Journal of Environmental and Occupational Science
www.jenvos.com
DOI: 10.5455/jeos.20150312010516

Review Article

Focused review of mathematical modeling of radiation-related abnormalities in the Techa River cohort

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Received: February 04, 2015
Accepted: March 12, 2015
Published: March 20, 2015

ABSTRACT

Mathematical models (MM) describe relationships between numerical values. Adequate models can make testable extrapolations. A requirement to a MM is its validity: Once construed, a model and the region of validity should be tested. Here reviewed a series of studies of the Techa River cohort, where MM were claimed to reveal relationships between the dynamics of the hemato and lymphopoiesis and the evolution of radiation dose rate over time. However, MM describe rather than reveal relationships. The use of MM without adequate verification may be conductive to the overestimation of biological effects of the low-dose low-rate ionizing radiation. Possible mechanisms of such overestimation are discussed.

KEY WORDS: Hematopoiesis, ionizing radiation, mathematical model, Techa River

INTRODUCTION

Mathematical models (MM) describe relationships between numerical values. One of the reasons for the modeling is that it helps to formalize ideas and facts known about a system [1]. Adequate MM can make testable predictions as to how a system would evolve under certain conditions [2]. In other words, MM make it possible to bridge gaps where data are missing, i.e., to make extrapolations [3]. MM have reached the highest level in physics; in some fields of biology they have played a smaller role because of the complexity of biological systems [2]. Sophisticated MM has been applied in certain fields of the radiation-related research, for example, the PARTRAC (PARticle TRACks) models [4,5]; in other fields of radiobiology, modeling has taken a softer role. A requirement to a MM is its validity [6]: once construed, a model and the region of validity [7], where it is supposed to be applicable, should be tested by reliable methods. Only thereafter, a model can be used for extrapolations especially in medico-biological sciences, where many quantitative relationships are stochastic. However, prior assumptions can be made in many cases, uniform assumptions probably being most applicable in many scenarios. In the recent article [8], dedicated to the Techa River cohort (TRC), it was stated "modeling studies revealed the relationship between the dynamics of the lymphocytopoietic system in the examined individuals and the variation of dose rate over the considered period of time." Note that MM describe rather than reveal relationships.

"The TRC consisted of over 30,000 people, who were born before the start of the radiation exposure in 1949 and lived along the Techa River [9]." Large discharges of radioactive waste into the river occurred during the years 1949-1956 [10,11]. "Doses due to external irradiation decreased in 1956, when residents of the upper reaches of the river were moved to new locations and the most highly contaminated parts of the flood plain were enclosed" [10]. The collective dose to the most exposed population from 1949 to 1956 was 6200 man Sv, with an average individual effective dose about 300 mSv, ranging from 36 to 1400 mSv (annual average from 4.5 to 175 mSv) [10]. The worldwide annual doses from the natural radiation background are generally expected to be within the range 1-10 mSv but can be higher [10,12]. Hence, a part of the TRC members received doses comparable to those from the natural radiation background. The doses received by the study subjects were not indicated in the articles [8,13].

In the author's opinion, certain quantitative risk estimates in the TRC have been questionable and conductive to exaggeration of the dose-effect relationships [14,15]. Another example of this is as follows. The cohort members have been generally aware of their dose estimates calculated on the basis of the age and residence history. Some of them were preoccupied with monetary compensations, others probably with radiation-related health problems. It can be reasonably assumed that people with higher dose estimates were on average more motivated to visit medical institutions and undergo examinations (a self-selection bias), being at the same time given more attention.

A similar phenomenon of the "dose-dependent participation of self-reported pre-screening cases" was mentioned in a study of the residents of contaminated territories after the chernobyl accident [16]. Detection probability of abnormalities, especially those without focal symptoms such as many hematological disorders, would be higher in people with higher dose estimates. Considering the above, a reason why a significant dose-response relationship for leukemias other than chronic lymphocytic leukemia (CLL), but not for CLL, was found in Krestinina *et al*., and Ivanov *et al*. [17,18] is evident: CLL is often accompanied by lymphadenopathy therefore remaining less frequently undiagnosed in the general population than other leukemias [15,19]. Therefore, screening for CLL would be probably less yielding than for other leukemias.

