ENDOCRINE-DISRUPTING CHEMICALS

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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, chemicals in plastic polymers (including breakdown products or constituents), food contact materials, cosmetics, and others. Common non-communicable diseases have been associated with environmentally-relevant doses of EDCs in human and animal populations, with differential exposure to EDCs emerging as a potential driver of observed health disparities based on race, ethnicity, and income. Research across different approaches and disciplines, including human, animal, and in vitro studies have unequivocally established causality between EDC exposure and effects and have often elucidated the endocrine mechanisms of action through which chemicals cause harm. 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 in the last decade.

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 diseases, particularly endocrine-related conditions. We strongly support the use of scientific knowledge in policies governing EDCs and other hazardous chemicals to improve public health.

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

[1] 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

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 relevant to human exposure ranges, yet not typically evaluated in government-sanctioned or internationally-recognized testing strategies.

The scientific consensus in EDC-2 and subsequent research shows that:

- EDCs contribute to the burden of many diseases and adverse health conditions, such as neurodevelopmental, reproductive and metabolic disorders, as well as some cancers, that have caused significant public health concern due to their increasing incidence.
- Non-linear and non-monotonic dose responses (NMDR) to EDCs are common and impair the assessment and management of risk when based on classical concepts of regulatory toxicology testing, such as potency, threshold, and the establishment of 'safe' doses of exposure.
- It is now well-established that the EDC effect depends upon when (i.e., at what life stage/s) the effect is assessed, with critical developmental periods of susceptibility, such as fetal development and infancy, influencing vulnerability to the effects of EDCs on later life outcomes.
- Regulatory hazard evaluation of EDCs is limited by the insufficient sensitivity of standard good laboratory practice (GLP) toxicology testing and OECD/EU guideline studies, as well as the omission of academic research, thereby leading to insufficient protection of public and environmental health with increased medical and other costs.
- New studies in humans have established associations between EDC exposures and numerous chronic diseases and adverse conditions. Furthermore, relationships between

epidemiological studies and mechanistic experimental studies of cells and animals have greatly expanded during the last decade, identifying certain modes of action.

National and international regulatory agencies such as the Organization for Economic Cooperation and Development (OECD), European Chemicals Agency (ECHA), European Food Safety Agency (EFSA), United Nations Environment Programme (UNEP), World Health Organization (WHO), United States Food & Drug Administration (FDA) 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 considerable 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, reflecting inadequate test strategies for critical human-relevant endpoints related to endocrine disruption, are inconsistent with peer-reviewed academic research, calling into question the rigor and effectiveness of regulatory approaches.

in 2017 the Endocrine Society established an Endocrine Disrupting Chemicals Advisory Group (EDC-AG) to improve the utilization of endocrine science in policies governing EDCs and help agencies address scientific and regulatory gaps, with oversight of member-led task forces operating in national, regional, and global policy environments. In 2024, the EDC-AG recommended the Society's Position Statement on EDCs be updated to reflect new regulatory policies and proposals.

BACKGROUND

Although the term "endocrine disruptor" was first used in 1991[2], the notion that environmental chemicals interfere with hormone actions emerged more than 70 years ago[3]. 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, as part of the Food Quality Protection Act, Congress mandated that EPA develop the Endocrine Disruptors Screening Program (EDSP). In 1999, the European Union (EU) established a

[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.

'Community strategy for endocrine disruptors with recommended actions to protect public health from EDC-related harm'[4]. In 2017, the EU adopted legal criteria to identify EDCs in pesticides and biocides, and then widened the applicability of these criteria by introducing new hazard classes for EDCs in the regulation on Classification, Labeling and Packaging (CLP). These classes are currently under discussion by the OECD as part of the process for adoption globally as part of the UN Global Harmonized System (GHS) for CLP.

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 environment[5]. 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. An update to the state of the science assessment is expected in 2025. Discussion of EDCs is also taking place in the context of multilateral environmental agreements (MEAs), such as the Intergovernmental Negotiating Committee (INC) on Plastic Pollution, which is negotiating a binding legal instrument, or treaty, to end plastic pollution, potentially with provisions on chemicals of concern including EDCs.

