

### Quick guide

# Endocrine-disrupting chemicals

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#### What are endocrine-disrupting chemicals?

The World Health Organisation defines an endocrine-disrupting chemical 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” (<https://apps.who.int/iris/handle/10665/67357>). In this definition, ‘adverse health effects’ describes any alteration to an organism’s morphology, physiology, and/or behaviour that impairs its ability to grow, develop, and/or reproduce. Of the approximately 140,000 chemicals registered under the European Union’s ‘Registration, Evaluation, Authorisation, and Restriction of Chemicals’ regulation, more than 1,000 are known, or suspected, to have endocrine-disrupting properties. However, most chemicals have not been tested for endocrine activity, meaning that there are likely many more endocrine-disrupting chemicals than are currently recognised. Nevertheless, the diversity of chemicals now known to disrupt the endocrine system is staggering (Figure 1).

Particularly well-known endocrine-disrupting chemicals include dichlorodiphenyltrichloroethane (DDT) and other organochlorine pesticides, antifouling agents such as tributyltin, and polychlorinated biphenyls (PCBs), which were used in the manufacture of electrical equipment but subsequently banned from use in many countries (since the 1970s). Per- and polyfluoroalkyl substances (PFASs), which are found in a variety of industrial products including fire-fighting foam, also have endocrine-disrupting properties, as do polybrominated diphenyl ethers (PBDEs), which are used as flame retardants in furnishings and electronics, alkylphenolic compounds (for example,

nonylphenols) used in the manufacture of surfactants, and plasticisers like bisphenols and phthalates, which are used to make plastics more pliable. In addition, various pharmaceuticals are extremely potent endocrine-disrupting chemicals, such as the synthetic androgen trenbolone, a growth-promoting steroid that is commonly administered to beef cattle.

#### How are wildlife and humans exposed to endocrine-disrupting chemicals?

Endocrine disruptors enter the environment from a myriad of sources. Pathways of these chemicals into ecosystems can be direct, such as drifting of spray during application of pesticides, herbicides, and fungicides to gardens and agricultural fields, or indirect, when chemicals developed for industrial or residential purposes — and/or their breakdown products — enter the environment due to inadequate waste management. For example, some endocrine disruptors can enter the environment in leachate from landfills, where items degrade and release chemicals (for example, the alkylphenols in cleaning products

and bisphenols in plastics). Another major source is wastewater, which is often contaminated with a variety of endocrine-disrupting chemicals (for instance, halogenated aromatic hydrocarbons in industrial effluent, and pharmaceuticals, illicit drugs, and hormones in residential wastewater). In addition to these relatively localised sources, runoff from agriculture, roads, and roofs is a widespread and spatially diffuse source of endocrine-disrupting chemicals (for example, steroids administered to agricultural animals and phthalates in road runoff). Once present in terrestrial and aquatic habitats, various endocrine-disrupting chemicals can persist for years or decades. Further, endocrine disruptors can be ‘pseudo-persistent’, meaning that although these contaminants are degradable, their continuous release into the environment leads to a constant environmental presence. This is seen, for example, in the case of receiving waters polluted by continuous release of pharmaceuticals with endocrine-disrupting properties. Wildlife can be exposed to these contaminants by a variety of routes including



**Figure 1. A wide variety of natural and synthetic chemicals have endocrine-disrupting properties, posing a threat to wildlife and humans alike.**

These endocrine-disrupting chemicals include (A) pesticides, herbicides, and fungicides applied to agricultural fields for crop protection, (B) brominated flame retardants used in consumer products and firefighting foam, (C) steroid hormones such as oestrogens found in the contraceptive pill that contaminate effluent-receiving waters, and (D) bisphenols and phthalates that are used in the production of plastics. Photo credits: (A) iStock.com/incposterco; (B) iStock.com/Avatar\_023; (C) iStock.com/aquatarkus; and (D) iStock.com/curtoicurto.

ingestion via food, inhalation or uptake via gills, and absorption through the body surface (such as through contact with sediment). Importantly, various endocrine-disrupting chemicals are also known to bioaccumulate (that is, they concentrate in biota tissues to a greater degree than in surrounding media) and/or biomagnify (when tissue concentrations in exposed biota increase at successively higher levels in a food chain).

Sources of human contamination with endocrine-disrupting chemicals are similarly numerous, with exposure mainly occurring by ingestion, as well as inhalation and dermal uptake. For instance, humans are continually exposed to endocrine-disrupting chemicals as a result of consuming food and drink from plastic (and plastic-lined) containers, as well as daily-use items such as clothing, furniture, electronics, insulation, cosmetics, and personal care products, with the latter often containing parabens and phthalates. Humans are also commonly contaminated with endocrine disruptors in the workplace, such as via exposure to industrial chemicals (such as PFASs), including various metals with endocrine-disrupting properties (mercury, lead), and pesticides, herbicides, and fungicides (methoxychlor, chlorpyrifos). Moreover, in most mammals, including humans, there is demonstrable placental and lactational transfer of many endocrine-disrupting chemicals. This is illustrated by the oestrogenic pharmaceutical diethylstilbestrol (DES), which was prescribed from the 1940s to the 1970s to millions of mothers to prevent miscarriage. Exposure to DES was linked to adverse pregnancy outcomes, infertility, and cancers in mothers, as well as their offspring — so-called ‘DES daughters’ and ‘DES sons’ — as a consequence of in utero exposure to this endocrine disruptor.

