Bundesinstitut für Risikobewertung

Questions and answers on endocrine disruptors

BfR FAQ of 17 March 2022

Consumers are routinely exposed to a plethora of substances, some of which may have undesirable effects on our health. This includes substances that disrupt the body's hormonal system (endocrine system), hence triggering detrimental health effects. These are referred to as endocrine disruptors or endocrine-disrupting substances.

Endocrine active substances may be encountered in all areas of daily life, both from natural and synthetic sources. Some of them are considered to be harmful to health hence called endocrine disruptors. The substances are regulated based on their potentially harmful activity, for example by imposing restrictions or bans on their use.

The German Federal Institute for Risk Assessment (BfR) has put together an FAQ concerning endocrine disruptors.

What are endocrine disruptors?

Multiple functions in humans and animals are controlled by specific messenger substances which we refer to as hormones. Together with the hormone producing and receiving tissues, this hormone system is called the endocrine system. The endocrine system controls different body functions such as temperature, water and salt balance, blood pressure, metabolism, the neuronal system as well as reproduction and development.

The regulation of blood glucose by the hormones insulin and glucagon is a well-known example. When the blood glucose level increases after a meal, the pancreas releases the hormone insulin which in turn decreases the blood sugar concentration. On the other hand, if the blood glucose level falls below the regular value, glucagon is released to mobilise existing reserves, resulting in a blood glucose increase.

The World Health Organisation (WHO) defines endocrine disruptors 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*.".

With this adverse outcome emphasised in the definition, endocrine disruptors differ from those substances which may or may not have an impact on the hormone system but do not disrupt the system in the long term. For example, the body can counteract against the effects of such substances as part of its homeostatic control mechanisms, or the impact is so slight that no harm is done or the effect may even be desirable. This means that not every substance acting on the hormone system is an endocrine disruptor. For a substance to be classified as an endocrine disruptor, it must have an adverse effect that cannot be compensated.

How do endocrine disruptors work?

Endocrine disruptors may influence the hormone system in different ways.
Some endocrine disruptors act directly by binding to a hormone receptor, where they mimic the effect of a hormone produced by the body. Other endocrine disruptors block hormone receptors directly or indirectly or alter their binding properties for their natural hormones, affecting the activity of the hormone.

In addition, other endocrine disruptors interfere with the synthesis, degradation, and/or elimination of hormones, and the transport of hormones in the body may be disturbed as well. Thus, endocrine disruptors either directly affect the corresponding hormone receptors or indirectly influence hormone (bio)availibility and/or concentration or the number of the cognate receptors in the body's target organs.

Due to many different existing mechanisms of action and hormonal systems, endocrine disruptors can hardly be characterised only by looking at a target effect or the chemical structure of the trigger substance, but rather by their mechanism of action and/or specific effects. What these mechanisms all have in common is that a hormonal system is functionally impaired from the outside and may be permanently disrupted. Accordingly, when considering possible endocrine disruptors, it is always investigated whether possible adverse/harmful health effects occur or not, and in which hormonal systems they are observed (thyroid, sexual hormones, etc.).

Which substances have the ability to interfere with the hormone system?
The endocrine systems in humans and animals may be affected by a plethora of naturally occurring or synthetic substances. Examples of natural, endocrine active substances include some secondary phytochemicals such as soybean or clover isoflavones, which among other things have oestrogenic effects. Many natural substances contained in our food possess potentially endocrine active properties which, however, does not necessarily mean that they act as endocrine disruptors; whether they do so substantially depends on the dose, similar to other toxins.

Additionally, there are drugs which specifically target elements of the hormone system or which are hormones themselves, e. g. the synthetic sexual hormone ethinylestradiol, which is used in contraceptive products. As for other substances, disturbances of the hormonal system are an unintentional secondary effect. The best-known synthetic substances with endocrine activity include components of plastic materials such as bisphenol A or softeners such as certain phthalates. Surfactants like nonylphenol or some flame retardants of the group of polybrominated diphenylethers or polychlorinated biphenyls (PCBs) or different pesticides and preservatives (butyl paraben) may also have different effects on the hormone system.

