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Environmental toxicology and ecotoxicology: How clean is clean? Rethinking dose-response analysis

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ABSTRACT

Global agendas for sustaining clean environments target remediation of multimedia contaminants, but how clean is clean? Environmental Toxicology and Ecotoxicology focus on issues concerning "clean". However, the models used to assess the effects of environmental multimedia on individual living organisms and communities or populations in Environmental Toxicology and Ecotoxicology may fail to provide reliable estimates for risk assessment and optimize health. Recent developments in low-dose effects research provide a novel means in Environmental Toxicology and Ecotoxicology to improve the quality of hazard and risk assessment.

1. Body

Global agendas for sustaining clean environments have involved vast public and private-sector investment actions. An early example is the 1990 report of the US Environmental Protection Agency (EPA), which showed that public and private pollution control activities in the US, over a period of 20 years, translated to an investment of $115 billion a year to protect and restore US air, water, and land (US EPA, 1990). The 1970–1990 period was one of growing environmental awareness. However, costs applied to environmental issues have been far greater on an annual basis since 1990. While these actions have centered on remediation of thousands of contaminated sites and related activities, the issue has been repeatedly raised as to how much remediation is needed for safe and acceptable environmental health and human use, yielding a two-fold question; how clean is clean, and what does clean mean?

How hazardous chemical, biological and physical agents that occur in soil, air and water media may affect individual living organisms is the core question of Environmental Toxicology, a multidisciplinary scientific field. Similarly, the effect of such agents on populations, communities and ecosystems is also the core of the multidisciplinary field of Ecotoxicology, which integrates ecology and toxicology and is a subdiscipline of Environmental Toxicology. Therefore, questions concerning the meaning of the word "clean" are a major challenge to Environmental Toxicology and Ecotoxicology. Hence, toxicological predictions of the two research fields are of profound importance for national economies and in maintaining ecological health and sustainability.

We believe that the models used by regulatory agencies to predict adverse effects of environmental contaminants and pollutants via exposure extrapolation and to set standards for protecting organisms against harmful effects, lack scientific validity and are therefore incapable of providing reliable estimates for risk assessment and optimizing health. Such failings have enormous implications, suggesting that essentially all environmental health standards have been inappropriately derived/based significantly compromising health, welfare and vast societal economic resources.

2. Traditional models: limitations

The dose-response relationships of hazardous substances are used by regulatory and drug agencies to generate predictive health/disease outcomes. Two traditional models, which prevailed in the scientific world throughout the 20th century, and adopted by worldwide

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regulatory agencies, are the Linear-Non-Threshold (LNT) and Threshold models. LNT assumes that toxicity increases from a zero exposure level proportionally with increasing levels of environmental stressors (Fig. 1a), whereas the Threshold model assumes that this linear increase starts after an exposure level below which no significant biological effects are assumed (Fig. 1b). However, recent scientific advancements lead us to believe that the most biologically plausible and validated model is hormesis which is characterized by a biphasic dose-response relationship in striking contrast to the threshold/LNT models (Fig. 1c). These developments suggest that LNT and threshold models that prevailed in Environmental Toxicology and Ecotoxicology fail to properly inform and guide risk assessment and risk management decisions to protect against low-exposure risks (Agathokleous and Calabrese, 2020; Shahid et al., 2020).

Environmental Toxicology received attention in the 1950–1960s with concerns of risks from applied agro and industrial chemicals (Koeman and Strik, 1981). The branch of Ecotoxicology was proposed in 1969 at a meeting of an ad-hoc Committee of the International Council of Scientific Unions (ICSU) in Stockholm (Truhaut, 1977). These fields were developed when hormesis was highly marginalized and the threshold model dominated the scientific world as well as the actions of regulatory agencies. The LNT model would become widely adopted in the 1970s following the proposal of the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation Committee Genetics Panel (BEAR I) to use the LNT model for germ cell mutations in 1956, and its reaffirmation and generalization to cancer by the NAS Biological Effects of Ionizing Radiation (BEIR) Committee in 1972 (Agathokleous and Calabrese, 2020). Hence, these two traditional models, which have long dominated Environmental Toxicology and Ecotoxicology, are typically based on only a few very high and environmentally unrealistic exposure levels in animal model studies (Agathokleous and Calabrese, 2020; Freixa et al., 2018).

