ED assessment under CLP and REACH: simplified guidance

Eurometaux, version 4.0, September 2025

(new: highlighted in blue)

Note: this document aims at presenting the "essentials of the ED hazard assessment" without delving going into the technical details required by of the assessment outlined in the recent ECHA Guidance on the application of the CLP criteria (November 2024) and the future REACH Information Requirements.

Its objective is to provide practical information on the requirements associated with the new ED hazard endpoint.

It initially focused on the CLP obligations, to explain the key relevant elements of the full ECHA CLP guidance, and to help users to have a quick overview of the implications of the CLP new feature.

It will be complemented by information on the REACH ED Information Requirements, currently discussed in the CARACAL Subgroup on ED/IR. As the initial Commission proposal triggers a lot of comments and discussions, the content of this section will be regularly updated.

It also highlights some metal specificities on which ways forward were identified or where further work will be needed.

Your comments are key to making it a useful document! Thanks for your help!

Table of Contents

ED under CLP

1. Introduction

1.1 A brief recap on the generic issues you need to know on classification under CLP

One of the main aims of the CLP Regulation (EC) No 1272/2008 is to determine **whether a substance or mixture is associated with inherent properties that trigger a classification as 'hazardous'** (i.e., causing harm). When relevant and reliable information (e.g. toxicological data) on a substance or mixture meets the classification criteria laid down in CLP, the hazard(s) of a substance or mixture are identified by assigning a certain hazard class and category.

The classification obligations under CLP depend on the role one has in the supply chain (manufacturer/importer, downstream user, distributor, producer of certain specific articles) and are detailed in ECHA's Introductory Guidance on the CLP Regulation.

In a nutshell, for manufacturer/importers and downstream users, key duties are to:

- **classify** substances and mixtures before they are placed on the market **according to the criteria published in the CLP legal text** (Title II)
- **ensure labels and packaging comply with the CLP requirements** (CLP Title III and Title IV respectively, including the correct hazard pictograms, signal words, hazard statements, appropriate precautionary statements and supplemental information). Safety data sheets shall reflect this information (REACH Annex II).
- take steps to ensure the classification and labelling **remain in line with new information** that becomes available and may affect the classification/labelling of the substance or mixture. In practice, a new hazard evaluation has to be carried out considering this new information and the related classification and labelling has to be updated where needed.
- **assemble and keep all information required** for the purposes of classification and labelling under the CLP for a period of at least 10 years after you have last supplied a substance or mixture (note: this is also a request under the REACH Regulation for registered substances).
- **notify** the (new) classification and labelling elements to the ECHA Classification and Labelling Inventory in case the substance placed on the market is not covered by a REACH registration. If the substance is covered by a REACH registration (by being member of a joint submission or having a letter of access), its classification is available via the REACH registration dossier.

The CLP Regulation includes provisions for two types of classification: **self-classifications** and **harmonised classifications**:

- Harmonised classifications are relevant for substances included in Table 3 of Part 3 of Annex VI of CLP and are mandatory classifications defined by EU regulatory decisions. They must be applied by all suppliers of the substance (manufacturers, importers of substances on their own or in mixtures, downstream users and distributors).
- Self-classifications have to be applied by the same actors for substances that do not have a harmonised classification or for endpoints not covered under a harmonised classification entry.

Note: mixtures are "**self-classified"** according to the best knowledge (i.e., data on mixture and ingredients, status of the science, existing rules on the data to use etc.).

A (harmonised/self-) classification for a substance may include a **Specific Concentration Limit (SCL) or a Multiplication Factor (M-Factor)**. If the substance is used in a **mixture** or is an **impurity in a substance**, the SCLs and M-factors for that substance should be considered when defining the classification. In the absence of a SCL, you need to apply the Generic Concentration Limit (GCL) defined in Annex I of the CLP (e.g. 0.1%).

ECHA or the local competent or enforcement authorities where a company is established may request all the information used for the purpose of classification and labelling under CLP. In case this information is included in the notification to the Classification and Labelling inventory or in the joint submission under REACH, this information is available to ECHA, and the competent authority needs to address its request to ECHA.

There are five basic steps for classifying substances and mixtures, starting from existing available data up to reviewing a classification if needed (e.g. if there are changes in the classification criteria or if new information on the substance is available):

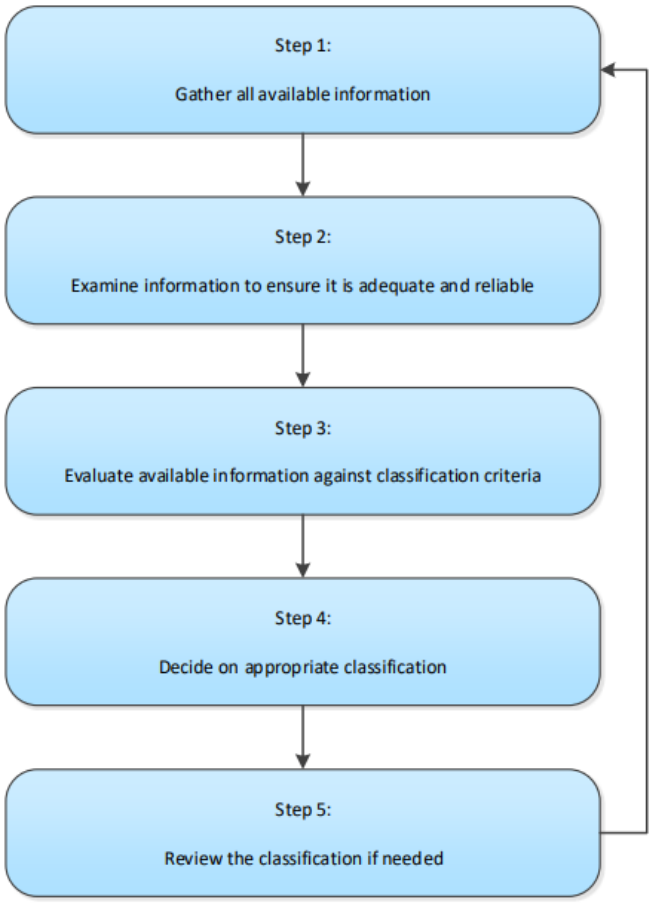


Figure 1 Five basic steps for classifying substances and mixtures

Please note that if your company is part of a joint submission under REACH, your consortium/association secretariat may perform Steps 1-3 and consult you with the outcomes of Step 3 on Steps 4 and 5 before providing you with the necessary information to support and document the classification. In some cases, company experts are also involved in Steps 1 and 2. In this scenario, the detailed ECHA Guidance on the application of the CLP criteria is the reference to look at. This 'simplified' guidance rather targets Steps 3, 4 and 5.

Note: The classification is based on **existing data.** And hence, the CLP text and guidance stipulate that testing in CLP for human or environmental hazards is **only** allowed **when one has exhausted all other means of generating information**, including the use of existing data, use of data from tests not carried out according to the principles of good laboratory practice, use of historical human data, application of weight of evidence and use of (quantitative) structure-activity relationships ((Q)SARs), *in vitro* methods and read-across. For the ED endpoint, additional constraints apply (see chapter 2).

2. Classification for the endocrine disrupting endpoint

2.1 What is the endocrine system and hazard?

The **'endocrine system'** in the CLP context consists of hormone-producing tissues and their associated hormones that regulate the functioning of the organism. It is a complex system made up of glands (e.g., adrenal, hypothalamus, pituitary, (para)thyroid, pineal, pancreas, ovary, and testes) and organs that produce, store, secrete and respond to hormones (e.g., adipose tissue, gastrointestinal tract, kidney, liver, placenta and heart). By acting at specific cells or tissues, hormones affect a variety of functions including growth, development, reproduction, sexual function, blood pressure, sleep, metabolism, mood etc. It is important to note that many aspects of the endocrine system are conserved across living organisms.

An **endocrine disruptor** (ED) is a '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' (WHO/IPCS, 2002). Endocrine disrupting chemicals (substances of mixtures) interfere with the hormonal system and thereby produce harmful effects in humans and/or wildlife. Those chemicals can be naturally occurring or man-made. They can mimic the function of natural hormones, block their activity, affect their production, storage, release, transport or breakdown and/or change tissue sensitivities to different hormones.

The definition of **adverse effect** used in the context of the ED assessment is generic and not specific to EDs[1] (i.e., IPCS 2009)

It has been suggested that ED substances and mixtures are found in pesticides, biocides, metals, additives, food contaminants and personal care products. Hence there are many routes of exposure.

2.2 Regulatory and legal context

Increasing scientific knowledge and societal concerns were a strong driver to address the ED hazard in the EU "2020 Chemicals Strategy for Sustainability towards a toxic-free environment" (Chemicals strategy - European Commission). Concerns included the possible association of EDs with certain disorders in humans, such as birth defects, developmental, reproductive or neurodevelopmental disorders, cancer, diabetes and obesity, with a high and increasing incidence in both children and adults.

The ED assessment of substances was at that time already performed under the Biocidal Product Regulation (BPR), Plant Protection Product Regulation (PPPR) and the Registration, Evaluation,

[1] See glossary

Authorisation, and Restriction of Chemicals (REACH) Regulation (i.e., REACH Article 57/ SVHC identification). The consequent Impact Assessment on the addition of new hazard classes (covering ED) and criteria in CLP to reflect current state of science concluded that ED assessments should be included in CLP for a better protection of living organism and the environment. This is in line with the one substance one assessment (OSOA) principle promoted by the EU Commission.

The new hazard classes were published in the Commission Delegated Regulation 2023/707

The new CLP (CLP 2.0) including the updated Annexes was published in November 2024 and entered into force on 10 December 2024.

The new hazard class for ED includes criteria for endocrine disruptors for humans (ED HH) and environment (ED ENV) in 2 categories: for known/presumed (ED category 1) and suspected (ED category 2) EDs (see table below).

Human Health

CLP, *Annex I,* Section *3.11.2.1*. *Hazard categories*

For classification for endocrine disruption for human health, substances shall be allocated to one of two categories.

Table 3.11.1.

Hazard categories for endocrine disruptors for human health

Categories	*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.
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.*

Environment

CLP, Annex I, *4.2.2.1. Hazard categories*

For the purpose of classification for endocrine disruption for the environment, substances shall be allocated to one of two categories.

Table 4.2.1

Hazard categories for endocrine disruptors for the environment

Categories	*Criteria*
CATEGORY 1	*Known or presumed endocrine disruptors for the environment* *The classification in Category 1 shall be largely based on evidence from at least one of the following:* *a) animal data;* *b) non-animal data providing an equivalent predictive capacity as data in point a.* *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 doubt about the relevance of the adverse effects identified at population or subpopulation level, classification in Category 2 may be more appropriate.*
CATEGORY 2	*Suspected endocrine disruptors for the environment*
	A substance shall be classified in Category 2 where all the following criteria are met: *(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.*

The ED classification requires evidence **fulfilling the three conditions** stipulated in the ED criteria (Section 2.3.). A **substance** is classified only **when sufficient evidence supports all 3 following elements:**

i) endocrine activity **and**
ii) adverse effect **and**
iii) biologically plausible link between adversity and endocrine activity is established.

If there is evidence for each of these elements, the overall strength of evidence will determine if the substance is classified as ED category 1 (known or presumed) or 2 (suspected).

Using that definition of an ED, logic dictates that if one of the three elements is not met, classification of the substance is not warranted.

A **mixture** will be classified based on the presence of an ingredient classified for ED at or above the generic or specific concentration limit for ED category 1 or 2.

