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New CLP hazard classes for endocrine disrupting properties for human health

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Overview

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- CLP classification criteria for EDs human health for substances and mixtures
- Hazard communication
- ECHA guidance on application of CLP criteria for ED HH classification and specific concepts to consider

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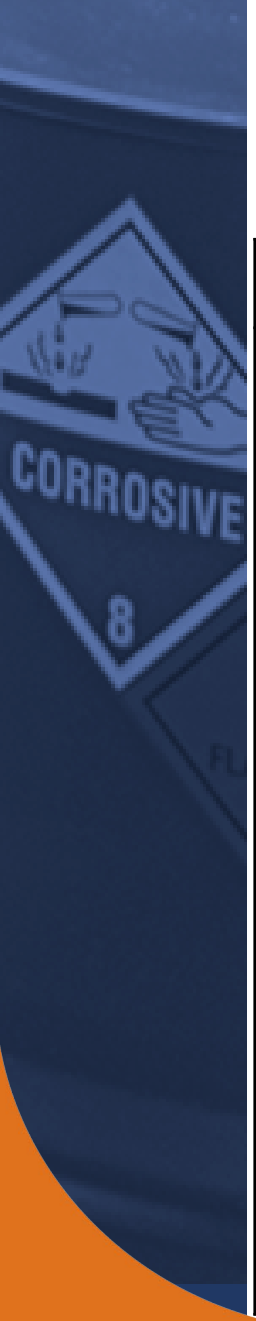
ED HH Classification Criteria

ED HH classification criteria in CLP Annex I Table 3.11.1; Category 1 (ED HH1)



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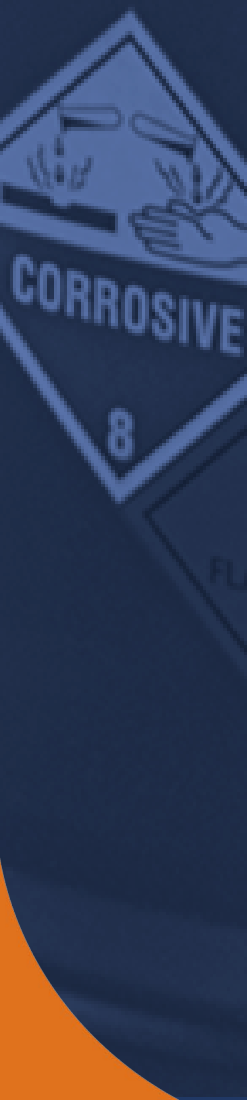
Category	Criteria
CATEGORY 1	**Known or presumed endocrine disruptors for human health** The classification in Category 1 shall be largely based on evidence from at least one of the following: a) human data; b) animal data; c) non-animal data providing an equivalent predictive capacity as data in points a or b. Such data shall provide evidence that the substance meets all the following criteria: a) endocrine **activity**; b) an **adverse effect** in an intact organism or its offspring or future generations; c) a **biologically plausible link** between the endocrine activity and the adverse effect. However, where there is information that raises serious doubts about the relevance of the adverse effects to humans, classification in Category 2 may be more appropriate.

ED HH classification criteria in CLP Annex I, Table 3.11.1; Category 2 (ED HH2)



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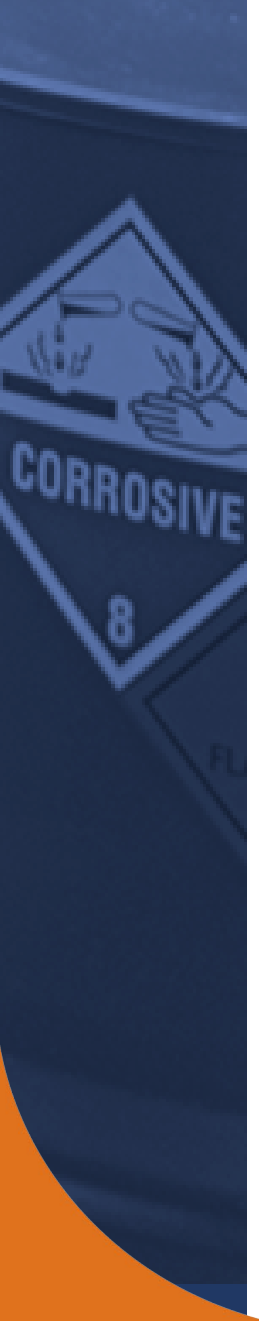
Category	Criteria
CATEGORY 2	**Suspected endocrine disruptors for human health** A substance shall be classified in Category 2 where all the following criteria are fulfilled: a) there is evidence of: i. an endocrine **activity**; and ii. an **adverse effect** in an intact organism or its offspring or future generations; b) the evidence referred to in point (a) is not sufficiently convincing to classify the substance in Category 1; c) there is evidence of a biologically plausible link between the endocrine activity and the adverse effect



