A Small Dose of Endocrine Disruptors
Or
An Introduction to the Health Effects of Endocrine Disruptors

Chapter 20
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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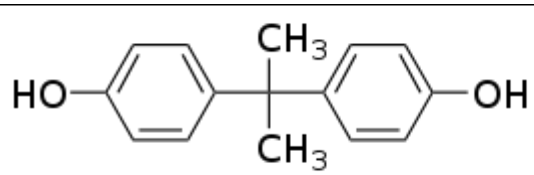
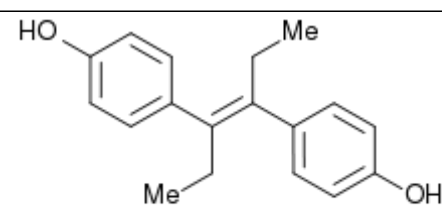
Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"

	
Bisphenol-A (BPA)	diethylstilbestrol

Dossier

<u>Endocrine Disruptors Chemicals (EDCs)</u>

Name: Endocrine Disruptors
Use: wide range of chemicals, pesticides, plastics, flame retardants, medicine
Source: synthetic chemistry, plants
Recommended daily intake: none (not essential)
Absorption: intestine, respiratory system (lungs), skin
Sensitive individuals: fetus and children
Toxicity/symptoms: endocrine system, mimic estrogen, anti-estrogenic, effects on hormone levels, sexual characteristics, reproduction, developmental effects
Regulatory facts: FDA and EPA are reviewing
General facts: billions of pounds used every year in wide range of products
Environmental: widely distributed in environment and can affect wild life
Recommendations: minimize use, avoid exposure to children, and consider alternatives, avoid any rubber ducks

From Wikipedia - https://en.wikipedia.org/wiki/Rubber_duck

Case Studies

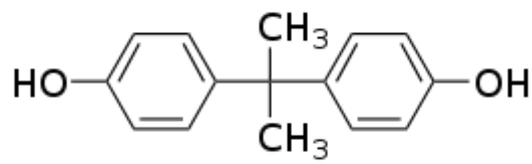
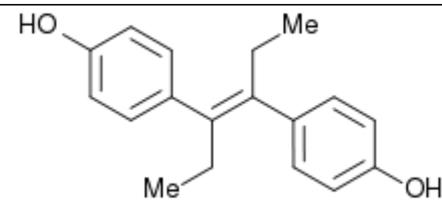
Hormonal Contraceptives

Oral contraceptives, the most widely used form of birth control, are used by millions of women throughout the world, are actually the ultimate endocrine disruptor. The search for a hormonal form of birth control began in the 1930s and was championed by women such as Margaret Sanger. An important breakthrough occurred in 1939, when Russell Marker discovered a way to synthesize progesterone from plants. Research on the use of hormones to disrupt female fertility accelerated in the 1950s. On May 9, 1960, the Food and Drug Administration approved "the Pill", a combination of an estrogen and a progesterone, taken by mouth to inhibit female fertility by preventing ovulation. Potential toxicity related to oral contraceptives was first reported in late 1961 with patient reports of blood clots and pulmonary embolism. Further research confirmed these reports and found that smokers were at greater risk. It was subsequently found that the levels of estrogen and progesterone could be significantly decreased and still effectively disrupt female fertility. There is growing concern about the excretion of these synthetic hormones (as well as natural ones) in the urine and their movement from sewage treatment plants into the environment, affecting wildlife, such as fish reproduction.

Synthetic Estrogens

A mildly estrogenic compound, Bisphenol-A (BPA), was first created in 1891 by Aleksandr Dianin, a Russian, who named it "Dianin's Compound". In 1938 the much more potent synthetic estrogen diethylstilbestrol (DES) was synthesized by Leon Golberg a graduate student at the University of Oxford in England. In 1941 the FDA approved its use for menopausal symptoms and in 1947 to prevent miscarriages. In 1953 the first study was published indicating that DES was not effective in preventing miscarriages. The manufacturers continued to markete DES for pregnant women until 1971, when the first study was published linking DES to vaginal cancer in female offspring. Between 1941 and 1971, millions of women and their offspring were exposed to DES.