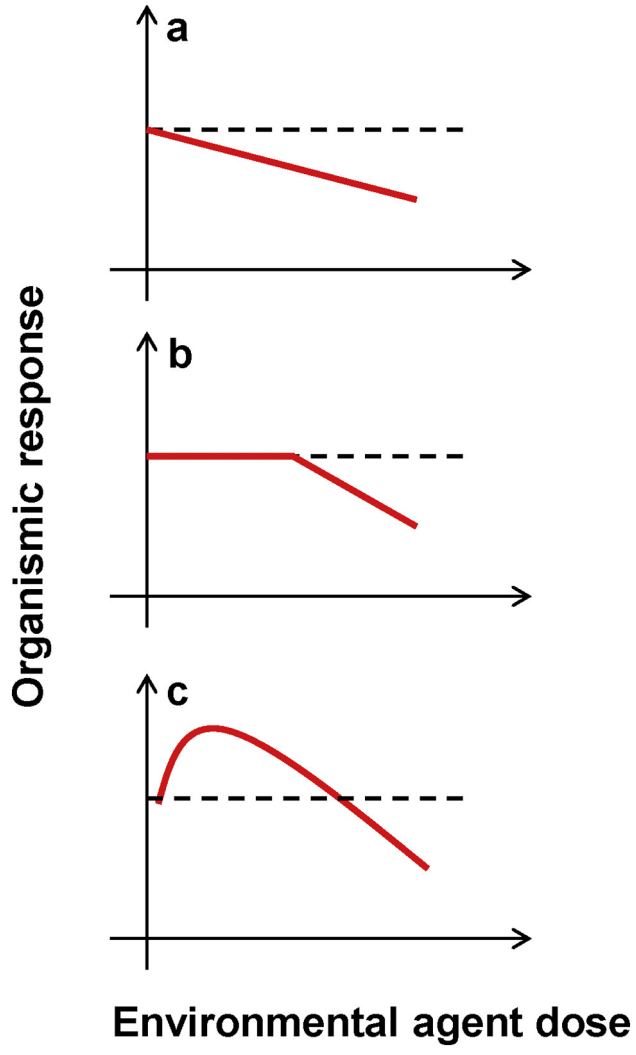

Fig. 1. Hypothetical dose-response models for (a) linear non-threshold (LNT), (b) threshold and (c) hormesis. The dashed line indicates the response of the control group (background response).

3. Hormesis: evolutionary-based and biologically plausible

Not only is it well documented that some environmental contaminants may not induce adverse/toxic effects at concentrations occurring in the environment nowadays (Agathokleous and Calabrese, 2020; Freixa et al., 2018), but it is also extensively demonstrated that multimedia contaminants upregulate adaptive responses in biological systems at low doses, displaying biphasic hormetic relationships (Agathokleous and Calabrese, 2020; Morkunas et al., 2018; Muszynska and Labudda, 2019; Shahid et al., 2020). Importantly, these observations are not restricted to the level of individual, which is the study of Environmental Toxicology, but also appear at higher levels of biological organization, such as at community level, including changes of community composition at low doses, which is the study of Ecotoxicology, in both aquatic and terrestrial environments (Agathokleous and Calabrese, 2020; Amaral et al., 2019; Colin et al., 2019; Li et al., 2020; Skubała and Zaleski, 2012; Su et al., 2019; Zheng et al., 2017; Wang et al., 2020). These advancements suggest that there are no absolutely toxic chemicals or other environmental stressors but only toxic doses/concentrations.

Hundreds of published papers, including extensive retrospective quantitative analyses published in the last 5 years, document that many environmental contaminants and pollutants induce hormesis. Many biological mechanisms of hormesis have been identified in various organisms subjected to many environmental stresses (Calabrese, 2013; Poschenrieder et al., 2013), but hormesis quantitative characteristics are independent of the biological mechanism (Calabrese and Mattson, 2017). Environmental stresses inducing hormesis include agrochemicals, human and veterinary pharmaceuticals, nanomaterials, radiation, rare earth elements, toxic ions, and many others (Agathokleous and Calabrese, 2020; Brito et al., 2018; Carvalho et al., 2020; Geihs et al., 2020; Iavicoli et al., 2018; Muszynska and Labudda, 2019; Poschenrieder et al., 2013; Shahid et al., 2020). Organic chemicals also induce hormesis, including not only chemicals occurring endogenously in organisms, e.g. carbohydrates, fats, polyphenols, reactive carbonyl species and resveratrol (Baur and Sinclair, 2004; Han et al., 2017; Juhasz et al., 2010; Lee et al., 2018; Martucci et al., 2017; Semchyshyn, 2020; Wall et al., 2015; Zemva et al., 2017), but also environmental organic contaminants/pollutants, e.g. carbon tetrachloride and polychlorinated biphenyls (Agathokleous and Calabrese, 2020; Hasmi et al., 2015; Ugazio et al., 1972). Low dose of ionizing radiation has been shown to display hormetic effects in plants, animal models (Calabrese, 2000; Calabrese and Blain, 2011) and humans in numerous epidemiological studies (Doss, 2013, 2018; Feinendegen and Cuttler, 2018; Scott, 2008).

