



Scientific Facts on Methods for the assessment of endocrine disruptors

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Level 2 - Details on Methods for the assessment of endocrine disruptors

1. **What are endocrine disruptors?.....2**
2. **What kind of substances can interfere with the endocrine system?.....2**
3. **Are there specific issues with the evaluation of endocrine disruptors?.....3**
4. **Are there specific criteria to define endocrine disruptive effects?3**
5. **Are there doses below which no endocrine effects are observed?.....4**
6. **How is the potential hazard of a chemical to act as an endocrine disruptor evaluated?4**
7. **What are the recommendations of the Scientific Committee regarding testing of endocrine disruptors?4**
8. **How can risk and level of concern be determined for endocrine disruptors?5**

This is a faithful summary of the leading report produced in 2013 by the European Food Safety Authority (EFSA):
"The scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment."

The full Digest is available at: <https://www.greenfacts.org/en/evaluation-endocrine-disruptors/>

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- Each question is answered in Level 1 with a short summary.
- These answers are developed in more detail in Level 2.
- Level 3 consists of the Source document, the internationally recognised scientific consensus report which is faithfully summarised in Level 2 and further in Level 1.

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1. What are endocrine disruptors?

Three specific questions were asked by the European Commission to the European Food Safety Authority, namely:

- What scientific criteria should be used to identify Endocrine Disruptors?
- What is an adverse effect and how can it be distinguished from physiological modulation?
- Are the existing toxicity testing methods appropriately covering the effects of endocrine active substances?

The opinion expressed is based on an extensive review of available information, including the recent „State of the Art Assessment of Endocrine Disruptors“ (Kortenkamp et al., 2011) report.

2. What kind of substances can interfere with the endocrine system?

The endocrine system is composed of various glands and organs in the body that play various roles in maintaining the good physiological status of the body. It includes for instance the adrenal glands, the thyroid, the testes and ovaries. The endocrine system influences almost every cell, organ, and function of an organism. It regulates, with the use of numerous molecular messengers, various vital functions such as metabolism, growth and development, tissue function, or mood, from conception through adulthood and into old age. This includes for example the development of the brain and nervous system, the growth and function of the reproductive system, or the regulation of blood sugar level.

The endocrine system can be, and often is affected by external factors.

A range of synthetic as well as naturally-occurring substances have been identified as interacting with the endocrine system. If the interaction of these external substances with the endocrine system leads to health problems in an intact organism or its offspring, these substances are referred to as “endocrine disruptors” (EDs). Overall, endocrine effects become adverse either by causing a biological response that goes outside of the natural range, or by changing the speed at which an organism goes through a transition phase (by accelerating or delaying sexual maturation, for instance). Meanwhile, the point at which endocrine modulation becomes an adverse effect cannot be determined on the basis of an absolute response value, but on the basis of a relative response (compared to the control/background response). The Scientific Committee is therefore of the opinion that, since “adversity” is the criteria for identifying a substance as an Endocrine Disruptor, it is necessary to determine when an interaction with the endocrine system becomes an adverse effect.

For this purpose, a substance that can interact or interfere with the endocrine system resulting in a biological effect, but not necessarily an adverse effect is defined as an endocrine active substance (EAS). Through that definition, by having an endocrine activity, it does not mean that a substance poses a toxicological or eco-toxicological hazard in itself. However, through this mode of action, it can potentially lead to adverse outcomes (endocrine disruption), and it is the hazard that needs to be assessed.

3. Are there specific issues with the evaluation of endocrine disruptors?

Many substances released into the environment through human activity can potentially interfere with the endocrine or hormonal systems of animals and humans. Such endocrine active substances (EASs) include synthetic drugs, pesticides, compounds used in industry and in consumer products, industrial by-products and pollutants, including some metals.

There is also a large number of substances of natural origin that can interact with the endocrine system. These substances occur in plants consumed as food or feed, and also as contaminants from fungi that may be present in food and. Examples of naturally occurring EASs are oestrogenic compounds in soy (e.g. genistein and daidzein), mycotoxins (e.g. zearalenone) in cereals, goitrogens in cabbage, which has the potential to inhibit iodine uptake (glucosinates), and glycyrrhizin in liquorice which has the potential to disturb the salt and water balance in the body.

The endocrine system includes reproduction and development regulation, as well as the regulation of the metabolism, and also all the signaling and regulating factors that influence it. The vast number of hormonal or signaling factors is divided into 5 major classes: amino acid derivatives, small neuropeptides, large proteins, steroid hormones and vitamin derivatives. Any molecule that resembles one of those compounds has the potential to disturb the endocrine system in an organism.