Meanwhile, in the 1940s and 1950s, the chemical industry discovered that BPA was an excellent hardener for epoxy resins and the plastic polycarbonate. It is now used in a wide range of products, from plastics to lining of food cans, with estimated use per year of 6 billion pounds. The CDC found that over 90% of people had BPA in their urine, with the highest exposure occurring in infants and children. Overt toxicity from exposure to BPA occurs at only very high doses but more subtle effects on the endocrine system occur at very low doses. Animal studies and limited human studies have found endocrine-related health effects but government agencies have been reluctant to ban or restrict the use of BPA. Recently local governments [examples] have moved to ban BPA from plastic baby bottles in an effort to reduce exposure to the most vulnerable.

	
Bisphenol-A (BPA)	diethylstilbestrol

<u>Atrazine</u>
Endocrine disruptors come in many forms, including herbicides like Atrazine, used to kill broadleaf and grassy weeds. It was introduced in 1958 and eventually banned in the European Union as a persistent ground water contaminant. Atrazine remains one of the most widely used herbicides in the United States. Several studies have found that Atrazine feminizes male frogs by disrupting the endocrine system. Other pesticides such DDT and organochlorines are also thought to be endocrine disruptors even at very low levels of exposure.

Introduction and History

> For example, recent work in the United States suggests that environmental levels of some EDCs are at least an order of magnitude greater in sewage sludge here than in Europe.
>
> Robert C. Hale
> Environmental Health Perspectives, August, 2003

Endocrine disrupting chemicals (EDCs) constitute a broad variety of chemicals that interact with the endocrine system sometimes at very low levels of exposure. Adverse effects include altered development such as feminization, reproductive system changes, decreased fertility, brain and behavior, impaired immune system, increased incidence of endometriosis, and some forms of cancer. The primary concerns regarding EDCs are 1) that they can produce adverse health effects at very low levels of exposure, 2) we are exposed to multiple EDC from conception and then throughout our lives, and 3) the chemicals are widely distributed in the environment affecting both humans and animals. Below is a small list of common chemicals thought to interact with the endocrine system.

Potential Endocrine Disruptors

Class	Chemical	Use
Pesticide	DDT	Insecticide (no longer allowed in US
	2,4-D	Herbicide
	Atrazine	Herbicide
Plastics additives	Bisphenol A	Harden in plastics
	Phthalates	Softener in plastics, solvent
Industrial chemical	Nonylphenol (breakdown product of nonylphenol ethoxylates	Detergents, paints, pesticides
Fire retardant	Polybrominated diphenyl ethers (PBDE)	Fire retardant
Drug	Diethylstilbesterol (DES)	No longer used to prevent miscarriages
Contaminants	Dioxin	Byproduct PVC plastics, incineration byproduct, contaminant in certain chlorinated compounds
	Arsenic, Lead, Mercury	Widespread contaminants
	Polychlorinated biphenyls (PCB)	Formerly used in transformer oils

Biological Properties

Endocrine System

The endocrine system is the body's chemical communication system, using the blood vessels to move chemicals throughout the body to communicate with different cells of the body. These naturally occurring chemicals, called hormones, are secreted by the by various glands throughout the body (see table below). Hormones move throughout the body, signaling specifically sensitive cells to respond. These chemicals regulate and influence almost all the basic functions of life such as growth, metabolism, reproduction, sexuality, fear response, anger, pregnancy, and many other big and small functions. In a complex feedback loop many hormones influence the secretion of other hormones. Finally, hormones are produced and can cause effects at incredibly low levels. Major hormone producing glands and examples of excreted hormones are listed in Table 2. However, many organs can secrete hormones as well, including kidneys, placenta, stomach, liver, and others.

