The Overestimation of Medical Consequences of Low-Dose Exposure to Ionizing Radiation, 2nd Edition

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INTRODUCTION

For many years we have tried to demonstrate that certain scientists tend to overestimate medical consequences of low-dose exposure to ionizing radiation (Jargin 2007, 2018), in accordance with the interests of companies and governments selling petroleum and natural gas. The overestimation contributes to the strangulation of nuclear energy, supporting appeals to dismantle nuclear power plants (NPPs). The use of atomic energy for electricity production is on the agenda today due to increasing energy needs of the humankind. Of note, health risks and environmental damage are maximal for coal and oil, lower for natural gas and much lower for atomic energy - the cleanest, safest and practically inexhaustible energy resource (Jaworowski 2010, Markandya and Wilkinson 2007).

The Chernobyl accident has been exploited to strangle the worldwide development of atomic energy; but it was necessary for a certain period: nuclear technologies should have been prevented from spreading to overpopulated countries governed by unstable regimes, swarming with actual and potential terrorists. Today, there are no thinkable alternatives to nuclear energy: non-renewable fossil fuels will become more expensive, contributing to excessive population growth in fossil fuel producing countries and poverty elsewhere. The worldwide introduction of the nuclear power is a necessity, but it will be possible only after a concentration of authority in a powerful international executive. It will enable construction of nuclear power plants in optimally suitable places, regardless of national borders, considering all socio-political, geological and other conditions. Moreover, durable peace is needed because nuclear facilities are potential targets.

The overpopulation leads to poverty, overcrowding, pollution of air and water. Ecological damage and depletion of non-renewable resources are proportional to the population size. Humankind can choose to check population growth by reducing the birth rate - instead of raising the death rate by means of wars, famine, and epidemics, as it was usual throughout the history. The ongoing industrial development of the previously underdeveloped countries is precarious because environment protection measures are observed less rigorously there and, most importantly, because of the large scale of this process, proportional to the population size. The exhaustion of fossil fuel resources and contamination of the environment provide another argument in favour of the nuclear energy. Producers of the fossil fuels are obviously interested in overestimation of biological effects of low-dose low-rate exposures to ionizing radiation to strangle the development of nuclear energy.

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CHAPTER 1

LOW DOSES, RADIATION SAFETY AND HORMESIS

Summary

Hormesis describes processes, where cells or organisms exhibit a biphasic response to increasing doses of a substance or condition; typically, low-dose exposures induce a beneficial response, while higher doses cause toxicity (Mattson and Calabrese 2010). Hormesis can be generally explained by evolutionary adaptation to the current level of a factor present in the natural environment or to some average from the past. This pertains also to ionizing radiation as the natural background has been decreasing during the time of life existence on the Earth. The DNA damage and repair are normally in a dynamic balance. The conservative nature of the DNA repair suggests that cells may have retained some capability to repair the damage from higher radiation levels than those existing today. According to this concept, the harm caused by a radioactive contamination would tend to zero with a dose rate tending to a wide range level of the natural radiation background. Existing evidence in favour of hormesis is substantial, experimental data being partly at variance with epidemiological studies. Potential bias, systematic errors and motives to exaggerate risks from the low-dose low-rate ionizing radiation are discussed here. In conclusion, current radiation safety norms are exceedingly restrictive and should be revised on the basis of scientific evidence. The elevation of limits must be accompanied by measures guaranteeing their observance.

Background

This chapter summarizes preceding articles on medical and biological effects of low-dose radiation coming to the conclusion that current radiation safety norms are exceedingly restrictive and should be revised to become more realistic and workable. The main goal is to emphasize the bias widespread in the epidemiological research on responses to radiation releases, which contributed to policy implementations perpetuating the use of the linear no-threshold theory (LNT) as the basis of radiation safety regulations. Current radiation safety norms are based on the LNT: extrapolations of a dose-response relationship down to low doses, where such relationships are unproven and can be reversed within a certain dose range. The evidence in favour of hormesis is considerable (Baldwin and Grantham 2015, Doss 2013, Scott 2008, Shibamoto and Nakamura 2018, Xu 2022). According to the regulations, an equivalent effective dose to individual members of the public should not exceed 1 mSv/year. The dose limits for exposed workers are 100 mSv in a consecutive 5-year period, with a maximum of 50 mSv in any single year. For comparison, worldwide annual exposures to natural radiation sources are generally expected to be in the range 1-10 mSv; the estimated global average being 2.4 mSv (UNSCEAR 2000).

Some assessments of the data on survivors of atomic explosions in Hiroshima and Nagasaki (A-bomb survivors) do not support the LNT and are consistent with hormesis (Doss 2016). For solid cancers and leukaemia, significant dose-response relationships were found among the A-bomb survivors exposed to ≤500 mSv but not ≤ 200 mSv (Little and Muirhead 1996, 1998, Heidenreich et al. 1997). The artificial neural network methods, applied to the data on A-bomb survivors, indicated the presence of thresholds around 200 mSv varying with organs (Sasaki et al. 2014, Sacks et al. 2016). The value 200 mSv has been mentioned in some reviews as a level, below which the cancer risk elevation is unproven (Heidenreich et al. 1997, González 2004). According to UNSCEAR (2010), a significant risk increase was observed at doses ≥100-200 mGy. This latter figure may be an underestimation due to bias in the epidemiological research.

