Food and Chemical Toxicology ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Cancer risk assessment: Optimizing human health through linear dose–response models

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ARTICLE INFO

Article history:
Received 27 February 2015
Accepted 18 April 2015
Available online

Keywords:
Risk assessment
Dose–response
Hormesis
Linearity
LNT
Precautionary principle

ABSTRACT

This paper proposes that generic cancer risk assessments be based on the integration of the Linear Non-Threshold (LNT) and hormetic dose–responses since optimal hormetic beneficial responses are estimated to occur at the dose associated with a 10^{-4} risk level based on the use of a LNT model as applied to animal cancer studies. The adoption of the 10^{-4} risk estimate provides a theoretical and practical integration of two competing risk assessment models whose predictions cannot be validated in human population studies or with standard chronic animal bioassay data. This model-integration reveals both substantial protection of the population from cancer effects (i.e. functional utility of the LNT model) while offering the possibility of significant reductions in cancer incidence should the hormetic dose–response model predictions be correct. The dose yielding the 10^{-4} cancer risk therefore yields the optimized toxicologically based "regulatory sweet spot".

1. Introduction

The assessment of cancer risks from exposure to ionizing radiation and chemical carcinogens by regulatory agencies worldwide is typically performed via the use of linear at low dose modeling. The linear non-threshold (LNT) approach for cancer risk assessment was first proposed for cancer risk assessment by the U.S. National Committee for Radiation Protection and Measurement (NCRPM) in 1958, following the recommendation of the U.S. National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel to switch from a threshold to a linear model for assessing genomic risk from ionizing radiation in 1956 (Jolly, 2003; Whitemore, 1986).

The LNT approach was later adopted by regulatory agencies starting in the late 1970s assessing risks for chemical carcinogens in all media (e.g. air, water, food and soil) (National Academy of Sciences (NAS), 1977). The initial transition from the threshold to the LNT approach in the mid more 1950s was made prior to the discovery of DNA repair, adaptive responses with chemical mutagens and ionizing radiation, apoptosis, pre-conditioning and the resurgence of the hormetic concept, all of which could affect the shape of the dose response in the low-dose zone. The clarification of different mechanisms of action for carcinogens has encouraged the development of cancer risk assessment methods that incorporate knowledge of species specificity and threshold. These approaches are often employed by the U.S. EPA and FDA and most European authorities for non-genotoxic carcinogens (Page et al., 1997; Whysner and Williams, 1992; Williams, 2001; Williams et al., 2012).

These developments have challenged the theoretical and mechanistic basis of the LNT, along with the recognition that epidemiological methods are in effect not capable of detecting risks below twice the normal background (Taubes, 1995). Furthermore, the massive mega-mouse study that used 24,000 animals was only able to estimate risk at the 1% level (ED01 study) (Bruce et al., 1981). Similar limitations were reported for a cancer bioassay study with >40,000 trout (Bailey et al., 2009). These methodological limitations along with the more recent developmental insights on the plethora of adaptive mechanisms that act at low doses have revealed limitations of the LNT model.

2. Developments

The dose–response model that has been shown to have biological plausibility, especially in the low dose zone, is hormesis, a biphasic dose–response. Current interest in hormesis can be traced back to the research of Thomas Luckey on radiation hormesis (Luckey, 1980) and on chemical hormesis by Tony Stebbing (Stebbing, 1982). These researchers stimulated the electric power utilities of Japan

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http://dx.doi.org/10.1016/j.fct.2015.04.023
0278-6915/

and the U.S. to conduct the first hormesis conference in August, 1985. These three events reactivated interest in the hormesis concept.

Since the initial hormesis conference mentioned here, multiple books have been published on hormesis (Calabrese, 1992, 1994; Costantini, 2014; Elliott, 2008; Luckey, 1992; Mattson and Calabrese, 2010; Rattan and LeBourg, 2014; Sanders, 2010; Stebbing, 2011). Also, many chapters on hormesis in toxicology and pharmacology texts have been produced; hormesis has been the focus of more than a dozen conferences; multiple symposia at major society meetings have addressed hormesis. It is the subject of more than 2000 scientific publications in peer-reviewed journals, and the object of more than 30,000 citations in the Web of Science/Knowledge. Extensive documentations of hormetic dose responses have been summarized from a large and continuously updated database (Calabrese and Blain, 2005, 2009, 2011).

The hormetic dose–response was also found to make more accurate predictions than the LNT or threshold dose–response models in head-to-head comparisons using large, independent data sets (Calabrese and Baldwin, 2003; Calabrese et al., 2006, 2008). Detailed mechanisms of 400 hormetic dose responses have recently been summarized (Calabrese, 2013). Additionally, the hormetic dose response therefore has been demonstrated to be highly generalizable, being independent of biological model (i.e., phylogenetically diverse – from bacteria to humans; in vitro and in vivo), level of biological organization (i.e., cell, organ and organism), endpoint, inducing agent and mechanism.

