

Thresholds and Endocrine Disruptors: An Endocrine Society Policy Perspective

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The concept of a threshold of adversity in toxicology is neither provable nor disprovable. As such, it is not a scientific question but a theoretical one. Yet, the belief in thresholds has led to traditional ways of interpreting data derived from regulatory guideline studies of the toxicity of chemicals. This includes, for example, the use of standard “uncertainty factors” when a “No Adverse Effect Level” (or similar “benchmark dose”) is either observed, or not observed. In the context of endocrine-disrupting chemicals (EDCs), this approach is demonstrably inappropriate. First, the efficacy of a hormone on different endpoints can vary by several orders of magnitude. This feature of hormone action also applies to EDCs that can interfere with that hormone. For this reason, we argue that the choice of endpoint for use in regulation is critical, but note that guideline studies were not designed with this in mind. Second, the biological events controlled by hormones in development not only change as development proceeds but are different from events controlled by hormones in the adult. Again, guideline endpoints were also not designed with this in mind, especially since the events controlled by hormones can be both temporally and spatially specific. The Endocrine Society has laid out this logic over several years and in several publications. Rather than being extreme views, they represent what is known about hormones and the chemicals that can interfere with them.

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Key Words: endocrine disrupting chemicals, threshold, toxicology, environmental regulations

In a commentary recently published in *Critical Reviews in Toxicology* [1], Dr Brescia lays out the logic to support a risk-based approach to regulating endocrine-disrupting chemicals (EDCs). Key to this approach is the assumption of a threshold of adversity. We, as members of the Endocrine Society’s Endocrine-Disrupting Chemicals (EDC) Advisory Group, would like to address two key scientific issues.

1. *Thresholds of adversity.* Key to risk assessment is the identification of a threshold of adversity, that is, the highest dose that does not produce an observable effect on a chosen endpoint. But, the choice of endpoint is key. For example, the concentration of lead required to affect measures of cognitive function in children is far less than the lethal dose

Abbreviations: EDC, endocrine-disrupting chemical; EPA, Environmental Protection Agency; OECD, Organization for Economic Co-operation and Development.

Received 23 June 2020

Accepted 7 July 2020

First Published Online 09 July 2020

Corrected and Typeset 10 September 2020

October 2020 | Vol. 4, Iss. 10

doi: 10.1210/jendso/bvaa085 | Journal of the Endocrine Society | 1–7

in adults (eg, [2, 3]) Since regulators initially developed safety determinations for lead exposures based on morbidity and lethality in adults, millions of children were harmed.

Lead toxicity presents another challenge: what should be done when no safe level of exposure can be identified [4-6]? This point could not be made any clearer than the United States Centers for Disease Control 2012 report on childhood lead poisoning prevention, which states, “New studies and re-interpretation of past studies have demonstrated that it is not possible to determine a threshold below which [blood lead level] is not inversely related to IQ” and “it is now clear that there is no known threshold below which adverse effects of lead are absent.” [7] In this case, it can be argued that a threshold for the effect of lead on brain development and IQ could exist, but one has not been demonstrated empirically. Given that the estimated “safe” level of chemical exposure often decreases as new data become available, it is clear that the early estimates of safety are often insufficient to protect human health [8].

Lead is not alone in its ability to have effects at even very low levels of exposure [9-13]. Unfortunately, documented low-dose effects exist for dozens, if not hundreds of chemicals, including EDCs. Despite the fact that human exposures are low, below the levels that cause mortality or other overt signs of toxicity in laboratory animals, epidemiological studies continue to document associations between EDCs and human disease outcomes in a manner that is concordant with mechanistic studies [14-22]. For EDCs, this reality was acknowledged in a 2017 report by the United States National Academy of Sciences [23], which provided recommendations on how the Environmental Protection Agency (EPA) should conduct investigations for low-dose effects of EDCs in a regulatory context. In addition, as professors Demeneix and Slama state in a report for the European Parliament [24], approaches used in regulatory toxicology still do not take into account the effects of chemical mixtures that impinge on the same endocrine signaling pathways or on interacting hormones [25]. All children are exposed both prenatally [26] and postnatally [27] to multiple xenobiotics, many of which have the potential to interfere with the endocrine system. This emphasizes the need for caution in the use of thresholds focused on individual chemicals.

During a consensus meeting that included regulators, toxicologists, epidemiologists, and endocrinologists, a consensus was reached on a series of scientific principles to identify EDCs [28]. It was agreed that the concept of thresholds should be further researched. The statement on this point concludes “that it may be difficult to distinguish a true threshold from an apparent threshold which merely arises from the limits of detection of the experimental system. Thus, the question of the existence of dose-thresholds for endocrine disruptors cannot be resolved through empirical dose-response studies alone but has to rely on mechanistic investigations and increased knowledge on the functions and programming of the endocrine system during specific windows of sensitivity.” Moreover, given that the estimated safe level of chemical exposure is often decreased as new data become available, the early estimates including uncertainty factors demonstrate that estimates of the true or practical threshold were overestimated [8].

