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THE DOSE AND DOSE-RATE EFFICIENCY FACTOR (DDREF): UNNEEDED, CONTROVERSIAL AND EPISTEMOLOGICALLY QUESTIONABLE

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Abstract

Purpose: The aim of the paper is to review the genesis and evolution of the concept termed *dose and dose rate effectiveness factor* or DDREF, to expose critiques on the concept and to suggest some curse of action on its use.

Material and methods: Mainly using the UNSCEAR reporting and ICRP recommendations as the main reference material, the paper describes the evolution (since the 70's) of the conundrum of inferring radiation risk at low dose and dose-rate. People are usually exposed to radiation at much lower doses and dose rates than those for which quantitative evaluations of incidence of radiation effects are available – a situation that tempted experts to search for a factor relating the epidemiological attribution of effects at high doses and dose-rates with the subjective inference of risk at low doses and dose-rates. The formal introduction and mathematical formulation of the concept by UNSCEAR and ICRP (in the 90's), is recalled. It is then underlined that the latest UNSCEAR radiation risk estimates did not use a DDREF concept, making it *de facto* unneeded for purposes of radiation risk attribution. The paper also summarizes the continuous use of the concept for radiation protection purposes and related concerns as well as some current public misunderstandings and apprehension on the DDREF (particularly the aftermath of the Fukushima Dai'ichi NPP accident). It finally discusses epistemological weaknesses of the concept itself.

Results: It seems that the DDREF has become superseded by scientific developments and its use has turned out to be unneeded for the purposes of radiation risk estimates. The concept also appears to be arguable for radiation protection purposes, visibly controversial and epistemologically questionable

Conclusions: It is suggested that: (i) the use of the DDREF can be definitely abandoned for radiation risk estimates; (ii) while recognizing that radiation protection has different purposes than radiation risk estimation, the discontinuation of using a DDREF for radiation protection might also be considered; (iii) for radiation exposure situations for which there are available epidemiological information that can be scientifically tested (namely which is confirmable and verifiable and therefore falsifiable), radiation risks should continue to be ***attributed*** in terms of *frequentistic* probabilities; and, (iv) for radiation exposure situations for which direct scientific evidence of effects is unavailable or unfeasible to obtain, radiation risks may need to be ***inferred*** on the basis of indirect evidence, scientific reasoning and professional judgment aimed at estimating their plausibility in terms of *subjective* probabilities.

Key words: *DDREF, low-dose, low-dose-rate, radiation-risk, linear-relationship, threshold-dose*

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1. Purpose

The paper is aimed at reviewing the genesis and evolution of the concept termed *dose and dose rate effectiveness factor* (which is usually represented in all languages by the English acronym, DDREF). It will expose critiques on the concept and to suggest some course of action on its use[1].

The concept had been internationally introduced more or less simultaneously in the 90's by the United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR [USCEAR, 1993] and the International Commission on Radiological Protection, ICRP [ICRP, 1991]. It should be emphasized, however, that the aims of UNSCEAR and ICRP in defining a DDREF were subtly different: while UNSCEAR used the concept for estimating risk of radiation exposure globally, ICRP recommended its use for purposes of radiation protection.

UNSCEAR and ICRP references to radiation health effects and risk were based on the available scientific information at high doses and dose rates and on the epidemiological studies based on that information. But such information was not sufficient for estimating unequivocally effects and risk at low doses and dose rates and, in particular, for estimating the presence of a threshold of dose below which effects will not occur[2].

The original call for a 'reduction factor', conceptually similar to what would became the DDREF, mainly aroused from the perceived need of estimating radiation risk at low dose and dose-rate on the base of the available factual information on radiation risk, which was assessed from exposures at high dose and dose-rate. While estimates of radiation health effects come largely from epidemiological studies involving exposures at high doses and dose rates, people are usually exposed to radiation at much lower levels. At low doses and dose rates epidemiological evidence is not available, and biological indicators of radiation-induced health effects associated to low doses exposures do not exist.

Thus, the issues of estimating risk at low doses from data available at high doses and the related DDREF concept have both a rather prolonged history. The first objective of this paper is to scrutinize that saga. This will facilitate to arrive to the ultimate objective of the paper: suggesting a future for the DDREF.

[1] Similar concepts were used by other relevant bodies, including the United States National Council on Radiation Protection and Measurements (NCRP) [NCRP, 1980], the Committee on Biological Effects of Ionizing Radiation of the National Research Council of the United States [NAS, 2006], the United States Nuclear Regulatory Commission [USNRC, 2005], and the (former) United Kingdom National Radiological Protection Board [NRPB 1988]. Since its inception the concept has been submerged in confusing terminology. It has been termed low-dose effectiveness factor (LDEF), dose-rate effectiveness factor (DREF), protraction factor, linear extrapolation overestimation factor, linear risk overestimation factor, low-dose extrapolation factor, risk ratio …etc [Rühm, 2015]. It was introduced by NCRP as DREF, although it used the term 'protraction factor' rather than DREF when the exposure extended over the lifetime, and in particular, when the effect was on life shortening. The names 'linear extrapolation overestimation factor (LEOF)' and the 'low dose extrapolation factor (LDEF)' were used in the literature [Pierce, D.A. and M. Vaeth, 1989].

[2] Since the problem started to be addressed, it was considered that proving or disproving the possible presence of a threshold dose, below which radiation effects could not occur, on the basis of epidemiological studies, was likely to be impossible due to statistical uncertainties in both the spontaneous and induced incidences of the effects. In confronting this difficulty, it was necessary to rely on general biological information and it was presumed that cellular targets exposed to ionizing radiation could be altered by single ionizing events, that such damage was unlikely to be error-free and that it may ultimately give rise to a health effects, and that, therefore, there might not be a dose or dose-rate threshold for such effects.

2. Material and methods

The UNSCEAR reporting and the ICRP recommendations are to be used as the main reference material. From 1958 to 1988, UNSCEAR reports had already included extensive discussions on the conundrum of deriving inference of radiation risk at low doses and dose rates from the incidence of radiation health effects resulting from epidemiological studies of radiation exposure situations involving high doses and dose rates. [UNSCEAR, 1958, 1962, 1964, 1969, 1972, 1977, 1982, 1986 and 1988]. Since the early 70's [ICRP, 1977] ICRP was also concerned with the same issue but for the different purpose of radiation protection. In 1980, a concept similar to the DDREF was introduced at the national level [NCRP,1980]. The 1993 UNSCEAR report and the ICRP Publication 60 would finally introduce formally the DDREF concept at the international level [UNSCEAR, 1993] [ICRP, 1990]. The 1996 UNSCEAR report made extensive references to DDREF but did not use it [UNSCEAR, 1996]. The latest UNSCEAR reporting on radiation risk did not use the DDREF concept for purposes of risk estimation [UNSCEAR, 2010, 2012, 2014]. The latest ICRP recommendations continue to use the concept for purposes of radiation protection [ICRP, 2003].

On the basis of these reference materials, the paper will follow the method of reviewing the genesis, evolution, formal introduction, mathematical formulation, quantification and a critique of the DDREF, including its eventual obsolescence, for purposes of estimating attributable risk and for purposes of radiation protection, as well as some other difficulties with the concept.

2.1. Genesis

The UNSCEAR struggle for understanding risk at low doses can be traced back to 1958, when it recognized that knowledge of effects at low radiation levels was lacking in quantity and quality, and that understanding of the basic mechanisms of damage produced at very low doses was needed [UNSCEAR, 1958].

In 1962 UNSCEAR was already expecting proportionality between doses and the incidence of malignancies 'down to the lowest doses" on the base of theoretical considerations and experimental data from cells and animals [UNSCEAR, 1962].

In 1964 occurs a first confusion between the UNSCEAR terms of reference and radiation protection. UNSCEAR confirms the use of radiation protection quantities for its estimates and indicates that linearity is the only approach which allows the use of mean doses in estimating risks, although recognizing that the assumption would likely result in overestimation of risk. [UNSCEAR, 1964].

In 1969, biological dosimetry is high in the agenda. A dose relationship for chromosomal aberrations is established and UNSCEAR introduces a warning that will reappear over the years: while the incidence of chromosome aberrations and that of tumors both seems to increase with increasing dose, but the relationship between the two effects is complex. [UNSCEAR, 1969]

In 1972 UNSCEAR had reported that the initial slope of the dose response was estimated to be lower than the slope at higher doses by a factor of about 2.5. UNSCEAR based that judgment on the analysis of data for leukaemia induction (all types of leukaemia pooled) in main cohort of survivors of the atomic bombing of Hiroshima and Nagasaki, termed the Life Span Study (LSS) [UNSCEAR, 1972].

