# A Note On The Dose-Rate-Effectiveness Factor and its Progeny DDREF*

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## Introduction

Our environment is pervaded by low levels of radiation and in space the levels are higher. In low-Earth orbit there is some protection from the galactic cosmic rays (GCR) by the magnetosphere but in deep space every visitor is exposed continuously to higher levels of GCR and sporadically but infrequently to radiation from the sun in the form of solar particle events (SPE). It is essential to have estimates of risk from exposure to radiation to facilitate the design of space vehicles that maximizes protection and for the planning of missions. To estimate the radiation risk it is necessary to know the potential total dose, the dose rate, the dose-response relationship and the radiation quality. Based on studies of chromosome aberrations Peng et al., (Health Physics 2012) they report that the effect of proton irradiation, independent of proton energy, is reduced by lowering the dose rate comparable to the dose-rate effect with gamma rays. Also, a small but significant reduction in the effect of 1GeV iron ions by lowering the dose rate was noted; a finding that invites further investigation Not only is the dose rate important, but since the exposure in space is continuous, so is the effect of protracted exposure to protons, heavy ions and secondary neutrons. In space protons are the most prevalent radiation and, except for a short period in very large solar particle events (SPE), the exposure is at a low dose- rate. Dose rate is of importance also in the derivation of risk estimates. There are not sufficient data for late effects, such as cancer, to estimate the risk posed by proton irradiation. The estimates have to be based mainly on the data from humans exposed to gamma rays, such as the atomic bomb survivors. Those exposures were at high dose-rates and are considered to

* An extensive and excellent report on DDREF has been prepared by the SENES group, Oak Ridge, Tennessee for NIOSH and has been submitted for external review.

possibly overestimate the risk to the general and working populations who are exposed to low dose-rate radiation or to multiple exposures to small doses and therefore a dose-rate effect correction factor is applied to the risk estimate based on the data from the atomic bomb survivors. It is the value of this factor that has been, and still is, a matter of contention.

## Solar Particle Events

In a SPE the proton dose rate increases and if it rises to a level that causes effects associated with exposure to high doses, such as vomiting, it would be a serious risk for astronauts without adequate shielding. In very large SPEs the dose rate rises rapidly and within a few hours may reach a high dose-rate (Parsons and Townsend 2000) The earliest effects that also have the lowest threshold are nausea and vomiting . The information about threshold dose rates for vomiting is inadequate. The only experimental animal found to be a suitable surrogate to study the threshold for vomiting is the ferret. Prevention of exposure for more than a couple of hours is required to ensure that early high-dose-rate effects do not occur in very large SPEs.

The ability of the bone marrow to withstand significant damage when the exposure to radiation is protracted at a low dose rate is well shown by Seed *et al.* (2002). In dogs exposed to 70 mGy gamma rays daily for most of their lifespan normal levels of red and white cells and platelets were maintained for more than one year. This was attributed to an acquired increase in radio-resistance involving adaptation shown by a broader shoulder of the survival curve of bone marrow progenitor cells. These results are consistent with those of Lamerton et al. (1960) for rats. The regulators have not set limits for acute tissue effects because the threshold doses are so much higher than the levels recommended to limit so-called stochastic effects (cancer and genetic effects), an exception is made in the case of the lens of the eye and the skin. In general a reduction in the dose rate reduces acute tissue effects, in some cases by about a factor of three.

## Dose-response relationships

The nature of the dose responses of the induction of cancer is central to the estimation of risks. Analyses have used linear no-threshold, linear quadratic, and quadratic models amongst others to describe the response to radiation.

The linear-quadratic model (LQ) $E= \alpha D + \beta D^2$, where alpha and beta coefficients represent the linear and the curved portions of the response has been widely used.
When the exposure is low the response is proportional to the number of nuclear traversals and the response is linear. With increasing exposure interactions can occur and the response, it is thought, becomes increasingly curved upward until some factor(s) reduces the response. If the exposure to low levels is protracted the response will remain linear. Similarly, if exposure to small levels is repeated (multiple fractions) and sufficiently separated in time the slope response will be the same as with small single doses and exposures at a low dose-rate. Radiation workers on Earth usually have sufficient time for recovery between daily exposures. In space the exposure is continuous but the difference in effect is not clear. A low dose-rate probably accounts for most of the effect of protraction but the difference between the effect of dose rate and protraction has not been made with clarity. The National Council on Radiation Protection and Measurements (NCRP 1980) used the term protraction factor rather than dose rate-effect factor (DREF) when the exposure extended over the lifetime, and in particular, when the effect was on life shortening. It is probable that protraction involves significant adaptive changes (Seed et al.,1982) and perhaps age changes in susceptibility to cancer induction (NIH 2003).

