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Subject: Addendum #7 to Hormesis Petition of 2/9/15
Date: Thu, 6 Jun 2019 19:26:26 -0700
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June 6, 2019

Dear Ms. Vietti-Cook:

Attached please find addendum #7 to my hormesis petition of 2/9/15. This addendum is the conclusion of an SNMMI Task Group on the issue of the Linear No-Threshold Hyporthesis.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

A Critical Assessment of the Linear No-Threshold Hypothesis

Its Validity and Applicability for Use in Risk Assessment and Radiation Protection

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Abstract: The Society of Nuclear Medicine and Molecular Imaging convened a task group to examine the evidence for the risk of carcinogenesis from low-dose radiation exposure and to assess evidence in the scientific literature related to the overall validity of the linear no-threshold (LNT) hypothesis and its applicability for use in risk assessment and radiation protection. In the low-dose and dose-rate region, the group concluded that the LNT hypothesis is invalid as it is not supported by the available scientific evidence and, instead, is actually refuted by published epidemiology and radiation biology. The task group concluded that the evidence does not support the use of LNT either for risk assessment or radiation protection in the low-dose and dose-rate region.

Key Words: linear no-threshold, ALARA, radiation carcinogenesis, risk assessment, radiation protection, radiophobia

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The Society of Nuclear Medicine and Molecular Imaging convened a task group to evaluate the dose-response relationship for radiation carcinogenesis at low doses and data in the relevant literature addressing the validity of the linear no-threshold (LNT) dose-response relationship for regulating radiation safety.

Although based on a thorough and critical review of the available scientific evidence, this article is purposely succinct to capture and maintain the attention of our readership. The task group comprised persons representing nuclear medicine, radiation oncology, radiation biology, medical physics, and health physics.

The first assignment of the task group was to assess the validity of the LNT hypothesis. The following question was posed: "Do the scientific data support or refute the linear no-threshold dose-response hypothesis?" The task group concluded after examining the available evidence that, in the low-dose and dose-rate region, the LNT hypothesis is not supported and, instead, is actually refuted by published epidemiology and radiation biology.

Next, the task group assessed whether the LNT hypothesis was appropriately applicable for use in risk assessment and as a model for radiation protection. The importance of this assessment is paramount, because the International Commission on Radiological Protection (ICRP) on page 43 of its Publication 103[1] unequivocally declared the LNT hypothesis to be "the best practical approach to managing risk from radiation exposure" commensurate with the "precautionary principle."[2] And further, despite evidence to the contrary, the Commission considered that the LNT hypothesis "remains a prudent basis for radiation protection at low doses and low dose rates."[3] The task group members concluded that the LNT model is not a practical basis for formulating radiation protection standards, and it does not provide "reliable" risk factors in the low-dose, dose-rate region; it is empirically false. No credible evidence shows that low-dose radiation exposure represents a significant toxin. Radiation at relatively high doses is a weak carcinogen, but this is not true at low doses. Credible evidence of low-dose (<100 mGy) carcinogenic risk is nonexistent; it is a hypothetical prediction derived from the LNT hypothesis. Further, the benefits of diagnostic imaging, using such low doses, far outweigh its claimed risks based on the LNT model.

THE LNT HYPOTHESIS IS NOT SUPPORTED BY EMPIRICAL EVIDENCE: IT SHOULD NOT BE USED FOR RISK ASSESSMENT

The task group's examination of the available scientific evidence identified substantial deficiencies in the underlying foundations of the LNT hypothesis:

1. The LNT hypothesis of radiation carcinogenesis postulates that all acute ionizing radiation exposure down to zero is proportionately detrimental with dose. Although cancer risk is understood at higher radiation dose levels delivered acutely, we find no unequivocal evidence of proportionate risk at lower doses (less than 100 mGy).[4–11] Low-dose risk over background incidence of cancer due to other causes can only be inferred and cannot be known with statistical confidence by linear extrapolation of the risk at high doses.
2. Whether or not low-dose damage is linearly proportionate to dose, the body's defensive responses are nonlinear, leaving the net result nonlinear.[12–14] The body deals with initial radiation damage through a set of well-known protective mechanisms at the cellular and suborgan levels, collectively called the adaptive protective responses, which provide cancer protection through DNA repair involving more than 150 genes, antioxidant production, apoptosis at the cellular level, bystander effects at the multicellular level, and immune system response involving removal of surviving but damaged cells on the organismal level.[15,16] These mechanisms defend the organism against both exogenous and endogenous DNA damage and enhance both survival and maintenance of genomic stability.[17]
3. DNA repair mechanisms may have evolved in a much higher background level of radiation and may have become quite efficient at repairing damage from low-dose exposure. At high

