NIEHS
National Institute of
Environmental Health Sciences

Endocrine Disruptors

Over the past decade, 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 humans, wildlife, fish or birds. Scientists often refer to these chemicals as "endocrine disruptors."

These chemicals are found in many of the everyday products we use including some plastic bottles, 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 while present in the environment at very low levels, have been shown to have adverse effects in wildlife species, as well as in laboratory animals at these low levels.

The difficulty of assessing public health effects is increased by the fact that people are typically exposed to multiple endocrine disruptors simultaneously. The National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) support research to understand how these chemicals work and to understand the effects that they may have in various animal and human populations with the long term goals of developing prevention and intervention strategies to reduce any adverse effects.

What are Endocrine Disruptors?

Endocrine disruptors are naturally occurring compounds or man-made chemicals that may interfere with the production or activity of hormones of the endocrine system leading to adverse health effects. Many of these chemicals have been linked with developmental, reproductive, neural, immune, and other problems in wildlife and laboratory animals.

Some scientists think these chemicals also are adversely affecting human health in similar ways resulting in declined fertility and increased incidences or progression of some diseases including endometriosis and cancers. 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.

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, 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.

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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, called homeostasis
- responses to surroundings, stress, and injury

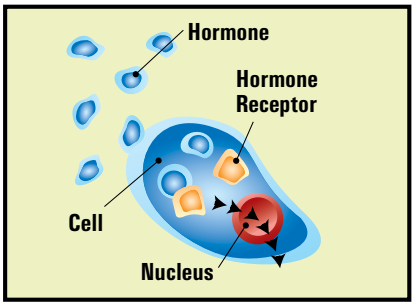
Endocrine disrupting chemicals may interfere with the body's own hormone signals because of their structure and activity.

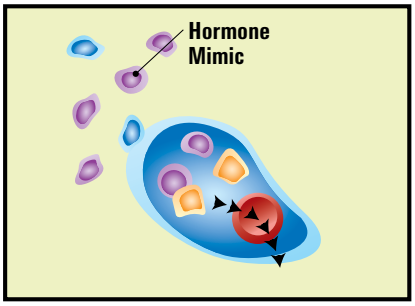
How do Endocrine Disruptors work?

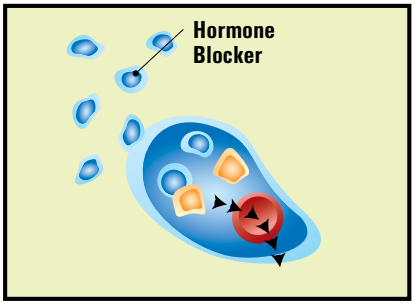
From animal studies, researchers have learned much about the mechanisms through which endocrine disruptors influence the endocrine system and alter hormonal functions.

Endocrine disruptors can:

- mimic or partly mimic naturally occurring hormones in the body like estrogens (the female sex hormone) and 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 or anti-androgens.
- interfere or block the way natural hormones or their receptors are made or controlled, for example by blocking their metabolism in the liver.







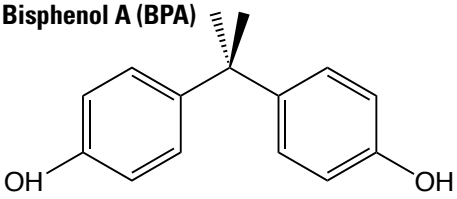
What are some examples of Endocrine Disruptors?

A wide and varied range of substances are thought to cause endocrine disruption. Chemicals that are known endocrine disruptors include diethylstilbesterol (the drug DES), dioxin and dioxin like compounds, PCBs, DDT, and some other pesticides. Some chemicals, particularly pesticides and plasticizers, such as Bisphenol A are suspected endocrine disruptors based on animal studies.

Bisphenol A (BPA) is a chemical produced in large quantities for use primarily in the production of polycarbonate plastics and epoxy resins.

Some endocrine disruptors occur among a group of chemicals referred to as phthalates, a class of chemicals that soften and increase the flexibility of polyvinyl chloride plastics.

Bisphenol A (BPA)



Di (2-ethylhexyl) phthalate (DEHP) An example of a phthalate is a compound called Di (2-ethylhexyl) phthalate (DEHP). 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 medical devices. Recently, an independent panel of experts assembled by the National Toxicology Program (NTP) found that DEHP may pose a risk to human development, especially critically ill male infants.[1]

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.

To specifically evaluate the effects that chemicals have on human reproduction, the National Toxicology Program (NTP) developed The Center for the Evaluation of Risks to Human Reproduction (CERHR). This center has evaluated the endocrine disruptor effects of seven phthalates and the phytoestrogen genistein found in soy infant formulas.[2]

How are People Exposed to Endocrine Disruptors?

People may be exposed to endocrine disruptors through the food and beverages they consume, medicine they take, and cosmetics they use. So, exposures may be through the diet, air, and skin. Some environmental endocrine disrupting chemicals, such as DDT, 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?

The 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 with the development of a rare form of vaginal cancer in the DES-daughters, 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.[3] NIEHS researchers also showed the effects of DES and other endocrine disruptors involved the estrogen receptor protein mechanism.[4] 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 disease and dysfunction later in life
- Conducting epidemiological studies in human populations
- Developing new assessment and biomarkers to determine exposure and toxicity levels, especially how mixtures of chemicals impact individuals
- Developing intervention and prevention strategies

Some examples of findings in important research areas are provided below.

Developmental Exposures

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.[5]

Researchers supported by NIEHS at the University of Cincinnati and the University of Illinois found that animals exposed to low doses of the natural human estrogen estradiol, or the environmental estrogen bisphenol A (BPA), during fetal development and estradiol as adults were more likely to develop a precursor of prostate cancer than those who were not exposed. This suggests that exposure to environmental and natural estrogens during fetal development could affect the way prostate genes behave, and may lead to higher rates of prostate disease during aging.[6]

Exposures at Low Levels

In 2000, an independent panel of experts convened by the NIEHS and the National Toxicology Program (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.[7] Although, there is little 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 diseases including fertility problems, early puberty, and early reproductive senescence
- increases in mammary, ovarian, and prostate cancers

There are data showing that exposure to Bisphenol A 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.

Transgenerational Effects

There is some evidence that endocrine disruptors may not only impact the individual directly exposed, but also future generations.

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.[8] Mechanisms involved in the transmission of disease were shown to involve epigenetic events.[9]

New research funded by the 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 two 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 two 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.[10]

The role of environmental endocrine disrupting chemicals in the transmission of disease from one generation to another is of great research interest to the NIEHS.

[1] *NTP Brief on the Potential Human Reproductive and Developmental Effects of Di (2-ethylhexyl) Phthalate (DEHP). Draft, May 2006.*

[2] *CERHR website.*

[3] *Endocrinology 147 (6) Supplement S11-S17, 2006.*

[4] *Developmental Biology. 2001. 238:224-238.*

[5] *Environmental Health Perspectives 103:83-87, 1995. Endocrinology 147 (6) Supplement S11-S17, 2006.*

[6] *Cancer Research. 2006 Jun 1;66(11):5624-32.*

[7] *National Toxicology Program's Report of the Endocrine Disruptors Low-Dose Peer Review, 2001.*

[8] *Carcinogenesis. 2000 Jul;21(7):1355-63. Carcinogenesis 19; 1655-1663.*

[9] *Cancer Research 2000 60-235-237.*

[10] *Science 3 June 20. Vol. 308. no. 5727, pp. 1466 - 1469.*