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General Comment

Please see the attached file.

Attachments

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PUBLIC INTEREST COMMENT

LINEAR NO-THRESHOLD MODEL AND STANDARDS FOR PROTECTION AGAINST RADIATION

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Rule Title Linear No-Threshold Model and Standards for Protection against Radiation
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The Regulatory Studies Program of the Mercatus Center at George Mason University is dedicated to understanding the effects of regulation on society. As part of its mission, the program employs contemporary economic scholarship to analyze and assess rulemaking proposals for their effects on economic opportunities and social well-being.

This comment before the Nuclear Regulatory Commission does not represent the views of any particular affected party or special interest group. It is instead 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.

I. 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

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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 recommendation: "(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 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.

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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

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

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 IQA guidelines. Further, the Commission should demonstrate how the studies that support its low-dose LNT assumption conform to the NRC's IQA guidelines.

II. 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

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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.

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 face 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 subthreshold, 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

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10. Edward J Calabrese and Linda A. Baldwin, "The Hormetic Dose-Response Model Is More Common Than the Threshold Model in Toxicology," *Toxicological Science* 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.

the effect of exposure to low-dose radiation on cancer risk is not different from zero.[14] Another study on the effect of radon exposure revealed beneficial effects from low-dose exposure.[15] These results were affirmed in a more recent study on radon exposure that detected the possibility of positive effects on lung cancer from low doses of radiation.[16] A multiple-country analysis of occupational exposure to X-rays and gamma rays in nuclear power plants did not detect negative health effects; instead it showed a rate of all cancer mortality lower in the exposed workers relative to the general population.[17]

Some toxicological studies have revealed hormetic dose responses in chemical carcinogens as well. In fact, a hormetic response is detected in nearly 2,000 chemical agents from about 245 different classes.[18] The hormetic responses exceeded those of the threshold by 2.5 to 1.[19] A reassessment of an animal study on the effect of the pesticide DDT, on which regulatory agencies had based their initial risk assessment, revealed a hormetic dose response function.[20] Hormesis has also been detected in exposure to low doses of air pollutants, namely particulate matter.[21]

Beyond estimating dose-response functions for federal policies, scientists in the field of health and safety find that hormesis has the potential to be used as a treatment and prevention for many diseases: "a better understanding of hormesis can also be important for the prevention of degenerative diseases and the development of safe, effective regimens for the treatment of cancer and other disorders."[22] The latter regimens refer to the field of "preconditioning" or "adaptive response."[23] Preconditioning and adaptive response research tests whether a low dose of a stressor induces, against higher doses of the same—or even other—stressors, a protective reaction in the body or helps the body to heal more quickly. The concept of vaccination is one example of preconditioning where exposures to small doses of a stressor are used to boost immunity against larger doses of the same stressor. Other stressors tested so far vary from environmental pollutants and chemical carcinogens to exercise and intermittent fasting. Obviously, radiation has also been the subject of considerable testing.[24] The ability of

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14 Zufan Tao et al., "Cancer Mortality in the High Background Radiation Areas of Yangjiang, China during the Period between 1979 and 1995," *Journal of Radiation Research* 41, Suppl. (2000): S31–S41.

15 Bernard L. Cohen, "Test of the Linear-No Threshold Theory of Radiation Carcinogenesis for Inhaled Radon Decay Products," *Health Physics* 68, no. 2 (1995): 157–74.

16 Richard E. Thompson et al., "Case-Control Study of Lung Cancer Risk from Residential Radon Exposure in Worcester County, Massachusetts," *Health Physics* 94, no. 3 (2008): 228–41.

17 Elizabeth Cardis et al., "The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks," *Radiation Research* 167, no. 4 (2007): 396–416.

18 Edward J. Calabrese and Robyn B. Blain, "The Hormesis Database: The Occurrence of Hormetic Dose Responses in the Toxicological Literature," *Regulatory Toxicology and Pharmacology* 61, no. 1 (2011): 73–81.

19 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.

20 Tokuo Sukata et al., "Detailed Low-Dose Study of 1, 1-b™ IS (p-chlorophenyl)-2, 2, 2-trichloroethane Carcinogenesis Suggests the Possibility of a Hormetic Effect," *International Journal of Cancer* 99, no. 1 (2002): 112–18.

21 Louis Anthony Tony Cox, "Hormesis for Fine Particulate Matter (PM 2.5)," *Dose-Response* 10, no. 2 (2012): 209–18.

22 Edward J. Calabrese et al., "Hormesis Predicts Low-Dose Responses Better Than Threshold Models," 309.

23 For a description of adaptive responses in toxicology and preconditioning in biomedicine and how they are subsets of a biphasic dose-response relationship (hormesis) see, for example, Edward J. Calabrese, "Converging Concepts: Adaptive Response, Preconditioning, and the Yerkes-Dodson Law are Manifestations of Hormesis," *Ageing Research Reviews* 7, no. 1 (2008): 8–20.

