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Mixtures Classification for Health Hazards

- Respiratory & Skin Sensitisation
- CMR
- STOT-SE & STOT-RE

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Respiratory and skin sensitisation (Chapter 3.4)

Ø Definition

- ü **Respiratory sensitiser: substance leading to hypersensitivity of the airways following inhalation** ← **R42**
- ü **Skin sensitiser: substance leading to an allergic response following skin contact.** ← **R43**

	Resp.Sensitisation Category 1, 1A/1B	Skin Sensitisation Category 1, 1A/1B
Pictogram		
Signal word	Danger	Warning
Hazard statement	**H334** May cause allergy or asthma symptoms or breathing difficulties if inhaled	**H317** May cause an allergic skin reaction

General procedure to classify mixtures for sensitizing effects

- Mixture Tested : same criteria as for substances but results need to be evaluated with care
- Similar tested mixtures: bridging principles
  - all Bridging Principles are applicable but possible interactions between components important to take into account
- Classification based on ingredients :
  - non-additivity approach : classified if sensitizing ingredient in concentration ≥ GCL or ≥ SCL

Respiratory sensitisation

Component classified as:	Generic concentration limits triggering classification of a mixture as:	
	Respiratory Sens. Cat.1	
	Solid/Liquid	Gas
Resp. Sens. Cat.1	**≥ 1.0 %**	**≥ 0.2 %**
Resp. Sens. Sub-cat.1A	≥ 0.1 %	≥ 0.1 %
Resp. Sens. Sub-cat.1B	≥ 1.0 %	≥ 0.2 %

nb: possibility to set SCL for sensitisation but for respiratory sensitisation:

Ø no possibility on the basis of animal data alone

Ø no concept available on the basis of human data

Some very low SCLs in Annex 6

Skin sensitisation

Component classified as:	Generic concentration limits triggering classification of a mixture as:
	Skin Sens.Cat.1 (all physical states)
Skin Sens. Cat.1	**≥ 1.0 %**
Skin Sens. Sub-cat.1A	≥ 0.1 %
Skin Sens. Sub-cat.1B	≥ 1.0 %

nb: possibility to set SCL for skin sensitisation based on animal data and on human data

(ECHA guidance : how to subcategorize and how to identify extreme sensitisers: SCL: 0.001 %)

Some very low SCLs in Annex 6

Respiratory or skin sensitisation

Component classified as:	Concentration limits for elicitation (Special labelling & SDS required)
Sensitiser Cat.1	**≥ 0.1 %**
Sensitiser Sub-cat.1A	**≥ 0.01 %**
Sensitiser Sub-cat.1B	**≥ 0.1 %**

nb: if SCL < 0.1%, the elicitation limit = 1/10 SCL

Ø **mixture not classified as sensitising:**

EUH 208 : Contains (name of sensitising substance). May produce an allergic reaction.

Ø **mixture classified as sensitising:**

The names of all sensitizing substances shall appear on the label.

Ø **mixture not classified and not intended for the general public**

EUH 210 : Safety data sheet available on request.

Example of classification

Ingredient	Skin sensitisation classification	Concentration (% w/w)	SCL
Substance A	Not class.	4,0	
Substance B	Skin Sens 1A	0,5	Not assigned
Substance C	Skin Sens 1	0,05	Skin Sens; H317: C ≥ 0.2 %
Substance D	Skin Sens 1B	0.05	Not assigned
Water	Not classified	94,9	

Classification mixture :

-Skin Sens 1 : - due to the content of Substance B: C ≥ GCL

Name of the substances on the label :

-Substance B (because it determines the classification)

CMR classification (Chapters 3.5, 3.6 and 3.7)

		Category 1 (1A/1B)	Category 2
Pictogram			
Signal word		Danger	Warning
Hazard statement	**M**	**H340 May cause genetic defects** (*)	**H341 Suspected of causing genetic defects** (*)
	C	**H350 May cause cancer** (*)	**H351 Suspected of causing cancer** (*)
	R	**H360 May damage fertility or the unborn child** (**) (*)	**H361 Suspected of damaging fertility or the unborn child** (**) (*)

