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What is the endocrine system?

The human endocrine system is a collection of glands and organs which secrete different types of hormones or molecular messengers into the bloodstream. It maintains a dynamic equilibrium in the body, and restores this equilibrium when the body is subjected to stress. The endocrine system regulates many aspects of health including *in utero* development, growth and metabolism, sexual development and reproduction, behaviour and immunity (see Figure 1).

There are around 50 different hormones found in the human body, including the steroid hormones oestrogen, progesterone and androgens. Oestrogens are responsible for female sexual development and reproduction. They are made in women's ovaries and placenta during pregnancy, in small amounts in men's testes, and in adrenal glands, the brain, and fat cells of women and men. There are three major forms made by women including 17-β oestradiol, oestrone and oestriol. Another, oestetrol, is made during pregnancy.

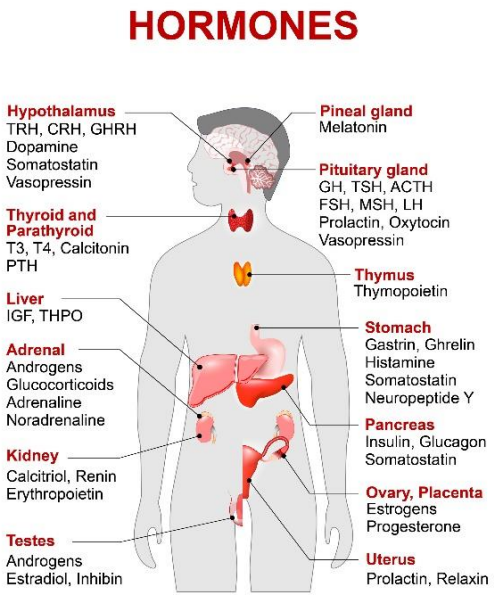

Figure 1: Major endocrine glands and hormones

An endocrine disrupting chemical is

"an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action"

Endocrine Society, 2012 (1)

Progesterone is also made in the ovaries (and placenta) and is associated with female sexual development and reproduction. Androgens, such as testosterone, are responsible for the development and maintenance of male sexual characteristics. They are made mainly in the testes, but also in women's ovaries, and in adrenal glands of both men and women.

Hormones circulate in the bloodstream and are transported to tissues and organs where they bind to hormone receptors (proteins) on cell surfaces, or inside cells. This binding triggers a chemical signalling cascade which initiates essential biological processes. For example when oestrogen binds to a receptor site inside a cell, it forms a hormone-receptor unit that moves into the nucleus, where it binds to DNA, and activates genes which produce proteins These proteins trigger cellular changes, resulting in oestrogen-controlled growth and development (2, 3).

Hormones are active at very low doses and their regulation is tightly controlled by the endocrine and central nervous systems. A healthy endocrine system is essential to the normal functioning of the human body.

Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are substances that interfere with the functioning of the endocrine system in humans and animals, altering hormone action, and resulting in harm to the health of the individual or that of subsequent generations (4). EDCs can negatively impact many aspects of human and animal health, affecting

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developmental, reproductive, neurological and immune system processes. They may also affect behaviour by affecting thyroid hormones and neurohormones such as dopamine, serotonin and endocannabinoids (5) Most EDCs are synthetic compounds although some, such as phytoestrogens found in plants, occur naturally.

How do EDCs exert their effects?

EDCs exert their effects either by changing the amount of hormone released, thereby altering the concentration of circulating hormones, or by interfering with hormone transport or hormone metabolism. Some EDCs are structurally similar to natural hormones and can bind to hormone receptors (6). After such binding one group of EDCs, known as "mimics" or "agonists", can induce the same biological processes associated with the hormone they mimic, but in an unregulated way; Another group, EDC "antagonists", prevent natural hormones from binding, thus blocking the triggering of the normal biological response.

Some EDCs can affect gene expression without altering the underlying DNA sequence of the gene. This can cause physical changes that are passed on to the next generation; a process known as "epigenetic" modification (7). If during pregnancy a mother is exposed to EDCs which exert these effects, the child's health may be at risk.

