



**Testimony
Before the Subcommittee on
Energy and Environment
Committee on Energy and Commerce
United States House of Representatives**

**Statement for hearing entitled,
“Biology’s Clock Interrupted: Endocrine
Disrupting Chemicals in Drinking Water”**

Statement of

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Mr. Chairman and distinguished members of the Subcommittee—I am pleased to appear before you today to present testimony on current understanding and ongoing research on endocrine disrupting chemicals (EDCs). I am Linda Birnbaum, the Director of the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health (NIH), as well as of the National Toxicology Program (NTP). NIH and NTP are entities of the U.S. Department of Health and Human Services.

Endocrine disruptors are naturally occurring or man-made substances that may mimic or interfere with the function of hormones in the body. Endocrine disruptors may turn on, shut off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs. NIEHS has had a longstanding interest in these chemicals with its support for research dating back to the beginning of the Institute in the 1960s.

Over the past fifty years, researchers observed increases in endocrine-sensitive health outcomes. Breast and prostatic cancer incidence increased between 1969 and 1986¹; there was a four-fold increase in ectopic pregnancies (development of the fertilized egg outside of the uterus) in the U.S. between 1970 and 1987²; the incidence of cryptorchidism (undescended testicles) doubled in the U.K. between 1960 and the mid 1980s³; and there was an approximately 42% decrease in sperm count worldwide between 1940 and 1990⁴.

These observations, set against the numerous observations of abnormalities of sexual development in amphibians and fish⁵ and the widespread detection of chemicals with endocrine disrupting properties in our bodies⁶, have led NIEHS to increase its support for research on the effects of chemical exposures on the various endocrine systems. The detection of numerous pharmaceutical agents and chemicals with endocrine disrupting potential in surface waters around the country⁷ has raised concern about drinking water as a significant route of exposure.

There are four aspects of exposure to endocrine disruption which I want to emphasize:

- First, the effect of low doses. Normal endocrine signaling involves very small changes in hormone levels, yet these changes can have significant biological effects. That means subtle disruptions of endocrine signaling is a plausible mechanism by which chemical exposures at low doses can have effects on the body.
- Second, the wide range of effects. Endocrine signals govern virtually every organ and process in the body. That means that when outside chemicals interfere with those systems,

¹ Hoel DG et al. J Natl Cancer Inst 84:313-320(1992)

² Nederlof KP et al. MMWR 39:9-17 (1990)

³ Group JRHCS. Br Med J 293:1401-1404(1986)

⁴ Carlsen E et al. Br Med J 305:609-613(1992)

⁵ e.g., Reeder et al., Environ Health Perspect 113(3) 261-265 (2005); Gross-Sorokin et al., Environ Health Perspect 114 (S-1):147-151 (2006)

⁶ CDC, Fourth National Report on Human Exposure to Environmental Chemicals (2009), <http://www.cdc.gov/exposurereport/>

⁷ USGS, Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams (2002); <http://toxics.usgs.gov/pubs/FS-027-02/>

the effects can be seen in many different diseases and conditions – some of which we are just learning to recognize as the result of endocrine disruption.

- Third, the persistence of effects. We are finding that the effects of exposure to endocrine disruptors can be observed long after the actual exposure has ceased. This is especially true for growth and development, processes that are very sensitive to endocrine regulation. The question of how these kinds of latent effects occur is an active area of investigation.
- Fourth, the ubiquity of exposure. Both naturally occurring and manmade substances can be endocrine disruptors. Some, e.g., arsenic and agricultural chemicals, are ubiquitous in the environment. In addition to the growing use of hormonally-active pharmaceuticals that pass through the bodies of those taking them and end up in water treatment systems and surface waters, many of the chemicals that are being found to have endocrine effects are components of a wide range of consumer products, including some water bottles, cosmetics, sunscreens, and other personal care products. Substances applied to the skin can be directly absorbed but also end up getting washed off our bodies and into our water systems. As a result, chemicals with endocrine disrupting activity are widely dispersed in our environment, often at levels plausibly associated with biological effects; exposure to humans is widespread.

Looking at these four points together, it is apparent that endocrine disruption is an important emerging public health concern. NIEHS is responding to the importance of this concern through our research investments, and we are starting to understand these health risks better, but there are still many gaps in our understanding. We are therefore gathering more information to help assess and manage EDCs appropriately.

Here are some examples to illustrate the first three of the take-home messages about endocrine disruption that I listed above. As for the fourth, I would point you to the Centers for Disease Control and Prevention's National Exposure Report⁸ for evidence of the widespread exposure to these chemicals.

