

## ENDOCRINE-DISRUPTING CHEMICALS

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### INTRODUCTION

Endocrine disrupting chemicals (EDCs) are broadly defined as chemicals that can interfere with hormone action. These chemicals are designed, produced, and marketed largely for specific industrial purposes (e.g., plasticizers, pesticides, etc). They are also found in some natural foods and may become further concentrated as foods are processed or can even contaminate foods during processing or storage. Public interest in possible health threats posed by EDCs is on the rise, leading to development of federal and state policies designed to regulate or mediate perceived EDC health risk. However, there is no comprehensive, coordinated approach to regulating EDCs in the US

The Endocrine Society — the premier professional organization for basic and clinical endocrine research and the treatment of endocrine disorders — is concerned that policy governing EDCs does not consider the full body of research into EDCs. To address this issue scientifically, the Society created a Task Force charged with summarizing current knowledge about EDCs, including possible mechanisms of action and potential health risks, and with recommending actions the Society could take to promote EDC research. The Task Force's work resulted in a comprehensive scientific document that is published in *Endocrine Reviews* as the Society's first Scientific Statement<sup>1</sup>. The Scientific Statement presents a review of the EDC literature, focused on the effects of low-dose exposure to EDCs on endocrine systems, and clearly elaborates a strong basis for concern about EDC health risks. Policies that fail to adequately consider these low-dose effects, many of which were identified through NIH-funded studies, could lead to regulatory decisions that inappropriately define safe levels for some EDCs. Furthermore, for many chemicals in use today, no data exist on their EDC activity due to a scarcity of rigorous scientific testing. Therefore, to be comprehensive and relevant to public health, EDC policy must be based on analysis of both low- and high-dose

actions, as well as both short- and long-term exposures and simultaneous exposure to multiple common EDCs. Moreover, research efforts to illuminate endocrine disrupting effects of all chemicals that enter the food chain or otherwise lead to human exposure should be expanded. Finally, it is critical that regulatory agencies understand that the consequences of EDC exposures will depend upon the timing of exposure. This is of particular concern when we consider the increased sensitivity and vulnerability of developing fetuses and infants to natural or artificial hormones.

### BACKGROUND

The understanding that environmental chemicals can interfere with hormone action has developed slowly over the past 50 years. Congress formally recognized EDCs as a public health concern in 1996 when it passed the Food Quality Protection Act and amendments to the Safe Drinking Water Act. These laws included a mandate to the US Environmental Protection Agency (EPA) to develop a program to identify EDCs to which the human population may be exposed.

In response to the mandate, the EPA has worked for more than 10 years to develop a formal system of screens and tests that would be used to identify potential EDCs in the environment. This Endocrine Disruptors Screening Program (EDSP) has yet to be finalized, but recent basic and clinical research into EDCs has provided significant new information about the mechanisms of EDCs on human health that could require modifications to the plan. Thus, there is concern that this plan, if implemented in its current form, will already be outdated.

### New Information on EDC Actions Has Emerged.

Endocrinological research into EDCs over the past decade has revealed important issues that have not yet been incorporated into the EDSP or into risk assessment paradigms employed by various government agencies, which concentrate on steroid and thyroid hormone receptor-based mechanisms. For example, it is now clear that other hormone receptor types and functions, including those involved in metabolism, obesity, and brain signaling, can be targets of EDCs.

EDCs may also act beyond the exposed individual. For example, exposures of pregnant women to EDCs can result in exposure of the fetus through placental transfer, and exposure can continue in the newborn through breastfeeding. The CDC has collected biomonitoring data indicating that several dozen industrial chemicals, including some



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EDCs, are routinely found in amniotic fluid.<sup>2</sup> Thus, nearly all babies born in the United States are exposed to industrial chemicals and are potentially at risk of EDC actions.

Recent reports show multi-generational effects of some EDCs (that is, the consequences of exposure are passed to future generations) through modification of DNA and other heritable mechanisms. Therefore, the endocrine disrupting potential of a compound extends far beyond actions at hormone receptors. It is therefore evident that EDCs need not bind to a hormone receptor in order to disrupt endocrine signaling in the exposed individual, her offspring, and subsequent generations, facets of EDC exposure that have not yet been incorporated into the EDSP or public policy in general.

### **EDC Effects Are Seen at Low Levels of Exposure.**

Current EDC policy relies largely on data produced from toxicological studies examining the effects of high doses of chemicals. A substance must show adverse effects that increase proportionally with dose in order to be considered dangerous by classical toxicological standards. However, many EDC effects occur at low doses even when high dose effects are not apparent. In fact, increasing amounts of hormone or 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 high levels of exposure. By excluding low-dose studies from policy considerations, the regulatory community may not be accounting for harmful EDC actions that exhibit hormone-like dose-response profiles.