It requires a considerable amount of data to define a dose-response relationship. Some of the more recent approaches including that of the National Research Council (NRC 2006) for estimating the effect of dose rate have assumed a linear-quadratic model. Findings from studies of the induction of chromosome aberrations by radiation, and belief of their importance in carcinogenesis have underpinned the use of the LQ model. However, with the new techniques the complexity of induction and the effect of dose rate have become clearer and yet more complex (Loucas et al 2004, Tawn et al. 2004).The results of Loucas et al (2004) are not consistent with a LQ model. In the case of mutations the response to dose rate is also not simple. For example, the deletions induced at the HPRT locus in human cells are larger with low dose-rate X-irradiation than high dose-rate (Colussi and Lohman 1997). In mouse spermatogonia the effect of dose rate is limited to the induction of the larger mutations (Russell and Hunsicker, 2012).

Nothing important is ever simple and it is optimistic to describe such a complex process as carcinogenesis, especially over a range of doses, by a simple model that does little to take into account what must be multiple

dose-dependent changes, including not only those involved in initiation but also their expression.

## Low Dose and Low Dose-Rate

What is considered a low dose and what is considered a low dose- rate depends on the approach taken (Rossi 1985). For example, if a low dose is defined as one in which only one track traverses a nucleus it would be less than about 0.2 mGy (UNSCEAR 1993, Goodhead 2009). A fundamental problem is that the size or number of targets for the initial events in the carcinogenic process is unknown but the evidence would suggest that they might vary depending on the type of tumor. If the nature of the targets does vary amongst organs it would be reasonable to believe that there is not a single dose response and therefore the value of a low dose and dose rate will depend on the specific cancer. What dose is considered small and what dose rate is considered low rate are obviously important questions. Scientific bodies such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Council on Radiological Protection (ICRP) and NCRP have answered them with single values, which while convenient for the setting of radiation limits, do not reflect differences in how different tissues respond. Based on epidemiological data there is a reasonable consensus that doses below 200 mGy, whatever the dose rate, can be considered to be low. In 1980 NCRP arbitrarily defined that a low dose was O-20 rads. In the case of cells in vitro effects have been noted at doses of about 40 mGy. The levels of dose rate defined as low dose-rate by the same organizations range from 0.5 Gy per year NCRP (1980) to 0.1 Gy per hour, ICRP (1991) and 144 mGy per day, UNSCEAR (1993). In 1993 Muirhead et al., suggested for radiation protection purposes that low doses were about 100 mGy or less and 0.1 m Gy/min a low dose-rate.

These figures do not reflect any organ-specific differences. In experiments designed to test the appropriateness of the LQ model and to get some estimate of the initial slope of the dose response it was shown that in mice that a low dose in the induction of breast cancer was between 10 and mGy (Ullrich et al. 1987)) somewhat greater for myeloid leukemia (Fry 1996) and substantially greater for lung tumors. (Ullrich et al. 1987). These results indicate a low dose is not the same for the induction of all cancers.

But it is not clear if, or how, the extent of the linear component of the dose-response curve is related to the size or number of targets involved in the induction of cancer.

Wakeford and Tawn (2010) suggested "that a low dose is a dose that produces an effect within the linear region of the dose response." This is sensible but as the results above show the level of the low dose varies with the type of cancer in mice. Also, the extent of the linear region of the dose responses are not known for individual human cancers.

It has been known for about seven decades that decreases in dose rate of low linear energy (LET) radiations such as X and gamma rays decrease biological effects such as chromosome aberrations (Sax, K. 1939, Marinelli. L. et al., (1942). In contrast, high-LET radiation, such as fractionated exposures to neutrons, did not cause a reduction of effect (Giles, N.H. 1943) It was the early studies on the induction of chromosome aberrations that led to the introduction of the LQ model to describe the dose-response relationship. This model was later used to describe the dose response for the induction of cancer by radiation and still is widely applied.

In most biological systems the effect decreases with decreasing dose rate down to a level, known as the limiting dose rate, below which the effect becomes independent of dose rate and only dependent on dose. Sacher, (1964) reported a limiting dose rate of about of about 20 rads/ day for life shortening. Using the same approach but a greater number of strains of mice and two hybrids Grahn et al, (1978) estimated the limiting dose rate to be closer to be 10 rads/day. In beagle dogs the results suggested a lower limiting dose rate for hematological diseases but for solid cancers total dose was more important than dose rate (Carnes and Fritz 1991). Bedford. J, and Mitchell, J. (1973) reported 5.2 Gy/day as the limiting rate for cell inactivation.