The effects of exposure to EDCs *in utero* can develop much later in life, which makes it very hard to show definitively the association between EDC exposure and adverse health impacts (6).

EDCs can act at multiple sites via multiple mechanisms of action (4). They are a very diverse group of chemicals (see Tables 1 and 2) belonging to many chemical classes, with greatly varied molecular structures. This makes it difficult to predict which chemicals might have endocrine disrupting properties.

Where are EDCs found?

EDCs are found in a variety of products including plastics, pesticides, cosmetics, food, toys, clothing, paints, medical equipment, cleaning products, furniture, soft furnishings, and electronics.

EDCs are widespread in the environment. They are found in rivers, estuaries, soil and air. Mostly they originate from human activities such as wastewater effluent discharge, agricultural runoff, landfill leaching, industrial and domestic pollution, and power station and car exhaust fumes.

EDCs enter the human body from contaminated food, water, and air. We also absorb them from personal care products through our skin and via exposure to soil or dust.

EDCs are commonly detected in wildlife and human body fluids and tissues (4, 5). For example BPA has been measured in human urine from across the world, and in blood, amniotic fluid and breast milk (8), Perfluoroalkyl substances have been measured in blood (9, 10) and phthalates are ubiquitous in urine (11) (see Table 1 for details).

Over 1400 compounds are suspected or known to have endocrine disrupting properties for wildlife or humans (12). Some of these are known to be detrimental to human health (5).

Pesticides often contain endocrine disrupting chemicals

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Table 1: Some recognised EDCs, adapted from Gore et al. 2015 (5).

Acronym/name	Use	Source	Effects	Exposure route
ATR atrazine	pesticide and herbicide	contaminated water and soil	liver, respiratory, nervous system damage	ingestion inhalation
BPA bisphenol A	plastics and epoxy resins	plastic bottles, toys, food can linings, till receipts	reproductive, developmental, neurological	ingestion inhalation dermal absorption
DDT Dichloro-diphenyl-trichloroethane	organochlorine pesticide	contaminated water, soil, and fish	carcinogen, organ, nervous system damage	ingestion inhalation dermal absorption
DES diethylstilbestrol	synthetic oestrogen, former anti-miscarriage pill; prostate cancer treatment	contaminated water	carcinogen (including breast cancer), teratogen	ingestion
EE2 ethinyloestradiol	synthetic oestrogen used in contraceptive & HRT	contaminated water	carcinogen (including breast cancer) brain health	ingestion
MXC methoxychlor	organochlorine insecticide	contaminated water, soil, and food	reproductive, developmental, organ, nervous system effects	ingestion, inhalation, dermal absorption
PCBs Polychlorinated biphenyls	organic chlorine compound once used widely in paint, electrical equipment, adhesives	contaminated air and food, old electronic equipment	carcinogen (including breast cancer), affects reproductive & nervous systems, thyroid, liver damage	ingestion, inhalation, dermal absorption
Phthalates	Plasticiser used in PVC, plastics, flooring, personal care products, medical devices, tubing	contaminated food and dust, and via application to skin	carcinogen, reproductive & developmental effects, liver damage	ingestion, inhalation, dermal absorption
PFASs poly- and perfluoro alkyl substances (e.g. PFOA)	Surfactants in firefighting foam, floor waxes, wiring, carpets, food wrappers, waterproofing & non-stick	contaminated food, water, and dust	carcinogen, developmental, immune system effects	ingestion, inhalation
TCDD 2,3,7,8-tetrachloro-dibenzodioxin	dioxin associated with smelting, herbicide production, chlorine bleaching of paper	occupational exposure, contaminated food	carcinogen, endocrine, reproductive and immune system effects	ingestion, inhalation
Vinclozolin	dicarboximide fungicide	occupational exposure, contaminated food	reproductive and neurological effects	ingestion, inhalation, dermal absorption

A number of EDCs are now banned or their use is restricted. These serve as helpful examples which enable scientists to study different mechanisms by which EDCs adversely affect human health. Many EDCs currently used are of particular concern (for more details see Table 2 and the section below on "Oestrogen mimics and breast cancer"). Examples include parabens (13, 14, 15) which are used as preservatives in personal care products and cosmetics and some food and medicines; triclosan (16, 17, 18) also used as a preservative, in some personal care products, household items, clothes, toys and carpets; and UV filters (19) used in sunscreen to protect skin against UV damage, and in some leave-on cosmetics and other products to reduce UV damage and prolong product life.