### **Basic Research Predicts 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. 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. However, current screening and testing guidelines often overlook delayed

effects such as those caused by DES or fail to incorporate complex endpoints of EDC actions to reveal adverse effects.

### **Scientific Controversy of EDCs Still Exists.**

While the effects of DES have been confirmed, controversy remains over the effects of other EDCs such as bisphenol A (BPA). In 2007 a group of 38 independent NIH-funded investigators determined that "...human exposure to BPA is within the range that is predicted to be biologically active in over 95% of people sampled."<sup>3</sup> In support of this position the Center for the Evaluation of Risks to Human Reproduction (CERHR) concluded in 2008 that there is "...some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A."<sup>4</sup> This concern is further supported by the recent demonstration that urinary BPA concentrations are significantly associated with diagnoses of type 2 diabetes and cardiovascular disease in humans.<sup>5</sup> Despite these opinions and scientific findings, the FDA ruled in 2008 that BPA is safe even for infants.<sup>6</sup> Similar controversies exist over other EDCs, such as perchlorate and phthalates.

Also controversial is the effect of fetal exposure to EDCs on the male reproductive system. Some studies have suggested poor semen quality and certain types of testicular cancer may be the result of fetal or early exposure to certain EDCs, but scientific interpretation of the studies varies, and conclusive data do not yet exist.

There are likely to be a number of explanations to account for the broadly divergent conclusions by different groups of scientists on these issues, but the reliance primarily on toxicological studies, including high-dose, short-term exposures, for public health risk assessment contributes to these uncertainties.

## CONSIDERATIONS

The scientific controversy over EDCs influences relevant policy decisions. The Endocrine Society encourages further research to resolve the 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 federal government to develop policies that protect people from the risk of exposure, or at the very least inform them of this risk.

<sup>2</sup> Barr D.B., Bishop A., Needham L.L. (2007) Concentrations of xenobiotic chemicals in the maternal-fetal unit. *Reprod Toxicol* 23:260-266

<sup>3</sup> vom Saal et al, *Reprod Toxicol*. 2007 Aug-Sep;24(2):131-8. Epub 2007 Jul 27

<sup>4</sup> Chapin et al, *Birth Defects Res B Dev Reprod Toxicol*. 2008 Jun;83(3):157-395

<sup>5</sup> Lang et al, *JAMA* 2008; 300:1303-10

<sup>6</sup> Tanne, *BMJ*. 2008 Aug 26;337:a1429. doi: 10.1136/bmj.a1429



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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, policies must be developed to consistently and comprehensively examine all chemicals for potential EDC activity.

Identifying direct links between EDC exposure and childhood or adult disease is difficult for many reasons, including the challenges of accurately assessing a lifetime of exposure to a complex mixture of potentially harmful agents. Furthermore, direct clinical investigations would be difficult and even unethical in many circumstances. It is therefore important that policy considerations include development and validation of animal model systems that, combined with detailed laboratory analyses of EDC mechanisms, will accurately predict and quantify potential effects in humans.

As more information about endocrine disruptor effects and mechanisms becomes available, it will be increasingly important to carefully quantify the extent of human exposure to EDCs and assess the inherent risk in that exposure. Additionally, it will become increasingly necessary to provide research funding so that scientists can further examine EDC effects.

Endocrine research is needed to 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 in order to ensure that a comprehensive examination of EDC exposure and its effects on human health is used as the basis for federal policy decisions.

### POSITIONS

The Endocrine Society is concerned that the public may be placed at risk because critical information about potential health effects of endocrine disrupting chemicals to which Americans are exposed is being overlooked in the development of federal guidelines and regulations. Endocrinologists, toxicologists, epidemiologists, and environmental scientists must work together with federal agencies and legislators to develop comprehensive screening programs for all chemicals and regulations governing EDCs in manufactured products, the food supply, or the environment.

Therefore, The Endocrine Society supports the following positions:

- Regulatory oversight of endocrine disrupting chemicals should be centralized such that regulations pass through a single office to ensure coordination among agencies. Coordination is required for comprehensive and consistent regulations among all relevant federal agencies setting guidelines for acceptable exposure, manufacturing, sale, and human use of EDCs.
- Policy should be based on comprehensive data covering both low-level and high-level exposures. Furthermore, tests and screens used to determine EDC activity of chemicals should be balanced between those that examine simple mechanisms and others that instead measure integrated biological outcomes, thereby encompassing substances that have effects through several mechanisms, whether known or unknown.
- Policy should be developed and revised under the direction of a collaborative group comprising endocrinologists, toxicologists, epidemiologists, and policymakers. The same group should identify knowledge gaps and recommend research directions to fill those gaps.
- Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC policy.
- The federal government should develop a public awareness campaign to inform the public of the risks and potential risks related to the presence of EDCs in the environment and in the food supply.
- The federal government 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.

*This position statement has been endorsed by the American Thyroid Association*