The author agrees with Mark P. Little (2016) that potentially biased studies and those of questionable reliability "should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here (Azizova et al. 2015a, Ivanov et al. 2006, Kashcheev et al. 2016, Moseeva et al. 2014)." This recommendation may be extended onto some other studies discussed in this book. For example, bias in data analyses from Mayak Production Association (MPA) has been caused by the contrast between the medical surveillance of nuclear workers compared with the rest of the population. About 41% of the MPA cohort migrated away by the end of 2005 and information on the cause of death for them were derived from various regions. The largest number of deaths in the years 1998-2010 happened not in Ozyorsk (where the Mayak facility is located) but elsewhere in Russia (Little et al. 2021). Moreover, the UNSCEAR evaluation of the low-dose radiation data seems to be prone to bias e.g. the overestimation of Chernobyl consequences; more details are in the next chapters. Today, when the literature is so abundant, research quality and potential conflicts of interest must be taken into account defining inclusion criteria of studies into reviews.

Chernobyl accident

Using the LNT, the Chernobyl accident (hereafter accident) was predicted to result in a considerable increase in radiation-induced cancer. In fact, there has been no cancer increase proven to be a consequence of the radiation exposure except for the thyroid carcinoma in people exposed at a young age (UNSCEAR 2008). Although the appearance of radiogenic thyroid cancers after the accident cannot be excluded, their number has been largely overestimated due to the following mechanisms. Prior to the accident, the registered incidence of paediatric thyroid malignancy was lower in the former Soviet Union (SU) compared to other developed countries apparently due to differences in diagnostic quality and coverage of the population by medical examinations (Lushnikov et al. 2006, Jargin 2009, 2011). Intensive screening in the contaminated territories after the accident found not only small tumours but also advanced neglected ones. There was a pressure to be registered as Chernobyl victims to get access to benefits and health care provisions (Bay and Oughton 2005). It can be reasonably assumed that some patients from non-contaminated areas were registered as Chernobyl victims on the basis of wrong information. There was no regular screening outside the contaminated areas, so that such cases must have been averagely more advanced. These phenomena were confirmed by the fact that the "first wave" thyroid cancers after the accident tended to be larger and less differentiated than those diagnosed after 10 years and later (Williams et al. 2004, Nikiforov and Gnepp 1994), when the pool of neglected cancers was gradually exhausted by the screening while the registration reliability was improved. Admixture of old neglected cases explains the fact that Chernobyl-associated thyroid cancers often behaved in an aggressive fashion. The following citation is illustrative: "The tumours 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" (Romanenko et al. 2007). There is an explanation: averagely earlier cancer detection in Western Europe.

The misclassification of neglected advanced cases as aggressive radiogenic cancers gave rise to the concept that the tumours supposed to be radiogenic, at least those from the "first wave" following the accident, were more aggressive than sporadic ones (Fridman et al. 2015, Iakovleva et al. 2008, Williams et al. 2004, Zablotska et al. 2015). This had consequences for the practice: although approaches varied, the surgical treatment of supposedly radiogenic cases was recommended to be "more radical" (Rumiantsev 2009). After 1998-1999, the surgery in some institutions switched to a more aggressive approach (Iakovleva et al. 2008, Demidchik et al. 2006), discussed below.

The following was recommended for Chernobyl-related paediatric thyroid carcinoma: "Radical thyroid surgery including total thyroidectomy combined with neck dissection followed by radioiodine ablation" (Demidchik et al. 2007) or external radiotherapy (40 Gy) (Mamchich and Pogorelov 1992). Some experts regarded subtotal thyroidectomy to be "oncologically not justified" and advocated total thyroidectomy with prophylactic neck dissection (Demidchik et al. 1996, Demidchik and Kontratovich 2003, Lushnikov et al. 2003, Rumiantsev 2009). Less extensive resections were regarded to be "only acceptable in exceptional cases of very small solitary intrathyroidal carcinomas without evidence of neck lymph node involvement on surgical revision" (Demidchik et al. 2006).

It was written in an instructive publication that bilateral neck dissection must be performed in all thyroid cancer cases independently of the tumour size, histology and lymph node status (Demidchik and Shelkovich 2016). This approach is at variance with a more conservative treatment of papillary thyroid carcinoma applied also in the settings of a nuclear accident (Sugitani 2017). The sources (La Quaglia et al. 1988, Segal et al. 1997) were misquoted by Demidchik and Kontratovich (2003) advocating total thyroidectomy with bilateral neck dissection for all cases of paediatric thyroid cancer. The sources (Arici et al. 2002, Danese et al. 1997, Giuffrida et al. 2002) were cited in support of the statement: "The most prevailing opinion calls for total thyroidectomy regardless of tumour size and histopathology" (Demidchik et al. 2006). In fact, subtotal thyroidectomy was applied or recommended in these studies, in some of them along with total thyroidectomy (Arici et al. 2002, Danese et al. 1997, Giuffrida et al. 2002).

Many thyroid patients were young females potentially concerned with the cosmetic aspect. Moreover, the total thyroidectomy with neck dissection is associated with complications such as hypoparathyroidism and recurrent laryngeal nerve palsy. In this connection, the high suicide rate noticed among patients with Chernobyl-related thyroid cancer (Contis and Foley 2015, Fridman et al. 2014) might be explained as a consequence of decreased life quality after the excessively radical surgery. Admittedly, other experts pointed out that “radiation history does not appear to significantly affect long-term treatment results, provided an appropriate, not principally different from that for sporadic thyroid cancer treatment and follow-up had been performed” (Saenko et al. 2017).

Mechanisms of false-positivity have been discussed previously (Jargin 2009, 2011); among others, the misinterpretation of nuclear pleomorphism as a malignancy criterion of thyroid nodules occurred in the former SU of the 1990s. If a thyroid nodule is found by the screening, a fine-needle aspiration is usually performed. The thyroid cytology is accompanied by some percentage of inconclusive results, when histological examination is indicated. In the former SU of the 1990s, this percentage was relatively high due to the insufficient experience with paediatric material, suboptimal quality of specimens and shortage of modern literature. The surgical specimen is sent to a pathologist, who may be sometimes prone, after in toto removal of the nodule, to confirm malignancy even in case of uncertainty. The fine-needle aspiration cytology was introduced into practice later than ultrasonography, which contributed to the overdiagnosis of malignancy especially during the 1990s.