Regarding communication and packaging, these new ED categories correspond to new EU **hazard phrases** to use in the hazard communication:

Hazard class and category code	Hazard statement code	Hazard statement
ED HH 1	EUH380	May cause endocrine disruption in humans
ED HH 2	EUH381	Suspected of causing endocrine disruption in humans
ED ENV 1	EUH430	May cause endocrine disruption in the environment
ED ENV 2	EUH431	Suspected of causing endocrine disruption in the environment

Precautionary statements are reported below:

Human Health

Classification	*Category 1*	*Category 2*
GHS Pictograms		
Signal Word	*Danger*	*Warning*
Hazard Statement	*EUH380: May cause endocrine disruption in humans*	*EUH381: Suspected of causing endocrine disruption in humans*
Precautionary Statement Prevention	*P201* *P202* *P263* *P280*	*P201* *P202* *P263* *P280*
Precautionary Statement Response	*P308 + P313*	*P308 + P313*
Precautionary Statement Storage	*P405*	*P405*
Precautionary Statement Disposal	*P501*	*P501*

Environment

Classification	*Category 1*	*Category 2*
GHS Pictograms		
Signal Word	*Danger*	*Warning*
Hazard Statement	*EUH430: May cause endocrine disruption in the environment*	*EUH431: Suspected of causing endocrine disruption in the environment*
Precautionary Statement Prevention	*P201* *P202* *P273*	*P201* *P202* *P273*
Precautionary Statement Response	*P391*	*P391*
Precautionary Statement Storage	*P405*	*P405*
Precautionary Statement Disposal	*P501*	*P501*

Currently there are **no pictograms** associated but they may be introduced at a later stage if adopted in the context of the UN GHS.

The **signal words** are 'Danger' for category 1 and 'Warning' for category 2 EDs.

2.3 Timelines

The ECHA visual on the timelines refers to **new quantities** placed on the market on or after 1 May 2025:

The Commission clarified in February that there will indeed be a transitional period for substances (quantities) that are already placed on the market (meaning: for the first time) before 1 May 2025. Those quantities will not need re-labelling (for the ED hazard class) before 1 November 2026. For new quantities placed on the market on or after 1 May 2025, those will need to comply with the new rules.

What does it mean for the REACH Registration dossiers?

In accordance with Article 22(f) of REACH, registrants have to update their registration 'without undue delay', in the case of 'any change in the classification and labelling'. The Commission Implementing Regulation (EU) 2020/1435 implements Article 22 of REACH. Article 6(2) of that Regulation is in particular relevant in this case as it provides that: *'In the case of a change falling within point (f) of Article 22(1) of Regulation (EC) No 1907/2006 that is due to an adaptation in the classification of a substance as a result of a new evaluation in accordance with Article 15 of Regulation (EC) No 1272/2008'*, the update and submission to the Agency needs to happen *'by no later than 6 months from the date when the decision to change the classification and labelling of the substance has been taken'*.

Since Delegated Regulation 2023/707 establishes 1 May 2025 as the date of application of the new hazard classes, the decision to classify should be taken by that day and consequently for classified substances the registration dossier should be updated at the latest by 1 November

2025. To avoid potential confusion on the market and ensure a smooth transition, registrants could include an explanatory note in their updated REACH registration dossier and SDS. This note could clarify that the updated classification and labelling information in the dossier may not yet be reflected on the labels of existing stocks, which are still covered by the transitional period under CLP. This explanation would help to prevent any misunderstandings and ensure that customers are aware of the transitional period.

This Commission clarification is in line with an informal clarification EBRC received from ECHA, i.e. that the application dates for the new hazard classes are not related to the REACH registration of substances.

In practice this means that

For substance A, placed on the market for the first time on 1 or 2 May 2025, it must be classified and labelled in accordance with the new hazard classes, as applicable.

For substance B, which has been on the market since 20 April 2018, the obligations depend on the "quantities". The amounts of substance B that were already on the EU market from 20 April 2018 to 30 April 2025 do not have to be re-classified or re-labelled until 1 November 2026, unless the formulation of the substance is changed. The new quantities of substance B, supplied as of 1May 2025 must be classified and labelled in accordance with the new hazard classes, as applicable.

Regarding IUCLID: Currently, IUCLID 6.9 does not foresee technical completeness check (TCC, as described in Article 20(2)) on the new hazard classes, but only quality warnings (QLT250) to remind users on the new CL requirements.

While aligning with the transition period between 1st May 2025 and 1st November 2026, ECHA will not make any change in the IUCLID validation rules that would affect the TCC process until the end of this timeline (or even beyond), to ensure that all registrants would be treated equally. Once the CLP implementation is finalised and new rules are introduced in IUCLID, ECHA will duly communicate on new TCC requirements.

2.3.1 Template for the communication to coregistrants

In view of the close linkages between EU REACH, EU CLP and EU e-SDS regulations and the importance of consistency/coherence in the proposed classification assessments, it is recommended to contact the co-registrants to raise awareness and propose phrases that can be added to the SDS documentation by the compliance date of 1 May 2025.

Please find herewith a suggested template for this communication, kindly shared by a metal consortium:

Summary on conducted assessment:

New CLP hazard classes for simple inorganic *specify metal* **substances**:

- PBT, vPvB, PMT and vPvM classes are not applicable.
- ED: include e.g.:
  - No available reliable data identified to indicate that *specify metal* substances are to be classified as endocrine disruptors, or
  - Available reliable data indicate that *specify metal* substances are to be classified as endocrine disruptors (cat 1 or cat 2), or
  - Assessment is still ongoing

Background:
The EU CLP regulation [1] introduced new hazard classes in 2023:

- ED HH in Category 1 and Category 2 (Endocrine disruption for human health)
- ED ENV in Category 1 and Category 2 (Endocrine disruption for the environment)
- PBT (persistent, bioaccumulative, toxic), vPvB (very persistent, very bioaccumulative)
- PMT (persistent, mobile, toxic), vPvM (very persistent, very mobile)

The assessment for EU CLP of whether a substance requires hazard classification for any of these new classes should be **conducted and concluded by 1 May 2025**. This is because it states on the ECHA website that *new quantities of existing substances* that are placed on the EU market from this date must be classified and labelled accordingly by that date (see visuals below).

PBT/vPvB, PMT/vPvM: According to the CLP Regulation, Annex I, section 4.3.2.3 and 4.4.2.3 and REACH Annex XIII, the hazard classes PBT, vPvB, PMT and vPvM do not apply to inorganic substances. Therefore, these hazard classes do not apply to the *specify metal* substances covered in this assessment (see list of substances below).

Regarding **Endocrine Disrupting properties**: The consortium performed an assessment of the possible endocrine disrupting properties of *specify metal* substances. The scope of the assessment is simple inorganic *specify metal* substances in which the *specify metal* moiety is the sole driver for any potential ED-related (eco)toxicological properties (list of substances attached overleaf). Other *specify metal* substances, such as organometallics, or composite materials with toxic moieties are not included in the scope.

The assessment followed guidance documents by ECHA [2], EFSA [3] and OECD [4] and ..[ ] *(add-delete).*

Provide a summary overview of the assessment referring to the available studies (references included below):

- A literature search was conducted based on e.g. the EFSA guidance [2], a paper by Escrivá et al. [4], *add if need so*. Approximately *number* publications were screened for relevance and for reliability for the assessment of endocrine disrupting properties of *specify metal* substances and included in the assessment as applicable.

- Assessment conclusion as of *date* 2025:
  - The consortium has reviewed available existing literature on endocrine disruption in accordance with pertinent guidance.
  - The toxicity assessment focused on the 'EATS' endocrinology endpoints of (anti) Estrogen, Androgen, Thyroid and Steroidogenesis. In a nutshell the outcome is *'No Classification'* or *'Classification as cat 1 or 2'* for EA & S *& (T)*. *Add if needed:* For T there is a potential data-gap, which may require further technical work in the future.
  - **Currently, no robust or reliable data has been identified that would indicate that *specify metal* substances have endocrine disrupting properties for humans or the environment** or **the identified data indicates that *specify metal* substances have endocrine disrupting properties**
  - The consortium will continue to closely follow the regulatory developments on "endocrine disruption", any changes to the CLP regulation or guidance documents, and possible new/future data requirements that are anticipated under the upcoming update of the EU REACH Regulation ("REACH 2.0", "REACH Revision").

For *specify metal* substances that require a safety datasheet (SDS), the following statements are suggested for you to include in your SDS by 1 May 2025 about the new CLP hazard classes:

SDS Section	Suggested statement
11.2 Information on other hazards	Currently (April 2025), no robust or reliable data has been identified that would indicate that *specify metal* substances have endocrine disrupting properties (human health). Or indicate ED classification if this is the conclusion of the assessment
12.5 Results of PBT and vPvB assessment	The PBT and vPvB criteria of REACH Annex XIII, and PBT, vPvB, PMT and vPvM criteria of CLP Annex I do not apply to inorganic substances. Therefore, an assessment or classification of this substance for these hazards is not required.
12.6 Endocrine disrupting properties	Currently (April 2025), no robust or reliable data has been identified that would indicate that *specify metal* substances have endocrine disrupting properties (environment). Or indicate ED classification if this is the conclusion of the assessment

This note was prepared by *names*

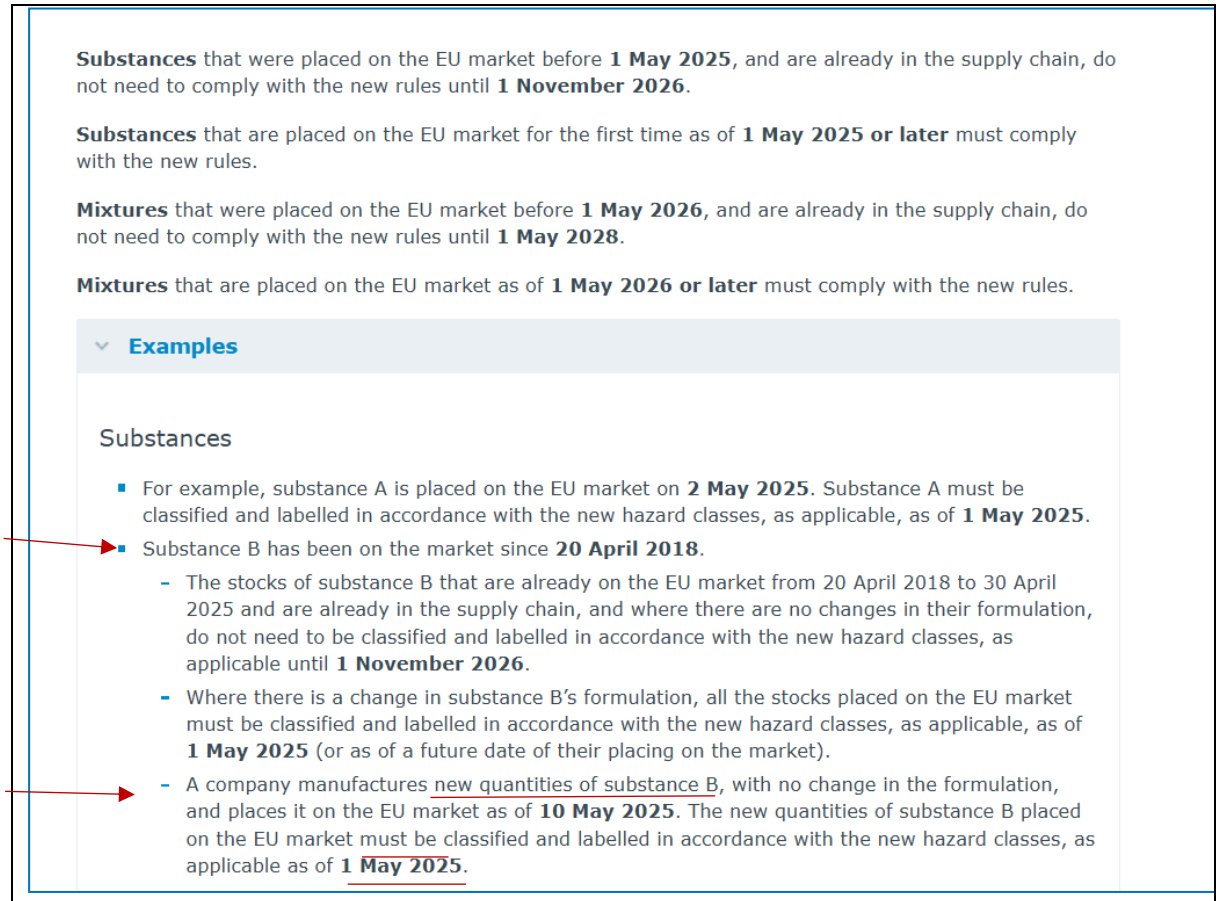
List of *specify metal* substances in scope of the assessment:

EC Substance name	EC No.	CAS No.