For radiation protection purposes a pragmatic approach has had to be taken to deal with the effects of low doses and the influence of dose rates and what level of a low dose and low dose-rate factor should be applied to risk estimates based on data from exposure to high doses. UNSCEAR (1993) concluded, from experimental animal studies, that a Dose and Low Dose-Rate Effect (DDREF) should be applied at a total dose of 200 mGy independent of dose rate and also at a dose rate of less than 0.1 mGy per

minute. The level of 200 mGy is one hundred times the estimate of the dose that would result in approximately a single track traversing a nucleus.

There has been no precise guidance on how to take into account the patterns of exposure to which working populations have been exposed. Such populations are continuously exposed to background radiation at a very low dose-rate to which is added in small doses at high dose-rate five days/week exposures over their working life span . The approach to the problem has been somewhat piecemeal and based on insufficient data. In 1972 UNSCEAR, based on the analysis by Edward Pochin of the data for leukemia induction (all types of leukemia pooled) in the Atomic Bomb Survivors, reported that the initial slope of the dose response was less than that at higher doses, by a factor of about 2.5. This low dose-factor, and an assumption that there would be about 5 times more solid cancers than leukemias (suggested by R.Mole), were the core of the risk estimate of radiation-induced cancer used for some years, including by ICRP (1977), until the data for solid cancers increased to a level that allowed estimates of the rate of induced total cancers.

In 1980 NCRP reported a systematic examination of the effect of dose rate on a broad range of biological endpoints in a wide variety of experimental systems, from mutations and chromosome aberrations to tumors and life shortening in animals. The study included the effects of dose rate on plants, mammalian cells in vitro, chromosome aberrations, tumors and life shortening in experimental animals The conclusion was that there was a generality about the reduction in effect as the dose rate was reduced, and in the case of tumor induction and life shortening the reduction ranged by a factor of 2 to10. Since there were insufficient data for a factor based on human studies it was suggested that a factor might be selected from the studies on surrogates. In the NCRP report, data for 5 types of solid tumors in either RFM or BALB/c mice, 2 sets of data for myeloid leukemia from RFM mice, life shortening in BALB/c mice and 2 types of tumors in rats were analyzed. The possible disadvantage in the choice of data from female mice and BALB/c mice is discussed later. A single value for the dose rate-effectiveness factor (DREF) for individual types of tumors was determined from the ratio of linear regression coefficients of the effects at high dose rate to that at low dose rate. It should be noted that the choice of a linear regression of the data for the exposure at high dose rate is a matter of simplification and ensures a single figure for an individual organ over the total dose response but not a single value for total cancers. If the assumption

of a linear dose response is not valid the estimated values of DREF will also not be valid.

Single values are favored for practical reasons by organizations responsible for radiation protection. At very low total doses the value would reach 1 but at different doses because, based on a LQ model being fitted to the data, the ratio of the linear and quadratic components for doses responses of different organs would differ.

In 1986 UNSCEAR stated " If the risk of tumor induction at 1 or 2 grays of sparsely ionizing radiation at a high dose-rate were extrapolated down to zero dose the procedure would overestimate the risk by a factor of up to 5 in typical situations" No mention was made of what typical situations were. In subsequent years there were a number of suggested values of DREF. For example, The National Institutes of Health (NIH) in its report on Radiobiological Tables in 1985 a value of 2.3 was used. In 1988 the National Radiological Protection Board (NRPB) suggested a value of 3 but in 1993 a value of 2. In 1989 NRC flirted with a value of 3.3 (excluding breast and thyroid) but subsequently in 1991 settled for a value of 2.0 BEIR V (NAS/NRC, 1990) used a LQ model in their analysis of leukemia from which they determined a DREF of 2. The term DREF seemed inappropriate as the analysis was quite different from that used by NCRP Report 64. This value was comparable to that obtained by BEIR III (NAS/NRC 1980 ) despite the fact that the latter used the old T65 estimates of the doses received by the atomic bomb survivors. For solid cancers, BEIR V thought that a factor of between 2 and 10 might apply, but chose to make no recommendation. BEIR V contended that there were four sets of data from which DREFs could be derived. These were: 1) specific locus mutation, 2) induction of reciprocal chromosome aberrations, 3) life shortening and 4) tumor induction in small mammals. It is not clear that anyone has used such a panel of data and, if so, how they weighted the importance of the individual sets of data.