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 can disrupt endocrine function by interacting with receptors other than estrogen, androgen and thyroid hormone receptors, such as the peroxisome proliferator-activated receptor gamma (PPARγ), estrogen-related receptor gamma (ERRγ), and the glucocorticoid receptor (GR), among others. EDCs also interact with membrane receptors such as the follicle-stimulating hormone receptor and the nicotinic acetylcholine receptor, which is expressed in many endocrine tissues. Moreover, many effects of EDCs are caused by direct actions of EDCs with other mechanistic components

[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.

of endocrine systems e.g., hormone distribution proteins in circulation, transmembrane hormone transporters, intracellular enzymes acting on hormones or their precursors and metabolites[6].

Despite these advances, 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 (THR), while those effects governed by other receptors and components of endocrine systems are not yet evaluated. Also, the OECD conceptual framework focuses narrowly on effects upon female and male reproductive systems, carcinogenicity and overt neurotoxicity; however, scientific evidence summarized in EDC-2 identified effects of EDCs on metabolism, thyroid hormone systems and neurodevelopment. Therefore, all major endocrine organs and their complex local systems at the cellular level are vulnerable to endocrine disruption, yet no testing guidelines related to endocrine pathologies have been developed, despite large increases in prevalence every year. An approach that utilizes the key characteristics of EDCs as a basis for hazard identification would recognize the breadth of chemical impacts on endocrine systems[7].

New evidence shows that 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. It is also 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. Furthermore, there are robust research data that have found EDC-related effects on neuroinflammation, synaptogenesis, mammary gland morphogenesis, stress signaling, and cardiac function amongst others. 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. There is also concern that pressure to move away from animal research in favor of in vitro, in silico, and other "new approach methodologies" (NAMs) for animal welfare reasons will further deplete

[6] La Merrill, M.A., Vandenberg, L.N., Smith, M.T. et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16, 45–57 (2020). https://doi.org/10.1038/s41574-019-0273-8

[7] La Merrill, M.A., Vandenberg, L.N., Smith, M.T. et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16, 45–57 (2020). https://doi.org/10.1038/s41574-019-0273-8

capacity to detect endocrine disruption, particularly during development and in sensitive but poorly modeled tissues such as the mammary gland, brain, and placenta. Despite the more labor- and technology-intensive nature of testing required to identify endocrine-disrupting properties of a substance, these assays 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 both hormones and EDCs. The presence of NMDR has been extensively demonstrated in animal and cellular models[8] and the diverse and complex molecular mechanisms underlying NMDR are beginning to be demonstrated[9]. Importantly, carefully designed epidemiological studies are starting to reveal their existence in human populations as well[6].

The existence of NMDR in evaluations of EDCs has significant consequences on regulatory toxicology, because NMDR does not guarantee that the lack of adverse effects at high doses also confirms safety at low doses. Common concepts of classical regulatory 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 or population will experience an adverse effect) is a function of the hazardous properties of the source, timing, and the level of exposure. When there is a monotonic relationship between dose and effect, risks associated with hazards are predicted to be reduced effectively by decreasing exposure. The existence of NMDR raises the possibility that reduced exposure may have uncertain effects on risk, with the possibility of no safe level of exposure. This feature supports regulatory application of hazard-based identification and management strategies for EDCs that consider the fundamental properties of the chemical in question.

Mixtures

[8] 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.

[9] 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

Individuals and populations are exposed to complex low-dose mixtures of EDCs, other chemicals, and additional environmental stressors[10] that may interact to produce complex and potentially synergistic effects[11]. Despite the validity of dose-additivity and the cumulative effects of exposure to EDCs and other environmental factors, 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. Hazard-based regulatory approaches may more effectively deal with the challenge of cumulative or mixture effects, and should be developed.

