Mixtures classification - practical application

Mixture classification and communicating safe use of mixtures. Advice for formulators and importers

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Tiered approach in classification of mixtures

- In general

1. Data available on the mixture itself

New!

2. Bridging principles

Most often used:

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

1. *Relevant, reliable and adequate* **data available on the mixture itself** ➔ use the data to classify

Note: expert judgement normally needed

2. **Bridging principles** – only where *relevant, reliable and adequate* data are available on similar tested mixtures and individual ingredients

Note:

- Animal studies are to be avoided.
- Available test data on substances and mixtures must be based on studies conducted using methods validated for the purpose.

Most often used:

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

Bridging principles – human health and environmental hazards only

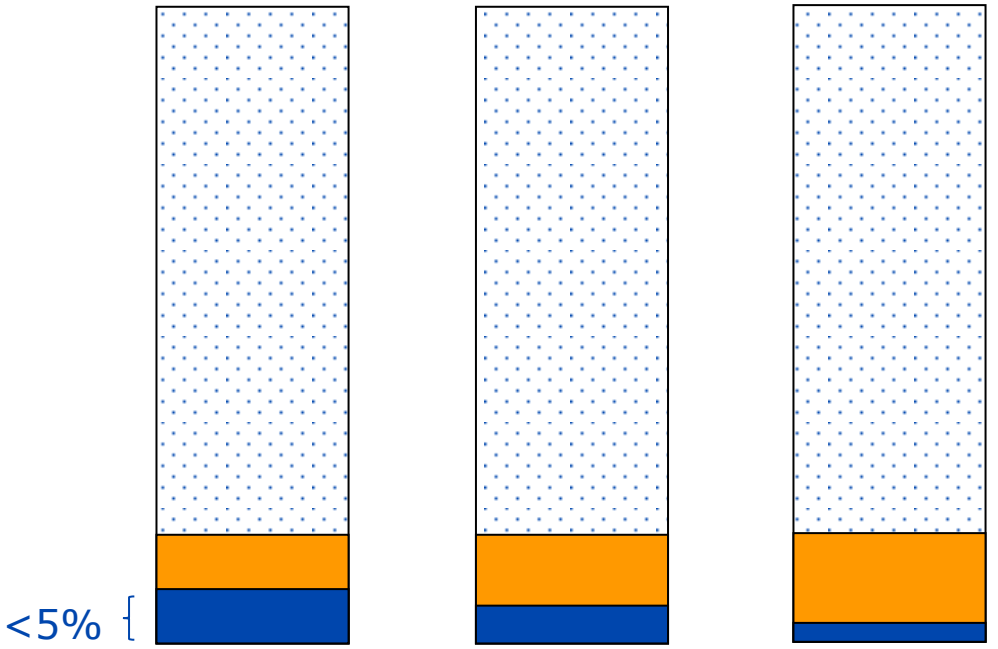
Bridging principle	Applicability
Dilution Batching A small change in the composition Substantiality similar mixtures	All hazard classes
Aerosols	Not applicable to CMR, aspiration hazard or environmental hazards
Concentration of highly hazardous mixtures Interpolation within one toxicity category	Not applicable to CMR-RS

➔ Simple mixtures or simple changes to a mixture

Interpolation

Orange: Skin Irrit. 2

Blue: Skin Corr . 1B



Mixture A
Skin Irrit. 2
Tested

Mixture C =?
Skin Irrit. 2
interpolated

Mixture B
Skin Irrit. 2
Tested

Tiered approach in classification of mixtures

- In general (but see below)

1. Data available on the mixture itself
2. Bridging principles

Most often used:

3. Classification based on hazards of the **individual ingredients** and their concentrations
   - Generally, the only approach for mixtures containing substances classified for carcinogenicity, mutagenicity or reproductive toxicity, and the only approach for bioaccumulation and biodegradation properties and for hazardous to the ozone layer.
   - In practice, also for mixtures containing sensitisers.

Classification based on ingredients

Specific/Generic Concentration Limits/M-factors

Concentration limits: concentrations of substances in a mixture which trigger classification of the mixture for a particular hazard.

M-factors: established to give increased weight to substances classified as Aquatic Acute 1 or Aquatic Chronic 1 when classifying mixtures for hazardous to aquatic environment.