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Table 2: Some commonly used oestrogenic EDCs that may be linked to breast cancer

Compound or group of compounds	Use
Triclosan	used as an anti-microbial agent in toothpaste, mouthwash, every day products such as liquid soaps and detergents, household items including chopping boards, children's toys, and carpets
Alkylphenols e.g. octylphenols	used in the production of resins and octylphenol ethoxylates; in rubber, inks, paints; pesticides, plastics; the EU has banned the use and production of certain alkylphenols e.g. nonylphenol
Bisphenols e.g. BPS, BPF, BPA	used in the manufacture of polycarbonate plastics, food and drink packaging, resins that line metal cans, CDs, computer casings, glasses, dental sealants, medical devices and thermal till receipts
UV filters (benzophenones, camphor derivatives, cinnamate derivatives)	used in sunscreen, to preserve some personal care products and prolong the life of
Metalloestrogens e.g. cadmium, nickel, aluminium	used for different functions or may be present as contaminants; found in everyday items such as cosmetics and personal care products, aluminium is the active ingredient in most antiperspirants
Flame retardants e.g. organophosphate	used to Firefighting foam, furniture and furnishings, fire-resistant clothing
Parabens e.g. methyl paraben	used as preservatives in personal care products and cosmetics, including shampoos, deodorants, moisturisers, makeup, skin cleansing products and mouth wash, and in some food and medicines

Why are EDCs cause for concern?

There is much scientific evidence that shows that exposure to certain EDCs can cause long term, irreversible damage to human health and the environment (4, 7, 20).

Many EDCs are persistent organic pollutants which degrade very slowly. At every step along the food chain they become more concentrated (4). The detrimental effects of EDCs on wildlife are well documented. They include cancers, reproductive disorders, adrenal and bone conditions, reduced biodiversity, population decline, greater susceptibility to infection, neurotoxicity and thyroid problems (4).

Research suggests that EDCs may cause adverse effects at extremely low levels (5, 21) although the scientific community is still debating this (6). Similar to natural hormones, EDCs may elicit "non-monotonic" (i.e. non-linear) dose responses. This could mean lower levels may be more harmful than higher levels (4). Scientists are also concerned that co-exposure to multiple EDCs may cause additive or other unpredictable effects (22).

Many scientists believe that the effects of long-term human exposure to EDCs are similar to the well documented detrimental effects in wildlife (4). Studies indicate that changing trends in human health, including increases in hormone sensitive cancers such as breast cancer, may be linked to EDC exposures (23).

Oestrogen, EDCs and breast cancer

Oestrogen and breast cancer

Oestrogen is a well-established risk factor for breast cancer. This is mainly because oestrogen encourages cells to divide more rapidly, and an increased rate of cell division of healthy cells raises the possibility of mutations occurring, including those that lead to breast cancer. In addition, some metabolites of oestrogen are carcinogenic, and these compounds may initiate breast cancer. By encouraging rapid cell division, oestrogen can also promote growth of existing breast cancer. Oestrogens can also induce epigenetic changes which affect expression of genes associated with breast cancer, e.g. they can turn off tumour suppressor genes, that help stop cells becoming cancerous (24, 25, 26, 27).

Breast cancer risk increases with age throughout our lives, in part due to cumulative exposure to natural oestrogen produced by our bodies. However, the rate of increase in risk declines after the menopause, as oestrogen is no longer produced in the ovaries, although a lower level of production continues in fat tissues (27).