3. Objective – Integration

Based on these features, it has been proposed that the hormetic dose–response should become the default model for risk assessment for both carcinogens and non-carcinogens. The hormesis database provides strong evidence that dose–response relationships for carcinogens (e.g., DDT, dioxin, multiple PAHs, ionizing radiation) and non-carcinogens typically display hormetic dose response patterns with similar quantitative features. While this line of argument has been made (Calabrese, 2004), this is not the purpose of this paper. The present paper proposes a "practical" and straightforward harmonization of both the LNT and hormetic models for cancer risk assessment. As is customary in such convergences, common ground is sought by various entities (e.g., regulatory agencies and regulated industries), while differences are still recognized and will remain unresolved for now.

We see the following reasons why integration of both models would be beneficial. First, if hormesis describes low-dose exposure impacts of chemicals/ionizing radiation more accurately than the LNT-model does, then the regulatory authorities should apply the best that the toxicological sciences have to offer. The hormetic dose response requires rigorous study designs in order to be properly evaluated, with large numbers of doses, with proper dose spacing, and often within a dose–time framework. When such data are available, the hormetic dose response has far outperformed the threshold and linearity dose response model for accuracy in estimating low dose effects (Calabrese and Baldwin, 2003; Calabrese et al., 2006, 2008).

Second, considering the developments in analytical chemistry, increasingly lower levels of chemicals can be detected. We have entered the realm of atto- (part per quintillion; 10^{-18}) and zeptomoles (part per sextillion; 10^{-21}) of detectable analytes (Pagnotti et al., 2011). Consequently, the unspoken 'logic' of the LNT-model infers that a 'clean bill of health' can never be truly given (Hanekamp et al., 2012). The technology-driven stringency of regulation in the context of the LNT-model can be attenuated with the aid of the biphasic dose–response model. As a result, regulatory expenditures will be reduced along with benefit optimization (Keeney, 1997).

Third, the biphasic dose–response model underscores the beneficial adaptability of organisms' responses to chemical exposure, whereby regulation that expresses the functional integration of both the LNT and hormetic models is better able to address society's fears of carcinogen exposure.

4. Integration – Roadmap

How then do we envision this integration, that is, the harmonization of the hormesis and LNT dose response models for cancer risk assessment? The reconciliation of these two divergent models can surprisingly be made in a direct and uncomplicated fashion.

1) The key aspect of the hormesis/LNT convergence is that when risks are based on chronic animal bioassay studies, the optimal protective effects (i.e., reduction in tumor incidence for the affected below the control group) is predicted to occur at the same dose at which the LNT predicts 10^{-4} risk.
2) To achieve this value, the hormetic-based approach would first estimate a 1% response from the animal bioassay via a BMD-type methodology. When this derived-dose is divided by factor of 100, it yields slightly less than a risk of 10^{-4}. This was shown to be the case for ten highly diverse data sets by Gaylor (1989). The hormetic risk assessment methodology of Calabrese and Cook (2005), which is optimized at the same dose that the LNT estimates a 10^{-4} risk level, predicts benefit while the LNT estimates enhanced cancer risk.
3) We propose that cancer risk assessment adopt an acceptable risk of 10^{-4} using the LNT model since this dose would also yield the optimal hormesis dose response benefit. This dose is the so-called regulatory "sweet-spot" that provides substantial protection against theoretical low dose risks that are far below the detection of even the most demanding epidemiological and toxicological studies/methods, while including benefits predicted by the hormetic dose response model (Fig. 1). This approach would also have the significant societal benefit of affecting a profound reduction in costs (i.e., financial and predicted adverse health), markedly affecting cost/benefit analyses.
4) In a population of one million people, the 10^{-4} risk predicts 100 people (i.e., 10^6 people $\times$ 10^{-4} risk = 100) affected with an organ-specific cancer (e.g., lung, kidney, bladder, etc.) by some deleterious agent that is added to the background for cancer of that organ (Fig. 1). Assuming a 25% tumor background

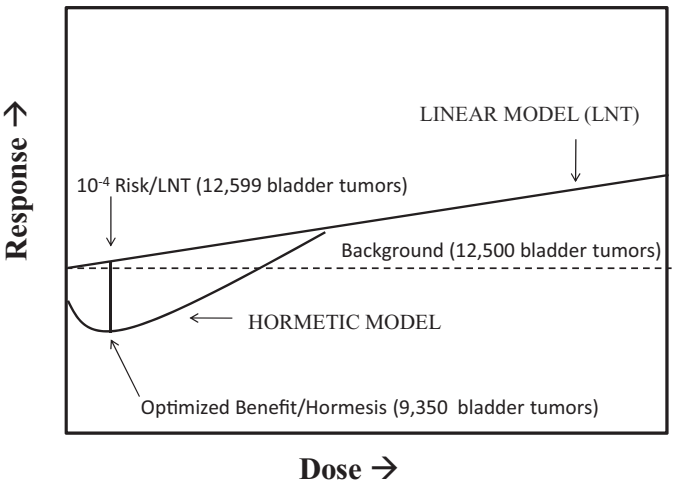

Fig. 1. Functional integration of hormesis and LNT for carcinogen risk assessment; derivation of the optimal regulatory strategy.

Please cite this article in press as: Edward J. Calabrese, Dima Yazji Shamoun, Jaap C. Hanekamp, Cancer risk assessment: Optimizing human health through linear dose–response models, Food and Chemical Toxicology (2015), doi: 10.1016/j.fct.2015.04.023