How can endocrine disruptors be identified?
Endocrine disruptors are identified through information about the mechanism of endocrine action as well as by observed harmful effects on organ systems and functions. This is typically based on obligatory animal studies within the framework of:

- the approval process for active substances in plant protection and biocidal products,
- the REACH Regulation for industrial chemicals, and
- other regulatory areas covering toys, food contact materials, and medical devices

In this context, it is important to demonstrate an adverse effect, which occurs as a consequence of endocrine activity.
In principle, this involves systematic checks for effects that point to possible endocrine-disrupting properties. This may include, for instance, the development of tumours in endocrine tissues or reduced reproductive capacity. In addition, the mechanism of action underlying these effects is explored in so-called mechanistic studies which typically rely on different cell culture systems. However, up to now, mainly mechanistic tests exist that identify the impact of substances on the sexual hormone system.

A scientific guideline (EFSA/ECHA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009) jointly prepared by the European Food Safety Authority (EFSA) and the European Chemical Agency (ECHA) deals with analysing the endocrine active potential of active substances in plant protection products and biocides. This is complemented by the OECD's general summary (Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption) of standardised methods used to detect endocrine disruptors. These include a multitude of techniques ranging from cell culture systems (*in vitro*) and animal models (*in vivo*) to computer-assisted computation methods (*in silico*).

Harmonised criteria for the identification of endocrine disruptors are currently under development at the European level, the aim being to allow a uniform assessment irrespective of the regulatory context in which a substance is considered, according to the principle "one substance – one assessment". It is intended that more and more alternative methods to animal experiments are to be used in the future when identifying endocrine disruptors, in an effort to minimise animal experiments or substitute them altogether. However, this remains a challenging task due to the lack of mechanical tests and also the complex nature of the endocrine system.

How are endocrine disruptors taken up?
Endocrine disruptors can enter the body in different ways: via food (which is referred to as oral uptake), via the skin (dermal uptake), and, in rare cases, by breathing (inhalation).

What should be kept in mind when discussing the health effects of endocrine disruptors?
The current public debate is mainly focused on substances that interfere with the sexual hormone system or the thyroid hormone system. Another point of debate is possible carcinogenic or obesity-promoting effects of certain endocrine disruptors.

Observations from epidemiological studies are often the focus of discussion. These observational studies analyse larger populations with respect to disease or other negative health effects, and possible causes thereof are investigated. However, it is usually difficult or impossible to prove clear cause-effect relationships between certain substances and an effect. This raises the question if the study findings are indeed based on a specific substance or if there may be other causes as well (such as alcohol consumption or nutrition). The frequency of a particular finding coinciding with a theoretical or established presence of a substance does not necessarily suggest a causal connection. As a general rule, additional mechanistic (*in vitro*) studies are therefore required to determine endocrine disruptors and their effects.

How is the risk of endocrine disruptors to consumer health assessed?
The health risk, i.e. the probability of adverse effects caused by endocrine disruptors to the hormonal system, depends on the endocrine-disrupting properties of a substance, its potency, efficacy, and effectiveness but also on the degree of uptake. The decisive factor for the assessment is the exposure (dose), i.e. the extent to which a person comes into contact with an endocrine-disrupting substance. The health risk is determined individually for every substance.