(*) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) (e.g. H350i)
(**) (state specific effect if known) (e.g. H360D)

General procedure to classify mixtures for CMR effects

- Based on ingredients : non-additivity approach (ingredient's concentration ≥ GCL or ≥ SCL).
- Mixtures tested : only on a case-by-case basis where CMR effects are non identified by the non-additivity approach (article 6, § 3)
- Bridging principles:
  - Dilution
  - Batching
  - Substantially similar mixtures

Germ cell mutagenicity (chapter 3.5)

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:		
	Category 1 mutagen		Category 2 mutagen
	Category 1A	Category 1B	
Muta 1A	≥ 0.1 %	/	/
Muta 1B	/	≥ 0.1 %	/
Muta 2	/	/	≥ 1.0 %

Solids and liquids (w/w units), Gases (v/v units)

Nb: there is no possibility to set SCL for germ cell mutagenicity

Carcinogenicity (chapter 3.6)

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:		
	Category 1 carcinogen		Category 2 carcinogen
	Category 1A	Category 1B	
Carc. 1A	≥ 0.1 %	/	/
Carc. 1B	/	≥ 0.1 %	/
Carc. 2	/	/	≥ 1.0 % (*)

Solids and liquids (w/w units), Gases (v/v units)

(*) : SDS upon request if Cat.2 substance in mixture in concentration ≥ 0.1 %

nb: possibility to set SCL for carcinogenicity : based on the T25 concept (http://ec.europa.eu/environment/archives/dansub/pdfs/potency.pdf)

(EUH 210 on the label if mixture not classified and not intended for the GP)

Overview of the T25 concept

- T25 = daily dose (mg /kg bw) inducing a tumour incidence of 25 % upon lifetime exposure
- Used for systemic carcinogens
- Carcinogens classified in three potency groups:
  - High potency (T25 value ≤ 1 mg/kg bw / day)
  - Medium potency (1 mg/kg/d < T25 ≤ 100 mg/kg/d)
  - Low potency (T25 value > 100 mg/kg bw / day)
- Consideration of elements modifying the preliminary potency evaluation

SCLs for substances in each potency group and classification category

		Category 1A	Category 1B	Category 2
	Dose (mg/kg bw/day)	SCL	SCL	SCL
Group 1 High potency	T25 ≤ 1	0.01%	0.01%	0.1%
Group 2 Medium potency	1 < T25 ≤ 100	0.1% (GCL)	0.1% (GCL)	1% (GCL)
Group 3 Low potency	T25 > 100	/	1%	1-5%

Reproductive toxicity (chapter 3.7)

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1		Category 2 Repr. Tox.	Lactation
	Repr.1A	Repr.1B		
Repr. 1A	≥ 0.3 % (*)			
Repr. 1B		≥ 0.3 % (*)		
Repr. 2			≥ 3.0% (*)	
Lact.				≥ 0.3 % (*)

Solids and liquids (w/w units), Gases (v/v units)

(*) : SDS upon request if classif. substance in mixture in concentration ≥ 0.1 %

(EUH 210 on the label if mixture not classified and not intended for the GP)

nb: possibility to set SCL for reproductive toxicity (see ECHA guidance)

Overview of the procedure to set SCLs for reproductive toxicity

- Based on the ED10
- ED10 = effective dose (mg /kg bw) with a 10 % effect level above the background
- Reproductive toxicants classified in three potency groups:
  - High potency (ED10 value ≤ 4 mg/kg bw / day)
  - Medium potency (4 mg/kg/d < ED10 ≤ 400 mg/kg/d)
  - Low potency (ED10 value > 400 mg/kg bw / day)
- Consideration of elements modifying the preliminary potency evaluation

SCLs for substances in each potency group and classification category

Proposals to remove old SCLs

		Category 1	Category 2
	Dose (mg/kg bw/day)	SCL	SCL
Group 1 High potency	ED10 ≤ 4	0.03% (factor of 10 lower for extremely potent repro.)	0.3% (factor of 10 lower for extremely potent repro.)
Group 2 Medium potency	4 < ED10 ≤ 400	0.3% (GCL)	3% (GCL)
Group 3 Low potency	ED10 > 400	3%	3-10%

Specific hazard statements

H360 : May damage fertility or the unborn child.
H361 : Suspected of damaging fertility or the unborn child.