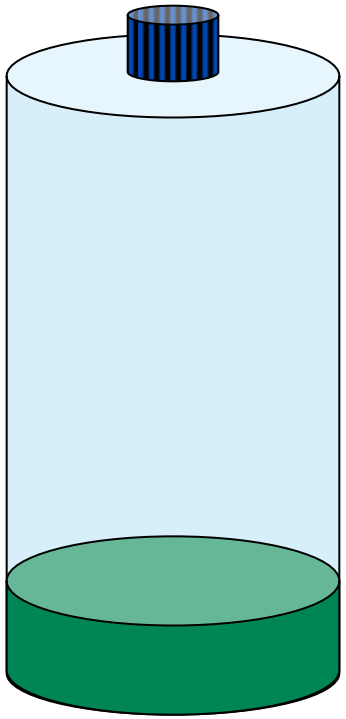
Generic cut off values

Minimum concentrations for substances *to be taken into account* for classification in a mixture, even if they do NOT trigger classification of the mixture directly.

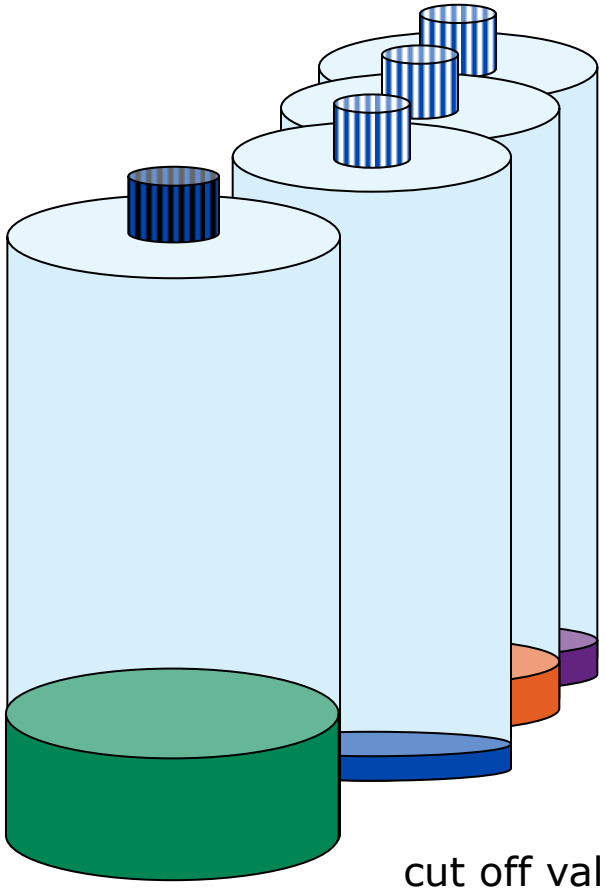
Additivity

Summation of the concentrations of all different ingredients classified for a particular hazard, which may contribute to the classification for some human health and both environmental hazard classes.

Classification based on ingredients



specific/generic concentration limit



cut off values

additivity

What are the GCLs and SCLs?

GCL – Generic Concentration Limits

- Apply to substances classified as hazardous to the ozone layer and for all human health hazards except acute toxicity.
- The actual GCLs are specified in the CLP Regulation for each applicable hazard.

SCL – Specific Concentration Limits

- SCLs take precedence over the GCLs - they ***must*** be applied for substances listed in Annex VI to CLP.
- SCLs are applicable to most health hazards.
- SCLs need to be set according to the methods outlined in ECHA guidance.
- SCLs lower than the GCLs ***have to*** be set if data justifies it.
- In **exceptional cases**, SCLs higher than GCLs **may** be set (Article 10).

Generic cut off values

Minimum concentrations for substances to be taken into account for classification of a mixture where additivity applies, even if they do NOT trigger classification of the mixture directly (Table 1.1 of the CLP Regulation).