Regarding low dose: Early studies of EDCs in sensitive animal models established examples in which no threshold dose could be detected; that is, effects were already apparent at the lowest doses tested.⁹ Moreover, there are some endocrine disrupting chemicals whose effects can be seen at low doses but not at high doses, in opposition to the usual dose-response curve familiar to toxicologists, which shows continually increasing responses with increases in dose. A 2007 NIEHS-sponsored review of studies of *in vivo* effects of Bisphenol A (BPA), for example, identified evidence for effects of low dose exposure during development on subsequent brain structure, function and behavior in rats and mice.¹⁰

An NIEHS-funded group at the Dartmouth College Superfund Research Program discovered that arsenic can act as a potent endocrine disruptor. They have shown that arsenic profoundly affects the function of five steroid hormone receptors (the receptors for glucocorticoid, androgen, progesterone, mineralocorticoid, and estrogen hormones) as well as the function of related

⁸ See <http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf> for most recent version of the report.

⁹ Sheehan DM et al., *Environ Health Perspect* 1999 Feb;107(2):155-9

¹⁰ Richter CA et al., *Reprod Toxicol* 24 (2007) pp. 199-224

nuclear receptors for thyroid hormone and retinoic acid.¹¹ These effects were observed at levels of 0.01 to 2.0 micromolars in cell culture and at or below 10 ppb in several animal models. They have also shown that arsenic has a significant effect on the ability of an activated hormone receptor to regulate gene expression, and that low level drinking water arsenic has strong, tissue-specific effects on expression of genes and proteins involved in the innate immune response in mouse lung.¹² They found that mice that were exposed to 100 ppb arsenic in drinking water had a significantly compromised response to H1N1 influenza infection.¹³

Regarding the broad range of effects: As our understanding of mechanisms has grown, so has our recognition of the many ways these compounds interact with the body and the many health outcomes that are influenced. The early work on endocrine disruption started out focusing mostly on outcomes that were known to be sensitive to the effects of steroid hormones, such as cancers of the reproductive system, and on mechanisms that involved hormonal receptors located in the cells' nuclei. However, in addition to working through normal nuclear hormone receptors such as estrogen, androgen, thyroid, and retinoid receptors, we find that these molecules interact with many other kinds of receptors, such as membrane (non-nuclear) receptors, neurotransmitter receptors, enzymatic pathways involved in steroid biosynthesis and metabolism, and all the other mechanisms that enable hormone systems to do the work they need to do, which in turn enables the organism to function normally and react to changes. So the universe of potential health effects has grown commensurately to include non-reproductive cancers, immune effects, metabolic effects, and brain development and behavior, in addition to non-cancer abnormalities of the reproductive system, such as reproductive tract abnormalities, precocious puberty, disorders of fertility and fecundity, and endometriosis.¹⁴ For example, endocrine control of glucose homeostasis can impact development of diabetes, obesity, and cardiovascular disease. Researchers have now identified model systems and mechanisms by which developmental exposure to EDCs such as tributyltin¹⁵, genistein and diethylstilbestrol¹⁶ may potentially cause weight gain in animals later in life. NIEHS-funded researchers are working on understanding biochemical and physiological aspects of environmental contributions to obesity, and we expect this work to have an impact on the development of interventions and preventive strategies to deal with this huge public health issue.

There are concerns about multiple possible health effects of BPA exposure. BPA is a selective endocrine modulator with widespread human exposure. The Department's Food and Drug Administration (FDA) recently announced that it has some concern about the potential effects of BPA, partly based on the conclusions of the NTP-CERHR Monograph on Potential Human Reproductive and Developmental Effects of Bisphenol A (see summary¹⁷), which in turn built on the earlier consensus statement report from the expert panel workshop convened by the NIEHS¹⁸. While much of the exposure to BPA in humans occurs through the diet, other sources of

¹¹ Davey JC et al. *Environ Health Perspect* (2008)116:165-172.

¹² Kozul CD et al. *Environ Health Perspect* (2009)117(7):1108-15.

¹³ Kozul CD et al. *Environ Health Perspect* (2009)117:1441-1447.

¹⁴ Diamanti-Kandarakis et al., *Endocrine Reviews* (2009) June;30(4):293-342

¹⁵ Grun F, Blumberg B. *Endocrinology* (2006) 147:S50-S55

¹⁶ Newbold RR et al. *Mol Cell Endocrinol* (2009) May 25;304(1-2):84-89

¹⁷ <http://www.niehs.nih.gov/news/media/questions/sya-bpa.cfm>

¹⁸ vom Saal et al. *Reprod Toxicol* (2007)24:131-138

exposure include air, dust, and water. NIEHS invested approximately \$20M in FY2009 to study health effects of BPA exposure, including \$10.7M from ARRA funding. We have developed a program to assess differences in routes of exposure and metabolism across species, as well as the replication and expansion of experiments that linked BPA exposure to disease endpoints such as cancers, ADHD, obesity/diabetes/metabolic syndrome, immune dysfunction, reproductive diseases and dyfunctions, and cardiovascular disease. In addition, an NTP study is being conducted with FDA measuring the effects of long term exposures to a wide dose range of BPA in rats.