CLP Annex I, Table 3.11.2. Generic concentration limits of components of a mixture classified as endocrine disruptor for human health that trigger classification of the mixture

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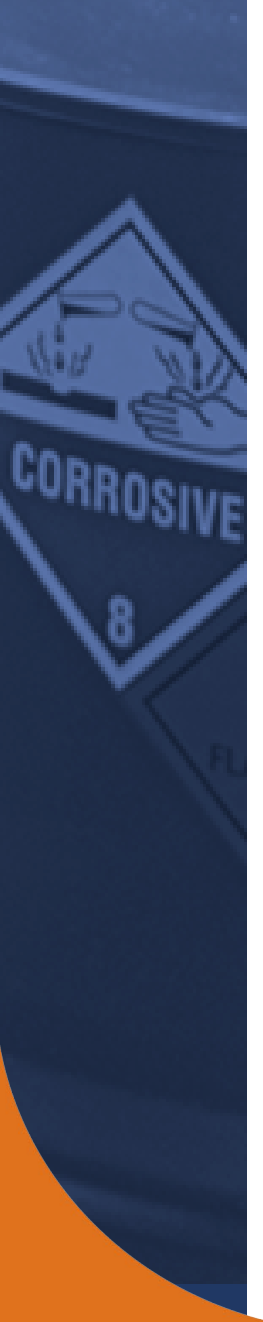
Component classified as:	Generic concentration limits triggering classification of a mixture as:	
	Category 1 Endocrine disruptor for human health	**Category 2** Endocrine disruptor for human health
Category 1 endocrine disruptor for human health	≥ 0,1 %	
Category 2 endocrine disruptor for human health		≥ 1 % [Note 1]

Note: The concentration limits in this Table apply to solids and liquids (w/w units) as well as gases (v/v units).
Note 1: If a Category 2 endocrine disruptor for human health is present in the mixture as an ingredient at a concentration ≥ 0,1 %, a SDS shall be available for the mixture upon request.



Classifying a mixture for ED HH

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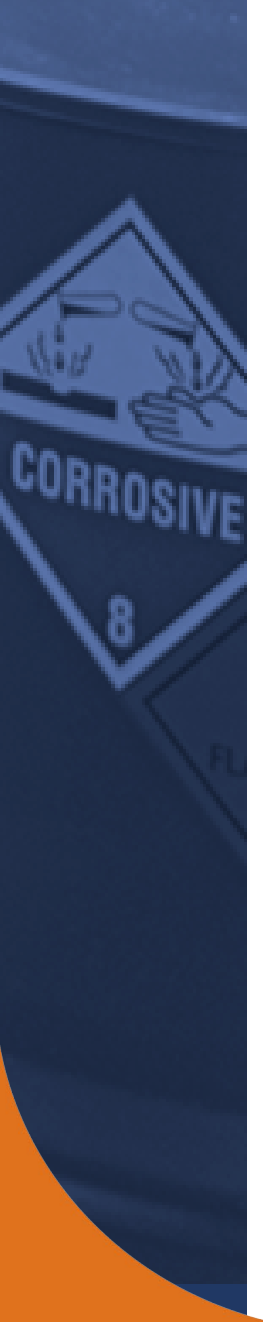
Classification is based on:

(i) the presence of a substance in the mixture, or

(ii) Data on mixture itself (to be used **only** when it demonstrates ED HH classification), or

(iii) Data on a similarly tested mixture (can be used applying the bridging principle)

