SETAC TIP

What is an Endocrine Disrupter?

PURPOSE: SETAC Technical Issue Papers (TIPs) provide a credible and balanced scientific discussion of important environmental issues.

Hormones typically trigger biological responses at very low concentrations.

Hormones and the Endocrine System

Hormones are molecules produced by endocrine glands that are transported by extracellular fluids such as the blood to other organs in the body. Hormones are essential for controlling many aspects of early development in humans and animals, including basic biological function in both vertebrate and invertebrate species. Plants also possess hormones but lack glands that produce and secrete hormones. Instead, each plant cell is capable of producing hormones.

Primary endocrine glands in vertebrates include the pituitary, thyroid, adrenal, gonads, and pancreas, but heart, fat, muscle, and liver tissues also produce hormones. Insulin is a well-known example of a hormone produced by the pancreas that controls blood glucose levels by promoting the uptake of sugars into cells. Estradiol and testosterone are examples of hormones needed for sexual development and reproduction, and thyroid hormones are critical for normal development and energy metabolism.

Hormones have effects on tissues through specialized, structurally specific proteins called receptors. It is via the binding of a hormone to a receptor that a biological response is initiated. Hormones typically trigger biological responses at very low concentrations (i.e., hormones can have high potency) because: (1) they are specific to a given receptor and have high affinity (binding) for that receptor and (2) hormones have relatively high efficacy to trigger a cellular response.

Endocrine systems also use complex positive and negative feedback mechanisms to control many functions in the body. For example, negative feedback loops are commonly employed in the endocrine system to maintain homeostatic conditions. In negative feedback loops, the release of a hormone triggers a response that is in turn recognized by other glands, and the release of additional hormone is decreased. Such negative feedback loops stabilize hormone actions, maintaining homeostatic conditions. Positive feedback loops in the endocrine system are employed more infrequently, and the increase of hormones occur during specific developmental stages or events (i.e., onset of puberty, labor associated with birth).

Hormones are believed to have relatively transient effects on tissues in adults (i.e., when the hormone is present, a response occurs, and when the hormone is removed, the response stops). In contrast, hormones program tissues in the fetus and neonate during sensitive windows of time, dictating how these tissues will develop and function in the adult. A relevant example here is the early development (including differentiation between the sexes) of gonads which in mature animals release sex hormones. Abnormal endocrine function may cause disease and developmental problems in humans and wildlife. Diabetes is an example of an endocrine disease due to inadequate insulin production or regulation.

There is a broad range of chemicals that are known or suspected to be EDs based on laboratory studies with animals, wildlife, and humans.

Endocrine Disrupters – The Scope of the Science

Many definitions of endocrine disrupters (EDs) exist. For example, the World Health Organization and United Nations Environment Programme (WHO/UNEP 2002) have defined an ED as an "…exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." A potential ED is an "exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations."

There is a broad range of chemicals that are known or suspected to be EDs based on laboratory studies with animals, wildlife, and humans. Some are industrial chemicals that include those no longer used or in restricted production (e.g., Stockholm Convention persistent organic pollutants like PCBs and DDT) while others remain in production or are being replaced in particular uses (e.g., some stain repellents, flame retardants, plasticizers, etc.). EDs also may include some human and veterinary pharmaceuticals, pesticides, preservatives, fragrances, surfactants, antimicrobials, and combustion by-products. In the case of some pharmaceuticals, the endocrine activity may be reflecting the intended mode-of-action of these chemicals as they were designed to interfere with the endocrine system of a specific organism group. In addition, some chemicals can be transformed by environmental or metabolic processes into potential EDs. Finally, EDs include a wide range of natural chemicals, which may be plant derived (e.g., phytoestrogens and caffeine) or naturally occurring in the earth's crust (elements such as cadmium).

How Do EDs Interact with the Endocrine System?

The natural and synthetic chemicals with endocrine activity in laboratory experiments are diverse in terms of structure, properties, and sources. Regardless of their chemical nature, a chemical substance needs sufficient molecular similarity, specificity (affinity), and efficacy to achieve a potency that would interfere with the endocrine system by either: (1) mimicking a hormone produced in the body or by (2) interfering with normal binding of the hormone to its receptor and through effects on transport, synthesis, breakdown, or excretion. Adverse effects of EDs may occur in humans and wildlife when the normal physiological function of the endocrine system is compromised or tissues are reprogrammed during early development. While many studies have focused on EDs that serve to mimic or block the actions of estrogens, androgens, or thyroid hormones, recent studies show that the action of several other hormones can also be affected by some natural and synthetic chemical substances.

What Are the Sources and Common Exposure Routes?