This is because the endocrine system functions, like many other systems in the body, in a 'lock and key' model, where a signaling molecule – in this case an hormone – is 'recognized' by a cellular structure named "a receptor " by fitting in it. For many hormones, these receptors are at the surface of the cells, and the biochemical message they carry tells the cell to do something specific, from growing to producing a specific compound, or to any of a myriad of functions a cell can accomplish. Any compound that either fits the « lock » instead of the hormone or prevents the 'key' from entering the lock e.g. by masking it, can potentially disturb the system by sending a false signal, or by preventing a signal from reaching its intended target.

4. Are there specific criteria to define endocrine disruptive effects?

Scientific criteria for what constitutes an "adverse effect" have not been defined in a standard way, the criteria for distinguishing between substances that are endocrine disruptors (EDs) and other groups of substances with different modes of action are also not well defined.

For the purpose of this assessment, the Scientific Committee is using the working definition of an endocrine disruptor set by the WHO/IPCS:

"An endocrine disrupter 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."

This definition implies:

- the presence of an adverse effect in an intact organism or a population;
- the presence of an endocrine activity (oestrogenic, androgenic, thyroid or steroidogenic) ;
- the presence of a plausible causal relationship between the two.

In general, but not always, transient, inconsistent and minor fluctuations at the biochemical and molecular level may be considered as being "normal" adaptations and, as such, non-adverse. However, changes at the cell-, organ-, organism-, or population-level resulting

in pathology or functional impairment as well as altered timing of development, may be considered as "adverse. In principle, no single assay is likely to provide all the information needed to decide whether a substance is an endocrine disruptor because of the need to provide information both at the cellular and molecular level, as well as on the reaction of the whole body. An expert judgment is required to assess on a case-by-case basis the health and environmental relevance of changes at the molecular, body or even population levels following exposure to an endocrine active substance.

5. Are there doses below which no endocrine effects are observed?

For most toxic substances, it is generally assumed that there is an amount below which there will be no biologically significant effect. It is assumed that the natural processes in the body and in cells can deal with this substance if its concentration is below this level, called the 'threshold'. For instance, since there are many receptors for a given hormone on the surface of a cell, it would be logical to think that it takes a certain amount of a disruptive substance to occupy the receptors and block the hormone's activity. However, most effects on the endocrine system happen at much lower concentrations than other toxic effects, and the current experimental approaches are not sensitive enough to detect the existence of these thresholds. Furthermore, when a large group of people is studied, the variation from one person to the other hides the possible threshold effect. For many potential endocrine disruptors, the exact mechanism of action is not known, and this complicates even more the determination of the presence or not of a threshold concentration below which there would be no effect on the body.

6. How is the potential hazard of a chemical to act as an endocrine disruptor evaluated?

There are a number of standard methods that have been compiled by the OECD into a "Conceptual Framework" which includes the currently available test methods, as well as those that are under development for the evaluation of chemicals for endocrine activity or disruption. These tests include computer models, as well as laboratory tests.

The Scientific Committee reviewed the current tests and concluded that a reasonably complete suite of standardised assays is available for testing the effects of endocrine active substance in mammals and fish (specifically for substances that mimic or disrupt the effect of oestrogens, androgens, thyroid and steroid hormones), with fewer tests being available for birds and amphibians.

The report however considers important to recognise that standardised assays for other parts of the endocrine system are not yet available and that a range of major groups of animals, such as reptiles, have not yet been considered by OECD for the development of any endocrine assays.

7. What are the recommendations of the Scientific Committee regarding testing of endocrine disruptors?

The Scientific Committee identified the need for further development of screening and testing methods as well as of strategies that will generate the data needed for the identification and assessment of endocrine disrupting properties. This is needed in particular for endocrine mechanisms that lie outside of the well-studied so-called "EATS » (Oestrogenic/Androgenic/Thyroid/Steroidogenic) systems.

A number of general issues related to the testing of substances have also been identified:

- current tests on mammals may not cover effects that could be induced by exposure during early development but may emerge during later life stages, even if fish lifecycle tests cover all relevant windows of exposure and can be expected to reveal the longer-term effects of developmental exposures at all stages of the lifecycle;
- combined exposure to multiple endocrine active substances could occur in such a way that combined toxicity could arise;
- the lack of consensus in the scientific community with regard to the existence and/or relevance of low-dose effects and threshold effects in connection with endocrine activity and endocrine disruption.

The Committee recommends, as a follow up activity, to clarify in a broader context the issues of biological thresholds and of criteria for 'adversity', as well as of combined exposure to multiple substances.

8. How can risk and level of concern be determined for endocrine disruptors?

The Scientific committee is of the opinion that risk management should be based on the effect that arises at the lowest concentration, no matter what the mode of action is.

The opinion of the committee is thus that for their risk assessment, EDs can be treated like most other substances of concern for human health and the environment. But, it adds that the level of concern is not determined exclusively by risk assessment but also by protection goals set by the risk management.