RSC INTEREST GROUP
TOXICOLOGY

Toxicology Topics in Brief
Endocrine Disruptors

Many essential biological processes in humans and other organisms are controlled by hormones. The hormone (or 'endocrine') system encompasses a large array of glands that secrete chemical messengers (hormones) into the blood that fulfil numerous functions, including regulating metabolism and growth, tissue function, mood, and reproduction.

Endocrine disrupting chemicals (EDCs) are chemicals that can interfere with the body's hormone system and have the potential to cause harm. Some can mimic natural hormones, although often only very weakly compared to the natural endogenous hormones. Others block or prevent the normal action of hormones, while others can work indirectly by increasing the removal of hormones from the blood by stimulating metabolism in the liver.

There is a concern that some chemicals used in everyday objects including furniture, building materials, cosmetics and food packaging, could have the potential to be EDCs.

Endocrine active substances are also naturally occurring, for example phytoestrogens which can be found in soya. Endocrine activity does not automatically mean a substance is an Endocrine disruptor. Some endocrine active substances are beneficial such as those used in pharmaceuticals, in the contraceptive pill and hormone replacement therapy (HRT).

The risk to humans from endocrine active chemicals is uncertain. Some scientists argue that they may be a cause of higher rates of illnesses and disorders; others argue that our exposure to these chemicals is too low to cause a problem and in reality, our body is not adversely affected.

Animal studies have shown that high doses of some of these chemicals can cause adverse health effects, but our real-life exposure is much lower than the amounts used in these studies.

Some scientists are convinced that even the low-level exposure that we experience can cause adverse health effects. This hypothesis is not universally accepted. It is vigorously debated and is the reason for much of the controversy in this area.

What are endocrine active and disrupting substances?

An endocrine active substance is a chemical that has the ability to interfere with the body's hormone system. Endocrine disruptors are a subset of endocrine active substances. They are chemicals that have the ability to interfere with the body's hormone system, and thereby cause harm in an intact organism. The World Health Organisation developed a definition that most global authorities are following "An endocrine disruptor is 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. "

It is possible for a chemical to interact with the endocrine system without any resulting harmful effects due to compensation by the normal biological control mechanisms.

Scientists and policy-makers agree that in order to be classified as an endocrine disruptor, a chemical has to be shown to be able to interfere with the endocrine system, and as a result of this cause harm. There are many chemicals that interact with the hormone system without causing harm. For example, when we eat sugar, the system responds by increasing the secretion of the hormone insulin by the pancreas.

Endocrine Disruptors are often sensationally referred to in the media as 'gender-bending chemicals' as many have some oestrogen like properties, but usually with low potency.

Wide variety of uses

We are potentially exposed to a variety of chemicals that are suspected endocrine disruptors in our homes, offices, cars and environment in general. Biomonitoring data can be used to establish actual exposure and highlight where action to reduce exposure to suspected EDCs is required.

For example: phthalates, which are chemicals that are used in the manufacture of polyvinyl chloride (PVC) plastic. PVC is used to make many household items (including toys), and it is also used in cars and building materials. Such uses are now being restricted as part of the implementation of the EU REACH and UK REACH regulations.

Did you know?

According to the World Health Organization, a substance should be regarded as an endocrine disruptor if it causes an adverse effect in an intact organism or (sub) population, by an endocrine mode of action.

What health effects have been linked to endocrine disruptors?

It is generally accepted that the link between these chemicals and health problems has not been conclusively proven. This remains a contentious topic, although the majority of the UK scientific community agree that current low exposures do not pose a concern for human health. It should be noted that in addition to the potential human health risks, endocrine disrupting chemicals can potentially cause damage to wildlife as well, there is more evidence of adverse effects seen in wildlife, than for humans.

However, some scientists are convinced that our exposure to certain chemicals causes a wide range of illnesses and disorders including cancer, autism, metabolism disorders (obesity) and reproductive problems as a result of their interaction with the hormone system. However, it is difficult for scientists to prove or disprove that endocrine disrupting chemicals cause higher rates of such illnesses.

Did you know?

Foetuses, babies, infants and children are considered to be most at risk to the potential harmful effects of endocrine disruptors. This is because they are still developing and growing, and the hormone system is central to this process.

RSC INTEREST GROUP
TOXICOLOGY

Should we be concerned about endocrine disruptors?

It is difficult to say with certainty whether endocrine disruptors should be a cause for great concern at the levels most of the population encounter

in their daily lives. The majority view in the UK is that current exposures are too low to be causing serious adverse effects. There is more evidence that endocrine disruptors have caused adverse effects in wildlife, particularly in the past.

Why is there so much uncertainty? There are many factors that can contribute to illnesses and disorders, such as lifestyle, diet and genetics. It is difficult to single out one factor from all the others. The fact that we are exposed to such a huge variety of chemicals also makes it difficult to pinpoint one chemical (or group of chemicals) that may be causing a problem. Also changes in reproductive behaviour such as mothers and fathers, being significantly older when they have children than in previous decades and the reduction in the number of children they have, may also explain some of the changes seen in reproduction.

