

ENDOCRINE-DISRUPTING CHEMICALS

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are defined as: “an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action”¹. These can include natural or manufactured chemicals, such as pesticides, biocides, plastics, food contact materials, cosmetics, and others. Individuals and populations are exposed to EDCs, and common non-communicable diseases have been associated with environmentally-relevant doses of EDCs in human epidemiological studies. International scientific studies in cellular and animal models have unequivocally established causality between EDC exposure and effects and have often elucidated the endocrine mechanisms of action through which chemicals cause harm. Recently, advances in scientific knowledge together with public interest prompted the design of policies to regulate the use of EDCs and prevent global health risks due to EDC.

As the world’s oldest and largest professional organization dedicated to the understanding of hormone systems and the care of patients with endocrine diseases, the Endocrine Society is committed to excellence in hormone science and incorporation of scientific knowledge into patient care and public health. Our members from over 120 countries are concerned about environmental chemical exposures and the role of EDCs in the etiology of endocrine-related diseases. We strongly support the use of scientific knowledge in policies governing EDCs.

Recognizing concerns about EDCs and their potential health effects, the Endocrine Society created a Task Force in 2008 to summarize scientific knowledge about EDCs. In 2009, the Task Force published the first Scientific Statement on EDCs, a landmark review of the science of EDCs, peer-reviewed and published in *Endocrine Reviews*. At the same time, the Society released the first position statement on EDCs, expressing its concern about the full translation of endocrine scientific knowledge into policies in the US.

Because the science of EDCs has grown exponentially since 2009, the Endocrine Society published a second Scientific Statement on EDCs (EDC-2) in 2015, reviewing more than 1300 scientific articles published after the first Scientific Statement. Both Scientific Statements together establish a strong basis for concern about health risks associated with exposure to EDCs and provide a mechanistic understanding of how EDCs alter hormone actions, particularly during development, and at low doses. In this context, “low-dose” refers to concentrations of EDCs that are consistent with human exposure ranges, yet not typically evaluated in government-sanctioned testing strategies.

The scientific consensus in EDC-2 showed that:

- The incidence of several conditions including neurodevelopmental, reproductive and metabolic disorders, as well as some cancers, has increased over past decades with evidence that exposure to EDCs has contributed to this increase.
- Low-dose and non-monotonic dose responses (NMDR) are common and challenge classical concepts of toxicology testing, such as potency, threshold, and the establishment of ‘safe’ doses of exposure during the process of risk assessment and subsequent management.
- It is now well-established that the nature of an effect also depends upon when, and how, the effect is assessed, complicating the prediction of the final outcome.
- Standard good laboratory practice (GLP) toxicology testing and guideline studies are not sufficiently sensitive to evaluate the hazards associated with EDCs, thereby leading to insufficient protection of public and environmental health with increased medical and other costs.
- There exist critical developmental periods of susceptibility, such as fetal development and infancy, when an organism is particularly vulnerable to EDC exposures.
- New studies in humans have established associations between EDC exposures and numerous chronic diseases. Furthermore, relationships between epidemiological studies and experimental mechanistic and/or cellular approaches and animal work have greatly expanded during the last decade, identifying certain modes of action.



POSITION STATEMENT

National and international regulatory agencies such as the Organization for Economic Cooperation and Development (OECD), European Food Safety Agency (EFSA) and the United States Environmental Protection Agency (EPA) have implemented programs to facilitate the translation of new scientific knowledge to governmental policies. However, there are serious deficiencies in these programs preventing the accurate identification of many EDCs and evaluation of their health risks. This has led to concern that regulatory agencies will incorrectly assert “safety” of a compound or establish “safe” levels of exposure for compounds that cause harm. In many cases, regulatory determinations based on guideline studies are inconsistent with academic research, calling into question the rigor and effectiveness of regulatory approaches.

To improve the utilization of endocrine science in policies governing EDCs and help agencies address scientific and regulatory gaps, in 2017 the Endocrine Society established an Endocrine Disrupting Chemicals Advisory Group (EDC-AG). The EDC-AG coordinates the activities of the Endocrine Society related to EDCs through the work of member-driven task forces. In 2018, the EDC-AG recommended that the original EDC Position Statement be updated to reflect new science and regulatory developments regarding EDCs.

BACKGROUND

Although the term “endocrine disruptor” was first used in 1991², the notion that environmental chemicals interfere with hormone actions emerged more than 50 years ago³. In the following years, as EDCs emerged as an important public health issue, national governments and international agencies attempted to address the regulatory challenges posed by EDCs. In 1996, the EPA assembled the Endocrine Disruption Screening and Testing Advisory Committee (EDSTAC), which led to the formation of the Endocrine Disruptors Screening Program (EDSP). In 1999, the European Union established a ‘Community strategy for endocrine disruptors’ with recommended actions to protect public health from EDC-related harm⁴. More recently, in 2012 the United Nations Environment Programme (UNEP) and the World Health Organization (WHO) published a revised assessment of the state of the science of endocrine disruptors, updating the previous version (2002), and advising of the potential risk that low-dose EDC exposures represent for human health and the environment⁵. This document emphasized the fact that EDCs represent a global threat and recognized the importance of a common global strategy to specifically

identify EDCs based on current scientific knowledge.