24 A quick Google Scholar search on "radiation" and adaptive response produces about 750,000 hits.

organisms to react adaptively to low doses of stressors has recently been demonstrated to play a fundamental role in evolution.[25]

Preconditioning and adaptive response may provide an important framework for the development of innovative and effective methods of treatment, such as the use of low doses of X-rays to treat pneumonia by promoting an anti-inflammatory response;[26] the use of low-dose radiotherapy to treat patients with shoulder tendonitis or bursitis;[27] the use of low-dose radiation to protect against kidney damage in diabetic patients;[28] the use of low-dose X-rays to initiate an adaptive response to both higher doses of radiation and to non-radiation stress, such as oxidative damage, a major cause of diabetic complications; and the use of low-dose light therapy to stimulate brain and muscle activity and sharpen memory,[29] to protect against subsequent heart attacks, to promote healing of surgical wounds, and to increase muscular function and physical performance.[30]

The LNT model assumes that there is no "safe" dose above zero. This assumption led to the management theory for ionizing radiation that aims to keep dosage as low as reasonably achievable (ALARA). Under the ALARA principle the goal is not for regulated entities to lower exposure to radiation and maintain an "adequate [level of] protection."[31] The goal instead is to continue pushing exposure levels *as low as reasonably achievable*.[32] If a threshold model is correct, then the continual drive to zero exposure becomes wasteful of valuable resources once levels are pushed beyond the threshold. Such lower levels of exposure would not be harmful to public health per se, but if they are beyond the adequate level necessary to achieve public health and safety protection, then the cost of resources expended to achieve these levels becomes relevant to the Commission. And if, as some literature suggests, a hormetic response is possible at low doses of ionizing radiation, then it may be possible to push the level below the optimal hormetic dose. This is because the ALARA management principle does not countenance the possibility that there may be either a threshold or a positive response at low doses.

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25 Mark P. Mattson and Edward J. Calabrese, eds., *Hormesis: A Revolution in Biology, Toxicology and Medicine* (New York: Humana Press, 2009).

26 Edward J. Calabrese, Gaurav Dhawan, and Rachna Kapoor, "Use of X-rays to Treat Shoulder Tendonitis/Bursitis: A Historical Assessment," *Archives of Toxicology* 88, no. 8 (2014): 1503–17.

27 Calabrese et al., "Use of X-rays to Treat Shoulder Tendonitis/Bursitis."

28 Minglong Shao et al., "Multiple Low-Dose Radiation Prevents Type 2 Diabetes-Induced Renal Damage through Attenuation of Dyslipidemia and Insulin Resistance and Subsequent Renal Inflammation and Oxidative Stress," *PLoS ONE* 9, no. 3 (2014): e92574.

29 Christopher R. Hayworth et al., "In Vivo Low-Level Light Therapy Increases Cytochrome Oxidase in Skeletal Muscle," *Photochemistry and Photobiology* 86, no. 3 (2010): 673–80.

30 Tanupriya Agrawal et al., "Pre-conditioning with Low-Level (Light) Therapy: Light before the Storm," *International Hormesis Society* 12, no. 4 (2014): 619–49.

31 Nuclear Regulatory Commission, "NRC Regulations (10 CFR): Part Index: Section 70.76 Backfitting."

32 Nuclear Regulatory Commission, Office of Nuclear Regulatory Research, *Regulatory Guide* 8.29, July 1981, http://pbadupws.nrc.gov/docs/ML0037/ML003739401.pdf.

III. STANDARDS FOR SELECTING ADEQUATE DEFAULTS IN RISK ASSESSMENTS

Choosing scientific defaults has been defined as "trans-science," meaning defaults fall into the category of "questions which can be asked of science and yet which cannot be answered by science."[33] By their nature, then, many of the default assumptions on which regulatory agencies generally rely for their risk assessments have been subject to controversy over the years.[34] This problem has been recognized in reports dating back to 1983, when the National Research Council (the Council) published *Risk Assessment in the Federal Government: Managing the Process*[35]—the famous Red Book—and the 1994 publication of *Science and Judgment in Risk Assessment*.[36]

In choosing a default standard, the Commission should use the well-recognized standards from government documents and other recommendations by the Council to help guide its choice. This section is meant to help the Commission apply these standards to the choice of a dose-response model as it sorts through a large body of research on dose response, much of which is not in agreement.

