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Updates to guidance documents for generation and evaluation of data

New CLP classifications and Biocide Bee guidance

May 2025

New hazard classes 2023

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
PBT	EUH440	Accumulates in the environment and living organisms including in humans
vPvB	EUH441	Strongly accumulates in the environment and living organisms including in humans
PMT	EUH450	Can cause long-lasting and diffuse contamination of water resources
vPvM	EUH451	Can cause very long-lasting and diffuse contamination of water resources

- The new hazard classes are:
- 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)
- New EU hazard statements:
-

Application dates
The new rules are in force as of 20 April 2023

Currently 5 entries on Registry of CLH intentions until outcome, for **ED** properties

CLH process

Which substances should be harmonised?

→ Focus on substances which are of **most concern to human health**, i.e.:

- Carcinogenic (C)
- Mutagenic (M)
- Reproductive toxicants (R)
- Respiratory sensitisers (RS)
- EDs and PBT PMTs in CLP revision end of 2024?

→ Other hazard classes can be harmonised on a case-by-case basis – justification needed, but…

→ Active substances in **plant protection products** (PPPs) **and biocidal products** (BPs) are normally harmonised

CLH proposal

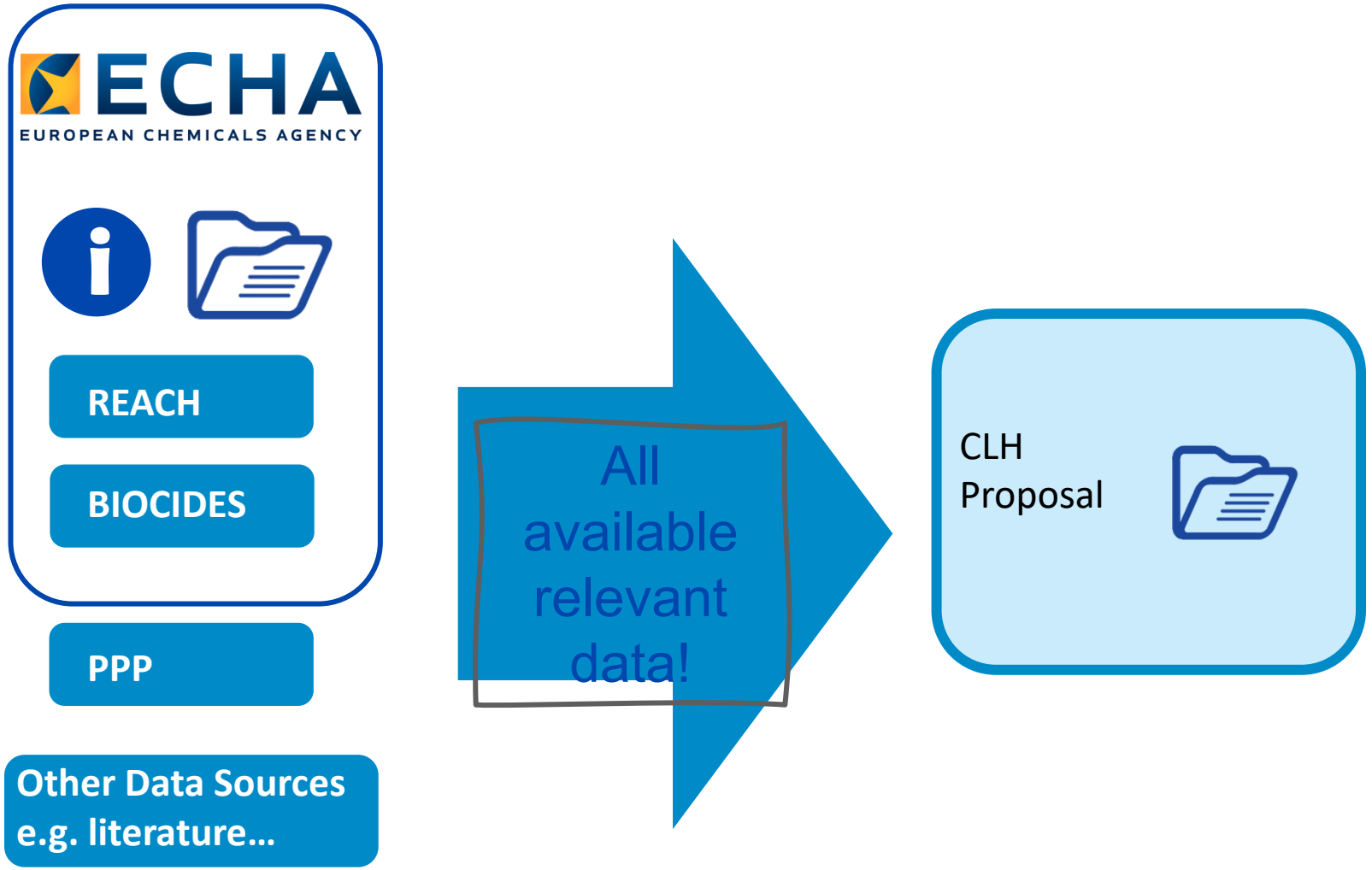
CLP2.0 revision will allow ECHA & EFSA to submit CLH proposals

→ Prepared by
- Member State Competent Authorities (MSCAs) ***most cases***
- ”Industry” (M/I/Dus)

→ Discussed and adopted by
- Risk Assessment Committee (RAC) – a Scientific committee composed of MS representatives where one member is appointed as a Rapporteur to prepare a draft opinion and defend it at the RAC.

