Commentary

The EPA Cancer Risk Assessment Default Model Proposal: Moving Away From the LNT

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Abstract

This article strongly supports the Environmental Protection Agency proposal to make significant changes in their cancer risk assessment principles and practices by moving away from the use of the linear nonthreshold (LNT) dose–response as the default model. An alternate approach is proposed based on model uncertainty which integrates the most scientifically supportable features of the threshold, hormesis, and LNT models to identify the doses that optimize population-based responses (ie, maximize health benefits/minimize health harm). This novel approach for cancer risk assessment represents a significant improvement to the current LNT default method from scientific and public health perspectives.

Keywords

cancer risk assessment, model uncertainty, LNT, hormesis, threshold, dose–response, US EPA

Linear Nonthreshold—Its Corrupt History and Scientific Flaws

The proposal by the Environmental Protection Agency (EPA)[1] to no longer use the linear nonthreshold (LNT) as the default model in cancer risk assessment is long overdue. It has been extensively documented that: (1) The LNT model has been based on flawed science (ie, Hermann J. Muller never induced point mutations but rather large gene deletions and other gross chromosomal aberrations[2]; (2) the LNT model has incorrect scientific interpretations (ie, Muller incorrectly assumed that his transgenerational phenotypic changes in Drosophila were due to gene mutations)[2]; and (3) the LNT single-hit theory has been formulated under the incorrect assumption that the, Muller X-ray induced gene mutation theory was sound.[3]

Further, the history of LNT has been ripe with deliberate misrepresentations of the scientific record, including (1) the incorrect dismissal of the Caspari threshold findings by Stern and Muller (see study by Calabrese[4]) contradicting a copious research record and substantial private correspondence between Muller and Stern[4]; (2) Muller's powerfully influential comments in his Nobel Prize Lecture were deliberately deceptive[5,6]; (3) scientific misconduct by the entire membership of the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel which lead to governmental adoption of the LNT (ie, publishing deliberately false information in the journal *Science* to enhance the acceptance of LNT; NAS BEAR I Genetics Panel, 1956[4,7]); and (4) serious errors on mutation risks that were introduced into the key Biological Effects of Ionizing Radiation (BEIR) I Report in 1972[8] which were adopted by the EPA in 1975 to justify the adoption of LNT for chemicals and radiation.[9,10]

It is only recently that the BEIR I mistakes and their perpetuation to the present by other US NAS BEIR Committees and their risk assessment implications were reported. The LNT cancer risk assessment policy, procedures, and belief system are based therefore upon a newly recognized series of corrupt actions and mistakes by key national leaders principally in the radiation genetics domain. These controlling deceptions and

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errors have guided the US cancer risk processes from the mid-1950s to the present. As important as these documented errors and deceptions for the LNT model are, a vast scientific literature exists that refutes the low-dose predictions of the LNT model.[11-13,22] Also, LNT falls outside the empirical, as no experiment would actually be possible to causally connect the perturbation of some part of the DNA by 1 ionizing photon/1 genotoxic molecule that subsequently would develop, over the organism's lifetime, into some disorder such as cancer. Linear nonthreshold simply assumes this by default.[14]

Given the present EPA proposal, its major challenge is whether a cancer risk assessment default model is needed, and, if so, what should it be? A default model in cancer risk assessment gets around the practical impossibility of testing agents for cancer risk over a large number of doses and with very large number of animals. This issue was well demonstrated in the now famous Food and Drug Administration ED-01 study that utilized some 24 000 mice.[15] Such studies take too long, are too costly, and they reduce the possibility that other agents get tested, since vast resources would be directed to the massively larger study(ies). In addition, the ED-01 study still could not explore the potential of very low risks without even a more substantial addition of mice.

Based on the history of chronic animal testing and the realization that large experiments were not practical, the National Toxicology Program (NTP) adopted the long-standing historical modus operandi of using the simple few/high doses approach to hazard assessment based on the inadequate assumption that the LNT model could make accurate predictions in the low-dose zone. These few and excessively high doses, however, made it impossible to challenge the LNT predictions as a cancer risk assessment model. Thus, the NTP and the EPA worked together to create a system of evaluation in which the LNT model would become the default for essentially all animal model cancer risk assessments.

The history of EPA risk assessment regulations has been based either on epidemiological or on animal model studies. In either case, knowledge of the nature of the response at low doses affecting normal humans is limited. For most regulated chemicals, adequate epidemiological studies don't exist, and even "adequate" studies have important limitations. The reality of this situation has resulted in regulatory agencies, such as EPA, basing their human exposure standards on high dose/few dose animal studies with mice and rats, needing to extrapolate to humans, often across many orders of magnitude of dose (eg, the history of volatile organic contaminants regulation illustrates this point). The question is how does the EPA find a way out of this regulatory quagmire of using the historically corrupt and scientifically flawed LNT model? The answer is not in basing regulations on mechanistic in vitro studies as helpful as they are, nor on limited and inadequate epidemiological studies as useful as they are, nor on the few/high-dose animal model approach. None of these approaches individually or collectively can offer a solution to the issue of cancer risk assessment.