New Approach Methods (NAMs)

Efforts to reduce and/or eliminate the use of animals in regulatory testing strategies have prompted the development of new approach methodologies (NAMs[12]) defined as technologies and approaches (including computational modelling, in vitro assays, and testing using alternative animal species such as c. elegans or zebrafish, and also sentinel animal species) to reduce the use of vertebrate animals in regulatory assessments and ensure a high level of human health protection[13][14]. Such approaches show promise in achieving more high-throughput screening of chemicals; however, NAMs have not been sufficiently developed to comprehensively assess biological complexity, including tissue cross-talk implicit in the endocrine system and sex as a biological variable, especially during highly sensitive and dynamic processes such as pregnancy. Moreover, certain endocrine processes, including many developmental pathways that, if perturbed, result in later-life effects, may never be sufficiently replicated via NAMs to achieve the high level of protection required. For example, non-animal methods do not adequately address the critical role of thyroid hormone in neurodevelopment.

Scientific controversies of EDCs

[10] Braud G, et al., Science 17 Oct 2024 Vol 386, Issue 6719 pp. 301-309 DOI: 10.1126/science.adq0336
[11] Martin O, et al., Environ Int. 2021 Jan:146:106206. doi: 10.1016/j.envint.2020.106206. Epub 2020 Oct 26.
[12] National Academies of Sciences, Engineering, and Medicine. 2023. *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.
[13] We note that NAMs should not be interpreted as non-animal methods, and regulatory agencies should make this distinction clear.
[14] National Academies of Sciences, Engineering, and Medicine. 2023. *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.

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 disruptor[15] 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. Drawing on the results of the CLARITY-BPA study[16], the European Food Safety Agency (EFSA) established a dramatically reduced tolerable daily intake level for BPA, indicating that average real-life human exposure is above levels EFSA considers safe, which prompted restrictions in consumer products and food contact materials[17].

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 EDC[18]. This affirms the scientific validity of the WHO, EU(CLP), and 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."[19] 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.

[15] 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.
[16] Heindel J, et al., Reprod Toxicol. 2020 Dec:98:29-60. doi: 10.1016/j.reprotox.2020.05.014. Epub 2020 Jul 16.
[17] FSA CEP Panel (EFSA Panel on Food Contact Materials, Enzymes andProcessing Aids), 2023. Scientific Opinion on the re-evaluation of the risks to public health related to the presence of bisphenol A (BPA)in foodstuffs. EFSA Journal 2023;21(4):6857, 392 pp.
[18] Solecki, R., Kortenkamp, A., Bergman, Å. et al. Arch Toxicol (2017) 91: 1001. https://doi.org/10.1007/s00204-016-1866-9
[19] SAICM/ICCM.4/15 Report of the International Conference on Chemicals Management on the work of its fourth sesión. 28 October 2015.

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 and expensive, 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 show 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 as demonstrated by DES. A precautionary approach to regulation, consistent with the EU constitution, may therefore be warranted in the absence of conclusive transgenerational data in humans.

CONSIDERATIONS

The Endocrine Society is concerned that regulatory agencies are prevented from making efficient and effective decisions regarding chemical safety due to delays and omissions in their incorporation of new scientific knowledge about EDCs. Stakeholders need to work together with agencies to utilize available scientific information and accelerate decision-making. There exist approximately 350,000 chemicals on the market with thousands of new chemicals produced every year[20]. 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. Often, such exposures are concentrated in sensitive populations who experience greater impacts due to cumulative and mixture effects which are not accounted for in a risk-based approach to chemicals management.

Regulatory agencies need to work with public health stakeholders to more accurately define the level of scientific evidence appropriate to act on chemicals of concern. Intervention studies and clinical research that would increase human exposure to hazardous chemicals would be unethical

[20] Wang, Z.; Walker, G. W.; Muir, D. C. G.; Nagatani-Yoshida, K. Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of Regulatory Industrial Chemical Invento- ries. Environ. Sci. Technol. 2020, 54 (5), 2575−2584

and should be considered unacceptable. Longitudinal epidemiological studies establishing causality in humans are difficult, expensive, and most importantly require long timeframes, especially when multigenerational effects must be studied. Therefore, when peer-reviewed scientific studies in cellular and animal models and/or epidemiological observational studies indicate a strong possibility of an adverse effect, authorities must develop regulatory strategies that protect public health, and in particular vulnerable populations; authorities must also conduct public outreach so that people can make informed decisions and be protected. We note that the cost of inaction is substantial, with annual healthcare cost and lost earnings in the U.S. that can be attributed to low-level daily exposure to endocrine-disrupting chemicals exceeds $340 billion[21].