At that time, ICRP was struggling in finding a paradigm to deal with radiation protection at low doses [ICRP, 1977]. ICRP was then considering effects defined according to the assumption that the probability of an effect occurring, rather than its severity could be regarded as a function of dose, without threshold, which were termed 'stochastic' effects. Unfortunately it was not clarified at the time that the qualifier 'stochastic' was use in reference to the randomness of the manifestation of the effect rather than of its generating event (these communication lapses would produce problems of interpretation). At the dose range involved in radiation protection, ICRP assumed that hereditary effects (namely, radiation induced health effect that occurs in a descendant of the exposed person) were stochastic, that some somatic effects (namely, radiation induced health effect that occurs in the exposed person) were considered stochastic and that, of these, carcinogenesis was considered to be the chief somatic risk of irradiation at low doses and therefore the main problem in radiation protection. [ICRP, 1977 (§6)]

Already at those early times, ICRP warned that the relationship between the dose received by an individual and any particular biological effect induced by irradiation was a complex matter on which much further work was needed. Then, ICRP prematurely recognized that, regarding stochastic effects and for radiation protection purposes, it was necessary to make *certain simplifying assumptions*, one being that, within the range of exposure conditions usually encountered in radiation work, *a linear relationship without threshold should be assumed between dose and the probability of an effect*. The ICRP then introduced a major warning: the simple summation of doses received by a tissue or organ as a measure of the total risk, and the calculation of the collective dose, as an index of the total detriment to a population, are valid *only on the basis of this assumption* and that the severity of each type of effect is independent of dose [ICRP, 1977)]. **This would become the basic radiation protection paradigm for years to come.**

Under the adopted paradigm, it was clear that the added risk from a given dose increment will depend on the slope of the dose-response relationship. At that time ICRP considered the dose-response relationship for stochastic processes to be in fact 'highly sigmoid' and thus, 'the risk from low doses could be overestimated by making a linear extrapolation from data obtained at high doses. ICRP then considered that there were radiobiological grounds for assuming that the dose-response curve for low-LET radiation will generally increase in slope with increasing dose and dose rate, over the absorbed dose range up to a few gray. The ICRP then introduced the mathematical formulation that will then be after many years used to define the DDREF, by indicating that for many effects studied experimentally, the response in this range could be represented by an expression of the form:

$$E = aD + bD^2 \quad (1)$$

Where:
E denotes the effect, and *D* the dose;
"a" and *"b"* are constants;
the quadratic term would 'predominate at high absorbed doses (generally above one gray) and high absorbed-dose rates (of the order of one gray per min), and;
the linear term and the slope that it represents come to 'predominate as the dose and dose rate are reduced'. [ICRP, 1977 (§ 28)]

ICRP then warned that, although a relationship of this form has been documented for a variety of effects, the relative values of the parameters *"a"* and *"b"* vary from one observation to another. ICRP concluded then that 'the extent to which the relationship may differ for other situations remains to be determined'. For human populations in particular, knowledge of dose-response relationships was too limited to enable confident prediction of the shapes and slopes of the curves at low doses and low dose rates. Nevertheless, ICRP indicated, in a few instances risk estimates can be based on results of irradiation of human populations involving single absorbed doses, of the order of 0.5 Gy or less, or to such doses repeated at intervals of a few days or more. In such cases it can be reasonably assumed that the *frequency* per unit absorbed dose of particular harmful effects resulting from such exposures is not likely to overestimate greatly the *frequency* of such effects in the dose range of concern in radiation protection, even though the latter may be received at much lower dose rates [ICRP, 1977 (§ 28)]. It is interesting to note that even at those early times ICRP made clear that the probabilities being searched where frequentistic probabilities.

Unsurprisingly, ICRP made then a fundamental warning indicating that 'in many instances, however, risk estimates depend on data derived from irradiation involving higher doses delivered at high dose rates' and that 'in these cases, it is *likely* that the *frequency* of effects per unit dose will be lower following exposure to low doses or to doses delivered at low dose rates, and it may be appropriate, therefore, ***to reduce these estimates by a factor to allow for the probable difference in risk***. [ICRP, 1977 (§ 29)]

Without naming it, ICRP thus introduced for the first time the concept of DDREF at the international level. Moreover, the ICRP made clear that its recommended 'risk factors' have therefore been chosen as far as possible to apply in practice for the purposes of radiation protection.

ICRP also introduced a further hypothesis, namely that 'the use of linear extrapolations, from the frequency of effects observed at high doses, may suffice to assess an upper limit of risk, with which the benefit of a practice, or the hazard of an alternative practice-not involving radiation exposure-may be compared'. However, ICRP indicated, 'the more cautious such an assumption of linearity is, the more important it becomes to recognize that it may lead to an overestimate of the radiation risks, which in turn could result in the choice of alternatives that are more hazardous than practices involving radiation exposures'. Thus, ICRP warned that in the choice of alternative practices, 'radiation risk estimates should be used only with great caution and with explicit recognition of the possibility that the actual risk at low doses may be lower than that implied by a deliberately cautious assumption of proportionality'. [ICRP, 1977 (§ 30)].

As the ICRP recommendations were being published in 1977, UNSCEAR addressed a number of similar estimates in its 1977 UNSCEAR Report. These can be summarized as follows: there was an increasing incidence of health effects with increasing dose up to a maximum, with a subsequent decline at higher doses, with assumed dose-response function with a number of common features including that data obtained from experimental animals appeared to be consistent with radiobiological effects occurring in single cells, such as cell killing, induction of mutations and chromosome aberrations. As a result there was an early recognition that: (i) information was needed on the extent to which both total dose and dose rate influence the induction of health effects in exposed individuals; and, (ii) the two features of the dose response that are most important for evaluation of the risk at low doses are the possible presence of a threshold dose, below which the effects could not occur, and the shape of the dose response [UNSCEAR, 1977 (particularly, Annex G, § 317 and 318)].

The 1977 UNSCEAR reporting inform of reduction factors ranging from 2 to 20 but noted that the LSS data suggested a reduction factor of 2 for the risk coefficient at lower doses as compared with that at the higher doses. Furthermore, in its final estimates, UNSCEAR then adopted a 'reduction factor' of 2.5 for estimating risk at low doses and low dose rates when extrapolating from high dose and dose-rate studies. An important conclusion of the UNSCEAR 1977 report is that the only secure basis for quantitative estimates of the *frequency* with which harmful effects may be produced in man must depend upon surveys of human populations who have been exposed to known doses of radiation. While obvious, this important consideration was not always taken into account seriously.

In summary, already in the early 70's, UNSCEAR discussed the conundrum of estimating risk at low dose and dose-rates from data at high dose and dose-rate and ICRP introduced *a factor for radiation protection purposes* to reduce estimates of *frequencies of effects* at high doses to allow for the probable difference in *risk at low doses*.

2.2. Evolution

The 80's was a time of reflection in relation of what it was going to be the evolution of the DDREF concept. The history was summarized in ICRP Publication 60 [ICRP, 1991 (§B55 et seq)]. Experimental information on dose-response relationships and the influence of dose rate had been comprehensively reviewed in a report by the National Council on Radiation Protection and Measurements [NCRP, 1980]. The general conclusion was that the shape of the dose-response relationship for high doses, at high dose rate was likely to be linear-quadratic in form in most biological systems. Thus, the basic paradigm that had been presented by ICRP a decade before was consolidated and will dominate in years to come was generated at the time. For exposure to low doses at low dose rate, the response was considered to be often effectively linear as is to be expected for a linear-quadratic response at low dose. In the linear-quadratic form, $E = aD + bD^2$, the effect initially

increases linearly with dose i.e. the effect per unit dose E/D = *a* is constant. Thereafter, the effect would increases more rapidly, i.e. the effect per unit dose increases linearly, as the quadratic term becomes operative (E/D = *b*D). At higher doses still, the effectiveness often declines again due to the effect of cell killing reducing the number of cells at risk. In the linear-quadratic equation, the ratio of the parameters for the linear and quadratic terms, *a/b*, has the dimension of dose and its value reflects the respective contributions of the linear and the quadratic term. Thus if *a/b* = 1 Gy, at 1 Gy the contributions to the response of the linear and quadratic terms would equal.

The NCRP thus defined a *dose-rate-effectiveness factor* (DREF), as the ratio of the slope of the linear no threshold fit to high dose, high dose-rate data, to the slope of the linear no threshold fit to low dose, low dose-rate data, and concluded that the DREF = 1 + *b/a* D. This will be the basis for the mathematical formulation of the DDREF that will be developed by UNSCEAR (see hereinafter) and of the surprising conclusion that the observed DREF in experimental situations would not be constant but depend on the dose range and the dose rate range over which the studies are performed. It would be smaller if these ranges are small. At the maximum in the dose-response relationship, which bends over due to cell killing, the DREF would also be a maximum. The NCRP report provided tables of data on DREF values in a wide variety of experimental biological systems, including tumours and life-shortening in animals. The NCRP concluded that values of DREF in experimental systems varied between 2 and 10 for individual tumour types and for life shortening in animals, as well as for a variety of other experimental endpoints.

