

ENDOCRINE-DISRUPTING CHEMICALS IN THE EUROPEAN UNION

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are chemicals, or mixtures of chemicals, that interfere with any aspect of hormone action. These chemicals are designed, produced, and marketed largely for specific industrial purposes (plasticizers, pesticides, food-packaging, etc). They are present in the environment, 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. Over the last decade, endocrine research has highlighted the potential impacts on human health and the environment following widespread exposure to EDCs. 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 aimed at phasing out endocrine disruptors in water, industrial chemicals, plant protection products and biocides¹. After many years of debate, the criteria to identify endocrine disruptors in the context of the EU biocides law were adopted in 2017, entering into force June 2018.

The Endocrine Society aims to ensure that policies governing EDCs consider the full body of research into EDCs. 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 Statementⁱⁱ, its 2012 Statement of Principlesⁱⁱⁱ, and in the 2015 Scientific Statement^{iv}, the Society calls for additional research and updated regulatory processes for the identification of EDCs, which overtly or potentially, depending on the chemicals and endpoints, pose a significant global public health threat. The evaluation of chemicals for endocrine effects must consider the scientific issues of latent and transgenerational effects, low-dose effects, non-monotonic dose responses (NMDR), and mixture effects. 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^v. For example, while the fish life-cycle toxicity test focuses on GnRH 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 aim of the Endocrine Society is human health protection; however, impacts on wildlife are also of concern. The idea that humans and wildlife share the same eco-systems is in line with the 'One Health' concept developed by the World Health Organization (WHO)^{vi}.

BACKGROUND

The understanding that environmental chemicals can interfere with hormone action has developed slowly over the past half century. The European Union has been engaged in policy work relevant to EDCs since the late 1990s^{vii}. Some milestones include Europe's Strategy on EDCs^{viii} (1999); the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals^x (REACH, 2007); pesticides regulation^x (2009); and biocides regulation^x (2011). In 2013, the European Parliament adopted a resolution on the protection of public health from endocrine disruptors^{xi} 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^{xii}.

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¹ European Commission Endocrine Disruptors Page. http://ec.europa.eu/environment/chemicals/endocrine/index_en.htm Accessed April 10, 2018.

ⁱⁱ Diamanti-Kandarakis et al., 2009. Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293–342

ⁱⁱⁱ 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

^{iv} A. C. Gore, et al., EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals, *Endocrine Reviews*, 36(6):E1–E150

^v 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.

^{vi} WHO 2017. <http://www.who.int/features/qa/one-health/en/> Accessed April 2, 2018.

^{vii} European Commission Public Health Website: https://ec.europa.eu/health/endocrine_disruptors/overview_en Accessed April 10, 2018

^{viii} 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

^{ix} European Commission Environment Website: http://ec.europa.eu/environment/chemicals/reach/legislation_en.htm#legal Accessed April 10, 2018.

^x European Commission Public Health Website: https://ec.europa.eu/health/biocides/policy_en and https://ec.europa.eu/food/plant/pesticides_en Accessed April 10, 2018.

^{xi} European Parliament resolution of 14 March 2013 on the protection of public health from endocrine disruptors. <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

^{xii} 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



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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^{xiii}. 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, 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 that is not reflected in the strategy. In July 2017, the European Commission announced that it would begin work on a new strategy to minimize exposure of EU citizens to endocrine disruptors, beyond pesticides and biocides.^{xiv} The new strategy is supposed to include consumer products such as toys, cosmetics, and food packaging regulated through specific EU legislation.

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^{xv}.

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.^{xvi,xvii,xviii} As is the case in the US, it is likely that nearly all babies born in the EU are exposed to industrial chemicals and are potentially at risk for EDC hazards^{xix}. 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 may

^{xiii} 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.

^{xiv} European Commission Press Release, Brussels, July 4 2017. http://europa.eu/rapid/press-release_IP-17-1906_en.htm Accessed April 10, 2018.

^{xv} 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.

^{xvi} DEMOCOPHES <http://www.eu-hbm.info/democophes> Accessed April 10, 2018.

^{xvii} 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.

^{xviii} Leino, O., et al: Pollutant concentrations in placenta. *Food and Chemical Toxicology* 54 (2013), 59-69.

^{xix} Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the US: NHANES 2003-2004. *Environ Health Perspect*. 2011;119:878-85.



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be 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.

What Constitutes “Proof?”

Several countries in North America and the EU have banned baby bottles and other baby food containers that contain bisphenol-A (BPA), a chemical used in many polycarbonate plastics, based on in vivo studies in humans and animals and other in vitro studies. Some companies have also taken independent measures to remove BPA from consumer products due to public concern over safety. However, no measures whatsoever have been taken so far to protect other vulnerable individuals such as pregnant women and adolescents. Similar concerns exist over other EDCs, such as perchlorate and phthalates.

Unlike pharmaceuticals, for which clinical trials are undertaken to prove benefits and rule out 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. 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^{xx}. 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^{xxi} and in a report by the United States National Academies^{xxii}.

CONSIDERATIONS

Emerging scientific discoveries on EDCs can influence relevant policy decisions. The Endocrine Society encourages further research to resolve scientific discrepancies and uncertainty, and recommends that policymakers consider taking a precautionary approach when developing policy about chemicals that may be harmful to the public. When conclusive evidence is lacking, but sound scientific studies indicate a strong possibility for adverse health effects, it is the responsibility of government to adopt measures that protect people from the risk of exposure to certain chemicals. While some chemicals have been shown to have endocrine-disrupting activity, there are no data on the universe of chemicals in use and in the environment today, including replacement chemicals for known EDCs. In many cases, replacements for harmful chemicals such as BPA include structural analogues with uncertain safety profiles. Thus, appropriate testing strategies must be developed to consistently and comprehensively examine all chemicals for potential EDC activity. 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

^{xx} Woodruff, T.J., 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.

^{xxi} 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

^{xxii} 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>.



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and assess the inherent risk in that exposure as far as this is possible. 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 comprehensive examination of EDC exposure and its effects on human health are used as the basis for policy decisions.

POSITIONS

The Endocrine Society is concerned that the European public may be placed at risk because critical information about potential health effects of endocrine-disrupting chemicals is being overlooked in the development of guidelines and regulations, hindering the efficient identification of EDCs. 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

- The EU Strategy on EDCs should be revised, taking into account new scientific information developed in recent years, and with the aim of minimizing exposure to hazardous EDCs throughout the environment and in consumer products.
- Regulations should be designed to protect the most vulnerable populations—including but not limited to fetuses, children, and adolescents—from irreversible effects.
- Regulatory decisions for EDCs should be science-based and should be applicable across all potential EDCs.
- Policy should be based on comprehensive data covering both low-level and high-level exposures, including cumulative and mixture effects. This includes synthesizing 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.

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.
- It cannot be assumed that there are thresholds below which EDC exposures are safe.
- 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.
- Guidance should ensure that regulatory agencies can identify chemicals that interfere with hormone action and define them as EDCs based on a realistic standard of scientific information, minimizing the potential for mischaracterization of harmful chemicals. Agencies should also have transparent processes in place for situations where they may not have sufficient information to evaluate a chemical for EDC effects.



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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^{xxiii}: 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.
 - Evaluate EDC outcomes at different life stages—not just adulthood.
 - Design studies to consider sex and gender differences in response to EDCs.
 - Perform longitudinal and multigenerational analyses in animals and humans.
 - Evaluate and implement emerging and sensitive testing systems, 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 “EDCs of interest” and to mixtures of low-dose EDCs.
 - 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, such as declining sperm counts.
 - 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.

^{xxiii} 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