ECHAs view on identification of up-to date practices for use of NAMs in ED identification, as well as needs and requirements for advancing methodologies, principles, and approaches

EURION final & ENKORE kick-off event

14 June 2024 (virtual)

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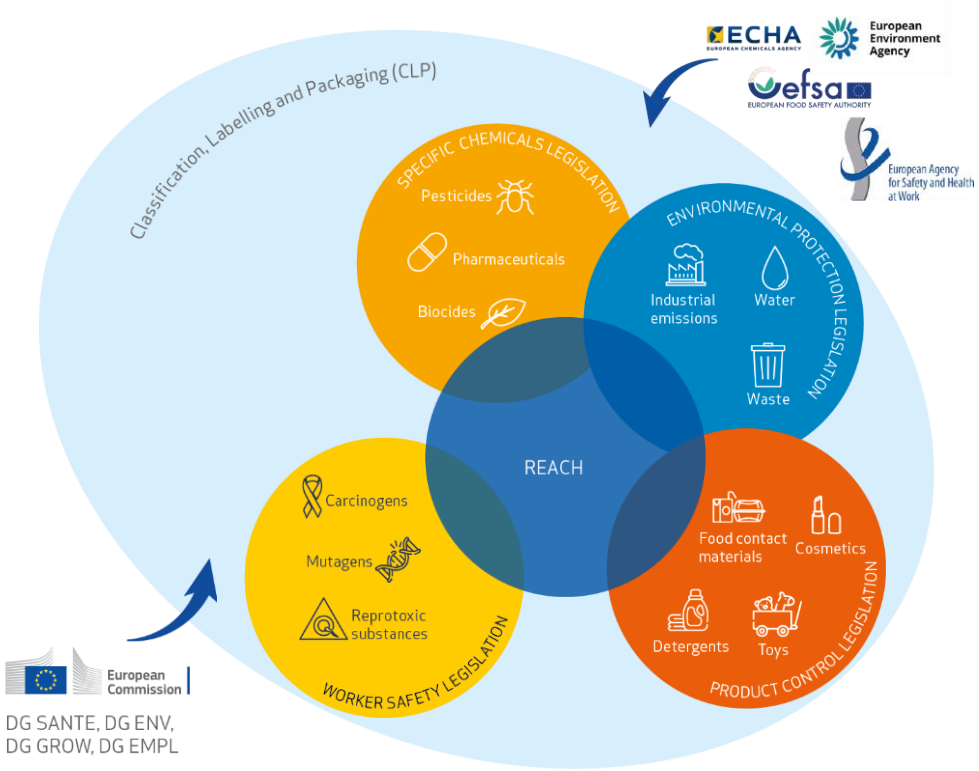
- → EU Chemicals legislation framework
  - Regulatory context - CLP
    - ED Guidance update status
  - Regulatory context - REACH
- → Starting point for the use of NAMs
- → NAMs in the regulatory system

EU Chemicals legislation framework



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Regulatory context – current system (CLP)

→ The regulatory system for industrial chemicals management relies on a **horizontal generic approach** based on the **identification of hazardous properties** of substances.

→ **Classification, Labelling and Packaging (CLP) Regulation** is the cornerstone legislation which:

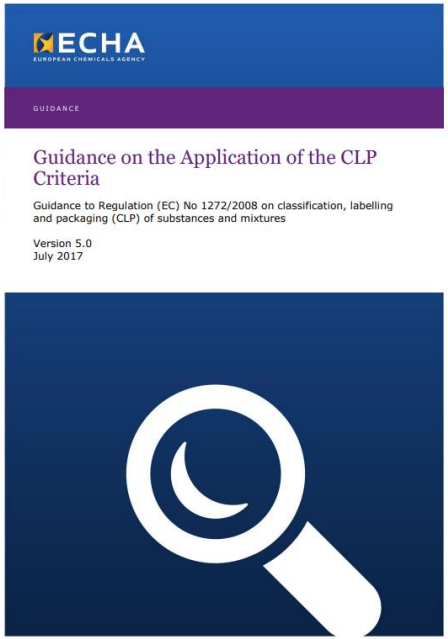
- Enables the **identification of hazardous properties and classification** based on adverse effects, **independently of exposure**, by applying specific criteria agreed at EU and international level (UN Global Harmonised System (GHS)),
- ensures, through **harmonised classification and labelling** that appropriate classification is consistently applied for most hazardous substances and can be easily enforced
- has **direct impact on other EU legislations**, including REACH, pesticide, biocide, cosmetic legislation, legislation regulating worker protection, etc.
- enables efficient **hazard communication** to workers, downstream users, consumers
- provides a **framework for generic risk management**.