Meanwhile, in 1982, UNSCEAR indicated some inconsistent outcomes in radiation risk estimates, but concluded that the overwhelming body of evidence at that time showed that at high doses of low LET radiation there was a life shortening essentially caused by an increased incidence of tumours. The effect of dose and dose rate, on the life-span shortening reported presented some conflicting results. By pooling many series of studies, an apparently linear relationship was obtained, which was understood to imply no dose-rate dependence, but the data could also be fitted with a linear-quadratic relationship, which would be consistent with the observation of a dose-rate effect [UNSCEAR, 1982].

In 1986, UNSCEAR reviewed evidence at the sub-cellular and cellular levels relevant to assessing the possible nature of the dose-response relationships for cancer initiation by radiation, studied how the initiation of cancerous clones and their progression to clinical tumours may affect the shape of the dose-response relationship and, examined various models of cancer induction and tested them for compatibility with epidemiological and experimental findings [UNSCEAR, 1986 (Annex B: Dose-response relationships for radiation-induced cancer)]. Three basic non-threshold models of the effect of radiation as a function of dose were considered with respect to both cellular effects and to cancer induction: the linear, the linear-quadratic and the pure quadratic models. UNSCEAR concluded that the vast majority of dose-response curves for induction of point mutations and chromosomal aberrations by low-LET radiation could be represented by a linear-quadratic model at low to intermediate doses; for high-LET radiation, after correction for cell killing, a linear model usually applied. In sum, after reviewing the available data again, in 1986 UNSCEAR came to the conclusion (based essentially on the same sources of experimental information) that responses at low dose and dose rate were less than those at high dose and dose rate by a factor of up to perhaps 5.

In 1988 UNSCEAR warned that assessment of the effects of low dose is clouded by the need for large samples, the difficulty of accurately estimating exposure and the growing importance of extraneous sources of variation and that precise direct estimation requires impracticably large samples, concluding that estimates of low-dose risks based largely on high-dose data must depend heavily on the assumptions about the shape of the dose-response curve and are, of necessity, no better than the applicability of the model used, suggesting that resolution of these difficulties would not be easy [UNSCEAR, 1988 (Annex F, particularly §68)]. In sum, while UNSCEAR at the time did not re-evaluate the data, it suggested the use of a factor of between 2 and 10, the implication being that the effect varied for different types of tumours.

During that decade many papers were published on matters associated with the DDREF concept, which were summarized by ICRP [ICRP, 1991 (§B55 et seq)]. In a report, experimental information included data on life-shortening and transformation in animal experiments, confirming reduction factors in the range of 2 to 10 [Liniecki, 1989]. Another report informed a maximum DREF of 5 for radiation-induced life-shortening due to tumours in mice after single, fractionated and continuous exposures [Thomson and Grahn, 1989]. Information on the A-bomb survivors for leukaemia suggested that the dose response fitted a linear-quadratic relationship best with an equivalent DREF of about 2 [NAS, 1990]. According to this reporting, for the solid cancers taken together, linearity provided the best fit [NAS, 1990] but individual tumour types show some differences in the slope of the dose response. A reanalysis however suggested that there was little difference in dose-response relationship for any of the different cancer sites including leukaemia, concluding that a DREF of up to 2 would be possible from the A-bomb survivor data but greater than 2 would be difficult to justify [Pierce and Vaeth, 1989]. Data from breast and thyroid studies showed little evidence of fractionation effects [Boice et al., 1979; Shore et al., 1984]. Another study on radiation-induced cancer in the breast showed a possible reduction factors of up to 3 [Miller et al., 1989]. Other study that found cancers induced by radioiodine in the thyroid were about 4 times less effectively than for acute x rays [Holm et al., 1988] but it also reported that factors other than dose rate (e.g., spatial distribution of dose and hormone balance) might also be involved. In another study, fractionated exposures in the lung failed to produce lung tumours even after several Gy (but did produce breast tumours) in contradistinction to the A-bomb survivor study, but no reduction factor could be derived [Davis et al., 1989].

While reporting on all these studies, ICRP noted at the time that linearity in dose response at doses of 1 Gy or more does not necessarily mean that no dose-rate effects are possible because of the different overall times of exposure involved when the dose is protracted. At such doses more than one ionising event can certainly occur in targets of molecular dimensions. A number of important experimental responses, such as life-shortening in mice, seem to show linear responses with different slopes for different fractionation or dose rate regimes but mainly over relatively high dose ranges (Thomson and Grahn, 1989). At very low doses, at which less than one event per sensitive target may occur, the response is expected to be linear. [ICRP, 1977 (§B60)]. Moreover, at that time ICRP already considered that theoretical considerations and most of the available experimental and epidemiological data did not support the idea of a threshold for the carcinogenic response to radiation involving low energy transfer (LET); nevertheless, ICRP warned that on statistical grounds a threshold for individual tumour types cannot be ruled out with certainty in either human or experimental systems, and that, if thresholds do exist, their values must be less than about 0.2 Gy for most human cancers and perhaps much less. [ICRP, 1977 (§B61)]

2.3. Formal Introduction

Finally, in 1993, the DDREF concept would be developed and introduced by UNSCEAR and ICRP more or less simultaneously. The DDREF was defined by UNSCEAR and ICRP (twice), adopted by the international standards established under the aegis of the IAEA and introduced in legislation of countries, e.g., the United States of America (US). The definitions used subtly different formulations, as follows:

- by UNSCEAR, as *the reduction in effect per unit dose observed at low doses and low dose rates, compared with effects at high doses and high dose rates* [UNSCEAR, 1993 (Annex F § 94 and 334)];
- by ICRP (at the time), *as a factor reducing the probability coefficient obtained directly from observations at high doses and high dose rates to give estimates of the probability of effects at low doses and low dose rates*; [ICRP, 1991 (§74)], and then, eventually,
- by ICRP (currently), as *a judged factor that generalises the usually lower biological effectiveness (per unit of dose) of radiation exposures at low doses and low dose rates as compared with exposures at high doses and high dose rates* [ICRP, 2007];
- by the IAEA (in its Safety Glossary, which establishes the terminology used by the international standards for nuclear safety and radiation protection), as *the ratio between the risk or radiation detriment per unit effective dose for high doses and/or dose rates and that for low doses and dose rates*, with the clarification that it is used in the estimation of risk coefficients for low doses and dose rates from observations and epidemiological findings at high doses and dose rates and that supersedes the dose rate effectiveness factor [IAEA, 2007]; and, ultimately, just as an example of definition in a national legislation,
- by the US Nuclear Regulatory Commission (USNRC), as *a factor applied to a risk model to modify the dose-risk relationship estimated by the model to account for the level of the dose and the rate at which the dose is incurred*; 'as used in the US Interactive Radio-Epidemiological Program (IREP)[3], a DDREF value of greater than one implies that chronic or low doses are less carcinogenic per unit of dose than acute or higher doses' [USNRC, 2017].

At the early 90's ICRP was consolidating a renewed radiation protection paradigm that would be developed as recommendations issued as ICRP Publication 60 [ICRP, 1991]. The basic assumption was that the simplest relationship between an increment in the dose incurred in an organ or tissue and the resulting increment in the probability of a defined stochastic effect was that of a straight line through the origin. But, as indicated before, ICRP warned that the human epidemiological data were not sufficiently precise to confirm or exclude that relationship and that almost all the data relating to stochastic changes in cells *in vitro* and in simple biological organisms and to the induction of many animal tumours showed curvilinear dose-effect relationships for radiations of low linear energy transfer (LET), with the slope at low doses being less than that at high doses.

In this context, ICRP indicated, low doses (and low dose rates) imply situations in which it was very unlikely that more than one ionising event will occur in the critical parts of a cell within the time during which repair mechanisms in the cell can operate. In such situations, ICRP postulated, the dose-response relationship will be linear. At higher doses and dose rates, two or more events may be able to combine, producing an enhanced effect reflected by a quadratic term in the dose-response relationship. At still higher doses, where cell killing becomes important, the slope would again decrease. [ICRP, 1991 (§72)]

In short, ICRP postulated at the time that for low LET radiations, the most characteristic form of the relationship between the dose in an organ or tissue and the probability of a resultant cancer is that of an initial proportional response at low values of dose, followed by a steeper rate of increase (slope) that can be represented by a quadratic term, followed finally by a decreasing slope due to cell killing. Furthermore, the ICRP suggested that there were no adequate grounds for assuming a real threshold in the relationship and that this form of response, while typical, is not necessarily the definitive form for all human cancers. According to ICRP, taken together with the linear approximation for increments over the dose due to natural background, the presumption provided a suitable basis for the use of a simple proportional relationship at all levels dose for purposes of dose limitation in radiation protection. [ICRP, 1991 (§73)]

On the basis of this reasoning, ICRP concluded that, in the context of radiation protection, there was sufficient evidence to justify its making an allowance for non-linearity when interpreting data for low LET radiation at high doses

[3] IREP is a US computer software program that uses information on the dose-response relationship, and specific factors such as a claimant's radiation exposure, gender, age at diagnosis, and age at exposure to calculate the probability of causation for a given pattern and level of radiation exposure.

and high dose rates to give estimates of the probability of effects at low doses and low dose rates. Thus, ICRP decided 'to reduce by a factor of 2 the probability coefficient obtained directly from observations at high doses and high dose rates, modified if necessary by an allowance for the effects of cell killing'. This would be the first attempted to quantify the DDREF. Because the wide spread in the data and the ICRP recognised 'that the choice of this value [of 2] is somewhat arbitrary and may be conservative'. The ICRP again indicated that this now defined DDREF was included in the probability coefficients for all doses below 0.2 Gy when the dose rate is less than 0.1 Gy per hour. [ICRP, 1991 (§74)].