Decision on Classification



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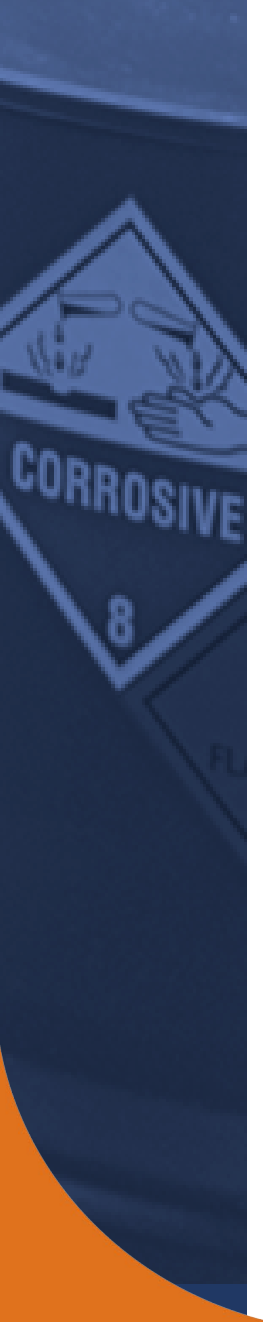
- Sufficient evidence on **all** three elements**;**
  - ✓Endocrine activity;
  - ✓Adverse effect;
  - ✓Biological plausible link.
- If any of the 3 not met ->No Classification
- Classification based on weight of evidence approach and expert judgement



Decision on Categorisation

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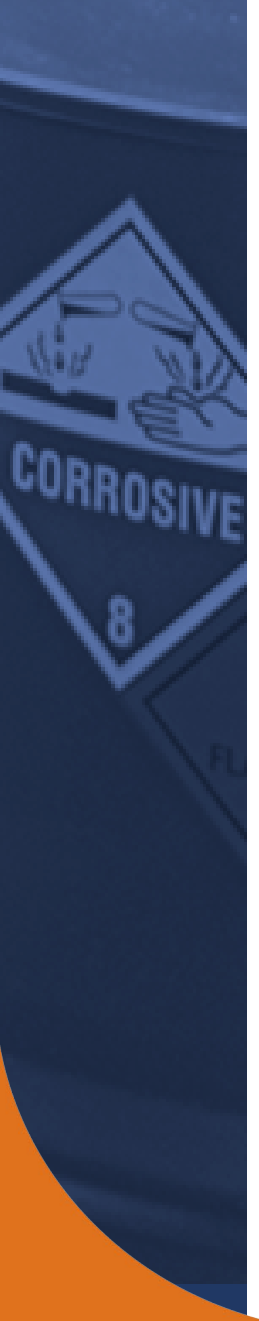
Depends on:

- Reliability
- Dosing/concentration settings
- Parameters covered
- Life-stage investigated or exposure duration
- Incidence of effects
- Divergences of results (i.e. lack of consistency)
- Chance, bias or confounding factors
- Doubts on human relevance

No detailed guidance yet on categorisation, more experience from CLH proposals and Risk Assessment Committee (RAC) needed.



Hazard Communication; Label elements of ED HH

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	Category 1	Category 2
Signal Word	**Danger**	**Warning**
Hazard Statement	**EUH380:** May cause endocrine disruption in humans	**EUH381:** Suspected of causing endocrine disruption in humans
Pictogram	- Currently no pictograms, may be introduced in GHS	- Currently no pictograms, may be introduced in GHS
Precautionary Statements (prevention, response, storage and disposal)	Outlined in Table 3.11.3 in CLP Annex I	Outlined in Table 3.11.3 in CLP Annex I

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Guidance on the Application of the CLP Criteria Part 3: Health Hazards