The following citations from a Russian-language professional publication are illustrative: “Practically all nodular thyroid lesions, independently of their size, were regarded at that time in children as potentially malignant tumours, requiring an urgent surgical operation” or “Aggressiveness of surgeons contributed to the shortening of the minimal latency period” (Lushnikov et al. 2006). Note that the term “latency period” is unsuitable if the cause-effect relationship is unproven; in the above context the latency should be understood as the time between the radiation exposure and surgery.

Radio- and cancerophobia contributed to the overdiagnosis of cancer. The number of detected nodules was additionally increased due to the iodine deficiency in the contaminated territories with the enhanced incidence of goitre and nodular lesions found by the screening providing more opportunities for the false-positive diagnoses. Frozen sections were sometimes used, which is suboptimal for histological diagnostics of thyroid nodules.

The facts discussed in this section seem to be camouflaged in the UNSCEAR reports. As mentioned above, the registered incidence of thyroid cancer in children and adolescents prior to the accident had been lower in the former SU than in other developed countries i.e. there was a pool of neglected cases. This is not clearly perceptible from UNSCEAR reports because the increased incidence 4-5 years after the accident was compared not with the pre-accident data but with those from the first years after the accident, when the registered incidence already started to increase (UNSCEAR 2008). Health checkups were started in the contaminated areas of Russia in 1986, while the risk of TC in children was known. Similar actions were conducted in Belarus. In Ukraine, the local cancer registry was established in 1987 in the radio-contaminated areas, which probably contributed to a better cancer detection and hence to the increase in the registered incidence.

Another example: the number of registered thyroid cancers in Ukraine prior to the accident as per UNSCEAR (2008) is greater than corresponding data published by IARC (Parkin et al. 1999): 39 cases for the period 1982-1985 vs. 25 cases for 1981-1985. These higher figures were published with references to "communications to the UNSCEAR Secretariat" (UNSCEAR 2008) and the paper by Tronko et al. (2002). However, this latter article could be found neither in online databases, nor on the website of the International Journal of Radiation Medicine (edited in Kiev), nor in libraries. According to the personal communication from the UNSCEAR Secretariat (22 October 2013), the UNSCEAR was provided with hard copies of this paper. Apparently, the paper by Tronko et al. (2002) has never been accessible to the international scientific community. The biased attitude within UNSCEAR may be conveyed by certain experts pushing through a prescribed notion.

Radioactive contamination in the Urals

Consequences of the radiocontamination in the Urals were summarily more significant than those after the Chernobyl disaster. The difference between contaminations in the Urals and Chernobyl areas is that the latter was due to an accident, but the former - a radiocontamination lasting over 70 years with several accidents in between. Apart from professional exposures, the disposal of radioactive substances into the river Techa, the 1957 Kyshtym accident and dispersion by winds from the lake Karachai in 1967, led to exposures of residents (Mould 2000). The East Urals Radioactive Trace (EURT) cohort included people exposed after the

Kyshtym accident. Large discharges of radioactive materials into the Techa river in the Southern Urals occurred between the years 1949 and 1956. The most exposed individuals were residents of villages along the river.

At earlier times (until 2005-2010), Russian researchers found no cancer increase in exposed populations of the Urals with average exposures below 0.5 Sv or among employees of the in general (Akleyev et al. 2001, 2004, Buldakov et al. 1990). The absolute risk of leukaemia per 1 Gy and 10000 man-years was found to be 3.5-fold smaller in the Techa river cohort (TRC) than in the life span study (LSS) of atomic bomb survivors in Japan. This was reasonably explained by a higher efficiency of the acute exposure compared to chronic and fractionated ones. Later on, the same experts reported comparable or even higher risks of cancer and other diseases in the cohorts from the Urals and in LSS (Akleev and Krestinina 2010, Krestinina et al. 2013a, Ostroumova et al. 2008).

An unofficial directive could have been behind this metamorphosis; potential motives are discussed in Chapter 13: financing, publication pressure and, most importantly, exaggeration of health risks from low-dose radiation in order to strangle atomic energy. Moreover, increased risks of non-malignant diseases - cardiovascular, respiratory, digestive - have been reported by the same and other scientists in the Urals and Chernobyl cohorts (Azizova et al. 2010, 2011, 2013, 2014a-c, 2015a,b, Ivanov et al. 2006, Kashcheev et al. 2016, Krestinina et al. 2013b, Moseeva et al. 2012, 2014, Yablokov 2009). For example, the incidence of cerebrovascular disease was significantly elevated among Mayak workers with a total external dose ≥0.1 Gy protracted over years (Simonetto et al. 2015). This is indicative of a bias, in particular, of dose-dependent self-selection, noticed also by other researchers in radiation-exposed cohorts (McGeoghegan et al. 2008, Zablotska et al. 2013). It can be reasonably assumed that individuals with higher dose estimates were on average more interested in medical examinations. In the health care system of the former SU, thoroughness of medical examination has often depended on a patient’s initiative. According to a personal communication with TRC expert Ludmila Krestinina (2014), exposed residents were preoccupied with monetary compensations. Most probably, individuals with higher dose estimates or those residing in more contaminated areas were more insistent at examinations, visited medical institutions more frequently, being at the same time given more attention. As a result of the screening effect, observation bias, dose-dependent selection and self-selection, diagnostics would be a priori more efficient in patients with higher doses, especially of diseases without local symptoms such as leukaemia; therefore, epidemiological studies alone do not prove causality for low doses.