Although the estimate of risk for radiation protection purposes was based on a linear fit to the data for "all cancers" in atomic bomb survivors it was considered that the dose response might be curvilinear. Considering a linear fit to the atomic bomb survivor has been used in estimating the cancer risk for radiation protection purposes it does not instill confidence that the curvature of the same dose response can also be used to derive DDREF. Also, what is the influence of pooling multiple dose-responses? In 1989

Pierce and Vaeth discussed dose responses and extrapolation to low doses. Applying the LQ model to the cancer for the atomic bomb survivors data the curvature was estimated from the ratio of $\beta/\alpha$, the coefficients for the curved portion and linear portion of the dose response respectively, and they called the value a linear extrapolation overestimation factor (LEOF) a term that morphed into Low Dose-Effect Factor (LDEF ).

The curvature of some responses of effects, such as chromosome aberrations, was determined using the same approach terming the factor derived as LDEF (Rossi 1990). For NASA this was an unfortunate choice of term because it was the acronym for a mission sometime ago, but it has stuck. In 1991 ICRP and NCRP in 1993 selected 2 as the most reasonable value for what was now termed DDREF. ICRP had decided to change the term from DREF but mainly used the values derived by NCRP.

In the latest recommendations by ICRP (2007), a value of 2 was selected again, a value that was thought to be supported by the fact that this was the value of the mean of the probabilistic uncertainty distribution for DDREF suggested by a number of committees The term DDREF appears to imply a linear-quadratic dose response instead of a linear response for high dose-rate radiation and that the effect of very low doses or small fractions would be equal to the effect of exposures at a low dose-rate.

In 2000 Pierce and Preston used the approach of Pierce and Vaeth (1989), described above, to determine the curvature of the dose-response curve of "all cancers" in the atomic bomb survivors and found the effect at low doses was 1.9 times less than estimated using a linear model. The validity of the accuracy of this value must depend on whether pooling of different dose responses is valid. Perhaps the importance of this finding, namely, 1.9, is that it is derived from data from humans and does not present any great pressure to reduce the current value of DDREF from 2.

In 2006 BEIR VII attempted to solve the difficult problem of deriving a single value of DDREF that was appropriate for use in radiation protection. They used the same data as Pierce and Preston (2000) but included the values for the LDEF determined from the dose responses of myeloid leukemia, lung tumors and Harderian gland tumors in male and female RFM mice; also, pituitary and uterine tumors in female RFM mice, lung and breast tumors and life shortening in female BALB/c mice and beagle dogs exposed to single doses of high dose-rate gamma rays.

Based on an a Bayesian analysis of the data pooled from the human and experimental animal data obtained a DDREF distribution with a point estimate of 1.5 and confidence limits of 0.8-2.7.

The selection of tumor dose responses was influenced by availability of data for dose responses after exposure to high dose-rate gamma rays suitable for Analysis. It was noted that each tumor type had different radiation dose-responses and that different DDREF values would apply to each case.

As with all analyses the validity lies in whether the data used in the analysis by BEIR VII are appropriate. There are two aspects that require attention. First, the use of Balb/c mice, a strain known for its radio sensitivity, the genetic basis of which is known and is described in the text of the report. Second, the murine ovary is very radiosensitive and when compromised or ablated results in hormonal imbalance, which in turn, alters tumor incidence. Unfortunately, there is little choice because of the lack of data for dose responses for tumors in both human and experimental animals. Furthermore, if each type of tumor has a different dose response is it appropriate to pool the data?

There is a general assumption that the LQ model is appropriate for all the responses including life shortening. The analysis based on this assumption provides an estimate of an LDEF and this was equated to be a DDREF. In the case of life shortening it is a pity that the extensive data from the studies at Argonne National Laboratory, (Grahn et al. 1995) were not discussed since they provided information about the effect of many small fractions protracted over a long period. For example, in the experiment with one exposure /week for 60 weeks the effect was reduced by a factor of about three.

Recent analyses of data from human populations exposed to protracted exposures of multiple small doses have been reported to indicate that they do not have lower risks per unit dose than the atomic bomb survivors (Jacob et.al. 2009, Preston 2011), Daniels and Schubauer-Berigan (2011, Daniels et al. 2012) have reported that the risk of leukemia in humans is not reduced by protraction.

A contrary view was expressed by EPRI (2009). Their report suggested that

while further epidemiological and radiobiological studies were required it was possible that the health effects of radiation may be significantly less after exposures at very low dose rates than currently estimated.