In fact, since the data at the time relating to high doses and high dose rates of low LET radiation, showed a lifetime fatality probability coefficient for a reference population of both sexes and of working age**,** of about 8 10^{-2} Sv^{-1} for the sum of all malignancies, this value, combined with the DDREF of 2, would lead to a nominal probability coefficient for workers of 4 10^{-2} Sv^{-1}. The corresponding values for the whole population, including children were estimated to be about 10 10^{-2} Sv^{-1} for high doses and dose rates and 5 10^{-2} Sv^{-1} for low dose and dose rates [ICRP, 1991 (§83)].

At the time, meanwhile, UNSCEAR was making very similar reasoning. Its radiation risk estimates were based on a number of assumptions, including that: radiation induces specific changes in the genetic code of cells simply by single tracks and by additional interaction of multiple tracks; the probability of this occurring could be expressed as the sum of two terms, one proportional to dose and the other proportional to the square of dose; at low doses with any dose rate and at high doses with low dose rate, only the term proportional to dose would be effective; at high doses with high dose rate, both terms are relevant; with densely ionizing radiation, there are fewer, but denser, tracks per unit dose, and each track is more likely to produce damage that is not successfully repaired; and, so, the relationship is more likely to be proportional to dose at all doses and dose rates [UNGA, 1993 (§25)].

On the basis of these presumptions, UNSCEAR informed the UN General Assembly in 1993 that the approach commonly used then in risk assessment was to fit a linear dose-response relationship to the data, a procedure that was usually considered to give an upper limit to the risk at low doses, because the quadratic term will increase the response at high doses with high-dose rates, forcing an increase in the slope of the fitted straight line; and that, from radiobiological considerations, it was then possible to assess the value of the factor by which the slope of the fitted curve should be reduced to give an estimate of the linear component of the linear-quadratic relationship [UNGA, 1993 (§43)].

Thus, the UN General Assembly was further informed that:

(i) an important element in the assessment of the radiation risks at low doses was then the reduction factor used to modify the direct linear (non-threshold) fit to the high-dose and high-dose-rate epidemiological data in order to estimate the slope of the linear component of the linear-quadratic function;

(ii) this factor was estimated with substantial uncertainty to be about 2 for the dose range providing most of the epidemiological data [UNGA, 1993 (§102)]; and,

(iii) the factor by which risk estimates derived from studies at high doses should be reduced when used to derive estimates for low doses was small with data suggesting a value not exceeding 2 [UNGA, 1993 (§107)].

The UNSCEAR judgements of 1993 were basically confirmed by UNSCEAR in 1994, although with the caveat that epidemiological studies on different human cohorts provide different quantitative results [UNSCEAR, 1994].

2.4. Mathematical formulation

A precise mathematical definition of the DDREF was elaborated by UNSCEAR at that early 90's [UNSECAR, 1993 (Appendix F, §31 to 38 and 89)]. It was based on the 70's above described assumptions on single-hit target theory and multitrack effects for the radiation-induced origins of health effects. Thus, it was presupposed that the probability of occurrence of effect, p_D, at a given dose, D, can be approximated by a potential expression of dose of the type:

$$p_D = (\alpha_1 D + \alpha_2 D^2 + \ldots . \alpha_n D^n) \exp[-(\beta_1 D + \beta_2 D^2 + \ldots \beta_n D^n)] \quad (2)$$

where:
the $\alpha_n D^n$ factors are coefficients for n terms for the induction of stochastic effects; and, the $\exp[-(\beta_1 D + \beta_2 D^2 + \ldots \beta_n D^n)]$ factor represents the disappearance of targets due to the killing of cells.

As the terms above 2 are considered trivial and the exponential term is not dominant except at very high doses, the above equation becomes linear quadratic and the (linear quadratic) probability, p_{lq}, results:

$$p_{lq} = \alpha_1 D + \alpha_2 D^2, \quad (3)$$

which is termed the *linear quadratic relationship*.

Since at very low doses the frequency of interaction is extremely low (an exposure to photonic radiation of around 1 MeV of energy and delivering a dose rate of around 1mSv/year, would be responsible of around 1 interaction/year/cell), $\alpha_2 D^2$ can be considered to be negligible at low doses and therefore the equation becomes linear with dose, and the (linear) probability, p_l, becomes:

$$p_l = \alpha_1 D, \quad (4)$$

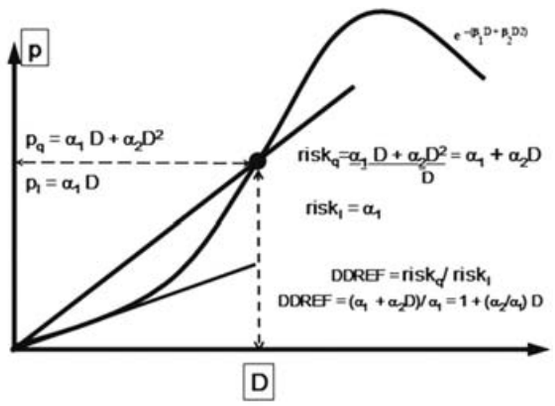
which have been generally termed *linear* (non-threshold) *relationship* or LNT.

Therefore, in a coordinate plane of probability, p_d, versus dose, D, it is possible to represent the probability, $p_{lq} = \alpha_1 D + \alpha_2 D^2$ resulting from the linear quadratic relationship and the probability $p_l = \alpha_1 D$ resulting from the linear relationship at low doses both as a function of the dose, D (see following Figure).

It may be observed that the risk per unit dose, $risk_q$, resulting from the linear quadratic relationship will be:

$$risk_q = (\alpha_1 D + \alpha_2 D^2) / D = \alpha_1 + \alpha_2 D \quad (5)$$

and the the risk per unit dose, $risk_l$, resulting from the linear relationship will be:



$$risk_l = \alpha_1. \quad (6)$$

Since the DDREF is defined as:

$$DDREF = risk_q / risk_l \quad (7)$$

It would result that:

$$\mathbf{DDREF = (\alpha_1 + \alpha_2 D)/ \alpha_1 = 1 + (\alpha_2/\alpha_1) D.} \quad (8)$$

Thus, as already discovered in the 70's, according to its mathematical formulation, the DDREF would not be constant with dose but it will increase linearly with the values of D at which the effects are observed. This would make the claim for a given constant value of DDREF mathematically unsustainable.

In fact, ICRP had observed at the same time that the DDREF in experimental situations will depend on the dose range and the dose rate range over which the studies are performed. It will be smaller if these ranges are small. At the maximum of the dose-response relationship (which bends over due to cell killing as noted above) the DDREF will also be a maximum. [ICRP, 1990 (§B56)]

2.5. Quantification

It is interesting to note, however, that the above mathematical formulation of DDREF could also lead to an estimation of a quasi constant DDREF. In fact, in order to maximize p_D it coud be differentiated with respect to D and equalized to zero. It was then deduced, under some assumptions at such maximizing value, that the DDREF would appear to be in the range of two to three. [Beninson, 1996]

Already in 1990, ICRP presented a comprehensive summary of DDREF suggested values [ICRP 1990 (§B64)]. While discussion choices of dose and dose rate effectiveness factor for low LET radiation, ICRP indicated that it was evident at the time that theoretical considerations, experimental results in animals and other biological organisms, and even some limited human experience suggest that cancer induction at low doses and low dose rates should be less than that observed after high doses and dose rates. The principal source of risk estimation were the Japanese survivors of the atomic bombs who were exposed to a range of doses at high dose rate and in whom statistically significant excess of cancer have been observed at doses down to 0.2 Gy. The ICRP therefore considered that a DDREF should therefore be applied to this data. In making a determination on the value to be used for this purpose the ICRP noted:

(i) that the full range of DDREF values obtained from studies in animals, namely 2-10, may extend over a broader dose range than human data and therefore include higher values than are relevant;

(ii) that some human experiences show little evidence of fractionation effects while others indicate possible effects of up to 3 or 4 at most;

(iii) that direct statistical assessment of the A-bomb survivor data does not seem to allow for much more than a factor of about 2 for the DDREF;

(iv) that DDREF ratios actually used for risk estimates in the past by others include UNSCEAR who used 2 and 2.5 in 1977 [UNSCEAR, 19977], suggested perhaps up to 5 in 1980 [UNSCEAR,1986], and recommended 2 to 10 in 1988 [UNSCEAR, 1988b]; the BEIR III Committee used a DDREF of 2.25 [NAS, 1980] but the BEIR V Committee recommended 2 or more but applied 2 only in the case of leukaemia and 1 for other cancers in deriving their numbers [NAS, 1990]; the US Nuclear Regulatory Commission used 3 [NUREG, 1989] and a group of the US National Institutes of Health used 2.3 [Rall et al., 1985].