Another passage which should be commented on: "It is found that the developed model is capable of reproducing the decreased level of blood lymphocyte concentration observed during the period of maximum radiation exposure, the recovery processes in the system observed during the period of decreasing dose rate, as well as the enhanced mitotic activity of bone marrow precursor cells in this hematopoietic lineage observed during the entire period under consideration" (i.e., years 1949-1956, emphasis added) [8]. It is at variance with the known fact that radiation can inhibit mitotic activity [20,21]. The matter should have been clarified by quantification of mitosis (e.g., counting mitotic figures) and cell death (apoptosis) [22] at different time points after the exposure in experiments with relevant radiation doses and dose rates. It was further commented on: "These modeling results imply that the additional increase in cell number caused by enhanced mitotic activity of the bone marrow precursor cells capable of dividing (X_1 cells) does not compensate completely the cell loss induced by radiation damage in the lymphocytopoietic system" [8]. This statement presupposes a simultaneous increase of mitosis and apoptosis rates, which may take place during some period after an exposure. This is however not a matter-of-course: many studies have reported enhanced cell growth, prolongation of cell lifespan, etc., under the impact of low-dose radiation [23]. This latter effect can be regarded as hormetic; it would disappear at higher doses inducing immunosuppression. According to the UNSCEAR 2006 Report, blood counts in humans after an acute whole body irradiation in the range 0.5-1 Gy can be normal or minimally depressed, while acute exposure to 2 Gy induces mild cytopenia with no significant bone marrow damage [23]. The doses 0.5-2 Gy are higher than the average in the TRC; while dose rates in the TRC were incomparably lower. There is evidence, albeit not without controversy that acute exposure to low linear energy transfer radiation is more efficient (at least in regard to mutagenesis and carcinogenesis) [23,24] than protracted or fractionated exposure: The sparing effects of dose protraction have been interpreted as reflecting increased repair of radiation-induced damage [24].

The following statement is from another article by the same researchers: "It is found that the models are capable of reproducing common regularities and peculiarities of the dynamics of systems on hand, including the decreased stationary levels of blood cell concentrations during the period of maximum radiation exposure, the recovery processes during the period of decrease of exposure dose rate, and the prevalence of younger bone marrow granulocytopoietic cells over more mature ones during the entire period [13]." The prevalence of young granulocytopoietic cells in the bone marrow combined with decreased levels of white blood cells are compatible with a maturation arrest that can be observed in myelodysplasia or neoplastic bone marrow conditions, the latter being rare stochastic outcomes especially after low dose exposures. Dysplastic and neoplastic changes can be spontaneous, i.e., unrelated to radiation. Direct radiation damage results in a decrease of stem and progenitor cell fraction resulting in bone marrow hypoplasia [23,25,26]. An increase in immature cells in the bone marrow as an immediate result of a radiation exposure or "during the entire period" of a protracted exposure [13] appears improbable and should have been proven by experiments, and not just postulated on the basis of a MM, which itself needs validation.

In regard to the MM used [8], the following should be commented on. The model does not take into account possible inhibition of mitotic activity of preserved cells, capable of dividing (X_1 cell compartment) under the impact of radiation. Admittedly, in conditions of low doses and dose rates, there can be no appreciable inhibition of mitotic activity. Under such conditions, it is an unproven supposition that the cell groups X_i^d (damaged cells that die within several days) and X_i^{hd} (heavily damaged cells that die within several hours) in the radiosensitive compartments X_i [6] would exist at all, or, in other words, the quantities of damaged cells would significantly increase as a result of the low dose/dose rate exposure. It could be verified by experiments *in vivo* and *in vitro* (cell cultures). Note that many experiments of that kind have applied higher doses [23,27,28] than those received on average by the TRC members.

The model under discussion is based on the "one-target-one-hit theory of cell damage" [8], presuming that the damage rate of radiosensitive cells would be proportional to the dose, which corresponds to the linear no-threshold (LNT) concept. According to this LNT concept, a linear dose-effect correlation proven to some extent at higher doses can be extrapolated down to very low doses. The LNT is corroborated by the following arguments: effects of ionizing radiation are of a stochastic nature; the more high-energy particles or photons hit a cell nucleus, the more DNA damage would occur and the higher the biological response 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; i.e., the response would decrease linearly with decreasing dose [29]." However, the LNT concept does not take into account the natural radiation background and the fact that DNA damage and repair are permanent processes that are normally in a dynamic equilibrium. Given the evolutionary prerequisite of the best fitness, it would be reasonable to assume that living organisms are best-adapted by the natural selection to the background levels of ionizing radiation [30]. This concept is in agreement with experimental and epidemiological evidence in favor of hormesis, i.e., beneficial action of low radiation doses [31-33]. Natural selection is a slow process; therefore,

