ENDOCRINE-DISRUPTING CHEMICALS IN THE EUROPEAN UNION JANUARY 2023

Introduction

Endocrine-disrupting chemicals (EDCs) are chemicals, or mixtures of chemicals, that interfere with any aspect of hormone action. With the exception of some compounds used as pharmaceuticals and pesticides, these chemicals are not designed to have effects on endocrine systems. Rather, they are designed, produced, and marketed for specific uses including in consumer products, food storage containers, personal care products and elsewhere. Some EDCs are also found in certain natural foods and may become further concentrated during processing. EDCs are often released into the environment, and over the last decade, endocrine research has highlighted the potential impacts on human health and the environment following widespread exposure to EDCs[i]. Consequently, public interest in possible health threats posed by EDCs has intensified in recent years, leading to the development of policies, laws and regulations designed to mitigate EDC related health risks. The European Union (EU) has introduced specific legislative obligations to eliminate EDCs in plant protection products and biocidal products[ii] and is considering further policy changes to minimize exposure to EDCs in consumer goods and prevent disease

The Endocrine Society aims to ensure that policies governing EDCs consider the full body of research into these chemicals. As the largest global professional organization for endocrine research and the clinical practice of endocrinology, the Society counts among its members the world's leading experts in endocrine science, including experts on EDCs and their effects. In its 2009 Scientific Statement[iii], its 2012 Statement of Principles[iv], and in the 2015 Scientific Statement[v], the Society calls for additional research and updated regulatory process for to assess and reduce exposure to EDCs. The evaluation of chemicals for endocrine effects must consider scientific principles including latent and transgenerational effects; the possibility of mixture effects; and the concept of multi-organ or multisystem effects leading to observed toxicity. Moreover, hormones achieve effects at extremely low levels and non-monotonic dose responses (NMDR), defined as a change in the sign (positive/negative) of the slope of a dose–response relationship over the range of doses tested, are often observed in endocrine systems. Therefore, regulators must evaluate chemicals for effects at extremely low levels and also consider the possibility of complex dose-response relationships, including NMDR. It is also critical that regulatory agencies appreciate that the consequences of EDC exposures depend upon the timing of exposure. Developmental stages—from prenatal life through adolescence—represent particularly vulnerable periods during which irreversible damage can result from exposure to low levels of EDCs. These scientific issues are not adequately addressed under the current Organization for Economic Cooperation and Development (OECD) screening guidelines, and require updated methodology and incorporation of newer, more sensitive endpoints for evaluating endocrine activity[vi]. For example, while the fish life-cycle toxicity test focuses on GnRH neuron development in the brain after chronic exposure, developmental neuroendocrine disruption may not alter GnRH neuron proliferation or structure directly, but rather through alteration of one or more neuromodulators controlling GnRH secretion. The primary research and clinical interest of the Endocrine Society is human health protection; however, impacts on wildlife are also of concern, in alignment with the 'One Health' concept adopted by the World Health Organization (WHO) and other national and international policymaking bodies[vii].

Background

The understanding that environmental chemicals can interfere with hormone action has gradually been understood by governments and applied to legislative and regulatory priorities over the past half century. The European Union has recognized EDCs in legislation since the late 1990s[viii]. Some milestones include Europe's Strategy on EDCs[ix] (1999); the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals[x] (REACH, 2007); plant protection products[7] (2009) and biocides regulation[xi] (2011), Chemicals Strategy for Sustainability (2020) and Europe's Beating Cancer Plan (2021). In 2013, the European Parliament adopted a resolution on the protection of public health from endocrine disruptors[xii] and the 7th Environmental Action Programme called for minimizing exposures to EDCs. After several years of debate in which the Endocrine Society actively participated, the Commission finally adopted criteria for the identification of endocrine disrupting biocides in

2017[xiii]. In 2019, the Petitions Committee of the European Parliament commissioned a report reviewing the scientific evidence regarding the concept of endocrine disruption, the extent of exposure, associated health effects and costs[xiv].

