CEFIC/EUROMETAUX/FECC/DUCC Workshop

How to classify Mixtures under CLP HEALTH HAZARDS

Acute Toxicity

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Brussels; 19 May 2014

Options/Decision Tree

- A. Apply **substance criteria** when **test data** for the **complete mixture** are available

- B. Apply "**bridging principles**", if applicable

- C. Estimate hazards using **ingredient information**
- D. **Translation** according to Annex VII (CLP specific)

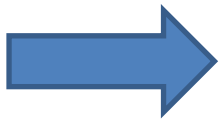
A. Test Data for the whole Mixture

Application of classification criteria for substances (Table 3.1.1)

Example 1:

A paint tested as aerosol (mist)

- Result. LC50 (rat): 4.7 mg/l/4h



Acute Tox.4; H 332=Harmful if inhaled

Rationale: For dusts and mists: (1 < ATE ≤ 5 mg/l/4h)

B. Bridging Principles
(Annex I 1.1.3)

Applicable bridging principles:

- Dilution
- Batching
- Concentration of highly hazardous mixtures
- Interpolation within one hazard category
- Substantially similar mixtures
- Changes in the composition of a mixture
- Aerosols

C. Use of Ingredient Information

Calculation Approach for Acute Toxicity:

Combined use of toxicities and concentrations of the components by a **weighting summation procedure** taking **ATE* values and** the **concentrations** of the relevant ingredients into account

ATE = Acute **T**oxicity **E**stimate (e.g. LD_{50} / LC_{50} = Median **L**ethal **D**ose/**C**oncentration)

Additivity Formula 1
(Annex I 3.1.3.6.1)

Data / Information available for all ingredients:

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$ (cf. UN Transport)

ATE = Acute Toxicity Estimate (e.g. LD_{50} /LC_{50})

C_i = Concentration of ingredient i

i = Individual Relevant ingredient from 1 to n

n = Number of ingredients

Application of Additivity formula 1 generally for one exposure route, unless relevant evidence of toxicity for other routes (Details Annex I 3.1.3.2)

Ingredients

Ingredients to be taken into account:

- Substances classified in one Acute toxicity Category.
- "Relevant Ingredients "= Concentrations to be taken into account:

  - GHS: 1%, unless suspect that relevant: < 1%

  - CLP ("Generic cut-off values"; Annex I Table 1.1):

    Cats.1-3: 0.1%

    Cat.4: 1%

- Substances with unknown acute toxicity: ≥ 1%

Ignored ingredients:

- Presumed not acutely toxic (e.g. water, sugar)

- Proven not to be classified based on valid data/information

- Substances with unknown acute toxicity if < 1%

Example 2

Acute oral data available for all ingredients:

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

A: 60%, ATE= LD 50= 250 mg/kg
B: 35%, ATE= LD 50= 750 mg/kg
C: 5%, water

$100 / ATE_{mix} = 60/250 + 35/750 + 0 = 0.2866$

$ATE_{mix} = 100/0.2866 = 349$ mg/kg

à **Cat. 4** (300< ATE ≤ 2,000 mg/kg; Table 3.1.1)

Options in Case of unknown Toxicity

Ingredients with unknown acute toxicity concerning a relevant exposure route (data gap):

- No respective test data
- "...without any useable information.."

- **Case 1:** Unknown ingredients < 1%
  Not relevant; not taken into consideration
- **Case 2**: Unknown ingredients ≥ 1% - 10%
  Application of Additivity formula 1
  à Dilution effect
- **Case 3**:Unknown ingredients > 10%
  Application of the modified Additivity formula 2 taking unknown ones into consideration
  à Potential impact on classification

Ingredients without respective acute toxicity test data, but with other useable information:

Derivation of a **converted** Acute Toxicity point Estimate **(cATpE)**

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Additivity Formula 2

Covering unknown Ingredients (§ 3.1.3.6.2.3)

$$\frac{100 - (\sum C \text{ unknown if } > 10\%)}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

