What is an endocrine disruptor (ED) and how are EDs identified?

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Endocrine disruptors (ED) - definition

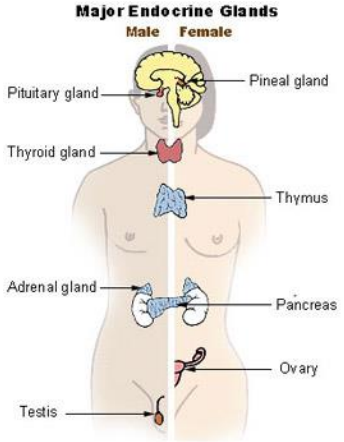
Endocrine disruptors are exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations.

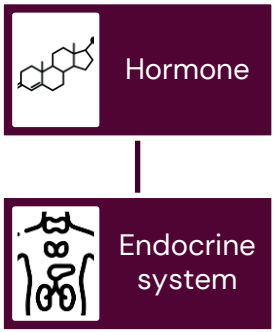
- WHO/IPCS 2002

Definition also adopted by the EU.

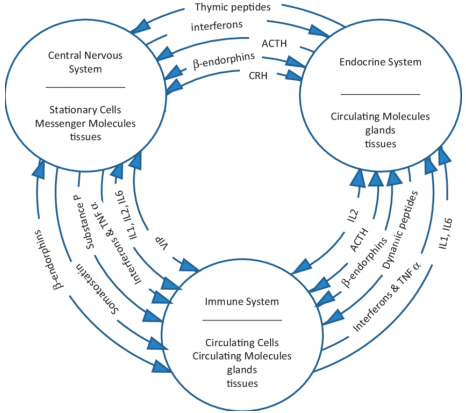
Definitions of hormones and endocrine system

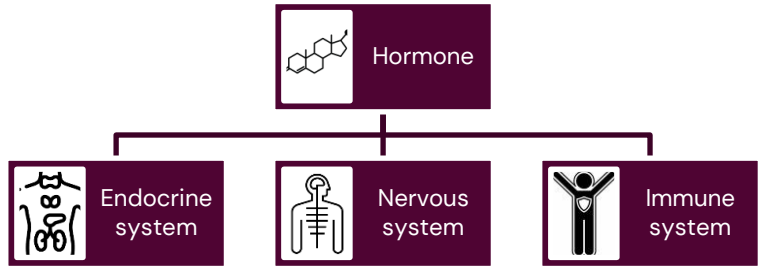
- *"A hormone is a substance produced by **glands** with **internal secretion**, which serve to carry **signals** through the **blood to target organs**."*
  – **Ernest Henry Starling** (1905)





- *"Any **substance** released by a cell that **acts on another cell near or far**, regardless of the singularity or ubiquity of the source, and **regardless of means of conveyance**."*
  – **Bahadoran** *et al.* (2019)





ED mechanisms

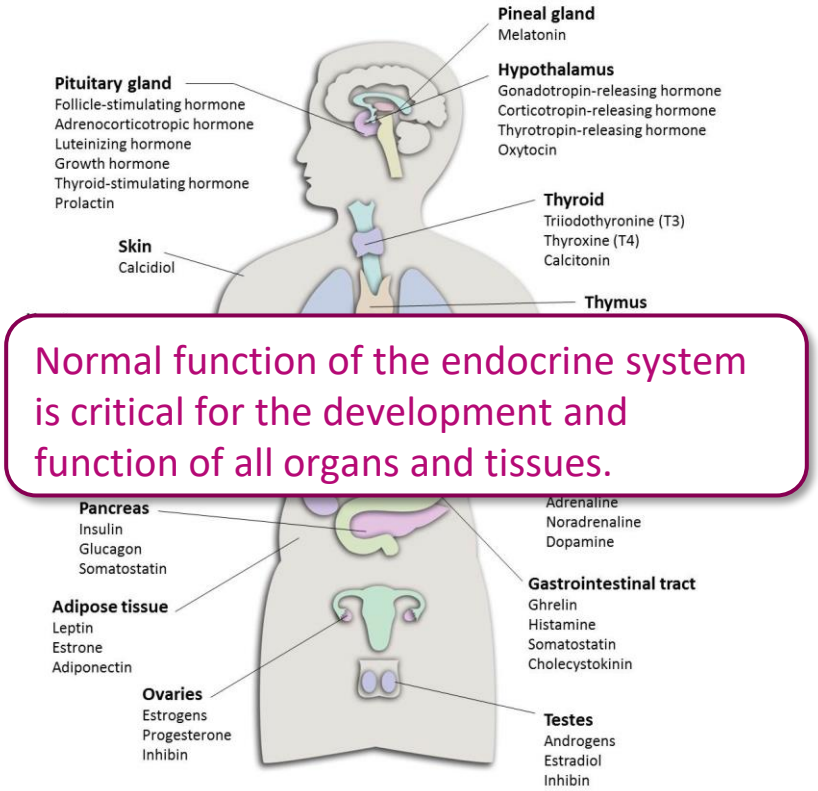
- Interactions with hormone receptors – agonsim or antagonism
- Interference with hormone production, transport, or metabolism