Major Glands and Examples of Hormones and Function

Gland (location)	Example hormone	Function
Pineal gland (brain)	Melatonin	Sleep
Pituitary gland (brain)	Growth hormone	Growth, cell reproduction
	Prolactin	Milk production, sexual gratification
	Thyroid-stimulating hormone	stimulates thyroid gland to secrete T3 and T4
	Luteinizing hormone	Female: ovulation Male: regulates testosterone
Thyroid gland (neck)	Thyroxine (T4)	Metabolism
	Triiodothyronine (T3)	Metabolism
Adrenal gland (kidney)	Glucocorticoids	Effects glucose uptake
	Adrenaline	Fight-or-flight response (range of effects)
Pancreas (kidney)	Insulin	Regulates glucose
Ovary (female)	Progesterone	Pregnancy, muscle relaxation, range of effects
	Estrogens	Growth, sexual characteristics
Testes (male)	Testosterone (androgen)	Muscle mass, bone density, sexual maturation

Health Effects

Introduction

There is growing evidence that exposure to EDCs during development is particularly hazardous. For example, early exposure to EDCs may result in cancer later in life (see Birnbaum and Fenton, 2003). For example, prenatal exposure to the synthetic estrogenic compound DES can result in vaginal cancers. Animal and human studies indicate that natural and synthetic estrogens can cause breast and vaginal cancers. Animal studies indicate that dioxin, an environmental contaminant, can interfere with breast tissue developmental and potentially lead to cancer.

Another organ vulnerable to endocrine disruptors is the thyroid and, by extension, the nervous system. The thyroid glands start development very early in gestation. A sensitive feedback system between the hypothalamus, pituitary, and thyroid gland regulates thyroid hormone production. Thyroid hormone is essential for normal brain development, influencing brain cell growth, migration, formation of connections between cells, development of supporting cells, and general functional development. Decreased thyroid hormone adversely affects all aspects of brain development. A wide range of chemicals can adversely interact with thyroid hormone (for additional information see Howdeshell, 2002). Normal thyroid function is also necessary for proper hearing development. There is growing concern that fetal and early exposure to EDCs results in neurodevelopmental disorders such as autism, reduced IQ, and hyperactivity disorders (ADHD).

Anabolic Steroid – Performance Enhancement

One of the many uses of anabolic steroids is for sports performance enhancement to increase muscle mass, strength, and endurance. The use of steroids is just one aspect of "doping" to enhance performance, which is defined as "the use of a drug or blood product to improve athletic performance." Doping covers the blood products such as injecting red blood cells to improve oxygen carrying capacity, which will not be covered in this chapter.

> **Ancient Greek Athletes -** "The Greek physician Galen is reputed to have prescribed 'the rear hooves of an Abyssinian ass, ground up, boiled in oil, and flavored with rose hips and rose petals' to improve performance."

The use of steroids to enhance performance started a long time ago when ancient Olympic athletes ate sheep testicles to boost testosterone (the most basic anabolic steroid). Research on testosterone and other steroids progressed rapidly in the 1930s, with synthesis of testosterone from cholesterol accomplished in 1935. It was quickly recognized that testosterone increased muscle mass, appetite, bone growth, induced male puberty, and could be used to treat chronic wasting conditions. However, there are a number of hazards associated with its use, including growth of the vocal cords and body hair, changes in cholesterol levels, acne, high blood pressure, liver damage, and testicular atrophy. Testosterone and synthetic derivatives (now more than 100) are used as performance enhancing drugs but are now generally banned and are tested for in professional sports.

Reducing Exposure

While it is not possible to entirely avoid exposure to endocrine disrupting chemicals some simple precautions can be taken. This is particularly important during fetal development and infancy. Avoid using plastic baby bottles or toys that contain BPA or phthalates. Reduce exposure to pesticides as much as possible by purchasing local organic foods or foods that use less pesticides. Chemicals such as lead and pesticides can be tracked indoors on shoes, so it is always recommended to remove your shoes before coming indoors.