ATE	=	Acute Toxicity Estimate (e.g. LD_{50} /LC_{50})
C_i	=	Concentration of ingredient i
i	=	Individual Relevant ingredient from 1 to n
n	=	Number of ingredients

Conversion
derived from relevant Information
(Table 3.1.2)

A. **Classification** category without respective toxicity data

B. Experimentally obtained acute **toxicity range values**
(e.g. for oral toxicity: 300 > LD50<2,000mg/kgbw)

C. **Other relevant information**:

- Extrapolation between routes
- Evidence from human exposure
- Evidence from other toxicity studies
- SARs

E X P E R T J U D G E M E N T !

Conversion Table

(Extract UN GHS;Table 3.1.2)

Exposure Routes	Classification Category or Acute Toxicity Range Estimates (ATE)	Converted Acute Toxicity point Estimates (cATpE)
oral (mg/kg body weight)	0 < Category 1 £ 5 5 < Category 2 £ 50 50 < Category 3 £ 300 300 < Category 4 £ 2 000 2000 < Category 5 £ 5 000	0,5 5 100 500 2500
dermal (mg/kg body weight)	0 < Category 1 £ 50 50 < Categoriy 2 £ 200 200 < Category 3 £ 1 000 1 000 < Category 4 £ 2 000 2000 < Category 5 £ 5 000	5 50 300 1 100 2500

Example 3-1
Acute dermal Toxicity

1.Data/information to be used in the additivity formula :

Ingredient	Concentration (%)	Test data	Classification	cATpE (mg/kg) (UN GHS Table 3.1.2)	Remarks
1	**17**			**n.a.**	**Unknown acute dermal toxicity**
2 (Mixture 1)	**35**		**5**	**2,500**	**Relevant only in UN GHS**
3 (Water)	**13**			**n.a.**	**Ignored, not acutely toxic**
4 (Mixture 2)	**15**		**4**	**1,100**	**4**
5	**19.2**	**Ø 2,000 mg/kgbw Ø (no toxic effects)**		**n.a.**	**Ignored, not acutely toxic**
6	**0.8**			**n.a.**	**Not a "Relevant ingredient"** since ≤ 1% and unknown

Example 3-2

Additivity formula 2 applies since > 10% unknown :

$$\frac{100\text{-unknown}}{ATE_{mix}} = \sum_{n} \frac{Ci}{ATE_i}$$

100-17 / ATE_{mix} = 35/2,500 + 0+ 15/1,100 + 0 + 0 = 0.027636

ATE_{mix} = 3,003 mg/kg

à **UN GHS: Cat. 5** (2,000 < ATE <= 5,000 mg/kg; UN GHS Tab. 3.1.1)

à **CLP: No classification**

Example 4

Application	**Different phases in inhalation exposure. Extrapolation**		
	Test Data	Classification	**Rationale**
Available information	Use /exposure as aerosol (mist) Animal data (rat): LC_{50} (mg/l/4h)		
Ingredient 1 solid (6%)		Category 4	**Conv. ATE (mg/l/4h) = 1.5 mg/1/4h**
Ingredient 2 solid (11%)	0.6	Category 3	**ATE = LC_{50}**
Ingredient 3 solid (10%)	6 (dust)	-	**Neglected, since not classified in any acute category.**
Ingredient 4 liquid (40 %)	11 (vapour)	Category 4	**Conv. ATE (mg/l/4h) = 1.5 mg/1/4h, assuming identical category for vapour and mist by expert judgement**
Ingredient 5 (33%)		-	**Water; neglected**
Rationale	**Use additivity formula in Annex I, 3.1.3.6.1, as information is available for all ingredients.** **$100/ATE_{mix} = 6/1.5+11/0.6+0+40/1.5+0 = 49$** à **$ATE_{mix}$ = 2.04 mg/l/4h à Category 4**		

