Following up on ED hazard classification: consequences and responsibilities

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Outline

- CLP & CLP Guidance on ED
  - Applicability
  - Transition periods
  - Definitions
  - Hazard identification and classification
- Implications for industry – actions needed
    - Business impact assessment
    - REACH, SDS, labels, PCN
    - Communication to workers, clients
    - Substitution (cover by Monika)
- Summary

ED and their hazard classes in CLP

EU / EES

CLP:

- The **C**lassification, **L**abelling and **P**ackaging Regulation (EC) No 1272/2008
  - based on UN GHS, but not identical!
  - No ED in UN GHS (yet?)

REACH:

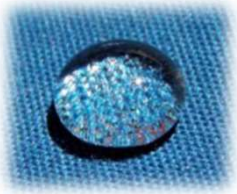
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the **R**egistration, **E**valuation, Authorisation and Restriction of **Ch**emicals (REACH)

Applicability

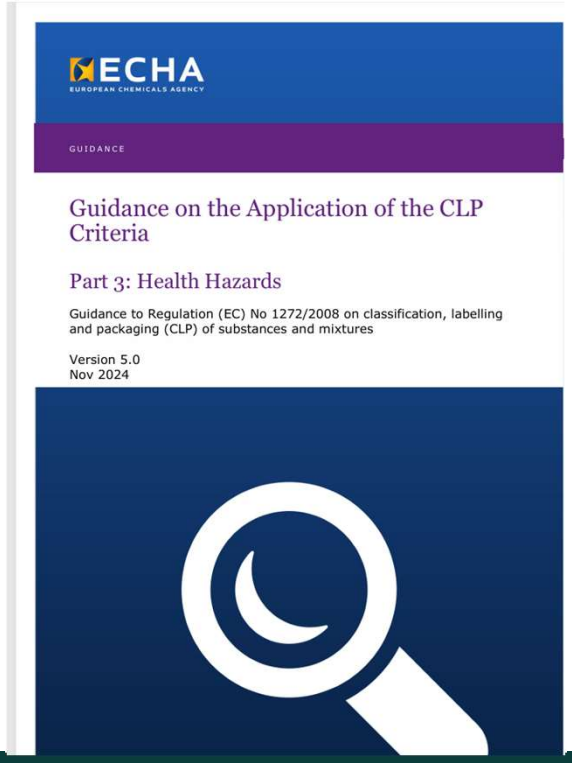
- 44 countries in Europe
- 27 countries in the European Union (EU)
  - Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden
  - CLP & REACH applies in all EU countries
- + Andorra, Monaco, San Marino, Serbia, Norway, Iceland, Liechtenstein

CLP is applicable for many sectors in EU

- Chemical industry
  - Chemicals (raw materials), mining & metals, hydrocarbon refining, nano, polymers
- Pharmaceutical industry
  - not the final drug
- Agricultural industry incl biocides
- Food & feed industry
- Cosmetics
  - not the finished cosmetic product
- Etc.



New CLP and New CLP Guidance



- CLP 2.0 was adopted by Council 14 Oct 2024 & published in OJ 20 Nov, 2024
  - Regulation (EU) 2024/2865 of the European Parliament and of the Council of 23 October 2024 amending Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (Text with EEA relevance)
- CLP Guidance in Nov 2024
  - Guidance on the Application of the CLP Criteria Part 3
  - Guidance on the Application of the CLP Criteria Part 4 & 5