ECHA (C4 and RAC secretariat) provides support to all actors during the process

CLH proposal – Data sources

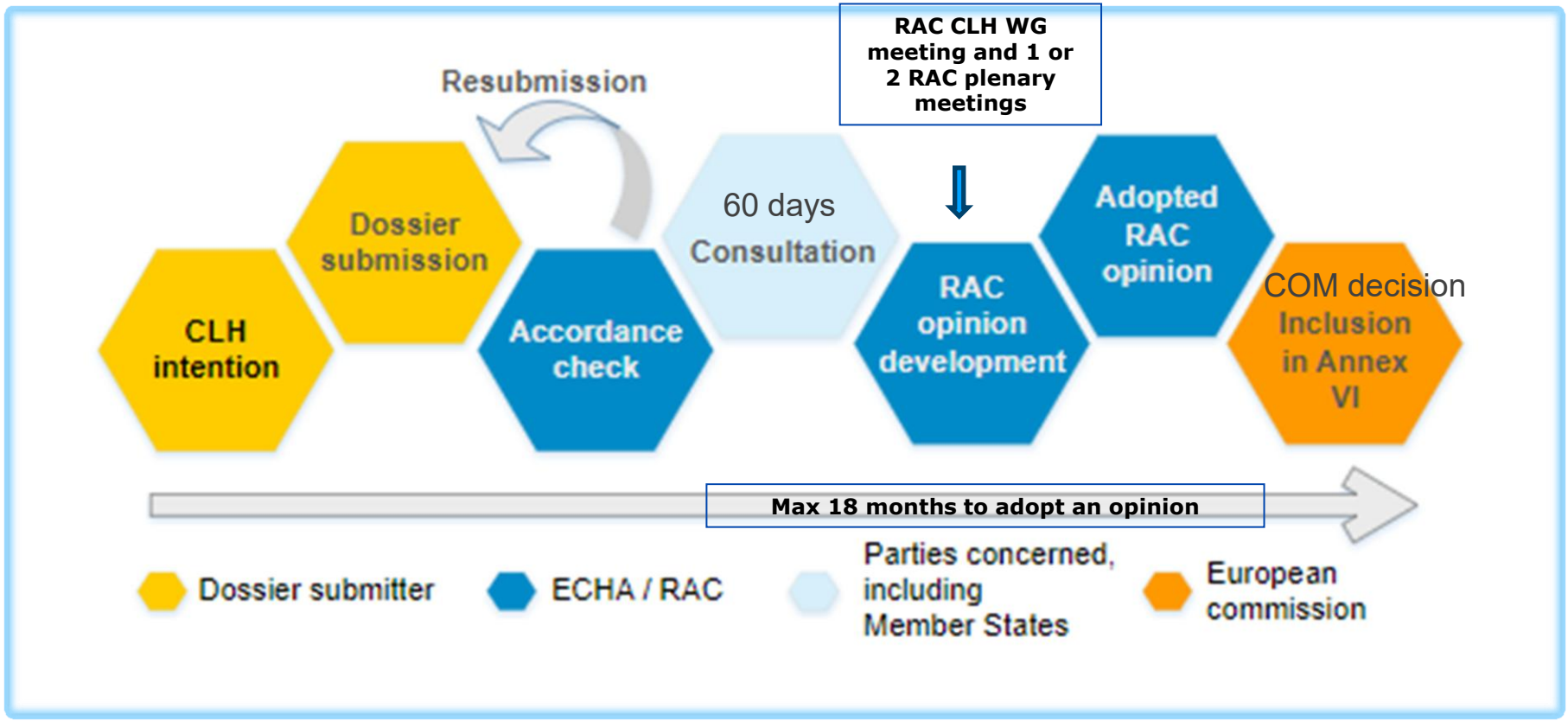


CLH proposals on EDs

- *MS can already make CLH proposals for new Hazard Classes*
- *CLH proposal template is revised*
- *Industry can self-classify*

There are application dates after which it will be mandatory to indicate if the substance is classified in any of the new hazard classes.
New hazard classes 2023 - ECHA (europa.eu)