Below is the explanation why the date is 1 May 2025 and not 1 November 2026, using information from the website of the European Chemicals Agency. See also simplified guidance of Eurometaux.

Although the ECHA graphic below indicates 1 November 2026 and indicates 'voluntary' application before that date:

When you then read the ECHA Examples Section for Substance B, it becomes clear the compliance date is in fact 1 May 2025:



Substances that were placed on the EU market before **1 May 2025**, and are already in the supply chain, do not need to comply with the new rules until **1 November 2026**.

Substances that are placed on the EU market for the first time as of **1 May 2025 or later** must comply with the new rules.

Mixtures that were placed on the EU market before **1 May 2026**, and are already in the supply chain, do not need to comply with the new rules until **1 May 2028**.

Mixtures that are placed on the EU market as of **1 May 2026 or later** must comply with the new rules.

Examples

Substances

- For example, substance A is placed on the EU market on **2 May 2025**. Substance A must be classified and labelled in accordance with the new hazard classes, as applicable, as of **1 May 2025**.
- Substance B has been on the market since **20 April 2018**.
  - The stocks of substance B that are already on the EU market from 20 April 2018 to 30 April 2025 and are already in the supply chain, and where there are no changes in their formulation, do not need to be classified and labelled in accordance with the new hazard classes, as applicable until **1 November 2026**.
  - Where there is a change in substance B's formulation, all the stocks placed on the EU market must be classified and labelled in accordance with the new hazard classes, as applicable, as of **1 May 2025** (or as of a future date of their placing on the market).
  - A company manufactures new quantities of substance B, with no change in the formulation, and places it on the EU market as of **10 May 2025**. The new quantities of substance B placed on the EU market must be classified and labelled in accordance with the new hazard classes, as applicable as of **1 May 2025**.

References *to complete*

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance). [Online]. Available: http://data.europa.eu/eli/reg/2008/1272/oj

[2] ECHA, 'Guidance on the Application of the CLP Criteria'. [Online]. Available: https://echa.europa.eu/guidance-documents/guidance-on-clp

[3] European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC) et al., 'Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009', EFS2, vol. 16, no. 6, Jun. 2018, doi: 10.2903/j.efsa.2018.5311.

[4] OECD, Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption. in OECD Series on Testing and Assessment. OECD, 2018. doi: 10.1787/9789264304741-en.

[5] L. Escrivá, E. Hessel, S. Gustafsson, R. Van Spronsen, M. Svanberg, and A. Beronius, 'A validated search filter for the identification of endocrine disruptors based on the ECHA/EFSA guidance recommendations', Environment International, vol. 142, p. 105828, Sep. 2020, doi: 10.1016/j.envint.2020.105828.

2.4 Specific provisions for substances already considered ED

There are specific rules for substances previously identified as ED under PPPR, BPR or REACH. Commission can immediately transfer these substances to Annex VI of the CLP:

- the ED conclusion based on the criteria under the BPR or PPP regulations correspond to ED Category 1 under CLP, and a direct transfer is foreseen.
- for biocidal and PPP active substances concluded not to meet ED criteria under BPR or PPPR, the outcomes under CLP will depend on the assessment (Category 1, Category 2 or 'No classification') depending on data available when re -assessed.
- for ED substances of very high concern (SVHC) (Article 57 of REACH), a direct transfer is foreseen to ED Category 1 under CLP.

2.5 ED guidance

The Guidance on application of CLP criteria for ED has been published in November 2024. It is available at Guidance on CLP - ECHA. Separate guidance is available for human health (HH) and environment (ENV). ECHA has announced that the guidance will be updated as experience with ED testing and assessments grows.

ECHA has also announced stakeholder workshops in 2025. A first webinar was hold in November (recording available at https://echa.europa.eu/-/introduction-to-echa-s-guidance-on-new-clp-hazard-classes).

Notes:

- ECHA/EFSA have published a guidance (2018) to help applicants and assessors of the competent authorities to comply with their obligations under the BPR and PPP Regulations (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311). The 2024 ECHA CLP guidance on EDs is largely similar to that guidance but mainly differs in that ED classification **does not require the generation of new data** and, therefore, needs to be based on available data. For hazard classification purposes, the 2024 ECHA CLP guidance shall be followed for all substances and mixtures.
- Assays and parameters are outlined in the "Revised Guidance Document (GD 150) on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption by the OECD" (OECD GD 150). This document provides guidance for evaluating chemicals in a regulatory context through new and revised OECD internationally harmonised test guidelines, assays validated at the national level and assays that are currently in the OECD validation process. Those assays to not per sé include metals in the validation process, raising questions with regard to their applicability (this is a topic identified as requiring longer-term work, see Annex 1 overview projects).
- The current ECHA CLP guidance **does not refer to any metal/inorganic specificities** like natural occurrence, bioavailability/speciation/complexation or essentiality. The Brix et

al. 2023 paper, which was submitted along the process drafting the ECHA guidance, provides a useful overview on metal specificities. ECHA has stated that as experience with ED testing and assessment grows, the need for additional guidance will be evaluated and guidance may be developed. For ED, the classification is based on the available relevant and reliable information. No new testing is required under CLP.

2.6 ED classification in a global context

At this stage, there is no ED hazard endpoint in the UN GHS classification system. An informal group of the GHS Sub-Committee was formally set up at the request of the EU Commission, supported by several EU Member States to introduce this additional endpoint in the UN GHS. This initiative aims to align GHS requirements to those in the EU CLP Regulation. The OECD was mandated to provide recommendations based on an assessment of the state of the science for both human health and environmental effects.

The first OECD ad hoc report (47th session, December 2024: ST/SG/AC.10/C.4/2024/20) concluded that while validated methods exist for many EATS modalities, major gaps remain for non-EATS modalities, that environmental methods are less developed, and that current GHS provisions do not explicitly allow the use of mechanistic data for identifying EDs.

A second update (48th session, July 2025: UN/SCEGHS/48/INF.32) incorporated EU and US pilot studies. These confirmed that although current GHS hazard classes can capture some adverse effects, they do not identify substances as ED. The EU found that most EDs identified under its regulations are not classified as such in GHS, while the US showed that certain chemicals with known endocrine are also not explicitly recognised as EDs. Transient endocrine effects remain poorly addressed. In response, options under discussion include expanding existing STOT, creating new stand-alone hazard classes for, or strengthening SDS. The informal group is therefore focussing on whether gaps exist in how the GHS currently addresses EDs, drawing on the pilot study results. There is still no consensus at GHS sub-committee level, and resolving the matter may take some time.

It should be noted that some countries around the world base their implementation of GHS on the CLP text (e.g. Chile) and as such requirements established in the EU can also apply in jurisdictions beyond those countries applying CLP in the European region. UNEP and WHO are also active on the issue, updating the 2012 State of the Science report on EDCs (scheduled for completion by late 2025). In parallel, UNEP is running a global project on lead and EDCs, titled "Addressing lead and Endocrine Disrupting Chemicals (EDCs)" as part of the broader initiative "Chemicals, Environment, and Health: Accelerating transition towards a toxic-free planet" (Project ID: 194919), involving stakeholder consultations, policy development, and pilot projects in ECOWAS, Asia-Pacific, and Africa focused on major sources.

3. Classification for human health

3.1 What do you need to know in a nutshell?

The classification for ED HH differs from the other hazard classes in that it refers to a specific (i.e. endocrine) mode of action (MoA) which leads to an adverse effect(s). It considers ED activity and its biological link to adversity ('biologically plausible link')[2].

Note that the classification of a substance as ED is separate from its classification for Carcinogenicity, Mutagenicity, Reproductive Toxicity, Specific Target Organ Toxicity (STOT). A substance can be classified as ED HH based on the same evidence used for other hazard classes irrespective of whether the substance is already classified for (one of) these hazard classes. This is a change from the current practice where usually (but not always) only one classification is triggered by a certain effect and a debate would occur what is the most appropriate classification. Under the ED endpoint, this approach changes and the same adverse effect in a study can trigger two parallel classification outcomes, e.g. for reproductive toxicity and endocrine properties via an effect on fertility.

Also, assessments for HH and ENV need to be performed separately, and in principle a substance can be classified as ED HH but not ED ENV (or vice versa), or as ED HH and ED ENV. In practice, separate classifications may be difficult to achieve (e.g., if you have a substance classified for environment, it may be difficult to demonstrate that the HH classification is not warranted.

More details are provided below.

3.2 Classification of substances

3.2.1 Classification steps

The process to classify a substance for the ED endpoint follows the 5 basic steps outlined in Figure 1.

- If your company is part of a joint submission under EU REACH (or you have a letter of access) for the substance you need to assess for ED, your consortium/association secretariat will likely perform Steps 1-3 and consult you on Steps 4 and 5 before providing you with the necessary information to implement and communicate the classification, document the classification and report the classification in the REACH registration dossier.

[2] See glossary

- If your company is not part of a joint submission you will have to perform steps 1-3 yourself, using the available data and assess in line with the detailed ECHA CLP Guidance (Guidance on the Application of the CLP Criteria Part 3 - section 3.11)

The 5 steps of the ED human health hazard are briefly explained below.

Step 1: gather all available information

For ED assessments, relevant data sources include guideline (company) studies, research (peer reviewed/published) studies and ED assessment performed by authorities (like EFSA or under BPR). Note that data might be collected from other databases (e.g. EASIS, which provides information on substances with potential ED properties) or from other substances (e.g. grouping and read-across approaches if justified https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across). Alternative methods, such as in chemico/in silico tools (e.g. (Q)SAR, docking, US EPA ToxCast database) are considered too on a case-by-case basis. These are not routine for PPPR or BPR as they are data-rich and are therefore highly relevant for REACH Databases. For investigating possible modes of action (MoAs), resources like AOP wiki (https://aopwiki.org/) should be consulted.

Literature searches/reviews are recommended to follow the principles outlined in section 3.2 and appendix F of the ECHA/EFSA (2018) guidance, including the "Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation EC N° 1107/2009" (EFSA, 2011). In addition, existing (eco)tox studies in current REACH dossiers could already contain relevant information related to ED and might thus be worthwhile to reassess for ED relevance.

Data to consider can be human (epidemiological or case) data, animal data or new/alternative approaches methodologies data (e.g., in vitro, in silico, omics, defined approaches, read-across, Q(S)AR, etc.).

Data should primarily focus on **Estrogen (E), Androgen (A), Thyroid (T), and Steroidogenesis (S)** modality, with the EAS and T modalities assessed separately. Standardised test guidelines and parameters for EATS modalities are outlined in OECD GD 150 and Conceptual Framework (Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption | OECD). However, data can also include non-guideline studies.

The CLP criteria apply to all endocrine modalities; therefore, data on non-EATS modalities should be collected and assessed too. These include, but are not limited to, hormones interfering with the neuroendocrine system, glucose homeostasis (insulin, glucagon, and glucagon-like peptides), retinoids, vitamin D, peroxisome proliferator-activated receptor-ɣ (PPARγ). The existing knowledge for non-EATS modalities is not as advanced as that for the EATS modalities and hence the ECHA Guidance focusses primarily on EATS. However, in some cases, it may be possible to reach a conclusion on the need to classify the substance based on a non-EATS MoA.

Previous regulatory assessments may serve as a starting point for additional literature search as well as information for other hazard classes.

Step 2: examine information to ensure relevance and reliability

Once the information has been collected, the **relevance and reliability of the data** should be assessed:

Relevant data implies that the data is suitable to assist in the assessment of the ED endpoint (i.e., if it informs on endocrine activity, adverse effects and/or a biologically plausible link).