adaptation to a changing environmental factor would lag behind its current value and correspond to some average from the past, especially for such an ancient mechanism as the DNA repair. Life evolved on earth with a radiation background that was higher than that existing today. Among others, natural background radiation decreased due to the radionuclide decay on the surface and oxygen accumulation in the atmosphere, resulting in the formation of the ozone layer. "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 [34]." The character of a dose-response relationship at the dose levels close to those from the natural radiation background can be predicted on the basis of general considerations. There are various factors influencing (inhibiting) lympho- and hematopoiesis. The lower the level of radioactive contamination, the less would be its contribution compared to the natural radioactive background, and the smaller would by the role of radiation compared to chemical and other exo- and endogenous noxious factors. Therefore, in the author's opinion, the LNT concept is not applicable to radiation doses comparable to those received from the natural background; more details are in [35]. However, the LNT is still the most accepted dose-response concept applied for radiation protection purposes. The generality of hormesis has been questioned [36,37]. There are theoretical considerations against hormesis, e.g., for pre-damaged cells [38] or in case of synergistic effects, when any additional noxious factor would possibly act according to a no-threshold pattern without hormesis. Synergistic or antagonistic effects of different agents need further consideration [39]. The topic of hormesis and LNT is viewed as controversial by many experts; discussion [29,36,39-42].

To verify the MM discussed here, the questions should be answered on the basis of experiments, whether radiation, administered with the doses and dose rates comparable to those received by the TRC members, can cause "enhanced mitotic activity of bone marrow precursor cells capable of dividing" [8] and "prevalence of younger cells over more mature cells of the granulocytic lineage in the bone marrow during the entire period of a protracted exposure" as per Smirnova *et al.* [13]. Moreover, the question should be clarified by experiments, in cell cultures or in vivo, whether the relevant doses and dose rates would cause any significant increase of cell death (apoptosis) compared to a control. In conclusion, the use of insufficiently verified MM based on the LNT concept can lead to overestimation of biological effects of the low-dose low-rate ionizing radiation.

