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RADIATION SAFETY STANDARDS AND HORMESIS

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Research

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CONFLICTS OF INTEREST
There are no conflicts of interest for any of the authors.

ABSTRACT

Strictly observed realistic safety standards are more helpful for the public health than excessive restrictions that would be disregarded. Today's radiation safety standards are based on the linear no-threshold theory (LNT): extrapolation of dose-response relationships down to low doses, where such relationships are unproven and can be inverse due to hormesis. Hormesis is theoretically founded for environmental factors causing adaptation to a background level or some average from the past when the natural background was higher. According to this concept, the harm caused by anthropogenic radiation would tend to zero with a dose rate decreasing down to a wide range level of the natural background. Hormesis concept should be applied with caution as hormetic stimuli may act without threshold on pre-damaged or atrophic tissues or act synergistically with other noxious agents. Experimental evidence in favor of hormesis is considerable but further studies are needed. Low doses should be analyzed separately from higher doses, which would prevent unfounded LNT-based extrapolations. Some reviews and metaanalises have analyzed studies of uneven quality. Questionable data on Chernobyl accident, Techa river and Mayak workers cohorts are discussed here along with motives to exaggerate consequences of low-dose low-rate exposures. Among the biases of epidemiological research, dose-dependent self-selection and recall bias are pointed out. In conclusion, current radiation safety standards are excessively restrictive and should be revised to become more realistic and workable. Revision of the limits should be based on reliable experiments and accompanied by measures guaranteeing observance.

KEYWORDS: ionizing radiation, safety standards, hormesis, Chernobyl accident, nuclear power

INTRODUCTION

Standards are only effective if they are properly applied in practice [1]. Unrealistic laws and regulations are often violated, which contributes to the disrespect for the law in general. Today's radiation safety standards are based on the linear no-threshold theory (LNT): extrapolations of a dose-response relationship down to the low doses, where such relationship is unproven and can become inverse due to hormesis [2-6]. According to the current standards, an equivalent effective dose to individual members of the public should not exceed 1 mSv/year. The limits of effective dose for exposed workers are 100 mSv in a consecutive 5-year period, with a maximum

effective dose of 50 mSv in any single year [1]. For comparison, worldwide annual exposures to natural radiation sources are generally expected to be in the range of 1-10 mSv, 2.4 mSv being a current estimate of the global average [7].

For solid cancers and leukemia, significant dose-response relationships were found in survivors of atomic explosions exposed to <500 mSv but not for doses < 200 mSv [7-10]. According to UNSCEAR, a statistically significant elevation of the cancer risk was observed in epidemiological studies at the doses >100-200 mGy [11]. There were also reports on dose-response relationships for lower doses [12,13] but validity was questioned [7]. Practical thresholds can in fact be higher due to biases in epidemiological research on stochastic effects of low doses [14-17]. The value 200 mSv has been regarded as a level, below which no excess cancers were proven [10,18]. Some reports contain poorly substantiated information (details are in [19,20]). The quality of the research is uneven; data trimming according to a preconceived idea appears to be probable in some studies [21]. Reviews and metaanalises discuss together studies of uneven quality [e.g., 22]; although in the latter review the unreliability of mortality data from the former Soviet Union (SU) was pointed out. We agree [23] with Prof. Little that "such data should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here [24-27]" [22]. This recommendation pertains apparently also to some other studies by the same and other researchers, discussed below. Today, when the literature is so abundant, research quality, possible biases and conflicts of interest should be taken into account defining inclusion criteria into metaanalyses and reviews.

CHERNOBYL ACCIDENT

Using the LNT, Chernobyl accident was predicted to result in a "virtual epidemic" of radiation-induced cancer. Instead, there was no cancer increase provably caused by radiation except for thyroid cancer (TC) [28,29]. TC in people exposed at a young age has been the only oncologic sequel of the Chernobyl accident widely believed to be proven [30]. It should be commented that the incidence of pediatric TC was much lower in the contaminated areas of the former SU compared to more developed countries obviously due to differences in diagnostic quality and coverage of the population by medical checkups (discussed in [31]). The mass screening after the accident detected not only small cancers but also advanced neglected TC accumulated in the population, classified as aggressive radiogenic cancers. Besides, some TC cases were brought from non-contaminated areas and registered as Chernobyl victims. As there was no screening outside the contaminated areas, such cases tended to be more advanced. These phenomena were confirmed by the fact that the 'first wave' TC after the accident were on average larger and less differentiated than later ones [32,33]. The following citation is illustrative: 'The tumors were randomly selected (successive cases) from the laboratories of Kiev and Valencia... [The cancers were] clearly more aggressive in the Ukrainian population in comparison with the Valencian cases' [34]. There is an explanation: averagely earlier cancer diagnostics in Valencia. Further details and references are in [31].