Low-dose induced stimulation is commonly up to 60% above the control response (Calabrese and Blain, 2011). The median maximum stimulation ranges between 120 and 125% for animals, microorganisms and plants (Calabrese et al., 2019). When there are more than 5 doses below the toxicological threshold, the median maximum stimulation in animals, microorganisms and plants increases to 160–190% above control (Calabrese et al., 2019). Because the entire toxicological literature suffers from inadequate dosing for permitting the detection of hormesis (Calabrese and Blain, 2011), the magnitude of the maximum stimulation might be underestimated (Calabrese et al., 2019). An analysis of the toxicological literature also revealed that the width of the

stimulatory zone was below 100 fold in 69–88% of 5668 dose-response relationships for animals, bacteria and plants (Calabrese and Blain, 2011). The ratio of toxicological threshold to the dose inducing maximum stimulation also was below 5 fold in 63% of 5325 dose-response relationships (Calabrese and Blain, 2011). These suggest that hormesis quantitative characteristics are highly generalized across organisms, stressors, endpoints and biological mechanisms (Agathokleous and Calabrese, 2020; Agathokleous et al., 2019a; Calabrese et al., 2019; Shahid et al., 2020). Hormesis also occurs frequently when the experimental design permits its detection, i.e. if not only high doses are incorporated in the experiment (Calabrese, 2017; Calabrese et al., 2006; Nascaerlla et al., 2009). Based on a priori entry and evaluative criteria, the hormetic model has been found to have a higher consistency with examined dose-response data than the threshold or LNT models in some cases (Calabrese, 2017; Calabrese et al., 2006; Nascaerlla et al., 2009).

Copious environmental stressors induce the accumulation of reactive oxygen species (ROS), with the potential to lead to adverse biological effects, including cell death, at high doses/exposures (Czarnocka and Karpiński, 2018). However, mild levels of ROS commonly enhance stress resistance, improve redox homeostasis and prolong lifespan, thus, being essential for healthy cellular functioning (Bazopoulou et al., 2019; Czarnocka and Karpiński, 2018; Geihs et al., 2020; Veskousis et al., 2020). ROS can promote mitohormesis, where low non-cytotoxic ROS concentrations promote mitochondrial homeostasis (Palmeira et al., 2019). These new understandings, along with further recent developments in stress biology, support a conclusion that the most biologically plausible and validated dose-response model is hormesis, not the LNT or Threshold models (Agathokleous and Calabrese, 2020; Geihs et al., 2020). Among others, mild exposures to heat and other environmental stressors can precondition organisms, and mediate heat-shock protein and a plethora of other gene products that function in response to stress, generating anti-proteotoxic mechanisms, inducing autophagy and prolonging lifespan, with potentially survival advantages to descendants (Kishimoto et al., 2017; Kourtis et al., 2012; Kumsta et al., 2019). Hence, environmental stressors have the potential to counterbalance the harm of all known toxins (Lee and Lee, 2019), and protect against more severe environmental challenges (Govindan et al., 2018; Wang et al., 2019).

The long-standing exclusion of the low-dose region in hazard assessment practices has led to incorrect toxicological predictions of below threshold responses that could be either harmful or beneficial (Agathokleous and Calabrese, 2020; see also Kim et al., 2018). Recognizing such hormetic developments, the EPA has recently questioned long-standing LNT-based assumptions about the risks of low-level exposure to radiation and environmental contaminants (Agathokleous et al., 2019b; Servick, 2018). The role of hormesis in ecotoxicology has been also debated in the previous decades (Kefford et al., 2008). However, the remarkable progress in the field in the recent years suggests that hormesis should be at the center of ecotoxicology as well as environmental toxicology. Hormesis model appears to be a standard model among several other models that occur within the current modeling framework of ecotoxicology or environmental toxicology (Ritz, 2010; Ritz et al., 2015). Hormesis provides the possibility to "let the data speak", i.e. decide between different models given that a study is designed to cover the full dose-response continuum. Assuming a certain model is always true and setting it default based on personal beliefs and dogmas, e.g. as is the case of the LNT model, can lead to hazard and risk assessment falling apart. Instead, the current science urges to move toward frameworks of data-based model selection characterized by objectivity rather than subjectivity.

4. Paradigm shift and implications

These recent advancements concerning the nature of the dose response in the low-dose zone and its mechanistic foundations suggest that the historically entrenched concept of "less is better" which embodies the all pervasive "Precautionary Principle" is incorrect, as demonstrated by thousands of hormetic biphasic dose-responses induced by numerous environmental contaminants on a vast array of life forms and at multiple organization levels (Agathokleous and Calabrese, 2020; Morkunas et al., 2018; Muszynska and Labudda, 2019; Shahid et al., 2020). The hormetic dose-response concept is also very general, with extensive documentation in the biomedical sciences with extremely broad applications and implications. These new dose-response findings, which are highly generalizable and evolutionary-based, offer Environmental Toxicology and Ecotoxicology the means to improve the quality of hazard and risk assessment.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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