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Linear No-Threshold model and standards for protection against radiation

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ABSTRACT

In response to the three petitions by Carol S. Marcus, Mark L. Miller, and Mohan Doss, dated February 9, February 13, and February 24, 2015, respectively, the Nuclear Regulatory Commission (NRC or the Commission) has announced that it is considering assessing its choice of dose–response model, the Linear No-Threshold (LNT) model, for exposure to ionizing radiation. This comment is designed to assist the Commission in evaluating the merits of a review of the default dose–response model it uses as the basis for the *Standards for Protection against Radiation* regulations. It extends the petitioners' argument in favor of reexamining the default hypothesis (LNT) and taking consideration of low-dose hormesis for two main reasons: 1) Failure to review the LNT hypothesis may jeopardize the NRC's mission to protect public health and safety; and 2) The National Research Council's guidelines for choosing adequate defaults indicate that the choice of low-dose default model is due for a reevaluation.

1. Introduction

In response to the three petitions by Carol S. Marcus, Mark L. Miller, and Mohan Doss, dated February 9, February 13, and February 24, 2015, respectively, the Nuclear Regulatory Commission (NRC or the Commission) has announced that it is considering assessing its choice of dose–response model, the Linear No-Threshold (LNT) model, for exposure to ionizing radiation. More precisely, the petitioners have proposed that the Commission amend 10 CFR Part 20, *Standards for Protection against Radiation*, to reflect the latest scientific understanding and evidence in support of low-dose radiation hormesis as a potentially more plausible default.

The petitioners argue that (1) the LNT assumption has never been validated and is still lacking scientific support; (2) there is vast scientific evidence, grounded in biology, genetics, clinical experiments, and ecological and epidemiological studies, in support of the existence of a low-dose radiation threshold and, even more so, of low-dose radiation hormesis; and (3) the LNT assumption is retarding public health by limiting the potential therapeutic application of low-dose ionizing radiation in treatment of diseases, especially cancer.[1]

In light of these claims, two of the petitioners have made the following recommendations: "1) Worker doses should remain at present levels, with allowance of up to 100 mSv (10 rem) effective dose per year if the doses are chronic. 2) ALARA [as low as reasonably achievable] should be removed entirely from the regulations…3) Public doses [exposure] should be raised to worker doses." One petitioner also requests that the regulation be changed to "4) end differential doses for pregnant women, embryos and fetuses, and children under 18 years of age."[2]

This comment extends the petitioners' argument in favor of reexamining the default hypothesis (LNT) and taking consideration of low-dose hormesis for the following reasons:

1) *Failure to review the LNT hypothesis may jeopardize the NRC's mission to protect public health and safety.* Research on hormesis suggests that low doses of ionizing radiation may be protective of public health. If true, regulating exposure to ionizing

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[1] "Linear No-Threshold Model and Standards for Protection against Radiation: Docket Folder Summary," Regulations.gov, accessed July 9, 2015, http://www.regulations.gov/#!docketDetail;D=NRC-2015-0057.

[2] "Linear No-Threshold Model and Standards for Protection against Radiation; Notice of Docketing and Request for Comment," Regulations.gov, accessed June 23, 2015, http://www.regulations.gov/#!documentDetail;D=NRC-2015-0057-0010.

radiation according to the ALARA principle may be harmful to public health if it regulates beneath the optimal hormetic dose.

2) *The National Research Council's guidelines for choosing adequate defaults indicate that the choice of low-dose default model is due for a reevaluation*. The NRC should conduct a systematic review of evidence, as recommended by the Council guidance, to determine the comparative weight of hormesis and LNT.[3]
   a. If the systematic review reveals hormesis to be "clearly superior" to LNT, then the NRC should abandon LNT and adopt hormesis.
   b. If the systematic review reveals hormesis to be "comparably plausible" to LNT, then, in light of both models, the NRC should conduct a quantitative model uncertainty analysis, present alternative risk assessments, and update its standards of protection accordingly.
   c. If the Commission decides to maintain adherence to LNT after, or without, conducting the systematic review of evidence, then the Commission should demonstrate why the body of evidence in favor of hormesis is inadequate for consideration under the NRC's Information Quality Act (IQA) guidelines. Further, the Commission should demonstrate how the studies that support its low-dose LNT assumption conform to the NRC's IQA guidelines.

2. Implications of the choice of the dose–response model on public health and safety

The regulation 10 CFR Part 20, *Standards for Protection against Radiation*, states that the NRC is to regulate "the receipt, possession, use, transfer, and disposal of licensed material by any licensee in such a manner that the total dose to an individual (including doses resulting from licensed and unlicensed radioactive material and from radiation sources other than background radiation) does not exceed the standards for protection against radiation."[4] The NRC derives its authority to regulate exposure to ionizing radiation under 10 CFR 20 from two acts, the Atomic Energy Act of 1954, as amended, and the Energy Reorganization Act of 1974, as amended. In these two acts, Congress authorized the NRC to set the appropriate standards necessary to achieve an adequate level of protection of public health and safety from the effects of exposure to ionizing radiation.[5]

When proposing rules designed to ensure "that the objective of compliance or adequate protection is met,"[6] the Atomic Energy Act is understood and interpreted by the courts to prohibit the NRC from considering economic costs of its rules.[7] Only when the rules propose a standard that would achieve a level of protection *beyond* adequate is the agency permitted to consider economic costs.[8] This comment takes no position on whether the default model, LNT, results in a level of protection beyond adequate when compared to plausible alternatives, and will instead base its arguments on the public health and safety implications of one plausible alternative model, hormesis, without reference to such costs.

