocketdyne (Atomics International). Radiat Res. 2011;176:244-258

Cardis et al. 2005 — 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. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ. 2005;331(7508):77

Cardis et al. 2007 — 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. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks. Radiat Res. 2007;167:396-416

Ivanow et al. 2006 — Ivanow VK, Tumanov KA, Kashcheev VV, Tsyb AF, Marchenko TA, Chekin SY, Maksioutov MA, Petrov AV, Biryukov AP. Mortality in Chernobyl clean-up workers: analysis of dose-effect relationship. Radiation and Risk. 2006;15:11-22 (Russian)

Ivanow et al. 2009 — Ivanov VK, Gorsky AI, Kashcheev VV, Maksioutov MA, Tumanov KA. Latent period in induction of radiogenic solid tumors in the cohort of emergency workers. Radiat Environ Biophys. 2009;48:247-252

Jacob et al. 2009 — Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H. Cancer risk of radiation workers larger than expected? Occup. Environ. Med. 2009 Jun 30 published online; doi:10.1136/oem.2008.043265

Krestinina et al. 2005 — Krestinina LY, Preston DL, Ostroumova EV, Degteva MO, Ron E, Vyushkova OV, Startsev NV, Kossenko MM, Akleyev AV. Protracted radiation exposure and cancer mortality in the Techa River Cohort. Radiat Res. 2005;164:602-611

Krestinina et al. 2007 — Krestinina LY, Davis F, Osroumova EV, Epifanova SB, Degteva MO, Preston DL, Akleyev AV. Solid cancer incidence and low-dose-rate radiation exposure in the Techa River cohort: 1956-2002. Int J Epid. 2007;36:1038-1046

Laurent et al. 2010 — Laurent O, Metz-Flamant C, Rogel A, Hubert D, Riedel A, Garcier Y, Laurier D. Relationship between occupational exposure to ionizing radiation and mortality at the Frenc electricity company, period 1961 - 2003. Int Arch Occup Environ Health. 2010;83:935-944

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|---|---|
| Muirhead et al. 2009 | Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, Zhang W. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Brit. J. Cancer. 2009;100:206-212 |
| Ozasa et al. 2012 | Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. Radiat Res. 2012;177:229-243 |
| Preston et al. 2004 | Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res. 2004;162:377-389 |
| Schonfeld et al. 2013 | Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL. Solid Cancer Mortality in the Techa River Cohort (1950-2007). Radiat Res. 2013;179:183-189 |
| Stayner et al. 2007 | Stayner L, Vrijheid M, Cardis E, Stram DO, Deltour I, Gilbert SJ, Howe G. A Monte Carlo Maximum Likelihood Method for Estimating Uncertainty Arising from Shared Errors in Exposures in Epidemiological Studies of Nuclear Workers. Radiat Res. 2007;168:757-763 |
| Wing and Richardson 2005 | Wing S and Richardson DB. Age at exposure to ionising radiation and cancer mortality among Hanford workers: follow up through 1994. Occup.Environ.Med. 2005;62:465-472 |


# 5 Basic scientific principles and other criteria relevant to radiation protection used to assess the DDREF

## Scientific principles

The DDREF was introduced to determine radiation risks due to exposure by low doses and low dose rates based on studies involving high doses and high dose rates. An assessment of the extent to which the use of a DDREF is justified and the value that should be assigned to is based on scientific findings pertaining to the radiation risk at various different doses and at various different dose rates. These findings are based on a range of different areas of research and require considerations as to which research results and which criteria should be used for the assessment and with which priority they should be used. The findings are set out below:

- **Radiobiological studies on molecular and cellular systems**

  For the last 50 years, the results of radiobiological studies formed the main basis for stipulating a DDREF, despite most – but not all – of them being based on studies involving several Gy. Here, studies were performed involving single cells or cell cultures in order to determine dose and dose-rate dependencies. These studies are still considered the most important source for justifying a DDREF greater than 1, even though they refer to high

doses. It remains to be seen whether and/or how these results can be extrapolated to the human tumour induction situation. This applies, in particular, with regard to more recent findings such as the bystander effect, genomic instability, adaptive response and their relevance regarding radiation effects at low doses and low dose rates. One aspect of these studies is the question of whether dose effects (deviation from a linear dose-response relationship) and dose rate effects are linked or whether they need to be treated as independently of one another.