Transition periods of new CLP and ED classification

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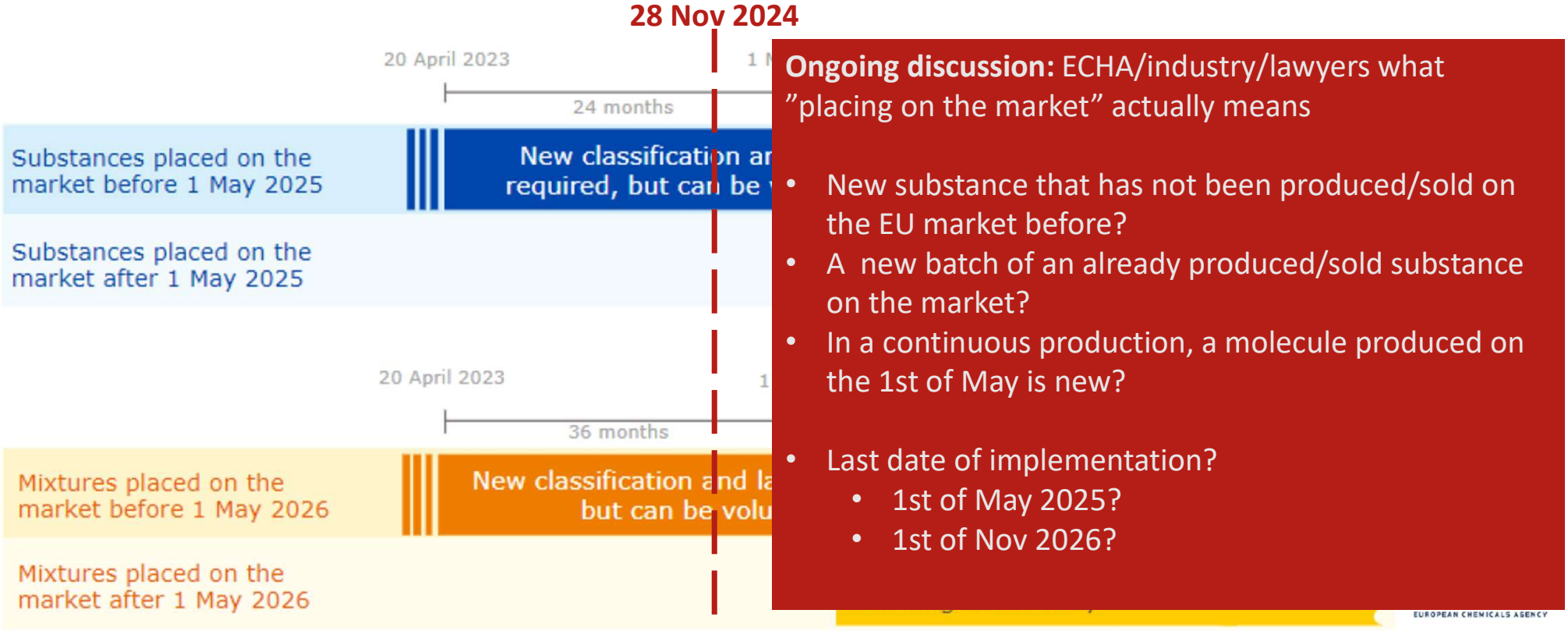

Ongoing discussion: ECHA/industry/lawyers what ”placing on the market” actually means

- New substance that has not been produced/sold on the EU market before?
- A new batch of an already produced/sold substance on the market?
- In a continuous production, a molecule produced on the 1st of May is new?

- Last date of implementation?
  - 1st of May 2025?
  - 1st of Nov 2026?

HH[1] & ENV[2] ED definitions identical

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

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

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

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

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

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

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HH & ENV ED definitions identical

Intact organism is explained more in detail in guidance

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Correlation is explained more in detail in guidance

EATS (and non-EATS)

- There are at least 50 hormones produced by the classical endocrine glands (i.e. adrenal, hypothalamus, pituitary, (para)thyroid, pineal gland, pancreas, ovary and testes).
- In addition, there are about 100 hormones produced by other tissues.
- CLP criteria do not differentiate between different modalities, thus covering all endocrine-disrupting MoAs
  - The CLP guidance mainly addresses the effects caused by **estrogen, androgen, thyroid, and steroidogenic (EATS)** modalities.
  - The EATS modalities are the pathways for which there is relatively good mechanistic understanding on how substance-induced perturbations may lead to adverse effects via an endocrine-disrupting MoA.