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doses, repair mechanisms are overwhelmed. The LNT hypothesis ignores potential evolutionary factors.[18]

4. The LNT model assumes that radiation damage and associated cancer risk are cumulative. This assumption incorrectly implies the absence of DNA damage repair and cellular turnover and elimination. To the contrary, the published scientific literature confirms the body's ability to respond to radiation-induced damage at low doses and dose rates.[16]
5. The LNT model assumes that radiation-induced risk is independent of dose rate. Although various scientific groups have proposed a dose and dose-rate effectiveness factor on the order of 1.5 to 2 as a response modifier,[19] this factor fails to adequately consider the well-known dose-rate effect,[9,20] such as demonstrated by the practice of fractionation of high-dose radiation therapy, which demonstrates that normal tissue recovery occurs between treatments. In addition to biological changes induced by low doses of acute radiation, it is important to recognize that dose-rate and dose distribution are very important in risk assessment; the same dose delivered at a low-dose rate or to only a part of the body is much less damaging than acute exposure to this same level.[21,22] Dose rate phenomena have been proven at all levels of biological organization from the molecular, cellular, tissue, organ, to whole organisms including humans.[12]
6. The LNT hypothesis assumes that any mutation may lead to a potentially lethal cancer. However, major paradigm shifts better explain recent data.[23] Although DNA damage in the form of initial genetic mutations may be a necessary prequel, single mutations are insufficient as causative factors in cancer induction.[24] The outdated "one mutation equals one cancer" theory has been replaced by the alternative concepts involving failure of multiple defense mechanisms, DNA misrepair, failures of cellular elimination, and loss of immune system function. Functional failures related to dose and dose rate have been demonstrated for the key events in critical carcinogenesis pathways.[25]
7. The average annual natural background radiation dose on Earth ranges from 1 to 260 mSv. Irrespective of the level of background exposure to a given population, no associated adverse health effects proportional to background dose have been documented anywhere in the world.[26] In contrast to LNT-based predictions, several high-background radiation areas (such as Denver, CO; Kerala, India; Yangjiang, China; Guarapari, Brazil; Ramsar, Iran) have the same or lower cancer rates compared with nearby areas with lower background rates.[27,28]
8. Various epidemiologic studies of populations exposed to low levels of radiation have documented benefit (reduced cancer incidence and increased longevity), and not just absence of harm, from radiation exposures.[4,8,14,29]

Upon careful critical review, many recent epidemiologic studies claiming to support the LNT hypothesis factually do not.[30–34] Their conclusions seem overreaching based on the data presented and analyses performed.[35–38]

In 2018, the National Council on Radiation Protection and Measurements (NCRP) published Commentary No. 27, Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection, which was intended to provide a critical review of 29 epidemiologic studies of populations exposed to radiation in the low-dose and low-dose rate range, mostly published within the last 10 years. Commentary No. 27 concluded that the more recent epidemiologic studies supported the idea of continued reliance on the LNT model for radiation protection purposes. According to NCRP Commentary No. 27, only 5 of the 29 studies provide strong support for the LNT model, including the Life Span[39] and International Nuclear Workers[33,34] studies. Several critical reviews by others, however, showed that the cited studies—instead of strong support—provide little if any foundational support for (and actually provided refuting evidence against) the LNT hypothesis.[11,38,40,41] Unfortunately, NCRP Commentary No. 27 chose to ignore these contradictory and inconclusive findings. Further, the Commentary's assessment that the updated analysis of the Japanese Life Span Study (LSS) data, as reported by Grant et al,[39] provided strong support for the LNT model for radiation protection was contradicted by this study's major conclusion:

> *"At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies."*

RISK MANAGEMENT VERSUS RISK ASSESSMENT

An important distinction may be made between use of the LNT model for radiation protection, as concluded by the NCRP Commentary, for formulating policy, and as a scientifically defensible hypothesis. This distinction is referred to as risk management versus risk assessment. Even regulatory agencies, as well as the NCRP, ICRP, and other advisory bodies, draw attention to this distinction and explicitly call for the LNT hypothesis to not be used for risk assessment,[1,42] but instead, only as a foundational assumption guiding radiation protection and regulation under the "As Low As Reasonably Achievable" (ALARA) concept.