CLH process



https://echa.europa.eu/regulations/clp/harmonised-classification-and-labelling

Actors and roles in the CLH process

→ **Dossier submitter**: Submits CLH intention to ECHA. Prepares dossier containing CLH proposal and responds to comments received during public consultation (PC)

→ **ECHA-secretariat**: Steers the CLH process and provides technical, administrative and scientific support

→ **Committee for Risk Assessment (RAC) and its Rapporteurs:** Examines the CLH proposals and prepares an **opinion** on the proposed harmonised classification for a substance

→ **Parties concerned:** Provide comments, possible additional data or identify themselves as parties concerned during consultation

→ **Commission:**

- decision on inclusion of the harmonised classification in Annex VI of CLP, based on **opinion** adopted by RAC
- representatives of the Commission act as observers at RAC meetings

CLH ED template

- → Version 1 very flexible
- → ECHA would like to collect experience from users
- → CLH report template:

https://echa.europa.eu/documents/10162/17220/clh_report_template_en.docx/b89cfbb2-aa3c-4a5c-9c15-0b1d7c166028?t=1683098745613

Relevant links

→ CLP Regulation (Annex I, 4.3 and 4.4 on new hazard classes)

- *https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1272-20230420*

→ Understanding Harmonised classification and labelling (CLH)

- *https://echa.europa.eu/regulations/clp/harmonised-classification-and-labelling*

→ CLH Registry of Intentions

- *https://echa.europa.eu/registry-of-clh-intentions-until-outcome*

ED New Guidance

Substances already concluded as EDs under PPPR, BPR or REACH (SVHC)

→ An ED conclusion based on the ED criteria for BPR or PPPR correspond to *Category 1 under CLP* – direct transfer foreseen

→ An active substance concluded not to meet the ED criteria under BPR or PPPR

- Can be Category 1, Category 2 or No classification under CLP, depending on data available when re-assessed

→ ED SVHCs correspond to *Category 1 under CLP* – direct transfer foreseen

Scope of the endocrine system and scope of the Guidance

→ The **CLP criteria apply to all endocrine modalities**

→ Approach taken:

- Since the CLP ED criteria does not limit the scope of the endocrine system neither should the guidance.
- Knowledge and test methods most advanced for EATS modalities. However, this does not exclude that there may be situations where the ED criteria are met for a non-EATS modality.
- Classification to be applied whenever data allows.

Solely non-specific consequences of other toxic effects

- Approach slightly different than ECHA/EFSA guidance.
- mostly on the wording 'specific' *vs.* 'non-specific' consequences of other toxic effects.

→ Approach taken:

- Text aligned with legal text and the related text for other hazard classes
- A '*non-specific consequence of the other toxic effects'* is understood as:
  - An endocrine-related adverse effect that is conclusively demonstrated to occur secondary to excessive toxicity; i.e. the co-occurring toxicity is so severe that the animals are suffering or dying.
  - In OECD TGs studies this situation should not normally occur.
- In all other situations, a comparative MoA analysis is needed to differentiate between an endocrine and non-endocrine MoA

Role of adverse outcome pathways (AOPs) in the mode of action (MoA) analysis

→ Approach taken:

- Clarify that an AOP can be the starting point for MoA analysis
- Differentiate between scientifically '*robust*' or '*OECD endorsed*' AOPs *vs.* '*other*' AOPs
- Clarify that for '*other*' less developed AOPs more data is needed to support the hypothesised sequence of events
- Clarify that data on the modified Bradford-Hill criteria increase the support for KERs. However, lack of data on these criteria should not be used to dismiss KERs.
  - Clarify that dose and time concordance important to support KEs
- Clarify that a MoA analysis needs to be supported by data; the amount of data is case-specific.

Human relevance

→ Approach taken:

- Follow the legal text:

CLP, Annex I, Section *3.11.1.2.1.* *Substances and mixtures fulfilling the criteria of endocrine disruptors for human health based on evidence referred to in Table 3.11.1 shall be considered to be known, presumed or suspected endocrine disruptors for human health unless there is evidence conclusively demonstrating that the adverse effects are not relevant to humans.*

- Text aligned with other sections of the guidance

Specific considerations of thyroid modality

→ No consensus reached on the thyroid modality

→ Approach taken:

- All thyroid related MoAs are relevant to humans
- Classification is warranted when a '*pattern of thyroid-related effects lead to the overall conclusion that they constitute an adverse effect*'
- When adverse effects are observed on the thyroid gland, additional mechanistic information is not necessarily required to meet the ED criteria.
  - This is because effects on thyroid weight and histopathology, which are 'T-mediated' parameters, provide intrinsic evidence of adverse effects via endocrine activity.

Examples

→ There were within the PEG and CARACAL diverging views on the usefulness of the examples, and on where the boundaries between the *ED HH 1*, *ED HH 2* and no classification are correctly illustrated by the examples.