– **Radiobiological studies on animals**

Studies on animals form part of discussions on determining a DDREF and generally involve observing a series of different end points (life shortening, tumour incidence, tumour mortality, etc.) in mice or rats. Although the extent to which the results of these studies can be extrapolated to human tumour induction remains to be seen, irradiation of an entire organism is more indicative of the human situation than irradiation of single cells. It should be noted, however, that the design of studies on animals (end points) and various influencing parameters when conducting studies have a major impact on the results, therefore making it difficult to make a general statement about DDREF.

– **Epidemiological studies**

Epidemiological data are also an important source for determining a DDREF, particularly as they directly refer to human cancer. Epidemiological studies also allow dose effects (LDEF)[1] and dose-rate effects (DREF)[2] to be investigated along with the question of whether they are independent of one another. While dose-response relationships can in principle be determined by studying a single exposed cohort, e.g. survivors of the Hiroshima and Nagasaki atomic bombings who received differing doses (LDEF), studies into the dose-rate effect (DREF) generally require comparable studies on various different populations exposed to differing dose rates. In contrast to doses above 100 mSv, current epidemiological studies into the risk of radiation-induced cancers are of little significance with doses of several 10 mSv. Studies involving low dose rates generally require long exposure and/or observation periods. This makes it difficult to make substantiated statements on the effect of low dose rates. In the last few years, however, a series of studies involving medium doses and dose rates have been conducted that enable more precise assessment. The combined investigation of individual studies in the form of meta-analyses may help to improve the situation further.

– **Mechanistic radiobiological models**

Extrapolations from high doses to low doses are required in order to provide statements regarding low doses and low dose rates which are important to radiation protection. Such extrapolations are often based on mathematically formulated mechanistic models which play a major part in interpreting experimental and epidemiological data. This includes, for example, the assumption of a purely linear or linear-quadratic dose-response relationship. In addition, the use of a multiplicative, additive or mixed risk model is also important when evaluating epidemiological data that also include the background risk. The extent to which age and gender dependencies (including even individual characteristics) of radiation risk need to be taken into consideration also has a part to play when estimating risk coefficients. Data uncertainty is also vital for the question of which model best describes present

[1] Low-Dose Effectiveness Factor, cf. Section 2.2
[2] Dose-Rate Effectiveness Factor, cf. Section 2.2

experimental and/or epidemiological data where data for the lowest observed doses and lowest dose rates generally exhibit the largest uncertainties. This greatly restricts the choice of model for best describing the data and leads to major uncertainties in determining a DDREF based on modelling.

## Radiation protection requirements criteria for operational implementation

As was the case several times in the past, an assessment to determine whether or not the DDREF value currently generally used in radiation protection to estimate radiation risk should be changed is not solely based on specified scientific findings in a narrow sense as it also includes other criteria pertaining to other key aspects of radiation protection and practical implementation. Assessment solely on the basis of scientific principles and criteria is not commensurate to the importance and function of DDREF, which is why the following criteria are used in the assessment along with scientific findings:

- **Influence of uncertainties**

  There are major uncertainties in terms of the determined risk values and DDREF derived therefrom, thus only allowing for the stipulation of a range of DDREF values (between 1 and 2, currently the subject of discussion) compatible with experimental and epidemiological data. Considerations as to whether to change the DDREF of 2 used to date therefore also have to take account of uncertainties. A decision is required to determine whether today's improved data situation (and reduced uncertainty) would give cause to introduce a DDREF (if there hadn't already been one) or whether the uncertainties are still as significant to be unable to clearly support the abolition of an existing DDREF.