Regarding persistence of biological effects: Because of the existence of special windows of susceptibility in developmental processes, we know that exposure to EDCs at very sensitive stages of development can result in profound changes in physiology and function that may not emerge clinically until much later in life.¹⁹ The exposure itself may cease, but the developmental impact and the subsequent adverse effect have already been set in motion. NIEHS leads the cross-NIH effort to understand how exposure-related changes in an individual's epigenetic status in one stage of their life can affect the health of the individual in later stages of their lifespan. Epigenetics is one recently discovered mechanism by which EDCs can produce these latent effects by altering the three dimensional structure of the chromosomes. The addition of methyl groups to DNA and changes to the histone proteins in chromosomes alter gene expression, leading to effects that can persist not just through one lifetime, but potentially for generations.

These delayed effects are the subject of a number of human studies funded by NIEHS. A group of researchers at Mt. Sinai School of Medicine recently reported that adverse behaviors of children aged 4-9 years (conduct or ADHD disorders) were associated with prenatal exposure to low molecular weight phthalates.²⁰ Other scientists at Columbia University's Center for Children's Environmental Health (co-funded by NIEHS and the Environmental Protection Agency (EPA)) examined cord blood exposure to polybrominated diphenyl ethers (PBDEs), which are ubiquitous flame retardants, and associations with neurodevelopment at ages 1-4 and 6 years. Children with higher concentrations of specific PBDEs while *in utero* scored lower on tests of mental and physical development.²¹ Previous data linking these compounds to altered thyroid hormones and thyroid function might provide a plausible mechanism for these effects.

The NIEHS Breast Cancer and Environment Research Program (co-funded with the NIH's National Cancer Institute) is investigating whether periods of susceptibility exist in the development of the mammary gland, when exposures to environmental agents may impact the breast and endocrine systems that can influence breast cancer risk in adulthood. It is examining the determinants of puberty in girls, integrating environmental, genetic, biologic, lifestyle, and socioeconomic factors, in recognition of the epidemiology linking breast cancer risk to pubertal maturation. A major area of study is the role of exposures to EDCs. Center scientists have measured 51 environmental agents and their metabolites in biospecimens from approximately

¹⁹ Diamanti-Kandarakis et alia, *Endocrine Reviews* (2009) June;30(4):293-342

²⁰ Engel SM et al. *Environ Health Perspect* 2010 Jan 8 [Epub ahead of print]

²¹ Herbstman JB et al. *Environ Health Perspect* 2010 Jan 4 [Epub ahead of print]

1,190 girls. The data include the first report in children of high levels of a number of hormonally active chemicals such as enterolactone, benzophenone-3, and monoethyl-phthalate.²²

A separate follow-up study is now in progress in response to observations of high perfluoroalkyl compound (PFC) levels measured in a geographically distinct subset of the Breast Cancer and the Environment Research Center cohort.²³ PFCs such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are of concern because of their presence in air, food, drinking water and human tissues, their persistence and long half-life, and their adverse effects on development in animal models. NIEHS is supporting numerous studies on these compounds. One of our intramural investigators is following up previous observations of an association between PFOS and PFOA and increased time-to-pregnancy (a measure of decreased fecundability).²⁴ At the request of the EPA, the NTP initiated a large research program on this class of compounds that includes PFOS, PFOA and shorter and longer chain perfluoroalkyl compounds.²⁵ These studies include an evaluation of multiple aspects of post-natal development following exposure *in utero* and will provide a sound basis for assessing cumulative human health risks for these ubiquitous contaminants.

New science to promote new understanding: Given our growing understanding of the myriad of cellular hormonal targets of EDCs, new approaches have to be developed in order to characterize the potential for environmental agents to perturb endocrine function. NTP's high throughput screening initiative (HTS) and Tox21 partnership, in collaboration with EPA and the NIH Chemical Genomics Center,²⁶ include multiple assays designed to assess activity of chemicals at hormonal targets. Initial results have shown that among the most active of hundreds of chemicals tested so far in these assay systems is BPA. Triclosan, an antimicrobial in hand soaps, toothpaste, cosmetics, and many other products, and one of the most frequently detected water contaminants, also exhibits endocrine activity in these tests and is one of the most active compounds across multiple assays.²⁷

By linking pre-existing and newly developed information on toxicological activity in whole animal studies of compounds registering as positive in these endocrine-relevant assays, we are able to explore the *in vivo* significance of signals picked up in HTS. As we move forward and develop and include additional assays for endocrine activity, HTS will help us decide which chemicals need further investigation.

