Radiation safety and hormesis

This is a summarizing update of several preceding publications (1 , 2) with special reference to the series of papers concerning the East Urals Radioactive Trace (EURT) (3 – 10). A realistic risk assessment and potential hormetic effects are of particular importance for the aerospace health and safety, where exposures to ionizing radiation may be unavoidable but not necessarily harmful. Hormesis is a biphasic dose response: low doses exert protective effects while higher doses are detrimental. Among environmental factors acting according to the hormetic pattern are numerous physical and chemical agents including products of water radiolysis (11 , 12). In the hormesis framework, mild exposures to various stressors elicit an adaptive response that enhances defenses and protects the organism. This protection may be associated with a performance increase that goes beyond that observed in untreated individuals (13). The term " hormesis" is rarely mentioned in publications on the field of radiation protection while the linear no-threshold (LNT) hypothesis is continued to be used. According to the LNT, the probability of developing cancer is proportional to the radiation dose; the dose-response relationships can be extrapolated down to low doses, where the correlations are unproven and can become inverse in accordance with the hormesis concept. In fact, to reject the LNT hypothesis, it would suffice to prove hormesis (14). The LNT is based on the following premise: the more particle tracks go through cell nuclei, the more DNA damage would occur and the higher the damage would be. This concept does not take into account that DNA damage and repair are permanent processes in the dynamic equilibrium. By analogy with other environmental factors, an evolutionary adaptation to the natural background radiation can be expected. The conservative nature of the DNA repair suggests that cells and

organisms may have retained some capability of repair from a higher radiation impact than that caused by the present background. Life evolved on the Earth with a radiation background that was higher than that existing today ([15] , [16]). The experimental evidence in favor of hormesis and adaptive responses to radiation is considerable ([13] , [17] , [18]); more details and references are in ([1] , [2] , [19]). This signifies that experimental data partly disagree with epidemiological studies. The main problem with the epidemiological research of low-dose radiation is potential bias, inter-study differences in quality, and reliability ([1] , [20]). Of particular significance is selection and self-selection: persons with higher doses or those residing in more contaminated areas would be averagely more preoccupied with their health, compensations, and provisions, being at the same time given more attention, the diagnostic quality thus being potentially dose-dependent. In case-control studies, the cases tend to recollect circumstances related to exposures better than controls (recall bias), which may result in dose-effect correlations ([1] , [21]).

Hormetic responses to therapeutics as compared to radiation hormesis should be briefly commented. Radiation is an environmental factor. There are no a priori grounds to expect biphasic dose-responses for factors that are absent in the natural environment. This general principle does not exclude a possibility that some substances, if even absent in the natural environment, can act according to the hormetic pattern due to some known or unknown mechanisms ([13] , [22] – [24]). Microorganisms may develop hormetic responses to antibiotics by a positive selection of resistant strains. The theoretic basis of some hormetic mechanisms was discussed within the

framework of stress response pathways (13 , 22). Of note, different kinds of stress are a part of the environmental impact on living organisms, the latter being accordingly adapted. On the other hand, some pharmacological and toxicological stimuli can have a cumulative effect or act synergistically with some noxious factors, for example, upon cells with a limited or lacking mitotic capacity such as cardiomyocytes or neurons. It can be of particular importance in conditions when such cells are pre-damaged, e. g., by ischemia, so that even a minor additional impact may act according to the no-threshold dose-response pattern without hormesis. Under such circumstances, which are common especially in gerontology, the hormesis concept can be precarious if used in the clinical decision-making. All clinically significant effects, hormetic or not, should be tested according to the principles of evidence-based medicine (25).