- **Implementation in real-life radiation protection**

  Continuity, consensus, comprehensibility and acceptance are very important to radiation protection. Frequent changes of concepts and regulations/guidelines can lead to unsettledness, particularly during implementation in real-life scenarios, that are counterproductive to radiation protection and should therefore be avoided whenever possible. Changes should only be pursued if there is sufficient scientific justification for doing so and if they are expected to lead to a major improvement in radiation protection, e.g. an improved protective effect and/or risk-benefit ratio.

- **International involvement**

  The current radiation protection concept is the result of an ongoing worldwide process. International agreement on radiation protection regulations has always been remarkably high, which is also the result of continuous efforts to achieve maximum international consensus. This far-reaching consensus also include estimates pertaining to the scientific basis of radiation protection such as radiobiology and radiation effect findings as well as questions relating to radiation protection conservatism. Active involvement in gaining international consensus is therefore a key aspect.

– **Consequences for stipulating limits**

  With its three "basic conceptional pillars", i.e. justification, optimisation and limitation, radiation protection has such a robust framework in place that quantitative fluctuations of one of the implemented factors (e.g. DDREF or weighting factors) do not necessarily require changes to limits, but could form the subject of discussion. Here, the problem of stipulating limits for occupationally exposed persons would inevitably be based on arguments where the radiation risk value and DDREF play a far greater part than the limit that applies to the general public. Justification for stipulating a limit for the public is largely based on the fact that it is within the fluctuation range of natural radiation exposure and that no risk statements can be made at levels of 1 mSv.

– **Risk communication**

  The general public is highly sensitive when it comes to radiation risk, but public debate regarding the effects of radiation and radiation risk levels are often governed by misconceptions. This is why careful and comprehensive communication is required every time a reassessment takes place.

  Public trust in the credibility of scientific bodies is a fundamental part of successful communication. Credibility can only be achieved by extensively discussing issues pertaining to higher risks. Such discussions and communication must take place within a context and in such a way that the general public is able to assess the relevance and value of new scientific findings[1].

# 6 Summary assessment

A statement on DDREF based on radiobiological studies involving cell cultures does not provide a clear picture. At molecular and cellular level (in vitro studies), a range of linear and non-linear effects can be observed. While effects at an "early" effect level, e.g. energy deposition, double-strand breaks and other radiation-induced DNA damage, have a linear relationship with dose, more complex "later" effects such as chromosome aberrations, repair processes and other effects on a subsequent effect level also reveal, at least in part, non-linear dose-response components. In addition to that, other biological mechanisms have an impact at low doses when compared with high doses. Dependencies on dose rate may be observed in a range of different effects, and there are no clear indications of a relationship between dose and dose-rate effects. This means that they can largely be observed "independently" of one another.

The effects of studies on animals indicate a large variability, meaning that it is not possible to determine clear dose-response relationships at low doses, nor is it possible to determine dose-rate dependencies. Overall, studies on animals provide little indication of a general deviation from a linear dose-response relationship or of a general dose rate dependency.

To date, radiobiological studies were the main argument in favour of a DDREF higher than 1. Non-linearities in terms of dose-response relationships and dose rate dependencies are still being observed in current studies. A large spectrum of differing dose-effect dependencies can be seen depending on the biological end point.

[1] The German Commission on Radiological Protection (SSK) has already dealt with this topic on several occasions: see SSK vol. 56 "Estimating, evaluating and managing risks" and SSK vol. 66 "Risks involving ionising and non-ionising radiation"

A comparison of the latest results of epidemiological studies involving low and high dose rates does not currently provide any indication that tumour risk is dependent on dose rate, i.e. on a DREF higher than 1. Most of the studies involving low dose rates use a linear dose-response relationship for analysis, which is why the dose-response relationship curve and a certain LDEF value cannot be determined. The latest study on atomic bomb survivors involving the effect of large dose rates does not provide any clear distinction between various types of dose-response relationship, e.g. linear or linear-quadratic, meaning that it is not currently possible to derive a LDEF value.