Guidance on the Application of the CLP Criteria

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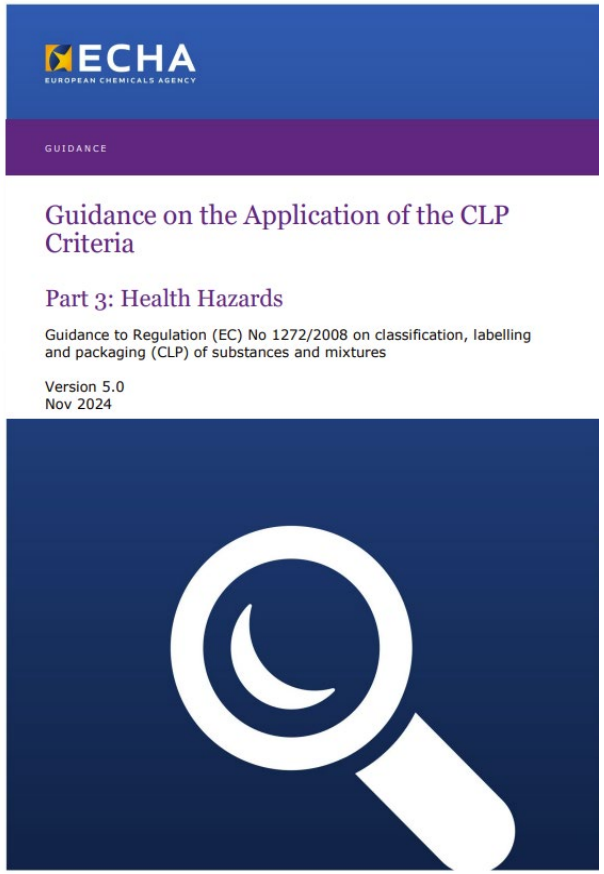
- Section 3.11, *Endocrine Disruption for Human Health,*

  Guidance on the Application of the CLP Criteria Part 3:

  Health Hazards, Version 5.0



- 3.11.1. **Definitions** and general considerations for endocrine disruption

- 3.11.2. **Classification of substances** for endocrine disruption for human health

- 3.11.3. **Classification of mixtures** for endocrine disruption for human health

3.11.1. Definitions

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CLP, Annex I, *Section 3.11.1.1.* *For the purposes of Section 3.11, the following definitions shall apply:*

(a) *'endocrine disruptor' means a substance or a mixture that alters one or more functions of the endocrine system and consequently causes adverse effects in an intact organism, its progeny, populations or subpopulations;*

(b) *'endocrine disruption' means the alteration of one or more functions of the endocrine system caused by an endocrine disruptor;*

(c) *'endocrine activity' means an interaction with the endocrine system that may result in a response of that system, of target organs or target tissues, and that confers on a substance or the mixture the potential to alter one or more functions of the endocrine system;*

(d) *'adverse effect' means a change in morphology, physiology, growth, development, reproduction or lifespan of an organism, system, population or subpopulation that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;*

(e) *'biologically plausible link' means the correlation between an endocrine activity and an adverse effect, based on biological processes, where the correlation is consistent with existing scientific knowledge.*

Data to be considered for classification; ECHA Guidance
Section 3.11.2.3. Evaluation of hazard information

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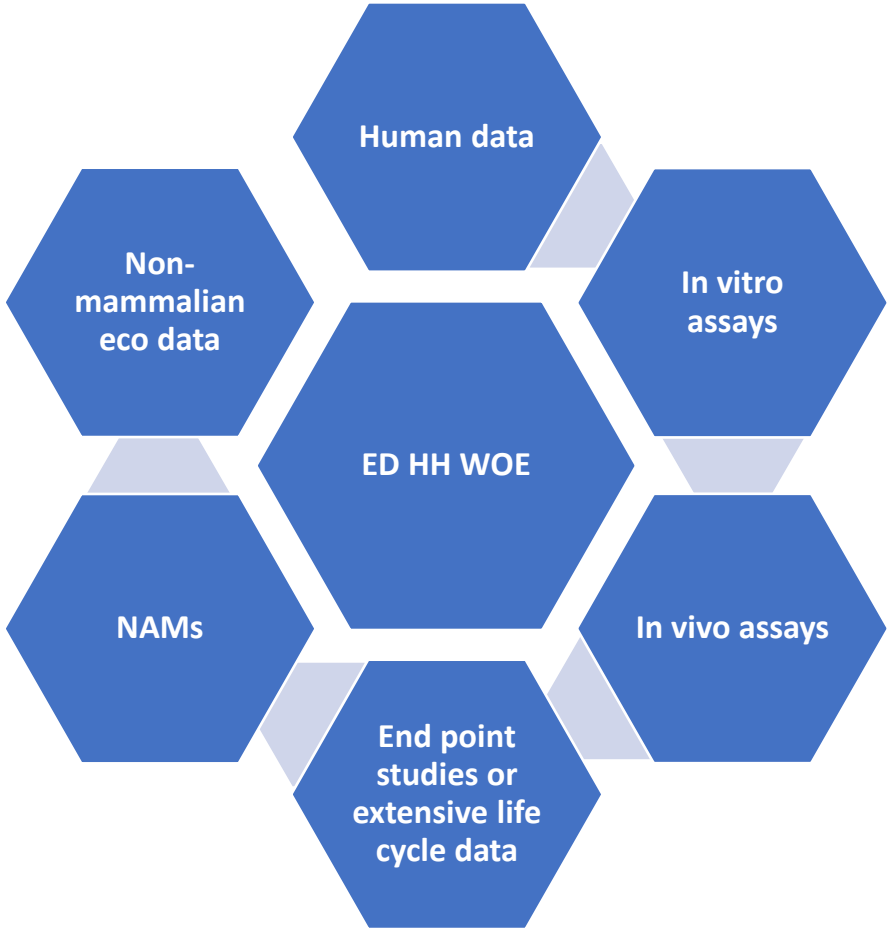