Along the same lines, an earlier study found a reduction of cancer mortality in the EURT populace (Kostyuchenko and Krestinina 1994). A review confirmed approximately the same level of both cancer-related and all-cause mortality in the EURT vs. control (Akleev et al. 2004). In a later report on the same cohort, the authors avoided direct comparisons but fitted the figures into a linear model. The configurations of dose-response curves depicted in this paper seem to be inconclusive but nevertheless an elevated cancer risk in the EURT population was claimed (Akleyev et al. 2017). In earlier reports, an incidence elevation of cardio- and cerebrovascular diseases in MPA, TRC and EURT populations was not accompanied by a mortality increase (Azizova 2012, 2015b, Soloviev and Krasnyuk 2018). This can be reasonably explained by a greater diagnostic effectiveness in people receiving higher doses, leading to detection of mild and questionable cases. A similar tendency for cancer was noticed among Chernobyl emergency workers (Kashcheev et al. 2015), commented previously (Jargin 2015). The mechanism was analogous: Chernobyl cleanup workers underwent repeated medical checkups. As a result, lesions were efficiently detected including small, dormant cancers and nodules with uncertain malignant potential. The early detection and treatment of diseases contributed to the diminution of mortality. Besides, some differentiated and borderline tumours, statistically filed as cancers, did not lead to death. However, in a recent paper based on the MPA cohort, an increased mortality risk from myocardial ischemia was claimed for the range of 5-50 mGy/year (Azizova et al. 2023). Presumably, some comments, though not cited, have been taken into account. The recent review (Koterov et al. 2023) has apparently been influenced by our comments cited by the same first author (Koterov 2017), commented previously (Jargin 2021), yet trying to shift responsibility for biased information onto foreign scientists: “In most sources, 2005-2021 (publications by M.P. Little with co-workers, and others) reveals an ideological bias towards the effects of low doses of radiation … In selected M.P. Little and co-authors sources for reviews and meta-analyses observed both absurd ERR values per 1 Gy and incorrect recalculations of the risk estimated in the originals at 0.1 Gy” (Koterov et al. 2023). Note that relevant papers co-authored by Prof. Little used the data provided by co-workers from Russia.

Enhanced risks of cardiovascular diseases were claimed for the cohorts from Chernobyl and the Urals, whereas average doses have been compatible with the natural radiation background (NRB). There are many populated areas on the Earth where annual dose rates from NRB are 10-100-fold greater than the worldwide average (2.4 mSv) with no health risks reliably detected (Sacks et al. 2016). The doses have been protracted over many years: studied MPA workers were employed since 1948-1982. Average doses of gamma radiation were around 0.54 Gy in males and 0.44 Gy in females in the MPA research, where the incidence of atherosclerosis in lower limbs correlated with the dose (Azizova et al. 2016a). Average doses in TRC were 34-35 mGy while the follow-up was since the 1950s (Krestinina et al. 2019), so that the dose rates were comparable with the natural background. The authors acknowledged that the risk for doses <0.1 Gy can be lower than that calculated using a linear model (Schonfeld et al. 2013). In particular, such data are unsuitable for computations of the dose and dose rate effectiveness factor (DDREF). Earlier Russian publications pointed out a higher biological efficiency of acute exposures compared to chronic ones (Akleyev et al. 2021); later on the same researchers claimed that the International Commission on Radiological Protection (ICRP) underestimates health risks from chronic exposures, and recommended the use of DDREF = 1.0 (Akleyev et al. 2022). This recommendation is obviously unfounded for the dose rates comparable with those from NRB.

It has been rightly noted in the recent review that “diagnosis (by a physician knowing the patient’s history) could vary with dose” and the “inter-study variation in unmeasured confounders or effect modifiers” (Little et al. 2023). Mild and borderline conditions are probably more often diagnosed in people with higher doses due to averagely more thorough examinations and patients’ attention to their own health. The high frequency of cardiovascular diseases in studied populations from Russia (Little et al. 2021) have been explained by unsubstantiated conclusions in unclear cases both post- and ante-mortem. At least in the former SU, there is a tendency: the lower the diagnostic quality, the higher the fraction of cardiovascular diseases among all causes of death. The same is true also for deceased people not undergoing autopsy, where cardiovascular diseases are often recorded as causes of death in questionable cases (Jargin 2017).

Another recent study based on the MPA cohort analyzed 9469 cases of cerebrovascular diseases including 2078 strokes (Azizova et al. 2022). The following statements seem to be contradictory: “Cerebrovascular diseases incidence was found to be significantly associated with cumulative radiation dose" and "No significant associations of either stroke or its types with cumulative gamma-ray dose of external exposure or alpha-particle dose of internal exposure were found" (Azizova et al. 2022). It can be reasonably expected that with more arterial occlusions and stenoses there would be more strokes. A possible explanation for the discrepancy is the dose-dependent diagnostic quality and a larger screening effect in individuals with higher doses. At that, mild and questionable conditions would be registered more often. On the contrary, strokes are usually diagnosed based on distinct morphological or clinical criteria, overdiagnosis being less probable. Moreover: "The estimates of the cerebrovascular diseases incidence risk significantly decreased with the increasing duration of employment for the entire cohort ($p < 0.001$)" and "In addition, a significant decrease in cerebrovascular diseases incidence risk with increasing attained age was observed in both males and females" (Azizova et al. 2022). The incidence of cerebrovascular diseases is known to increase with age; so that the above quotes are compatible with a protective (hormetic) effect of radiation. Hormesis is mentioned neither in the paper by Azizova et al. (2022) nor in other above-cited articles by the same researchers. In the author's opinion (2023), Azizova et al. (2022) should have discussed harmful cerebrovascular diseases (strokes) and concluded that there was no increase of strokes after low-dose low-rate exposures. This is common knowledge. By including harmless and unreliably diagnosed conditions, they were able to make a sensational conclusion that low doses elevate the frequency of cerebrovascular diseases.