The European Chemicals Agency (ECHA) and European Food Safety Agency (EFSA) are charged with providing guidance to establish the details of the scientific information needed for identifying an EDC based on its adverse effect, endocrine activity and plausible link between the two. The Endocrine Society has argued that identification strategies should not restrict "endocrine-mediated action" to perturbation of a single class or system of hormones interacting with a receptor[xv]. Cells need to react to a wide variety of hormones, and hormone-receptor interaction can activate many different endocrine pathways, which are typically linked via mutual interrelationships and crosstalk. A single chemical or class of chemicals can interact with different endocrine pathways, disrupting regulatory mechanisms, altering homeostasis and predisposing individuals to endocrine diseases. Therefore, "endocrine-mediated" should specifically indicate that the adverse outcome is plausibly caused by a substance interfering with hormone synthesis, transport, metabolism, excretion, and/or receptor-mediated action. Receptor-mediated action should recognize that many hormones have multiple receptor isoforms including nuclear and/or membrane or other receptors that convert an extracellular signal into a specific cellular response. It should also reflect the World Health Organization's International Program on Chemical Safety (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.

While the original EU strategy on EDCs from 1999 identified important short, medium, and long-term actions to address EDCs and their public health consequences, new scientific information has emerged in recent years and policymakers have begun the process of updating relevant laws. In July 2017, the European Commission recognized the importance of more comprehensively assessing and minimizing exposure to EDCs in consumer products and other products, beyond plant protection products and biocides, including toys, cosmetics, and food packaging materials through the regulation on Classification, Labeling and Packaging (CLP) and regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). On December 19, 2022, the Commission proposed a revision to the CLP regulation that included a specific hazard class for EDCs, with multiple categories based on the strength of evidence.[xvi]

Science of EDC Actions Has Advanced.
EU policymakers need to protect citizens from harmful chemical exposures, and they rely on scientific experts to help them determine how best to do this. Endocrinological research into EDCs over the past 20 years has revealed important issues that have not yet been incorporated into testing paradigms, guideline studies, or in regulatory analyses. It is now clear that multiple hormone systems, including those involved in fetal development, immune response, reproduction, metabolism, obesity, and brain development, can be targets of EDCs. Furthermore, EDCs can produce effects that do not exactly mimic or block those of natural hormones[xvii].

EDCs can also act on multiple generations simultaneously. For example, exposure of pregnant women to EDCs can act on the pregnant woman, her fetus, and on the fetal gametes, affecting three generations. Individuals exposed to EDCs in the womb face a greater risk of disease later in life, and some EDCs have multi-generational effects through epigenetic modification of DNA and other heritable mechanisms, thereby placing future generations at higher risk of disease. In the case of the female fetus, germ cell numbers are maximized by 7 months gestation and EDC exposure can alter the germ cells during this critical developmental period. Therefore, the endocrine-disrupting potential of a compound extends far beyond actions at hormone receptors, and testing paradigms and public policy must incorporate these aspects of EDC exposure. Recent biomonitoring studies from across Europe have shown that people in the general population are typically exposed to multiple chemicals throughout their life.[xviii,xix,xx] As is the case in the US, it is likely that all babies born in the EU are exposed to industrial chemicals and are at risk for EDC hazards[xxi]. Regulatory paradigms must incorporate new endpoints that reflect the sensitivity of organisms to endocrine disruption and are relevant to disease states to which exposure has been linked.

EDC Effects Are Seen at Low Levels of Exposure.
Current EDC policy relies largely on data produced from guideline studies examining the effects of high doses of chemicals, relative to human exposure. A substance must show evidence of a narrow set of adverse effects that increase proportionally with dose in order to be considered dangerous by classical standards. However, many EDC effects occur at low doses irrespective of effects seen at high doses. In fact, increasing amounts of hormone or a hormone mimic can squelch a measured adverse effect by overwhelming or down-regulating the

endocrine system's ability to respond. In this circumstance, an effect seen at low levels of exposure would not be observed at higher levels of exposure. By eliminating low-dose studies from policy considerations, the regulatory community is excluding crucial evidence of harmful EDC actions that exhibit hormone-like dose-response profiles.

Basic Research Predicts or Confirms Human Disease.
EDC effects may not be detectable until years after the initial exposure occurs and may affect the offspring of the exposed individual. This was first demonstrated for diethylstilbestrol (DES), which was given to pregnant women in the mid-20th century with the intention of preventing miscarriage. However, DES caused male and female reproductive abnormalities. Additionally, in early adulthood, the daughters of these women were observed to develop a rare cancer at a higher rate than women who had not been exposed to DES before birth. The observation led to basic research studies in animal models that confirmed the causal relationship of prenatal DES exposure to the development of cancer later in life. The confirmation of DES' effects illustrates in reverse the power of research in appropriate animal models.

