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NIEHS
National Institute of
Environmental Health Sciences

Endocrine Disruptors

A growing body of evidence suggests that numerous chemicals, both natural and man-made, may interfere with the endocrine system and produce adverse effects in laboratory animals, wildlife, and humans. Scientists often refer to these chemicals as "endocrine disruptors." Endocrine disruption is an important public health concern that is being addressed by the National Institute of Environmental Health Sciences (NIEHS).

These chemicals are found in many of the everyday products we use, including some plastic bottles and containers, liners of metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides. Although limited scientific information is available on the potential adverse human health effects, concern arises because endocrine disrupting chemicals present in the environment at very low levels have been shown to have adverse effects in wildlife species as well as in laboratory animals. The difficulty of assessing public health effects is increased by the fact that people are typically exposed to multiple endocrine disruptors simultaneously.

NIEHS and the National Toxicology Program (NTP) support research to understand how these chemicals work, and to understand the effects they may have in various animal and human populations, with the long term goal of developing prevention and intervention strategies to reduce any adverse effects.

What are endocrine disruptors?

Endocrine disruptors are naturally occurring compounds 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, which may affect the normal functions of tissues and organs. Many of these substances have been linked with developmental, reproductive, neural, immune, and other problems in wildlife and laboratory animals.

Some research suggests that these substances are also adversely affecting human health in similar ways, resulting in reduced fertility and increased incidences or progression of some diseases, including obesity, diabetes, endometriosis, and some cancers.

The endocrine system keeps our bodies in balance, maintaining homoestasis and guiding proper growth and development.

These chemicals have also been referred to as endocrine modulators, environmental hormones, and endocrine active compounds. Environmental chemicals with estrogenic activity are probably the most well studied, however chemicals with anti-estrogen, androgen, anti-androgen, progesterone, or thyroid-like activity have also been identified.

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What is the endocrine system and why is it important?

The endocrine system is one of the body's main communication networks and is responsible for controlling and coordinating numerous body functions. Hormones are first produced by the endocrine tissues, such as the ovaries, testes, adrenal, pituitary, thyroid, and pancreas, and then secreted into the blood to act as the body's chemical messengers where they direct communication and coordination among other tissues throughout the body.

For example, hormones work with the nervous system, reproductive system, kidneys, gut, liver, and fat to help maintain and control:

- Body energy levels
- Reproduction
- Growth and development
- Internal balance of body systems, or homeostasis
- Response to surroundings, stress, and injury

Endocrine disrupting chemicals may interfere with the body's own hormone signals because of their structure and activity.

How are people exposed to endocrine disruptors?

People may be exposed to endocrine disruptors through the food and beverages they consume, medicine they take, pesticides they apply, and cosmetics they use. So, exposures may be through the diet, air, skin, and water.

Some environmental endocrine disrupting chemicals, such as the pesticide DDT, dioxins, and polychlorinated biphenyls (PCBs) used in electrical equipment, are highly persistent and slow to degrade in the environment making them potentially hazardous over an extended period of time.

What is NIEHS research telling us about endocrine disruptors?

NIEHS has been a pioneer in conducting research on the health effects of endocrine disruptors for more than three decades, starting with the endocrine-disrupting effects of the pharmaceutical, diethylstilbestrol (DES).

From the 1940s–1970s, DES was used to treat women with high-risk pregnancies, with the mistaken belief that it prevented miscarriage. In 1972, prenatal exposure to DES was linked to the development of a rare form of vaginal cancer in daughters whose mother received DES, and with numerous non-cancerous changes in both sons and daughters. NIEHS researchers developed animal models of DES exposure that successfully replicated and predicted human health problems, and have been useful in studying the mechanisms involved in DES toxic effects.[1] NIEHS researchers also showed that the effects of DES and other endocrine disruptors involved the estrogen receptor.[2]

In addition to the fact that we now know that endocrine disruptors are widely dispersed in our environment, some other key points about exposure to endocrine disruptors have emerged.

Four points about endocrine disruption:

- **Low dose matters**
- **Wide range of health effects**
- **Persistence of biological effects**
- **Ubiquitous exposure**

Exposures at low levels count.

The body's own normal endocrine signaling involves very small changes in hormone levels, yet we know these changes can have significant biological effects. This leads scientists to think that chemical exposures, even at low doses, can disrupt the body's delicate endocrine system and lead to disease.

In 2000, an independent panel of experts convened by NIEHS and NTP found that there was "credible evidence" that some hormone-like chemicals can affect test animals' bodily functions at very low levels — well below the "no effect" levels determined by traditional testing.[3]

Endocrine disrupting chemicals may impact a broad range of health effects.

Although there is limited evidence to prove that low-dose exposures are causing adverse human health effects, there is a large body of research in experimental animals and wildlife suggesting that endocrine disruptors may cause:

- Reductions in male fertility and declines in the numbers of males born.
- Abnormalities in male reproductive organs.
- Female reproductive health issues, including fertility problems, early puberty, and early reproductive senescence.
- Increases in mammary, ovarian, and prostate cancers.
- Increases in immune and autoimmune diseases, and some neurodegenerative diseases.

There are data showing that exposure to BPA, as well as other endocrine disrupting chemicals with estrogenic activity, may have effects on obesity and diabetes. These data, while preliminary and only in animals, indicate the potential for endocrine disrupting agents to have effects on other endocrine systems not yet fully examined.

