Rethinking subthreshold effects in regulatory chemical risk assessments

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A great number of dose-response studies indicate that hormesis is a common phenomenon, occurring in numerous organisms exposed to singular or combined environmental stressors, such as pharmaceuticals, heavy metals, micro/nanoplastics, organic flame retardants, pesticides, and rare earths [1–6]. While biological responses to low exposure levels are often beneficial, exposure to doses below the no-observed-adverse-effect-level (NOAEL; hereafter subthreshold doses) does not always translate to beneficial responses[2,4]. For example, subthreshold contaminant doses can enhance the virulence of phytopathogenic microbes and promote the resistance of crop pests with significant implications for crop production [2,7,8]. Subthreshold contaminant exposures can also stimulate infectious animal/human pathogens and promote their resistance to antibiotics and other drugs, threatening long term sustainability. Importantly, the hormetic function of common pathways that regulate cancer progress indicate that current regulatory standards may not protect adequately against cancer risks [9–11].

Current risk assessment frameworks used around the world to assess exposure and effects are largely based on scientific developments from the mid-to-late 20th century, which frequently included only very high (often environmentally unrealistic) doses and the broad assumption of linearity in the response in the absence of evidence of alternative dose-response relationships (Fig. 1) [12–16]. How representative and realistic this approach is increasingly being challenged, in a modern era of analytical advances enabling measurement of low doses and hormetic responses. An expanding scientific literature provides evidence of significant effects of subthreshold contaminant doses on numerous animals, plants, and microbes [1–6]. We opine that regulatory risk assessments on exposure and effects should not be based upon outdated science and biologically-unsupported assumptions regarding linearity. Instead, subthreshold effects and dose-response behavior should be included in the regulatory risk assessment. We urge for this approach to be adopted as part of a more real-life risk simulation approach [17], especially in the light of the growing evidence of genotoxicity of chemicals such as fluoride and arsenic [18,19].

Currently, subthreshold responses/effects in regulatory frameworks are largely not considered in worldwide risk assessments, impeding their identification and evaluation (Supporting Information). In the USA, the US Environmental Protection Agency (EPA) does permit non-linear approaches where adequate evidence is provided to prove divergence from the default linear assumption. However, a recent proposal for the inclusion of subthreshold responses and non-default dose-response models in the risk assessment was not implemented [20]. In 2017 the National Institute for Occupational Safety and Health (NIOSH) acknowledged the dilemma regarding linear extrapolation and endorsed the consideration of non-linear responses for carcinogens in recent new guidelines [21]. The US Food and Drug Administration (FDA) also recognized non-linear responses in 2018 in its guidance document on the assessment and control of mutagenic substances, and permits deviation from the linear-no-threshold (LNT) dose-response model if protective mechanisms exist [22].

In Europe, the European Food Safety Authority (EFSA) has made efforts to evaluate the relevance of subthreshold effects and non-linear responses in recent years [23]. For example, EFSA's scientific committees recently acknowledged subthreshold effects and non-linear responses for bisphenol A and bis(2-ethylhexyl phthalate) and called for internationally-coordinated efforts to identify and address such responses as part of the risk assessment process [24]. The European Chemicals Agency (ECHA) also focuses on threshold and non-threshold events, but does not clearly acknowledge or consider subthreshold effects in its guidelines. It does, however, allow the best-fit dose-response model to be used instead of enforcing default dose-response models [25]. In 2019, China's Ministry of Ecology and Environment published its trial 'Framework Guide to the Technology Methods of Environmental Risk Assessment for

Chemical Substances' [20]. The framework is based on either threshold or linear no-threshold dose-response models, and does not allow for subthreshold responses/effects or more relevant dose-response modeling based on best fit to specific data sets [20].

We strongly advocate the consideration of potential subthreshold effects in chemical risk assessment should no longer be postponed. We opine there is an urgent need for regulatory authorities around the world to be inclusive of the most up-to-date science by (re)considering (i) potential subthreshold responses, (ii) non-linear dose-response models able to detect subthreshold responses, and (iii) abandoning the default use of linear dose-response models for all risk assessments. The current lack of subthreshold responses inclusion in the risk assessment of chemicals undermines the accuracy of the risk assessment process, and consequent remediation practices and actions applied. As a recent example, the hormetic model can predict potential subthreshold effects of disinfectants widely introduced into the environment during the COVID-19 pandemic, unlike the linear-no-threshold and threshold models [5].