Regulatory Approaches Should Address Gaps in Protection
Market forces have driven several countries to ban the use of bisphenol A (BPA) in baby bottles and other baby food containers. However, these measures do not account for other sources of BPA. Moreover, science indicates that chemicals used as replacements (e.g., BPF, BPS) have been shown to have similar effects on endocrine systems. Similar concerns exist over other EDCs, such as perchlorate and phthalates.

Unlike pharmaceuticals, for which clinical trials are undertaken to prove benefits and define adverse effects, it would be unethical to perform human studies to uncover harmful EDC effects. One cannot imagine a scenario in which DES would have been given to pregnant women after animal studies revealed its harmful effects. Thus, calls for "definitive proof of harm to humans" present an unachievable goal. It is imperative that strong evidence from animal models be heavily weighted in assessment paradigms.

Identifying direct links between EDC exposure and childhood or adult disease is difficult for many reasons, including the challenge of accurately assessing a lifetime of exposure to a complex mixture of potentially harmful agents, including many that reside in the body for long periods of time. However, the reality is that humans and wildlife are already exposed to many EDCs on a daily basis and their future health is in question today. It is therefore important to synthesize information from animal model systems, detailed laboratory analyses of EDC mechanisms, and epidemiological studies to predict and quantify potential effects in humans so that exposure reductions can be taken where needed[xxii]. Endocrine scientists have unique expertise and experience in experimental endocrinology, and this expertise is critical for high-quality evaluation of endocrine studies by advisory committees and other groups that provide insight on regulatory policy for EDCs.

Systematic Review Can Improve the Reliability of Chemical Evaluations
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 approaches, such as "weight of evidence" evaluations. Systematic review methodologies relevant to endocrine-disrupting chemicals have been developed, including the SYRINA method[xxiii] and in a report by the United States National Academies[xxiv]. While systematic review can reduce bias, it remains important for individuals with expertise in hormone biology to be involved where expert judgement is required, e.g., defining criteria for including/excluding studies.

Considerations

Scientific discoveries on EDCs should influence relevant policy decisions. While the Endocrine Society encourages further research to further elucidate chemical effects on endocrine systems, there is already sufficient evidence to support regulatory action on many EDCs. Where there exists uncertainty, we support the precautionary principle and recommend that policymakers and regulators adopt approaches that allow for multiple classes of EDCs, depending on the strength of available evidence. Research and testing strategies should prioritize generating information on endocrine hazards for chemicals where there is currently limited evidence, including for proposed substitute chemicals. In many cases, replacements for harmful chemicals such as BPA include structural analogues with uncertain safety profiles. Testing strategies should consistently and comprehensively examine all chemicals for potential EDC activity;

however, if this is impractical, group-based approaches to chemical regulation should be adopted. Widely applicable, science-based criteria for identification of EDCs are required.

As more information about EDC effects and mechanisms becomes available, it will be increasingly important to carefully assess the extent of human exposure to EDCs, especially for communities that may experience disproportionate exposures or impacts due to racial/ethnic, socioeconomic, or other sources of inequality. Additionally, it will become necessary to provide research funding so that scientists can further examine EDC effects, in particular those already manifesting in people.

To better inform EU guidelines, endocrine research is needed to further elucidate the mechanisms whereby EDCs interfere with endocrine systems necessary for normal development and physiology, including the sources of low-dose effects and NMDR. Toxicologic research is needed to understand the dose-response relationship between general endpoints of toxicity and chemical exposures that typically involve doses higher than those which alter endocrine systems. Epidemiologic research is needed to identify and quantify levels of human exposure that correlate with disease development. Environmental science is needed to identify sources of exposure. Research on "green" chemistry approaches are needed to identify safer chemical alternatives. All disciplines must work together with policymakers, non-governmental organizations, scientific societies, and other stakeholders to ensure that a thorough examination of EDC exposure and effects on human health are used as the basis for policy decisions.

Positions

The Endocrine Society is concerned that the European public is at increased risk from ongoing exposure to EDCs. There is substantial scientific evidence of harm to human health and the environment from EDCs, illustrating the need for policymakers in the EU to act with urgency. EDC effects know no disciplinary boundaries; teams of scientists, including endocrine scientists, toxicologists, epidemiologists, chemists, environmental scientists and others, must work together to inform EDC-related policies. Legislators, regulators, and others involved in EDC-related policies must develop comprehensive programs for all chemicals and regulations governing EDCs in manufactured products, the food supply, and the environment.