REFERENCES

1. Green MH. Introduction to modeling. J Nutr 1992;122:690-4.
2. Umulis DM, Othmer HG. The importance of geometry in mathematical models of developing systems. Curr Opin Genet Dev 2012;22:547-52.
3. Sible JC, Tyson JJ. Mathematical modeling as a tool for investigating cell cycle control networks. Methods 2007;41:238-47.
4. Alloni D, Campa A, Friedland W, Mariotti L, Ottolenghi A. Track structure, radiation quality and initial radiobiological events: Considerations based on the PARTRAC code experience. Int J Radiat Biol 2012;88:77-86.
5. Friedland W, Kundrát P. Track structure based modelling of chromosome aberrations after photon and alpha-particle irradiation. Mutat Res 2013;756:213-23.
6. Bratus AS, Novozhilov AS, Platonov AP. Dynamic systems and models in biology. Moscow, Russia: Fizmatlit; 2010.
7. Cross M, Moscardini AO. Learning the art of mathematical modeling. Chichester, UK: Ellis Horwood; 1985.
8. Smirnova OA, Akleyev AV, Dimov GP. Modeling analysis of the lymphocytopoiesis dynamics in chronically irradiated residents of Techa riverside villages. Radiat Environ Biophys 2014;53:515-23.
9. Napier BA. Joint U.S./Russian studies of population exposures resulting from nuclear production activities in the southern Urals. Health Phys 2014;106:294-304.
10. UNSCEAR. 2008 Report to the General Assembly. Sources and effects of ionizing radiation. Annex B. Exposures of the public and workers from various sources of radiation. New York, NY, USA: United Nations; 2008.
11. Schonfeld SJ, Krestinina LY, Epifanova S, Degteva MO, Akleyev AV, Preston DL. Solid cancer mortality in the techa river cohort (1950-2007). Radiat Res 2013;179:183-9.
12. UNSCEAR. 2010 Report to the General Assembly. Summary of low-dose radiation effects on health. New York, NY, USA: United Nations; 2010.
13. Smirnova OA, Akleyev AV, Dimov GP. Analysis of hematopoiesis dynamics in residents of Techa riverside villages chronically exposed to nonuniform radiation: Modeling approach. Health Phys 2014;106:445-58.
14. Jargin SV. On the low-dose-radiation exposure in the Techa River Cohort and mortality from circulatory diseases. Radiat Environ Biophys 2013;52:419-20.
15. Jargin SV. Leukemia and cardiovascular diseases in the Techa river cohort: New interpretation required. J Environ Occup Sci 2014;3:63-4.
16. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, *et al.* Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. Br J Cancer 2011;104:181-7.
17. Krestinina L, Preston DL, Davis FG, Epifanova S, Ostroumova E, Ron E, *et al.* Leukemia incidence among people exposed to chronic radiation from the contaminated Techa River, 1953-2005. Radiat Environ Biophys 2010;49:195-201.
18. Ivanov VK, Tsyb AF, Khait SE, Kashcheev VV, Chekin SY, Maksioutov MA, *et al.* Leukemia incidence in the Russian cohort of Chernobyl emergency workers. Radiat Environ Biophys 2012;51:143-9.
19. Jargin SV. On the radiation-leukemia dose-response relationship among recovery workers after the chernobyl accident. Dose Response 2014;12:162-5.
20. Selzer E, Hebar A. Basic principles of molecular effects of irradiation. Wien Med Wochenschr 2012;162:47-54.
21. Deckbar D, Jeggo PA, Löbrich M. Understanding the limitations of radiation-induced cell cycle checkpoints. Crit Rev Biochem Mol Biol 2011;46:271-83.
22. Vignon C, Debeissat C, Georget MT, Bouscary D, Gyan E, Rosset P, *et al.* Flow cytometric quantification of all phases of the cell cycle and apoptosis in a two-color fluorescence plot. PLoS One 2013;8:e68425.
23. UNSCEAR. 2006 Report to the General Assembly. Effects of ionizing radiation. Annex A. Epidemiological studies of radiation and cancer. Annex D: Effects of ionizing radiation on the immune system. New York, NY, USA: United Nations; 2006.
24. UNSCEAR. 1993 Report to the General Assembly. Sources and effects of ionizing radiation. Annex F. Influence of dose and dose rate on stochastic effects of radiation. New York, NY, USA: United Nations; 1993.
25. Farhi DC, Chai CC, Edelman AS, Parveen T, Vo TT. Pathology of Bone Marrow and Blood Cells. Philadelphia: Lippincott Williams & Wilkins; 2004.
26. Young NS. Current concepts in the pathophysiology and treatment of aplastic anemia. Hematology Am Soc Hematol Educ Program 2013;2013:76-81.
27. Dainiak N. Hematologic consequences of exposure to ionizing radiation. Exp Hematol 2002;30:513-28.
28. Schofield R. Assessment of cytotoxic injury to bone marrow. Br J Cancer Suppl 1986;7:115-25.
29. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, *et al.* Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. Proc Natl Acad Sci U S A 2003;100:13761-6.

30. Johansson L. Hormesis, an update of the present position. Eur J Nucl Med Mol Imaging 2003;30:921-33.
31. Mitchel RE. The dose window for radiation-induced protective adaptive responses. Dose Response 2009;8:192-208.
32. Calabrese EJ, Baldwin LA. Radiation hormesis: The demise of a legitimate hypothesis. Hum Exp Toxicol 2000;19:76-84.
33. Jaworowski Z. Radiation hormesis – A remedy for fear. Hum Exp Toxicol 2010;29:263-70.
34. Karam PA, Leslie SA. Calculations of background beta-gamma radiation dose through geologic time. Health Phys 1999;77:662-7.
35. Jargin SV. On the genetic effects of low-dose radiation. J Environ Occup Sci 2014;3:199-203.
36. Ulsh BA. The new radiobiology: Returning to our roots. Dose Response 2012;10:593-609.
37. Thayer KA, Melnick R, Burns K, Davis D, Huff J. Fundamental flaws of hormesis for public health decisions. Environ Health Perspect 2005;113:1271-6.
38. Jargin SV. Hormesis and homeopathy: The artificial twins. J Intercult Ethnopharmacol 2015;4:74-7.
39. Mothersill C, Seymour C. Implications for human and environmental health of low doses of ionising radiation. J Environ Radioact 2014;133:5-9.
40. Rose KS. Lower limits of radiosensitivity in organisms, excluding man. J Environ Radioact 1991;15:113-33.
41. Tubiana M, Aurengo A, Averbeck D, Masse R. Recent reports on the effect of low doses of ionizing radiation and its dose-effect relationship. Radiat Environ Biophys 2006;44:245-51.
42. Breckow J. Linear-no-threshold is a radiation-protection standard rather than a mechanistic effect model. Radiat Environ Biophys 2006;44:257-60.

Source of Support: Nil, Conflict of Interest: None declared.