Hazard class	Hazard category	Generic cut-off values
Acute toxicity	1-3	0,1%
	4	1%
Skin corrosion/ irritation	All	1%*
Serious damage to the eye/eye irritation	All	1%*
Hazardous to the aquatic environment	Acute 1	0,1%#
	Chronic 1	0,1%#
	Chronic 2-4	1%

These minimum concentrations apply, unless there is a presumption that an ingredient present at <1 % (*) or 0.1 % (#) can still be relevant for classifying the mixture

Additivity (1/2)

For some human health and both environmental hazard classes, the concentrations of all different ingredients classified for a particular hazard may contribute to the classification for that hazard

- Generic cut off values to be considered
- Only applicable to some hazard classes - for example, not applicable to the CMRs
- Not applicable in all cases for some hazards
  - For example, ingredients whose chemical characteristics make this approach unworkable, and which are classified for skin corrosion or irritation and eye damage or irritation

Additivity (2/2)

Hazard class	Reference in Annex I to CLP
STOT SE 3 (respiratory tract irritation/ narcotic effects only)	3.8.3.4.5
Acute toxicity	3.1.3.6.1
Serious skin corrosion/ irritation	3.2.3.3
Serious eye damage/ eye irritation	3.3.3.2
Aspiration hazards	3.10.3
Aquatic acute and chronic	4.1.3

Generic concentration Limits (GCL)

(Hazards where additivity does not apply)

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 %	-

Generic concentration limits for skin corrosion/ irritation

(Table 3.2.3, CLP) – where additivity applies

Sum of ingredients classified as:	Concentration triggering classification of the mixture as:	
	Skin corrosive (Cat 1A, 1B or 1C)	Skin irritant (Cat 2)
Skin corrosive Cat 1A, 1B or 1C	≥ 5 %	≥ 1 % but < 5 %
Skin irritant Cat 2	-	≥ 10 %
(10 x Skin corrosive Cat 1A, 1B or 1C) + Skin irritant Cat 2	-	≥ 10 %

Example: skin corrosive/irritant?

Summation method

Sum concentrations of corrosive ingredients	x 10
Sum concentration skin irritants	x 1

Mixture with two ingredients, one classified as skin irritant, the other presumed to be skin corrosive at concentrations lower than the generic cut off value

	Concentration	Classification	Weighting	Summation
Ingredient A	7 %	Skin Irrit. 2	x1	7 %
Ingredient B	0.5 %	Skin Corrosive	x10	5 %
Total hazardous ingredients				**12 %**

(≥ 10 %, the GCL for Skin Irrit. 2)

→ SKIN IRRIT. 2

Generic concentration limits for eye damage/ irritation

(Table 3.3.3, CLP) – where additivity applies

Sum of ingredients classified as:	Concentration triggering classification of the mixture for effects on the eye:	
	Irreversible eye effects Cat 1	Reversible eye effects Cat 2
Eye effects Cat 1 or Skin corrosive Cat 1A, 1B or 1C	≥ 3 %	≥ 1 % but < 3 %
Eye effects Cat 2	-	≥ 10 %
(10 x Eye effects Cat 1) + Eye effects Cat 2	-	≥ 10 %
(Skin corrosive Cat 1A, 1B or 1C) + Eye effects Cat 2	≥ 3 %	≥ 1 % but < 3 %
10 x (Skin corrosive Cat 1A, 1B or 1C + Eye effects Cat 1) + Eye effects Cat 2	-	≥ 10 %

Additivity formula for acute toxicity

- The **ATE** is the **A**cute **T**oxicity **E**stimate which is
  1. an LD_{50} or LC_{50}-value, or (if not known)
  2. converted value (point estimate) for acute toxicity from Table 3.1.2 in Annex I, either from a range test or from a classification category
- The **ATE** of a mixture is determined by calculation from the ATE values for the relevant ingredients (for all three routes of exposure)

$$\frac{100}{ATE_{mixture}} = \sum_{n} \frac{C_{ingredient}}{ATE_{ingredient}}$$

C = concentration

n = the number of ingredients

Example 1: Additivity for acute toxicity (1/2)

Mixture with two hazardous ingredients

It is assumed that the mixture contains no other acutely hazardous ingredients, and that the LD50 values have been derived using the oral route.

	Concentration	LD50 (mg/kg)	Classification
Ingredient 1	40%	400	Acute Tox 4
Ingredient 2	12%	30	Acute Tox 2

Example 1: Additivity for acute toxicity (2/2)

Insert the values into the formula:

$$\frac{100}{ATE} = \frac{40}{400} + \frac{12}{30}$$

Therefore, for the mixture:

$$\mathbf{ATE} = \frac{100}{(\frac{40}{400})+(\frac{12}{30})} = \mathbf{200}\ \boldsymbol{mg/kg}$$

Result: Since the resulting ATE value for the mixture by the oral route is within the range 50 < ATE ≤ 300 (mg/kg) , the mixture is classified as **Acute Tox 3; H301**

Example 2: Additivity for acute toxicity (1/2)

Mixture with two hazardous ingredients

It is assumed that the mixture contains no other hazardous ingredients, and that the LD50 values by the oral route are not known.