H360F : May damage fertility.
H360D : May damage the unborn child.
H361f : Suspected of damaging fertility
H361d : Suspected of damaging the unborn child.
H360FD : May damage fertility. May damage the unborn child.
H361fd : Suspected of damaging fertility. Suspected of damaging the unborn child.
H360Fd : May damage fertility. Suspected of damaging the unborn child.
H360Df : May damage the unborn child. Suspected of damaging fertility

Precision brought by the 4th ATP

"Hazard statements H360 and H361 indicate a general concern for effects on fertility and/or development.

These general hazard statements can be replaced by the HS indicating a specific effect.

When the other differentiation is not mentioned, this is due to

- ü evidence proving no such effect,
- ü inconclusive data, or
- ü no data.

The obligations to classify for the other differentiation still apply.

Example of classification.

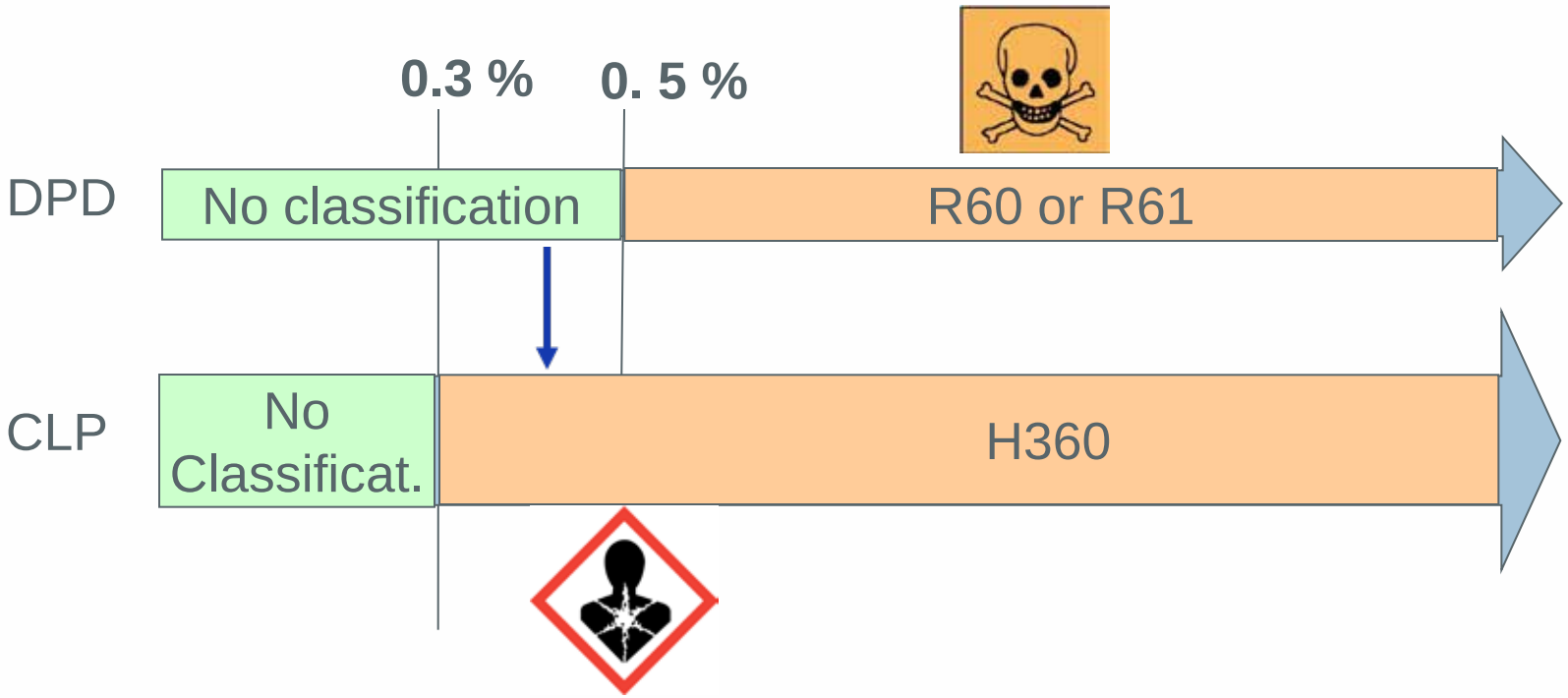
Ingredient	Repro classification	Concentration (% w/w)	SCL
Substance A	Repro 1B, H360Df	0.05	D: not assigned
			f: 0.3%
Substance B	Repro 2, H361fd	2	d: not assigned
			f: not assigned
Substance C	Repro 2, H361d	3.5	d: 4%
			f: not assigned
Substance D	Not classified	36	/
Water	Not classified	58.45	/

