CLP: methodology for classification of mixtures

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CLP applies to both substances and mixtures:

Substances

- → Definition: In natural state or obtained by any manufacturing process, incl. any additive necessary to preserve its stability + impurities
- → Annex VI is list of harmonised classifications → binding at EU level.
- → These are relevant to the classification of mixtures containing these substances
- → Some substances can also be described as mixtures

Mixtures

- → Definition: A mixture or solution composed of two or more substances
- → Formulations are mixtures
- → Classification can be based on information
  - on the mixture itself (e.g. acute toxicity, irritation), or
  - on similar tested mixtures (bridging priciples)
  - from the substances in the mixture used for classification and labelling

Classification criteria are provided in CLP per hazard class

Classification of mixtures

Mixture classification

Art. 9 of CLP

A tiered approach applies to the classification of mixtures:

1. Data available on the mixture itself (Art. 9.2 and 9.3)

2. Bridging principles (Art. 9.4)
(i.e. data for similar tested mixtures)

3. Classification based on hazards of the individual ingredients and their concentrations (Art. 9.4)
(cut-off values, concentration limits, multiplying factors-calculations)

1. Data available on the mixture itself

- Use same criteria as for substances, CLP Annex 1
- Hazard classes other than CMR, mainly “low tier” endpoints
- Must be critically assessed
  - Tests not normally/ necessarily validated for mixtures
  - Standard tests not suitable for certain mixtures, see e.g CLP guidance on mixture testing of LLNA & classification

2. Bridging principles

- In case of *relevant, reliable and adequate* data on similar tested mixtures and individual hazardous ingredients
- Simple mixtures or simple changes to a mixture
- Clarification anticipated in the CLP Revision

1. Dilution
2. Batching
3. Concentration of highly hazardous mixtures
4. Interpolation within one toxicity category
5. Substantially similar mixtures
6. A small change in the composition
7. Aerosols

3. Classification based on hazards of the individual ingredients and their concentrations

They are used for **mixture** classification **when**:

- *test data for the whole mixture are not available*
- *bridging principles cannot be applied*

Primary approach for mixtures containing CMR substances

They are also used for classification of **substances** when they contain hazardous additives or contaminants.

Concentration thresholds in CLP

- **Generic Concentration Limits**
  (Article 10, Tables in section 3-5, Annex I)

- **Specific Concentration Limits**
  (Article 10, Table 3.1, Annex VI, and «self-classification»)

- **M-factor** *for aquatic environmental hazards*
  (Article 10, Part 4, Annex I)

Also generic cut-off values are the minimum concentration that «shall be taken into account for the classification»
(Article 11 and Table. 1.1.)

Generic and specific concentration limits

- Generic concentration limits (GCLs) are defined in CLP for most health hazard classes (in Part 3, Annex I, CLP)
- For high and low potency substances specific concentration limits (SCLs) can be set – based on data
- Concentration above GCL/SCL lead to classification
  - In case of additive effects, the sum of concentrations of constituents

Generic concentration limits for classification

Ingredient classification			Category 1, 1A or 1B	Category 2
Mutagenicity or Carcinogenicity		1A or 1B	≥ 0,1 %	-
		2	-	≥ 1,0 %
Reproductive toxicity		1A or 1B	≥ 0,3 %	-
		2	-	≥ 3,0 %
STOT (SE & RE)		1	≥ 10 %	1,0 % ≤ concentration < 10 %
		2	-	≥ 10 %
Resp. Sens.	solid/ liquid	1A	≥ 0,1 %	-
		1, 1B	≥ 1,0 %	-
	gas	1A	≥ 0,1 %	-
		1, 1B	≥ 0,2 %	-
Skin sensitisation		1A	≥ 0,1 %	-
		1, 1B	≥ 1,0 %	-

Additivity formulae
Human health hazard: Acute toxicity

A calculation formula is used which is based on acute toxicity estimates and concentrations:

If the unknown ingredients are ≤ 10%

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

where:
Ci = concentration of ingredient i (% w/w or % v/v)
i = the individual ingredient from 1 to n
n = the number of ingredients
ATEi = Acute Toxicity Estimate of ingredient i