	Concentration	LD50 (mg/kg)	Classification	Converted ATE (mg/kg)
Ingredient 1	40%	?	Acute Tox 4	500
Ingredient 2	12%	?	Acute Tox 2	5

Example 2: Additivity for acute toxicity (2/2)

In the event that the LD50 values are *not* known, insert the converted ATE values into the formula:

$$\frac{100}{ATE} = \frac{40}{500} + \frac{12}{5}$$

Therefore, for the mixture:

$$\mathbf{ATE} = \frac{100}{(\frac{40}{500})+(\frac{12}{5})} = \mathbf{40}\ mg/kg$$

Result: Since the resulting ATE value for the mixture by the oral route is within the range 5 < ATE ≤ 50 (mg/kg), the mixture is classified as **Acute Tox 2;H300**

What about a mixture within a mixture?

Example: What is the classification of Mixture A?

Details:

- Mixture A contains 1% mixture B and 99% mixture C
- Mixture C is not hazardous. Mixture B is classified Carc. 1B because 1% of it is an impurity classified as Carc. 1B, with no SCL assigned. The GCL for Carc. 1B is 0.1%.
- Other components of mixture B are known not to be carcinogenic.

Classification:

Since mixture A only contains 0.01% of the Carc. 1B substance, it need not be classified

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.

Example: Additivity for environmental classification (1/3)

Summation method

INFORMATION ON INGREDIENTS CLASSIFICATION AND CONCENTRATION					
	Acute aquatic hazard	**M**	**Long-term aquatic hazard**	**M**	**C (%)**
Astralamid	Acute 1	10	Chronic 1	10	1
Bastralamid	Acute 1	1	Chronic 2	-	3
Castralamid	Not classified	-	Chronic 2	-	10
Dastralamid	Not classified	-	Chronic 3	-	10
Estralamid	Not classified	-	Not classified	-	10
Festralamid	Not classified	-	Not classified	-	66

M = M-factor; C = Concentration

(Example from CLP Guidance)

Example: Additivity for environmental classification (2/3)

Acute aquatic hazard – summation method

- Information on classification including associated M-factors and the % of the components in the mixture are available.
- Classify for acute hazard if: Σ (Acute 1 × M) ≥ 25%

Conclusion on classification for acute aquatic hazard

Using the classification of the components of the mixture: (1 × 10) + (3 × 1) = 13 (which is < 25%).

Hence, **no classification for acute aquatic hazard** is warranted.

Example: Additivity for environmental classification (3/3)

Long-term aquatic hazard: Summation method

- Step 1: Classify as Chronic 1 if: Σ (Chronic 1 × M) ≥ 25% (if not, then go to Step 2).
- Step 2: Classify as Chronic 2 if: Σ (10 × Chronic 1 × M) + Σ (Chronic 2) ≥ 25% (if not, then go to Step 3).
- Step 3: Classify as Chronic 3 if: Σ (100 × Chronic 1 × M) + Σ (10 × Chronic 2) + Σ (Chronic 3) ≥ 25% (if not, then go to Step 4).
- Step 4: Classify as Chronic 4 if: Σ (Chronic 1) + Σ (Chronic 2) + Σ (Chronic 3) + Σ (Chronic 4) ≥ 25%

Conclusion on classification for chronic aquatic hazard

Using the classification of the components of the mixture:

Step 1: (1 × 10) = 10 (which is <25%), therefore → Step 2.

Step 2: (10 × 1 × 10) + 3+10 = 113 (which is >25%). Hence, **classify as Aquatic Chronic 2**.

Summary

- Use the systematic approach for classification of mixtures in CLP.
- Consider all the available information.
- In most cases, classification of the mixture is based on hazards of the individual ingredients and their concentrations.
- Utilise available guidance and resources.

Appropriate classification, labelling and packaging of the mixtures are intended to ensure their safe use

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