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Letter to the Editor

Dose and dose-rate effectiveness of radiation: first objectivity then conclusions

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ABSTRACT

This letter comments on the ongoing re-evaluation of the dose and dose rate effectiveness factor (DDREF) equal to 2.0, currently recommended by the International Commission on Radiological Protection. The topics of DDREF and threshold are related to the linear no-threshold theory (LNT), which does not take into account that DNA damage and repair are in dynamic equilibrium probably reached in a long term. Living organisms must have been adapted by natural selection to the today's background level of radiation or to some average from the past, when the radiation background was higher. Dose-dependent self-selection of exposed people and other biases common in epidemiological studies, cited in support of the DDREF lowering, are discussed here. In conclusion, the LNT and under-estimation of DDREF tend to exaggerate radiation-related health risks at low dose and dose rates exposures. Future risk estimates should be based on direct comparisons of experimental data from acute and protracted exposures.

KEY WORDS: Ionizing radiation; Dose rate; Chernobyl; Cancer risk

INTRODUCTION

The dose and dose rate effectiveness factor (DDREF) is used for adjustment of risk estimates at acute radiation exposures to continuous (low dose rate) exposures [1]. This letter refers to the ongoing discussion of the DDREF equal to 2.0, currently recommended by the International Commission on Radiological Protection (ICRP) [2]. The topics of the threshold, hormesis and DDREF are interrelated with the linear no-threshold theory (LNT). Hormesis and the LNT are considered controversial by many scientists; discussion is in [3-8]. Only the LNT is discussed below, but the same arguments pertain also to other no-threshold models. In particular, the linear-quadratic model does not fit all experimental data well [9].

The biophysical rationale of the LNT is as follows. The more tracks pass through a cell nucleus, the more DNA damage would result and the higher the risk of malignant transformation would be. Tracks of particles produce damage and consequent cellular changes. Decreasing the number of damaged cells by a factor of 10 would decrease the biological response by the same factor. Consequently, the risk of radiation-induced endpoints would decrease linearly, without a threshold, down to minimal doses [10]. This concept does not take into account that DNA damage and repair are permanent processes being in dynamic equilibrium most probably reached in a long term. There is an ecologically based argument against the LNT: given the evolutionary prerequisite of the best fitness, living organisms must be adapted by natural selection to a background level of ionizing radiation [11]. Accordingly, there would be an optimal exposure level, as it is for many environmental factors: visible and ultraviolet light, various chemical elements and compounds [12] as well as products from radiolysis of water participating in physiological processes [13]. Evolutionary adaptation to a changing environmental factor would probably lag behind its current value and correspond to some average from the past. Natural background radiation has been decreasing during the time of life existence [14]. It can be argued that resistance against radiation carcinogenesis may not be acquired by natural selection because the reproductive and cancer-developing ages in humans are averagely different. However, the conservative nature of mutation repair suggests that this mechanism evolved in the distant past, before the appearance of humans as a species, so that living organisms may have retained some capability to repair damage from higher radiation levels than those existing today [14]. Admittedly, the concept of radioactivity as an environmental factor with an optimal exposure level remains largely in the theory requiring corroboration by experimentally based scientific knowledge.

DISCUSSION

Obviously, if a dose is split into fractions, a biological system would have time for repair. With the dose protraction, damage caused by a given track would less frequently interact with that induced by a subsequent track, resulting damage thus being lower [15]. Effects of high linear energy transfer (LET) radiation were reported to have a small or no dose rate dependence in contrast to low LET radiation, where lowering of the dose rate can significantly reduce efficiency [16-18]. X- and γ-rays are sparsely ionizing; they

are termed low-LET radiation. In contrast, α-particles and neutrons are high-LET radiations. Electrons (β-rays) are generally sparsely ionizing i.e. low-LET, while protons are, at moderate energies, densely ionizing. Dependence between LET and relative biological effectiveness (RBE) is non-linear possibly with a peak at higher LET values; however, comparing low-LET and high-LET radiation, the latter is characterized by a higher RBE. The high-LET radiation causes more damage per unit absorbed dose [17,19]; a cell death can be produced by a few tracks or even a single one [15]. Moreover, the high-LET radiation, being a minor component of the natural radiation background except for radon, has probably induced less adaptation of internal organs other than lungs. This might explain why lowering the dose rate of low-LET radiation generally reduces carcinogenic effectiveness while that of high-LET radiation dose does not [18,20,21].