Risk assessment is the scientific process of characterizing the nature and magnitude of radiation effects, but the scientific evidence does not support the use of the LNT hypothesis to accurately assess or establish the level of associated risk at low doses. Thus, LNT use is restricted to, and due to its mathematical simplicity assumed to be a prudent model for, radiation protection, that is, the management of risks from low-dose radiation exposure. The authors of NCRP Commentary No. 27 also agreed, stating on page 139 that "the epidemiologic data do not justify using the LNT model and collective doses to estimate the numbers of excess cancers in some large population who received small individual doses."

In 1980, Lauriston Taylor (past president of the NCRP) observed that LNT-based predictive calculations, which continue to be misused, were based on a literal application of the hypothesis, treating it as fact even without statistical or other scientific verification.[43] Such claims, he said, are "deeply immoral uses of our scientific knowledge."

In the United States, regulators have frequently acknowledged deficiencies in the LNT hypothesis, but have continued to accept it and to use it for regulatory language due to (1) ongoing advocation by both NCRP and ICRP, and (2) being unable to find any alternative model.

THE NULL HYPOTHESIS AND BURDEN OF PROOF

Attempting to disprove a null hypothesis may confound correct data interpretation to support or refute the LNT hypothesis. This may be illustrated in the recent epidemiological update of solid cancer incidence among the LSS cohort of Japanese atomic bomb survivors as reported by Grant et al[39] in 2017. In that analysis, the LNT hypothesis was selected as the null hypothesis. Grant et al found that the atomic bomb survivor data did not permit rejection of the null hypothesis (that estimates for thresholds derived from the LSS data cannot be distinguished statistically from zero). However, we maintain that failure to reject a null hypothesis is not the same as confirming its validity,[44] because failure to reject may only result from insufficient confirmatory data rather than from the validity of the null hypothesis. In the case of the LSS, the data were insufficient to reject the null hypothesis due to large uncertainties.

Inability to reject the LNT model (based on insufficient data) should not, as asserted, "preclude definitive conclusions to confidently guide radiation protection policies."

Current regulatory opinion needs to be modified and updated because regulators continue to ignore or dismiss the scientific literature on dose-response, existence of thresholds, and adaptive hormetic effects. Such considerations may reveal that alternative dose-response relationships are more plausible and consistent with the low-dose data than is the LNT hypothesis. Because many epidemiologic studies[5,6,8,29] and various analyses of the LSS data[40,41] have actually documented benefit at low doses, and not just absence of harm, the burden of proof may need to be shifted to those asserting that the LNT hypothesis is correct.

THE LNT MODEL AND RISK MANAGEMENT

According to the ICRP, the LNT model provides a prudent basis for practical application of radiological protection guidelines, meaning proper management of potential risk from low-dose radiation exposure.[3] Risk management, the key driver for policy setting, involves use of the LNT model as well as subjective value judgments.[1] Value judgments may consider practicality, public sentiment, and economic and political considerations. But a regulatory protection policy can only be legitimate when based on correct science. To properly manage risk at low radiation doses, the complete spectrum of possible health outcomes must be acknowledged, including the potential for beneficial effects and dose-and-dose-rate thresholds below which the biological effect cannot be detected. Use of the LNT model effectively excludes these considerations in policy and rulemaking.

Current radiation protection policy accepts the LNT paradigm (based mainly on the Japanese atomic bomb survivor cohort, a population exposed instantaneously to the blast). Individual absorbed doses for survivors in the LSS cohort can only be estimated from survivor-provided information pertaining to their location at the time of the bombing and terrain shielding data.[39] These potentially imprecise and inaccurate bomb survivor doses may have also been underestimated because they were based solely on the initial blast radiation; fallout radioactivity was not accounted for in survivor dosimetry calculations.[45] This omission likely impacted the excess relative risk estimates, leading to an overestimated cancer risk in the cohort—particularly at low doses. According to a 2012 analysis of the LSS data reported by Ozasa et al,[46] there is "insufficient information about fallout or residual radiation to completely rule out this possibility." Given the many uncertainties and incomplete information, the LSS data are not consistent with, and therefore do not support, the LNT model. As previously noted, the shape of the most current derived dose-response relationship reported by Grant et al[39] essentially precluded use of the LNT model to confidently guide radiation protection policies; earlier analyses have also not supported the LNT model.[8,9]