Pathways/modalities

- → Estrogen
- → Androgen
- → Thyroid
- → Steroidogenesis
- → Many more!

”EATS”

EDs can cause serious and varied health effects



Normal function of the endocrine system is critical for the development and function of all organs and tissues.

- Effects on development and function of the female and male reproductive systems
  - → E.g. oocyte development, estrous cyclicity, poor sperm quality, hypospadias, cryptorchidism
- Effects on neurodevelopment
- Cardiovascular disease
- Metabolic disorders
- Bone disorders
- Immune function and disease

Strict EU regulation

REACH (2006)

- endocrine disrupting chemicals are considered of similar regulatory concern as substances of very high concern

Plant protection products and biocides (2009/2012)

- endocrine disrupting chemicals shall not be approved unless exposure is negligible

Classification, Labeling and Packaging (CLP) (2023)

- ED hazard classes (human health and environment)

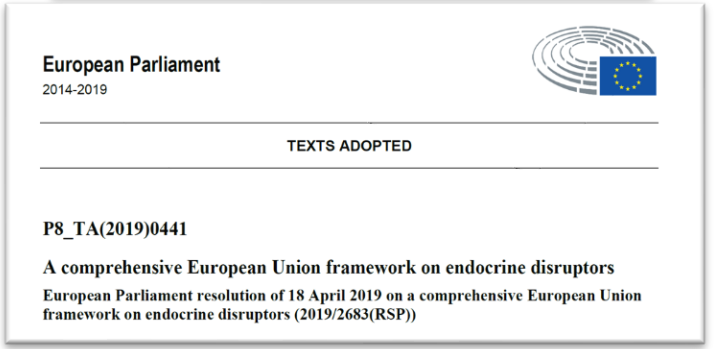
Note: no ED hazard class in the Globally Harmonized System for Classification and Labelling of chemicals (GHS)


EUROPEAN COMMISSION

Brussels, 7.11.2018
COM(2018) 734 final

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Towards a comprehensive European Union framework on endocrine disruptors


European Parliament
2014-2019

TEXTS ADOPTED

P8_TA(2019)0441

A comprehensive European Union framework on endocrine disruptors

European Parliament resolution of 18 April 2019 on a comprehensive European Union framework on endocrine disruptors (2019/2683(RSP))

Criteria for identification of ED and regulation in the EU

- Implemented for **biocides** (Regulation (EU) No 2017/2100) and **plant protection products** (Regulation (EU) No 2018/605) in 2018, and for **CLP** in April 2023.
- Based on the WHO/IPCS definition.
- In general, a substance is an ED if it meets the following criteria:

1. it is known to cause an **adverse effect** in an intact organism, its offspring, future generations
2. it has **endocrine activity**
3. there is a **biologically plausible link** between the endocrine activity and the adverse effect

Toxicity testing to identify EDs

OECD Conceptual Framework (OECD 2018)

Focus on EATS pathways

Level 1 Existing data, non-test methods	Physical and chemcial properties, existing (eco)toxicity data (e.g. scientific literature), *in silico* predictions (read-across, QSAR)
Level 2 *In vitro* assays for selected pathways	Estrogen and androgen receptor bindning assays, receptor transactivation assays (OECD TG 455, 458), steroidogenesis assay (OECD TG 456), aromatase assay (OPPTS 890.1200), US EPA ToxCast estrogen receptor pathway model*, newly validated thyroid assays*
Level 3 *In vivo* assays for selected endocrine mechanisms	Uterotrophic Assay (OECD TG 440), Hershberger assay (OECD TG 441), amphibian metamorphosis assay (AMA) (OECD TG 231)
Level 4 *In vivo* methods for endocrine-related adverse effects	Repeated dose toxicity (OECD TG 407, 408), prenatal development (OECD TG 414), Combined chronic toxicity and carcinogenicity studies (OECD TG 451-453), Reproduction/developmental toxicity screening test (OECD TG 421), Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), Developmental neurotoxicity study (OECD TG 426), pubertal development in male and female rats (OPPTS 890.1500, OPPTS 890.1450)
Level 5 *In vivo* methods for adverse effects in more complex endpoints	Extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443), Two-generation reproduction toxicity study (OECD TG 416)

*validated after 2018

WoE

Supports assessment of endocrine activity

Biologically plausible link?