Environmental classification M-factors

Annex I: *Table 4.1.3*

Multiplying factors for highly toxic components of mixtures

Acute toxicity	M factor	Chronic toxicity	M factor	
$L(E)C_{50}$ value		NOEC value	NRD[a] components	RD[b] components
$0,1 < L(E)C_{50} \leq 1$	1	$0,01 < NOEC \leq 0,1$	1	-
$0,01 < L(E)C_{50} \leq 0,1$	10	$0,001 < NOEC \leq 0,01$	10	1
$0,001 < L(E)C_{50} \leq 0,01$	100	$0,0001 < NOEC \leq 0,001$	100	10
$0,0001 < L(E)C_{50} \leq 0,001$	1000	$0,00001 < NOEC \leq 0,0001$	1000	100
$0,00001 < L(E)C_{50} \leq 0,0001$	10000	$0,000001 < NOEC \leq 0,00001$	10000	1000
(continue in factor 10 intervals)		(continue in factor 10 intervals)		

[a] Non-rapidly degradable.

[b] Rapidly degradable.

Mixture classification of CMR

CLP Regulation

→ The mixture shall be classified as a [CMR] when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 [CMR] and is present at or above the appropriate generic or specific concentration limit as shown in Table [3.5.2, 3.6.2 or 3.7.2] for Category 1A, Category 1B and Category 2 respectively.

Concerning classification of mixtures when data are available for the complete mixture

→ On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components/ ingredients.

→ In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of [CMR] test systems.

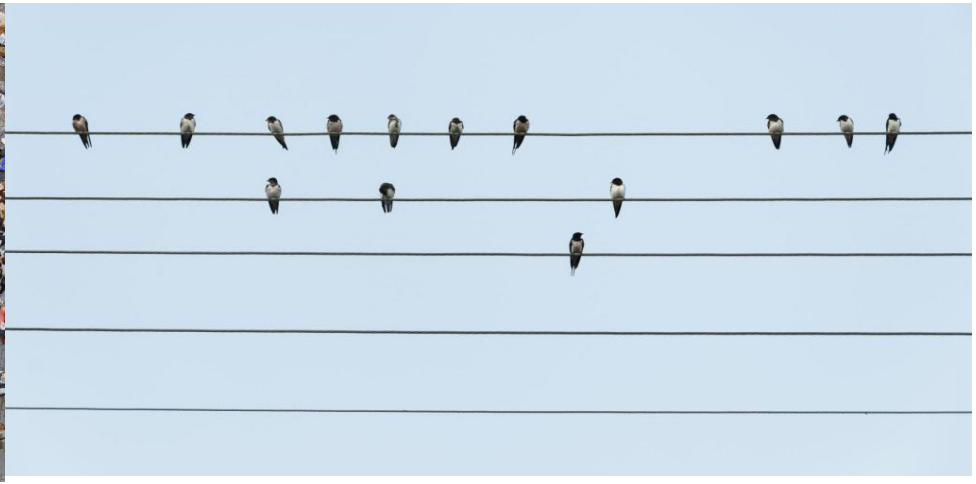
→ Adequate documentation supporting the classification shall be retained and made available for review upon request

Why not test & classify the mixture directly for CMR? Scientific basis

→ Studies on animals have a certain (statistical) **power to identify effects**

→ A study on a sufficient number of animals is a surrogate for the exposed human population

- 50 animals/sex/dose for a ”life-time” carcinogenicity study
- Controls + at least 3 doses -> highest dose elicits some toxicity
- Confidence in the results (negative and positive)



Conclusions

- → Provisions in CLP are expected to lead to adequate protection of the community from hazardous properties of substances and mixtures.
- → Sufficiently high (statistical) power in an appropriately designed test is key to making informed decisions about the safety of substances and mixtures.
  - Hazardous potential of substances is usually also exhibited by the substance when it is in a mixture
  - Data from testing mixtures not very informative for CMR hazards; results can be difficult to interpret
    - Lack of effect likely to be due to inability to detect effects
  - -> CMR mixture classification needs to be based on the properties of the constituents
  - If the GCL are adequately conservative, classification and its downstream consequences are adequately protective
- → New hazard classes introduced into CLP ensures more complete "capture" of toxic substances by the regulation and therefore toxicity of mixtures is also more comprehensively addressed

Available CLP guidance

Guidance documents

- Introductory Guidance on the CLP Regulation
  (basic features and procedures laid down in Regulation (EC) No 1272/2008)
- Guidance on the application of the CLP criteria
- Guidance on the preparation of dossiers for harmonised classification and labelling

Link to guidance documents:

https://echa.europa.eu/guidance-documents/guidance-on-clp

ECHA Website – links to further information

Harmonised classification and labelling (CLH) - ECHA (europa.eu)

Mixture classification - ECHA (europa.eu)

Thank you

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