Theoretically, mechanistic models can provide a way of deriving a functional relationship between dose and effect, which is why they play a major part in extrapolating from high to low doses. The linear-quadratic dose-response relationship was originally designed as a mechanistic model, thus making it a strong indicator of a DDREF > 1. Even if this model now barely claims to realistically describe a response mechanism, it has still retained some of its validity.

However, mechanistic models generally only map a segment of the highly complex yet largely unknown response curve between the primary event (ionisation) and the end point (cancer). It is unlikely that the entire carcinogenesis process can be described by one of these models if it is to extend beyond simple data fitting. This is why models only have a limited part to play in deciding on an appropriate DDREF value.

Uncertainties have a major impact on justifying a DDREF. No single scientific criterion is sufficient to provide a clear DDREF value. Instead, the many variabilities of the various study approaches as well as their results and uncertainties only allow a DDREF to be limited to a value of less than 2. However, an assessment of the scientific findings does not permit any specification of the DDREF with more precision.

As described in Chapter 2, the DDREF is a very subtle design factor in terms of influence and function. In light of the current level of scientific knowledge and major radiation risk uncertainty, various scientific criteria indicate that such a factor would not be introduced if it were not already in place. Ensuring maximum continuity in terms of radiation protection gives rise to the question of whether weaker evidence based on current scientific assessment provides sufficient justification for abolishing a DDREF and any potentially resulting consequences, or whether the uncertainties permit a value between 1 and 2 that cannot be decided upon, therefore rendering it debatable. It should also be noted that the conceptional construct of radiation protection is based on the three fundamental principles, i.e. “justification”, “optimisation” and “limitation”, and therefore not largely based on knowing the exact radiation risk at low doses.

In view of the continuity criterion described above, implementation within practical radiation protection requires meticulous considerations as to whether the DDREF value should be changed. Such considerations should only take place with international consensus.

Based on current scientific findings, the German Commission on Radiological Protection (SSK) no longer considers there to be sufficient justification for the DDREF used in radiation protection. If a reduction or abolition of the DDREF is the subject of consideration for scientific reasons, however, it must be justified such that this scientific motive is sufficient, especially if the purported radiation protection improvement cannot be clearly stated. On the other hand, consideration should be given in terms of the extent to which a potential underestimate of the risk of cancer at low doses and low dose rates could be in line with the precautionary principle customary to radiation protection.

The German Commission on Radiological Protection (Strahlenschutzkommission, SSK) sets great store on the scientific basis of its statements and recommendations. SSK considers maximum scientific objectivity and constant efforts to incorporate all current research results paramount to gaining and building the necessary trust of the general public in its assessments.

The SSK also takes this view when it comes to changing the DDREF on the basis of new scientific findings. Beyond its commitment to scientific objectivity, the SSK considers its mission to observe issues regarding public perception and take account of them in frequent ongoing communication.

In radiation protection the most important factors are damage associated with exposure (carcinogenesis and genetic mutation) and their likelihood of occurrence. These factors are quantified by the "detriment" (damage to health), which is a weighted probability of damage including, among others, risk coefficients (including a DDREF) (see Chapter 1). However, the detriment also includes a number of other parameters, such as probability of survival, quality of life and loss of life expectancy. These parameters are subject to development over time. Improved living conditions and medical progress could, for example, lead to an increase in probability of survival in the case of developing cancer, an improvement in quality of life and a reduction in loss of life expectancy. All of these parameters need to be taken into account when further assessing the health effects of a certain exposure. An isolated view of the risk coefficient and/or DDREF is not sufficient to take account of the overall situation.