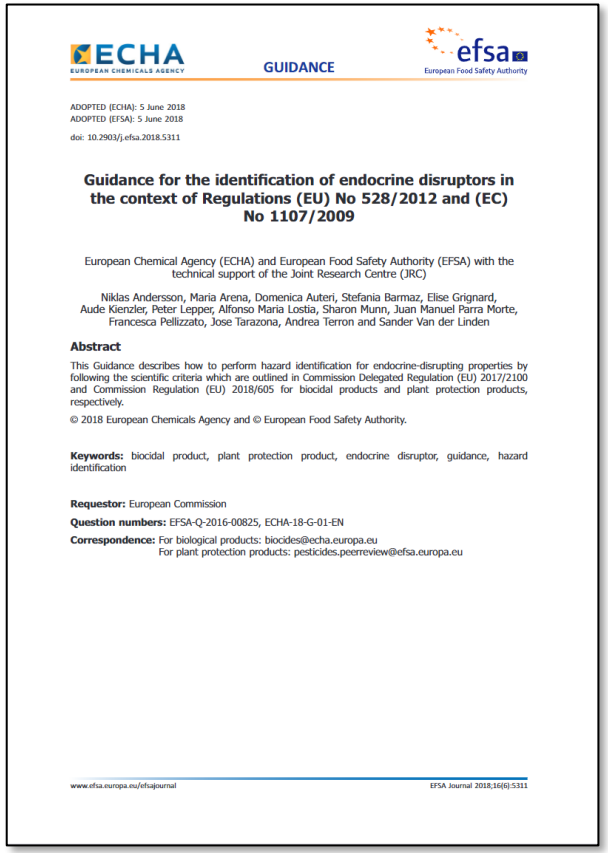
WoE

Supports assessment of adversity

Expert judgment!

OECD Guidance document 150 (2018). https://doi.org/10.1787/9789264304741-en.

Guidance



ECHA EUROPEAN CHEMICALS AGENCY

GUIDANCE

efsa European Food Safety Authority

ADOPTED (ECHA): 5 June 2018
ADOPTED (EFSA): 5 June 2018

doi: 10.2903/j.efsa.2018.5311

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Niklas Andersson, Maria Arena, Domenica Auteri, Stefania Barmaz, Elise Grignard, Aude Kienzler, Peter Lepper, Alfonso Maria Lostia, Sharon Munn, Juan Manuel Parra Morte, Francesca Pellizzato, Jose Tarazona, Andrea Terron and Sander Van der Linden

Abstract

This Guidance describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

Keywords: biocidal product, plant protection product, endocrine disruptor, guidance, hazard identification

Requestor: European Commission

Question numbers: EFSA-Q-2016-00825, ECHA-18-G-01-EN

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ECHA EUROPEAN CHEMICALS AGENCY

GUIDANCE

Guidance on the Application of the CLP Criteria

Part 3: Health Hazards

Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures

Version 5.0
Nov 2024

ECHA EUROPEAN CHEMICALS AGENCY

GUIDANCE

Guidance on the Application of the CLP Criteria

Part 4: Environmental hazards
and
Part 5: Additional Hazards

Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures

Version 4.0
Nov 2024

Reflections

- A high level of evidence is required to identify a substance as ED
- Extensive animal data on complex endpoints needed
- Identification of non-EATS EDs?

- ”next generation” assessment of EDs, reducing the need for animal tests, *equivalent predictive capacity*

IMM seminar, 12 December, 13.00.
Information and registration:
https://news.ki.se/calendar/towards-next-generation-assessment-and-identification-of-endocrine-disruptors

Open Research Europe
Open Research Europe 2024, 4:68 Last updated: 14 JUN 2024

Check for updates

OPEN LETTER

Enhanced identification of endocrine disruptors through integration of science-based regulatory practices and innovative methodologies: The MERLON Project [version 1; peer review: 2 approved]

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Thank you for your attention

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