Classification mixture : H360? H360 Df? H361? H361fd? H361d? H361f? Not classified?

Development ?
Fertility ?

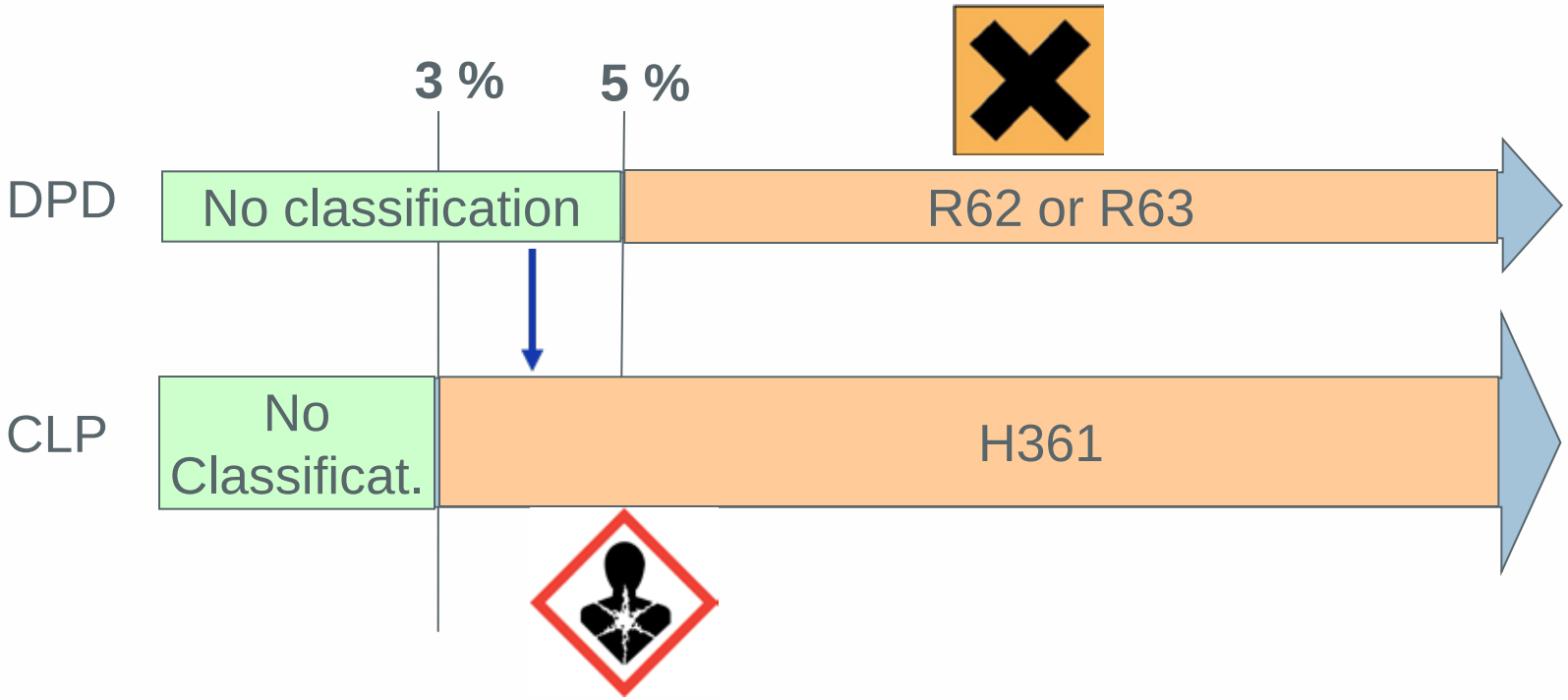
CLP vs DPD for mixtures.