Therefore, the Endocrine Society supports the following positions:

Policy

- Regulatory decisions to minimize exposure to hazardous EDCs should be science-based and take into account new scientific information over time. They should apply to all potential known or suspected EDCs
- Regulations should be designed to protect all populations from irreversible adverse effects by assessing impacts on particularly vulnerable populations, including but not limited to infants, pregnant women, individuals undergoing puberty, and genetically-susceptible individuals.
- Policy should be based on comprehensive data covering both low-level and high-level exposures and including basic science (comprising animal and in vitro studies), clinical observations, and epidemiological data.
- All processes governing the identification of EDCs should ideally include endocrine scientists with expertise in the biological systems and mechanisms at play to ensure comprehensive understanding of the effects and endpoints to be examined.
- To avoid regrettable substitutions, group-based restrictions should be explored for chemicals with similar structure or toxicologic effects.

Assessment

- Rigorous standards and protocols should be developed for characterization of study populations and collection, storage, and processing of biological samples for measurements of EDCs and byproducts.
- Thresholds below which EDC exposures are safe cannot be simply defined by extrapolating from exposure to high doses, and policymakers and regulators should consider that there may be no safe threshold of exposure. Consistent with the current state of the art of endocrine science, the default approach to assess a potential EDC must include study of low doses with possibly no threshold and no definitive potency due to variations depending on hormonal systems and many other factors.
- Tests and screens used to determine EDC activity should be balanced between those that examine simple mechanisms and others that measure integrated biological outcomes at different periods of life, thereby encompassing both known and unknown effects.
- EDC identification methods should incorporate the most sensitive endpoints, and endpoints relevant to human and ecological health. Guidance for identification should incorporate hormonal systems beyond estrogen, androgen, and steroidogenesis, including thyroid hormone pathways.
- Systematic review should be used wherever possible to identify EDCs. The results of EDC identification

processes should be transparent and publicly available.

- The Endocrine Society welcomes the proposed CLP revision and supports multiple categories of EDCs based on the level of evidence. We urge swift adoption of the Commission's proposal, and the development of guidance on CLP implementation that ensures that regulatory agencies can identify chemicals that interfere with hormone action and define them as EDCs with the level of evidence required for identification proportionate to the levels of data available and be based on predictions of adverse effects.
- Chemicals should be evaluated for cumulative and mixture effects.
- Agencies should implement regulatory approaches that allow for multiple classes for EDCs, based on the strength of available evidence, and with regulatory consequences for identified EDCs.

Research

- The European Commission and agencies should support further research into EDCs in alignment with the proposed revision to the EU strategy on EDCs, specifically including the research areas identified by the Endocrine Society's Second Scientific Statement on EDCs. These and other research areas are provided in the appendix following this statement.

Appendix[xxv]: Recommendations for Additional Research

- Mechanistic studies of EDC actions on nuclear hormone receptors need to be extended beyond ERs, AR, PR, GR, ThR, and PPARs to the aryl hydrocarbon receptor (AhR), other nuclear hormone superfamily members and to membrane steroid hormone receptors.
- Investigate EDC effects on enzymes involved in steroidogenesis, hormone metabolism, and protein processing in humans and animal models.
- EDC interference with local and tissue-specific activation/inactivation of hormones, precursors of hormones, and hormone transport systems across cellular membranes.
- Translate research from rodents into nonhuman primates, sheep, and other species; and take advantage of transgenic (especially humanized) animals, keeping in mind the need for a better understanding of hormones and early-life development in humans.
- Test additional critical periods beyond prenatal and early postnatal—e.g., adolescence as an additional sensitive developmental window, though aging populations should not be overlooked in testing strategies.
- Evaluate EDC outcomes at different life stages–not just adulthood.
- Design studies to consider sex and gender differences in response to EDCs.
- Support longitudinal and multigenerational studies in animals and humans that evaluate how early-life exposures may result in effects later in life, including in aged/aging populations.
- Evaluate and implement emerging and sensitive testing systems (e.g., organoids, spheroids), including high-throughput systems, for hazard assessment, screening, and prioritization.
- In humans, consider genetic diversity and population differences in exposures and outcomes. This should include racial, ethnic, socioeconomic, and geographic variables.
- Expand research to emerging categories of EDCs (e.g., PFAS) and with the aim of investigating mixture effects and environmentally-relevant concentration levels. The team science approach, including teams of basic, translational, and clinical scientists; epidemiologists; health care providers; and public health professionals, needs to be a priority for future research and funding.
- Study the contribution of EDCs to reproductive health issues in males and females, including effects on fertility status e.g., declining sperm count, and infertility.
- Better understanding of cumulative and synergistic effects of EDCs; storage of EDCs in the body and effects of exercise and weight loss on EDC storage; accumulation of EDCs in recycled products and exposure via new pathways such as nanoplastic particles.