In view of these considerations and especially that limited human information suggests a DDREF in the low region of the range, the ICRP had decided at the time to recommend that for radiation protection purposes the value 2 be used for the DDREF, recognising that the choice is somewhat arbitrary and may be conservative. However, the ICRP warned that, obviously, its recommendation at that time can be expected to change if new, more definitive information becomes available in the future. [ICRP, 1991]

In 2000 [UNSCEAR, 2000] and in 2006 [UNSCEAR, 2006] presented comprehensive reviews of epidemiological studies of health effects of radiation. The reports also addressed comprehensively the issue of DDREF. The 2006 reporting introduced around forty mentions to the concept and summarizing values that were being used, which were ranging from 2 to 10 although with most values being around 2 to 3. [UNSCEAR 2006, Annex A, Table 8]

2.6. Disregarding DDREF for estimating attributable radiation risks

However, in spite of the long referencing to the DDREF in the UNSCEAR 2006 Report, UNSCEAR notably not considered necessary continuing to use of a DDREF for its risk estimates. The report indicated that its estimates implicitly adjust for extrapolation to low doses so that no extra application of a DDREF was needed [UNSCEAR, 2006 (§593)]. The use of DDREF, therefore, was evitable for estimating attributable radiation effects and risks and, therefore, the concept would be disregarded and would enter into a state of *de facto* obsolescence, at least for the purpose of the UNSCEAR estimates.

It should be recognized however that while in 2006 UNSCEAR took distance from the DDREF for the first time, the reporting continued to be confused as it indicated that the chosen approaches implicitly took account of

extrapolation of dose (if not dose rate), so that to some extent they take account of DDREF.

In 2010 UNSCEAR summarised the state of knowledge on low-dose radiation effects on health [UNSCEAR, 2010]. It informed the UN General Assembly that mathematically based models were used to address the risk at low doses and after recalling that '*an adjustment factor known as the dose and dose-rate effectiveness factor is often used to take into account the comparative reduction in effect due to low doses and dose rates;* reconfirmed that, *however, in the 2006 report of the Committee a linear-quadratic model was used directly for extrapolation to estimate risks at low doses, and so no dose and dose-rate effectiveness factor was applicable*'. [UNCEAR, 2010 (§31)]

An important departure from the use of the DDREF for risk estimates took place in 2013. The World Health Organization issued a health risk assessment from the nuclear accident of the Fukushima Dai'ichi NPP in Japan based on a preliminary dose estimation and did not use a DDREF concept [WHO, 2013]. UNSCEAR indicated that the WHO decision was consistent with its estimates of cancer risks after acute doses and with a meta-analysis of low-dose-rate, moderate-dose exposures [UNSCEAR 2014]

2.7. Reconsidering DDREF for radiation risk estimates

The reconsideration on the necessity of using of DDREF for radiation risk estimates was a response to many scientific developments, which occurred during the quarter of a century elapsing since the concept was introduced. These developments naturally lead to the need of reviewing the use of the DDREF in radiation risk estimates. The scientific developments include those in the area of statistical analysis, radio-epidemiology and radio-biology.

2.7.1. Statistical developments

In 2006 UNSCEAR introduced the use of sophisticated statistical tools for its risk estimates including techniques of Bayesian analysis. It moreover used a system of rolling reviews of all the studies of radiation-associated cancer incidence in irradiated human populations, giving particular attention to the soundness of study design, including consideration of a wide range of potential confounding factors, statistical power to reveal excess incidence of effects and consideration of the characteristics differences between the studied populations. The renewed statistical analysis includes assessing potential for systematic error and other sources of uncertainty. In addition, UNSCEAR has recently published a comprehensive review of uncertainties in risk estimates for radiation-induced cancer [UNSCEAR, 2012 (Annex B: Uncertainties in risk estimates for radiation-induced cancer)].

The estimates are made on the bases of which are *frequentistic probabilities*, namely they express the limit of the relative frequency of health effects found in cohorts exposed to radiation. They are usually offered as *excess risks/rates,* that measure the statistical relationship between a given risk factor and a specific outcome and, depending on the context, presented as *excess relative risk*, or *excess absolute risk*, or, perhaps most appropriately, to estimates of the risk over some period of time, such as *lifetime risk*, associated with an exposure of interest[4].

It is underlined that all these risk related quantities, namely relative risk, absolute risk, lifetime risk and assigned share, require that a factual 'rate' had been observed. The probabilities involved in these concepts are *frequentistic* by definition. The fact that Bayesian techniques have been used in the calculation does not retract the reality that the estimation are based on *frequentistic* probabilities and that that estimation did not need the use of a DDREF.

2.7.2. New epidemiological information

Meanwhile, new epidemiological studies are becoming available on exposure situations involving lower doses and dose rates. The UN General Assembly has been recently informed on ongoing evaluations of epidemiological studies of cancer incidence from low-dose-rate exposures due to environmental sources of radiations [UNGA, 2016 (§14)].

[4] These quantities are derived from *frequentistic* probabilities and are defined as follows:

- The excess relative risk/rate, or ERR, is the relative risk/rate minus one, namely the ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0; the ERR is often expressed as the excess relative risk per unit dose.
- The excess absolute risk/rate, or EAR, is the difference between the hazard rate in an exposed population and the "baseline rate" in that population, namely, EAR is the rate of disease incidence or mortality in an exposed population minus the corresponding disease rate in an unexposed population; the EAR is often expressed as the additive excess rate per unit dose.
- The lifetime risk, or LR, is the risk over a lifetime that an individual will develop, or die from, a specific disease caused by an exposure and can be calculated with several types of estimates as follows: (i) the excess lifetime risk (ELR) which is the difference between the proportion of people who develop or die from the disease in an exposed population and the corresponding proportion in a similar population without the exposure; (ii) the risk of exposure-induced death (REID) which is defined as the difference in a cause-specific death rate for exposed and unexposed populations of a given sex and a given age at exposure, as an additional cause of death introduced into a population; (iii) loss of life expectancy (LLE) which describes the decrease in life expectancy due to the exposure of interest; and (iv) lifetime attributable risk (LAR) which is an approximation of the REID and describes excess deaths (or disease cases) over a follow-up period with population background rates determined by the experience of unexposed individuals (The LAR is used to estimate lifetime risks in recommendations and standards for radiation protection.)

UNSCEAR has also defined the so-termed *assigned share*, which is defined as the probability that an observed health effect in an individual was caused by a specific radiation exposure [ILO, 2010].The assigned share is a concept that can be important for legal/technical purpose of imputing (or acquitting) those responsible of radiation exposure situations of causing health effects. Imputation means ascribing to a generator of radiation exposure (e.g. a nuclear installation) to cause something bad (e.g., health effects) to a recipient of the exposure (e.g. a worker). Imputation has been mainly related to occupational compensation claims, for example as part of a multi-stage test for legal liability associated with the causal relationship between the conduct of employers of occupationally exposed workers and the occupational harm that those workers may have experienced. The assigned share is equal to the fraction of the total number of cases of a specific type of cancer diagnosed among individuals which is in excess to the baseline number of cases for persons who share the same attributes, such as absorbed organ dose, age, time since last exposure, sex, smoking history, etc. The assigned share (AS) is quantified as AS= excess relative risk/relative risk and is often (confusedly) referred to as the attributable fraction or probability of causation assuming that the calculated excess relative risk represents the net consequences of mechanisms of disease manifestation for a given individual diagnosed with disease.

2.7.3. Advances in radiobiology

Significant progresses are being achieved in the understanding of the biological mechanisms that initiate and propagate detrimental effects following radiation exposure at low-dose and low-dose rate.

Already in 1996, UNSCEAR had described a number of so-called non-targeted and delayed effects of radiation exposure [UNSCEAR, 2006 (Annex C)] and the UN General Assembly was then informed that those non-targeted and delayed effects of radiation exposure may influence the mechanistic judgements required for the estimation of risk at low doses and dose rates [UNGA, 2006 (§29 et seq)].