Along with the elevated cancer risk, an increased risk of non-cancer outcomes has been reported, e. g., in the EURT cohorts (3 – 9). For example, the incidence of cerebrovascular diseases (CVD) was significantly elevated among Mayak facility workers with accumulated external gamma-ray doses ≥0. 2 Gy compared to those exposed to lower doses (3). The risk estimate in (3) was higher than in other studies. Nonetheless, in a later publication, a significantly enhanced CVD risk was reported for the doses as low as ≥0. 1 Gy (4). The excess relative risk of CVD per 1 Gy in Mayak workers turned out to be even higher than among atomic bomb survivors (5 , 6), where the exposure was acute and hence presumably more efficient per dose unit. Elevated risks compared to those calculated using the LNT model have been found in the Techa River cohort for the total of

cardiovascular diseases and separately for ischemic heart disease (7). The average total cumulated gamma-ray dose to male Mayak workers studied in (6 , 8) was ~0. 91 Gy while ≥90% of the Techa river cohort received ≤0. 1 Gy (7). For comparison, an increased risk of heart disease in patients receiving radiation therapy has been associated with mediastinal doses ≥40 Gy and breast doses 40–50 Gy (26), i. e., fractionated but still high-dose-rate exposures. According to the BEIR VII (Biologic Effects of Ionizing Radiation) Report, radiation has been demonstrated to increase the risk of diseases other than cancer, particularly cardiovascular disease, in patients exposed to high therapeutic doses and in A-bomb survivors exposed to more modest doses. However, there is no direct evidence of increased risk of non-cancer diseases at low doses (27). According to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), existing evidence is not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses ≤1–2 Gy (26). The threshold may be underestimated due to bias in the epidemiological research. Doses associated with cardiovascular damage in experiments have been generally higher than averages in human populations exposed due to accidents and other anthropogenic contaminations, overviewed in (1 , 2). Reported dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases cast doubt on such relationships for cancer found by the same researchers.

Certain reports on the enhanced cancer risk appear doubtful. For example, a significant increase in the skin cancer risk was found among Mayak et al. (10). A bias was not excluded: the workers and medical personnel knew

individual work histories wherefrom cumulated doses could be estimated possibly influencing the diagnostic thoroughness and self-reporting. Skin doses were unknown (10). The workers were exposed predominantly to gamma rays having a relatively high penetration distance, so that the portion of energy absorbed by the skin must have been correspondingly low. Not surprisingly, the " pre-malignant skin lesions and actinic keratoses… were very rare in members of the study cohort" (10). Other questionable results and conclusions have been cited previously (2), for example: " CVD incidence was significantly higher among workers with total absorbed external γ-ray doses greater than 0. 1 Gy compared to those exposed to lower doses and that CVD incidence was also significantly higher among workers with total absorbed internal alpha-particle doses to the liver from incorporated plutonium greater than 0. 01 Gy compared to those exposed to lower doses" (9). Considering the dose comparisons above and in (1), such results are probably caused by bias. Finally, unverified LNT-based mathematical models have been applied to the EURT data contributing to the overestimation of medical consequences of low-dose low-rate exposures to ionizing radiation (28) commented previously (29). Potential motives have been discussed elsewhere (1 , 2).

Conclusion

The monitoring of populations exposed to low-dose low-rate radiation is important but will hardly add much reliable information on the health risks. It can be reasonably assumed that the screening, increased attention of exposed people to their health, and biased research will result in new reports on the elevated detection rate of cancer and other diseases in exposed

populations. A constructive alternative for the future work would be large-scale animal experiments. The life duration is known to be a sensitive endpoint attributable to radiation exposures. Low-dose exposures were reported to extend the lifespan of mice and some invertebrates (13). Cardiovascular effects and hormesis could be measured in chronic experiments applying exercise tolerance (time to fatigue) and other functional tests. The spectrometry describing changes in the heart proteome may provide valuable information. Promising data in favor of radiation hormesis have been received also in the research of brain tissues (18). Moreover, the question should be clarified in cell cultures and *in vivo* whether relevant doses cause an increase in cell death, i. e., apoptosis. To enable extrapolations to humans, the doses and dose rates in experiments must be comparable to those in corresponding human populations, taking into account the radiosensitivity and life span of given species. Further experiments with different animal species would contribute to a better quantification of their radiosensitivity, thus enabling more precise extrapolations to humans.

Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Disclaimer

The statements presented in this publication are solely the responsibility of the author.

Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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