An Improved Default Model Approach: Model Uncertainty

The best answer, for the foreseeable future, from theoretical data support and public health perspectives is the use of dose–response model uncertainty, that is, using the leading dose–response models and determining where they optimally converge to yield the so-called regulatory sweet spot. This "sweet spot" is the dose where health benefits are optimized, and risks are minimized. The resultant of these converging science-driven processes will yield the optimal public health dose, with changes in dose going either up or down yielding less benefit/more public health harm, thus the sweet spot concept (note 1). In practice, this involves finding a practical and scientific means to integrate the threshold, LNT, and hormetic dose–response models, the 3 models with the most toxicological gravitas based on the peer-reviewed published literature. Each model has its strengths and limits, its advocates, and its detractors. In the interest of full disclosure, the authors strongly favor the hormesis model and feel it is far superior to the threshold model and even more so to the LNT model.[16-18] Nonetheless, it is argued here that the combination and integration of these 3 most substantial dose–response models into a dynamic risk assessment framework works best because it has the potential to integrate the best scientific features of the 3 models while limiting/minimizing the possibility of error.

This process describes/predicts what happens if hormesis is correct or incorrect and the same for the LNT as these 2 models provide the bounds of harm or benefit. The case for this integrated dose–response approach has been published in several peer-reviewed chemical and radiation health risk assessment publications.[4,19,20] Attractive features of this integrative approach are that the nadir of the hormetic dose response, based on a large number of studies in the hormetic database,[11] and the "safe" exposure estimate using the threshold dose–response model with a standard 100-fold uncertainty factor yield essentially the same value. Thus, these 2 models provide an agreement, although they offer a different toxicological interpretation (ie no effect/safe threshold interpretation versus beneficial hormetic interpretation). At this same dose, the LNT model was found to yield a cancer risk approximately 10^{-4} (or 1 per 10 000 people over an 80-year lifespan). This value represents a low risk within society, which is not detectable via epidemiological evaluation under the best of research conditions. It is also about 500-fold lower than the cancer risk from background (ie, spontaneous tumors). Figure 1 provides a description of the integration of the threshold, LNT, and hormesis models within a model uncertainty framework, showing the optimized dose (ie, the regulatory sweet spot). If the hormetic dose–response model predictions are correct, then the benefits to society in terms of disease reduction would be substantial. However, if hormesis was wrong and LNT is correct, the effects would be undetectable, again showing the regulatory sweet spot.

The integration of the 3 most credible scientific models within a model uncertainty suggests that more research still

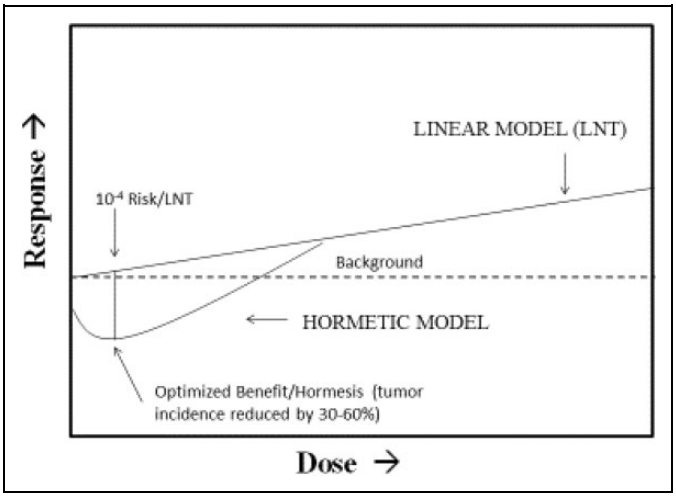

Figure 1. Integration of hormesis and LNT for risk assessment. LNT indicates linear nonthreshold.

needs to be undertaken to improve the reliability of model-based, low-dose estimates. It also raises the possibility that this general approach might be able to be refined and fine-tuned so as to be applied to specific agents. For example, it is possible/likely that the hormetic optima may vary somewhat depending on the specific agent. Despite the remaining uncertainties of this proposed model uncertainty and dose optimization regulatory sweet spot approach, it offers considerable scientific and societal advances over the present LNT model and should be adopted by the US EPA and other environmental regulatory agencies in other countries. It offers a strong scientific foundation, the integrated estimates of the 3 most evaluated models and it errs on the side of safety, while allowing society to capitalize on the potential of significant public health benefits. This perspective is far superior to the current LNT-default risk assessment both from scientific and from public health perspectives. The EPA proposal should be accepted and implemented across all programs involving risk assessment as soon as possible.

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Note

1. It is worth noting that the "optimal dose" or the "sweet spot" proposed in this article is only based on the dose–response science in cancer risk assessment. A work in progress by Dima Shamoun and Richard Williams expands on this idea of optimal dose by marrying economic analysis (in the form of benefit–cost analysis) with dose–response modeling. The idea is that the optimal dose occurs where the marginal cost is equal to the marginal benefit of the reduction in dose. This *economically* optimal dose would take into account regulatory costs, various administrative costs, compliance costs, and risk–risk trade-offs and health–health trade-offs. As a result of this comprehensive calculus, the economically optimal dose may occur at a dose higher than the optimal dose proposed here yet maximizing the net benefits of a risk-based regulation. See, for example, Keeney.[21]

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