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Oestrogen mimics and breast cancer

Some EDCs can mimic the hormone oestrogen. These EDCs are known as “oestrogenic EDCs" or oestrogen mimics (28). Oestrogenic EDCs can bind to oestrogen receptors, which are found in different tissues throughout the body, including breast tissue. Binding may initiate the expression of oestrogen-responsive genes which encourage breast epithelial cells to divide more rapidly (29). This is one of the ways that oestrogenic EDCs may increase breast cancer risk.

The risk from exposure to oestrogenic EDCs is greater during times when breast tissue is developing at different life stages: foetal development (for more see our webpage on *in utero* exposures); at puberty; during pregnancy. Exposure during these critical periods in particular increases the risk of breast cancer later in life (30).

High levels of synthetic oestrogens, including those used in hormone replacement therapy (HRT), the contraceptive pill, and DES (a treatment to prevent miscarriage no longer used for this purpose), have all been shown to increase breast cancer risk (31, 32) (see Table 1).

Other oestrogenic EDCs linked to an increased risk of breast cancer are described in Table 2. They include the flame retardants TCDD and PFOA (5), phthalates (33, 34), parabens (35, 36), BPA (37, 38) and bisphenol substitutes (39), triclosan (16, 40, 41), octylphenol (40), the three main groups of UV filters (benzophenones, camphor derivatives and cinnamate derivatives) (42, 43), and a number of metals or “metalloestrogens”, including cadmium, nickel and aluminium (44, 45, 46).

Exposure to multiple EDCs simultaneously may be potentially more harmful than individual chemical exposures. One recent study (47) found when BPA, methyl paraben and PFOA (at levels commonly detected in human body fluids) were exposed to human breast cells grown in cell culture, the potentially harmful effects increased to a greater degree than the effects of individual exposures. Furthermore, the effects of the mixtures corresponded to three “hallmarks” or common traits of cancer, including increased breast cell proliferation, evasion of programmed cell death and overriding normal cell control mechanisms.

There are a number of widely accepted tests which are used to determine how oestrogenic a substance is (48, 49; see Appendix 1 for details).

Non-oestrogenic EDCs and breast cancer

As EDCs are so chemically varied and can disrupt many different hormonal pathways, it is a challenge to develop methods of testing which will identify all EDCs. *In vitro* tests have been developed to identify EDCs that affect certain hormones for example oestrogens, androgens, progesterone and thyroid hormones. However more research is needed to develop a more comprehensive range of tests (50).

Hormones other than oestrogen, such as progesterone, prolactin and testosterone, can also affect breast cancer risk (27). EDCs which affect pathways associated with these hormones may also affect risk. The UV filter benzophenone-3 is an oestrogen mimic suspected of increasing breast cancer. This compound is also an androgen agonist and affects progesterone receptor function (43).

HRT contains synthetic hormones that can increase breast cancer risk

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EDCs and other human diseases

Exposure of the human population to EDCs may be leading to an increase in the incidence of many human diseases (5). This is difficult to show definitively, although research suggests associations between various suspected or confirmed EDCs and human illnesses or diseases. For example obesity, type 2 diabetes and cardiovascular disease have been linked to exposure to BPA, certain phthalates, the dioxin TCDD, some PFASs, some PCBs and persistent organic pollutants (5, 51, 52) (see Table 1).

Female reproductive health problems, including early puberty, infertility, abnormal menstrual cycles, premature ovarian failure and menopause, polycystic ovary syndrome, endometriosis, fibroids and adverse pregnancy outcomes, have been linked to exposure to BPA, phthalates and some pesticides (5, 53). Male reproductive health problems, including declining sperm counts, increased numbers of male children born with genital malformations (23), testicular and prostate cancer and reduced fertility, have been associated with exposure to BPA, certain phthalates, the pesticide metabolite DDE, and dioxins (53, 54). Other possible EDC exposure effects include thyroid disruption, which has been linked to PCBs, certain flame retardants, dioxins, UV filters, triclosan, BPA, and phthalates (55, 56), and developmental, neuro-behavioural and cognitive difficulties which have been linked to BPA, organophosphate pesticides, PCBs and phthalates (5, 57, 58).