Guidance update

- ’Guidance on the Application of the CLP Criteria’
  - New classes and criteria
  - Part 3
    - 3.11 ED for HH
  - Part 4
    - 4.2 ED for ENV
    - (4.3 PBT/vPvB & PMT/vPvM)

Further updates in future with more experience

ED guidance publication:
Estimated October 2024



Before publication, EFSA/ECHA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and EC No 1107/2009 may be used for Cat 1
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311

Timeline for the guidance

- → May 2023: ED EG meeting & consultation (>1000 comments)
- → Sept 2023: PEG consultation (>2000 comments)
  - Parallel consultation of ECHA Committees (RAC, MSC, BPC)
- → Dec 2023: PEG meeting
- → Jan 2023: PEG comments to RCOM, PEG WGs
- → May 2024: targeted PEG consultation (>800 comment)
- → July-Aug 2024: CARACAL consultation
- → Oct 2024: Publishing

Start	End	Task
02/07/2024		Presentation of the ED guidance to CARACAL
01/07/2024	**18/08/2024**	**Written consultation of CARACAL**
19/08/2024	19/09/2024	ECHA addresses CARACAL comments
20/09/2024		Final guidance to communications
04/10/2024		Publication of guidance

→ Consultation procedure, 9/2023 version publicly available
https://echa.europa.eu/support/guidance/consultation-procedure/ongoing-clp

Regulatory context – current system (REACH)

→ **REACH** feeds into CLP and ensures that industry provides adequate data for hazard assessment, including classification and labelling by:

- specifying **standard information requirements**;
- requiring data to be generated using **standardised and broadly accepted testing methods** (e.g. at OECD level), which:
  - enable the identification of adverse effects and comparison with CLP/GHS criteria
  - enable the derivation of safety levels to be compared with external exposure levels and decide on appropriate company level and regulatory risk management
  - the level of uncertainty related to the results obtained by these methods is considered 'acceptable' for regulators
  - allow mutual acceptance of data between different EU legislations and internationally.

The starting point for the use of NAMs

While considering a system based on non-animal test methods, main elements of the horizontal system should be maintained:

- Defined **hazard classes** based on clear criteria
  - ✓ worldwide harmonisation via GHS
  - ✓ with associated generic risk management measures (EU)
- **Standard information requirements** allowing conclusive outcome for:
  - ✓ classification & labelling (C&L)
  - ✓ reference doses for risk assessment
- **Quality data** for decision making:
  - ✓ reliable comparable and re-usable
  - ✓ allowing mutual acceptance of data

→ **Currently we don't have NAM based solutions able to cover these 3 main elements for complex tox endpoints!**

NAMs in the regulatory system

- A possible way forward -

1) **To close major gaps**
2) **To gain experience**
3) **To propose a new "NAM friendly" system?**

Define

Identify critical needs transit to animal free system to steer NAM development

Demonstrate

Apply already available NAMs under the current system

Re-design

Re-think the overall system to enable NAMs & **Redefine** the main elements of the horizontal approach

Time

Now | Short-term | Mid-term | Long-term

Step 1: identify (and address) critical needs

Demonstrate NAMs can derive protection levels comparable with current ones

- **Hazard identification:** Ability to demonstrate that NAMs, (e.g. an integrated *in vitro/in silico* system) can be used to allow a conclusive outcome on the (lack of) hazardous properties for a given regulatory endpoint
- **Hazard characterisation:** Ability to reliably identify hazard based on changes at the molecular/cellular level instead of observed adversity in an organism
- **Extrapolation:** Ability to reliably convert nominal concentrations measured or predicted by NAMs into external doses used to set safety levels, to communicate the hazard and assess the risks

Step 2: Apply NAMs under current system

There is significant potential for **refinement** and **reduction**, using tools already available in the following areas:

For lower tier endpoints

- **Developments of *in silico* methods (e.g. QSARs)** with higher predictive capacity and broader applicability domain for hazard and risk assessment

For higher tier endpoints

- Better utilisation of **'omics** to support **read-across and grouping**
- Introduction of ***TG+*** studies (**omics enhanced bioassays)** to generate molecular data in an entire biological system
- Introduction of the **in vitro toxicokinetic measurements +** generic **PBK model** to allow IVIVe and identify potential for bioaccumulation in air breathers

Step 3: Adapt overall system (if necessary)

Potential areas for consideration are:
While closing critical gaps identified in step 1 and gaining confidence in step 2, we can start considering what is needed for a new framework.

- How to derive reference values for risk assessment from **molecular data** (not adverse effects)
- How to **calibrate** the system against expected and well-defined **protection goals**
- Revision or **development of C&L criteria which are suitable for NAMs**
- Throughput/performance and cost **optimisation**

Thank you

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While developing and testing new methodology we are trying to address the following problems:

→ **Toxicological significance of the model used to generate NAM data**

- Is the model capable of expressing relevant toxicity?
- How to define criteria for it?

→ **What is similar and what not**

- What level of similarity in molecular response should be considered to justify toxicological similarity?
- How to define it (e.g. can we define feature space to cover whole tox space relevant for given endpoint)?

→ **Interpretation of molecular data to substantiate the grouping hypothesis**

- How feasible is the interpretation of the NAM data to substantiate a grouping hypothesis, considering specific endpoint that is being read across?
- How to develop criteria for it?