Effects of endocrine disruptors may begin early and be persistent.

Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural systems are developing. In animals, adverse consequences, such as subfertility, premature reproductive senescence, and cancer, are linked to early exposure, but they may not be apparent until much later in life.[45]

Research from NIEHS investigators have shown that the adverse effects of DES in mice can be passed to subsequent generations even though they were not directly exposed. The increased susceptibility for tumors was seen in both the granddaughters and grandsons of mice who were developmentally exposed to DES.[67] Mechanisms involved in the transmission of disease were shown to involve epigenetic events — that is altering gene function without altering DNA sequence.[8]

New research funded by NIEHS also found that endocrine disruptors may affect not just the offspring of mothers exposed during pregnancy, but future offspring as well. The researchers found that several endocrine disrupting chemicals caused fertility defects in male rats that were passed down to nearly every male in subsequent generations. This study suggests that the compounds may have caused changes in the developing male germ cells, and that endocrine disruptors may be able to reprogram or change the expression of genes without mutating DNA.[9] The role of environmental endocrine disrupting chemicals in the transmission of disease from one generation to another is of great research interest to NIEHS.

What are some current areas of Research NIEHS is pursuing?

Researchers are playing a lead role in uncovering the mechanisms of action of endocrine disruptors. Today, scientists are:

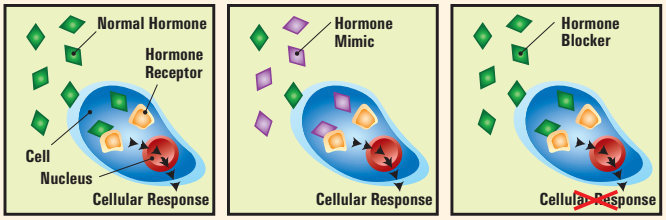
- Developing new models and tools to better understand how endocrine disruptors work.
- Developing high throughput assays to determine which chemicals have endocrine disrupting activity.
- Examining the long-term effects of exposure to various endocrine disrupting compounds during development and on diseases later in life.
- Conducting epidemiological studies in human populations.
- Developing new assessments and biomarkers to determine exposure and toxicity levels — especially how mixtures of chemicals impact individuals.
- Developing intervention and prevention strategies.

How do endocrine disruptors work?

From animal studies, researchers have learned much about the mechanisms through which endocrine disruptors influence the endocrine system and alter hormonal functions.

Endocrine disruptors can:

- Mimic or partly mimic naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones, potentially producing overstimulation.
- Bind to a receptor within a cell and block the endogenous hormone from binding. The normal signal then fails to occur and the body fails to respond properly. Examples of chemicals that block or antagonize hormones are anti-estrogens and anti-androgens.
- Interfere or block the way natural hormones or their receptors are made or controlled, for example, by altering their metabolism in the liver.

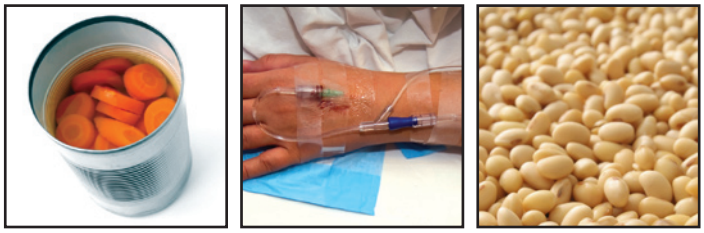


When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right).

What are some examples of endocrine disruptors?

A wide and varied range of substances are thought to cause endocrine disruption.

Chemicals that are known endocrine disruptors include diethylstilbestrol (the synethetic estrogen DES), dioxin and dioxin-like compounds, polychlorinated biphenyls (PCBs), DDT, and some other pesticides.



Bisphenol A (BPA) is a chemical produced in large quantities for use primarily in the production of polycarbonate plastics and epoxy resins. The NTP Center for the Evaluation of Risks to Human Reproduction completed a review of BPA in September 2008. The NTP expressed "*some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A." [10]

Di(2-ethylhexyl) phthalate (DEHP) is a high production volume chemical used in the manufacture of a wide variety of consumer food packaging, some children's products, and some polyvinyl chloride (PVC) medical devices. In 2006, the NTP found that DEHP may pose a risk to human development, especially critically ill male infants.[11]

Phytoestrogens are naturally occurring substances in plants that have hormone-like activity. Examples of phytoestrogens are genistein and daidzein, which can be found in soy-derived products.

1 Endocrinology. 2006. 147(6):S11-S17.

2 Developmental Biology. 2001. 238:224-238.

3 National Toxicology Program's Report of the Endocrine Disruptors Low-Dose Peer Review. 2001.

4 Environmental Health Perspectives. 1995. 103:83-87.

5 Endocrinology. 2006. 147(6):S11-S17.

6 Carcinogenesis. 2000. 21(7):1355-1363.

7 Carcinogenesis. 1998. 19:1655-1663.

8 Cancer Research. 2000. 60:235-237.

9 Science. 2005. 308(5727):1466-1469.

10 NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08-5994. September 2008.

11 NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di(2-ethylhexyl) Phthalate (DEHP). NIH Publication No. 06-4476. November 2006.