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Critiques Of The Current Radiation Protection System: Short Review of Research Fields Recommended By ICRP

BOR, Doğan [1]

[1] *Ankara University Retired Faculty Member.*

Correspondence:
Doğan BOR Ankara University Retired Faculty Member.
doganbor@gmail.com

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ABSTRACT

The cancer risk caused by low-level radiation is one of the most frequently encountered questions by medical physicists. When all the factors affecting cancer formation are considered, it is quite difficult to calculate the effect of radiation alone. In addition, there is no theory explaining the effects of radiation on health. Due to the need for a philosophy of radiation protection, the Linear Non-threshold Theory was put forward. In this review paper, I will mention the debates about the validity of LNT theory and try to summarize the new suggestions and research studies regarding to some of the concepts mentioned in the above paragraph.

Keywords: *Radiation, low dose, Linear non-threshold theory, radiation protection*

INTRODUCTION

As a medical physicist, one of the questions I mostly encounter is the health effects of low-level radiation, particularly the risk of cancer. I am sure my colleagues are also facing with similar questions. It is difficult to answer these questions because we express the health effects that can be attributed to radiation, such as cancer, with some risk factors. However, the perception and definition of risk factors are different for us and those who are not experts in the subject. Another problem is the lack of a theory that fully explains the health effects of low-level radiation. High uncertainties in dose measurements, the presence of many confounding factors and biases which are inherent in human epidemiological studies and as well as in animal and in-vitro research are the important reasons why a reliable theory could not be established on this subject. Due to the need for a standard radiation protection philosophy for the public, radiation workers, patients receiving diagnosis and treatment using radiation and also for nonhuman biota and ecosystems, international organizations put forward the "Linear Non-threshold Theory (LNT) some years ago. This theory is presently the most widely applied model for radiation risk assessment [1, 2]. The International Commission on Radiological Protection (ICRP) is an independent, international scientific organization providing recommendations and guidance on all aspects of protection against ionizing radiation. Although they advise the use of LNT as a general model, a revision of the system of Radiological Protection that will update the 2007 general recommendations in ICRP Publication 103 is suggested now [3, 4]. This is the beginning of a process that will take several years, involving open and transparent engagement with organizations and individuals around the world. Many areas are identified for potential review including: classification of effects, with particular focus on tissue reactions; reformulation of detriment, potentially including non-cancer diseases; re-evaluation of the relationship between detriment and effective dose, and the possibility of defining detriments for males and females of different ages; individual variation in the response to radiation exposure; heritable effects; and effects and risks in nonhuman biota and ecosystems. Some of the basic concepts are also being considered, including the framework for bringing together the protection of people and the environment,

incremental improvements to the fundamental principles of justification and optimization, a broader approach to the protection of individuals, and clarification of the exposure situations introduced in 2007. In this review paper, I will mention the debates about the validity of LNT theory and try to summarize the new suggestions and research studies regarding some of the concepts mentioned in the above paragraph.

Categorization of Radiation Health Effects

When we talk about the health effects of ionizing radiation, it is necessary to make a distinction between two major classes of health effects [1, 2]):

Tissue reaction: Deterministic effects – impairment of organ/tissue function occurring above dose thresholds, with severity increasing with increasing dose.

Stochastic effects: Cancers and heritable diseases – predominantly the risk of cancer occurring in exposed populations, with increasing frequency (but not severity) with increasing dose, and assuming that there is no threshold below which there is no risk.

However current scientific research indicated that this simple classification may require reconsideration, for better understanding of tissue responses, their variation between individuals, and the relationships between dose and the probability of occurrence or the severity of effects [3]. The classification of these effects for protection purposes should be revisited to ensure that it remains fit for purpose. For example, it may be useful to distinguish between severe and other tissue reactions, or between short-term and long-term health effects. Some health effects may not fit well into either category (e.g. cataract diseases of the circulatory system). Whatever classification is adopted, it will be necessary to assess the impact on the management of radiological risks in terms of the tolerability range of risks and as well as borders of unacceptable risk levels putting them into perspective with other risks [3, 5-7].