This article does not suggest that toxicity thresholds are overly conservative and that risk necessarily exists below current limits, but that subthreshold positive or negative effects exist that are not captured by current threshold and LNT models and need to be part of the evaluation and assessment process. Hence, instead of assuming a specific dose-response model *a priori*, the most suitable/effective model to fit or describe the actual data would be selected *ad hoc*. Such a policy would prevent enforcing the exclusion of subthreshold doses and would allow identification of subthreshold effects, as applicable. Furthermore, as lead regulatory agencies increasingly acknowledge subthreshold responses/effects and non-linear dose responses, scientific research should shift the focus to the effects of lower and environmentally realistic doses to facilitate the development of more accurate risk assessments in the future.

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Supporting Information: Additional text detailing regulatory risk assessment situations in the US (Supporting Text 1), the EU (Supporting Text 2), and China (Supporting Text 3).

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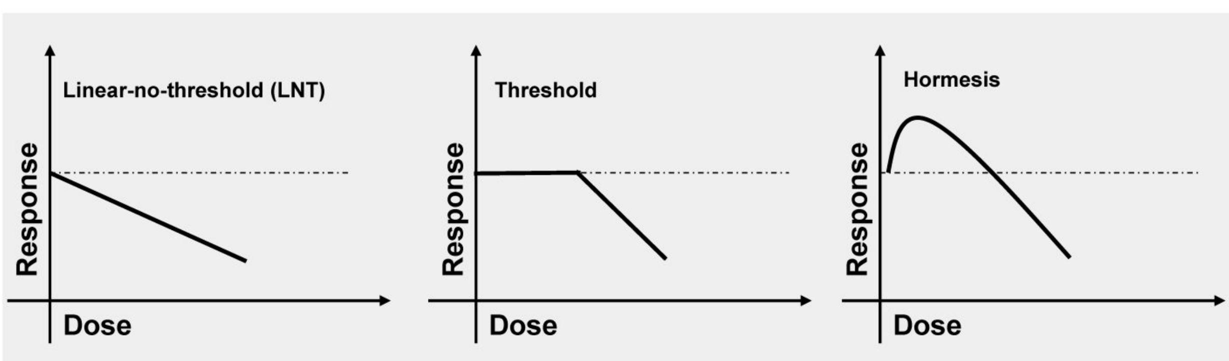
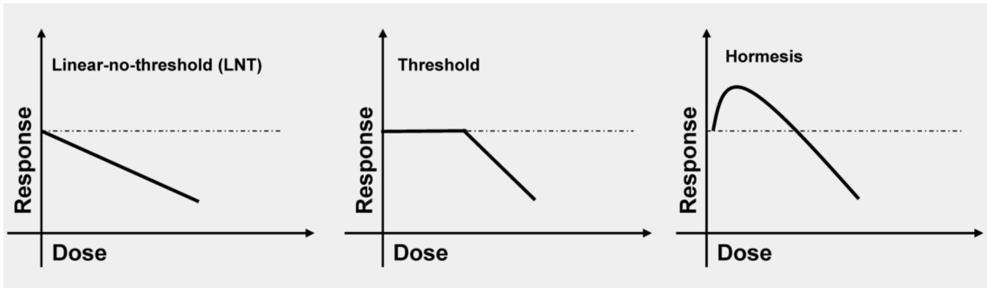
Figure & caption

Figure 1. Common dose-response relationships. Linear-no-threshold (LNT) excludes biological repair mechanisms, toxicological threshold, and significant sub-NOAEL (no-observed-adverse-effect-level) responses. Threshold excludes significant sub-NOAEL responses, while after NOAEL predicting effects similarly to LNT. Hormesis acknowledges significant sub- and super-NOAEL effects. The dashed line indicates the control response. The relationship's direction is endpoint-specific.





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