- There is **no practical experience** on the application of the CLP ED criteria.
- The decision on classification is based on the **overall strength of evidence** and decided on a case-by-case basis.
- Disclaimer: the **examples are illustrative -** do not pre-empt decisions on classification.

→ ECHA took a decision to delete Cat 2 and no classification examples from the guidance based on the CARACAL comments. Further experience is needed to be able to provide examples.

Examples

→ There are good examples for HH and ecotox regarding classification as ED 1. There are also examples on setting SCL and for ED adversity.

→ Examples how to classify mixtures are absent but the schemas are clear.

→ Potency has returned for non-mammalian data and features in SCL setting.

Issues with the guidance (Industry)

The ECHA ED guidance reflects the evolving landscape of endocrine disruptors, and the uncertainties associated with ED assessment.

- Use of NAMs increasingly encouraged with acknowledgement that more validation is need before they can be used for adversity
- ED assessment includes new non-EATs modalities despite limited mechanistic Knowledge and lack of validated methods

The ECHA ED guidance does not address some uncertainties about the classifications

- Limited clarity on how to differentiate between Cat 1, Cat 2 and no classification
- No indication concerning data sufficiency and or strength of evidence
- How to address human (non-relevance)for the T-modality

MS's View

- → ED assessment a part of substance evaluation since 2018
- → CLP inclusion inevitable? But problematic
- → Categories
- → Guidance published 12th Nov 2024 (Guidance on the Application of the CLP Criteria Part 3: Health Hazards)
- → CLP proposal including ED available on submission of MS AR currently.
- → Formal process starts at dossier submission; timelines followed once dossier is found in accordance
- → ED EG discussion on, e.g. data sufficiency, prior to CLH dossier submission possible

PBT/vPvB and PMT/vPvM Information

- See EFSA document - Guidance on the Application of the CLP Criteria Part 4: Environmental hazards for further detail on definitions and general considerations on PBT/vPvB and PMT/vPvM substance classification.

- Summary tables are provided below.

Persistence criteria

Annex I: 4.3.2.1.1. and 4.4.2.1.1. A substance shall be considered to fulfil the persistence criterion (P) where any of the following conditions is met:

(a) the degradation half-life in marine water is higher than 60 days;

(b) the degradation half-life in fresh or estuarine water is higher than 40 days;

(c) the degradation half-life in marine sediment is higher than 180 days;

(d) the degradation half-life in fresh or estuarine water sediment is higher than 120 days;

(e) the degradation half-life in soil is higher than 120 days.

Annex I: 4.3.2.2.1 and 4.4.2.2.1 A substance shall be considered to fulfil the 'very persistent' criterion (vP) where any of the following situations is met:

(a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days;

(b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days;

(c) the degradation half-life in soil is higher than 180 days.

Bioaccumulation criteria

Annex I: 4.3.2.1.2. A substance shall be considered to fulfil the bioaccumulation criterion (B) where the bioconcentration factor in aquatic species is higher than 2000.

Annex I: 4.3.2.2.2. A substance shall be considered to fulfil the "very bioaccumulative" criterion (vB) where the bioconcentration factor in aquatic species is higher than 5 000.

Mobility criteria

Annex I: 4.4.2.1.2. A substance shall be considered to fulfil the mobility criterion (M) when the log K_{OC} is less than 3. For an ionisable substance, the mobility criterion shall be considered fulfilled when the lowest log K_{OC} value for pH between 4 and 9 is less than 3.

Annex I: 4.4.2.2.2. A substance shall be considered to fulfil the 'very mobile' criterion (vM) when the log K_{OC} is less than 2. For an ionisable substance, the mobility criterion shall be considered fulfilled when the lowest log K_{OC} value for pH between 4 and 9 is less than 2.

Toxicity Criteria

Annex I: 4.3.2.1.3. and 4.4.2.1.3. A substance shall be considered to fulfil the toxicity criterion (T) in any of the following situations:

(a) the long-term no-observed effect concentration (NOEC) or ECx (e.g EC10) for marine or freshwater organisms is less than 0,01 mg/l;

(b) the substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B, or 2) according to sections 3.5, 3.6 or 3.7;

(c) there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification as specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Section 3.9;

(d) the substance meets the criteria for classification as endocrine disruptor (category 1) for human health or the environment according to sections 3.11 or 4.2.

Revision of Biocide Guidance Vol III Parts B+C Assessment and Evaluation

Provisional timeline :

→ PEG meeting: February 2025
→ COM/CA consultation: Spring 2025
→ Publication: Q3 2025

Dietary risk assessment:

→ The need was identified to separate the dietary RA part from the main guidance
→ The process was detached from the finalisation of the main guidance
→ More expertise needed from ARTFood
→ DRA guidance will be published separately, with some delay