Critiques of The Current Radiation Protection System

Shape of the dose-response function:

As a stochastic effect, cancer is the main disease of radiation. In order to discriminate cancer related to radiation from the other carcinogen factors, epidemiological studies are made to compare cancer rates between the cohorts that have been exposed and unexposed to radiation [4]. It is necessary to include persons exposed to high and low levels of radiation in these studies. So, risk factors are derived for different dose ranges specific to different cancer sites. The results are plotted radiation dose versus excess risk (risk attributable to radiation only) and called as dose-response function. Epidemiological studies including the victims of atomic bombs in Japan (LSS – Life Span Study) have provided the calculation of risk factors from background radiations up to lethal doses. Statistical reliability of this study is quite high due to the wide range of dose interval, availability of a suitable control cohort and high numbers of persons in these cohorts and acceptable accuracy of retrospective dosimetry. Dose response function of this study is shown in Figure 1 [8]. The risk versus dose behavior is linear at the high dose interval, starting approximately from 100 mGy. However, the shape of the function cannot be well defined at the low dose region. So, risk factors for leukemia and solid cancers (also each type of organ cancers) were derived from the high dose part due to the statistical confidence of the data. Cancer risk reduces with dose but high uncertainties at data points at the low dose part does not allow for determine of reliable risk factors specific to this region. But it is very important to have risk factors for this low dose region, because there is a huge number of populations exposed to this radiation levels: The background radiation from manmade and natural sources that we live in is a low-level radiation. Patients undergoing nuclear medicine and diagnostic radiology (not some of the interventional procedures) examinations are exposed to low level- radiation. There are also occupationally exposed people working in medical and industrial sectors. Since it is not possible to reliably fit dose-response curve at the low dose region to a known function, majority of the international scientific organizations have accepted that the shape of dose response function is also linear in this low radiation range and have recommended extrapolating the risk factors obtained from the high dose region to low dose region. In order to reduce the risk levels, these factors are reduced by a certain number, called "Dose - Rate Effectiveness factor (DREF)" [9-11]. The assumption of linearity of risk factors between zero and high doses without any dose threshold is called as "linear-no-threshold (LNT) theory". In the current system, linear models are used to reflect the relationship between dose and the risk of solid cancers, and a linear-quadratic model is used to reflect the relationship between dose and the risk of leukemia. LNT theory is taken as prudent approach to radiation protection system for purposes of constructing radiation protection principles,

standards, guidelines and regulations [2]. Due to the reasons stated below, this theory has been debated in the scientific community for years [12-17].