Furthermore, there are several additional reasons why the validated endpoints employed in the Organization for Economic Co-operation and Development (OECD) guidelines may fail to provide clear information about whether or not a threshold exists. First, there is the sensitivity of the biological outcomes evaluated. For example, the uterotrophic assay focuses on organ weight, even though many endocrine-disrupting effects do not entail any change in the overall organ weight (see [29] for an example). Second, the variability in results obtained in studies such as the uterotrophic assay depends on protocol differences, all permitted within validated guidelines, including the use of rats or mice and their different strains, or injection versus gavage [30]. Third, there is the assumption

of a monotonic dose response in regulatory testing that influences all aspects of study design; monotonicity is an unlikely default assumption for most EDCs [13].

The commentary concludes that “a threshold approach to the risk assessment of [EDCs] is scientifically justified.” However, it can only be justified if you ignore that endpoints of adversity in standard toxicological studies are not sensitive to EDCs [31, 32], that uncertainty factors often overestimate the theoretical threshold, and that mixture effects are not considered.

2. *Hormones and development.* (Brescia, 2020) also makes the statement that it is an “extreme position” to hold that the developing organism has “homeostatic mechanisms [that] are not sufficiently developed such that a threshold of adversity cannot be assumed for EDCs acting during the developmental stages of the life cycle.” The commentary further states that this position is “not supported by decades of observations and safety testing of developmental toxicants, with little evidence suggesting that the fundamental rules governing endocrine function cease to apply during this life stage...”.

To be clear, framing the position of the Endocrine Society [33] as extreme throws into sharp relief the difference between the author’s perception of regulatory toxicology and that of fundamental science. The Endocrine Society is the largest and oldest society of clinicians and scientists focused on understanding hormone systems in health and disease. It has more than 18 000 members and was founded over 100 years ago. We are further concerned about the juxtaposition in the article of the consensus position of a longstanding medical and scientific society with commentary from industry consultants. Moreover, use of the term “endocrine function” in the statement above is ambiguous. Because the human fetus does not have a functional thyroid gland during the first trimester of development, despite having a requirement for thyroid hormone for normal development during this period [34, 35], endocrine function obviously changes through development. Perhaps instead what (Brescia, 2020) refers to is “endocrine action.” Clearly, we are well aware that the fundamental rules of endocrine actions are the same throughout the life cycle (eg, [36, 37]). Rather than being an extreme view [33], it is uniformly held by scientific societies that fetal development represents a very complex time of hormone action. Thus, the downstream actions of hormones are often quite different during development compared with the adult, the sensitivity of the fetus to the same hormone is often much greater during development, and the effects downstream of hormone action are often not reversible [38-41].

The crux of our perspective, supported by decades of endocrine science, is that if a chemical interferes with the action of a specific hormone, the effects of exposure will be consistent with those actions. For example, an antiandrogenic chemical exposure during fetal development would interfere with testosterone action in the brain and produce effects that in some cases would not be observed until adulthood [32]. Moreover, because the developing brain is very sensitive to testosterone, the dose at which an antiandrogenic chemical would produce adverse effects in the fetus would be lower than those required to interfere with testosterone actions in the adult.

We specifically note that many of the adverse outcomes of EDCs are not evaluated in standard regulatory toxicology testing such as altered neurite outgrowth, neuronal migration, and myelination (and more) in the brain following thyroid hormone disruption. Further, there is no guideline study that evaluates brain sexual dimorphisms, or sensitive social behaviors in rodents that have had alterations to these sensitive brain regions [42-44]. While the US EPA defines an adverse neurodevelopmental effect as “an adverse change in the structure or function of the central and/or peripheral nervous system...” [45], there are no sensitive markers of these events in current test guidelines. Also, no regulatory toxicology tests exist that evaluate the impacts of environmental chemicals on mammary gland morphology or development, and the evaluation of outcomes relevant to breast cancer are recognized to be insufficient [46-49].

Even though the US EPA defines an adverse effect as “a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or **reduces an organism’s ability to respond to an additional environmental challenge,**” [[50] emphasis added], there are no guideline studies that evaluate whether exposures to EDCs alter the response of animals to environmental stressors. Yet, numerous studies show that animals exposed to EDCs are more sensitive to hormones, carcinogens, allergens, and other environmental challenges (eg, [51-54]). The recognition of these weaknesses in EDC testing was the basis for a major effort in the European Union funded by Horizon 2020 to identify better endpoints that can be captured by OECD test guidelines [55]. These are hardly extreme positions.

