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Model Uncertainty via the Integration of Hormesis and LNT as the Default in Cancer Risk Assessment

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Abstract

On June 23, 2015, the US Nuclear Regulatory Commission (NRC) issued a formal notice in the *Federal Register* that it would consider whether "it should amend its 'Standards for Protection Against Radiation' regulations from the linear nonthreshold (LNT) model of radiation protection to the hormesis model." The present commentary supports this recommendation based on the (1) flawed and deceptive history of the adoption of LNT by the US National Academy of Sciences (NAS) in 1956; (2) the documented capacity of hormesis to make more accurate predictions of biological responses for diverse biological end points in the low-dose zone; (3) the occurrence of extensive hormetic data from the peer-reviewed biomedical literature that revealed hormetic responses are highly generalizable, being independent of biological model, end point measured, inducing agent, level of biological organization, and mechanism; and (4) the integration of hormesis and LNT models via a model uncertainty methodology that optimizes public health responses at 10^{-4}. Thus, both LNT and hormesis can be integratively used for risk assessment purposes, and this integration defines the so-called "regulatory sweet spot."

Keywords

hormesis, LNT, cancer risk assessment, dose–response, biphasic, adaptive response

Overview

The comments offered here assess the scientific foundations of the 3 petitions (Carol Marcus, Michael Miller, and Mohan Doss) to the Nuclear Regulatory Commission (NRC) proposing a change in the use of the linear nonthreshold (LNT) for risk assessment to the hormesis dose–response. This assessment includes the scientific and historical foundations of the LNT recommendation by the National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Committee, Genetics Panel in 1956 for regulatory agencies to adopt linearity at low dose for ionizing radiation risk assessment, how this occurred, and what it means today for NRC regulations. The comments also assess the scientific foundations of hormesis, including how accurately it predicts low-dose effects and how this model compares with other dose–response models such as the LNT and threshold models. Finally, it will be shown how hormesis could be applied to cancer risk assessment and how this may be used to optimize the health of radiation-exposed workers and the general public.

The Scientific Foundations of LNT as Adopted by Regulatory Agencies, Including the NRC, Are Based on a Fabrication and Falsification of the Research Record by the US NAS BEAR I Committee, Genetics Panel (1956)

The use of the LNT for radiation-induced mutation originated in 1928 with a publication by the famous physical chemist Gilbert Lewis in the journal *Nature*.[1] The article offered a mechanism for the theory of evolution. Although this specific hypothesis of Lewis would not be generally accepted, subsequent research by

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several students of Herman J. Muller provided support for a linearity response for gonadal mutation in male fruit flies at very high doses (ie, several hundred thousand-fold greater than normal background). Muller would refer to this linear response as the proportionality rule. This was the term used throughout the 1930s and 1940s for what would now be called the LNT. The proportionality rule (ie, LNT) became linked to a mechanism in the mid-1930s via the collaboration of leading radiation geneticists and several prominent physicists, yielding the LNT single-hit theory. The single-hit mechanism was based entirely on ''hit theory.'' This early history is described and critiqued in detail by Calabrese.[1] During World War II, the US Atomic Energy Commission (AEC) funded research at the University of Rochester to determine the shape of the dose–response in the low-dose zone. The principal research was done under the direction of Curt Stern. This research and related activities are told in considerable detail by Calabrese.[2] The Stern research is central as it was upon these findings that the LNT would be based and accepted by US regulatory agencies. Thus, a careful assessment of their research is essential for an evaluation of the 3 petitions to the NRC. Calabrese[2] has shown that the interpretations of Stern and his manipulations of the publication process led to ideologically based deliberate distortions of the nature of the dose–response in the low-dose zone. The history of the LNT and the roles of Stern and Muller are assessed in detailed by Calabrese.[2-4] These findings reflect documented deceptive actions by Muller on multiple occasions in order to ensure acceptance of the LNT. These publications provide a fundamental backdrop for the critical actions of the BEAR I Committee, Genetics Panel, which is now summarized.