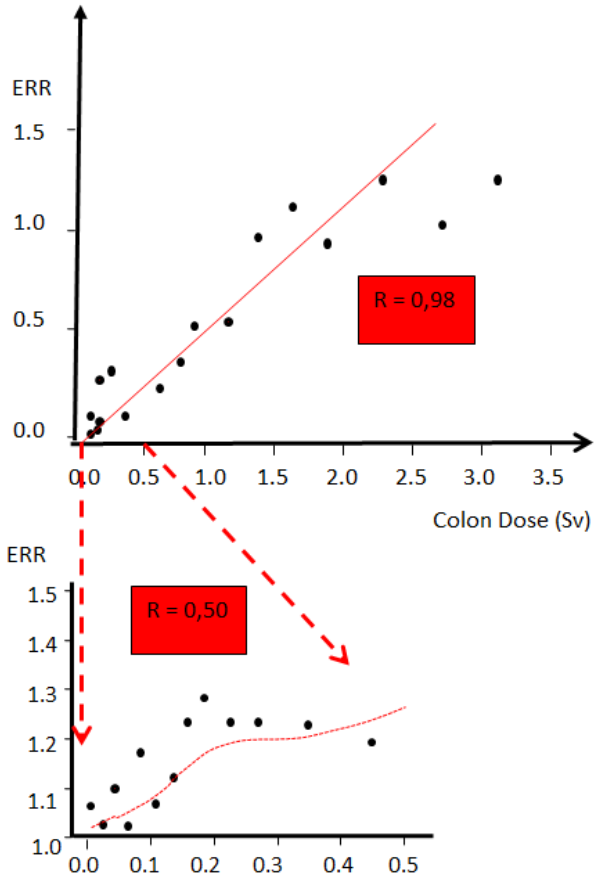

Figure 1: Dose-response function. Excess Relative Risk (ERR) versus Colon Dose. Obtained from epidemiology study on Japanese population affected by atomic bomb. Colon doses are taken as examples. The figure below shows the risks of low intensity radiation in more detail. The lethal effect of radiation is over 2.5 Sv. The dose-risk behavior is linear over the entire dose scale but non-linear in the low dose region [8].

There are high levels of uncertainties in epidemiological studies carried out at low radiation doses due to the confounding factors such as lifestyle, preexisting dis¬eases, age, sex, ethnicity, multiple exposures, uncertainties in exposure and dose reconstruction, as well as a lack of suffi¬ciently large population datasets to achieve statistical power. But combining the data of similar epidemiological studies and evaluating them as a whole improves confidence of the results. It is shown that majority of this meta-analysis supports the linearity of dose-response function [7, 18]. On the other hand, over the past two decades, our understanding of radiation biology has undergone a fundamental shift in paradigms away from single "hit–effect" relationships and towards complex ongoing "cellular responses". Molecular and cellular investigations carried out on irradiated cells give non-linear dose-response relationships due to Non-Targeted Effects (NTE) of radiation [19, 20]. Some animal studies also confirmed these findings [21]. Radiation induced bystander effects (RIBE) (observed in un-irradiated cells that are in close proximity to irradiated cells as a result of communication with irradiated cells) Radiation induced genomic instability (RIGI) (temporary or long-term increase in the rate of genetic changes in the genome of irradiated cells over many cell generations) and Abscopal effects (AE) (transmitted effect between irradiated and un-irradiated tissues outside of the irradiated volume via systemic signaling) are the types of Non-Targeted Effects. These effects imply that radiation may also affect targets (cells) other than the directly irradiated cells. These cells even did not receive any energy deposition from the incoming radiation, they suffer the same damage as directly affected cells. Since radiation interacts with a single cell, but the effect spreads to many cells, indicates that the dose response function is not linear on cellular basis. LNT theory is simple, states that a single particle of radiation hitting a single DNA molecule in a single cell nucleus initiates cancer. An important problem with this simple argument is the ignorance of biological defense mechanisms of human bodies that prevent the vast majority of events that may cause cancer. Some of the most important examples include [22]: induction of DNA repair enzymes; apoptosis, a process by which damaged cells "commit suicide"; immune system stimulation; and delaying mitosis and thus extending the time before it occurs, during which damage repair is most effective. Besides immediate defenses against detrimental effects in irradiated cells, a stimulation of defenses is observed in neighboring hit and non-hit cells. These adaptive responses are also observed in cell and animal studies. Another important issue is the abundant evidence that low-level radiation stimulates the immune system, while high level doses depress the immune response [21]. According to LNT, if a 1 Gy dose gives a cancer risk R, the risk from a dose of 0.01 Gy is R/100, the risk from 0.00001 Gy is R/100,000, and so on. Does extrapolating the dose response curve to zero dose mean that even a few radiation particles can cause cancer? This is also another draw back of LNT theory. This low dose interval, corresponds to background radiation region. None of the epidemiological work up to now, investigating the effect of background radiation to human health,