(ECHA CLP Guidance)

Mixtures in Mixtures (1)

Option 1 : Treat all constituents (i.e. also added mixtures) like substance ingredients :

1. Conversion of acute toxicity hazard categories of the ingredient mixture to **c**onverted **A**cute**T**oxicity **p**oint **E**stimates = c**AT**p**E**s according to table 3.1.2

2. Application of Additivity formula(e) with known ATEs and/or c**AT**p**E**s of the constituent mixture(s).

   ⇒ **ATE of the new mixture**

3. Use Table 3.1.1 with ATE

⇒ **Hazard category of the new mixture**

A Mixture in a Mixture

Example 5: Option 1

Data given:

Mixture A: 92% Ingredient 1(LD50>2000 mg/kgbw; NC)+8% Mixture 1

Mix 1: 88% Ingr. 2(ATE= 145; Cat. 3) +12% Ingr. 3 (ATE=320; Cat. 4)

What is the ATE (oral) of the new mixture A (Ingr.1+mixture 1) ?

Option 1:Treatment of mixture 1 like a substance ingredient:

- Mixture 1= 100%: (%Ingr.2 /ATE Ingr. 2+ %Ingr.3/ATE Ingr. 3) = 100:(88/145+ 12/320)=>155 mg/kgbw
- Mix A= 100/ ATE Mix 1: 8/155> ATE 1,936 mg/kgbw

à Cat. 4

Mixtures in Mixtures (2)

Option 2: “Break down“ the added mixture into its relevant ingredients:

Identification of all individual ingredient substances with their absolute concentrations in the final mixture, then application of the Additivity formula

- Necessary information
  - Composition (relevant ingredients)
  - Classification of the constituents
  - Toxicity data of the constituents/ingredients

- If complete information available à Exact classification
- Problem: CBI , import

Therefore trustful cooperation between DU/formulator and manufacturer/importer

Choice of appropriate option dependent on data base

SCLs in Acute Toxicity ?

No!

The SCL concept is not compatible with the approach using the GHS Additivity formula, which takes the toxic potency directly via the ATE into account.

Entries in Annex VI:

- Table 3.1 (GHS): No SCLs
- Table 3.2 (DSD): SCLs, e.g. Xylene 12.5%

Special Cases/Pitfalls (1)

1) **Classification as Acute Tox. in Annex VI, which is not warranted by robust data**:

- E.g. Xylene (601-022-00-9) R 20/…
- LC 50: 29 mg/l/4h (Key 1 study in CSB)
- How to procede?

  - No consideration of xylene as ingredient: Not allowed
  - Use cATpE (Table 3.1.2): Not necessary.
  - Use the valid test value, i.e. 29 mg/l/4h: No consistency with criteria
  - Use upper limit for Acute toxicity classification (Inhalation; vapour), i.e. 20 mg/l/4h: Proposed

Special Cases/Pitfalls (2)

2) **No acute classification in Annex VI** at all or none concerning a specific route

à No certainty that non-classification is proven, i.e. based on data

Check literature for test data or other relevant information, e.g. in ECHA Registered substances; SDSs

3) **Range % values** for harzardous ingredients: Basis for Additivity formula(e) is 100%

Ingred.	Conc.(%)	ATE (Oral)
1	20-50	250
2	30-60	350

$$\frac{50 \text{ or } 100 \text{ or } 110}{ATE_{mix}}$$

= 20/250 + 30/350 ? or

= 50/250 + 60/350 ? or?