The higher risks of cerebrovascular diseases at higher doses in females than in males (Azizova et al. 2022) agrees with the known tendency that women in Russia care more than men about their health and are generally given more attention by medical personnel. Hence the worldwide highest gender gaps in the life expectancy: countries of the former SU crown the list (World Bank Group 2020). Accordingly, the diagnostics in women must be on average more efficient and reliable than in men. This notion doesn't contradict to the higher relative risk in some low-dose male groups: Tables 1 and 1S in (Azizova et al. 2022). Cerebrovascular diseases are more frequent in men, among others, thanks to alcohol and smoking. Some overdiagnosis of mild conditions may occur just because these conditions are expected. For example, the author encountered descriptions of age- and hypertension-related changes of retinal vessels in a medical record of a middle-aged man after a dispensarization (yearly workplace examination) whereas his eye grounds had not been inspected. As for post mortems, supposedly age-related changes (aortal, coronary, cerebral or basilar atherosclerosis) have been habitually written without sufficient evidence in autopsy reports and death certificates (Jargin 2017). In higher-dose groups the diagnostics would be more reliable resulting in a more pronounced screening effect especially in women but less frequent unsubstantiated recordings especially in men.

Among members of the MPA cohort who received gamma-ray doses more than 0.1 Gy, the incidence of circulatory diseases was found to be higher than in people exposed to lower doses (Azizova et al. 2014a, Simonetto et al. 2015). The excess relative risk (ERR/Gy) of cerebrovascular conditions in MPA employees was claimed to be even higher than among atomic bomb survivors in Japan (Azizova et al. 2014a, 2018a), where dose-dependent selection could have taken place like in other epidemiological studies. Some data assessments of life span study (LSS) of atomic bomb survivors are compatible with hormesis (Doss 2016, Grant et al. 2021, Luckey 2008, Little and Muirhead 1996). For solid cancers, a dose-response association was detected among the survivors who received doses ≤0.5 Sv but not below 0.2 Sv (Heidenreich et al. 1997, Grant et al. 2017, Little and Muirhead 1996, 1998). For example, the data about renal cancer in men indicated hormesis: U-shaped dose-response with negative ERR estimates at low-to-moderate doses, while those in women did not (Grant et al. 2021). The authors noted that these findings could have been observed by chance. A preceding article by the same researchers also showed different shapes of dose response curves for males and females (Grant et al. 2017). When studies based on the same cohort report different dose responses, reliability should be doubted. Other studies found no significant risks for kidney cancer from low doses (Boice et al. 2022, Haylock et al. 2018). Apparently, epidemiological data have too many uncertainties to reliably evaluate hormesis; large-scale animal experiments would be more informative.

Finally, a significantly increased risk of non-melanoma skin cancer was reported in MPA workers exposed to radiation at doses ≥2.0 Sv accumulated over prolonged periods (Azizova et al. 2018a). The Japanese A-bomb survivor non-melanoma skin cancer dataset was consistent with a threshold at about 1.0 Sv of acute exposure (Little and Charles 1997). However, an observation bias seems to be probable in (Azizova et al. 2018a). The workers and some medical personnel knew the individual work histories, from which accumulated doses could be approximately inferred, potentially influencing the diagnostic thoroughness. The skin doses were unknown in (Azizova et al. 2018a). The subjects were exposed mainly to gamma-rays having a relatively high penetration distance in tissues, so that the absorbed doses within the skin must have been relatively low. Accordingly, the premalignant skin lesions and actinic keratoses were "very rare" in members of the cohort by Azizova et al. (2018a). It is known that radiation exposure is associated with premalignant epidermal changes; in particular, actinic keratosis may be caused by X-ray and radiotherapy. Therefore, a cause-effect relationship between radiation and skin tumors in the study by Azizova et al. (2018a) is improbable.

Considering the above, the following statements by the same scientists may create biased impression. The statements cited below, not specifying dose levels, are inapplicable to the cohorts from the Urals and to low radiation doses in general, being suggestive of bias. Here follow the examples:

> "It was shown that ionizing radiation is one of the promoters of the development of atherosclerosis" (Rybkina and Azizova 2016).

> "It is concluded that this study provides evidence for an association of lower extremity arterial disease incidence with dose from external gamma-rays" (Azizova et al. 2016a).

> "This study provides strong evidence of ischemic heart disease incidence and mortality association with external gamma-ray exposure and some evidence of ischemic heart disease incidence and mortality association with internal alpha-radiation exposure" (Azizova 2015a).

> "A significant increasing trend in circulatory diseases mortality with increasing dose from internal alpha-radiation to the liver was observed" (Azizova 2015c).

> "Significant associations were observed between doses from external gamma-rays and ischemic heart disease and cerebrovascular disease incidence and also between internal doses from alpha-radiation and ischemic heart disease mortality and cerebrovascular disease incidence" (Moseeva et al. 2014).

> "Findings are that aortal atherosclerosis prevalence was higher in males and females underwent external gamma-irradiation of total dose over 0.5 Gy, in males and females underwent internal alpha-irradiation from incorporated plutonium of total absorbed radiation dose in liver over 0.025 Gy" (Azivova et al. 2011).

> "There was a significantly increasing trend (ERR/Gy) of ischemic heart disease mortality with the total absorbed dose to liver from internal alpha-radiation due to incorporated plutonium" (Azizova et al. 2012).