Substantial research has recently shown that the NAS BEAR I Committee, Genetics Panel misrepresented the research record in its key technical publication in *Science* (June 1956)[5] that recommended the switch from threshold to LNT for risk assessment. This scientific misconduct has now been extensively documented in peer-reviewed publications.[6-8] As is presented in the paper by Calabrese,[7] the Panel was extremely concerned that their recommendation to switch to the LNT model be accepted. However, there were very strong misgivings among the panelists that their LNT recommendations would not be accepted if the Panel's uncertainties and fundamental scientific disagreements concerning transgenerational genetic risks were made known via their publications to the scientific community and the general public. These fears are documented in the papers by Calabrese[3,4,7] via letters and other correspondence of Panel members. In the 1956 *Science* paper[5] of the Panel, it is written that all geneticists on the Panel (ie, 12) were challenged to estimate the number of adverse reproductive genetic outcomes that would occur over 10 generations of US residents at a given level of gonadal radiation exposure. Of the 12, 9 provided detailed reports with estimates. All such written documentations are publically available and provide key documentation to support the conclusions of the paper by Calabrese.[7] The evidence shows that the estimates of the expert Panelists wildly varied, revealing great uncertainty both within and between expert geneticists. Such profoundly large inconsistencies and disagreements were disturbing, and a non-scientific ideologically based decision was made to drop the 3 estimates showing the lowest damage. This significantly reduced the ''appearance'' of uncertainty. Yet, when the 1956 *Science* paper[5] was published, the authors (ie, NAS Genetics Panel) stated that of the 12 geneticists on the Panel only 6 took up the challenge and provided estimates. However, we now know that this was not true and can be shown to be a demonstrably false statement. Dropping of the 3 lowest genetic damage estimates reduced a significant amount of variation, yet excessive uncertainty still remained. For the remaining 6 estimates, the uncertainly range was 750-fold and was still considered too excessive and was feared this could jeopardize acceptance for the LNT recommendation. Thus, the Panel then falsified the *Science* paper by stating their range of uncertainty to be only 100-fold. This falsification of the research record would have been discovered if the data had been published. However, the Panel formally voted not to make the data public, and therefore, it became impossible to challenge the falsification of the *Science* paper since no Panel member revealed these deceptions. Finally, there were 3 Panel geneticists who refused to provide estimates because the process was excessively uncertain and could not be relied upon. These perspectives were also deliberately omitted as well from the *Science* paper, further misleading the *Science* journal readership.

The documentation of these actions is well established within the papers by Calabrese. It shows that the key actions of the BEAR I Genetics Panel were dishonest, and yet, it was upon their recommendation that the linearity paradigm became accepted, adopted, and implemented within the United States and worldwide. Thus, the foundation of the LNT was based on misrepresentations, intending to mislead regulatory agencies and others. In fact, the NRC publication of 1981 addressing[9] cancer risk assessment makes note of the 1956 Genetics Panel activity, using this deception-based activity as foundational material. As history demonstrates, the Genetics Panel was successful in their deceptions because of the great authority of the NAS and the willingness of the regulatory and scientific communities to accept what they were told without examining the basis for the recommendation. Although these accusations seem harsh, the documentation supports each statement. The problem is that it has taken some 6 decades for these deceptions to be revealed. Thus, the regulatory process was literally taken hostage by leading radiation geneticists acting via the prestigious US NAS much like a highly infectious virus in order to manipulate and direct the actions of regulatory agencies in the United States and elsewhere to their own ideological viewpoint.

Refusal of the NAS Genetics Panel to Document the Basis of the LNT Recommendation

The BEAR I Genetics Panel deliberately refused to provide any documentation to describe the scientific basis for their recommendation that the LNT be adopted by regulatory agencies.

Newly uncovered documents reveal that this decision was made in order not to show profound disagreements on uncertainty in risk estimation and to focus on the identification of self-serving grant funding opportunities. The basis of their decision is given in the study by Calabrese.[6] More specifically, some 6 months after publication of their landmark 1956 report,[10] the BEAR Genetics Panel was challenged by a number of distinguished biologists to provide the documentation upon which it based its linearity decision. It should be known that the NAS Genetics Panel had never developed any written basis for the linearity decision. It was simply by proclamation within the Panel as seen by a reading of the Panel transcripts. Now when forced to confront the reality that it had no written basis, the Panel decided that it would not provide one. This outrageous and arrogant decision was shared in writing with the President of the NAS at the time (Dr Detlev Bronk), thereby making him fully aware of this decision. Yet, he would do nothing to reverse it, making him a party to this decision.

Following the acceptance of LNT, cancer risk assessment would become strongly model driven as is seen in the later Biological Effects of Ionizing Radiation (BEIR) Committee reports starting in 1972. Once the LNT concept was accepted as a scientific and inaccessible belief, it was transformed into a model-based construct that could not be proven wrong or easily modified. This was the case even after the discovery of DNA repair, apoptosis, adaptive response, hormesis, and other new concepts, all of which could profoundly affect the shape of the dose–response in the low-dose zone.