Hazard identification and assessment

- What ED data is available?
  - No requirement for new ED data generation, but battery of OECD tests available
    - No single test can be expected to detect all types of endocrine activity
    - No data – no hazard (classification)?
- Need to **meet all three criteria**
  - Endocrine activity
    - Data in *in vivo* or *in vitro* mechanistic studies
  - Adverse effects
    - Data in animal studies with repeated exposures (RAx/analogy), according to OECD TGs (414, 421/422, 443), at or close to limit dose of 1000 mg/kg
  - Biologically plausible link
    - AOPs can be helpful, but not needed.
- HH: Human data
- ENV: Fish or mammalian data
- Research data

Hazard categories:
Cat 1: Known/presumed vs Cat 2: Suspected

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 doubt 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.

HH: Adverse effects in humans

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.

ENV: Adverse effects at population level

Hazard classification:
New ED hazard statements

Independent HH/ENV

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

Classification: WoE & expert judgement

3.11.2.3.1. Classification as an endocrine disruptor for human health is made on the basis of an assessment of the total weight of evidence using expert judgment (see Section 1.1.1). This means that all available information that bears on the determination of endocrine disruption for human health is considered together, such as:

(a) in vivo studies or other studies (e.g. in vitro, in silico studies) predictive of adverse effects, endocrine activity or biologically plausible link in humans or animals;

(b) data from analogue substances using structure-activity relationships (SAR);

(c) evaluation of substances chemically related to the substance under study may also be included (grouping, read-across), particularly when information on the substance is scarce;

(d) any additional relevant and acceptable scientific data.

4.2.2.3.2. In applying the weight of evidence determination and expert judgement, the assessment of the scientific evidence referred to in Section 4.2.2.3.1 shall, in particular, consider all of the following factors:

(a) both positive and negative results;

(b) the relevance of the study design for the assessment of adverse effects and its relevance at the population or subpopulation level, and for the assessment of the endocrine activity;

(c) the adverse effects on reproduction, growth/development, and other relevant adverse effects which are likely to impact on populations or subpopulations;

(d) the quality and consistency of the data, considering the pattern and coherence of the results within and between studies of a similar design and across different species;

(e) the route of exposure, toxicokinetic and metabolism studies;

(f) the concept of the limit dose (concentration), and international guidelines on maximum recommended doses (concentrations) and for assessing confounding effects of excessive toxicity;

(g) where available, adequate, reliable and representative field or monitoring data or results from population models.

Hazard classification: ED is different than other hazard classes

- The classification for ED HH differs from the other hazard classes in that it refers to a specific MoA which leads to an adverse effect(s).
  - Ex. A substance can be classified as Toxic to Reproduction (litter size is significantly reduced due to a chemical exposure). The MoA behind this adverse effect can be known or unknown. If known, it *could* be an endocrine MoA. But the MoA could also *not* be affecting the endocrine system.
  - Substance is classified Repro 1B
    - ED MoA -> Repro 1B + ED Cat 1/2
    - Non-ED MoA -> Repro 1B only
    - No data on MoA -> Repro 1B only
  - Same for Carc and STOT RE

Hazard classification: Mixtures

- Use of Generic Concentration Limits (**GCLs**) of the components, Table 3.11.2
- Specific Concentration Limits (**SCLs**) for ED properties are set based on the potency of the adverse effect
- On a case-by-case basis, test data on the mixture as a whole may be used for classification

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 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]

CLP Guidance classification examples

- ED HH/ENV cat 1 examples given
- But not ED HH/ENV cat 2!
  - PEG divergent views
  - Await ECHA Committee for Risk Assessment (RAC) ED HH cat 2 decisions (?)
- Will be updated “soon” with more experience

