Avens Publishing Group
J Environ Stud
February 2016 Vol.:2, Issue:1

Biological Effectiveness of Ionizing Radiation: Acute vs. Protracted Exposures

Open Access Editorial Article

Journal of Environmental Studies

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Submission: 23 January, 2016
Accepted: 18 February, 2016
Published: 23 February, 2016

Reviewed & Approved by: Dr. Jim Clarke, Practice of Civil & Environmental Engineering, Vanderbilt University, USA

Keywords: Ionizing radiation; Dose rate; Chernobyl; Cancer risk

Abstract

This letter refers to the current discussion around re-evaluation of the dose and dose rate effectiveness factor (DDREF) equal to 2, presently recommended by the International Commission on Radiological Protection. The topics of the threshold, hormesis and DDREF are interrelated with the linear no-threshold theory (LNT). The LNT does not take into account that DNA damage and repair are permanent processes in dynamic equilibrium. Given the evolutionary prerequisite of best fitness, it would be reasonable to assume that living organisms have been adapted by the natural selection to the background levels of ionizing radiation. Accordingly, there must be an optimal exposure level, as it is for many environmental factors. Several studies cited in the literature in support of the LNT and lowering of the DDREF down to 1 are discussed here. In the author's opinion, the dose-effect relationships with non-neoplastic diseases found in certain exposed populations call in question dose-effect relationships with cancer. Self-selection and other biases in epidemiological studies are discussed. The dose-response relationships should be clarified in large-scale experiments involving different animal species. In conclusion, the LNT and under-estimation of DDREF tend to exaggerate radiation-related health risks at low radiation doses and dose rates.

Arguments against Linear No-Threshold Theory (LNT)

Radiation-related cancer risk estimates have been primarily based on the data from atomic bomb survivors. To adjust the risk estimates at acute exposures to low dose and continuous (low dose rate) exposures, a dose and dose rate effectiveness factor (DDREF) is used [1]. This letter refers to the discussion around re-evaluation of the DDREF value equal to 2, 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 LNT are considered controversial by many scientists; discussion is in [3-8]. The LNT is corroborated by the following arguments: the more tracks go through a cell nucleus, the more DNA damage would result and the higher the risk of malignant transformation would be. "Decreasing the number of damaged cells by a factor of 10 would be expected to decrease the biological response by the same factor of 10" [9]. This concept does not take into account that DNA damage and repair are permanent processes in dynamic equilibrium. Given the evolutionary prerequisite of best fitness, it would be reasonable to assume that living organisms have been adapted by the natural selection to background levels of ionizing radiation [10]. Accordingly, there must be an optimal exposure level, as it is for many environmental factors: visible and ultraviolet light, different chemical elements and compounds [11], as well as the products from radiolysis of water [12]. Evolutionary adaptation to a changing environmental factor would lag behind its current value and correspond to some average of historic levels. Natural background radiation has probably been decreasing during the time of life existence on the Earth. It can be argued that resistance against radiation carcinogenesis may not be acquired by natural selection because the average reproductive and cancer-developing ages in humans differ considerably. However, DNA repair is an ancient mechanism that had developed long time before the appearance of the human species. The double-strand breaks in DNA, induced by radiation, can be repaired by error-free or error-prone repair mechanisms [13]. Mutations and carcinogenesis are caused by many factors; it might be hypothesized that a low-dose radiation exposure would contribute to expression of repair-related genes, which would enhance the error-free repair of the damage induced by different mutagens. The conservative nature of mutation repair mechanisms suggest that they have evolved in the distant past so that modern organisms may have retained some of the capability of efficiently repairing damage from higher radiation levels than those currently existing [14].

Discussion around Dose and Dose Rate Effectiveness Factor (DDREF)

Understandably, if a dose is split into fractions, a biological system would have time for repair, so that resulting damage would be lower. However, high LET radiation has generally been regarded to show a small or no dose-rate dependence in contrast to low LET radiation where low dose-rate can significantly reduce effects [15-17]. It can be reasonably assumed that high LET radiation, constituting a minor component of the natural radiation background except for the gas radon, has induced less adaptation of internal organs other than the lung. Besides, a track of densely ionizing radiation is generally much more destructive [18]. Accordingly, lowering the dose rate of low-LET radiation reduces carcinogenic effectiveness, whereas fractionation of high-LET radiation dose does not [19-21].

Several studies were cited in [2] directly [22-24] or through the review [25] in support of the no-threshold concept and lowering