The LSS data-generated radiation cancer risk estimates have unfortunately been assumed to apply to chronic radiation exposures as well as instantaneous exposures. The total dose from nuclear medicine procedures, for example, is protracted; low-dose rates with chronic exposure are known to reduce risk compared with acute exposure of the same total dose.[21] The dose rate and dose distribution from internally deposited radioactive materials are much less effective in producing either life-shortening or increasing cancer frequency compared with the same acute whole-body dose.[47]

Application of the precautionary principle excludes empiric low-dose radiation research. Effective risk management and risk communication may thus be compromised in low-dose scenarios unless it is recognized that use of LNT, and its corollary, ALARA, may not err on the side of caution, but rather result in significant collateral negative consequences, as detailed below.

1. The number of disaster-related deaths resulting from the misguided LNT-based evacuation policy for nearby residents after the 2011 Fukushima Daiichi nuclear accident reached almost 2000, as of 2016. This number exceeds the number of Fukushima residents who were killed directly by the earthquake and tsunami.[48]
2. Fear of radiation at low doses (radiophobia)[14,49] caused many Japanese to avoid important radiologic medical examinations needed to diagnose a traumatic injury or other diseases, such as cancer.[50,51] Without radiological examinations or if the examinations were performed using a radiation exposure that was too low, patients may have been undiagnosed or misdiagnosed.[52,53] Using alternative methods (eg, longer-duration magnetic resonance imaging in place of computed tomography)[54] may be less accurate, and may expose patients to greater risks, such as use of anesthesia for the examination.[51]
3. Focusing on potential risks of diagnostic imaging while ignoring benefits is improper and could even be harmful since the hypothetically projected risks of low-dose radiation exposure are far lower than its actual benefits.[14,55] Such benefits may include the valuable information provided (enabling more accurate and rapid diagnoses, evaluation of extent of disease, or patients' peace of mind for negative examinations), lives saved, improved quality of life, avoidance of unnecessary surgeries, reduced hospital stays, and reduced costs.[56–58]
4. The application of highly conservative radiation dose limits required to achieve adequate remediation or cleanup in the aftermath of contamination or a nuclear accident provide questionable benefit. Excessive amounts of shielding that may be required are expensive and incur unnecessary injuries and deaths from mining lead.

Thus, effective risk management and communication with respect to diagnostic medical imaging and other low-dose uses and scenarios are not possible until LNT and its corollary, ALARA, are universally viewed as being scientifically indefensible.

CONCLUSIONS

Conventional thinking among national and international scientific committees and regulators holds that the LNT dose-response hypothesis cannot be proven or disproven due to large statistical uncertainties, competing causes of cancer, and numerous other confounding factors, such as radiation quality, dose rate, dose distribution, subject age and sex, and various tissue radiosensitivities and responses. However, such thinking discounts the substantial volume of scientific evidence showing the numerous mechanisms by which natural biological processes protect living organisms against low-dose and dose-rate radiation. From a mechanistic molecular and cellular perspective, linear extrapolation from high-dose cancer data to predict the cancer frequency in the low-dose range cannot be supported as a valid biological mechanism, and therefore, is not a valid assessment of risk of radiation carcinogenesis.

Consequently, since LNT has been disproven, it should not be used for risk assessment and in radiation protection simply because it is erroneously thought to err on the side of caution. Focusing on potential risks of diagnostic imaging while ignoring its far greater actual benefits is improper and could even be harmful. In light of the uncertainties and other considerations, the LNT hypothesis and risk factors derived therefrom should not be used to estimate cancer risks for individual patients or patient populations undergoing diagnostic imaging procedures and should not be used

to limit such procedures to clinically manage individual patients. As a corollary to this point, although it is important to record individual patient doses to provide data for future epidemiologic studies and analyses, it is inadvisable to use a patient's dose history to assess the propriety of a planned imaging procedure. The decision to perform imaging should be based solely on medical necessity.

Automatic application of LNT as a model for radiation protection may produce other harms unrelated to dose, such as overly conservative clean-up standards and evacuation requirements after a nuclear accident. No scientific evidence supports the assumed probabilities of cancer in the low dose and low-dose rate region. There are demonstrated dose and dose-rate thresholds below which no adverse effects can be detected. The common opinion that any amount of radiation can be harmful, no matter how small, is a false perception that must be corrected.

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