Notes on the relevance of the data:

- it is assumed by default that effects observed in mammalian studies are relevant to humans, unless one can explicitly demonstrate the non-relevance for humans (but there is no specific guidance on this).
- negative human data will normally not overrule positive good quality non-human (animal) data leading to ED classification; human data are often considered as flawed by a too low number of individuals investigated, inadequate exposure assessment, co-exposures etc.)
- considering the high level of conservation of the endocrine system across taxonomic groups, non-mammalian data may also be relevant to support the ED conclusion for humans. Negative environmental data cannot be used in isolation as an argument for non ED-classification for human health.

Reliable data means that the study/test method fulfils necessary quality criteria, such as compliance with international guidelines (like OECD or GLP), provides an adequate description of test materials & observations and a good reporting of analytical values/observations (including in the case of EDs relevant parameters for the ED assessment). The reliability of a study is often assessed using Klimisch criteria (Klimisch, 1997).

Only data that are relevant and reliable should be considered for further ED assessment. It is proposed however to keep track of all studies with their reliability criteria as one may consider studies of lower reliability (e.g. Klimisch (K)3) may still serve as 'supportive data' if they provide valuable context to the overall assessment, e.g. for the MoA analysis. In addition, some of the ECHA CLP Guidance examples also consider K3 studies.

Important notes:

- since classification is based on all available, reliable and relevant data, the dose levels in the studies are to be considered as provided. All dose levels, including those tested above the limit dose of a test guideline or above the Maximum Tolerated Dose (MTD), may still be relevant for classification.
- The presence of **other toxicity** must not be used to dismiss classification unless it can be justified that the ED-related adverse effect(s) are **solely non-specific consequences**

of other excessive toxicity (e.g., prostration, severe inappetence, mortality), demonstrated using individual animal data. The excessive toxicity should occur at lower or the same doses as ED–related effect(s). Similarly, excessive toxicity should precede the ED-related effect(s). Both dose and temporal concordance are necessary to support a claim that ED-related effect(s) are a consequence of the other toxic effects, and this is best illustrated by a comparative assessment. There is currently a paradox in that ECHA notes that, according to the international test guidelines, the top dose should not induce excessive toxicity, and studies which cause excessive toxicity should not be conducted (cf. importance of proper dose setting). In case less than excessive other toxicity is observed, a comparative MoA analysis needed to differentiate between ED and non- ED mechanism of action.

Step 3: evaluate available information against classification criteria

The ED classification criteria are included in Annex 1I of the CLP and detailed in the ECHA CLP guidance (2024). All available relevant and reliable information collected in Step 1 has to be considered and assessed in a weight-of-evidence (WoE) approach.

A 'WoE' approach considers multiple data sources deemed relevant and reliable in the assessment, and refers to expert judgement to interpret the whole dataset and come to a hazard conclusion. The WoE methodology, is used to

1) Evaluate the line(s) of evidence for adversity and/or endocrine activity from all available relevant information collected in Step 1
2) For the MoA analysis (MoA), if triggered.

Different frameworks are accepted to establish a MoA. The ECHA/EFSA (2018) guidance suggests the International Programme on Chemical Safety (IPCS 2014) (https://pubmed.ncbi.nlm.nih.gov/24166207/) or the OECD Adverse Outcome Pathway (AOP) activity).

The guidance states that ED classification may be warranted when there is evidence that the criteria (a) endocrine activity, (b) adverse effect(s), (c) plausible link are met, even if there is not enough information to postulate a detailed MoA. This highlights the key importance of 'adversity' and 'activity' when compared to 'MoA' as driving element in ED assessments.

Since the adversity, endocrine activity and MoA are rarely conclusively covered in a single study and since most metals are associated with an extensive experimental database relevant for ED assessment, multiple studies need to be assessed in parallel. The considered studies and their interpretation need to be well and transparently documented for later updating or regulatory scrutiny. The ECHA/EFSA guidance (2018) includes an Appendix E that can help doing so, but alternative formats can be used to discuss the studies and their reliability.

Note that the CLP criteria apply to all endocrine modalities: EATS and non EATS.

Step 4: Decide on appropriate classification

The ED assessment needs to consider a possible adverse effect, ED activity and a biologically plausible link between the observed activity and adversity. If evidence from sufficiently investigated data concludes positively on each of these three elements, the substance needs classification as ED.

In a next step, a decision on the categorisation needs to be taken. The conclusion on ED Cat 1 or Cat 2 is only dependent on the strength and consistency of the available evidence, i.e., how convincing are the data. Allocation to category 1 is warranted when the evidence is sufficiently convincing when considering all relevant and reliable evidence in a weight of evidence approach. However, if the evidence for either adverse effect(s) or endocrine activity or both is not sufficiently convincing (e.g. if there are concerns regarding the study design or conduct) and if there is insufficient information to make a conclusion on category 1, the substance shall be classified as ED the category 2 (or even no classification may be warranted).

It is very uncertain on how to distinguish between category 1 vs. 2 based on strength on the data, and there is currently no detailed guidance available. It should be noted that the views of EU regulatory experts on this topic are highly divergent, and this aspect will be monitored closely in the upcoming classification discussions.

If the data do not support (at least) one of the ED classification elements (with a major focus on 'activity' and 'adversity'), a 'no ED classification' can be concluded. Defending a category 2 classification based on 'weak' evidence will be difficult.

As experience with regulatory ED assessment grows, the CLP guidance for ED will be updated and clarity on ED assessments and categorisations will hopefully be included.

The current CLP guidance identifies some conditions for concluding on **no ED classification** of a substance. For example:

- no adverse effect is observed (this includes adaptative responses demonstrated not to be adverse per se or not leading to adverse effects), or
- no endocrine activity is observed, or
- no biological plausible link can be established, or
- adverse effect(s) are solely a non-specific consequence of other toxic effects, or
- a non-endocrine MoA as a result of a comparative MoA analysis demonstrated to be most likely explanation of observed adverse effect(s), or
- adverse effects conclusively demonstrated not to be relevant for humans.

If the evaluation of the hazard information shows that the substance meets the criteria for ED classification, then one needs to assign the respective category and the appropriate labelling

elements for hazard communication (like Safety Data Sheets (SDS)) via the appropriate signal word, hazard statements, hazard pictograms, and precautionary statements.

Step 5. Review the classification if needed

New data might become available over time via e.g. scientific research (cf. peer reviewed publications) or contract research (cf. testing requirements triggered by regulations like REACH). If such new data are relevant and reliable for ED assessment, they need to be considered in the hazard assessment. These data might confirm the current (non-)classification but might as well trigger a different classification. This can be an 'up-classification' as well as a 'down-classification' compared to the preceding assessment. Again, steps 1 to 4 need to be performed, and the proper hazard conclusion needs to be implemented and communicated by the industry.

3.2.2 Concentration limits

Specific and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance (e.g. as impurity) or in a mixture leads to the classification of the substance or mixture as hazardous.

The generic concentration limit (GCL) value for ED is **0.1%** for an ED category 1 and **1%** for an ED category 2 (aligning with the carcinogenicity and mutagenicity endpoints rather than with reproductive toxicity).

Specific concentration limits (SCLs) are set using similar procedures as for carcinogenicity, reproductive toxicity and specific target organ toxicity with small modifications, depending on type of data available. They are based on the observed potency for ED of the substance in the available studies. Only one SCL is to be selected for the ED HH endpoint.

Usually, SCLs are lower than the GCL. The guidance states that in exceptional cases, a higher SCL than the GCL can be set but only when there is adequate, reliable and conclusive scientific information that the hazard of the classified substance is *clearly* above the GCL.

3.2.3 Read-across and grouping of substances

For most metals and metal compounds, alternative approaches like grouping and read-across are applied. This approach can also be used for ED, as for Carcinogen Mutagen Reprotoxic (CMR) substances:

- The assumption that the metal ion is the driver of the ED effects will justify grouping and read-across for the ED human health endpoints (cfr. using the ECHA Read-Across Assessment Framework (RAAF) criteria). Note that the possible contribution of the counter-ions in the observed effect need to be assessed and compared to the metal ion.

- Read-across and grouping of metal and metal compounds considers different metal-specific elements like speciation, complexation, valence etc. These factors may affect the release of the metal ion, its bioavailability and hence its toxicity. Again, a proper consideration of all these factors is recommended in line with the ECHA RAAF or the OECD Guidance on the Grouping of Chemicals (to be published in 2025).
- Note that the ED effect may be a threshold or a non-threshold effect. A JRC report reflects the work of an expert group on the issue in 2013, which did not manage to reach consensus. Several other publications have been identified, supporting -or not- the existence of a threshold. It was recently shown that for some well-studied EDCs, dose–response relationships and thresholds (NOAELs/LOAELs) can be established for endocrine-mediated adversity, supporting the threshold principle (Choi et al. 2024). Other research and expert opinions (e.g. Borgert et al. 2018; Zhao and Fent 2024) suggest that the presence of endogenous hormones and their products in vivo creates a biological context where only sufficiently high concentrations of EDCs can elicit effects, implying a practical threshold. The human-relevant potency threshold (HRPT) concept further proposes that only chemicals with mechanistic potency above a certain level, relative to these endogenous hormones, are likely to cause adverse effects in humans. However, for weak EDCs or in cases of high sensitivity (e.g., during development), thresholds may be extremely low or difficult to determine, and some effects may occur at very low exposures, making its precise quantification difficult. Hence, being conservative, authorities may consider the **non-threshold mechanism as a default**. A non-threshold approach may mean that -in theory- there is no 'safe' exposure level below which no ED effect is expected for a substance. On the other hand, the concentration limits proposed by the EU CLP and UN GHS (see 3.2.3) can be considered as pragmatic thresholds.
- Considering the above, but also the CLP guidance that stresses that "*concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation",* it is recommended to bring together different lines of evidence when proposing a different grouping of e.g. a metal vs. its metal compounds, based on the 'negligible bioavailability of the metal ion' from the metal compared to the metal compounds. Structural analogy and physico-chemical properties cannot be used on their own to conclude on a different assessment for EDs. Data on the toxicological profile, toxicokinetics, data on ED activity and/or adversity of the metal that clearly differentiate it from the metal compounds can however be used to build a weight-of-evidence case concluding on a different hazard assessment. The reasoning should be clear, scientifically defensible and transparent.

The identification and justification of a threshold, compatible with metal specificities like "essentiality", but also with the pragmatic thresholds used in CLP (e.g., GCL, SCL) will be further worked on by the Human Health and Environment Taskforces, HeTAP and ETAP (see Annex 1).

3.2.4 Can testing of substances be done?

The ED classification is based on the respective classification criteria and consideration of all available relevant and reliable information. No data generation is triggered by the CLP for the ED endpoint.

Further testing can however be considered e.g., under other legislations. Note though that vertebrate testing is not allowed under some regulations like EU REACH (unless triggered under REACH Annexes VII-VIII), unless a testing proposal is included, submitted and approved by ECHA. Vertebrate testing can however be triggered by EU authorities (e.g. as part of an EU REACH evaluation or under the BPR).

In vitro/in silico testing can always be considered. Several assays (e.g. *in vitro*) are available as official OECD guideline studies and offered by research labs (although not always under GLP). These assays mostly focus on MoA investigations or ED activity. However, metal specificities might complicate this testing and/or the evaluation of the test data: metals might e.g. react with media constituents and precipitate or re-complex. Also, *in vitro* dosing and metal uptake might be excessive and irrelevant for *in vivo* testing conditions. These factors (and maybe others) need to be well investigated and considered before initiating a testing program.

3.3 Classification of mixtures

3.3.1 Classification steps

Classification of mixtures is based on a component[3]-based approach (i.e. on data for the ingredients). Each component in a mixture is compared separately to the respective GCL and/or SCL to conclude on the classification of the mixture, unless the additivity principle applies (see below).