The European Union (EU) is currently concluding a long process to establish criteria to identify EDCs in pesticides and biocides mandated by EU biocides and pesticides laws. To date, the European Food and Safety Authority (EFSA) has applied “interim criteria” to the evaluation of these chemicals; however, these criteria are limited to certain pathways and are insufficient to protect European citizens from all EDC-related health hazards.

New Information on EDC Action

New research has clarified and resolved several scientific issues and controversies discussed in the Society’s 2009 Position Statement, and many previously disputed concepts have become widely accepted by the scientific community. For example, it is now well-established that EDCs interact with receptors other than estrogen, androgen and thyroid hormone receptors, such as the peroxisome proliferator-activated receptor gamma (PPAR γ), aryl hydrocarbon receptor (AhR), estrogen-related receptor gamma (ERR γ), and the glucocorticoid receptor (GR), among others. Moreover, EDCs also interact with membrane receptors such as the nicotinic acetylcholine receptor, which is expressed in many endocrine tissues. Despite these advancements, OECD test guidelines and the EU criteria for pesticides and biocides are still almost exclusively focused on effects occurring via interactions with nuclear estrogen, androgen and thyroid hormone receptors, while those effects governed by other receptors are not yet evaluated. Also, the OECD conceptual framework focuses narrowly on effects on female and male reproductive systems, carcinogenicity and overt neurotoxicity; however, scientific evidence summarized in EDC-2 identified EDC-related effects on obesity, diabetes mellitus, thyroid disruption and neurodevelopment. Therefore, all major endocrine organs are vulnerable to endocrine disruption, yet no testing guidelines related to endocrine pathologies have been developed, despite large increases in prevalence every year.

It is now well established that developmental exposure to EDCs can alter the epigenome of offspring, affecting gene expression and organogenesis, thereby altering an organism’s sensitivity to disease later in life. Emerging data also reveal EDC-related effects on neuroinflammation, synaptogenesis, mammary gland morphogenesis and cardiac function. These alterations are frequently subtle, as they are manifested at the cellular or behavioral level that requires expertise beyond standard toxicity testing, yet they are biologically meaningful and can enhance individuals’ susceptibility to chronic diseases. These types of endpoints require more sensitive assays and endocrine expertise than those used in the classical apical toxicological assays that typically evaluate for the presence of dramatic morphological alterations or (at the extreme) the death of laboratory animals. Despite the more labor-intensive nature of testing required to identify endocrine-disrupting properties of a substance, these assays

² Schug, T., et al., Minireview: Endocrine Disruptors: Past Lessons and Future Directions, *Molecular Endocrinology*, (2016) 30(8): 833–847.

³ Gassner FX, et al., Effects of hormones on growth, fattening, and meat production potential of livestock. *Recent Prog Horm Res*. 1958;14.

⁴ Communication From the Commission to the Council and the European Parliament. COM (99)706 <http://ec.europa.eu/environment/archives/docum/99706sm.htm>. Accessed April 2, 2018

⁵ WHO/UNEP (2012) State of the Science of Endocrine Disrupting Chemicals – 2012. <http://www.who.int/ceh/publications/endocrine/en/> Accessed April 2, 2018.



POSITION STATEMENT

are paramount for inclusion in testing protocols to ensure that harmful effects at human-relevant doses are identified.

Non-Monotonic Dose-Responses

Non-monotonic dose responses (NMDR) occur when the slope of the curve relating dose and effect changes sign at some point within the range of the doses examined. This phenomenon is particularly common in the case of hormones and EDCs. The presence of NMDR has been extensively demonstrated in animal and cellular models⁶ and the diverse and complex molecular mechanisms underlying NMDR are beginning to be demonstrated⁷. Importantly, current epidemiological studies are starting to reveal their existence in human populations as well⁶.

The existence of NMDR in evaluations of EDCs has significant consequences on regulatory toxicology, because it does not guarantee that the lack of adverse effects at high doses also confirms safety at low doses. Common concepts of classical toxicology, such as potency and threshold also do not easily transfer to the non-monotonic behaviour of EDCs. The concept of risk (i.e., the chance that a person will experience an adverse effect) is a function of the hazardous properties of the source and the level of exposure. When there is a monotonic relationship between dose and effect, risks associated with hazards can be greatly reduced by decreasing exposure. The existence of NMDR raises the possibility that reduced exposure may have uncertain effects on risk, making it very difficult to predict a safe level of exposure. In this case, it might be necessary to eliminate the hazard entirely to ensure safety. This feature of EDCs supports the development of hazard-based identification strategies for EDCs that consider the fundamental properties of the chemical in question.