EATS mediated parameters

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- Effect caused by **estrogen**, **androgen, thyroid** and **steroidogenic** modalities
- Most studied and understood mechanism of actions
- The only internationally accepted standard methods or test guidelines for assessment of this endpoint are ones that investigate EATS modalities
- Examples of EATS mediated parameters in humans:
  - Effects on uterine weight
  - Disturbed estrous cyclicity
  - Increase in thyroid gland weight
  - Changes in histopathology of the follicular cells of thyroid gland

Non-EATS mediated parameters

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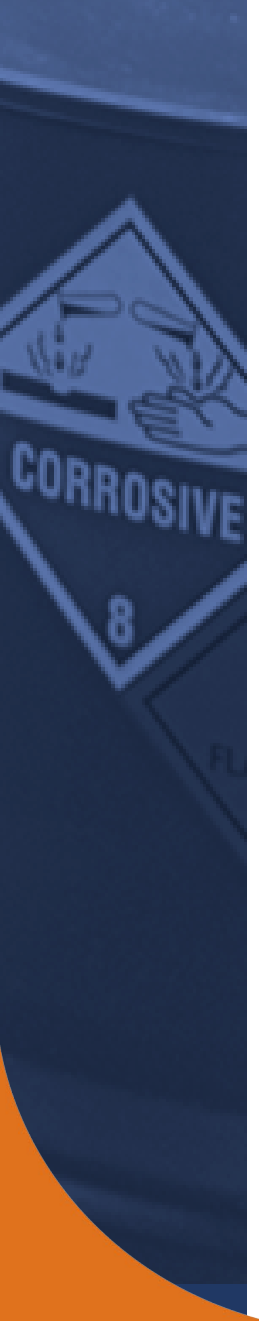
- **All** hormones not covered by EATS

- Knowledge of these modalities is limited but can still be used to reach a conclusion on ED potential

- Examples of Non-EATS mediated parameters in humans:
  - Hormones interfering with neuroendocrine system
  - Hormones interfering with Vitamin A and D
  - Hormones interfering with glucose homeostasis

Human relevance



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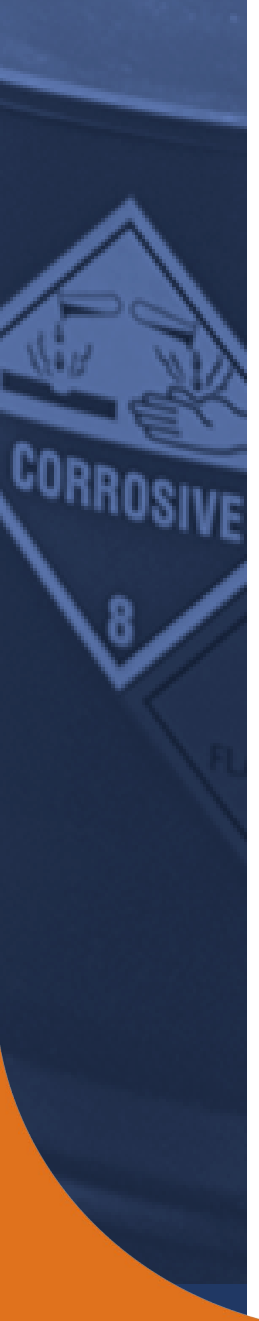
- **CLP, Annex I, Section 3.11.1.2.1;**