Several studies were cited in [2] directly [22-24], through the review [25], or mentioned as entire research series e.g. of Techa river and Mayak facility worker cohorts, adding evidence in support of the no-threshold concept and lowering of the DDREF. In the study of atomic bomb (A-bomb) survivors, it was concluded that the estimated lowest dose range with a significant excess relative risk (ERR) for all solid cancers was 0 to 0.20 Gy, while a dose-threshold analysis indicated no threshold [22]. This conclusion was doubted as the analysis had a priori restricted possible functional forms using only linear and linear-quadratic dose-dependences [6,26,27]. If a more generalized functional form was used, the lower bounds of the 95% confidence intervals would be under zero for low doses. This does not prove existence of a threshold, but demonstrates that the data variability is too high to suggest that the threshold is zero; more details are in [6,27]. Fitting of mathematical models is of limited value for determining whether or not a threshold and a cause-effect relationship exist; understanding of underlying mechanisms and verification by reliable methods are necessary, which is true also for chemical carcinogens [28,29]. The artificial neural networks method, applied to the cancer databases of A-bomb survivors, demonstrated the presence of a threshold that varied with organ, gender and age at exposure [30].

Papers overestimating medical consequences of the Chernobyl accident have been reviewed previously [31,32]. In the author's opinion, there is also a tendency to exaggerate the cause-effect relationship between radiation and certain diseases in the Techa river and Mayak facility worker cohorts [33,34]. In some earlier publications no increase in cancer incidence was reported at the doses below 0.52 Sv [35] or among all studied Mayak workers [36], while existence of a threshold was held possible [37]. It was pointed out that excessive absolute risk of leukemia had been 3.5 times lower in the Techa river cohort than among A-bomb survivors [38,39] i.e. the risk from acute exposure had been higher than that from protracted exposure at comparable doses. However, later reports by the same scientists have repeatedly stressed comparability of the data from Japan and the Urals and, correspondingly, a similar level of cancer risk from acute and protracted exposures both for leukemia and for solid cancers [23,24,40]. An unofficial directive can have been behind this change of accents; discussed in [32]. Along with the elevated cancer risk, an increased risk of non-neoplastic diseases (circulatory, respiratory, gastrointestinal) has been reported by the same researchers [22]. This can be seen as a circumstantial evidence in favor of biases e.g. the self-selection bias: dose-related differences in self-reporting and medical surveillance, a phenomenon noticed also by other researchers [41,42] discussed in [43]. Individuals knowing their higher doses would probably be more motivated to visit medical institutions, being at the same time given more attention. A relationship of aortic atherosclerosis and cerebrovascular diseases with low-dose exposures was reported from the Mayak facility, where the incidence of both conditions was increased in workers exposed to external γ-rays at a total dose above 0.5 Gy and/or to internal α-radiation from incorporated plutonium at liver dose above 0.025 Gy [44,45]. The ERR per 1 Gy for cerebrovascular diseases in the cohort of Mayak workers was even higher than in A-bomb survivors [46], where the self-selection bias could have been active as well. Incidence of cerebrovascular diseases was reported to be significantly higher among workers with total external γ-ray doses over 0.2 Gy compared to those exposed to lower doses [47]. In a later publication, the same was reported for the dose 0.1 Gy [48], which can hardly be caused by radiation considering the dose comparisons given in the next paragraph. In the author's opinion, the dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases [44-54] call in question such relationships for cancer reported by the same and other scientists [23,24,40,41,55-60], which pertains also to the studies cited in [2,25] directly or indirectly in support of the DDREF lowering.

Average total doses to male Mayak facility workers studied in [46] were 0.91 Gy; over 90% of the Techa river cohort received < 0.1 Gy [52] protracted over many years. For comparison, some studies found no evidence for excess morbidity and mortality from coronary artery disease in women treated with radiotherapy for the left breast cancer compared to patients with right-side tumors [61]. An increased risk of heart disease has been related to breast tumor doses of 40-50 Gy and mediastinal doses in excess of 40 Gy [62]. The 7th Report of the Committee on the Biological Effects of Ionizing Radiation (BEIR VII) [17] summarized that "there may be some risk of cardiovascular morbidity and mortality for very high doses and high-dose-rate exposures" [17]. According to the judgment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), given the inconsistent epidemiological data and the lack of a biologically plausible mechanism, the present data are not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses of less than 1-2 Gy [62]. In the author's opinion, the latter figures are understated as some epidemiological data are probably biased e.g. by dose-dependent self-selection [12,31,34,43], while doses

associated with functional or morphological cardiovascular changes in experiments were much higher [63-65]. Finally, evaluating data on cardiovascular mortality, it should be taken into account that cardiovascular diseases are sometimes overdiagnosed post mortem in unclear cases [66], which may be a confounding factor.

Conscious or subconscious dose-dependent changes in behavior have probably contributed to the dose-effect relationships found in many epidemiological studies: one additional X-ray, endoscopy or blood count can lead to a diagnosis thus influencing statistics. Among other biases of epidemiological research are "dose lagging, odds averaging over wide dose ranges when evaluating odds ratios, and forcing a positive slope to the relative risk dose-response curve" [7]. Besides, studies of radiation effects in humans may be prone to a recall bias: cases would probably recollect facts related to the exposure better than controls, especially if they are informed on carcinogenicity of radiation. Furthermore, biases and limitations of epidemiological studies on low dose exposures included a priori classification of spontaneous conditions as radiation-induced, discussion of doses disregarding natural radiation background, conclusions about incidence increase without adequate comparisons with a control, data trimming etc., commented in [31,32]. Some experiments, where no effects had been found in exposed animals, were excluded from databases [67]; other studies with lesser or no impacts of radiation have not been cited in reviews [68] etc. All that contributed to overestimation of low dose effects. Today, when the literature is so abundant, research quality and possible biases should be taken into account defining inclusion criteria for studies into pooled analyses and reviews.