Mixtures

Individuals and populations are exposed to complex low-dose mixtures of EDCs, other chemicals, and additional environmental stressors. These exposures may interact producing complicated effects that are difficult to predict. In spite of this, chemical safety-levels are based on single-chemical studies often using environmentally irrelevant doses. The potential health effects of combined exposures make the risk assessment process more complex compared to the assessment of single chemicals. Therefore, new methods must be developed to fill these gaps and incorporate combined exposures into EDC hazard and risk assessments.

Scientific Controversies of EDCs

It is important to note that some controversies addressed in the previous 2009 Position Statement have been resolved. For example, the Member State Committee of the EU unanimously agreed in 2017 that Bisphenol A is an endocrine disruptor⁸ after supporting the French (ANSES) proposal to identify Bisphenol A as a substance of very high concern specifically because of its endocrine disrupting properties in humans.

In addition, an international group of experts supported by the German Risk Assessment Agency unanimously agreed that potency of an EDC is not relevant for identification of a chemical as an EDC⁹. This affirms the scientific validity of the Endocrine Society's definition of an EDC. Also, the ICCM4 conference in 2015 "welcome[d] the report by the United Nations Environment Programme and the World Health Organization entitled State of the Science of Endocrine Disrupting Chemicals—2012, which identifies concerns, including evidence in humans, laboratory animals and wildlife that exposure to endocrine-disrupting chemicals can result in adverse effects."¹⁰ A small number of industry-aligned groups disagreed with the ICCM4 resolution.

Scientific knowledge since 2009, reviewed in EDC-2, identifies EDCs as contributors to increases in the incidence of: impaired reproduction, neurodevelopment alterations, thyroid dysfunction, obesity, autoimmune disease, diabetes mellitus and increased susceptibility for hormone-sensitive cancers. While the contribution to disease burden in the human population is difficult to measure unequivocally, evidence of a role for EDCs in these diseases continues to build from cross-sectional epidemiological studies and small numbers of prospective and intervention studies. Assessment of causality remains heavily dependent on experimental studies in animal and cellular models, where translation to humans is not always straightforward. To avoid a protracted risk evaluation process, and to maximize consistency and transparency, it is necessary to establish *a priori* when the level of evidence has achieved a point at which action should be taken.

Increasing evidence in laboratory animals suggest that EDCs lead to transgenerational effects, affecting multiple generations following exposure. Epidemiologic data in humans demonstrating transgenerational effects will take decades to collect; yet ongoing exposures may be causing harm to future generations. A precautionary

⁶ Vandenberg, LN, et al., Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses *Endocr Rev.* 2012 Jun;33(3):378-455. doi: 10.1210/er.2011-1050.

⁷ Villar-Pazos, S, et al., Molecular mechanisms involved in the non-monotonic effect of bisphenol-a on ca2+ entry in mouse pancreatic β -cells *Sci Rep.* 2017 Sep 18;7(1):11770. doi: 10.1038/s41598-017-11995-3

⁸ ECHA/PR/17/12 MSC unanimously agrees that Bisphenol A is an endocrine disruptor. <https://echa.europa.eu/-/msc-unanimously-agrees-that-bisphenol-a-is-an-endocrine-disruptor> Accessed April 2, 2018.

⁹ Solecki, R., Kortenkamp, A., Bergman, Å, et al. *Arch Toxicol* (2017) 91: 1001. <https://doi.org/10.1007/s00204-016-1866-9>

¹⁰ SAICM/ICCM.4/15 Report of the International Conference on Chemicals Management on the work of its fourth session. 28 October 2015.



POSITION STATEMENT

approach to regulation may therefore be warranted in the absence of conclusive transgenerational data in humans.

CONSIDERATIONS

The Endocrine Society is concerned that delays in the incorporation of new scientific knowledge about EDCs has prevented regulatory agencies from making efficient and effective decisions regarding chemical safety. Stakeholders need to work together to help agencies utilize available scientific information and accelerate decision-making. There exist approximately 100,000 chemicals on the market with thousands of new chemicals produced every year. Remarkably, affirmative pre-market safety determinations are not made for the vast majority of these chemicals, meaning that populations are exposed to chemicals with the potential to cause harm without their knowledge.