In the meantime, there continue to appear reports on Chernobyl material, where the cause-effect relationship between dose estimates and a cancer risk is discussed as a matter-of-fact [35-38]. Without repeating the previously published arguments [20,31], the following should be stressed. Among the motives of the exaggeration of Chernobyl consequences were writing of numerous dissertations, financing, international help and scientific cooperation with overseas voyages, etc. Moreover, Chernobyl accident was misused to strangle the nuclear power [39] thus contributing to higher fossil fuel prices. Furthermore, the mechanisms of false-positive diagnosis of malignancy have been discussed previously [40,41]. Among others, misinterpretation of cellular pleomorphism as a malignancy criterion of thyroid nodules was not uncommon in the 1990s. In the urinary bladder, inflammatory reactive atypia was obviously misinterpreted as dysplasia or carcinoma in situ [40,43,44]. On the basis of morphological descriptions and images from Russian-language editions on tumor pathology of that time, no reliable differential diagnosis could be made; some images were reproduced in [43,45]. In the author's opinion, based also on interviews with pathologists and other experts involved in the diagnostics of Chernobyl-related cancer, trimming of statistics contributed to the overestimation of Chernobyl consequences. A circumstantial evidence thereof is the large number of papers reporting unrealistic data, partly referenced in [46] and commented in [19].

The exaggeration of Chernobyl consequences may lead to the overestimation of carcinogenicity of certain radionuclides. Moreover, the exaggeration caused anxiety contributing to enhanced abortion rate [47]. Chernobyl accident has been exploited to strangle the worldwide development of nuclear power, the cleanest, safest and practically inexhaustible means to meet the global energy needs [41,48]. However, it was necessary for the time be-

ing: the nuclear technology should have been prevented from spreading to densely populated regions, where conflicts and terrorism are not excluded. The worldwide introduction of nuclear energy will be possible only after a concentration of authority in the most developed parts of the world. It will make possible the construction of nuclear reactors in optimally suitable places, considering all sociopolitical, geographical, and geological conditions, attitudes of workers and engineers to their duties [31], which would prevent accidents like Fukushima and Chernobyl.

TECHA RIVER, MAYAK FACILITY AND OTHER EPIDEMIOLOGICAL RESEARCH

There is a tendency to exaggerate cause-effect relationships between radiation and certain diseases in studies of the Techa river and Mayak workers cohorts in the Ural region of Russia [49]. It should be noted that dimensions of radiocontamination in the Urals were larger than that after Chernobyl. The Mayak complex, located 70 km to the north from the million city of Chelyabinsk, included the Facility A, the reactor, and Facility B, a radiochemical plant. The main source of exposure at the Facility A was gamma radiation, while overage total doses for workers in the period 1949-1954 were estimated to be 1220 mSv. The major radiation components at Facility B were external gamma irradiation and ^{229}Pu aerosols. The average total doses for workers of this facility in the period 1949-1953 were 2450 mSv [50]. Waste disposal into the Techa river system, the Kyshtym accident (1957), resuspension by winds from the waste repository lake Karachai (1967) and other accidents contributed to exposures of surrounding population. About 7500 evacuees from the Techa river area received average doses in the range 35-1700 mSv. Especially high doses were received in the village Metlino, where some residents obtained red bone marrow doses 3000-4000 mSv [50]. The relatively large discharges of radioactive materials into the Techa river occurred between the years 1949 and 1956. The Techa river cohort consists of over 30,000 people who were born before the start of exposure in 1949 and lived along the Techa river; more details and references are in [49]. The difference between Chernobyl and the East Urals radioactive trace is that the former was an accident, but the latter - a contamination tolerated over decades, with several accidents in between.

The tendency to exaggerate medical consequences of the East Urals radioactive trace seems to be rather new: in earlier papers no increase in cancer incidence was reported at the doses <0.52 Sv [51] or among all studied Mayak workers [52], while existence of a threshold was regarded possible [53]. 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 [54,55] i.e. the risk from acute exposure had been higher than that from protracted exposures at comparable doses. However, later works by the same scientists have repeatedly stressed comparability of the data from Japan and the Ural region and, correspondingly, a similar level of cancer risk from acute and protracted exposures both for leukemia and for solid cancers [56-58]. An unofficial directive could have been behind this metamorphosis. Along with the elevated cancer risk, an increased risk of non-neoplastic diseases (circulatory, respiratory, gastrointestinal) has been reported by the same and other researchers [24-27, 59-69]. For example, cerebrovascular disease incidence was significantly elevated in workers with a total external dose 0.1 Gy protracted over years [70]. This can be seen as a circumstantial evidence in favor of biases e.g. self-selection: dose-related differences in self-reporting and medical surveillance, a phenomenon noticed also by other researchers in exposed populations [71,72], discussed in [73]. Individuals knowing their higher doses would probably be more motivated to visit medical institutions, being on average given more attention. Besides, studies in humans may be prone to a recall bias: cases would recollect facts related to the exposure better than controls. The dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases [24-27,59-69] call in question such relationships for cancer reported by the same and other scientists e.g. [74-80]. Although there may be some risk of cardiovascular disease at high dose and dose-rate exposures [81], existing data do not confirm a cause-effect relationship between radiation and cardiovascular diseases at doses <1-2 Gy, while plausible biological mechanisms are unknown [16]. The latter value seems to be an underestimation due to the biases in the epidemiological research. Note that patients treated by radiotherapy who received doses >40 Gy to parts of the heart may develop cardiovascular complications later in life; some sources mention also lower doses [82,83], which are still much higher than the average doses in Chernobyl and Ural cohorts. The doses associated with cardiovascular alterations in animal experiments have been also considerably higher [84,85].