[i] Gubbi S, Wurth R, Hannah-Shmouni F, Koch CA. Environmental Endocrinology - Basic concepts. in Pivonello R, Diamanti-Kandarakis E (eds), Environmental Endocrinology and Endocrine Disruptors, Endocrinology, Springer 2022.

[ii] European Commission Endocrine Disruptors Page. http://ec.europa.eu/environment/chemicals/endocrine/index_en.htm Accessed April 10, 2018.
[iii] Diamanti-Kandrakis et al., 2009. Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293–342
[iv] Zoeller et al. 2012. Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society. *Endocrinology*, September 2012, 153(9):4097–4110
[v] A. C. Gore, et al., EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals, *Endocrine Reviews*, 36(6):E1–E150
[vi] OECD 2012. Draft Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption. http://www.oecd.org/chemicalsafety/testing/50459967.pdf Accessed April 10, 2018.
[vii] WHO 2017. http://www.who.int/features/qa/one-health/en/ Accessed April 2, 2018.
[viii] European Commission Public Health Website: https://ec.europa.eu/health/endocrine_disruptors/overview_en Accessed April 10, 2018
[ix] Communication from the Commission to the Council and the European Parliament. COM (99)706. Community Strategy for Endocrine Disruptors http://ec.europa.eu/environment/archives/docum/99706sm.htm Accessed April 10, 2018
[x] European Commission Environment Website: http://ec.europa.eu/environment/chemicals/reach/legislation_en.htm#legal Accessed April 10, 2018.
[xi] European Commission Public Health Website: https://ec.europa.eu/health/biocides/policy_en Accessed April 10, 2018.
[xii] European Parliament resolution of 14 March 2013 on the protection of public health from endocrine disrupters. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2013-0091+0+DOC+XML+V0//EN Accessed April 2, 2018
[xiii] COMMISSION DELEGATED REGULATION (EU) 2017/2100. Setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council. (2017) *Official Journal of the European Union* L301/1
[xiv] https://www.europarl.europa.eu/RegData/etudes/STUD/2019/608866/IPOL_STU(2019)608866_EN.pdf
[xv] Endocrine Society 2017. https://www.endocrine.org/-/media/endosociety/files/advocacy-and-outreach/society-letters/2018/20180131-endocrine-society-response-to-public-consultation-on-draft-edc-criteria-guidance-document.pdf?la=en Accessed April 10, 2018.
[xvi] European Commission Press Release, Brussels, July 4 2017. http://europa.eu/rapid/press-release_IP-17-1906_en.htm) Accessed April 10, 2018.
[xvii] Sutton, P., et al: Toxic environmental chemicals: the role of reproductive health professionals in preventing harmful exposures. *American Journal of Obstetrics and Gynecology*. 2012 Sep;207(3):164-73.
[xviii] DEMOCOPHES http://www.eu-hbm.info/democophes Accessed April 10, 2018.
[xix] Casas M., et al: Exposure to brominated flame retardants, perfluorinated compounds, phthalates and phenols in European birth cohorts:, *International Journal of Hygiene and Environmental Health* 216 (2013) 230-242.
[xx] Leino, O., et al: Polluant concentrations in placenta. *Food and Chemical Toxicology* 54 (2013), 59-69.
[xxi] Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the US: NHANES 2003-2004. *Environ Health Perspect*. 2011;119:878–85.
[xxii] Woodruff, TJ., and Sutton, P.: The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. *Environmental Health Perspectives*. 2014 Oct;122(10):1007-14.
[xxiii] Beronius and Vandenberg, 2016. Using systematic review for hazard and risk assessment of endocrine disrupting chemicals. *Rev. Endocr Metab Disord*. 2015 Dec;16(4):273-87
[xxiv] 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.
[xxv] Adapted from: A. C. Gore, et al., EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals, *Endocrine Reviews*, 36(6):E1–E150