Substances and mixtures fulfilling the criteria of endocrine disruptors for human health based on evidence referred to in Table 3.11.1 shall be considered to be known, presumed or suspected endocrine disruptors for human health unless there is evidence conclusively demonstrating that the adverse effects are not relevant to humans.

- **What does this mean?**
  - Default assumption; observed effects in mammalians are relevant to humans.
  - Justification is needed where MoA is known as not relevant or relevance is doubted.
  - Additional experimental studies needed to prove non-human relevance.

Classification in presence of other toxic effects



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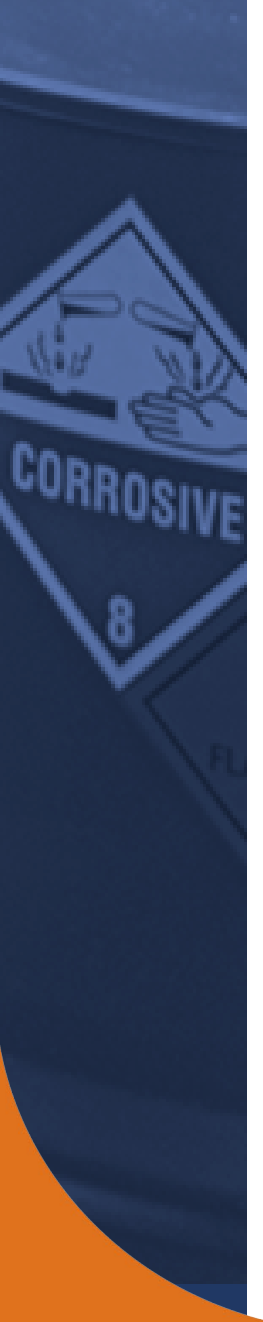
- **CLP, Annex I: 3.11.2.2.2.;**

Adverse effects that are solely non-specific consequences of other toxic effects shall not be considered for the identification of a substance as endocrine disruptor for human health.

- Severe toxicity i.e., total body collapse and all types of adverse effects appear; ED classification can be dismissed
- Excessive toxicity should not occur if tests are performed in accordance with OECD test guidelines
- Effects at top dose or maximum tolerable dose should be considered
- Case by case comparative analysis of mechanism of action (MoA) may be required



Example:

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- 10% decrease in body weight in maternal rats in a reproductive toxicity test ≠excessive toxic
- At the same dose, ED effects occur in their offspring, e.g., effects on thyroid weights
- Comparative analysis of mechanism of action is required to confirm ED effects

Specific considerations: Thyroid modality

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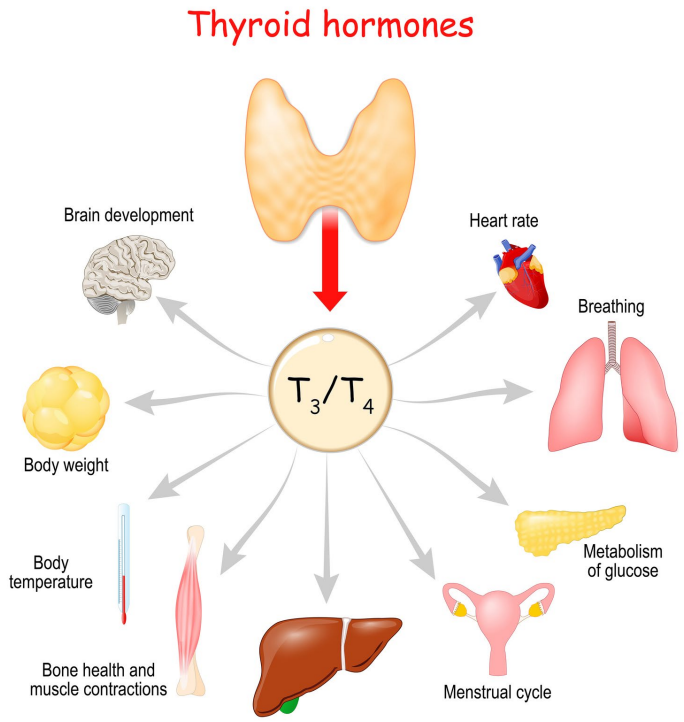
- Thyroid hormones act on almost all cells in the body
- EDs can adversely affect thyroid function
- All thyroid related mechanisms of action are relevant for ED classification
- Examples:
  - Increased thyroid weight
  - Histopathological findings in thyroid cells
  - Increased levels of total cholesterol