What is the evidence?

In animal studies, it has been shown that exposure to high levels of some endocrine disrupting chemicals can result in various health effects, including fertility and developmental issues.

This raises concern, but does not necessarily mean that these chemicals are posing a risk to humans. This is because under normal circumstances, humans are not exposed to the same high levels of endocrine disrupting chemicals used in animal studies.

A Controversial Debate

In 2012, an informal expert group of academics produced a review on the State of the Science of Endocrine Disrupting Chemicals (Bergman et.al. WHO/UNEP 2013) This was published by, although not officially endorsed by the WHO. It concluded that the evidence supports the idea that exposure to endocrine disruptors plays a role in the increased incidences of reproductive diseases, certain cancers, behavioural problems such as ADHD and maybe even obesity and diabetes.

However, the report and its conclusions have not been universally accepted. A detailed peer reviewed critique of the report was published by another expert group of academics (Lamb et al 2014). This was very critical of the review by Bergman et.al. (WHO/UNEP 2013) which raised questions about the conclusions (based on the methodology used). This expert group which was funded by industry, included two of the authors of the original 2002 WHO Report on this topic (WHO 2002).

Did you know?

Sometimes chemicals are purposefully designed to interact with the hormone system. For example: the synthetic oestrogens used in the oral contraceptive pill mimic natural oestrogen.

Endocrine disruptors and low dose effects

In traditional toxicology 'the dose makes the poison'. This means that there is a lower threshold below which a substance does not cause harm. For example, selenium is a naturally occurring chemical element that is essential to human health in trace amounts. However, at high doses selenium is toxic. In extreme cases, too much of the element can lead to cirrhosis of the liver, pulmonary oedema and even death.

However, some scientists suggest that endocrine disrupting chemicals do not obey the 'dose makes the poison' rule. Their view is that endocrine disruptors can cause health problems at extremely low doses, without any health problems necessarily being seen at higher dose levels. This is known as the 'Low Dose Hypothesis'. (Vandenberg et.al. 2012)

These scientists contend that there is no safe level of endocrine disruptors as there is for other chemicals.

This 'Low Dose Hypothesis' continues to be controversial within the scientific community. The European Food Safety Authority and the Food and Drug Administration in the US agree that existence of low dose effects has not been conclusively established. Concerns have been raised about the risk that exposure to low levels of several EDCs, the concern being what is the combined effect, particularly if they potentially affect the same aspect of the endocrine systems by different mechanisms. This is part of the general concern about the possible risks from the exposure to low levels of a large mixture of chemicals via the environment. There is much research activity on this topic and the way this concern can be incorporated into regulatory risk assessment.

Suspected endocrine disruptors

Many substances which are endocrine active / suspected endocrine disruptors are used in the manufacture of everyday items. In many cases, the European Union has taken precautionary measures to reduce the exposure of the most vulnerable members of society. Other governments have also taken action to reduce exposure to these substances. While human beings have evolved in an environment where they are exposed to natural endocrine active substances, the concern is now increased exposure to synthetic chemicals which are endocrine active and potentially endocrine disruptors.

The table below provides details on some of these.

	Uses	What's being done?
Phthalates	Mainly used in PVC plastic. PVC is used in a wide range of items, including food packaging, toys, building materials and medical devices.	Several phthalates are now being phased out in Europe. The use of phthalates in toys has also been restricted.
Bisphenol A (BPA)	BPA is used in the manufacture of polycarbonate plastic which can be found in re-usable kitchenware (plates, mugs etc.). It is also used to produce epoxy resins in the inner lining of food and drink cans.	BPA is not permitted to be used in baby bottles in the EU. Several countries have put in place similar restrictions. Also from 2020 it use in thermal paper is banned.

Parabens	Parabens are a group of chemicals used primarily in cosmetics as preservatives. They prevent bacterial growth.	Since January 2014, certain parabens have not been permitted in cosmetics in the EU. (isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben) Others (Methyl, ethyl, propyl and butyl) are still widely used in cosmetics and since 2020 are being reviewed in the EU. However, paraben-free cosmetics are also widely available.
Flame Retardants	Flame retardants are chemicals that are used in the manufacture of items such as furniture and electronics to make them less flammable.	There have been concerns about the health effects of some flame retardants which are suspected endocrine disruptors. The most potentially hazardous flame retardants have now been banned in the EU. These include specific Brominated organo halogen flame retardants. Older furniture may still contain these.
Dioxins	Dioxins are chemicals that are made unintentionally and released into the environment in certain circumstances during combustion, e.g., from incinerators.	Our exposure to dioxins has decreased significantly over the last 20 years following the introduction of environmental legislation.
Pesticides	Pesticides are used to protect plants and crops from pests. They are important for our food security. However, quite a few chemicals that have been used as pesticides are suspected endocrine disruptors.	The latest EU legislation says that pesticides which are considered to be endocrine disruptors will not be approved for use.
Biocides	Biocides are chemical substances or microorganisms intended to destroy, deter, render harmless, or exert a controlling effect on any harmful organism.	The latest EU legislation says that biocidal active ingredients which are considered to be endocrine disruptors will not be approved. Although there may be derogations in very limited cases.
Naturally Occurring	There are many naturally occurring chemicals which would fall under the definition of endocrine disruptor. Phytoestrogens are naturally occurring oestrogens, e.g., isoflavones which are found in soya beans.	Most of us probably regularly eat naturally occurring oestrogens with no harmful effects. However, some experts suggest that babies and infants should not be fed exclusively with soya milk as a precaution.