> "The incidence data point to higher risk estimates (in MPA workers) compared to those from the Japanese A-bomb survivors" (Moseeva et al. 2012).

> "The categorical analyses showed that cerebrovascular disease incidence was significantly higher among workers with total absorbed external gamma-ray doses greater than 0.1 Gy compared to those exposed to lower doses and that cerebrovascular disease 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" (Azizova 2014a).

The risk estimates by Tamara Azizova et al. (2011) were found to be significantly higher than those in other studies (Ruehm et al. 2020). Among members of the MPA cohort who received gamma-ray doses ≥0.1 Gy, the incidence of circulatory diseases was found to be greater than in people exposed to lower doses (Azizova 2014a, Simonetto 2015). Cause-effect relationships are improbable at such a low dose level, considering dose comparisons quoted below and elsewhere in this book. The UNSCEAR (2006) could not reach a final conclusion concerning causality between exposures ≤1-2 Gy and cardiovascular diseases. Apparently, the level 1-2 Gy is an underestimation due to the screening effect, selection and other bias in epidemiological research. Political and economical interests sometimes overweigh scientific objectivity, which is perceivable from certain documents issued by highly esteemed international organizations. As mentioned above, Chernobyl accident has been exploited to strangulate worldwide development of atomic industry (Jaworowski 2010).

Dose levels associated with cardiac derangements in experimental animals and in humans after radiotherapy have been much greater than average values in Chernobyl and Urals populations (Authors on behalf of ICRP et al. 2012, Boerma et al. 2016, Puukila et al. 2017, Schultz-Hector 1992). Results of animal experiments are generally compatible with hormesis, i.e. favorable effect within a certain low-dose range, with possible exception of genetically modified cancer-prone animals. In some experimental and epidemiological studies, low doses turned out to be protective against cardiovascular diseases (Authors on behalf of ICRP et al. 2012). As mentioned above, the evidence in favour of hormesis is considerable (Baldwin and Grantham 2015, Doss 2013, Scott 2008, Shibamoto and Nakamura 2018, Xu 2022). In humans after radiotherapy, myocardial fibrosis developed at the doses above 30 Gy. An increased risk of coronary heart disease after radiotherapy was noted after exposures to 7.6-18.4 Gy (Puukila et al. 2017), which is much higher than mean doses in the cohorts from Chernobyl and the Urals. Finally, the recall bias should be mentioned: cancer patients remember facts related to radiation more often than healthy controls (Jorgensen 2013), which may lead to overestimation of doses and dose-effect correlations. It should be stressed in conclusion of this section that unrealistic cardiovascular risks at low-dose exposures call in questions cancer risks reported by the same and other researchers.

Cataracts

Similar tendencies have been noticed in regard to cataracts. Results of the studies reporting correlations between the cumulative radiation dose and cataract incidence among MPA workers (Azizova et al. 2016b, 2018b, Bragin et al. 2017) have been questioned (Tukov and Kashirina 2018, Soloviev and Krasnyuk 2018). The risk in higher dose groups starting from 0.25-0.50 Sv was found to be significantly higher than that in the control group with doses ≤0.25 Sv. The average doses were 0.54±0.061 Gy in males and 0.46±0.01 Gy in females (Azizova et al. 2016b). Dose-effect relationships were claimed for cataracts; but the well-known association of the latter with diabetes mellitus was not confirmed (Azizova et al. 2016b, Bragin et al. 2017, Soloviev and Krasnyuk 2018). This called into question the biological relevance of other results by the same researchers. Supposedly after the criticism (Soloviev and Krasnyuk 2018), the data on diabetes did not reappear in a subsequent article (Azizova et al. 2018c). Remarkably, there were no significant associations of the radiation dose with cataract surgeries (Azizova et al. 2019). The cataracts including mild cases not requiring surgery must have been diagnosed on the average more efficiently in individuals with higher doses due to an increased attention to their own health and/or attention on the part of medics. Earlier publications with participation of the same researchers reported that radiation-induced cataracts developed among MPA workers only after exposures ≥4 Gy (Okladnikova et al. 2007). A review of data from Russia indicated that chronic exposures ≤ 2 Gy were not associated with cataracts (Guskova 1999).

In animal experiments, the doses were higher than the averages in Chernobyl, MPA and Techa river populations. Some experiments in rodents investigated low doses and suggested that genetic factors have an influence on the susceptibility to radiation-induced lens opacities (Authors on behalf of ICRP et al. 2012, McCarron et al. 2022, Worgul et al. 2005). According to the UNSCEAR (1982), a minimum of 3-5 Gy is required to produce significant opacities in animals which are, like humans, not prone to the cataract development. More dose is needed when fractionated. The threshold for chronic exposures was supposed to be in the range 6-14 Gy. Later on, lower thresholds and the no-threshold model have been discussed. Based predominantly on epidemiological studies, the International Commission on Radiological Protection (ICRP) revised preceding recommendations and proposed a threshold of 0.5 Gy for low linear energy transfer radiation. However, some epidemiological studies do not support this lower threshold for cataracts (Authors on behalf of ICRP et al. 2012). “A threshold for highly fractionated or protracted exposure was judged as <0.5 Gy mainly from one paper (Worgul et al. 2007) on cataracts at 12-14 years after exposure in Chernobyl clean-up workers” (Hamada et al. 2020), where a possibility of “underestimation of uncertainties” in dosimetry was acknowledged (Worgul et al. 2007). A threshold for chronic exposures is regarded to be uncertain for lack of evidence (Hamada et al. 2020).

