INTRODUCTION
Endocrine-disrupting chemicals (EDCs) are defined as 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.

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 biocides. The European Commission is charged with developing science-based criteria for endocrine disruptors. However, the EU has struggled to define criteria to identify EDCs, and EU laws governing EDCs are inconsistent in their management of these chemicals.

The Endocrine Society wants to ensure that policies governing EDCs consider the full body of research into EDCs. As the largest global professional organization for basic and clinical endocrine research and the treatment of endocrine disorders, the Society counts among its members the world’s leading experts in endocrinology, including experts on EDCs and their effects. In its 2009 Scientific Statement and its 2012 Statement of Principles, the Society calls for greater 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 take into account the scientific issues of latent and transgenerational effects, low-dose effects, non-monotonic dose responses, and mixture effects. It is also critical that regulatory agencies understand 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 even low levels of EDCs. These scientific issues are not adequately addressed under the current Organization for Economic Cooperation and Development (OECD) — screening guidelines, which rely on outdated methodology and insensitive endpoints for evaluating endocrine activity.

For example, while the fish life-cycle toxicity test focuses on GnRH development in 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. We note that the primary aim of the Endocrine Society is human health; however, this should not be taken to mean that impacts on wildlife are not of concern.

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. Some milestones include Europe’s Strategy on EDCs (1999); the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH, 2007); pesticides regulation (2009); and biocides regulation (2011). More recently the European Parliament adopted a resolution on the protection of public health from endocrine disruptors; the 7th Environmental Action Programme was published in 2013 and calls for minimizing exposures to EDCs.

Currently, the European Commission seeks to define criteria for the identification of substances as EDCs. Among these criteria, “endocrine-mediated action” cannot be restricted to perturbing a single class or system of hormones interacting with a receptor, since a single chemical or class of chemicals can interact with different endocrine pathways, and endocrine systems are often linked. Therefore, “endocrine-mediated” action criteria to identify EDCs, and EU laws governing EDCs are inconsistent in their management of these chemicals.

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should specifically indicate that the adverse outcome is plausibly caused by a substance interfering with hormone action. By “hormone action”, we mean “hormone receptor activation”, recognizing that many hormones have multiple receptor isoforms including nuclear and/or membrane or other receptors that “transduce” hormone signals into cellular actions that affect development and/or physiology. It should also reflect the 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.

**SCIENCE OF EDC ACTIONS HAS ADVANCED.**

EU policymakers are invested in protecting their constituents 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, reproduction, metabolism, obesity, and brain development, can be targets of EDCs. Furthermore, EDCs can produce effects that do not exactly mimic those of natural hormones.

EDCs can also act on multiple generations. For example, exposure of pregnant women to EDCs will result in exposure of the fetus through placental transfer, and exposure can continue in the newborn through breast-feeding. Recent biomonitoring studies from across Europe have shown that people in the general population are typically contaminated with several chemicals. 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.

Individuals exposed to EDCs in the womb face elevated risk of disease later in life. Additionally, some EDCs have multi-generational effects through 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 seven months gestation and higher risk of disease. In the case of the female fetus, germ cell numbers are maximized by seven months gestation and higher risk of disease later in life. Additionally, some EDCs have multi-generational effects through modification of DNA and other heritable mechanisms, thereby placing future generations at higher risk of disease.

**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 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?”**

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 therefore imperative that strong evidence from animal models be heavily weighed 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\footnote{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.}.

While a number of 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 \textit{in vivo} studies in humans and animals and other \textit{in vitro} studies, no measures whatsoever have been taken so far to protect other vulnerable individuals such as pregnant women and adolescents. Similar controversies exist over other EDCs, such as perchlorate and phthalates.

There are likely to be a number of explanations to account for the broadly divergent conclusions by different groups of scientists on some issues, but the lack of representation of endocrine scientists with expertise in hormonal action and hormonal effects on EDC advisory groups is a crucial consideration. Endocrine scientists have unique expertise and experience in experimental endocrinology, and this expertise is critical for high-quality evaluation of endocrine studies which cannot be assessed by scientists with different discipline-specific expertise.

\section*{CONSIDERATIONS}

The scientific controversy over EDCs has stimulated scientists to raise new questions and to accumulate evidence that can no longer be denied by the scientific community or by policymakers. 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 the government to adopt measures that protect people from the risk of exposure to certain chemicals. Furthermore, while some chemicals have been shown to have endocrine-disrupting activity, there are no data on the vast majority of the thousands of compounds in use and in the environment today. 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 endocrine disruptor effects and mechanisms becomes available, it will be increasingly important to carefully assess the extent of human exposure to EDCs and assess the inherent risk in that exposure as far as this is possible. Additionally, it will become increasingly 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. 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. All disciplines must work together with policymakers, non-governmental organizations, scientific societies, and other stakeholders in order to ensure that a comprehensive examination of EDC exposure and its effects on human health are used as the basis for policy decisions.

\section*{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. EDC effects know no disciplinary boundaries. Teams of scientists, including endocrine scientists, toxicologists, epidemiologists, 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:

\begin{itemize}
  \item 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.
  \item Regulations should be designed to protect the most vulnerable populations — including but not limited to fetuses, children, and adolescents — from irreversible effects.
  \item Definition and criteria for EDCs should be science-based, not economics-based, and should be applicable across all potential EDCs.
  \item The Endocrine Society opposes the inclusion of a “potency” cutoff as an element of hazard characterization because the concept as it is applied in this context is inconsistent with endocrine science and fails to account for developmental windows or whether the appropriate endpoint is used\footnote{Endocrine Society Comments to European Commission Public Consultation on EDCs. Accessed February 4, 2015.}.\end{itemize}
POSITION STATEMENT

• It cannot be assumed that there are thresholds below which EDC exposures are safe.
• 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.
• Consistent with the current state of the art of endocrine science, the default approach to assessing potential EDCs must include low-dose studies relative to human exposures and below those dose ranges used for traditional toxicity testing. Assessments should take into account that there may be no detectable threshold below which EDC can be presumed to be safe, and that potency is an inaccurate predictor for toxic effects, 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.
• 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.
• The results of EDC identification processes should be transparent and publicly available.
• The European Commission and agencies should support further research into EDCs, including the development of high-throughput assays that would allow the testing of many chemicals for EDC activity at a full range of concentrations and in both males and females. Such assays must be anchored to biologically relevant endpoints that reflect actual effects on human health and the environment.