indicated a harm effect [4]. Another issue is the upper border of low dose region. Could we define a low dose range that radiation has no harmful effects on health? Some literature refers this low dose interval as <100 mGy of low-LET radiation to organs and tissues and low dose rates as <5 mGy/h [23]. But there is growing evidence from epidemiologic studies of dose–risk relationships at dose levels down to about 100 mGy or less, for all cancers and for several specific cancer site (see for example [8, 2, 25-29]. In-vitro laboratory and animal studies also investigating the shape of this response function. However, they are not fully supporting to LNT theory (Figure 2) [12, 30]. Due to all these uncertainties, different hypotheses regarding to the shape of dose response at low doses whether it is linear, linear with a threshold, sub-linear, supra-linear or even hermetic i.e., beneficial for health have been suggested. This beneficial effect of radiation is called as Radiation Hormesis and defined as the stimulating effect of small doses. Up-regulation of protective mechanisms at the cell and tissue by low doses can function against spontaneous cancer other than radi¬ation-induced carcinogenesis [14]. Various scientific organizations and research groups are recommending further research by combining the animal, in vitro and human (epidemiological) studies for an optimum solution of low-level effects [3, 31].

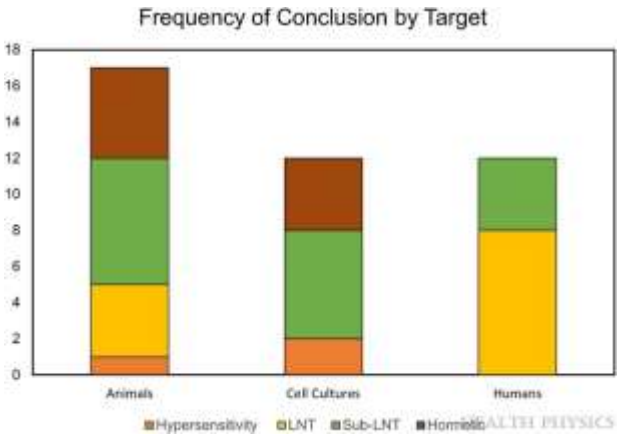

Figure 2: Different findings of animal, cell and human studies investigating the shape of the Dose-Response function. Human studies include epidemiological studies of populations exposed to radiation occupationally, it is interesting to note that human findings are supporting both LNT and sub-LNT (with the permission of C. Wilson 2024) [12].

Dose rate and transfer of risk factors

Japanese atomic bomb survivors were exposed acute doses and risk factors derived from the high dose region of the dose-response function. These factors are used for low dose and low dose rate cases after they reduced by DREF value in the current radiation protection system. But the question of whether low dose-rate exposures are less carcinogenic than high dose-rate exposures, given the same dose, have not answered yet [11, 32, 33]. Therefore, use of single DREF factor (ICRP recommends DREF of two) for the reduction of risk factors brings another uncertainty. It has been proposed that it will be more appropriate to consider both a low dose effectiveness factor (LDEF) and a dose-rate effectiveness factor (DREF) for risk estimate calculations. It is also recommended that further epidemiological studies especially for low dose rates and protracted exposures with extended follow-up will provide new insight on these uncertainties [11]. The rate of base line cancer and cancer cites are different among the populations, therefore transfer of risk estimates between different populations is uncertain. Expansion of risk data specific to gender and age at irradiation for each cancer site is also needed [24, 34].

Dosimetric quantities

ICRP is also aiming to simplify the use of dose quantities for protection against tissue reactions and stochastic effects [3]. A clear distinction is needed between absorbed dose (in Gray-Gy) and equivalent dose (in Sievert-Sv) in order to prevent the confusion between equivalent dose and effective dose expressed in the same units (Sv) [35]. The proposal is to use Gray for the assessment of individual organ and tissue doses and equivalent dose would no longer be used to set the limits for the tissue reactions, but will be in used for the calculation of effective dose. In this case, radiation weighting factors will be considered separately for the calculation of radiation-weighted absorbed dose in Gy and effective dose in Sv respectively. Another recommendation is related to effective dose. ICRP recommends a lifetime fatal cancer risk of about 5% per Sievert applies at low doses or low dose-rates (that is 1 in 20,000 per mSv). Effective dose is defined for a population of all ages and both sexes, on the basis of mean doses to a reference man and a reference woman [1, 2]. However, it is found that the risk coefficient for a specific age band, sex, and examination could differ by up to a factor of 10, but that for most examinations' estimates are within ±50% of the more detailed organ-dose-based risk assessments.