Regulatory agencies need to work with public health stakeholders to more accurately define the level of scientific evidence appropriate to take action on chemicals of concern. Longitudinal epidemiological studies establishing causality in humans are difficult, expensive, and require long timeframes, especially when multigenerational effects must be studied. Such studies also inherently require “harm” to individuals and human populations; this should be considered unacceptable. Intervention and clinical studies are also challenging and may be unethical. Therefore, when peer-reviewed scientific studies in cellular and animal models and/or epidemiological evidence indicate a strong possibility of an adverse effect, authorities must develop regulatory strategies that better protect public health, and in particular vulnerable populations; authorities must also conduct public outreach so that people can make informed decisions and be protected.

Systematic review is an approach to the evaluation of scientific data and literature that ensures that the evaluation of information is conducted in a transparent, unbiased, and reproducible method. Key features of systematic review include a clearly stated set of objectives with pre-defined eligibility criteria for study inclusion; an explicit, reproducible methodology for identifying relevant literature; an assessment of the validity and/or quality of the findings of each included study; and a systematic presentation, and synthesis, of the characteristics and findings of the included studies. Taken together, these features lead to more reproducible results between different groups of experts than earlier out-dated approaches, such as “weight of evidence” evaluations. Systematic review methodologies relevant to endocrine-disrupting chemicals have been developed, including the SYRINA method¹¹ and the Navigation guide¹², which was utilized by a panel of the United States National Academies to evaluate EDCs¹³.

Testing must incorporate the latest endocrine science and the expertise of endocrine scientists in combination with classical regulatory toxicology. Endocrine research has proven that NMDRs exist and therefore, toxicological

assumptions such as linear potency and threshold should not be assumed. Moreover, newer EDC-sensitive endpoints should be identified and incorporated into testing strategies to capture relevant chemical effects.

In recent years scientists from many disciplines including toxicologists, epidemiologists, environmental scientists and endocrinologists have worked together to understand how EDCs act and how to translate this knowledge into policy. In the EU, this has resulted in new regulations and strategies that, although far from perfect, are recognizable steps in the right direction. Broader adoption of these regulations and strategies, with continued improvement, is needed to advance public health and reduce harms due to EDC exposures worldwide.

POSITIONS

The Endocrine Society is concerned that human health is at risk because the current extensive scientific knowledge on EDCs and their health effects is not effectively translated to regulatory policies that fully protect populations from EDC exposures. Accumulating evidence points to the fact that EDCs contribute to the etiology of chronic diseases. The increase in the prevalence and morbidity and mortality of chronic diseases imposes a major impact on the efficiency of health systems. Regulatory test guidelines must advance to incorporate updated endocrinology concepts and rapidly integrate them into reliable testing.

Therefore, the Endocrine Society supports the following positions

- Regulatory toxicology should implement endocrine concepts such as low dose and NMDR without further delay. Because of the presence of NMDR, it cannot be assumed that there are thresholds below which EDC exposures are safe.
- The Endocrine Society opposes the use of “potency” cutoffs as an element of hazard identification; this concept is inconsistent with endocrine science and fails to account for variation in sensitivity across development and different tissue types.
- Regulatory strategies for EDCs, including identification and risk reduction, should be science-based, not economics-based, and should be applicable across all potential EDCs.

¹¹ L.N. Vandenberg et al., A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals, *Environ Health* 15(1) (2016) 74.

¹² T.J. Woodruff, P. Sutton, The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes, *Environmental Health Perspectives* 122 (2014) 1007-14.

¹³ National Academies of Sciences, Engineering, and Medicine. 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24758>.



POSITION STATEMENT

- Regulations should be designed to protect the most vulnerable populations—including but not limited to foetuses, children, pregnant women, adolescents, and the elderly—from irreversible effects.
- EDC regulatory strategies should incorporate the most sensitive endpoints for EDCs that are relevant to human and ecological health. The currently battery of classical guideline studies are insufficient.
- Policy should be based on comprehensive data covering both low-level and high-level exposures, including cumulative effects, mixture effects, and other stressors. This includes synthesizing basic science (comprising animal and in vitro studies), clinical observations, and epidemiological data.
- A precautionary approach to regulation may be warranted in the absence of conclusive data in humans.
- Systematic review should be used in chemical assessments and to identify EDCs. Studies should be evaluated in a transparent manner using the same criteria. Consistent with the principles of systematic review, the studies and information about relevant endpoints used to make decisions should be reported and made publicly available.
- All processes governing EDC assessments should include endocrine scientists with expertise in the hormonal systems and biological mechanisms for each endpoint to ensure comprehensive understanding of the effects and endpoints under examination by testing.
- EDCs are a global issue. Health issues related to EDCs cannot be geographically compartmentalized and should be addressed by intergovernmental actions. The Endocrine Society supports the cooperative actions described in the Strategic Approach to International Chemicals Management Endocrine Disrupting Chemicals Workplan for 2016-2020¹⁴.

¹⁴ SAICM/ICCM.5/Bureau.1/INF/3