In practice: if a mixture contains a component classified as ED cat 1 at a concentration ≥0.1% or a component classified as ED cat 2 at a concentration ≥1%, the mixture will carry the classification as ED cat 1 or cat 2, respectively. When components have SCLs[4], those should be used instead of the GCLs.

[3] Please note that the words "component", "ingredient", "constituent" are used interchangeably in the ECHA CLP guidance

[4] More guidance on the setting of specific concentration limits (SCLs) can be found here

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***		
Component classified as:	*Generic concentration limits triggering classification of a mixture as:*	
Category	*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 shall 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.*		

Can test data on the whole mixture be used? Mixtures containing components classified as ED must normally be classified using **only** the available relevant and reliable information for the individual ingredients in the mixture. Only in cases where available test data on the mixture itself demonstrate ED effects not retrieved from the information on the ingredients, then this data must be taken into account[5]. **In other words, data on tested mixtures can be used only when it demonstrates a classification for ED, and not for demonstrating a lower or no classification.**

What is the additivity principle?

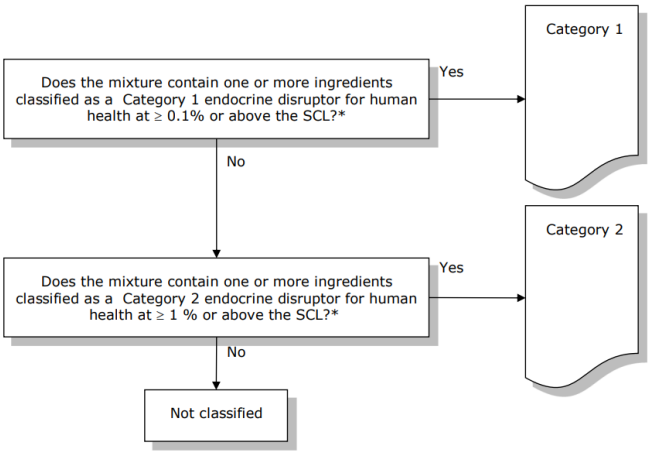
The consideration behind is that exposure to EDs with both similar and different modes of action can lead to combination effects if they affect the same physiological process(es) or have the same target organ(s) for toxicity. For ED, it is reasonable to assume additivity for substances with similar mechanism or mode of action or adverse outcome, unless there are specific reasons not to do so[6].

What is the decision logic to classify mixtures?

[5] In such cases the test results for the mixture as a whole must show to be conclusive taking into account dose (concentration) and other factors such as duration, observations, sensitivity and statistical analysis of the test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request

[6] Additivity is already applied for other CLP endpoints where the MoA of the substances is assumed to be the same: e.g., reprotoxicity of substances releasing boron ions, skin sensitisation by nickel substances. When the MoA is different, there may be some cases where it is deemed appropriate to assume additive or synergistic effects. In other cases, there may be no cause for additivity.

Figure 3.12 Decision logic for classification of mixtures based on individual ingredients of the mixture



*Applicability of additivity approach should also be considered.

3.3.2 Bridging

CLP states that when a mixture itself has not been tested to determine its properties for ED HH but there are sufficient data on the individual components and similar tested mixtures, these data can be used in accordance with bridging principles to classify the mixture. For EDs, however, bridging principles **will only be used on a case-by-case basis** and data on a similar mixture can only be used when it demonstrates classification, not for a lower or no classification.

What does this mean for metal mixtures like **'alloys'**? Given the vast number of alloys that need to be self-classified by the manufacturers and reviewed by regulators under CLP (and GHS), some consideration needs to be given on how to group alloys with similar characteristics to define which similar alloys are covered by the same classification.

Some guidance on grouping has been drafted in the context of the bioelution/metal release discussions. It proposes a stepwise approach that starts from the composition of the alloys (i.e., its ingredients), and hence is in line with the CLP that states that the ED classification is based on the ingredients' classifications. This ingredients' information is to be complemented with other available information on the alloy such as alloy production processing, applications of the alloy, specifications, and other sources of information (physical form, galvanic series, surface composition, microstructure and inclusions, corrosion data…), and/or information on the pure metals as supportive information for the grouping. The following template can be used to organise the data:

	Alloy 1				Alloy 2			
	Ingredient 1	Ingredient 2	Ingredient 3	Ingredient x	Ingredient 1	Ingredient 2	Ingredient 3	Ingredient x
Concentration %								
Classifications								
ED cat (incl. GCL/SCL)								
Other information on alloy								
Presence of ingredients that influence corrosion								
Physical form								
Applications								
Others. E.g., galvanic series, surface composition, microstructure and inclusions, and/or on the pure metals (e.g., Pourbaix diagrams								
Metal release (µg/g sample)* -medium x -medium y								

*Provide details about the tests: fluid composition, loadings, sample characteristics, etc.

The sector will further work on practical guidance on how to group alloys in view of the mixtures' deadline.

3.3.3 Can testing of mixtures be done?

Article 6(3) of the CLP prevents to test mixtures and to use whole mixture test results for the CMR and ED endpoints. "*For the evaluation of mixtures pursuant to chapter 2 of this Title in relation to the "germ cell mutagenicity", "carcinogenicity", "reproductive toxicity", "endocrine disruption for human health" and "endocrine disruption for the environment" hazard classes referred to in sections 3.5.3.1, 3.6.3.1, 3.7.3.1, 3.11.3.1 and 4.2.3.1 of Annex I, the manufacturer, importer and downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture and not for the mixture itself*."

Note: "Metal release" information refers to the metal ion releases from the components of the mixture/alloy and hence does not fall under Article 6(3): *[...the manufacturer, importer and*

downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture and not for the mixture itself].

3.4 Classification of a complex material: use of MeClas

The MeClas tool allows classifying complex inorganic materials like ores and concentrates, complex intermediates or UVCBs, all considered as 'More than One Constituent Substances' (MOCs) in the 2024 CLP. MOCs should be evaluated and classified following the same classification rules as mixtures. MeClas (www.meclas.eu) follows the legal ruling but recognises also the specific properties and assessment techniques for inorganics, uses the most updated information on toxicity references and self-classifications and provides on that basis a classification output that can be used and communicated.

Regarding the ED endpoint, the Generic Concentration Limits that trigger the classification based on the individual constituents are taken over in MeClas as 0.1% (ED category 1) and 1% (ED category 2). Currently -at the time of publication of this document- as no substance in the MeClas database has been classified for ED, the MeClas output displays '*under construction*' when the classification of a MOC is determined.

Tiers 0 and 1 of MeClas use only the composition and the generic concentration limits to determine the ED classification.
Tier 2 considers a "bioaccessibility correction" for the oral route (systemic effects) to which EDs belong. This correction uses the relative metal release in a bioelution test, calculated by comparing the release from the metal compound when present as constituent in a mixture with the release from a "reference sample". This reference sample should be selected based on the same form and on the existence of toxicological information and/or oral reference values. In absence of these data, a default 100% release can also be put in MeClas.

Eq 3

$$Relative\ metal\ release\left(\%\right) = \frac{mg\ metal\ ion\ released\ (measured\ in\ extract)/g\ Test\ sample}{mg\ metal\ ion\ released\ (measured\ in\ extract)/g\ Reference\ sample}\ \boldsymbol{x\ 100}$$

4. Classification for environment

4.1 What do you need to know in a nutshell?

Similarly, as for human health, classification for the environment refers to a specific ED mode of action (MoA) leading to adverse effects at the population level.

The classification requires evidence for 3 elements, as for human health and a **substance** is as such only classified **when there is sufficient evidence on the 3 following elements:**

i) endocrine activity **and**

ii) adverse effect **and**
iii) biologically plausible link between adversity and endocrine activity is established.

If there is evidence for each of these elements, the overall strength of evidence will determine if the substance is classified as ED category 1 (known or presumed) or 2 (suspected).

The definition of an ED also implies that if one of the three elements is not met, classification of the substance is not warranted.

A **mixture** will be classified based on the presence of an ingredient classified for ED at or above the generic or specific concentration limit for ED category 1 or 2.

Notes:

- The classification as ED environment is intended to indicate that a substance may cause an endocrine-related adverse effect. The sensitivity to such effects may depend on the life-stage investigated.
- To classify a substance as ED environment, the adverse effects need to be relevant at the population level.
- The CLP legal text and the ECHA CLP guidance do not refer to metal specificities like essentiality, the diversity of modes of action, the distinction between endocrine modulation and endocrine disruption... Those aspects may be addressed in later updates of the ECHA CLP Guidance. In the meantime, the metals sector believes it is crucial to apply as far as possible a common approach to the ED environment hazard, highlighting these metal specificities where relevant, supported by the best science and data. Key scientific references were submitted to ECHA along the guidance drafting process (Brix et al. 2023).

4.2 Classification of substances

4.2.1 Classification steps

The process to classify a substance for the ED endpoint follows the 5 basic steps outlined in Figure 1 and explained under 3.1 Classification of substances ED Human Health:

- If your company is part of a joint submission under EU REACH (or you have a letter of access) for the substance you need to assess for ED, your consortium/association secretariat will likely perform Steps 1-3 and consult you on Steps 4 and 5 before providing you with the necessary information to implement and communicate the classification, document the classification and report the classification in the REACH registration dossier. This information package will include the required information and references to support the approach followed by the metals sector to factor in the relevant metal specificities.

- If your company is not part of a joint submission you will have to perform steps 1-3 yourself, using the available data and assess in line with the detailed ECHA CLP Guidance (Guidance on the Application of the CLP Criteria Part 3 - section 3.11)

The 5 steps of the ED environmental hazard are briefly recalled below.

Step 1: gather all available information

For ED assessments, relevant data sources include guideline (company) studies, research (peer reviewed/published) studies and ED assessment performed by authorities (like EFSA or under BPR). Note that data might be collected from other substances too (e.g. grouping and read-across approaches if justified) as well as alternative methods such as in silico predictions. For investigating possible modes of actions (MoAs), resources like AOP Wiki (https://aopwiki.org/) should be consulted. A literature search and review are recommended following the principles outlined in section 3.2 and Appendix F of ECHA/EFSA (2018) Guidance, including the "Submission of scientific peer-review literature for the approval of pesticide active substances under Regulation EC N° 1107/2009" (EFSA, 2011).

Data should primarily focus on **estrogen (E), androgen (A), steroidogenesis (S) and thyroid (T)** (EATS) modalities. However, the scope is not limited to EATS modalities, i.e., the data collection and later hazard assessment can also refer to non-EATS modalities. But because the current knowledge is more advanced on EATS modalities, the ECHA CLP guidance and criteria focus on these modalities.

Notes:

- Animal studies to be considered for classification of substances as ED ENV are outlined in the OECD GD 150 'Revised guidance document on standardised test guidelines for evaluating substances for endocrine disruption'. It includes the 'OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Substances' (OECD, 2012) which lists the OECD test guidelines and standardised test methods available in 2018 that can be used to evaluate substances for endocrine disruption

What taxa are covered?

The focus is mainly on vertebrates especially fish and amphibians, and also mammals. If available, information on invertebrates or other vertebrates (like birds and reptiles) should also be considered.

Overall data on mammals and other taxa should be considered together in a holistic approach to reach a hazard conclusion for the substance.

Step 2: examine information to ensure relevance and reliability

Only data that are relevant and reliable should be considered for further assessment. This is particularly important for the ED ENV assessment since there are ample metals data reported in non-guideline studies. All studies should first be analysed for reliability (does the study fulfil the necessary quality criteria?) and relevance (is the data suitable to assist in the assessment of the hazard endpoint?), and only data meeting both criteria should be used.

On the **relevance** of the data:

- The CLP criteria stipulate that **population relevance is assumed by default** unless there is evidence conclusively demonstrating that adverse effects identified are not relevant at population or subpopulation level. More details are provided in the ECHA CLP Guidance.
- Effects on growth, development and reproduction in a single species as well as behavioural endpoints that affect the population.
  Effects in non-reproductive organs can be relevant at the population level on a case-by-case basis, e.g. when accompanied by a pattern of effects which are all related to same mode of action.