ISSN: 2471-4879

of the recommended DDREF value down to 1. Some of these papers are discussed below. So, epidemiological studies based on the best fitting of functional forms do not necessarily prove a cause-effect relationship. In the study of Hiroshima and Nagasaki survivors [22], it was concluded that zero dose is the best estimate for the dose threshold, thus validating the LNT. This conclusion is, however, regarded questionable as the analysis had a priori restricted the possible functional forms of the dose-response relationship, resulting in the conclusion on a zero dose threshold [5,26]. If a more generalized functional form was used, the conclusion would have been different, as the lower bounds of the 95% confidence intervals would have been below zero for low doses; more details are in [5]. The artificial neural networks method was reported to have circumvented the limitation of [22] and demonstrated the presence of a threshold of excess relative risk in humans exposed to ionizing radiation [27]. Along with the elevated risk of cancer mortality, an increased risk of non-neoplastic diseases including those of circulatory, respiratory (pneumonia, influenza etc.) and digestive systems, was reported in [22], which can be seen as circumstantial evidence in favor of dose-related differences in medical surveillance and self-reporting, a phenomenon noticed also by other researchers in populations exposed to radiation [28], discussed in [29]. In the author's opinion, the dose-effect relationships with non-neoplastic diseases [30-34] call in question such relationships with cancer, reported e.g. in the studies [23,24,35-43] including those cited in [2,25] in support of the DDREF lowering. Although there may be some risk of cardiovascular disease at high dose and dose-rate exposures [16], existing data are insufficient to confirm a cause-effect relationship between radiation and cardiovascular diseases at doses below 1-2 Gy, while plausible biological mechanisms are unknown [44]. Average doses in the epidemiological studies [30-34] were lower. As mentioned above, people knowing their relatively high dose estimates would probably be on average more motivated to visit medical institutions (self-selection bias), being at the same time given more attention. Conscious or subconscious dose-dependent behavioral changes have probably contributed to the dose-effect correlations found in epidemiological studies: one additional X-ray, endoscopy or blood count can lead to a cancer diagnosis thus influencing statistics. The same mechanism can cause in future an increase in the registered cancer incidence in the high natural background radiation areas (Guarapari, Brazil; Kerala, India; Ramsar, Iran; Yangjiang, China), where no cancer increase has been detected so far [2,45-48]; although singular reports on enhanced cancer risk in such areas have already appeared [45,49].

A tendency to exaggerate medical consequences of Chernobyl accident in some professional publications was noticed in the 1990s [50,51]. Biases and conflicts of interests could have influenced results and conclusions by some researchers, e.g. [52-56], as discussed in [29,50,51,53,57]. This may pertain also to some reports cited in [2,25]. Similar biases might have been active in some studies correlating radiation exposure and minisatellite mutations in the offspring of exposed parents [58,59]. Studies of that kind have been commented previously [11,60]. More details are in [61-65]. There is also a tendency to emphasize radiation-related pathology in the Techa River and Mayak nuclear facility cohorts, although in some publications no increase in cancer or other potentially radiation-related conditions were reported [66-68]; and existence of a threshold was held possible [68]. It was concluded, for example, that: "The number of radiation-induced cancers in the Techa river cohort has been lower than among Japanese A-bomb survivors" [69], which means that the risk from acute exposure is higher than from protracted one at the same dose. Other works stress similarities between the data from Japan and the Urals i.e. similar level of cancer risk from acute and low-rate exposures [70]. Accordingly, with regard to DDREF, the more recent papers concluded that carcinogenic risk resulting from low-rate exposure is not lower than that from acute exposure of A-bomb survivors [71] i.e. the DDREF value must be close to 1. 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, meta-analyses and reviews. For example, certain reports on Chernobyl-related thyroid cancer can be conductive to over-estimation of carcinogenic properties of radioiodine; discussed in [72].

On the Dose-Response Relationship

A dose-effect curve for low doses and dose rates can be construed theoretically. There are numerous carcinogenic factors, both environmental and endogenous. The lower would be the level of added radioactivity due to contamination, the smaller would be its contribution compared to the natural radiation background, and the less significant would be the role of radiation in general compared to other carcinogens. Accordingly, the dose-effect curve would deviate from linearity with the dose and dose rate decreasing down to the background levels; the relationship can even become inverse in accordance with hormesis. A corresponding graph plotted on the basis of experimental data is presented in [73] with a comment that the window for maximum adaptive response protection occurs at doses between 1 and 100 mGy, where risk is reduced below the spontaneous level of cancer risk [73]. It means that a large part of experimental data is at variance with results of epidemiological studies discussed in [2,43]. Admittedly, data obtained in small animals as well as adaptive responses detected at the cellular level cannot be directly extrapolated to humans. Some animal experiments do not support the hormesis concept showing, for example, no life lengthening in mice continuously exposed to radiation at low dose rates [74] (critically discussed in [75]). Other researchers did report life lengthening of mice in analogous experiments [76]. In any case, the hormesis concept should be applied with caution 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 [77-79]. In this connection, the petition to remove the phrase "As low as reasonably achievable" (ALARA) from the radiation safety regulations [80] is hardly justified, as exposures are unpredictable during a human life, while effects of exposures may accumulate. Hormesis cannot be used in the radiation safety regulations without compelling experimental evidence from large-scale animal experiments using different species. Epidemiological studies in humans would be less informative because of the relatively low sensitivity and biases [7,81], in particular, dose-dependent quality of medical surveillance and more frequent self-reporting of people with higher doses (self-selection bias). The dose-response

ISSN: 2471-4879

relationships should be clarified in large-scale experiments involving different animal species.

DDREF under-estimation: about motives

If vested interests cannot be excluded, the question cui bono? (to whose profit?) should be discussed. The LNT and under-estimation of DDREF down to the values below 2 [17] tend to exaggerate radiation-related health risks at low doses and dose rates. Such exaggeration is conductive to strangulation of nuclear energy, the cleanest, safest (if everything is done properly) and practically inexhaustible means to meet the world's energy needs [52]. This would agree with the interest of fossil fuel producers. Nuclear power has returned to the agenda because of the concerns over increasing global energy demand, declining fossil fuel reserves and global climate changes. Nuclear energy emits virtually no greenhouse gases in comparison to coal, oil or gas [82]. In the author's opinion [83], revision and possible elevation of the dose limits both for the public and for professional exposures is indicated, which must be accompanied by measures guaranteeing adherence to the regulations. More international trust and cooperation would enable construction of nuclear power plants in optimally suitable places, notwithstanding national borders, considering all sociopolitical, geographic, geologic factors, attitude of workers and engineers to their duties [64,82] interrelated with their proficiency, moods, motivations and observance of human rights. Consideration of all these factors would make nuclear accidents improbable.

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