What's being done?

As previously emphasized, there is still a great deal of uncertainty surrounding this subject. The risk (and its extent) is still largely unknown. However, in many cases where there is a perceived higher risk, action has been taken by the European Union and others to reduce our exposure.

Under the EU REACH regulations SVHC (Substances of Very High Concern) are identified and added to a candidate list. The data on these substances is then reviewed at EU level to identify what restrictions are required to limit human exposure. This list is primarily for Carcinogen, Mutagens and Reproductive toxicants, but Endocrine Disrupting chemicals are also included as "substances of equivalent concern". This can then result in either specific Restrictions of their use or for an Authorisation process for specific limited uses by specific companies, which have to be renewed every few years. This is only where substitutes are not available, the UK adopted a similar approach following the end of the Brexit transition period, from January 2021 but may potentially take a different view than the EU in the longer term.

Many scientists and campaigners have called on various governments to take precautionary action and restrict or ban the use of many suspected endocrine disruptors. (Kortenkamp et. al. 2011) The EU takes this approach with suspected Endocrine Disruptors being placed on the SVHC candidate list for expert review.

Other groups of experts have called on governments to take a risk-based approach using the best possible science and implementing due precaution in risk management measures. This is because they feel that there are issues and complexities with the scientific evidence and that the banning or restricting of endocrine active chemicals would not be justified or proportionate. Chemicals shown to be endocrine disrupting according to the WHO definition, causing adverse effects in an intact organism, would need to be appropriately risk managed. The Royal Society of Chemistry has published a Policy Position supporting a risk-based evidence informed approach to regulation of EDCs (RSC 2020)

Some experts are also concerned about the potential risks associated with replacing suspected endocrine disruptors with chemicals that we know much less about in terms of safety.

However, despite the controversy within the scientific community, it seems likely that in future further legislation will be put in place to ensure that the substances of concern are adequately regulated and the products on the market can continue to be safely used. There is ongoing international research to enable a fuller understanding of the risk from Endocrine Disrupting chemicals to both human health and wildlife.

RSC INTEREST GROUP TOXICOLOGY

Further Reading

Lamb James C., IV, Paolo Boffetta, Warren G. Foster, Julie E. Goodman, Karyn L. Hentz, Lorenz R. Rhomberg, Jane Staveley, Gerard Swaen, Glen Van Der Kraak, Amy L. Williams. Critical comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012. Regulatory Toxicology and Pharmacology 69 (2014) 22–40. https://www.sciencedirect.com/science/article/pii/S0273230014000269?via%3Dihub

Kortenkamp A, Martin O, Faust M, Evans R, McKinlay R, Orton F, et al. State of the Art Assessment of Endocrine Disruptors. Final Report.(2011). http://ec.europa.eu/environment/endocrine/documents/4_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs Jr., D.R., Lee, D.H., Shioda, T., Soto, A.M., Vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose. Endocr Review 2012 June; 33(3) 378-455 Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses (nih.gov)

WHO (World Health Organization) International Programme on Chemical Safety. Global Assessment of the State-of-the-Science of Endocrine Disruptors. Geneva:World Health Organization. (2002). Available: http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

WHO (World Health Organization)/UNEP (United Nations Environment Programme) The State-of-the-Science of Endocrine Disrupting Chemicals - 2012 (Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, eds). Geneva:UNEP/WHO. (2013). Available: http://www.who.int/ceh/publications/endocrine/en/index.html

RSC (Royal Society of Chemistry) Policy Position: Risk-based Regulation for Endocrine Disrupting Chemicals (EDCs) 2020. . https://www.rsc.org/globalassets/04-campaigning-outreach/policy/policy/environment-health-safety-policy/edc-policy-position-final-sep-2020.pdf

This text was originally produced by a working party of the Environment, Health and Safety Committee (EHSC) of the Royal Society of Chemistry. This updated version was prepared by the RSC Toxicology Group Committee in June 2022. This document does not represent an official opinion or policy position of the Royal Society of Chemistry. The information in this publication is intended to be an introduction into this topic and is not exhaustive, and was correct at the time of publication. The RSC Toxicology Group Committee accepts no liability for actions taken on the basis of the information in this document.

For more information on the RSC Toxicology Group, please visit https://www.rsc.org/membership-and-community/connect-with-others/through-interests/interest-groups/toxicology/