Average total doses to male workers of the Mayak facility were 0.91 Gy [46]; over 90% of the Techa river cohort received < 0.1 Gy [52] protracted over many years. A relationship of aortic atherosclerosis and cerebrovascular diseases with low-dose exposures was reported from the Mayak facility, where both conditions were increased in workers exposed to external gamma-rays at total doses >0.5 Gy protracted over years [59,65]. The excess relative risk (ERR) per Gy for cerebrovascular diseases in the cohort of Mayak workers was reportedly

even higher than that in A-bomb survivors [61], where the self-selection bias could have been active as well.

Epidemiological studies have a limited statistical power to detect the risk of cardiovascular disease after exposures <0.5 Gy [82]. In particular, the research based on the best fitting of mathematical models e.g. [57,58,86] does not necessarily prove a cause-effect relationship. For example, a study of atomic bomb survivors concluded that the estimated lowest dose range with a significant ERR for all solid cancers was 0 to 0.20 Gy, while a dose-threshold analysis indicated no threshold [86]. This conclusion was questioned as the analysis had restricted possible functional forms using only linear and linear-quadratic dependences [87-89]. If a more generalized functional form had been used to fit the data, the lower bounds of the 95% confidence intervals would have been under zero for low doses i.e. a threshold cannot be excluded. The artificial neural networks, applied to the cancer databases of A-bomb survivors, demonstrated the presence of thresholds for the ERR varying with organs, gender and age at exposure [90].

Furthermore, biases and limitations of epidemiological studies have included a priori classification of spontaneous diseases as radiation-induced, discussion of doses disregarding natural radiation background, conclusions about incidence increase without adequate comparisons with a control, "dose lagging, odds averaging over wide dose ranges when evaluating odds ratios, and forcing a positive slope to the relative risk dose-response curve" [91], data trimming etc., commented in [20,21]. Some experiments, where no effects had been found in exposed animals, were excluded from databases [92]; other studies with negative results have not been cited in reviews [93] etc. All that contributed to overestimation of the low dose effects.

HORMESIS AND RADIATION SAFETY NORMS

Hormesis describes any process in which a cell or organism(s) exhibit a biphasic response to exposure to increasing amounts of a substance or condition; typically, low-dose exposures elicit a beneficial response, whereas high doses cause toxicity [6]. Among hormetic agents (hormetins) are numerous chemical substances and elements, vitamins, heat, light, ultraviolet, ionizing radiation and products of water radiolysis [94], exercise, and different kinds of stress [95]. For factors that are present in the natural environment, hormesis is generally conceivable as it can be caused by adaptation to an environmental level. This pertains also to ionizing radiation. Nonetheless, the LNT has been used as a basis of the safety standards. The LNT is based on the idea that cells are randomly altered by ionizing radiation events causing mutations: the more particle tracks go through cell nuclei, the higher would be the risk of malignant transformation [28,96]. This concept does not take into account that DNA damage and repair are permanent processes in dynamic equilibrium. Natural background radiation has been decreasing over the time of life existence on the Earth among others due to the decay of radionuclides and formation of the ozone layer. It was reported, for example, that the radiation dose from internal ^{40}K has decreased by a factor of about eight over the past 4 billion years. Radiation exposure from geologic materials has decreased from about 1.6 mGy/year to 0.66 mGy/year over the same period; while exposure to an organism with a potassium concentration of 250 mmol/liter has decreased from about 5.5 to about 0.70 mGy/year. Accordingly, background radiation exposure from these two sources has dropped from about 7.0 to 1.35 mGy/year during the time of the life existence [97]. The conservative nature of mutation repair mechanisms in modern organisms suggest that these mechanisms may have evolved in the distant past and that organisms may retain some of the capability of efficiently repairing damage from higher radiation levels than exist at present [97]. By analogy with other environmental factors, there may be adaptation [14] i.e. an optimal impact level. The natural selection is a slow process; therefore, current adaptation would correspond to some average from the past when the natural radiation background was higher. Exposure levels corresponding to the maximal adaptation may be expected to act as hormetic stimuli.