Reliable data means that the study/test method fulfils necessary quality criteria, such as compliance with international guidelines (like OECD or GLP), provides an adequate description of test materials & observations and a good reporting of analytical values/observations (including in the case of EDs relevant parameters for the ED assessment). The reliability of a study is often assessed using Klimisch criteria (Klimisch, 1997).

Only data that are relevant and reliable should be considered for further ED assessment. It is proposed however to keep track of all studies with their reliability criteria as one may consider studies of lower reliability (e.g. Klimisch (K)3) may still serve as 'supportive data' if they provide valuable context to the overall assessment, e.g. for the MoA analysis. In addition, some of the ECHA CLP Guidance examples also consider K3 studies.

<u>Step 3: evaluate available information against classification criteria</u>

The ED classification criteria are included in Annex I of the CLP and detailed in the ECHA Guidance.

All available relevant and reliable information collected in Step 1 (related to endocrine-related 'adversity', 'activity' and/or 'MoA') has to be considered and assessed in a weight-of-evidence (WoE) approach. A WoE approach considers multiple data sources deemed relevant and reliable and uses expert judgement is required to interpret the whole dataset and come to a hazard conclusion.

The WoE methodology, is used to

1) Evaluate the line(s) of evidence for adversity and/or endocrine activity from all available relevant information collected in Step 1

2) For the MoA analysis (MoA), if triggered.

Different frameworks are accepted to establish a MoA. The ECHA/EFSA (2018) guidance suggests the International Programme on Chemical Safety (IPCS 2014) ((https://pubmed.ncbi.nlm.nih.gov/24166207/) or the OECD Adverse Outcome Pathway (AOP) activity).

The guidance states that ED classification may be warranted when there is evidence that the criteria (a) endocrine activity, (b) adverse effect(s), (c) plausible link are met, even if there is not enough information to postulate a detailed MoA. This highlights the key importance of 'adversity' and 'activity' when compared to 'MoA' as driving element in ED assessments.

Since the three lines of evidence for ED assessment (adversity, activity and MoA) are rarely conclusively covered in a single study and since most metals are associated with an extensive experimental database relevant for ED assessment, multiple studies need to be assessed in parallel. The considered lines of evidence and their interpretation need to be well and transparently documented for later updating or regulatory scrutiny.

Note that the CLP criteria apply to all endocrine modalities: EATS and non-EATS.

Step 4: Decide on appropriate classification

The ED assessment needs to consider a possible related effect, ED activity and a biologically plausible link between the observed activity and adversity. If evidence from sufficiently investigated data concludes positively on each of these three elements and the effects are relevant at population level, the substance needs classification as ED.

In a next step, a decision on the categorisation needs to be taken. The conclusion on ED Cat 1 or Cat 2 is only dependent on the strength and consistency of the available evidence. Allocation to category 1 is warranted when the evidence is sufficiently convincing when considering all relevant and reliable evidence in a weight of evidence approach.

When the evidence for either adverse effect(s) or endocrine activity or both is not sufficiently convincing to place the substance in Category 1, then Category 2 or no classification may be warranted. This may be caused by issues related to reliability, dosing/concentration settings, parameters covered, life-stage investigated or exposure duration, serious doubts on the relevance at the level of population, incidence of the effects, divergencies between results in different studies if not explainable by differences in study design (i.e. lack of consistency), inconsistent pattern of effects, etc., or when chance, bias or confounding factors cannot be ruled out with reasonable confidence in Step 2.

Where there is evidence conclusively demonstrating that the adverse effects are not relevant at the population level, the substance should not be considered an ED for the environment. As for human health, as experience with regulatory ED assessment grows, the CLP ED guidance will be updated and more clarity on ED assessments and categorisations will hopefully be included.

If the evaluation of the hazard information shows that the substance meets the criteria for ED classification, then one needs to assign the respective category and the appropriate labelling elements for hazard communication (like SDS) via the appropriate signal word, hazard statements, hazard pictograms, and precautionary statements.

Step 5. Review the classification if needed

New data might become available over time via e.g. scientific research (cf. peer reviewed publications) or contract research (cf. testing requirements triggered by regulations like REACH). If such new data are relevant and reliable for ED assessment, they need to be considered in the hazard assessment. These data might confirm the current (non-)classification but might as well trigger a different classification. This can be an 'up-classification' as well as a 'down-classification' compared to the preceding assessment. Again, steps 1 to 4 need to be performed, and the proper hazard conclusion needs to be implemented and communicated by the industry.

Important notes:

The classification for ED environment is independent of other environmental classifications, and the ED classifications for environment (category 1 or 2) and for human health (category 1 or 2) are also independent. This means that an ED classification for human health does not automatically translate to a classification for ED environment, and vice-versa.

Substances shall not be classified as ED, if an adverse effect is solely a consequence of a non-ED effect. But the presence of other toxic effects i.e. (adverse) effects other than endocrine related adverse effects, shall not be used to negate findings of endocrine-related adverse effects. If ED effects are observed with co-occurring other toxic effects, a case-by-case evaluation is needed. To consider an ED-related adverse effect **solely** as a non-specific consequence of other toxic effects, there must be evidence for a biologically plausible sequence of events demonstrating that it is solely a non-ED MoA that causes the adverse effect, and which also excludes the endocrine MoA as the most likely cause for the observed adverse effect(s).

4.2.2 No M-Factors but concentration limits

The M-factors assigned to the aquatic hazard endpoint do not apply to the ED endpoint. Instead, concentration limits (as GCL or SCL) are set and align the protection levels for human health and environment. These limits are assigned to a substance and indicate the threshold at or above which the presence of that substance in another substance or in a mixture (as identified impurity, additive or individual constituent) leads to the classification of the substance or mixture as ED.

The generic concentration limit (GCL) value for ED is **0.1%** for an ED category 1 and **1%** for an ED category 2 (as for ED HH). .

4.2.3 Read-across and grouping

For most metals and metal compounds, alternative approaches like grouping and read-across are applied. This approach can also be used for ED, as for CMR substances:

- The assumption that the metal ion is the driver of the ED effects will justify grouping and read-across for the ED ENV endpoints (cfr. using the ECHA Read-Across Assessment Framework (RAAF) criteria). Note that the possible contribution of the counter-ions in the observed effect need to be assessed and compared to the metal ion.
- Read-across and grouping of metal and metal compounds considers different metal-specific elements like speciation, complexation, valence etc. These factors may affect the release of the metal ion, its bioavailability and hence its toxicity. Again, a proper consideration of all these factors is recommended in line with the ECHA RAAF or the OECD Guidance on the Grouping of Chemicals (to be published in 2025).
- Note that the ED effect ED effect may be a threshold or a non-threshold effect. A JRC report reflects the work of an expert group on the issue in 2013, which did not manage to reach consensus. It was recently shown that for some well-studied EDCs, dose–response relationships and thresholds (NOAELs/LOAELs) can be established for endocrine-mediated adversity, supporting the threshold principle (Choi et al. 2024). Other research and expert opinions (e.g. Borgert et al. 2018; Zhao and Fent 2024) suggest that the presence of endogenous hormones and their products in vivo creates a biological context where only sufficiently high concentrations of EDCs can elicit effects, implying a practical threshold. The human-relevant potency threshold (HRPT) concept further proposes that only chemicals with mechanistic potency above a certain level, relative to these endogenous hormones, are likely to cause adverse effects in humans. However, for weak EDCs or in cases of high sensitivity (e.g., during development), thresholds may be extremely low or difficult to determine, and some effects may occur at very low exposures, making its precise quantification difficult. Hence, being conservative, authorities may consider the **non-threshold mechanism as a default**. A non-threshold approach may mean that -in theory- there is no 'safe' exposure level below which no ED effect is expected for a substance. On the other hand, the concentration limits proposed by the EU CLP and UN GHS (see 3.2.3) can be considered as pragmatic thresholds.
- Considering the above, but also the CLP guidance that stresses that "*concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation",* it is recommended to bring together and document different lines of evidence when proposing a different grouping of e.g. a metal vs. its metal compounds, based on the 'negligible bioavailability of the metal ion' from the metal compared to the metal compounds. Structural analogy and physico-chemical properties cannot be used on their own to conclude on a different assessment for EDs. Data on the toxicological profile, toxicokinetics, data on ED activity and/or adversity of the metal that clearly differentiate it from the metal compounds can however be used to build a weight-of-

evidence case concluding on a different hazard assessment. The reasoning should be clear, scientifically defensible and transparent.

The identification and justification of a threshold, compatible with metal specificities like "essentiality", but also with the pragmatic thresholds used in CLP (e.g., GCL, SCL) will be further worked on by the Human Health and Environment Taskforces, HeTAP and ETAP (see Annex 1).

4.2.4 Can testing be done?

The ED classification is based on the respective classification criteria and consideration of all available relevant and reliable information. No data generation is triggered by the CLP for the ED endpoint.

Further testing can however be considered e.g., under other legislations. Note though that vertebrate testing is not allowed under some regulations like EU REACH (unless triggered under REACH Annexes VII-VIII), unless a testing proposal is included, submitted and approved by ECHA. Vertebrate testing can however be triggered by EU authorities (e.g. as part of an EU REACH evaluation or under the BPR).

In vitro/in silico testing can always be considered. Several assays (e.g. *in vitro*) are available as official OECD guideline studies and offered by research labs (although not always under GLP). These assays mostly focus on MoA investigations or ED activity. However, metal specificities might complicate this testing and/or the evaluation of the test data: metals might e.g. react with media constituents and precipitate or re-complex. Also, *in vitro* dosing and metal uptake might be excessive and irrelevant for true environmental testing conditions. These factors (and maybe others) need to be well investigated and considered before initiating a testing program.

4.3 Classification of mixtures

4.3.1 Classification steps

Classification of mixtures is based on a component[7]-based approach (i.e. on data for the ingredients). Each component in a mixture is compared separately to the respective GCL and SCL to conclude on the classification of the mixture, unless the additivity principle applies (see below).

In practice: if a mixture contains a component classified as ED cat 1 at a concentration ≥0.1% or a component classified as ED cat 2 at a concentration ≥1%, the mixture will carry the classification as ED cat 1 or cat 2, respectively. When components have SCLs, those should be used instead of the GCLs.

[7] Please note that the words "component", "ingredient", "constituent" are used interchangeably in the ECHA CLP guidance

CLP, Annex I: *Table 4.2.2*

Generic concentration limits of components of a mixture classified as endocrine disruptor for the environment that trigger classification of the mixture

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

Note: The concentration limits in this Table shall apply to solids and liquids (w/w units) as well as gases (v/v units).

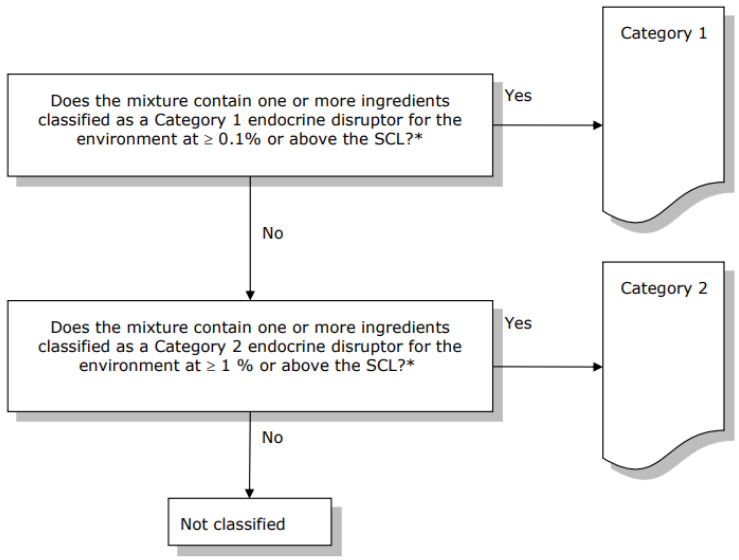
Note 1: If a Category 2 endocrine disruptor for the environment is present in the mixture as an ingredient at a concentration ≥ 0,1 % a SDS shall be available for the mixture upon request.