This aspect is important when deciding whether or not to change the DDREF as both effects may have a complex interactive effect that could lead to a compensatory tendency: The abolition of the DDREF would in itself lead to an increase in radiation-induced detriment, whereas adjusting the above parameters to meet current statistics could lead to a reduction of the detriment.

## Recommendation of the German Commission on Radiological Protection

Based on current scientific findings, the German Commission on Radiological Protection (Strahlenschutzkommission, SSK) no longer considers the justification for the DDREF used in radiation protection as being sufficient.

In view of the assessments set out in this report, 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 the impact on radiation protection, in the case of adjusting the DDREF, the SSK also recommends that all of the other parameters pertaining to the detriment be adapted to the latest scientific findings.

The SSK means that an international agreement in these issues is urgently necessary and recommends that its assessment be used as a basis for international discussions on these issues.

## List of figures

*Fig. 2.1: Dose-rate effect: Based on a linear-quadratic dose-response relationship (equations (2.1) and (2.2), here: $\alpha/\beta$ = 1 Sv), fractionation, i.e. exposure involving several single doses, has less of an effect (solid line) than that caused by a single exposure with the same dose (dotted and dashed line). At the limit to very many fractions, the effect follows the linear component (dashed line) of the linear-quadratic curve.*

*Fig. 2.2: Linear-quadratic dose-response relationships for radiation types with a low (left) and a high LET (right). The quotient $\alpha/\beta$ depends on the LET and describes the dose at which the linear and quadratic terms are the same size. N.B.: The quadratic component (dotted line) is the same on both charts.*

*Fig. 2.3: Dependence of the LDEF on the $\alpha/\beta$ ratio of a linear-quadratic dose-response relationship (equation 2.2) when extrapolating from a dose of 1 Sv (dashed line) or 600 mSv (solid line).*

*Fig. 3.1: Number of breakpoints per cell in chromosome exchange aberrations depending on the dose at various different dose rates. The parameters $\alpha$ and $\beta$ represent the linear and quadratic terms in the linear-quadratic relationship (see equation 2.1), while c is the polynomial axis intercept. Triangles represent "complex" aberrations (several breakpoints per exchange), while circles indicate "simple" aberrations (one or a few breakpoints per exchange).*

*(Source: Loucas et al. 2004, Fig. 4, p. 343. This figure is republished with the permission of the journal "Radiation Research". The original title is: Exchange breakpoints as a function of acute and chronic dose. Triangular symbols represent the dose response for total exchanges (simple plus complex). Circular symbols show the response for simple exchanges alone. For both high and low dose rates, the induction of simple exchanges is fitted well by a linear model. At high dose rates virtually all of the curvature in the shape of the dose response is due to breakpoints from complex exchanges, whose contribution to total damage becomes significant above 2 Gy. At limiting low dose rates all evidence of upward curvature is gone, and the dose responses for total and simple exchanges are almost superimposable, demonstrating that the relative contribution of complex aberrations is small. Nevertheless, complex aberrations are formed under these conditions, accounting for roughly 10 to 15% of the total exchange breakpoints.*

*Fig. 4.1: Excess relative risk (ERR) for all tumours as a function of the colon dose (gamma absorbed dose plus the neutron absorbed dose weighted by a factor of 10). The black dots correspond to ERR values with the corresponding 95% confidence intervals (CI) for the selected dose groups. Solid lines: Linear model (L) (incl. 95% CI, represented as dashed lines) and linear-quadratic (LQ) model, each for the total dose range, and the linear-quadratic (LQ(< 2 Gy)) model for doses between 0 Gy and 2 Gy.*

*(Source: Ozasa et al. 2012, Fig. 4, p. 237. This figure is republished with the permission of the journal "Radiation Research". The original title is: Excess relative risk (ERR) for all solid cancer in relation to radiation exposure. The black circles represent ERR and 95% CI for the dose categories, together with trend estimates based on linear (L) with 95% CI (dotted lines) and linear-quadratic (LQ) models using the full dose range, and LQ model for the data restricted to dose <2 Gy.)*