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Regulatory Standards

In 1996, the U.S. Food Quality Protection Act and the Safe Drinking Water Act directed the EPA to establish a program to test for endocrine disruption chemicals. In 1998 the EPA established the Endocrine Disruptor Screening Program and took the first step to define and validate tests for endocrine disrupting chemicals. The tests include cell-based (*in vitro*) screening tests suitable to rapidly examine the approximately 85,000 chemicals in use prior to more sophisticated animal-based tests. The program has progressed very slowly and it was not until 2007 that testing began.

There has also be considerable controversy over the endocrine effects of Bisphenol-A, which is used in plastics and to line food cans. The Food and Drug Administration is in the process of reviewing the many studies on the health effects of BPA.

Recommendation and Conclusions

There is an abundance of evidence that the endocrine system is very sensitive and essential for normal development. Adverse effects include cancer and neurodevelopmental disorders such as reduced IQ. We are unavoidably exposed to a wide range of naturally occurring and synthetic EDCs. The developing fetus and infant are especially sensitive to EDCs and exposure should reduced as much as possible. Unfortunately many common products needlessly contain EDCs chemicals, such as baby bottles, plastic toys and can lining. When possible avoid these products and urge manufacture to use alternatives. The government should also be encouraged to proceed with EDC screening and issue appropriate regulations to control exposure. A precautionary approach is warranted when a chemical is suspected of being an endocrine disruptor and especially if there is likely to be wide exposure to susceptible populations.

More Information and References

<u>Slide Presentation</u>

- A Small Dose of Endocrine Disruptors presentation material and references online: http://www.asmalldoseoftoxicology.org or Web site contains presentation material related to the health effects of Endocrine Disruptors.

<u>European, Asian, and International Agencies</u>

- European Union – Chemicals and Pesticides Information. Online: < https://www.europarl.europa.eu/factsheets/en/sheet/78/chemicals-and-pesticides > (accessed: 12 October 2020).
  Site contains policy and other information on the use of pesticides in agriculture.

- World Health Organization - WHO Pesticide Evaluation Scheme (WHOPES). Online: < https://www.who.int/whopes/resources > (accessed: 12 October 2020). WHOPES is an "international programme which promotes and coordinates the testing and evaluation of new pesticides proposed for public health use."

- International Programme on Chemical Safety (IPCS). Online: http://www.ilo.org/safework/info/WCMS_111391/lang--en/index.htm (accessed: 12 October 2020).
  WHO is the Executing Agency of the IPCS, whose main roles are to establish the scientific basis for safe use of chemicals, and to strengthen national capabilities and capacities for chemical safety.

North American Agencies

- NTP-CERHR Monograph on the Potential Human Reproductive and Development al Effects of Bisphenol-A (2008) Online: < https://pubmed.ncbi.nlm.nih.gov/19407859 > (accessed: 12 October 2020).

- US EPA Endocrine Disruption and Endocrine Disruptor Screening Program (EDSP). Online: http://www.epa.gov/endo/ (accessed: 12 October 2020). Describes the program, efforts to develop the screening test, and prioritization of chemicals to be tested.

- US National Institutes of Environmental Health Sciences (NIEHS), National Institutes of Health - Endocrine Disruptors. Online: http://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm. (accessed: 12 October 2020).
  Provides an overview of endocrine disruptors and recent research.

Non-Government Organizations

- The Endocrine Disruption Exchange, Inc. (TEDX). Online: < http://www.endocrinedisruption.com/> (accessed: 12 October 2020).

A non-profit organization that compiles and disseminates information on the health effects of endocrine disruptors. Now closed but still a source o f very relevant information.

- Endocrine Disruptors. Natural Resources Defense Council. Online: https://www.nrdc.org/stories/9-ways-avoid-hormone-disrupting-chemicals (accessed: 12 October 2020).
  General information on endocrine disruptors.

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