**How do endocrine-disrupting chemicals act?** Endocrine-disrupting chemicals can act in the body in a variety of ways. Most interact with hormone receptors to either stimulate a hormonal response (acting as a receptor agonist) or inhibit such a response (acting as a receptor antagonist). Endocrine disruptors acting as hormone receptor agonists

generally share strong chemical structural identity with the natural hormone for that receptor. Hormone receptor antagonists work by binding to a receptor, blocking its activity. In the case of nuclear hormone receptors, this involves binding of the hormone/receptor complex to DNA to stimulate transcription of gene cascades. Endocrine disruptors can also have effects by interacting with, and either stimulating or antagonising, processes mediated by membrane receptor systems, which tend to be faster-acting pathways. In addition, some endocrine-disrupting chemicals interfere with enzymes that synthesise or break down hormones, whereas others act through multiple targets to cause hormone disruption, as shown for the surfactant nonylphenol, which acts simultaneously as both a weak oestrogen receptor agonist and androgen receptor antagonist. Much of the original work on endocrine-disrupting chemicals was focused on sex steroid pathways, but other hormonal pathways are now also known to be targeted, including the thyroid system, the stress axis (for example, corticosteroids), and various hormonal regulatory networks for energy processes and neural function. Endocrine disruptors can also have effects via molecular epigenetic programming. The laying down of epigenetic ‘marks’ sometimes has immediate effects, but in other cases can change the developmental trajectory and lead to latent and often long-term effects. This latter point underscores the particular vulnerability of developing organisms to endocrine-disrupting chemicals.

**What effects do endocrine-disrupting chemicals have?** Exposure to endocrine-disrupting chemicals can produce a remarkable range of biological effects that can vary depending upon factors such as species, sex, and age of exposure. Many of these effects occur via oestrogenic and anti-androgenic mechanisms particularly affecting reproduction, which in all vertebrates is tightly regulated by hormone release at the appropriate timing and levels. Moreover, sex differences in production of endogenous oestrogens and androgens, and the balance between them, are crucial for normal

sexual differentiation and development. Malformed genitalia in alligators, compromised oviduct function leading to poor eggshell quality in egg-laying species, misshapen uteri in mammals, ovulatory problems in females and spermatogenesis defects in males of diverse taxa, and even the presence of developing eggs in the testis of males, are all associated with endocrine-disrupting chemical exposures. At the population level, these sublethal effects can have dire consequences. A stand-out example of this is a seven-year, whole-lake study carried out by Kidd and colleagues, in which fathead minnows (*Pimephales promelas*) inhabiting an experimental lake system were chronically exposed to the oestrogenic endocrine disruptor 17 $\alpha$ -ethinyloestradiol (a common ingredient in the birth control pill). Contamination of the lake led to feminisation of male fish, altered gonadal development and intersex in males, disrupted oogenesis in females and, ultimately, collapse of the fish population in the lake.

Other components of endocrine systems have also emerged as being highly sensitive to exposures. For instance, laboratory animal studies, field work on wildlife, and human epidemiological and clinical work, have demonstrated links between endocrine-disrupting chemicals and thyroid disease, cardiovascular and metabolic disorders, obesity, diabetes, and hormone-sensitive cancers. In particular, thyroid disruptors, which can act through thyroid hormone receptors or by interfering with the biosynthesis of thyroid hormones, can lead to failure of amphibians to undergo metamorphosis, and disrupt metabolic processes in mammals. In addition, insulin homeostasis and glucose regulation are influenced by endocrine-disrupting chemicals. Insulin resistance can be induced by exposure to bisphenols and persistent organic pollutants in animals, and epidemiological studies in humans show an association between higher serum concentrations of endocrine-disrupting chemicals and type-II diabetes mellitus.

**How can we reduce the effects of endocrine-disrupting chemicals on wildlife and human health?** Because endocrine-disrupting

chemicals include a wide array of environmental chemicals, reducing their presence and impacts is a formidable task. Undoubtedly, limiting industrial production, use, and release of endocrine-disrupting chemicals is fundamental to reducing the extent to which wildlife and humans are exposed to these contaminants. In the European Union, new chemicals must generally undergo a program of assessment, including testing for harmful endocrine-related effects on reproduction and disease. However, endocrine disruption is still not addressed under the European Union chemical classification system and no agreed-upon test methods exist to identify whether a chemical has endocrine-disrupting properties. Furthermore, current approaches used to restrict the production of endocrine-disrupting chemicals are susceptible to the issue of ‘regrettable substitution’, where one harmful chemical is replaced by another that is equally (or more) harmful. This was seen, for example, in the case of flame-retardant chemicals used in furniture manufacturing, where polybrominated biphenyls (PBBs) were identified as hazardous and replaced with PBDEs, which have a similar chemical structure and also have endocrine-disrupting properties.

Encouragingly, there is increasing interest in using a chemical class approach in regulation, partly driven by concern over the toxicity of PFASs. There is also a growing call from the scientific community for regulatory agencies to better account for the risks posed by mixtures of chemicals, given that wildlife and humans are often exposed to these contaminants as chemical cocktails. In addition to improving regulatory measures, another approach to reducing the prevalence of endocrine-disrupting chemicals revolves around green chemistry — that is, the development of new chemicals that both have the desired technical performance and are inherently non-toxic to humans and the environment. Although this approach holds great promise for environmental protection, with few exceptions the field of green chemistry has, to date, largely overlooked the issue of endocrine disruption. This is, therefore, a crucially important area for future research.

### Where can I find out more?

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