Mixture containing a substance R60 or R61 / Repr.1B



CLP vs DPD for mixtures.

Mixture containing a substance R62 or R63 / Repr.2



Specific target organ toxicity (Chapters 3.8 and 3.9)

- Specific target organ toxicity – Single Exposure
  - STOT-SE : 3 categories
- Specific target organ toxicity – Repeated Exposure
  - STOT-RE : 2 categories

STOT-SE (Chapter 3.8)

Ø Definition

ü Specific, non lethal target organ toxicity after a single exposure

	Category 1	Category 2	Category 3
Pictogram			
Signal word	Danger	Warning	Warning
Hazard statement	**H370 Causes damage to organs** (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	**H371 May cause damage to organs** (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	**H335 May cause respiratory irritation**; or **H336 May cause drowsiness or dizziness**

R39/23/24/25 or R39/26/27/28 **R68/20/21/22** **R37 or R67**

General procedure to classify mixtures for STOT-SE effects

- Mixture Tested : same criteria as for substances
- Similar tested mixtures: bridging principles
  - all Br.Princ. are applicable
- Classification based on ingredients :
  - non-additivity approach : STOT SE 1 & 2
    classification of the mixture if ingredient classified in 1 or 2 in concentration ≥ GCL or ≥ SCL
  - additivity approach : STOT SE 3

GCL: generic concentration limits;
SCL: specific concentration limits.

STOT-SE : Categories 1 & 2

Non-additivity approach

Ingredient classified as:	General concentration limits triggering classification of a mixture as:	
	Cat.1	Cat.2
STOT-SE 1	≥ 10 %	1.0 ≤ c < 10 %
STOT-SE 2	/	≥ 10 % *(*)*

(*) : SDS upon request if Cat.2 substance in mixture in concentration ≥ 1 %

(EUH 210 on the label if mixture not classified and not intended for the GP)

Ø *Care for the potentiation or synergistic effects (3.8.3.4.4)*

Ø *Possibility to set SCL for STOT-SE (see ECHA guidance)*

Ø *Target organs and route of exposure are not specified, when classification of the mixture is based on ingredients. (Echa guidance)*

Overview of the procedure to set SCLs for STOT-SE

- only appropriate to fix SCLs for substances classified in STOT-SE Cat.1
- Based on the ED
- SCLs only if ED at a dose level or concentration clearly (more than one magnitude) below the guidance values , e.g. below 30 mg/kg bodyweight from the oral single exposure study.
- equation to fix SCL triggering classification of the mixture in STOT-SE1

  SCL_{cat1} = ED/GV1 x 100%
- equation to fix SCL triggering classification of the mixture in STOT-SE2