Can data on the whole mixture be used? Mixtures containing components classified as EDs must normally be classified using **only** the available relevant and reliable information for the individual ingredients in the mixture. Only in cases where available test data on the mixture itself demonstrate ED effects not retrieved from the information on the ingredients, then this data must be taken into account[8]. **In other words, data on tested mixtures can be used only when it demonstrates a classification for ED ENV, and not for demonstrating a lower or no classification.**

What is the decision logic to classify mixtures?

[8] In such cases the test results for the mixture as a whole must shown to be conclusive taking into account dose(concentration) and other factors such as duration, observations, sensitivity and statistical analysis of the test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request

Figure 4.2.3 Decision logic for classification of mixtures based on individual ingredients of the mixture



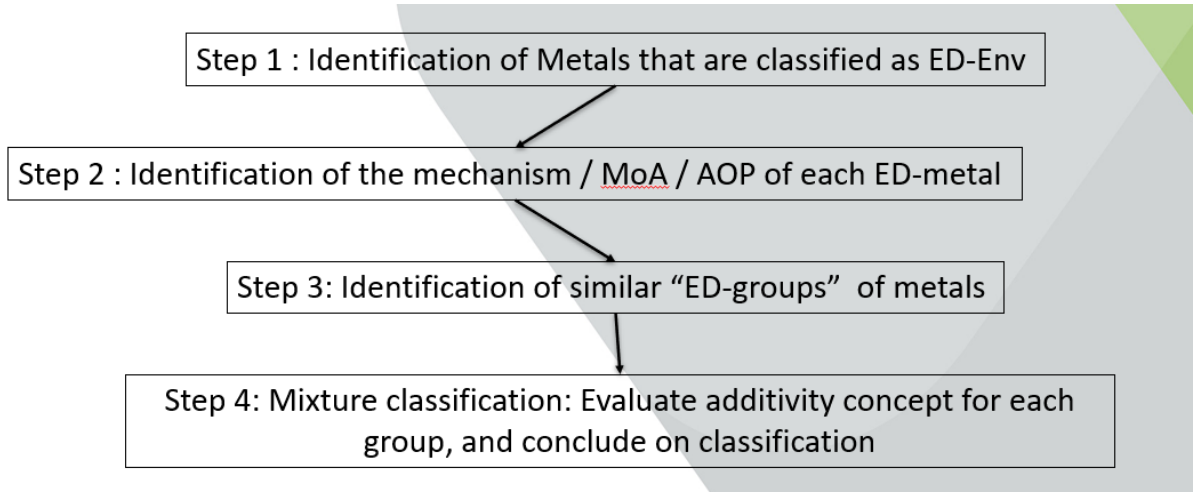
*Applicability of additivity approach should also be considered.

How to consider additivity?

As for human health, the consideration behind is that exposure to EDs with both similar and dissimilar modes of action can lead to combination effects if they affect the same physiological process(es) or have the same target organs for toxicity. For ED, it is reasonable to assume additivity for substances with similar mechanism or mode of action or adverse outcome, unless there are specific reasons not to do it[9]. The ECHA Guidance stipulates that the mechanism does not need to be the same; the same adverse outcome between substances can already suggest additivity. It is important in the assessment of potential additivity to consider if constituents with the same biological targets have different effects or mechanism behind the effects (e.g. they may have agonistic or antagonistic activity or even partial activity at the same receptor). In this case a careful assessment is needed since also dissimilar modes of action can cause the same adverse outcomes in an additive manner.

[9] Additivity is already applied for other CLP endpoints where the MoA of the substances is assumed to be the same: e.g., reprotoxicity of substances releasing boron ions, skin sensitisation by nickel substances. When the MoA is different, there may be some cases where it is deemed appropriate to assume additive or synergistic effects. In other cases, there may be no cause for additivity.

It is proposed to proceed along the following lines:



And in step 4, it is proposed to go for a Toxic Unit-like approach, bringing in the release of the metals in environmentally relevant conditions and concentration limits:
The mixture should be classified if:

$$\textbf{Classified if:} \quad \frac{\text{Conc. Me}_A}{\text{SCL/GCL of Me}_A} + \frac{\text{Conc. Me}_B}{\text{SCL/GCL of Me}_B} + \ldots > 1$$

Each metal's bioavailable concentration is divided by its specific or generic concentration limit, and the results are added together but only for metals that share the same mode of action (MoA) or same adverse outcome pathway (AOP). If the total exceeds 1, the mixture is classified.

For example:

- Me_A = Cat.1, moderate potency (GCL of 0.1%) in a mixture at concentration of 0.08 %
- Me_B = Cat.1, very high potency (SCL of 0.001%) in a mixture at concentration of 0.0006%

$Conc.Me_A/GCL\ Me_A + Conc.Me_B/SCL\ Me_B$ = 0/08%/0.1%. + 0.00021%/0.001% = 0.8 +0.21 = 1.01

⇨ Classification of the mixture

4.3.2 Bridging

CLP states that when a mixture itself has not been tested to determine its properties for HH but there are sufficient data on the individual components and similar tested mixtures, this data can be used in accordance with bridging principles to classify the mixture. For EDs, however, bridging

principles **will only be used on a case-by-case basis** and data on similar mixture can only be used when it demonstrates classification, not for 'no classification'.

What does this mean for metal mixtures like **'alloys'**? Given the vast number of alloys that need to be self-classified by the manufacturers and reviewed by regulators under CLP (and GHS), some consideration has been given on how to group alloys with similar characteristics to define which similar alloys are covered by the same classification.

Some guidance on grouping has been drafted in the context of the bioelution discussions. It includes a stepwise approach that starts from the composition of the alloys (i.e., its ingredients), and hence is in line with the CLP that states that the ED classification is based on the ingredients' classifications. It is to be complemented with other available information on the alloy such as alloy production processing, applications of the alloy, specifications, and other sources of information (physical form, galvanic series, surface composition, microstructure and inclusions, corrosion data), and/or information on the pure metals as supportive information for the grouping. The following template can be used to organise the data:

	Alloy 1				**Alloy 2**			
	Ingredient 1	Ingredient 2	Ingredient 3	Ingredient x	Ingredient 1	Ingredient 2	Ingredient 3	Ingredient x
Concentration %								
Classifications								
ED cat (incl. GCL/SCL)								
Other information on alloy								
Presence of ingredients that influence corrosion								
Physical form								
Applications								
Others. E.g., galvanic series, surface composition, microstructure and inclusions, and/or on the pure metals (e.g., Pourbaix diagrams								
Metal release (µg/g sample)* -medium x -medium y								

*Provide details about the tests: fluid composition, loadings, sample characteristics, etc.

4.3.3 Can testing be done?

Article 6(3) of the CLP prevents to test mixtures and to use whole mixture test results for the CMR and ED endpoints. "*For the evaluation of mixtures pursuant to chapter 2 of this Title in relation to the "germ cell mutagenicity", "carcinogenicity", "reproductive toxicity", "endocrine disruption for human health" and "endocrine disruption for the environment" hazard classes referred to in sections 3.5.3.1, 3.6.3.1, 3.7.3.1, 3.11.3.1 and 4.2.3.1 of Annex I, the manufacturer, importer and downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture and not for the mixture itself*."

Note: "Metal release" information refers to the metal ion releases from the components of the alloy and hence does not fall under Article 6(3): *[…the manufacturer, importer and downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture and not for the mixture itself]*.

4.4 Classification of complex materials with MeClas

The MeClas tool allows classifying complex inorganic materials like ores and concentrates, complex intermediates, UVCBs, all considered as more than one constituent substances (MOCs) in the 2024 CLP. MOCs should be evaluated and classified following the same classification rules as mixtures. MeClas follows the legal ruling but recognises also the specific properties and assessment techniques for inorganics. It uses the most updated information on toxicity references and self-classifications available and provides an output that can be communicated.

Regarding the ED endpoint, the Generic Concentration Limits that trigger the classification based on the individual constituents are built in MeClas (0.1% for ED category 1 and 1% for ED category 2). Currently -at the time of publication of this document- as no substance in the MeClas database has been classified for ED, the MeClas output displays 'under construction' when the classification of a MOC is determined.

Tiers 0 and 1 of MeClas use only the composition and the generic concentration limits to determine the ED classification.
Tier 2 considers a "bioavailability correction" using Transformation Dissolution results. Transformation dissolution tests (TDp) are conducted to determine the rate and extent to which metals and sparingly soluble metal compounds dissolve to soluble, available ionic species in aqueous test media under a set of standard laboratory conditions, representative of those generally occurring in the environment.

Classification is subsequently corrected by considering the bioavailable elemental concentration instead of the assumption of 100% soluble constituent concentration (=reference material, considered as worst-case) as in Tiers 0 and 1. For example, a material containing 1%

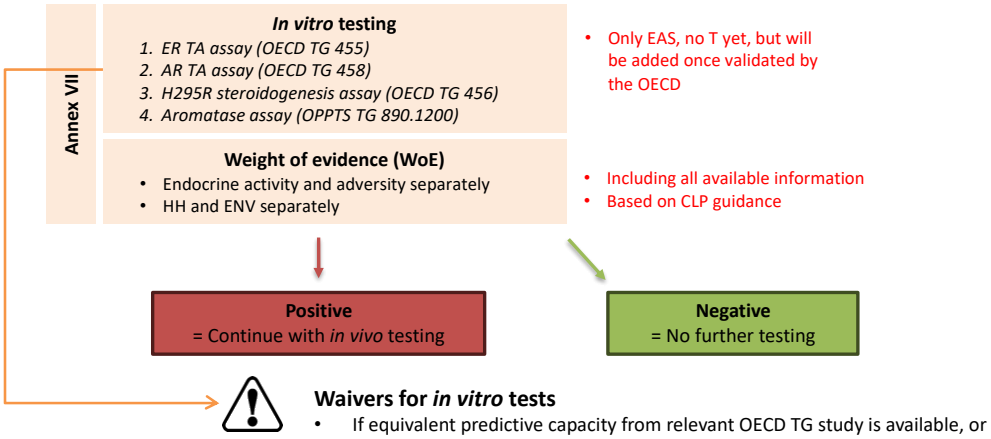
cobalt metal of which only 0.2% is released after 28 days (long term aquatic hazard) will result in an available, soluble cobalt concentration of 1% x 0.2% = 0.002% for further consideration in the environmental mixtures rules (CLP and UN GHS) .

The MeClas tool will be amended in 2025 to include this reasoning for the ED environmental classification of complex materials.

5. EDs in REACH

The Commission proposal outlined below dates from the 4th of February 2025 and was discussed with the CARACAL subgroup on the 18th of February 2025. No further meetings have taken place.

