ENDOCRINE SOCIETY
Hormone Science to Health

Endocrine Society Public Consult Comments
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2.1.1. Have you conducted or are you aware of an assessment of substances which would be identified as endocrine disruptors according to option 1?

No

2.1.2. Are you aware of any assessment(s) of substitutability of the identified substances?

No

2.1.3. Are you aware of any assessment(s) of the socio-economic impact if the identified substances were regulated without further risk assessment?

No

Note, we also answer **no** to questions 2.2.1, 2.2.2, 2.2.3, 2.3.1., 2,3,2., 2.3.3., 2.4.1., 2.4.2., 2.4.3.

2.1.4. Please, provide us with any other comments you may have regarding option 1:

The Endocrine Society is a global organization with more than 18,000 members in more than 100 countries dedicated to research on hormones and treatment of patients with endocrine diseases and disorders. The Endocrine Society has developed comprehensive reports on EDC science, including its 2009 Scientific Statement on EDCs [1] and its 2012 Statement of Principles for Public Health Protection, which highlights how current regulatory approaches are insufficient to identify EDCs [2]. This same conclusion was also derived for the European system by a major report requested by the European Commission [3]. The Society expects to publish a new Scientific Statement on EDCs before the close of the impact assessment.

The Society considers Option 1 to be inappropriate, as the status quo does not provide adequate assessment of endocrine activity for the tens of thousands of chemicals already on the market, or for new chemicals. Unlike for carcinogens and reprotoxins, which fall under cut-off criteria, language in current regulations regarding endocrine disruptors is not well defined. Therefore, significant ambiguity remains as to the definition of, and potential regulatory action for EDCs. Furthermore, interim criteria are not fit-for-purpose because they do not identify the full range of EDCs. Examples of regulatory failures include PCBs, whose production was banned by legislation, and now we know that PCB exposures produced adverse effects on children (e.g., [2]) through an endocrine-mediated pathway. Similar evidence is likewise accruing for flame retardants (e.g., [4]) and plasticizers (e.g., [5, 6]). The case studies highlighted in “Late Lessons from Early Warnings” emphasize these points [7].

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EDC criteria should apply generally to chemicals regulations, and not only to those for biocides and pesticides. Therefore, science-based criteria should be developed and applied to all current and future regulations.

2.2.4. Please, provide us with any other comments you may have regarding option 2.

The Endocrine Society largely supports the scientific approach outlined in Options 2 and 3. However, we prefer Option 3, due to certain weaknesses in Option 2, specified below.

In subsections a)i), and e)iv), the term "endocrine-mediated" is not clear, consequently it is used by different parties to mean different things. Often "endocrine-mediated action" is used to convey the idea that a chemical can produce an adverse effect by perturbing a single class or system of hormones interacting with a receptor. However, this is inconsistent with the observation that a single chemical or class of chemicals can interact with different endocrine pathways, and that endocrine systems are often linked.

Therefore, the term "endocrine-mediated" should be clarified to specifically indicate that the adverse outcome was plausibly caused by a substance interfering with hormone action. By "hormone action", we mean "hormone receptor activation", recognizing that many hormones have multiple receptor isoforms including nuclear and/or membrane or other receptors that "transduce" hormone signals into cellular actions that affect development and/or physiology. It should also reflect the WHO-IPCS definition, which encompasses all endocrine systems and effects including a) receptor-mediated effects; b) interference with endogenous ligand delivery to the receptor; and c) epigenetic effects.

Subsection a)ii) should not limit the evidence to that from experimental studies but should explicitly allow the incorporation of human epidemiological data into data assessment, in combination with experimental evidence, laboratory data from animal models, and other model systems and high-throughput and modeling approaches.

Subsection c) The term "adverse effects" must include effects not only during and after exposure throughout an individual's lifetime, but also possible effects on future generations (i.e. transgenerational effects). The science suggesting that this can happen in some cases has advanced in both laboratory animals and humans [9-14].

Subsection d) should specify the information needed to demonstrate that effects are clearly not relevant to human health in the contexts described. It should be made clear that a simple lack of evidence of relevance does not constitute a clear demonstration of non relevance. Moreover, it is important to discriminate between an endocrine mechanism being not relevant to humans versus an endpoint being non relevant. For example, the mechanism of ovulation in the female rodent depends on the hypothalamus to a greater extent than in primates including humans. However, this does not mean that EDCs lead to ovulatory disorders in the female rodent but not in humans. This means that reproductive failure after EDC exposure involves different species-dependent mechanisms.

The default assumption should be that an effect seen in mammalian animals should always be considered as relevant for humans. Establishing lack of relevance would require the ethical investigation of both the effects and the mechanisms of a given EDC throughout the lifespan of an organism, and detailed knowledge that such mechanisms certainly do not operate in the human. The lack of evidence for an effect in humans from epidemiological studies should not replace and negate the evidence from animal studies.