  SCL_{cat2} = ED/GV2 x 100%

STOT-SE : guidance values

GUIDANCE VALUE RANGES FOR SINGLE-DOSE EXPOSURES

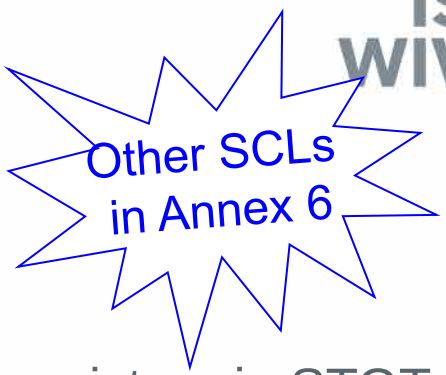
Category 1

Route of exposure	Units	
Oral (rat)	mg/kg bw	c ≤ 300
Dermal (rat or rabbit)	mg/kg bw	c ≤ 1000
Inhalation (rat) gas	ppm	c ≤ 2500
Inhalation (rat) vapour	mg/l	c ≤ 10
Inhalation (rat) dust/mist/fume	mg/l/4h	c ≤ 1.0

Category 2

Route of exposure	Units	
Oral (rat)	mg/kg bw	300 < c ≤ 2000
Dermal (rat or rabbit)	mg/kg bw	1000 < c ≤ 2000
Inhalation (rat) gas	ppmV	2500 < c ≤ 20000
Inhalation (rat) vapour	mg/l	10 < c < 20
Inhalation (rat) dust/mist/fume	mg/l/4h	1.0 < c ≤ 5.0

SCLs for STOT-SE (Cat.1): example



Substance classified in STOT-SE, Cat.1
ED = 7 mg/kg bw (oral route):

Ø equation to fix SCL triggering classification of the mixture in STOT-SE1

$SCL_{cat1} = ED/GV1 \times 100\%$

$SCL_{Cat.1} = \frac{7 \text{ mg/kg bw}}{300 \text{ mg/kg bw}} \times 100\ \% = 2.3\ \%$ ⇢ 2 %

Ø equation to fix SCL triggering classification of the mixture in STOT-SE2

$SCL_{cat2} = ED/GV2 \times 100\%$

$SCL_{Cat.1} = \frac{7 \text{ mg/kg bw}}{2000 \text{ mg/kg bw}} \times 100\ \% = 0.35\ \%$ ⇢ 0.2 %

n.b.: The resulting SCL is rounded down to the nearest preferred value (1,2 or 5)

STOT-SE : Category 3

Additivity approach

Respiratory Tract Irritation (RTI) : STOT-SE 3; H335
Narcotic effects : STOT-SE3; H336

- Ø additivity approach *(concentration value for the relevant ingredients not yet specified but 1% proposed in GHS)*
- Ø ingredients with the same hazard (RTI or narcotic effects) totalled separately
- Ø GCL : 20 % (higher or lower SCLs)
- Ø expert judgement

Example of classification.

Ingredient	STOT-SE classification	Concentration (% w/w)	SCL
Substance A	Not classified	4,0	
Substance B	STOT-SE 1	2,0	Not assigned
Substance C	STOT-SE 2	8,5	Not assigned
Substance D	STOT-SE 2	5,5	Not assigned
Substance E	STOT-SE 3, H335	3,5	Not assigned
Substance F	STOT-SE 3, H336	15	Not assigned
Substance G	STOT-SE 3, H336	15	Not assigned
Water	Not classified	46,5	

Classification mixture :

STOT SE 1 ? No because …

STOT SE 2 ? Yes because …

STOT SE 3, H335 ? ... H336 ? …

STOT-RE (Chapter 3.9)

ø Definition

ü Specific, target organ toxicity after a repeated exposure

	Category 1	Category 2
Pictogram		
Signal word	Danger	Warning
Hazard statement	**H372** **Causes damage to organs** (state all organs affected, if known) **through prolonged or repeated exposure** (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	**H373** **May cause damage to organs** (state all organs affected, if known) **through prolonged or repeated exposure** (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

R48/23/24/25 **R48/20/21/22**

General procedure to classify mixtures for STOT-RE effects

- Mixture Tested : same criteria as for substances
- Similar tested mixtures: bridging principles
  - all Br.Princ. are applicable
- Classification based on ingredients :
  - non-additivity approach : STOT RE 1 & 2 classification of the mixture if ingredient classified in 1 or 2 in concentration ≥ GCL or ≥ SCL