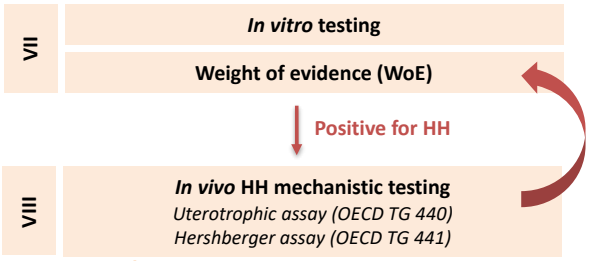
Information requirements – General



Waivers for *in vitro* tests

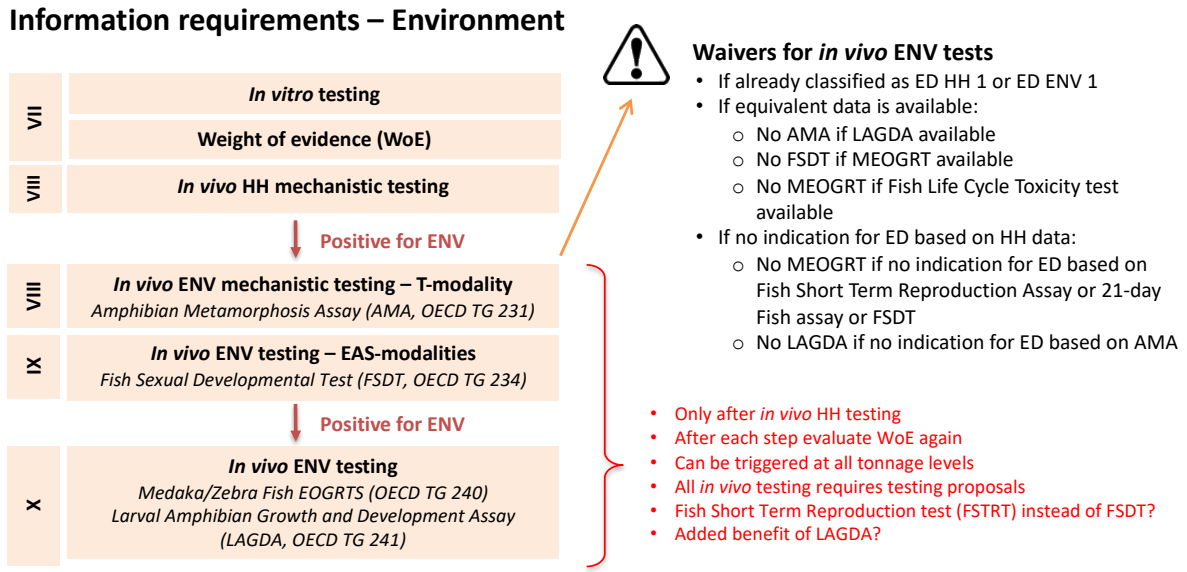
- If equivalent predictive capacity from relevant OECD TG study is available, or
- If clear indications for EAS activity in *in vivo* OECD TG studies, or
- If no endocrine-related adversity in EOGRTS (OECD TG 443)

Information requirements – Human Health



Waivers for *in vivo* HH tests

- If already classified as ED HH 1
- If equivalent data is available (e.g. ToxCast ER for Uterotrophic) ToxCast data reliable?
- If no E or A related adversity in EOGRTS



The **standard information requirements** at Annex VII for ED will include:

- Four *in vitro* assays (OECD 455, 458, 456 and OPPTS 890.1200) covering estrogen, androgen and steroidogenesis. Thyroid assays (currently omitted) are not validated yet but will be added in the future.
- A weight of evidence (WoE) analysis based on all available information (including the 4 in vitro assays, and literature data). The EC refers for the WoE analysis to the CLP guidance on how that should be done.

If the **WoE is positive**, then additional testing will be required for human health and the environment:

- Annex VIII:
  - Uterorophic and Hershberger: two *in vivo* assays on E and A-modality for human health
  - Amphibian Metamorphosis Asssay (AMA): *in vivo* assay on T-modality for environment
- Annex IX:
  - Fish sexual development test (FSTRA): *in vivo* assay on EAS-modalities for environment
- Annex X:
  - Medaka EOGRT or Zebrafish EOGRT
  - LAGDA: The EC is aware of the shortcomings of this test, but argue this could be due to lack of experience and lack for alternative tests (such as an extended AMA which is not yet validated and taken up in the OECD framework)

Important notes:

- If the **WoE at any point is negative**, then no further testing is required.
- If the **WoE is positive**, then all further testing can already be triggered starting from Annex VII (including MEOGRT, LAGDA, FSTRA, AMA, ...), so not according to the annexes under which they will be listed and as is shown above! This means that tonnage bands do not really matter for ED.

- All *in vivo* testing will require **testing proposals**
- HH tests have to be conducted before going to ENV testing
- **Specific waivers** are foreseen, but only for Annex VII substances:
    - If it is already possible to classify ED for HH Cat. 1, then no further testing for ENV is required (if risk management practices have also been implemented)
    - Specific waivers based on half-life and potency. However, there was a lot of pushbacks from Member States regarding these waivers, particularly concerning half-life, i.e. daily exposure leading to lifelong exposure, concentration levels, and the extrapolation *in vitro*/*in vivo*. Arguments to keep potency as a waiver were also raised (mainly from industry).
    - It is still unclear how these specific waivers will be implemented.

The Commission is aiming to publish its proposal by **Q4 2025-Q1 2026**, which will also include an updated impact assessment.

6. More information & references

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- OECD 2018. Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption OECD Series on Testing and Assessment, https://www.oecd.org/en/publications/guidance-document-on-standardised-test-guidelines-for-evaluating-chemicals-for-endocrine-disruption-2nd-edition_9789264304741-en.html Framework
- RAAF (Read-Across Assessment Framework) 2017. https://echa.europa.eu/documents/10162/17221/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a
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Presentations provided by Kevin Brix to the Science Forum (and available on request from lee@eurometaux.be)

- **Part 1**
  - Overview of the endocrine system
  - Metal essentiality and the endocrine system
- **Part 2**
  - Types of potential interactions between metals and the endocrine system
  - Indirect effects
  - Endocrine disruption
  - Endocrine modulation
- **Part 3**
  - Assessment Tools
  - AOP Networks
  - Computational Tools
  - Experimental Approaches

7. Glossary

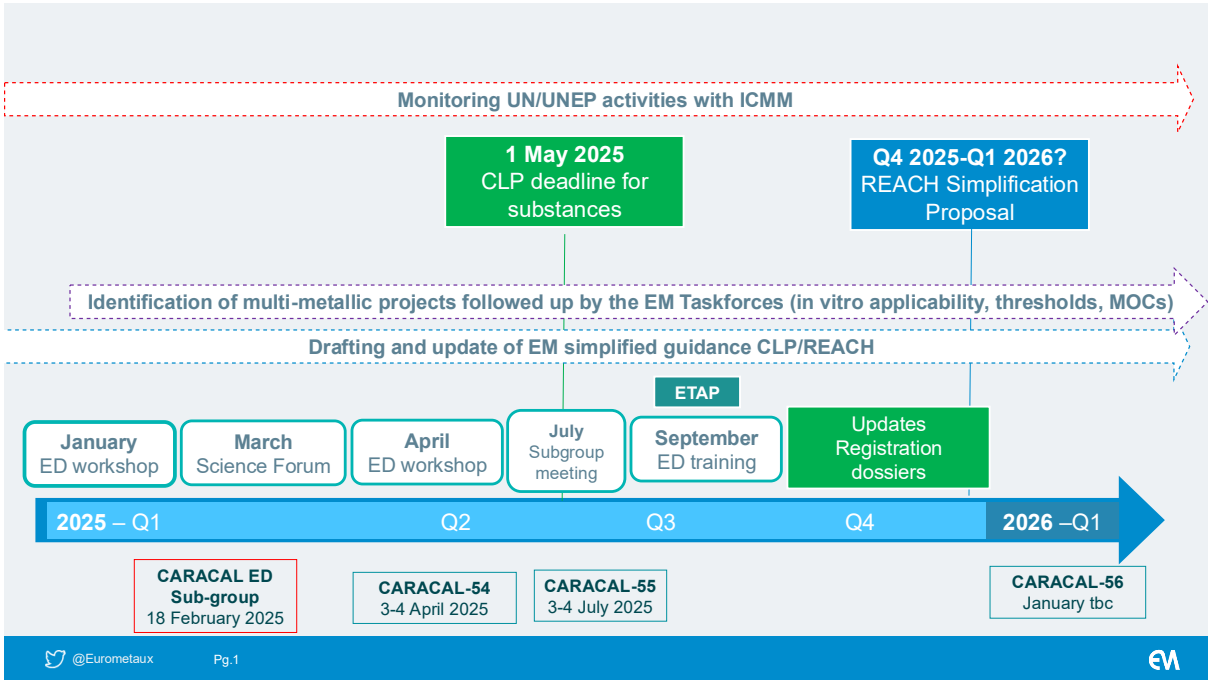
Adversity	IPCS/WHO defined in 2009 an adverse effect as a "change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences." Note that the ECHA/EFSA (2018) guidance or the OECD GD 150 refer more specifically to "EATS-mediated adversity", which is a more specific definition.
AOP	Adverse Outcome Pathway
Biological plausibility	The 'biologically plausible link' relies on an understanding of the fundamental biological processes involved and whether they are consistent with the sequence of the events proposed. Note that the biologically plausible link is assumed in case there is endocrine activity and EATS-mediated adverse effects, in the absence of information demonstrating the contrary (i.e. a fully developed non-ED MoA that is proven to be more important than the next most plausible ED MoA).
BPR	Biocides Products Regulation
CLP	Classification, Labelling and Packaging Regulation
CMR	Carcinogens Mutagens Reprotoxic
ED activity	A substance that has an 'endocrine activity' has the potential to interact with and alter the function(s) of the endocrine system, target organs and tissues. This interaction may occur at any level in a biologically plausible sequence of events leading to an adverse effect
EASIS	Endocrine Active Substances Information System https://easis.jrc.ec.europa.eu/
EATS	Estrogen (E), Androgen (A), Thyroid (T) and Steroidogenesis (S)
ED	Endocrine Disruptor
ENV	Environment
EFSA	European Food Safety Authority
GCL	Generic Concentration Limit
GD	Guidance Document
HH	Human Health
MoA	Mode of Action
MOCs	More than One Constituent
MTD	Maximum Tolerated Dose
OECD	Organization for Economic Co-operation and Development
PPPR	Regulation (EC) 1107/2009 on authorisation and marketing of pesticides
RAAF	Read-Across Assessment Framework
QSAR	Quantitative structure-activity relationship
SCL	Specific Concentration Limit
STOT	Specific Target Organ Toxicity
SVHC	Substances of Very High Concern

UVCBs	Unknown or variable composition, complex reaction products or of biological materials
UN GHS	United Nations Globally Harmonized System of Classification and Labelling of Chemicals
WoE	Weight of Evidence

Annex 1: multi-metallic topics for which projects/cooperation with expert panels (ETAP, HeTAP) are considered, ongoing:

- Relevance of *in vitro* assays and applicability to metals/inorganics
- Exploration of the (non-)threshold issue and use of bioavailability, consideration of essentiality
    - Subgroup meeting in July 2025:
        - identification of several references for further analysis and discussion: e.g. Choi et al. 2024, Borgert et al. 2024, Matthiessen et. al., 2016; Borgert et. al., 2013; Brescia, 2020; Day et. al., 2018; Lamb IV, et. al., 2014; Hass et al., 2019; JRC, 2013; Endocrine Society, 2018; Demeneix et al., 2020; KemI, 2013; example of bromide (mandate under Article 75(1)g of the BPR by eCA DK – providing differing views on the existence of a threshold for EDs
        - discussion on how natural occurrence and essentiality may play a role => need to assess existence of a threshold on a case-by-case basis, depending also on e.g. interactions with receptors, quantification will remain a challenge
        - pragmatic approach: use of concentration limits
        - agreement to continue discussion in ETAP, collect data on mode of action and physiological role
        - discussion of secondary effects
- Correction Tier 2 MeClas for complex materials including consideration of additivity
    - subgroup meeting in July 2025, outcomes included in this updated version
    - correction to be approved by the MeClas Steering Committee in autumn 2025
- Grouping of alloys and other complex materials (read-across, bridging)
- ...

Annex 2: overall timeline


Monitoring UN/UNEP activities with ICMM
1 May 2025
CLP deadline for substances
Q4 2025-Q1 2026?
REACH Simplification Proposal
Identification of multi-metallic projects followed up by the EM Taskforces (in vitro applicability, thresholds, MOCs)
Drafting and update of EM simplified guidance CLP/REACH
ETAP
January
ED workshop
March
Science Forum
April
ED workshop
July
Subgroup meeting
September
ED training
Updates
Registration dossiers
2025 – Q1
Q2
Q3
Q4
2026 –Q1
CARACAL ED Sub-group
18 February 2025
CARACAL-54
3-4 April 2025
CARACAL-55
3-4 July 2025
CARACAL-56
January tbc
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