The National Research Council has dedicated numerous publications to risk assessment over the past three decades. In 2009, the Council released *Science and Decisions: Advancing Risk Assessment*, in which an entire chapter was dedicated to the "Selection and Use of Defaults."[37] The chapter can be summarized by the following four recommendations:

1. Have a clear choice of defaults to prevent inconsistency resulting from an ad hoc interpretation of the data across the agency's analysis.[38] Further, a default assumption may be well chosen in general, but it is necessary to maintain flexibility in the application of defaults, as substance-specific (here ionizing radiation) data may justify a departure from defaults.[39]

2. Invoke defaults for the steps of the risk assessment where it is necessary to make "inferences beyond those that can be clearly drawn from the available data or to otherwise fill common data gaps."[40] Also, "inferences are needed when underlying biologic knowledge is uncertain or absent."[41]

3. Maintain criteria "available for judging whether, in specific cases, data are adequate for direct use or to support an inference in place of a default."[42]

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33 Wendy E. Wagner, "The Science Charade in Toxic Risk Regulation," *Columbia Law Review* 95, no. 7 (1995) 1613.
34 Committee on Improving Risk Analysis Approaches Used by the U.S. EPA et al., *Science and Decisions: Advancing Risk Assessment* (Washington, DC: National Academies Press, February 24, 2009)
35 Committee on the Institutional Means for Assessment of Risks to Public Health et al., *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC: National Academies Press, 1983)
36 Committee on Risk Assessment of Hazardous Air Pollutants, Board on Environmental Studies and Toxicology, Commission on Life Sciences, and National Research Council, *Science and Judgment in Risk Assessment* (Washington, DC: National Academies Press, 1994)
37 Committee on Improving Risk Analysis Approaches Used by the U.S. EPA et al., *Science and Decisions*, ch. 6
38 Ibid., 190
39 Ibid., 189
40 Ibid., 192
41 Ibid.
42 Ibid.

4. Report and compare alternative risk estimates in the presence of a "comparably plausible" alternative assumption; abandon a default assumption in favor of an alternative assumption when the latter is determined to be "clearly superior" to the former, when "its plausibility clearly exceeds the plausibility of the default."[43]

Consistent with the recommendations from the Council outlined above, I will detail why the NRC may make a fresh assessment of its default assumption, and I propose a solution to the special case where the Commission finds the LNT and hormesis models to be comparatively plausible.

1. Choosing a default may be necessary in cases where data is lacking; yet, even when a default is widely used for other substances and by other agencies, the Commission is not precluded from changing its default assumptions. The Council encourages abandoning a default for an alternative when evidence accumulates and identifies the latter as a more appropriate alternative assumption.

2. In the case of selecting a default model of dose response, the Commission's only explicit justification for adopting the LNT as the default dose-response model for ionizing radiation apparently dates from the July 1981 Regulatory Guide 8.29 titled *Instruction Concerning Risk from Occupational Radiation Exposure*. In this guide, the Commission stated the following:

> Below about 100 rems, studies have not been able to accurately measure the risk, primarily because of the small numbers of exposed people and because the effect is small compared to differences in the normal incidence from year to year and place to place. Most scientists believe that there is some degree of risk no matter how small the dose. Some scientists believe that the risk drops off to zero at some low dose, the threshold effect. A few believe that risk levels off so that even very small doses imply a significant risk. The majority of scientists today endorse either the linear model or the linear-quadratic model. The NRC endorses the linear model, which shows the number of effects decreasing as the dose decreases, for radiation protection purposes.
>
> It is prudent to assume that smaller doses have some chance of causing cancer. This is as true for natural cancer-causers such as sunlight and natural radiation as it is for those that are man made such as cigarette smoke, smog, and

43 Ibid., 201 NRC makes the analogy between the "clearly superior" standard for alternatives and the legal concept of "evidence beyond reasonable doubt." A similar analogy can be drawn for this point where "comparably plausible" can be interpreted as the legal parlance "preponderance of evidence," or the 50 percent range of plausibility The two points can be reasonably summarized as follows when an alternative is comparatively plausible, quantitative model uncertainty should be characterized and presented in the risk assessment, on the other hand, when an alternative is *clearly superior*, it should, then, replace the default Also in a footnote on page 201, the NRC further clarifies the clearly superior standard "The term *clearly superior* should not be interpreted quantitatively, but the committee notes that statistical P values can also be used as an analogy For example, rejecting the null in favor of the alternative only when P<0 05 could be viewed as insisting that the alternative hypothesis is 'clearly superior' to the 'default null'"

man-made radiation. As even very small doses may entail some small risk, it follows that no dose should be taken without a reason. Thus a principle of radiation protection is to do more than merely meet the allowed regulatory limits; doses should be kept as low as is reasonable achievable (ALARA).[44]

Throughout Regulatory Guide 8.29 the NRC is clear about the uncertainties that make its validation of the LNT assumption very difficult. Namely, the biological evidence on the carcinogenic mode of action of radiation is unclear,[45] and the effect of low doses of radiation has to be extrapolated from epidemiological and clinical studies of extremely high doses—hundreds of rems higher than the occupational limit of the time of less than 5 rems per year.