The 2012 UNSCEAR White Paper provided a comprehensive review of the biological mechanisms of radiation actions at low doses [UNSCEAR, 2012]. Recently the UN General Assembly has been informed that UNSCEAR envisages to direct its future work mainly at – *inter alia* –, improving the understanding of mechanisms of radiation action and biological reaction at all levels of biological organization, i.e. from the molecular level to the population level, and obtaining more definitive evidence relating to health effects, in particular health effects from low-dose-range and chronic exposure [UNGA, 2016 (§21)].

2.8. The use of DDREF in radiation protection

2.8.1. Evolution

As indicated before, since 1990, the ICRP policy was to include the DDREF in the probability coefficients for all equivalent doses resulting from absorbed doses below 0.2 Gy and from higher absorbed doses when the dose rate was less than 0.1 Gy per hour. [ICRP, 1990 (§74)]

In 2004, ICRP would issue a full publication on the issue of low-dose extrapolation of radiation-related cancer risk: ICRP Publication 99 [ICRP, 2005]. This report considers the evidence relating to cancer risk associated with exposure to low doses of low LET, focus on evidence regarding the so-called linear, non-threshold (LNT) hypothesis, namely on linearity at low doses of the dose–response relationship for all cancers considered as a group, but not necessarily individually, and looks at the possibility of establishing a universal threshold dose below which there is no risk of radiation-related cancer. The report underlines the fundamental role of radiation-induced DNA damage in the induction of mutations and chromosome aberrations indicating that it provides a framework for the analysis of risks at low radiation doses and low-dose-rate exposures and indicates that, although cells have a vast array of damage response mechanisms, these mechanisms are not foolproof, and it is clear that damaged or altered cells are capable of escaping these pathways and propagating, proved consequences include chromosome aberrations and somatic cell mutations. The report concludes that current understanding of mechanisms and quantitative data on dose and time–dose relationships support the LNT hypothesis.

ICRP Publication 99, however, recognizes that emerging results with regard to radiation-related adaptive responses, genomic instability, and bystander effects suggest that the risk of low-level exposure to ionising radiation is uncertain, and a simple extrapolation from high-dose effects may not be wholly justified in all instances. However, it judges that although there are intrinsic uncertainties at low doses and low dose rates, direct epidemiological measures of radiation cancer risk necessarily reflect all mechanistic contributions including those from induced genomic instability, bystander effects, and, in some cases, adaptive responses, and therefore may provide insights about these contributions. It therefore insists that experimental approaches using animal models support the view that the response for early initiating events is likely to correspond to that for the induction of cytogenetic damage, that, on this basis, mechanistic arguments support a linear response in the low-dose region, and that quantitative analyses of dose responses for tumourigenesis and for life shortening in laboratory animals also support this prediction. Significantly, ICRP Publication 99 indicates that these studies also support a DDREF in the range of about 2 when data are extrapolated to low doses from effects induced by doses in the range of 2–3 Gy.

ICRP Publication 99 also includes a formal quantitative uncertainty analysis combining the different uncertain components of estimated radiation-related cancer risk with and without allowing for the uncertain possibility of a universal low-dose threshold. Unless the existence of a threshold is assumed to be virtually certain, the effect of introducing the uncertain possibility of a threshold is equivalent to that of an uncertain increase in the value of DDREF, i.e. merely a variation on the result obtained by ignoring the possibility of a threshold.

ICRP Publication 99 concludes that while existence of a low-dose threshold does not seem to be unlikely for radiation-related cancers of certain tissues, the evidence does not favour the existence of a universal threshold. The LNT hypothesis, combined with an uncertain DDREF for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates.

The policy on DDREF in the new (and current) ICRP recommendations [ICRP, 2007] would be based on the outcomes of ICRP Publication 99. The ICRP concept would now be re-defined as *a judged factor that generalises the usually lower biological effectiveness (per unit of dose) of radiation exposures at low doses and low dose rates as compared with exposures at high doses and high dose rates* [ICRP, 2007]. ICRP thus decides to continue to use the DDREF for radiation protection purposes, judging that the most probable dose-response relationships was linear quadratic, *where the linear coefficient at low doses or low dose rates is obtained from the high dose, high dose rate estimates of risk by dividing by a DDREF of 2* [ICRP, 2007]. From the analysis conducted in ICRP Publication 99 [ICRP, 2005], the ICRP considered that the adoption of the *linear non-threshold model combined with a judged value of a DDREF provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure*. In sum, the ICRP made the broad judgment that *a DDREF of 2 should be applied for the general purposes of radiological protection*.

2.8.2. Debate

Notwithstanding the current formal position of ICRP regarding the use of a DDREF, the concept, and in particular its value, is being discussed and argued among professionals from the radiation protection community. The current situation on the use of the concept for radiation protection was considered unsatisfactory by some [e.g.: Fry, 2013]. It has been further questioned whether a DDREF is really needed for radiation protection purposes following exposure to low total radiation doses delivered at low dose-rates [Brooks, 2013]

The DDREF was also discussed in the framework of Melodi, the European Platform dedicated to low dose radiation risk research[5]. In a comprehensive discussion that took place in Melodi 2011, the view was presented that there was 'little reason to use DDREF for radiation protection at this time'. [Preston, 2011]

Responding to concerns about the DDREF, on February 2014, the German Commission on Radiological Protection (Strahlenschutzkommission, SSK) issued recommendations indicating that the SSK no longer considers justifications for the DDREF used in radiation protection as being sufficient. The SSK set out assessments that leaded it to recommend abolishing the DDREF or adjusting it to bring it into line with more recent findings. Due to the DDREF 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, meaning 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. [SSK, 2014]

A comprehensive discussion on the DDREF in the light of radiological protection dose took place in the framework of an *ad hoc* workshop on DDREF jointly organized by ICRP and Japan NUS Co., Ltd. (JANUS)[6], in Kyoto, Japan on May 22, 2015 [Rühm et al., 2015]. Some basic questions were discussed at this event, including: Should DREF and LDEF be separated or combined as DDREF? Should a DREF also be applied to leukemia? How robust are the scientific results obtained from human epidemiological studies at low doses and low dose rates? How variable are other factors besides radiation in animal studies? Are animal data applicable to humans? Which endpoints are relevant in radiobiological studies? How to integrate information (especially animal vs. human data)?

The workshop reflected a problem governing the discussions on DDREF from its origin: the complexities of the induction of radiation health effects at low doses *vis-à-vis* the need of a DDREF concept. These are different issued although they are subtlety related.

Under this framework the workshop concluded that 'extrapolation of biological effects observed at high doses and high dose rates to low doses and low dose rates of ionizing radiation typical for radiological protection settings has become a central issue', and from this fact, it was judged, there is the need to reassess the DDREF concept which combines dose and dose-rate effects for radiological protection purposes, with the rationale being to keep radiological protection simple and practical. In particular, the suggestion was made that 'dose and dose-rate effects should be considered separately, at all levels of biological effect, keeping, for example, in mind that the linear term in an linear quadratic dose–response curve might depend on dose rate', however not excluding that in the end, for the sake of simplification, ICRP will 'continue to use a combined single factor to describe extrapolation of risks from high doses and dose rates to low doses and dose rates typical for most radiological protection scenarios'.

The Workshop also addressed endpoints at molecular and cellular levels and concluded that it is still unclear which endpoint is most relevant to the DDREF discussion. Many newly discovered biological phenomena, such as genomic instability, bystander effects, and adaptive response seems to show different dose–response behavior at low doses, highlighting the complicated action of ionizing radiation, and making unclear to what extent such effects are of relevance for radiation protection. A significant challenge is presented by the lapse of time between the induction of effects at molecular and cellular levels, and the development and manifestation of malignancies.

The Workshop also considered that, while animal experiments may offer some potential, the question of how to transfer results obtained in experimental animals to humans is still unresolved.

In relation to ongoing studies on human cohorts exposed to radiation, which regularly produce updates of the observed health effects with increasing follow-up period, the Workshop proposed to combine these studies in pooled studies or meta-analyses, which presumably would be closest to what is 'interested in radiological protection'. But it was emphasized, however, that the results that can be obtained at dose and dose rate relevant to radiological protection 'will be difficult to quantify with high precision, because the probability of occurrence of stochastic effects such as the incidence of cancer or leukemia at those low doses and dose rates is low, and spontaneous incidence of cancer in the human population is high'.

More recently, it was warned that there are fields in radiation protection that need clarification in spite of current insight into radiation risk, particularly at the low dose range where biological effects like mutations or chromosomal aberrations are detectable but it is unclear whether these biological effects translate into health effects. Thus, for radiation protection purposes, assumptions have to made that must be reappraised on the basis of new findings. The DDREF would be one of the concepts affected by new insights [Müller, 2015].

[5] In 2010 MELODI was founded as a registered association with the objective of proposing research and development priorities for Europe in the field of low radiation doses, seeking the views of stakeholders on the priorities for research, keeping them informed on progress made, and contributing to the dissemination of knowledge.