Hormesis cannot be used in the radiation safety regulations without unequivocal experimental evidence from large-scale animal experiments. Current evidence in favor of hormesis is, however, considerable [87,91,98,99], which means that a part of experimental data is at variance with epidemiological studies cited above. Admittedly, some animal experiments did not support hormesis e.g. showing no life lengthening of mice continuously exposed to low dose radiation [100]. Other researchers did report life lengthening of mice in low dose rate experiments [e.g., 101]. In small animals, minimal doses associated with carcinogenesis are generally higher than those in the Chernobyl and Ural cohorts, being in the range of hundreds or thousands of mGy [7,102-104]. Hormesis is assumed to work on molecular (stimulating DNA repair) and cellular levels. Eukaryotic cells display cell-type-specific adaptive responses enhancing their radioresistance after a low-dose priming irradiation [3,4,105-107]; details of these mechanisms are outside the scope of this review.

Although the value of experiments for extrapolation to humans is controversial [108], for such a universal mechanism as DNA repair the extrapolation would probably be permissible if various animal species are used. Further work can quantify sensitivity of different species enabling more precise extrapolations to humans [109]. Outstanding data e.g. 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" [96], 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 [110] should be verified by experiments. The same applies to the data on the excess radiation-related cancer deaths related to the doses below the occupational limits [111]. In any case, the hormesis concept should be applied cautiously as hormetic stimuli may act without threshold on pre-damaged or atrophic tissues and/or synergistically with other noxious agents including carcinogens [112-115].

The benefit from a moderate exposure to ionizing radiation was demonstrated epidemiologically among survivors of atomic explosions [116], although these data might be not free from biases e.g. due to a better medical surveillance of the survivors. Occupational exposures were repeatedly shown to be associated with better health [3,4], which, however, can at least in part be explained by the healthy worker effect [4]. The cancer mortality was found to be lower in high-elevation areas, where the natural radiation background is increased due to the higher intensity of cosmic rays [3,117]. However, better medical surveillance, increasing attention of people to their health, and biased research may cause one day enhanced registered cancer incidence in the areas with high natural radiation background, which would prove no cause-effect relationship. Certainly, knowledge on hormesis is incomplete. The most promising way to reliable data on the dose-effect relationships for low doses would be large-scale experiments. Note that animal experiments are ethically inadmissible without integrity of all participants of the research.

Discussing the exclusion of hormesis from the risk assessment, Zbigniew Jaworowski wrote: "It seems to me that the driving force was (and still is) ... the antinuclear power lobby, concerned that demonstration of the beneficial effects of small radiation doses, and thus of the existence of a threshold for harmful effects occurring near this dose region, will destroy their raison d'être" [2]. The raison d'être should probably be replaced by cui bono (for whose benefit?): strangulation of the nuclear power in the wake of Chernobyl contributed to higher prices for fossil fuels. The motives for overestimation of Chernobyl consequences in the former SU were discussed above and in [20,31]. In many countries, among the motives were antinuclear sentiments supported by the Green movement, well in agreement with the interests of fossil fuel producers. Today, however, there are no alternatives to the nuclear power: in the long run, nonrenewable fossil fuels will become increasingly expensive, contributing to the uncontrolled population growth in oil-producing countries and poverty in the rest of the world.

CONCLUSION

Summarizing the above and previously published arguments [118,119], the harm caused by anthropogenic radiation would tend to zero with a dose rate decreasing down to a wide range level of the natural background. Within a certain range, the dose-effect relationship would be inverse in accordance with hormesis. A corresponding graph, plotted on the basis of experimental data, with a sagging of the dose-effect curve below the background cancer risk in the range 0.1-700 mGy, is depicted in [103]. However, hormesis cannot be used in radiation safety regulations without consistent experimental evidence obtained in large-scale experiments using different animal species, under controlled conditions to exclude biases and conflicts of interest. Low doses should be analyzed separately from higher doses [120,121], which would prevent unfounded LNT-based extrapolations such as prediction of millions of deaths from nuclear accidents, e.g. [122].

The current radiation safety standards are exceedingly restrictive and should be revised to become more realistic and workable. Elevation of the limits must be accompanied by measures guaranteeing their strict observance, and by openness of dosimetric data. We found no contraindications to an elevation of the total equivalent effective doses to individual members of the public up to 5 mSv/year. The dose rate would remain within the range of the natural background radiation. Considering inevitable global spread of the nuclear power to meet the energy needs of the mankind [41,123], elevation of the limits for professional exposures should be considered as well. The revision must be based on reliable experiments and accompanied by measures guaranteeing observance. Strictly observed realistic safety standards are more helpful for the public health than excessive restrictions that would be disregarded.

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