How are consumers protected from health hazards posed by endocrine disruptors?
Endocrine disruptors are regulated in different areas at the EU level in an effort to prevent risks to human health and the environment. Specific measures or options for the identification, assessment, and management of endocrine disruptors are provided in the legislation for

plant protection products and biocidal products, as well as for chemicals in general under the REACH Regulation, regulations covering cosmetics, regulations for medical devices, and the Water Framework Directive. Where a synthetic substance is found to have endocrine disrupting properties that substance will be subject to regulation in accordance with the applicable statutory provisions in the EU. Moreover, most of the potential health effects of endocrine disruptors are, in principle, also covered and regulated by existing regulations, regardless of whether the trigger substance actually is an endocrine disruptor or not. This includes substances that are potentially carcinogenic or toxic to reproduction or which interfere with development. Therefore, there is already a very high level of protection for consumers and the risk of taking up a harmful amount of a substance classified as an endocrine disruptor is low. For plant protection products and biocidal products, the endocrine-disrupting properties are examined and assessed during the approval procedure. If the active substance is determined to be an endocrine disruptor, this constitutes an exclusion criterion (so-called "cut-off" criterion), meaning the active substance will be denied approval. This is unless it can be shown that exposure to that active substance is negligible or that a biocidal product is required to avert serious threats to humans and animals or the environment.

The REACH Regulation provides a framework for the assessment of risks posed by endocrine disruptors to humans and the environment, and their incorporation in consumer products (including mixtures and manufactures) thus endocrine disruptors can be subject to limitations or bans based on an Annex XVII restriction. These restrictions can then be applied to all products on the European market. Endocrine disruptors may also be identified as substances of very high concern (SVHC). Uses of endocrine disruptors identified as SVHC are, therefore, i.e. after inclusion in Annex XIV of the REACH Regulation, subject to approval for all European manufacturers / users. On top of this, the European Chemicals Agency (ECHA) is required to assess the need for and initiate a restriction of the incorporation in consumer products, which includes also all imported goods.

Consumer products such as children's toys are analysed for such substances in order to protect consumers from the harmful effects of endocrine disruptors. For food contact materials, maximum quantities of release from such materials are derived and characterised to be not harmful to human health (migration limit values). No health impairments are expected as long as these values are not exceeded.

The risk assessment carried out by the Scientific Committee for Consumer Safety of the European Commission (SCCS) on cosmetic products, too, takes endocrine-disrupting effects into account. Since 2019, substances used in cosmetic products which are suspected to have endocrine effects are re-evaluated with an eye specifically to these potential endocrine effects.

Which activities currently undertaken by the BfR with regard to endocrine disruptors?
The BfR has long been involved in the development of methods for identifying endocrine disruptors and their effects, in which it has worked with other public authorities and research institutes both at the EU and global level. As a scientific institution of the federal government, the BfR is represented in a number of national and international expert panels dealing with endocrine disruptors.

The BfR uses strict standards in its risk assessments in a bid to ensure a high level of consumer health protection and safety of the use of substances.

How is public awareness raised of identified endocrine disruptors?
This may be through publications or press releases or generally via databases or registries.

As for plant protection agents and foodstuff contact materials, the assessment result is published in the EFSA journal (https://efsa.onlinelibrary.wiley.com) of the European Food Safety Authority.

For biocidal agents, the assessment result can be found in the statements of the Biocidal Products Committee (https://echa.europa.eu/de/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval).

The status of the assessment of endocrine disruptors and of substance assessments under the REACH regulation, as well as the information on whether the ECHA's Expert Group on Endocrine Disruptors has already looked at a biocidal agent and released a statement is published in the "Endocrine disruptor assessment list" of the European Chemicals Agency (ECHA).

The ECHA website "Endocrine Disruptor Lists", which is also publicly accessible, informs stakeholders about substances identified as endocrine disruptors or under investigation for endocrine-disrupting properties. Information on the regulation of select endocrine disruptors is provided on the website of the European Chemicals Agency (ECHA) under the procedures Restrictions, SVHC identification and Annex XIV to the REACH Regulation.

Further information on endocrine disruptors and hormone-like substances on the BfR website

Endocrine disruptors - some publications

https://www.bfr.bund.de/en/a-z_index/endocrine_disruptors_and_hormone_like_substances-130013.html

BfR “Statements app”

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the federal states (‘Länder’) on questions of food, chemical and product safety. The BfR conducts independent research on topics that are closely linked to its assessment tasks.