In the study of radiologic technologists, the cumulative occupational exposure was associated with self-reported cataracts, but not with the cataract surgery. “The population of radiologic technologists… is medically literate” (Little et al. 2020). The self-reporting might have been related to a professional awareness associated with a longer work experience and hence with a cumulative dose. A similar pattern of significant excess relative risk (ERR) for cataract morbidity but not surgery has been reported in MPA workers (Azizova 2018c, 2019). This agrees with the concept of a dose-dependent diagnostic efficiency with the recording of mild cases not requiring surgery in persons with higher doses. A significantly increased risk of the cataract surgery as a function of radiation dose has hitherto been reported only in LSS of atomic bomb survivors (Ainsbury et al. 2021), where the effect of acute exposure could have been indeed significant. Of note, the reports by Azizova (2018c, 2019) on “a clear and significant increased ERR/Sv in females compared to males” among MPA workers were designated as “the most striking study observing sex effects relating to radiation induced cataract incidence” (Barnard and Hamada 2023). The sex differences can be attributed to a gender-related attitude in the Russian healthcare. It is well known that middle-aged and elderly men visit health care centers (polyclinics) on the average less frequently than women. Middle-aged men sometimes encounter an unfriendly attitude in governmental medical institutions especially if supposed to be alcoholics. Some of them don’t seek medical help if they have symptoms or chronic disease. Hence the worldwide highest gender gaps in the life expectancy: countries of the former Soviet Union crown the list (World Bank Group 2020). A higher frequency of cataracts in females than in males was found also in a study of the Techa river cohort (Mikryukova and Akleyev 2017).

It should be stressed in conclusion that ionizing radiation is a proven cataractogen; but doses and dose rates associated with risks, i.e. potential thresholds, should be further investigated. The number of studies that provide explicit biological and mechanistic evidence at doses ≤2 Gy is very small (Ainsbury et al. 2016, 2021). Reliable information can be obtained in animal experiments.

Hormesis and radiation safety regulations

Hormesis describes processes, where a cell or organism exhibits a biphasic response to increasing doses of a substance or condition; typically, low-dose exposures induce a beneficial response, while higher doses cause toxicity (Mattson and Calabrese 2010). Among hormetic factors are various substances and chemical elements, vitamins, light, ultraviolet, ionizing radiation and products of water radiolysis, as well as different kinds of stress (Kaludercic et al. 2014, Le Bourg and Rattan 2014). For factors that are present in the natural environment, hormesis can be explained by an adaptation to a current environmental level or some average from the past. This pertains also to ionizing radiation. The LNT is based on the concept that cells are altered by ionizing radiation: the more tracks pass through cell nuclei, the higher would be the risk of malignant transformation. This concept does not take into account that DNA damage and repair are normally in a dynamic equilibrium. The natural background radiation has been decreasing over the time of life existence on the Earth. The conservative nature of the DNA repair suggests that cells may have retained some capability to repair damage from higher radiation levels than those existing today (Karam and Leslie 1999).

The evolutionary adaptation to ionizing radiation was explained by the increased synthesis of DNA repair enzymes, activated endogenous radioprotective mechanisms, achieved e.g. by accumulation of sulfhydryl compounds and antimutagens, as well as an increase of the reserve of off-cycle cells (Burlakova et al. 2016). Eukaryotic cells display an adaptive response that enhances their radio-resistance after a low-dose priming irradiation (Marples and Skov 1996). The repair of DNA damage is enhanced in cells irradiated with a priming dose of 0.25 Gy followed by 2 Gy compared with those irradiated with 2 Gy only (Le et al. 1998). Doses 50-75 mGy significantly enhanced proliferation of cultured cells via activation of signaling pathways (Liang et al. 2011). Furthermore, the bystander effect (a biological response of a cell resulting from an event in a nearby cell) may play a role in radiobiological responses to low dose irradiation. A review by Mitchel (2004) concluded that below 100 mGy, the bystander effect reduced rather than increased the risk of radiation-induced damage and hence of genetic instability. Details of these mechanisms are beyond the scope of this book. Results of animal experiments (apart from genetically modified animals) are generally compatible with hormesis. Among others, there is evidence in favour of hormetic effects of low-dose radiation such as activation of DNA repair and apoptosis, suppression of inflammation and protection from inflammatory diseases, stimulation of anticancer and other immunity. There is experimental evidence that low-dose exposure slows ageing and prolongs life (Scott 2014, Caratero et al. 1998).

In animals, doses associated with carcinogenesis have been higher than those in the Chernobyl and EURT cohorts, amounting to hundreds or thousands mGy (UNSCEAR 1986, 2000, Mitchel 2009, Moskalev 1983). It should be mentioned that radiation hormesis was demonstrated also for synergistic interactions. For example, residential radon and some professional exposures may protect against lung cancer in smokers; in the Mayak facility cohort, radiation hormesis apparently protected not only against spontaneous lung cancer but also against that associated with the cigarette smoking (Sanders and Scott 2006). In vitro, eukaryotic cells show adaptive responses enhancing their radioresistance after a low-dose priming irradiation (Jolly and Meyer 2009, Klammer et al. 2012, Nenoi et al. 2015, Ojima et al. 2011). For such ancient biological phenomena as hormesis and DNA repair, the data may be generalized across species (Baldwin and Grantham 2015, Calabrese 2015). Further research could quantify radiosensitivity of different animal species thus enabling more precise extrapolations to humans (Higley et al. 2012).