Subsection e)iii) refers to "expert judgement". The Endocrine Society strongly supports the involvement of experts in the evaluation of studies to ensure that studies are of sufficient quality and relevance to have contributed to the knowledge base of the field. We assert that for EDCs, endocrine scientists need to be involved in these processes. We define "endocrine scientists" in this context as individuals with a research-based understanding of relevant endocrine system(s) and mechanisms, and who have recently made or are currently making significant contributions to the advancement of knowledge in the field of hormone action.

Q2.3.4 - Please, provide us with any other comments you may have regarding option 3.

This option follows the scientific approach outlined in Option 2, with the added benefit of multiple categories of chemicals based on current scientific evidence. This approach provides the necessary framework to incorporate evolving knowledge to assign levels based on currently available scientific evidence. It should be made clear that assignment to one or another category is not a "final decision" but rather an interim decision based on currently available evidence. It also should be made clear at what time intervals a chemical will be re-evaluated for potential assignment in a new category, as new evidence becomes available.

A critical issue is the "level of evidence" needed for category assignment, but there are no criteria proposed for differentiating between the different categories of demonstrated, highly suspected or potential EDCs. Such criteria depend on the chemical and the endpoint studied, among other issues. If two rare conditions are associated, for example a rare cancer of the reproductive tract in young women, and exposure to DES, the rarity of the individual conditions increases the overall level of evidence. Considering that BPA is ubiquitous and obesity and metabolic syndrome are multifactorial conditions, it is difficult to envisage a sufficient level of evidence will ever be achieved to get absolute proof of cause and effect that BPA is an obesogenic and diabetogenic EDC in humans. The interpretation of evidence will therefore depend greatly on the expertise of those who review the data.

2.4.4. Please, provide us with any other comments you may have regarding option 4.

The Endocrine Society opposes the inclusion of "potency" as an element of hazard characterization because the concept as it is applied is not science based.

Ultimate effects of hormones are produced through a cascade of events that includes regulation of hormone production, delivery of the hormone to the site of action, and the molecular events leading to the observable effects. Empirical data to support a theoretical framework that describes how a multi-step process from hormone binding to a nuclear receptor through expression of the gene under hormonal regulation is sparse [15]. However, existing data indicates that while the relationship between hormone concentration and gene expression remains first order, the curve can be shifted significantly to the left (or right), or with higher (or lower) maximum effects, simply by very small changes in co-factor concentration [15]. This is amplified by changes in hormone receptor concentration [16]. Thus, the "potency" of a hormone or EDC on different endpoints can vary by multiple orders of magnitude – much greater than the "uncertainty" factors built in to risk assessment. There is good evidence for the glucocorticoid receptor that the hormone-receptor complex can produce long-term changes in gene expression despite a very transient residence time on the regulatory element of the gene (so-called "hit-and-run") [17, 18]. The sum of this evidence fully supports rejecting potency as an element of hazard characterization.

4.1 - Please provide any other data or information that could help the Commission to conduct its impact assessment.

The Endocrine Society appreciates the opportunity to provide input on the public consultation of the Commission's impact assessment on EDCs. Endocrinologists across the globe are continually advancing our knowledge of the health effects of endocrine disrupting chemicals and the mechanisms through which they cause harm, and are developing appropriate methodologies to measure the potential for undesired effects. The pace of discovery on EDCs has increased exponentially in recent years, as has our knowledge of new windows of vulnerability for interference with hormone action, and the Commission should ensure that the expertise of endocrinologists is incorporated into its work on EDCs. Endocrinologists are the experts who create new knowledge in the field of Endocrinology and Endocrine Disruption, and also are those who work on the front lines of endocrine diseases. As endocrinologists, we believe that the implications of the following characteristics of EDCs should be considered:

- A single hormone will have changing effects at different times and places in the body during development and with different sensitivity. Therefore sensitive endpoints with predictive ability must be prioritized to identify endocrine disruptors.
- Hormones act at very low concentrations so the effects of very small amounts of endocrine disruptors need to be taken into account systematically.
- Chemical interference with hormone actions during early development can have long-lasting, even permanent, consequences that might manifest years later and endocrine disruptors can set up the body for mis-adaptation.
- Multiple chemicals can affect a single hormone pathway, and humans and wildlife are exposed to mixtures of chemicals throughout their life cycles. Therefore, assessment of endocrine disruption should include examination of the effects of mixtures of chemicals and not only one chemical at a time.

Finally, the impact assessment should consider not only the cost to industry due to action, but also the cost to society due to inaction. We urge the commission to consider currently available reports from the Health and Environment Alliance and The Nordic Council on the economic costs of EDCs [19,20].

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