Industry implications

Industry actions required during transition period and implementation

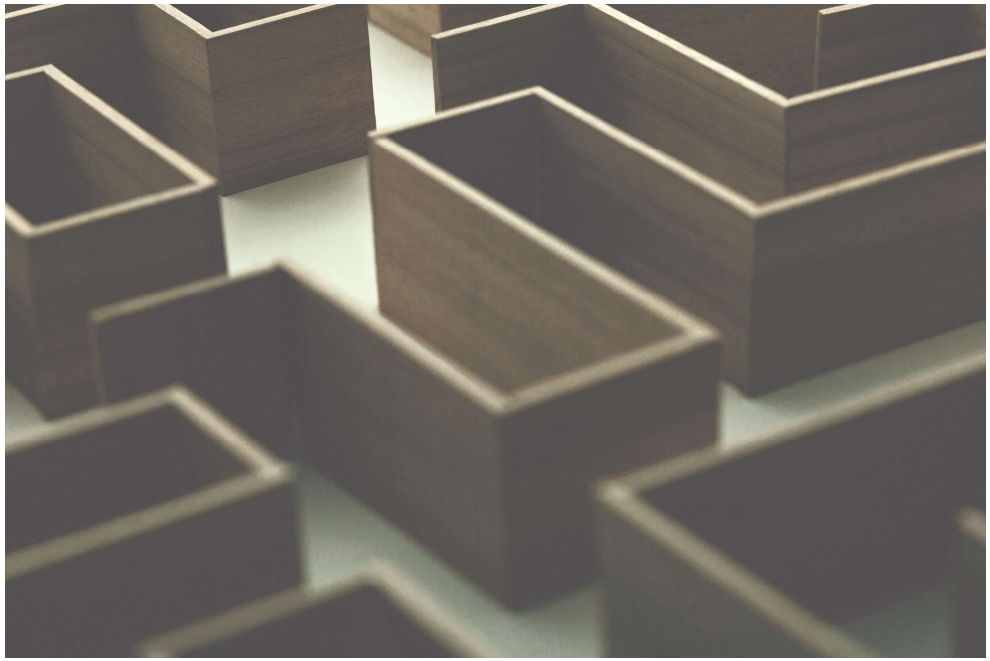
1.	Business impact assessment	All*
2.	Hazard identification	M*/I*/all
3.	Hazard classification	All
4.	Update of REACH dossier for substances (within 12 months)	M/I
5.	Update of ECHA C&L inventory	M/I
6.	Update Safety Data Sheets (SDS)	All
7.	Update of Poison Centre Notifications (PCN) in all EU countries where sold	All (as applicable)
8.	Update of product hazard labels	All (as applicable)
9.	Add new labels to products, pipes, tanks, etc	All (as applicable)
10.	Communicate to customers (letter, SDS, label)	All (as applicable)
11.	Keep an eye on SVHC candidate list and Substitute (Monika)	All (as applicable)

* roles in supply chain: M:Manufacturer, I:Importer, All: M+I+formulator/downstream user+ distributor/retailer

REACH: **A**uthorisation

Authorisation

- Aims to ensure that substances of very high concern (SVHCs) are progressively replaced by less dangerous substances or technologies where technically and economically feasible alternatives are available.
- Substances with the following hazard properties may be identified as SVHCs:
  - Carcinogenic, mutagenic or toxic for reproduction (CMR) category 1A or 1B in accordance with the CLP Regulation.
  - Persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) according to REACH Annex XIII.
  - Substances on a case-by-case basis, that cause an as CMR or PBT/vPvB substances. **equivalent level of concern**



Summary

- Not globally harmonised; EU-specific regulation as ED building blocks not (yet?) in UN
- Read new CLP guidance(s) back and forth
- Send questions to ECHA PCN and SDS/REACH helpdesk
- Keep an eye on transitional periods
- Initiate business impact assessment of new CLP requirements to understand the coming workload
- To learn more; join ECHA workshop on new hazard classes that will be held during 2025

- No data – no classification!
  - How to avoid regrettable substitution… next speaker Monika

Thank you!

Questions?

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