Sources of EDs

Endocrine disrupters may be found in a range of commercial products and foodstuffs, and in the environment, and include both man-made chemicals and natural products (e.g., some substances in plants known as phytoestrogens). Some reported sources of synthetic EDs relevant to human exposure include building materials, furniture, electronics (e.g., e-waste), and food packaging. In terms of ecological exposures, common sources of EDs can include sewage treatment plant effluent and may also include run-off from agricultural operations. Moreover, some EDs are present globally because of international trade and long-range transport and deposition by wind and water currents. Overall, humans and wildlife can be exposed to natural and synthetic endocrine active chemicals from a variety of sources, both diffuse (e.g., food or agricultural or urban runoff) and discrete (e.g., pharmaceutical treatment or from a sewage effluent outfall).

Common Exposure Routes

Humans can be exposed to EDs through diverse routes including orally through food and drinking water, inadvertent ingestion of soils, inhalation of dust, and uptake through the skin. What and how much chemical we are exposed to is highly dependent upon dietary habits, occupation, and other lifestyle factors such as age and where we live. Fetal exposure through the placenta and exposure of the newborn through breast milk may be

Boat bottom with anti-fouling paint and barnacles.

Reductions in the use of tributyltin compounds have led to recoveries of impacted mollusk populations and the associated recovery of commercial shellfish populations.

of particular concern because of the possible sensitivity or lower threshold for response to some EDs in these early life stages as compared to adults.

Non-human species are also exposed to EDs through food, water, inhalation, and maternal transfer to the fetus, and the concentrations found in their tissues also depend on their diet, age, and location. For example, higher concentrations of some poorly metabolized, fat-soluble EDs may be found in older animals that are higher up in the food chain (e.g., predatory fish or fish eating birds and mammals).

Which Effects in Humans and Wildlife Have Been Linked to Endocrine Disrupters in the Laboratory?

Humans

Globally, disease trends in humans are causing significant concern. Some disorders and diseases of the endocrine system such as Type II diabetes, testicular and breast cancer, thyroid disorders, and genital malformations in baby boys appear to be increasing. This raises concerns as to whether environmental or occupational exposure to EDs may be associated with these diseases. While animal models in laboratory studies can provide important insights as to whether this might be the case, human epidemiology studies typically have not yet been able to make direct linkages between cause (exposure to specific EDs) and effects. The strongest evidence of adverse ED effects in humans has been observed in sons and daughters of mothers who used the synthetic estrogen diethylstilbestrol (DES) to prevent miscarriages during the 1950s-70s. Children exposed to DES in the womb have elevated rates of uterine cancer and numerous reproductive tract abnormalities (including fibroids, endometriosis, and non-descended testes).

Wildlife

Reproductive health disorders also occur in wildlife, and some have been linked to chemical exposure through long-term studies. For example, marine mollusks living in harbors and coastal waters have been exposed to harmful levels of tributyltin-based anti-fouling products which were extensively used in ship paints until recent years. Some of these animals developed imposex (development of male genitalia in females) and infertility, leading to species declines. Reductions in the use of tributyltin compounds have led to recoveries of impacted mollusk populations and the associated recovery of commercial shellfish populations. Another well-characterized occurrence of endocrine effects in a wildlife species involves feminization of male fish living downstream of sewage treatment plant effluent discharges. Evidence of fish feminization includes development of eggs (oocytes) in the testes and inappropriate production of the egg yolk protein vitellogenin in male fish. These feminization responses in exposed fish have been associated with the presence of natural and synthetic steroidal estrogens, including 17β-estradiol (a natural estrogen) and 17α-ethinylestradiol (the active ingredient in the birth control pill), as well as weak estrogen mimics like alkylphenol surfactants.

Assessing Risks and Developing Regulations for EDs

Recently, there has been a global effort to supplement existing test approaches for assessing chemicals with standardized tools that focus on the specific detection of EDs as a basis for evaluating their potential hazards to humans and wildlife (Matthiessen 2013). A large, internationally harmonized program of test method development and validation has been conducted over the last decade by the Organization for Economic Cooperation and Development (OECD). The resulting suite of both screening and higher-tier testing methods can be used with confidence to assess chemicals which may have estrogen-, androgen-, or thyroid-disrupting properties. The screening tests have completed a formal, multi-step scientific validation process while some of the higher-tier methods are undergoing final scientific validation. A guidance document describing these standardized test guidelines (and guideline drafts) for evaluating chemicals for endocrine disruption and the possible outcome scenarios of the tests has been published in the OECD Series on Testing and Assessment (OECD 2012; see http://www.oecd.org/env/ehs/testing/oecd-guidelinesforthetestingofchemicals.htm)

Regulatory authorities throughout the world also continue to work on approaches to define

Researchers at the Duluth USEPA lab evaluate effects of EDCs on fish.

Given the understandable public concern over health implications for humans and wildlife, EDs have received significant research attention over the past few years.

overall ED risks to human and wildlife. For example, in the US, a screening and testing program has been launched that has focused initially on components of pesticide formulations with a high potential for human and environmental exposure. A subset of about 50 of these chemicals has been screened for hazard using 11 different assays (which include several developed through the OECD effort) to identify those with the potential to interact with the estrogen, androgen, and thyroid systems (results from these Tier 1 assays are intended to be used as a weight of evidence rather than a single result). In the US program, if a chemical substance is deemed to have endocrine activity in a Tier 1 assessment, the substance then proceeds to more extensive Tier 2 assays, designed to examine the possibility for adverse effects that may result from the endocrine activity. An important purpose of the Tier 2 tests is to generate dose-response data appropriate for formal risk assessment.