GCL: generic concentration limits
SCL: specific concentration limits

STOT-RE (chapter 3.9)

Ingredient classified as:	General concentration limits triggering classification of a mixture as:	
	Cat.1	Cat.2
STOT-RE 1	≥ 10 %	1.0 ≤ c < 10 %
STOT-RE 2	/	≥ 10 % *(*)*

(*) : SDS upon request if Cat.2 substance in mixture in concentration ≥ 1 %
(EUH 210 on the label if mixture not classified and not intended for the GP)

Ø *Care for the potentiation or synergistic effects (3.9.3.4.4)*

Ø *Possibility to set SCL for STOT-RE (see ECHA guidance)*

Ø *Target organs and route of exposure are not specified, when classification of the mixture is based on ingredients. (Echa guidance)*

Overview of the procedure to set SCLs for STOT-RE

- only appropriate to fix SCLs for substances classified in STOT-RE Cat.1
- Based on the ED
- SCLs only if ED at a dose level or concentration clearly (more than one magnitude) below the guidance values, e.g. below 1 mg/kg bodyweight from the 90-day oral study.
- equation to fix SCL triggering classification of the mixture in STOT-RE1

  SCL_{cat1} = ED/GV1 x 100%
- equation to fix SCL triggering classification of the mixture in STOT-RE2

  SCL_{cat2} = ED/GV2 x 100%

STOT-RE : guidance values

GUIDANCE VALUE RANGES FOR REPEATED-DOSE EXPOSURES (90-days)

Category 1

Route of exposure	Units	
Oral (rat)	mg/kg bw	$c \leq 10$
Dermal (rat or rabbit)	mg/kg bw	$c \leq 20$
Inhalation (rat) gas	ppm	$c \leq 50$
Inhalation (rat) vapour	mg/l/6h/day	$c \leq 0.2$
Inhalation (rat) dust/mist/fume	mg/l/6h/day	$c \leq 0.02$

Category 2

Route of exposure	Units	
Oral (rat)	mg/kg bw	$10 < c \leq 100$
Dermal (rat or rabbit)	mg/kg bw	$20 < c \leq 200$
Inhalation (rat) gas	ppmV/6h/day	$50 < c \leq 250$
Inhalation (rat) vapour	mg/l/6h/day	$0.2 < c < 1.0$
Inhalation (rat) dust/mist/fume	mg/l/6h/day	$0.02 < c \leq 0.2$

SCLs for STOT-RE : example

Substance classified in STOT-RE, Cat.1
ED = 0.12 mg/kg bw (oral route):

Ø equation to fix SCL triggering classification of the mixture in STOT-RE1

SCLcat1 = ED/GV1 x 100%

$$SCL_{Cat.1} = \frac{0.12 \text{ mg/kg bw}}{10 \text{ mg/kg bw}} \times 100\ \% = 1.2\ \% \dashrightarrow 1\ \%$$

Ø equation to fix SCL triggering classification of the mixture in STOT-RE2

SCL_{cat2} = ED/GV2 x 100%

$$SCL_{Cat.1} = \frac{0.12 \text{ mg/kg bw}}{100 \text{ mg/kg bw}} \times 100\ \% = 0.12\ \% \dashrightarrow 0.1\%$$

n.b.: The resulting SCL is rounded down to the nearest preferred value (1,2 or 5)

Useful links

ECHA: Guidance on CLP:
http://echa.europa.eu/web/guest/guidance-documents/guidance-on-clp

ECHA : C&L inventory:
http://echa.europa.eu/web/guest/information-on-chemicals

Institute for Health and Consumer protection:
http://...
Taken over by ECHA.
No more development, no more support.

Help for translation of terms used in REACH and CLP
http://echa.cdt.europa.eu/SearchByQueryLoad.do;jsessionid=DEE2A13D470564377D2D1364DDB09777?method=load

CLP National Helpdesk :

Federal Public Service (FPS) Health, Food Chain Safety and Environment

Contact Center: +32 (0)2 524.97.97

E-mail: info@health.fgov.be

Website