- Ask supplier for more exact information ("Suppliers… shall cooperate…"; CLP § 4.9)
- Apply worst case, i.e. use highest concentration from given range/and or from most hazardous ingredient
- Perform separate evaluations with calculated maximum values for a category taking 100% for calculation

Special Cases/Pitfalls (3)

4. Calculation of the maximum concentration in a certain category:

Inhalation vapour:

1. Data given: Cat. 4 for ingredient A; no respective classification for the other ingredients

   Calculation:

   100/20* = x/11**--> **x= 55%**

   20*= upper cut-off for classification of vapours in Cat. 4

   11**: cATpE for substances classified in Cat.4, but without toxicity data (s. Table 3.1.2)

2. Data given: LC 50 available for ingredient B: LC50: 15 mg/l/4h); no respective classification for the other ingredients

   Calculation:

   100/20* = x/15 --> **x=75 %**

Conclusion :

1. No classification for mixtures without tox data containing < 55 %
2. No classification for mixtures with toxicity data < 75 %

Comparison with pre-CLP: Acc. to DPD no classification only if ingredients A or B < 25% , provided there are no other acutely toxic ingredients

Special Cases/Pitfalls (4)

5) **Non-appropriate ATEs from animal data** for use in the Additivity formula:

a) Methanol: LD50 oral (rat) > 10,000 mg/kgbw, but basis for Acute Tox.3 is human evidence (lowest valid Lethal dose:

300 mg/kgbw)

Options:

- Use cATpE: 100 mg/kgbw
- Use robust human data without “uncertainty default “:

300 mg/kgbw. Proposed (see ECHA CLP Guidance)

b) Other LD50 values from certain substance classes

Aromatic amines or nitro compounds:

e.g. Aniline LD50 oral (rat): 930 mg/kgbw (ECHA CSB, Key 01)

Use cATpEs **100 mg/kgbw** via classification as Acute Tox.3

c) Some chlorinated hydrocarbons

Special Cases/Pitfalls (5)

6. Impact of **form or physical state** concerning **Inhalation**

- Consideration as vapour: LC_{50} **<** SVC (saturated vapour conc.)
- Consideration as mist: LC_{50} close to or > SVC
  (SVC=0.0412 x MW x vapour pressure (hPa at 20°C)
- Evaluation of **vapour form/phase**:
  Ingredients which can be ignored
  - Solids (no sublimation assumed) in liquid mixtures
    e.g. polymers, salts
  - Pastes, highly viscous substances
- Evaluation of **mist (aerosol) form** of liquid mixtures: solids (dust data) cannot be ignored
  Remark: Justification for ignoring ingredients necessary

Special Cases/Pitfalls (6)

- Non-appropriate toxicity range values
  e.g. 200 < LD_{50} (oral) ≤ 2,000 mg/kgbw
  Issue: ATE ≤ or > 300 mg/kgbw ?

Options:

§ Classify in Cat. 3 or

§ Ask for full test report

- Check which oservations (lethality, significant clinical signs) at 200 and 2,000 mg/kgbw)
- Decision of category (expert judgement)
- If Cat. 4: à Use cATpE of 500 mg/kgbw

Comparison CLP vs. DPD

CLP	DPD
Preference for test results with whole mixture Possibility of use all **Bridging principles** provided necessary data are available	**Preference for test results** with whole mixture **Only the Bridging principle for changes in the composition** of a mixture is applicable
Use of an **additivity principle** for an ingredient based classification procedure: - Specific **additivity formula** taking toxicity via ATEs directly into account (sliding system) **Separate consideration of all exposure routes** with **relevant evidence** of toxicity	Use of an **additivity principle** for an ingredient- based classification procedure : **-Staggered summation using a weighting system based on classification** **Combined consideration of** all **exposure routes** with a classification
Data gaps: <10% of the ingredients: not taken into consideration in calculation, but a diluting effect > 10% ingredients: taken into consideration in calculation with **potential impact on classification (generally more severe)**	**Data gaps:** Not taken into consideration. Generally a diluting effect
Options for classification procedures	**No such options**

Conclusion

- Only little correspondence with DPD criteria
- New, partly complex procedures
- Optional approaches
- Sometimes expert judgement needed
- The clock is running - although still one more year for mixture classification acc. to GHS/CLP.

Thank you!

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