[6] The abbreviated name of this company is that of the ancient Roman god, Janus, who has two faces, one facing forward and the other backward, and is known as the god who stands between the beginning and end of things, between the past and the future: an allegory probable applicable to the DDREF concept.

Responding to these developments, the ICRP created a task group *on radiation risk inference at low-dose and low-dose rate exposure for radiological protection purposes*. Its aim is – *interalia* – recommending whether it is desirable to continue to estimate risk at low doses by assessing the slope of the dose response at high doses and then applying a DDREF reduction factor or *to adopt the UNSCEAR approach of inferring the risk coefficients at low doses by using all available information and techniques of Bayesian analysis for estimating the best expert judgment* [ICRP, 2015]. The Group is currently 'going beyond BEIR VII and including a more detailed analysis of more animal data, performing a meta analysis on total solid cancers, selected cancer sites including leukemia (incl. sensitivity analyses and comparison with adjusted LSS data), performing an analysis of dose response curves (L vs. LQ models), discussing further (e.g., methodological) aspects, scrutinizing biolgocial studies at molecular and cellular level, and evaluating the radiobiological evidence for treating dose and dose rate effects separately [Rühm, 2015]. The final outcome of the deliberations of this group is expected.

2.9. Additional Difficulties with the DDREF concept

While the latest reports UNSCEAR were *de facto* abandoning the use of the DDREF for its radiation risk estimates, and the radiation protection community was expressing concerns on the use of the concept even for radiation protection purposes, the DDREF has also been argued in other scenarios, including among the media and the public and in the field of epistemology.

2.9.1. Media and public concern

The DDREF has also been questioned by the public media, mainly in relation to its credibility. For instance, the concept was a point of controversy in the aftermath of the nuclear accident at the Fukushima Dai'ichi nuclear power plant. Following interviews of qualified scientists on the DDREF and its use, the media concluded that the risk of health effects induced by radiation was greater than those derived from the risk coefficients used internationally. This misunderstanding was reinforced during several television programmes with a wide audience, which added to the public concern and confusion.

Following the accident, the ICRP convened a task group to compile lessons learned and its members reported their views including many references to confusion and misapprehension about the DDREF[7][González et al., 2013]. The reporting indicates that misunderstandings about DDREF were due in part to the rather convoluted wording of its definition (particularly reinforced when translated into other languages – e.g., Japanese in the case of the accident). People were informed on the steps used for estimating risk of cancer, including the adjustment downward by a DDREF of 2 to account for the assumed ameliorating effect when radiation is received at a low dose and low dose rate, but the concept was notably misunderstood. While trying to explain to the lay public the concept of radiation risk was a daunting challenge, claims propagated by media coverage that low risk estimates resulted from applying the DDREF contributed to misunderstanding, confusion and anxiety.

A recent international assessment of the accident consequences refers to associated psychological problems in some vulnerable groups of the affected population [IAEA, 2015][8] and UNSCEAR had already estimated that the most important health effect from the accident was on mental and social well-being, related to *interalia* the fear and stigma related to the perceived risk of exposure to ionizing radiation [UNSCEAR, 2014][9]. The confusion on DDREF could have contributed to this undesirable situation.

2.9.2. Epistemological difficulties

In addition to its apparent needlessness and to the controversies on its use, it could be deduced from the relatively recent UNSCEAR report on attribution of effects and inference of risk [UNSCEAR, 2015 (Annex A: Attributing health effects to ionizing radiation exposure and inferring risks)] that the DDREF concept might present some conceptual difficulties. A major epistemological output of that report is a clear distinction between attribution and inference, i.e., between scientific provability (namely, scientific demonstration by evidence) and scientific judgment (namely, scientific ability to make considered decisions or form sensible opinions, even in the absence of direct evidence). Attribution requires demonstration and attestation that can be confirmable and verifiable and therefore falsifiable. Epidemiological assessments of cohorts exposed to relatively high doses may offer, for stochastic effects, *frequentistic* probabilities complying with such condition. If such scientific information is absent, as it is the case in low doses, risk may still be inferred from a scientific judgment that take account of all the available information however indirect, which can be quantified as a *subjective* probability or 'degree of believe' or 'credence' by qualified experts.

Thus, attribution and inference are two related by distinct concepts. For stochastic effects, attribution can be quantified with *frequentistic* probabilities and inference with *subjective* probabilities.

In fact, the DDREF is defined as a factor relating these two probabilities (both per unit dose): the nominator is a probability assessed at high doses on the bases of factual epidemiological information, and the numerator is a probability inferred at low doses on the bases of scientific judgment. These two probabilities may be considered to be mathematically consistent but they are conceptually diverse, as follows:

[7] González et al., 2013. González A.J., Akashi M., Boice J.D., Jr., Chino M., Homma T., Ishigure N., Kai M., Kusumi S., Lee, J.-K., Menzel H.-G., Niwa O., Sakai K., Weiss W., Yamashita S., Yonekura, Y., Radiological Protection Issues Arising During and After the Fukushima Nuclear Reactor Accident, J. Radiol. Prot. 33 3 (2013) 497–571.

[8] IAEA, 2015. The Fukushima Daiichi Accident. Report by the Director General. Document GOV/2015/26. International Atomic Energy Agency, Vienna, 2015.

[9] UNSCEAR, 2014. Sources, Effects and Risks of Ionizing Radiation. Volume I: Report to the General Assembly and Scientific Annex A. UNSCEAR 2013 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.14.IX.1. United Nations, New York, 2014. {U876}

- At high doses, the available epidemiological information allows for assessing *frequentistic probabilities* and to define EAR and ERR, throughout rigorous statistical and probabilistic assessments based on frequencies. Such estimates are confirmable and verifiable and also falsifiable. They can be proved to be correct (or incorrect) by following strict quality criteria.
- At low doses, the concept of frequentistic probability is epistemologically inapplicable because at such doses radiation effects can not be epidemiologically attributed to radiation. Therefore, only subjective probabilities can be assigned, which cannot reflect direct observational data but rather judgments or 'degree of believe' or 'credence' by qualified experts.

The scientific appropriateness of a factor relating these two dissimilar concepts of probabilities may be epistemologically debatable.

The 2012 UNSCEAR report on attributing health effects to ionizing radiation exposure and inferring risks concluded that [UNSCEAR, 2012]: *An increased incidence of stochastic effects in a population could be attributed to radiation exposure through epidemiological analysis — provided that, inter alia, the increased incidence of cases of the stochastic effect were sufficient to overcome the inherent statistical uncertainties…… Although demonstrated in animal studies, an increase in the incidence of hereditary effects in human populations cannot at present be attributed to radiation exposure… In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation.*

3. Result

The analyses heretofore show that over the last century a perception developed that radiation risk per unit dose is higher at high dose and dose-rate than at low dose and dose-rate. This discernment was supported by indirect information but could not be scientifically confirmed and verified. The search for a factor relating those two risks was an unavoidable scientific temptation and the DDREF concept was maturing over a long time and then formally established by the end of the century and even its mathematical formulation was developed. Since then, few low radiation-related concepts have been more scrutinized that the DDREF. The Mendelay database alone registers 109 papers on DDREF [Mendelay, 2017].

A common denominator of the long saga of the DDREF concept seems to be some kind of 'inbreeding' or 'endogamy' among the participating experts. There were two different, although connected, intentions:

- on the one side, there was a genuine interest and a formal responsibility (e.g., in UNSCEAR) in estimating radiation risk, namely 'guessing' probabilities of harm, following exposure at low level doses, at which scientific evidence was not available (and was even suspected that it might be unavailable for times to come); and,
- on the other hand, there was a genuine interest (e.g., in ICRP) for 'concocting' a paradigm for protecting people against radiation risk at any dose, even at doses at which scientific evidence of radiation effects was unavailable, following strict ethical values including deontological principles.

These two objectives are interrelated but fundamentally diverse. However, many of the experts who developed the basic philosophy both in UNSCEAR and ICRP were the same people representing two distinct interests. Thus, inbreeding (i.e. leading from closely related people) and endogamy (i.e., interacting only within the limits of the community) became unavoidable. In the author's own experience, it is extremely difficult to seat in both UNSCEAR and ICRP and isolate oneself from what is going on in the one/other organization.

Thus, in the DDREF saga there was a mixture between the interest of apprehending the science of radiation effects and the ethical responsibility of protecting people against radiation exposure. In order to deal with the DDREF concept and its consequences it might be wise to consider these two issued separately.

The attribution of risk of stochastic radiation effects at high dose and dose-rate and the inference of plausible risk at low dose and dose-rate could be treated as being conceptually interconnected but epistemologically independent one of each other. The first can be attributed to radiation exposure situations by using conventional scientific tools, mainly radio-epidemiology science, for provability, demonstration and attestation; the second is only inferable through scientific judgment. It seems inappropriate to use a simple factor relating these two different entities as it could easily be misunderstood as pretending that equal scientific value can be assigned to both of them.