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 that rely on "expert judgement" and are often insufficiently transparent. Systematic review methodologies relevant to endocrine-disrupting chemicals have been developed, including the SYRINA method[22] and the Navigation guide[23], which was utilized by a panel of the United States National Academies to evaluate EDCs[24].

Testing must incorporate the latest endocrine science and the expertise of endocrine scientists; endocrine research has proven that NMDRs exist and therefore, assumptions such as linear potency

[21] Attina, T. M. et al. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. The Lancet Diabetes & Endocrinology, Volume 4, Issue 12, 996 - 1003

[22] 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.

[23] 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.

[24] 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.

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

At present, some NAMs may be suitable for screening to identify hazards currently uncharacterized by animal studies[25]. However, due to their numerous, well-characterized limitations, NAMs should not be used to determine that a chemical is safe without substantiation from traditional methods. We are concerned that regulatory agencies have not described how they will validate NAMs or published a framework for how they will accept and use hazard data from NAMs as a basis for restrictions and other controls, or lack thereof, on EDCs. Absent clear plans from regulatory agencies, we note that high-throughput testing could also be achieved while reducing animal testing for example by adopting class-based approaches utilizing read-across and group assessments to apply positive hazard data from one chemical to others in the same group, or by making better use of academic data, including human cohort studies, in regulatory assessments.

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 and/or exacerbate the etiology of numerous chronic diseases. The increase in the prevalence, morbidity and mortality of chronic diseases imposes a major impact on the efficiency and cost of health systems. Regulatory test guidelines must advance to incorporate updated endocrinology concepts and rapidly integrate them into reliable EDC testing.

[25] National Academies of Sciences, Engineering, and Medicine. 2023. *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.

Therefore, the Endocrine Society supports the following positions

- Regulatory toxicology should implement endocrine concepts such as low dose effects and NMDR without further delay. Because 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 hazard identification and risk reduction, should be science-based and applicable across all potential EDCs, not based on the economic impact on manufacturers or commercial enterprise, which fails to prioritize human health burden and associated costs to patients and communities.
- Regulations should be designed to protect the most vulnerable populations – including but not limited to fetuses, children, pregnant women, adolescents, socioeconomically disadvantaged populations, and the elderly – from irreversible effects of EDCs.
- EDC testing 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.
- We support the development and application of NAMs for regulatory purposes when they demonstrably reflect biological understanding as well as or better than traditional methods. Currently, some NAMs may be appropriate for screening chemicals to identify hazards, but they should not be used to invalidate positive results from human or animal studies, nor should NAMs be evaluated in isolation to determine that a chemical is safe. Most NAMs remain unvalidated and unable to assess sex as a biological variable, let alone endocrine tissue cross-talk, developmental stages or genetic variability.
- Policy should be based on comprehensive data covering both low-level and high-level exposures, including cumulative EDC effects, EDC mixture effects, and other stressors

combined with EDCs. This includes synthesizing basic science (comprising human, 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 risk assessments and to identify EDCs. Studies should be evaluated in a transparent manner using current standardised criteria. Consistent with the principles of systematic review, the included and excluded studies as well as information about relevant endpoints used to make risk and EDC identification decisions should be reported and made publicly available.
- All processes governing EDC assessments should include endocrine scientists with expertise in the hormonal systems and other biological mechanisms relevant to each endpoint to ensure comprehensive understanding of the effects and endpoints under examination by chemical testing.
- EDCs are a global issue. Health issues related to EDCs cannot be geographically compartmentalized, may occur globally, 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 2016-2020[26].
- The "One Health" approach, recognizing the impact of EDCs on biodiversity and ecological health in addition to human health, should be considered in policies governing management of hazardous chemicals.

[26] SAICM/ICCM.5/Bureau.1/INF/3