It is extremely difficult, if not impossible in some instances, to validate the dose–response function at low doses where thousands of subjects would be needed to uncover either a small response or a relatively infrequent event. This is particularly true when the adverse effect, such as cancer, occurs in both the test and the control group.[9] This task is made even harder when one potential response in the test group is a decrease in the incidence of the adverse event—a hormetic response. To uncover such an effect would require a study design that would allow for such a response; the use of the LNT assumption in fact makes it impossible to detect such an effect.

A more familiar difficulty for a dose–response researcher is extrapolation. Because researchers must often predict health effects at the low doses, they must extrapolate from higher test doses to low doses. This is true for both animal and human epidemiological studies.

The choices of models in the low dose region have generally fallen into three categories: a linear extrapolation from high dose through the origin; a threshold below which no harm exists; and a sub-threshold, or hormetic, dose where there are actual beneficial effects. Efforts to discover where there are either threshold or hormetic doses are as difficult as attempting to validate the LNT.

For instance, the hormetic effect detected in multiple studies is generally modest, ranging 30–60 percent greater than control values.[10] Given the small ratio of signal to noise and the modesty of the effect, it is difficult to replicate hormesis and to distinguish between a threshold and a hormetic model in the low-dose region.[11] As described in one paper, "the use of different default models has important implications in many areas, including the establishment of limits for chemical exposures."[12] Considering the significance of health implications of correctly identifying the type of dose–response model, efforts to design better studies have continued.

Recent advances in clinical studies have begun to allow researchers to overcome some of the aforementioned obstacles. For example, shifting focus from the whole animal to cell-level investigation has allowed for a wider range of doses to be tested and for more results to be replicated. The shift in focus has also allowed for results that are more relevant to humans and that rely less on extrapolation.[13] These and other recent advances suggest that the dynamics of the low-dose region may be more nuanced than the default LNT model predicts. While a full review of recent literature on threshold and hormetic models is beyond the scope of this comment, a brief description of some of the research follows.

Regarding the possibility of a threshold or hormetic response to exposure to radiation, four epidemiological studies of subjects who were naturally exposed to background radiation did not detect any increase in cancer risk, and one detected a positive response to low-dose radiation. This particular study lacked statistical significance but remains important for consideration because it implies a possible threshold, as the lack of statistical significance means that

[3] The same methodology can be adopted for testing the weight of a threshold model relative to LNT or hormesis.

[4] Nuclear Regulatory Commission, "NRC Regulations (10 CFR): Part 20—Standards for Protection against Radiation," accessed July 23, 2015, http://www.nrc.gov/reading-rm/doc-collections/cfr/part020/full-text.html.

[5] Nuclear Regulatory Commission, "NRC Regulations (10 CFR): Part 20."

[6] Nuclear Regulatory Commission, "NRC Regulations (10 CFR): Part Index: Section 70.76 Backfitting," accessed July 10, 2014, http://www.nrc.gov/reading-rm/doc-collections/cfr/part070/part070-0076.html.

[7] Curtis W. Copeland, "Economic Analysis and Independent Regulatory Agencies," Administrative Conference of the United States, March 29, 2013.

[8] "NRC Regulations (10 CFR): Part Index: Section 70.76 Backfitting"; Curtis Copeland, "Economic Analysis and Independent Regulatory Agencies."

[9] Robert A. Scala, "Risk Assessment," in *Casarett and Doull's Toxicology*: *The Basic Science of Poisons*, ed. Mary O. Amdur, John Doull, and Curtis D. Klaassen (New York: Pergamon Press, 1991), 985–96.

[10] Edward J. Calabrese and Linda A. Baldwin, "The Hormetic Dose-Response Model Is More Common Than the Threshold Model in Toxicology," *Toxicological Sciences* 71, no. 2 (2003): 246–50.

[11] Edward J. Calabrese and Mark P. Mattson, "Hormesis Provides a Generalized Quantitative Estimate of Biological Plasticity," *Journal of Cell Communication and Signaling* 5, no. 1 (2011): 25–38.

[12] Edward J. Calabrese et al., "Hormesis Predicts Low-Dose Responses Better Than Threshold Models," *International Journal of Toxicology* 27, no. 5 (2008): 369–78.

[13] Food and Drug Administration, Advances in the Development of Alternatives to Whole Animal (Vertebrate) Testing, 1993.