There is considerable pressure, especially in Europe, to reduce DDREF to 1. Without new data it is hard to see that the problem of the value of DDREF will be solved to the satisfaction of everybody. Schimmerling and Cucinottta (2006), cognizant of the needs of NASA, expressed concern that the derivation of DDREF did not take into account many of the factors of importance to NASA. They could have added the possible importance of the difference between dose rate and protraction. Importantly, in their opinion, data from animal experiments were not appropriate for the estimation of DDREF to be used in radiation protection standards for humans. Goodhead (2000) noted the diversity of animal-tumor dose responses and that, " on their own would be unlikely to lead to low-LET generalizations of linear-quadratic at high dose rate and the same linear term alone at low dose rates" That questions the use of LDEF in the selection of a value for DDREF. Preston (2011) considered the evidence for a DDREF greater than one unconvincing, but recommended that the uncertainties in the epidemiological data needed to be characterized.

If it is decided, that current or planned studies of humans exposed to sufficiently low doses of low-LET radiation will not provide the necessary data and that data from experimental systems will have to be used, the use of life-shortening in mice should be examined. The lack of adequate data from human experience to determine the effect of dose rate on the risk of radiation-induced cancer has resulted in the use of experimental data, mainly, the effect of dose rate on cancer induction in mice.

Apart from the inherent problem of extrapolation of data across species there are significant problems in the estimation of risk in the experimental animals. The dose-responses, which differ amongst tissues, and particularly, the initial slopes are very expensive to define with sufficient precision. The use of DREF (NCRP 1980) had two advantages: first, a linear fit to both the data obtained for the effects of high and low dose-rate exposures eliminated the need to define the initial slope and second, this made it possible to derive a single factor (DREF) independent of dose. A linear fit might be accepted on statistical grounds, at least for some cancers, because the data are not sufficient to define the dose response. If, as the evidence suggests, the dose responses after high dose-rate exposures are curvilinear, at least for some

solid cancers and myeloid leukemia, the choice of a single factor, independent of dose, does not reflect the complete picture of the effect of dose rate.

The change in name from DREF to DDREF (ICRP 1991) without explanation did not reduce the complexities, but because it is applied to low doses it has been suggested that the dose response for radiation-induced cancer is curvilinear and the term DDREF has been applied to the factor LDEF, derived from the curvature of the dose response for cancer induction (NRC 2006). The recommendation of a single value for DDREF is not valid if the dose response is curvilinear, but because of the uncertainties and the practical advantage, a single value is considered suitable for use in the setting of radiation limits. The selection of the value is more a committee decision than a strict interpretation of the data. The question is can the selection be improved? Obviously the ideal would be to have adequate data from humans exposed either at low dose rates or to multiple small doses. Based on a linear-quadratic dose response model the effect of these two exposure patterns would be the same.

## Conclusions

The current situation is unsatisfactory with the value of 2 for DDREF accepted by ICRP, NCRP and used in the estimate of risk for radiation protection but questioned by BEIR VII and others. As a start it would be helpful if the assumptions made in the use of terms such as DDREF and LDEF and the uncertainties were clarified. The recommendation of BEIR VII that DDREF of 1.5 should be considered is based on the assumption that the dose responses for all the cancers considered and life shortening are linear quadratic. Furthermore, LDEFs are based on the response to high dose-rate exposure and therefore do not take into account any effect of protraction. NCRP (1980) used the term Protraction Factor to describe the effect on life span of life-long exposures on the assumption that extensive protraction had some effect other than dose rate. The question of whether there are effects of protraction separate from dose rate and their importance has not been fully answered. The importance of protraction of space radiation has been discussed by Curtis et al., (2004). A much better picture of the molecular, cellular and tissue responses that contribute to and determine the nature of the dose responses of the induction of cancer in

different organs surely must be possible. The picture as it relates to radiation protection has not changed sufficiently in decades.

There does not seem to be a consensus on whether epidemiological studies can provide the relevant data. If epidemiology cannot provide an estimate of the risk at low doses or low dose-rates experimental data will have to be used. If experimental animal data are to be used there should be agreement on how extrapolation across species can be accomplished. Either by examination of existing data, or obtaining new data, any differences in the effect of dose rate and protraction over long periods such as the working lifetime should be determined. There are a number of advantages in using life shortening, especially because although the majority of life shortening is due to excess tumors it integrates all the causes in a single value. Furthermore, a method of extrapolating the risk across species has been proposed (Carnes et al.2003). As the data from the study of the atomic bomb survivors increase testing of methods of extrapolation improves.

To estimate the risk to people exposed for protracted periods in space to protons of various energies at low dose rates, low fluencies of a gallimaufry of heavy ions, and possibly a period(s) of exposure to protons at a high dose rate, from risk estimates based, mainly on data from atomic bomb survivors exposed to high energy gamma rays over a very short period, is a daunting but not an impossible task.

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