In sum, following the analysis heretofore, the results are:

- The epistemology of the DDREF concept appears to be clearer now, it is becoming understood that,
  - estimation of radiation risk is different than radiation protection, and
  - attribution of risk is different than inference of risk.
- It seems that the DDREF for estimating radiation risk has become superseded by the scientific developments in this area and its use has turned out to be unnecessary for this purpose.
- The use of the concept for inferring radiation risk for radiation protection purpose also appears to have become confusing, controversial for the media and the public and questionable for epistemology.

4. Conclusion

4.1. Abandoning the use of the DDREF

Following the analyses heretofore, it seems that the more reasonable conclusion is that the use of the DDREF can be definitively abandoned for purposes of radiation risk estimates. In specific radiation exposure situations, if frequentistic probabilities are available, effects can be ***attributable*** and could be expressed as EAR, ERR or any other convenient quantity. If *frequentistic* probabilities are not available radiation risk may be ***inferable*** through the use of subjective probabilities (see hereinafter). In both cases using a DDREF is unneeded, controversial and epistemologically questionable.

The discontinuation of using a DDREF for radiation protection purposes should also be considered. While recognizing that radiation protection has different reasons, principles, rationales, functions, uses and intentions than those of radiation risk estimation, the approaches for attributing factual effects and inferring subjective risks described hereinafter might also applicable to radiation protection. The outcome can in principle be perfected in both cases by estimating a detriment-adjusted risk, namely the frequentistic probabilities assessed for attributing effects and the subjective probabilities estimated for inferring risk can both be modified for radiation protection purposes to allow for the different components of the detriment in order to express the severity of either attributable or inferred consequences.

4.2. Attributing radiation effects

For radiation exposure situations for which there are available epidemiological data that can be scientifically tested (namely which are confirmable and verifiable and therefore falsifiable), radiation risk should continue to be ***attributed*** in terms of frequentistic probabilities. These can be presented as EAR, ERR or any other convenient quantity. The process should be substantiated by applying strict quality criteria and using all systematic statistical and probabilistic techniques available.

4.3. Inference of radiation risks

For radiation exposure situations for which direct scientific evidence of effects is unavailable or unfeasible to obtain, radiation risk may still need to be ***inferred***. Such inference should be substantiated on the basis of indirect evidence, scientific reasoning and professional judgment. The aim would be assigning plausible risks in terms of subjective probabilities that are usually described as '*degree of belief*' or '*credibility*'.

For inferring radiation risk all indirect but relevant available data should be considered, including: pertinent radiobiological information; experiments exposing animals to radiation; responses by cells and tissues to irradiation; and, last but not least, the available epidemiological information. It should be emphasized however that the epidemiological information for supporting the inference of risk at low doses and dose-rates should preferably be based on new epidemiological studies dealing more directly with the exposure situation under consideration and that risk transfer from different exposure situations, such as those at high dose and high dose rates, should preferably be avoided.

5. Epilogue

Following developments with the DDREF, UNSCEAR discussed the issue during its sixty-third session (27 June-1 July 2016). It was reported to the seventy-first session of United Nations General Assembly that a short paper would be prepared on the scientific view of the Scientific Committee on the DDREF [UNGA, 2016 (§28)]. The issue will be further discussed at the sixty-fourth session of UNSCEAR.

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Коэффициент эффективности (DDREF) дозы и мощности доз: ненужные, спорные и противоречивые вопросы

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Abstract

Цель: Целью данной статьи является обзор происхождения и эволюции понятия, называемого коэффициент эффективности дозы и мощности дозы облучения (DDREF), критический анализ этого понятия, а также предложения по его использованию.

Материал и методы: Взяв за основу отчеты НКДАР ООН и рекомендации МКРЗ, автор в данной статье описал эволюцию (с 70-х гг. прошлого века) понимания вопросов радиационного риска при облучении в малых дозах и при низких мощностях доз. Население обычно облучается в дозах намного меньших (и с более низкой мощностью дозы), чем те группы лиц, для которых имеются количественные оценки радиационных эффектов. Впервые предложение о введении «коэффициента уменьшения», аналогичного DDREF, возникло в связи с необходимостью оценки радиационного риска при малых дозах и низких мощностях доз на базе имеющихся фактических данных о радиационном риске, который оценивался при больших дозах и высоких мощностях доз. Оценки радиационных эффектов для здоровья получены в основном из эпидемиологических исследований, рассматривающих облучение в больших дозах при высоких мощностях доз, однако люди обычно подвергаются радиационному облучению при значительно более низких уровнях. Для малых доз и низких мощностей доз нет эпидемиологических данных об эффектах их действия. Не существует и биологических индикаторов радиационно-индуцированных эффектов на здоровье при облучении в малых дозах. Сравниваются официальное представление и математическая формулировка понятия DDREF в документах НКДАР ООН и МКРЗ (в 1990-х гг.). В статье подчеркивается, что в настоящее время при оценках радиационного риска НКДАР ООН не используют понятие DDREF, делая его тем самым де факто ненужным для целей определения радиационного риска. В статье обобщается использование концепции DDREF для целей радиационной защиты, а также степень понимания и связанные с этим опасения по поводу DDREF (в особенности после аварии на атомной станции Фукусима-1). В заключение, в статье обсуждаются эпистемологические недостатки самого понятия.

В 1980-е гг. продолжался анализ того, каким должна быть эволюция понятия DDREF. В Публикации 60 МКРЗ обобщена история вопроса. Экспериментальные данные о зависимости «доза–эффект» и влиянии мощности дозы были всесторонне пересмотрены в отчете Национального Совета по Радиационной Защите и Измерениям США. Был сделан вывод, что форма зависимости «доза–эффект» для больших доз и высоких мощностей доз была, вероятно, линейно-квадратичной в большинстве биологических систем. Таким образом, базовая парадигма, представленная МКРЗ десятилетием ранее, была закреплена, и она доминировала в последующие годы. Для облучения в малых дозах при низких мощностях доз ответ считался часто эффективно линейным, как ожидалось, соответствующим линейно-квадратичному ответу при малых дозах. В линейно-квадратичной форме, $E = aD + bD^2$, эффект изначально увеличивается линейно с дозой, т.е. значение эффекта на единицу дозы $E/D = a$ является постоянным. Далее эффект возрастает быстрее, т.к. вклад квадратичной части зависимости начинает перевешивать вклад линейного участка. При более высоких дозах эффективность часто снова снижается в связи с эффектом клеточной гибели, что, в свою очередь, снижает количество подверженных риску клеток. В линейно-квадратичном уравнении отношение параметров для линейных и квадратичных членов *a/b имеет размер дозы, и ее значение отражает относительный вклад линейного и квадратичного члена*. Таким образом, если $a/b = 1$ Гр, то при 1 Гр вклады в эффект линейного и квадратичного члена будут равны. Комитет NCRP определил коэффициент мощности дозы (DREF) как отношение наклона кривой «доза–эффект» в диапазоне высоких доз к наклону кривой «доза–эффект» в диапазоне малых доз ионизирующего излучения.

Тогда $DREF = 1 + b/a\ D$. Это станет основой для математической формулировки DDREF, которая будет разработана НКДАР ООН, и будет сделан неожиданный вывод, что наблюдаемый DREF в экспериментальных ситуациях не является константой, а зависит от диапазона доз и мощности доз в проведенных исследованиях.

Пересмотр необходимости использования DDREF для оценки радиационного риска произошел в результате многочисленных научных достижений, происшедших в течение четверти века после введения данного понятия. Эти научные достижения в области статистического анализа, радиоэпидемиологии и радиобиологии привели к тому, что возникла необходимость пересмотра использования DDREF при оценке радиационного риска. По-видимому, DDREF вытеснили научные разработки, и его использование стало ненужным для оценки радиационного риска. Понятие также представляется спорным для целей радиационной защиты, очевидно, неоднозначным и эпистемологически сомнительным.

Заключение**:** Представляется целесообразным, что: (i) можно определенно прекратить использовать DDREF для оценок радиационного риска; (ii) с учетом того, что цели радиационной защиты отличаются от задач оценки радиационного риска, можно также рассмотреть прекращение использования DDREF для радиационной защиты; (iii) для ситуаций радиационного облучения с имеющимися эпидемиологическими данными, которые можно научно проверить (а именно, данными, которые можно подтвердить и верифицировать, а, следовательно, опровергнуть) радиационные риски следует продолжать считать как вероятностными (стохастическими) явлениями; а также, (iv) для радиационных ситуаций, где нет прямых научных доказательств эффектов, либо их невозможно получить, радиационные риски необходимо предполагать на основании косвенных доказательств, научных выводов и профессиональной оценки, с целью оценки их правдоподобия относительно субъективных вероятностей.

Ключевые слова: *облучение, дозы, мощности доз, коэффициент эффективности, оценки радиогенных рисков, стохастические эффекты радиационного воздействия*

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