The suggestion that fetuses, neonates, and infants have sufficient “homeostatic” functions to protect them from environmental pollutants is in fact an example of an extreme position that is not supported by evidence. There are numerous studies documenting that the fetal compartment acts as a depot for some chemicals including EDCs (eg, perfluorinated compounds [56], polybrominated diphenyl ethers [57]). Furthermore, regulatory toxicologists acknowledge the insufficiency of homeostatic functions at different life stages when using adjustment factors to account for life stage during risk assessments. Yet, even the standard default uncertainty factor of 10, which is typically used to acknowledge the increased vulnerability of fetuses, neonates, infants, and children, is often insufficient; numerous studies provide evidence that individuals at these vulnerable stages of development are more than 10-times more sensitive than adults [58, 59]. This reality has also been acknowledged by regulators in the United States [60].

Endocrinology is a scientific field that relies upon the theory of falsifiability (sometimes also referred to as the Popper framework). In our field of study, for a hypothesis to be credible, it must be disprovable. In contrast, (Brescia, 2020) describes a framework where the demonstration of a true threshold would “entail studying an infinite number of organisms of the species in question... using infinitely precise measures... and an infinite number of doses...” The author acknowledges that “hypotheses regarding where on the dose-response curve the true threshold lies are beyond the ability of science to resolve” and is therefore not a scientific question.

The Endocrine Society holds that rigorous scientific evidence, including fundamental features of endocrinology, should inform safety determinations, even when these features challenge and force us to rethink conventional concepts in toxicology. Thus, it is essential to identify the threshold of empirical data required to identify safe levels of chemicals to which we expose the entire human population.

Acknowledgments

The authors wish to thank Dr Joe Laakso, director of science policy for the Endocrine Society and Dr Shirlee Tan, toxicologist with Public Health—Seattle & King County for their careful review and comment on this commentary.

Additional information

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Disclosures & Disclaimers: This letter was drafted in response to the commentary by Dr Brescia, “Thresholds of adversity and their applicability to endocrine disrupting chemicals”. This response is submitted by the authors (Barbara Demeneix, Laura Vandenberg, Richard Ivell, and R. Thomas Zoeller) on behalf of the Endocrine Society’s Endocrine-Disrupting Chemicals Expert Advisory Group and the members of this Advisory Group.

The Endocrine Society's EDC Advisory Group provides coordinated oversight and guidance on Society activities related to Endocrine-Disrupting Chemicals (EDCs) covering all relevant Society functions, including publications, education, and policy. The EDC-related positions and priorities that the Endocrine Society advocates for are described in our Position Statement on EDCs (<https://www.endocrine.org/advocacy/position-statements/endocrine-disrupting-chemicals>) and Position Statement on EDCs in the EU (<https://www.endocrine.org/advocacy/position-statements/endocrine-disrupting-chemicals-in-the-european-union>).

None of the authors received funding from any source for this commentary. The views expressed here are the professional opinions of the authors and do not necessarily reflect those of their employers or any agencies that have funded their work. There are no contractual relations or proprietary considerations that restrict the authors' publication or dissemination of the findings described in the manuscript.

Dr Demeneix is currently the chair of the Endocrine Society's EDC Advisory Group and is co-chair of one of its Task Force groups. Her EDC-related research has been funded by government and EU agencies and foundations. Dr Demeneix holds a patent under the name "Transgenic clawed frog embryos and use thereof as detectors of endocrine disruptors in the environment" filed in 2002 (number FR020669) and extended by a Patent Cooperation Treaty filed in 2003.

Dr Vandenberg is currently a member of the Endocrine Society's EDC Advisory Group, is co-chair of one of its Task Force groups, and a member of 2 other Task Forces. She is also a member of the US EPA's Science Advisory Board Chemical Assessment Advisory Committee and a scientific advisor (unpaid) to 2 Horizon 2020 EDC grants. Her travel has been sponsored by various government, academic, and industry groups to present findings of her research. Dr Vandenberg's EDC-related research has been funded by US government agencies, the University of Massachusetts Amherst, and nongovernmental organization including the Cornell Douglas Foundation and the Great Neck Breast Cancer Coalition.

Dr Ivell is currently a member of the Endocrine Society's EDC Advisory Group and is Editor-in-Chief of the specialty section "Reproduction" for the journals *Frontiers in Physiology* and *Frontiers in Endocrinology*. His EDC-related research has been funded by government and academic agencies.

Dr Zoeller has served on various advisory boards and panels of the US EPA, the National Institutes of Health and Pew Charitable Trusts in relation to issues of EDCs. He is currently a member of the Endocrine Society's EDC Advisory Group and is co-chair of one of its Task Force groups. His travel has been sponsored by various government, academic, and industry groups to present findings of his research. Dr Zoeller's research has been funded by government agencies in the United States and the European Union.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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