The NTP is employing *in vitro* and short term animal models to detect perturbations in endocrine function that can be used as a basis for deciding whether to conduct more rigorous long-term studies. Short term models are also being used to address questions of cumulative risk, that is, whether exposure to mixtures of similar compounds causes additive or synergistic (whole greater than the sum of the parts) effects. For example, through a collaborative arrangement with EPA's

²² Wolff MS et al. Environ Health Perspect 2007, 115(1):116-121

²³ R21ES017176 PI: Susan Pinney, Univ of Cincinnati. Exposure biomarkers of polyfluoroalkyl compounds in persons living in the Ohio River valley.

²⁴ PI: Matthew Longnecker, NIEHS. Perfluorinated alkyls and fecundability.

²⁵ <http://ntp.niehs.nih.gov/files/PFOAConcept.pdf>

²⁶ <http://ntp.niehs.nih.gov/go/28213>

²⁷ http://www.epa.gov/ncct/practice_community/category_priority.html

Office of Research and Development, the NTP is conducting studies to evaluate effects on male reproductive endpoints for many combinations of phthalates to allow more precise comparisons of potency and a better understanding of cumulative risk for this class of compounds found in many plastics.

The NTP is also planning new research relevant specifically to EDCs in drinking water. One set of studies will investigate the potential for mixtures of chemicals known to occur in drinking water to impact pre- and early post-natal development. These studies will focus on structurally dissimilar drugs and other industrial chemicals that perturb a common biological pathway, e.g. cholesterol and lipid metabolism.

New information on endocrine activity has led the NTP to develop toxicological research programs on additional compounds such as bisphenol AF,²⁸ used to make certain industrial polymers; butylparaben,²⁹ a preservative used in cosmetics; oxybenzone,³⁰ a sunscreen ingredient; and triclosan.³¹ The relevance of cosmetics, sunscreens and other personal care products to drinking water exposures has previously been highlighted. Endocrine activity is also of potential concern for herbal products taken as dietary supplements. NTP research programs on several of these, such as gum guggul, Dong quai, and valerian, includes evaluations of hormonal activity.

In addition to generating new knowledge, we also need to make sure our science is shared with those who need to use it. This includes other Federal, state and local agencies as well as communities and individuals. Many of our research efforts are done in partnership with the agencies who will be the consumers of the research. We have also supported some excellent scientific forums for sharing this information with government and non-government scientists. For example, the NIEHS/NTP, along with other NIH components, FDA, CDC, the Agency for Toxic Substances and Disease Registry, EPA, the Society of Toxicology, the World Health Organization, and the European Environment Agency, recently sponsored a workshop on prenatal programming and toxicology entitled, "PPTOXII: Role of environmental stressors in the developmental origins of disease." The meeting, attended by 280 scientists, focused on the developmental origins of disease with the goal of stimulating collaborations in the area of effects of endocrine disrupting chemicals on developmental toxicity. We are also mindful of the need to keep dialog open with affected communities. In our Breast Cancer and Environmental Research Program, researchers have created public messages to convey information about endocrine disrupting chemicals and their potential role in the prevention and understanding of breast cancer, including fact sheets for clinicians and the public on likely sources of exposures.

In conclusion, let me stress that I believe this area of environmental health sciences to be of the utmost importance. Our endocrine systems keep our bodies in balance, maintaining homeostasis and guiding proper growth and development. With NIEHS's leadership, we are learning more and more about how these finely tuned systems are sensitive to unanticipated effects from

²⁸<http://ntp.niehs.nih.gov/index.cfm?objectid=F609B028-F1F6-975E-715EE7E97E4CCB16>

²⁹<http://ntp.niehs.nih.gov/files/ButylparabenConcept.pdf>

³⁰<http://ntp.niehs.nih.gov/index.cfm?objectid=072CEB9A-A49B-F6AA-91E25964528B914A>

³¹<http://ntp.niehs.nih.gov/index.cfm?objectid=F610E7F7-F1F6-975E-76E92BC0B5CC47B3>

chemical exposures. This information is critically important for creating effective strategies to prevent disease and promote better health, as well as to ensure safe drinking water.

Thank you for the opportunity to present information on this important topic. I would be happy to answer your questions.