Specific considerations: Neurotoxicity & immunotoxicity

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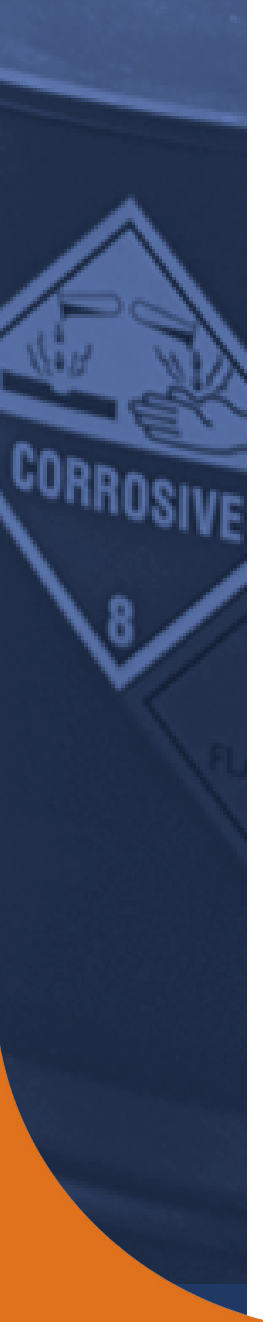
- Neurotoxic and immunotoxic effects must be considered for classification as ED HH
- Assessment done on a case-by-case basis
- Example of ED neurotoxicity: altered cochlear development and hearing loss
- Example of ED effects on immune system:
  - Increased susceptibility to infections and tumours
  - Inflammatory chronic diseases such as allergy, asthma
  - Autoimmune disorders

Specific concentration limits (SCLs)



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- Specific concentration limits (SCLs) must be derived for extremely potent EDs in favour of Generic concentration level (GCL) i.e. applying a SCL
- Detailed instructions outlined in section **3.11.2.6,** ECHA Guidance
- SCLs are set based on potency of adverse effect from available data
- Calculation method depends on type of effect e.g. STOT RE or Reproductive Toxicity
- Potency needs to be adjusted as ED GCL is lower

  e.g. Cat 1. ED GCL; 0.1% versus Cat 1. Repr.Tox GCL; 0.3%

- If several calculation methods available, **the lowest SCL should be selected for classification and only one SCL can be set for ED HH**

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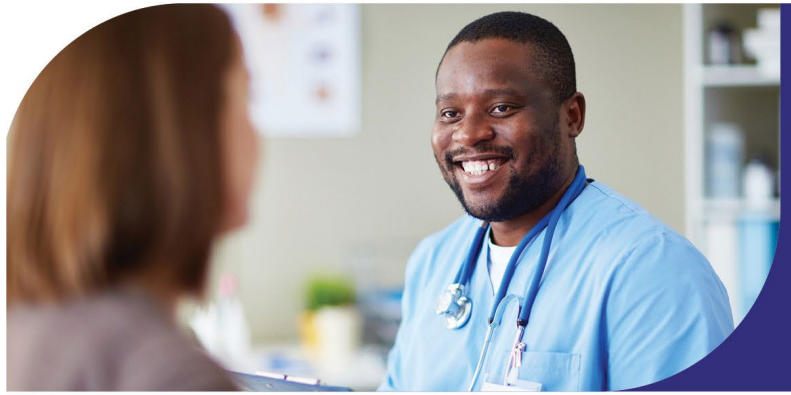
Thank you



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