Another potential argument in favor of DDREF lowering is the significant increase in the minisatellite DNA mutation rate found in children of workers at the Mayak facility (mean parental gonadal dose 1.65 Gy protracted over many years) [69] or residents of contaminated territories after the Chernobyl accident [70-74] (mean whole-body doses in different areas up to 18 mSv, overviewed in [12]). At the same time, minisatellite mutations were not observed after acute external irradiation in the offspring of cancer survivors, of A-bomb survivors, or after protracted exposures of Chernobyl clean-up workers [75]. In particular, the studies [74,75] found no significant differences in mutation rates between children of exposed and unexposed parents. The mean parental gonadal dose was 1.9 Sv in [76] and >1 Sv in [77]. It was concluded that a single acute exposure of spermatogonial cells in humans does not result in discernible mutation induction at minisatellite loci [77]. The review [75] concluded that there is a weight of evidence that acute high dose paternal exposures have not led to detectable increase in minisatellite mutations in the offspring of humans. Results from [70-74] are also in contrast with [78] and other studies overviewed in [78,79]. Possible biases in [70-74], questioning other results by the same researchers, have been discussed previously [12,80]. Importantly, the available evidence suggests that human health has not been significantly affected by transgenerational effects of radiation [75].

As for hormesis, it cannot be used in the radiation safety regulations without unequivocal experimental evidence. Due to the relatively low sensitivity of epidemiological studies and biases discussed here and in the literature [7,75] epidemiological studies would be hardly helpful in overcoming this barrier. The same attitude was expressed by the UNSCEAR e.g. in regard to potentially radiation-related circulatory diseases at doses less than 1-2 Gy [62]. Some studies [e.g. 76] showed a diminished risk of heart disease associated with radiotherapy for breast cancer, but longer follow-up is deemed to be needed [62]. Large-scale animal experiments using different species would be required for the further study of the dose-effect relationships and hormesis in view of its potential application in the safety regulations. Current experimental evidence in favor of adaptive response to low dose radiation and hormesis is considerable [4-7,82,83], which means that a part of experimental data is at variance with results of epidemiological studies discussed above and cited in [2,25]. Some animal experiments did not support the hormesis concept showing, for example, no life lengthening in mice continuously exposed to radiation at low dose rates [84]. Other researchers did report life lengthening of mice in low dose experiments [e.g., 85]. Although the value of animal experiments for extrapolation to humans is controversial [86], for such a universal mechanism as DNA repair the extrapolation would be probably admissible if different animal species are used. Further work in this direction could quantify sensitivity of different species enabling more precise extrapolations to humans [87]. Outstanding data on harmful effects of low doses should be verified by experiments, for example, that "above doses of 50-100 mSv (protracted exposure) or 10-50 mSv (acute exposure), direct epidemiological evidence from human populations demonstrates that exposure to ionizing radiation increases the risk of some cancers" [10], or four-fold increase in the incidence of thyroid cancer and twofold increase of benign thyroid tumors in children linked to a thyroid dose of 90 mGy [88]. The same applies to the data on the excess radiation-related cancer deaths occurring at doses below the current occupational limits [89]. In any case, the hormesis concept should be applied cautiously as hormetic stimuli may act without threshold upon pre-damaged or atrophic tissues, or act synergistically with other known or unknown noxious agents including carcinogens [90-94]. In this connection, the petition to remove the phrase "As low as reasonably achievable" (ALARA) from the radiation safety regulations [95] is hardly justified, as exposures are unpredictable while their effects may accumulate.

CONCLUSION

There is evidence that protracted exposures are safer than current estimates. The results of animal experiments, with doses similar to or somewhat higher than the dose range

to which the A-bomb survivors were exposed, and dose rates that varied by factors 100-1000 or more, produced DDREF values 1-10 or more with a central value about 4 [18]. A range of models suggests that protracted exposures are between 2.0 and infinitely times safer than acute exposures at comparable doses [9]. Indeed, according to the hypothesis of evolutionary adaptation to the natural radiation background, with the dose rate tending to the background level, radiation-related risks would tend to zero, and can even fall below zero within some dose range in accordance with hormesis. However, future risk estimates should be based on direct comparisons of data from acute and protracted exposures, rather than on extrapolations by models [9]. In conclusion, the LNT and under-estimation of DDREF tend to overestimate radiation-related health risks of low dose and dose rates exposures.

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