In subsequent documents the Commission still has not found scientific justification for maintaining its LNT assumption. In the face of scientific uncertainty, prudence and conservatism are commonly invoked by an agency as applications of the precautionary principle. In the 2011 *Fact Sheet on Biological Effects of Radiation*, the NRC stated, "The LNT hypothesis is accepted by the NRC as a conservative model for determining radiation dose standards, recognizing that the model may over estimate radiation risk."[46] And its 2014 statement *Radiation Exposure and Cancer* said that "the U.S. Nuclear Regulatory Commission (NRC) accepts the LNT hypothesis as a conservative model for estimating radiation risk."[47]

3. To follow an objective process for determining the appropriate default, the Commission should consider both the evidence that validates the LNT and the evidence that suggests hormesis for a dose-response function for ionizing radiation.[48] In both cases, the Commission should examine the evidence using the NRC's own Information Quality Act guidelines.[49] In short, the NRC should conduct a systematic review of evidence to determine whether the data available support the use of alternative inferences, such as hormesis or threshold, in place of LNT.[50]

4. If, upon completing the systematic review of evidence, the Commission identifies a "clearly superior" default model, then the Commission should adopt that model. If the Commission does not deem either the LNT or the hormetic model as "clearly

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44. Office of Nuclear Regulatory Research, *Regulatory Guide* 8.29, 3–5. It is also worth noting that especially with reference to natural carcinogens, such as sunlight, there is evidence suggesting that too little exposure causes a wide range of cancers owing to vitamin D deficiency. For example, see Cedric F. Garland et al., "The Role of Vitamin D in Cancer Prevention," *American Journal of Public Health* 96, no. 2 (2006): 252–61.
45. Office of Nuclear Regulatory Research, *Regulatory Guide* 8.29, 3–4.
46. Nuclear Regulatory Commission, "Fact Sheet on Biological Effects of Radiation," last modified December 12, 2014.
47. Nuclear Regulatory Commission, "Radiation Exposure and Cancer," last modified October 17, 2014.
48. It is important to note here that studies that simply extrapolate from high to low doses do not constitute evidence of validation of LNT, but merely an application of the hypothesis. For example, in the title of this article in *Nature*, mathematical extrapolation using LNT was implied as validating evidence: "Researchers pin down risks of low-dose radiation." Alison Abbott, "Researchers Pin Down Risks of Low-Dose Radiation," *Nature* 523, no. 7558 (2015): 17–18.
49. Nuclear Regulatory Commission, "NRC Information Quality Guidelines," last modified August 28, 2014.
50. Systematic review of evidence, instead of weight of evidence, is the latest recommendation from the Council Committee to Review EPA's Draft IRIS Assessment of Formaldehyde et al., *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (Washington, DC: National Academies Press, 2011).

superior," and the systematic review instead reveals them to be "comparatively plausible," then the NRC should develop a quantitative model uncertainty analysis in its risk assessment of ionizing radiation, and it should update the protection standards accordingly. That is not to say that a determination that one model is clearly superior to another precludes a quantitative uncertainty analysis—there are many reasons to conduct such an analysis beyond model uncertainty. To that end, I recommend for consideration of the Commission a recent paper coauthored by Edward J. Calabrese, Jaap Hanekamp, and me, titled "Cancer Risk Assessment: Optimizing Human Health through Linear Dose–Response Models."[51] In this paper we propose a method for setting protection standards to maximize public health and safety while harmonizing hormesis and LNT. We argue that, given our inability to validate the dose-response in human populations, if both models are found to be "comparatively plausible," then the prudent course of action is to minimize the harm associated with choosing the wrong one. Based on a diverse dataset, it has been observed that the nadir of the hormetic curve (the point that maximizes the protective hormetic response) is approximately aligned with the dose corresponding to a 10^{-4} response on the LNT curve. Therefore, adopting a 10^{-4} risk estimate offers maximal health protection from cancer by capitalizing on the protective health effects of hormesis while maintaining the functional utility of LNT.

IV. CONCLUSION

After reviewing the NRC's mission, its legislative mandates and constraints, and recent research on low-dose radiation, there appears to be strong evidence to support reconsidering the LNT as the default dose-response model for ionizing radiation.

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 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:[52]

   a. If the systematic review reveals hormesis to be "clearly superior" to LNT, then the NRC should abandon LNT and adopt hormesis.

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51 Edward J. Calabrese, Dıma Yazjı Shamoun, and Jaap C. Hanekamp, "Cancer Rısk Assessment: Optımızıng Human Health through Lınear Dose–Response Models," *Food and Chemıcal Toxıcology* 81 (2015): 137–40.

52 The same methodology can be adopted for testing the weight of a threshold model relative to LNT or 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 IQA guidelines. It should further demonstrate how the studies on which the Commission relies to support its low-dose LNT assumption conform with the NRC's IQA guidelines.