The regulation of EDCs

EDCs are regulated at the European Union (EU) level. The regulation of EDCs across the EU is complex and inconsistent. Although there has been some progress in recent years, EDCs continue to be used widely across Europe in a range of different products.

Under REACH, the EU's main chemicals regulation, substances with endocrine disrupting properties for which there is evidence of probable serious effects to human health or the environment require authorisation and/or replacement. However, most chemicals have not been tested for their endocrine disrupting properties and as a result very few are subject to the REACH authorisation procedure.

A further complication is that currently EDCs are treated differently under different EU legislation. To introduce greater consistency, the European Commission developed criteria for identifying EDCs, which were adopted in 2018 (59).

However, the criteria are not ideal, as the burden of proof required to identify a substance as an EDC has been set too high. Currently the criteria apply to EDCs used in plant protection product (PPPs) and biocides. The Commission is now developing a new EDC strategy that will cover areas such as toys, cosmetics, and food packaging.

Breast Cancer UK is working with partners in Europe to press for a robust and comprehensive EDC strategy that promotes the phase-out of potential and suspected EDCs and their replacement with safer alternatives. See our EDC Policy page for more on our work in this area.

EDCs are found in a range of everyday products

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Breast Cancer UK Position

• A new EDC strategy that delivers a high level of protection for human health and includes a timetable to implement EDC criteria in all relevant EU laws;
• Support for implementation of the EU Plastics Strategy by banning EDCs in plastics;
• The grouping of harmful chemicals with similar structures and potential uses in chemical regulation to avoid regrettable substitution;
• The extension of EU Article 60 (3) of the REACH Regulation, to ensure EDCs are, by default, classed as Substances of Very High Concern (SVHC), for which no safe thresholds can be determined;
• An increase in funding for research into the environmental and chemical causes of breast cancer

How can you reduce your risk of exposure to EDCs and breast cancer?

There are many risk factors for breast cancer and so many actions you can take that can help reduce your risk. One of these is to reduce your exposure to potentially harmful chemicals including EDCs, especially those which can mimic oestrogen. Exposures come from many sources e.g. cosmetics and personal care products, plastic containers, food packaging, confectionary, tinned food, garden sprays, household cleaners, soft furnishings and other household items. We recommend that you get to know the names of chemicals to avoid and identify safer alternatives. Details are available on the reduce your risk section of our website.

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Breast Cancer UK works to save lives and reduce breast cancer rates by tackling environmental and chemical causes of the disease.

For further information on how harmful chemicals may be linked to breast cancer and full references please visit our website www.breastcanceruk.org.uk

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Appendix 1 Oestrogenicity tests

Substances suspected of being oestrogenic EDCs can be tested for their ability to mimic oestrogen (oestrogenicity). There are widely accepted tests (assays) which are used to determine a substance's level of oestrogenicity (48). These include tests using rodents (rodent uterotrophic assays), and a range of *in vitro* tests on cells grown under laboratory conditions. Oestrogen receptor binding assays measure the ability of a substance to bind to oestrogen receptors, and compare this to the binding with natural oestrogen (expressed as the relative binding affinity); cell proliferation assays, also known as the E screen (49), measure an increase in the number of oestrogen-sensitive human breast cancer cells on exposure to the test chemical; and reporter gene assays measure the ability of the test chemical to stimulate the first stage of oestrogen-receptor-dependent gene expression, which influences a cell's function. These tests are replicated using oestrogen (normally 17-β oestradiol), and with no addition of either oestrogen or the chemical being tested, and results compared with the chemical addition test. Many of the *in vitro* tests use oestrogen receptor positive human breast cancer cells because they are especially sensitive to oestrogen and other oestrogenic substances. Although these tests use breast cancer cells, tests are not specifically designed to test if a substance could cause breast cancer directly.