Using the reference person anatomy, limits the use of effective doses for individual patients as well as for some specific group of people. This can be the case for patients with impaired organ function or for patients with organ ablation (e.g. thyroid), as well as for some examinations conducted only for patients of a specific sex (like mammography, or diagnosis of prostate cancer) [6]. A dose quantity similar to effective dose could instead be specified separately for males and females of different ages, taking account of differences in radiation detriment with age at exposure, and allowing consideration of differences from reference body sizes [3]. Although effective dose, is not recommended to be used for patient, a number of organizations have published coefficients that can be used in the calculation of organ/tissue doses and effective doses for radiological procedures [36. 37]. However, there are differences of up to 25% in some data caused by the use of different phantoms and dose conversion coefficients [38]. It should be keep in mind that, limited part of the body is exposed in radiological examinations (CT etc.) and the use of general risk factor of 5 x 10-2/Sv may give an idea for all the cancer sites but may under estimate the risk of organ cancer directly exposed to radiation since the dose is multiplied by a tissue factor for this organ which is less than one. There are software's and tabulated data for organ dose calculations but none considers the radiosensitivity of individuals. For example, at the level of effective dose of 100 mSv, many organs have the potential to obtain doses of 100 mGy or more [39]. Recognizing the need to help standardize such dose calculations, the ICRP is planning for future to provide reference dose coefficients for specified radiographic and CT procedures (see ICRP Task Group 113 [40]). Calculation of effective dose in relation to an individual patient's exposure instead of standard human anatomies could be more useful. It is also planned to provide these coefficients for exposures at all ages, including the developing fetus.

Tissue weigting factors (WT)

The wT values are rounded and have only four different numerical values. They do not represent scientific best judgments for any specific age group. It is also suggested that wT values be derived to be valid for certain age groups and both sexes, including embryos/fetuses and infants [41].

Relative biological effectiveness (RBE), and radiation weighting factors

It is also important to reconsider the values of current radiation weighting factors since they do not fully reflect the new evidence of RBE of different type of radiations (ICRU 2020). More research is needed to better understand the effectiveness of low energy electrons produced by low energy photons [42].

Effects of radiation from in utero exposure

The issue of health effects of in utero radiation exposure are especially important for the medical profession. Much of the current guidance relies on animal research and limited epidemiological data [43], but some new results from the meta-analytic studies have been published in the recent years are quite interesting. There are studies showing an increased risk of leukemia and some types of childhood cancer among individuals exposed to whole-body doses of less than 100 mGy during childhood [28, 29]. Further research is needed for a greater understanding of biological mechanisms to derive definitive conclusions for specific types of cancer in understanding the long-term health effects from in utero low dose exposures.

Heritable effects of radiation on offspring and next generations

The issue of potential effects for the offspring and subsequent generations is a recurrent major concern for the general public and a particular one for parents (and potential future parents) exposed to ionizing radiation from occupational, medical, or environmental sources. Today, there is little evidence from epidemiological studies to suggest the existence of heritable deleterious effects resulting from radiation exposure in humans [44, 45]. However, heritable risks are included in overall stochastic risks based on evidence in experimental animals [46].

Genomic instability

The induction of genomic instability was observed in recent research studies resulting in the loss of genetic control and the observation of multiple genetic alterations in cell population and in some animal studies. This condition was induced by high acute exposure to radiation. Following radiation exposure, no changes are observed for several cell divisions. After multiple cell divisions, the cells lose genetic

control and many types of biological changes are observed, for example chromosome aberrations, polyploidy, apoptosis, and formation of clones with defined chromosome damage and multiple mutations. Multiple studies have attempted to demonstrate the induction of genomic instability in normal human cells or human populations and have not been able to demonstrate it [47, 48]. Because of the lack of low dose and low-dose rate data, it is not possible to estimate the impact of dose-rate on the induction of genomic instability. Thus, there remains a controversy on the role of low dose radiation induced genomic instability and cancer induction. This is an area that requires additional research.