The benefit from a moderate exposure to ionizing radiation was reported in A-bomb survivors (Luckey 2008), although these data might not be free from bias due to a better monitoring of the survivors. Occupational exposures were reported to be associated with better health (Prekeges 2003, Jolly and Meyer 2009), which at least in part can be explained by the healthy worker effect. Cancer mortality was found to be lower in high-elevation areas, where the natural radiation background is enhanced due to a higher intensity of the cosmic radiation (Hart 2010, Prekeges 2003, UNSCEAR 2010). There are many places in the world where the dose rate from natural background radiation is 10-100 times higher than the average e.g. 260 mGy/year in Ramsar, Iran; yet no higher incidence of cancer or other radiation-related diseases has been found in such areas (Sacks et al. 2016). The residents of Mississippi receive ~2 mGy per year from natural radiation, while those living in Colorado receive ~8 mGy per year. Nevertheless, epidemiological studies demonstrated that the cancer rate mortality in Colorado is 30% less than in Mississippi after correcting for confounding factors (Sanders 2017). The screening effect and increasing attention of people to their own health may result one day in an increase of the registered cancer incidence in areas with enhanced radiation background, which would prove no causal relationship. The most promising way to gather reliable information on low dose effects would be large-scale animal experiments. However, the integrity of all participants is needed for that. A mixture of reliable und unreliable studies assessed together remains a problem of reviews and meta-analyses. Large-scale experiments must be inexpensive. It is unnecessary to examine each mouse and perform necropsies (Little 2018, Tran and Little 2017). It would suffice to maintain in equal conditions large murine populations - unexposed and exposed to different dose rates - and to register the average life duration. Such an experiment, being simple and relatively inexpensive, would objectively characterize the dose-response pattern and hormesis.

The tumour risk from dental diagnostic X-ray exposures

Finally a few words about dentistry (Jargin 2022). Dental diagnostic X-rays in oral and maxillofacial care were reported to be associated with an increased risk of meningioma (Claus et al. 2012, Lin et al. 2013) but not of malignant brain tumours (gliomas) (Lin et al. 2013). Malignant gliomas grow relatively rapidly. Meningioma, a benign tumour, grows slowly, it may persist over many years without symptoms, or produce mild transitory pains e.g. trigeminalgia (Niwant et al. 2015, Aiken 1981) sometimes perceived on a conscious or subconscious level as pertaining to teeth, provoking a patient to go to the dentist, hence more dental diagnostic X-rays. Furthermore, meningioma may be associated with epilepsy (Lin et al. 2013). It is known that seizures in meningioma may precede other symptoms. Such patients may undergo diagnostic X-rays within the scope of the examination for epilepsy and, again, go more frequently to a dentist because of injuries to teeth or oral mucosa. Therefore, association between dental X-rays and meningioma can be explained by more frequent visits to dentists. Slow non-invasive growth of a benign tumour over many years is actually an argument against the cause-effect relationship between radiation and meningioma because X-rays with a higher probability would be performed when the tumour had already existed. Potentially carcinogenic doses of ionizing radiation i.e. thresholds were discussed in Chapters 1 and 2. A carcinogenic effect has never been proven for the dose levels associated with routine diagnostic X-rays including the cone beam CT (CBCT) applied in dentistry (Al-Okshi et al. 2015, Mettler et al. 2008). The above considerations pertain also to vestibular schwannoma (VS) reported to be associated with dental x-rays (Han et al. 2012). Remarkably, an enhanced risk of VS was also found in people who started using cell phones before the age of 20 (Han et al. 2012). As discussed previously, there is neither compelling evidence nor theoretic plausibility for the concept that radio-frequency electromagnetic fields are more harmful than infrared radiation, which is ubiquitous and harmless up to the thermal damage (Jargin 2020). The reported association may be caused by selection, self-selection, recall bias etc. The bias must be stronger in case of ionizing radiation than for electromagnetic fields as the general public is informed of carcinogenicity of the former. Among limitations of epidemiological studies 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” (Scott 2008). The matter should be clarified by large-scale animal experiments. All said, the following conclusion by Lin et al. (2013) should be agreed with: “Protection from ionizing radiation is as important as the diagnostic benefit to patients”, among other things, because exposures may be unpredictable and their effects may accumulate. Fortunately, radiation exposures associated with dental x-rays have decreased over the last decades.

Conclusion

Summarizing the above and previously published arguments (Jargin 2009-2018), the harm caused by radioactive contamination would tend to zero with a dose rate tending to a wide range level of the natural radiation background. Within a certain range, the dose-effect relationship may become reversed due to hormesis. A graph, plotted on the basis of experimental data, with a sagging of the dose-effect curve below the background cancer risk within the range 0.1-700 mGy, was presented in the review by Mitchel (2009). Low doses should be analysed separately from higher doses (Rozhdestvenskii 2008, 2011) to prevent unfounded LNT-based prognostications e.g. of millions of victims from nuclear accidents (Bertell 2006).

With regard to radiation safety regulations, a new approach is needed - to determine the threshold dose using large-scale animal experiments and establish regulations to ensure that doses are kept well below the threshold level (Doss 2016). In our opinion, current radiation safety norms are exceedingly restrictive and should be revised to become more realistic and practical. An elevation of limits must be accompanied by measures guaranteeing their observance. No contraindications have been found to an elevation of the total doses to individual members of the public up to 5 mSv/year. The dose rate would thus remain within the range of the natural background. Considering that development of nuclear technologies is needed to meet the global energy needs (Jaworowski 2010), a doubling of limits for professional exposures should be considered as well. Strictly observed realistic safety norms will bring more benefit for the public health than excessive restrictions that might be neglected in conditions of disrespect for laws and regulations. Note that negligence and disregard of written instructions was among the causes of the Chernobyl accident (Beliaev 2006, Kamenev 1995, Mould 2000). The worldwide development of nuclear technologies will be possible only after a concentration of authority in the most developed parts of the world, the science-informed harmonization of global radiation regulatory standards and globalized control of the nuclear industry.

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