Not all regulatory jurisdictions will necessarily use the same approach as the US. For example, for many years European chemicals regulation has been built on the scientific risk assessment approach which combines Predicted Effect Concentration (PEC) information with knowledge of the Predicted No-Effect Concentration (PNEC). However, the European Union (EU) has recently adopted legislation for biocides and pesticides that would evaluate and regulate with a focus on hazard alone if there is evidence of ED activity and associated adverse effects in validated biological testing procedures (unless human exposure is negligible). This hazard-based approach for biocides and pesticides does not consider exposure, although the established risk assessment approach continues to be used in other areas of EU policy such as for human and veterinary medicines. Some believe the new EU hazard-based approach may lead to certain biocides and pesticides being banned in Europe based on the intrinsic property of possessing endocrine activity in laboratory experiments alone. Consequently, there are ongoing discussions as to the feasibility of this new approach for science-based risk assessment, and at this time it is unclear how such regulations will be implemented in EU member countries.

Research Needs

Given the understandable public concern over health implications for humans and wildlife, EDs have received significant research attention over the past few years. This research has focused on:

- Exposure to and possible effects of androgens, estrogens, and thyroid hormone disrupters in both humans and wildlife;
- Relating observed adverse effects (e.g., increases in certain types of cancers in humans, feminization and subsequent reproductive effects in fish) to exposures to specific endocrine-active chemicals so that effective chemical-specific regulatory controls can be implemented.

However, these types of epidemiology-oriented studies, either in humans or wildlife, are very challenging to conduct and at present seldom definitive, so work in this area continues.

Another very active area of research involves the development of efficient and sensitive analytical techniques and bioassays to detect EDs both in the environment and in 'new' products entering commerce. Finally, while most regulatory efforts are currently focusing on estrogen, androgen, and thyroid activity, work is also underway to develop assessment and testing methods for other possible pathways of endocrine disruption of relevance to human disease (e.g. cancer and diabetes) and wildlife health (especially developmental and reproductive health, and response to stress).

References

Matthiessen P. 2013. Endocrine Disrupters: Hazard Testing and Assessment Methods. Hoboken (NJ): John Wiley & Sons, Inc. 398 pp.

OECD. 2012. Guidance Document on Standardized Test Guidelines For Evaluating Chemicals for Endocrine Disruption. Series on Testing and Assessment No. 150. Paris (FR): OECD. Reference ENV/JM/MONO(2012)22.

WHO/UNEP. 2002. Global Assessment of the State of the Science of Endocrine Disruptors. Damstra T, Barlow S, Bergman A, Kavlock R, Van Der Kraak G, editors. Geneva (CH): World Health Organization. Publication no. WHO/PCS/EDC/02.2

Aknowledgements

Thank you to the SETAC global advisory group on Endocrine Disrupter Testing and Risk Assessment for their contributions to this document!

About this Document

When referring to this text, please use the following citation:

[SETAC] Society of Environmental Toxicology and Chemistry. 2014. Technical Issue Paper: What is an Endocrine Disrupter? Pensacola (FL): SETAC. 5 pp.

About SETAC

SETAC is a not-for-profit, global professional organization comprised of some 6,000 individual members and institutions from academia, business and government. Since 1979, the Society has provided a forum where scientists, managers and other professionals exchange information and ideas on the study, analysis and solution of environmental problems, the management and regulation of natural resources, research and development, and environmental education.

SETAC's founding principles are:

» Multidisciplinary approaches to solving environmental problems
» Tripartite balance among academia, business and government
» Science-based objectivity

SETAC is implementing this mission worldwide.

SETAC publications, which include Technical Issue Papers (TIPs), workshop summaries, newsletters (*SETAC Globe* and *SETAC News*), and journals (*Environmental Toxicology and Chemistry* and *Integrated Environmental Assessment and Management*), are useful to environmental scientists in research, research management, chemical manufacturing and regulation, risk assessment, and education, as well as to students considering or preparing for careers in these areas. The publications provide information for keeping abreast of recent developments in familiar subject areas and for rapid introduction to principles and approaches in new subject areas.

Contact Information

For further information, contact the Pensacola office if you live in Latin America, Asia/Pacific, or North America or the Brussels office if you live in Europe or Africa:

229 S Baylen St., 2nd Floor
Pensacola, FL, 32502 USA
T +1 850 469 1500
F +1 850 469 9778
E setac@setac.org

Avenue de la Toison d'Or 67
B-1060 Brussels, Belgium
T +32 2 772 72 81
F +32 2 770 53 86
E setaceu@setac.org