AOP Steps	Key Events
Interaction with Radiation Energy Deposition	Exposure of Target Tissue
Macro-Molecular Alterations	Single, double and multiple DNA breaks
	Base modifications
	Protein Oxidation
	Free Radical Formation
	Chromosome Alterations
Celular Responses	Gene Activation
	Protein production
	Altered Signaling
	Cell killing and Tissue Disruption
Organ Responses	Altered Physiology
	Disrupted Homeostasis
	Altered Tissue Development/Function
Adverse Outcome	Impaired Development
	Impaired Reproduction
	Cancer and Non-cancer Effects

Figure 3: Schematic representation of an adverse outcome pathway for ionizing radiation-induced cancer and non-cancer diseases showing each step along the proposed pathway and associated key events.

Adverse Outcome Pathway (AOP)

One of the important suggestions is to use adverse outcome pathway (AOP) concept. It is a model that identifies the sequence of molecular and cellular events having potential to produce a harmful effect when an organism is exposed to radiation. AOP is structured representation of biological events leading to adverse effect (undesired harmful effect resulting from a medication) and is considered relevant to risk assessment. It begins with molecular initiating effect (i.e., radiation induced DNA break) and is followed by measurable key events that map out a hypothetical path to adverse outcome via key event relationships. Thus, these key events are empirically observable precursor steps and provide a proposed connectivity from initiating effect to an adverse outcome [49, 50]. The AOP framework is gaining traction within the radiation risk assessment community as the framework provides a linkage between experimentally derived biological data at different levels of biological organization with disease progression. Current radiation protection principles are built on population-based risk mainly derived from physical contributors, such as exposure type (internal, external or both), dose, dose rate and radiation quality. These principles do not reflect specific individual's exposure risk which depends upon the biological contributors i.e., tissue sensitivity, confounders (genetic, life style, socio-economic status) and risk types (radiosensitive, normal, radioresistant).

In this context, the AOP concept may provide a strategy for integrating complex biology of an individual with the physical attributes of a radiation insult by identifying early key events of relevance to phenotypic changes [50]. Radiation AOPs would help enhance our understanding of crucial molecular, cellular, tissue and organismal-level events that are detectable and relevant to adverse effects progression. Bringing data together in formalized frameworks would also support: (1) increasing understanding of tissue- level sensitivities; (2) identifying bioindicators and biomarkers to increase understanding of disease progression or its detection; (3) linking low dose and low dose-rate effects to health outcomes to facilitate risk characterization using disease-based guidance; and (4) refining hazard and risk assessment for co-exposure scenarios, decrease the uncertainty in radiation risk assessment. Radiation-induced cancer occurs years after irradiation. This latency period is about 10 years for solid organ cancers and the risk continues with a decreasing trend throughout life time. The organism can be exposed to many different carcinogens during this period. Therefore, it is not possible to attribute a

cancer case to a past radiation exposure. We should also keep in mind that, chemical, physical mutagens even natural organism stress elicit similar stress responses as ionizing radiation. They induce oxidative stress and lesions in DNA, RNA and proteins and signaling of the damage to neighbor cells. All these stress responses can cause inflammations which is a hall mark of cancer.

CONCLUSION

When I was asked to write a paper for the medical physicists, I decided to select this topic. One of my aims is to emphasize the arguments regarding to the concept of LNT. This is because the effective dose used to express cancer risk in the stochastic effects of radiation was derived from this theory. The risk of cancer attributable to radiation has recently become an important factor fueling radiation phobia in society. This issue started to become a nightmare for families, especially in computerized tomography examinations of children and young people. So, as a medical physicist, when we talk about the stochastic risk of radiation, we should know the limitations of the current radiation protection system and how to use risk concepts appropriately and correctly [51]. The second aim of this review is to give some information about the changes planning to be made in the radiation protection system in the coming years and suggested research topics. As I stated in the last paragraph of introduction session, many areas are identified in this respect, but I covered only the topics that seemed to be important for urgent needs of our society. I hope this article will be a guide for my young colleagues in their career search.

Conflict of Interest

There are no conflicts of interest and no acknowledgements.

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