Hormesis Outcompetes LNT and Threshold

Hormesis, including radiation hormesis, has a long history going back over 100 years. Calabrese and Baldwin[11-15] have summarized these early developments in detail. In fact, as early as 1917, ionizing radiation was shown to significantly enhance the lifespan of the insect model, the confused flour beetle, in an extremely well-designed study that has been repeatedly confirmed.

Thousands of studies have been published over the past several decades on hormesis and show it to be reproducible, generalized, and independent of biological model, agent, end point, and mechanism. In multiple direct head-to-head comparisons, the hormetic model has strikingly outperformed LNT and threshold models for accuracy in low-dose predictions.[16-20] It is important to note that the many valid hormesis studies not only clearly show the strengths of hormesis but also demonstrate serious flaws in the LNT model and establish that it cannot be used as a default, that is, if the LNT cannot be shown to provide accurate estimates in so many experimental systems and for a wide range of end points, including those affecting the process of cancer, then it is not possible to rely upon it as a default dose–response risk assessment model. Although it is widely quoted that a single valid study can discredit a powerful theory, LNT has been shown to be invalid in not one but multiple thousands of peer-reviewed and reproducible studies, affecting a very broad spectrum of biological models and end points, including each key stage of the process of carcinogenesis including tumor formation. With such extensive documentation showing the limitations of the LNT model, it is not scientifically possible to use the LNT as the default model for risk assessment and the basis for regulatory decision making. The LNT model has always been impossible to prove correct, but it could be proven to be incorrect. This is literally what this massive set of published papers on hormesis does.

The Hormesis Database

Although the LNT model is being criticized in these comments for its fraudulent origin and integration into US regulatory agencies and its discrediting by a very large number of valid hormesis studies, the proposal that the NRC is considering is to switch to the hormetic dose–response model. The NRC should note that a hormesis database was created nearly 20 years ago via funding from multiple sources but principally via the US Air Force to the University of Massachusetts at Amherst. This database is being continuously expanded and now there are several different types of hormetic databases which serve differing purposes. In 2005, Calabrese and Blain[21] first published a detailed description of the original hormesis database. This article has been updated on 2 occasions (2009 and 2011).[22,23] The hormesis database provides detailed information on each hormetic dose experiment that first passes rigorous evaluative criteria. The findings indicate that hormesis is highly generalizable and is independent of biological model, level of biological organization (ie, cell, organ, and organism), end points measured, inducing agent (eg, chemical class, physical agents such as ionizing radiation, etc), developmental processes, gender, and mechanism. The quantitative features of the hormetic dose–response are similar across all of the above-mentioned parameters, suggesting that the hormetic response is constrained by the limits of biological plasticity.[24] Thus, hormesis is fundamental, generalizable, quantifiable, and mechanistically explained. Also, unlike the LNT model, it can be tested in the observable range and accepted or rejected for any specific experiment. This is a very valuable feature as one does not have to rely on extrapolative modeling but on empirical data.

In the early 2000s, the most significant concern with the hormesis model was that it needed to be explained in mechanistic terms. Today, this is not a concern and is useful only as a historical note. For example, in 2013, Calabrese[25] provided specific mechanisms for 400 different hormetic dose–responses, where the response was mediated by a specific receptor and/or cell signaling pathway. No other dose–response model has had such a plethora of mechanistic documentation to support and explain it. Further, a new hormesis mechanism paper by Calabrese is in its final stages of preparation prior to submittal to a journal. This new paper will contain nearly 600 additional hormetic dose–responses with clearly identified molecular mechanisms. Thus, about 1000 dose–responses for hormesis are now available with mechanisms.

These developments of the past 2 decades have provided information on the occurrence of hormetic dose–responses, their frequency, generalizability, and mechanisms. It provides a sound foundation upon which to build a regulatory program, especially given the fact that its conclusions and predictions are testable. These features make the hormetic dose–response a sound choice upon which to base risk assessments upon, including cancer and noncancer end points.

The New Goal: Using Hormesis to Optimize Worker Health and the Public Health

These goals can be achieved best at present via the integration of LNT and hormesis models via a model uncertainty methodology. Recent papers by Calabrese et al[26,27] demonstrate that the public health would be optimized at an LNT-based risk of 10^{-4}, the dose of the hormetic nadir in animal studies. This integration yields the optimal public health response within the context of both defining and minimizing risk model uncertainty, with LNT providing the upper bound and hormesis the lower bound of risks. Thus, the NRC should change from an LNT model-based risk assessment as a default to the integrated LNT–Hormesis model as described by Calabrese et al.[26,27] This model could also be applied to epidemiological data with slight modification.

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