Human Health Classification: General Considerations and Overview

Key considerations for GHS Classifications

- Focuses on **Self Classification** by industry
- Identify **Physical State** – e.g., metal salt, oxide, sulfide, etc.
- Identify **Relevant Properties**: Key physical-chemical parameters (e.g., solubility, adsorptivity, particle size, transformation/dissolution, and critical surface area)
- Classify using data from the **chemical form/species** that is biologically relevant
  - Do not use data from a soluble species when classifying an insoluble compound if it results in classification unless …..

Key considerations for GHS Classifications

- Identify appropriateness of **read-across** (Note - not all territories recognize-read across & not all read-across methods are appropriate)

- Use **Weight of Evidence** approach
  - Consider all available information together to make a classification
  - Consider quality and consistency of data
  - Consider site and mechanisms of action; positive and negative data; and synergistic, additive, and antagonistic effects

- Use **expert judgment** to interpret the available data for classification purposes

Health Hazards Classification - Summary

Health Hazard Classes	Hazard Category
Acute Toxicity, Oral	1 2 3 4 5
Acute Toxicity, Dermal	1 2 3 4 5
Acute Toxicity, Inhalation	1 2 3 4 5
Skin Corrosion/Irritation	1 1A/B/C 2 3
Eye Damage/Irritation	1 2 2A/B
Respiratory Sensitisation	1
Skin Sensitisation	1
Germ Cell Mutagenicity	1 1A/B 2
Carcinogenicity	1 1A/B 2
Reproductive Toxicity	1 1A/B 2 Lactation
Target Organ ST – Single Dose	1 2 3
Target Organ ST – Repeat Dose	1 2
Aspiration Hazard	1 2

Optional Sub Categories
Sub Categories
Separate Classifications

1 is more severe than 5

1. Acute Toxicity

adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours

Acute Toxicity: Major or Key differences from the EU system

- Acute Toxicity Category Cut-Offs changed, plus extra Category (but no Cat 5 unlike UN GHS)
- Mixtures classification process changed for Acute Effects- no Specific Concentration Limits – Bridging
- Conversion to an estimated Acute Toxicity point Estimate
- Hazard Communication – symbols change

Acute Toxicity: Classification Criteria for Substances

Acute toxicity hazard categories based on Acute Toxicity Estimate (e.g.. actual LD50/LC50 values or ATE based on range test)

Route	Unit	Cat. 1	Cat. 2	Cat. 3	Cat. 4	Cat. 5**
Oral	mg/kg	≤ 5	≤ 50	≤ 300	≤ 2000	≤ 5000
Dermal	mg/kg	≤ 50	≤ 200	≤ 1000	≤ 2000	≤ 5000*
Inhalation						
Gas	ppm	≤ 100	≤ 500	≤ 2500	≤ 20000	*
Vapour	mg/l/4h	≤ 0.5	≤ 2	≤ 10	≤ 20	*
Dust/Mist	mg/l/4h	≤ 0.05	≤ 0.5	≤ 1	≤ 5	*

** Cat 5 – Optional: For identification of substances of relative low toxicity which may present a danger to vulnerable populations, not taken up by the EU

* Equivalent doses to oral and dermal levels for Cat 5 – may vary with Regulatory Authority

Acute Toxicity: Comparison to the 67/548/EEC Criteria

1272/2008 Regulation			67/549/EEC		
Hazard Category	LD_{50} mg/kg		Risk Phrase	LD_{50} mg/kg	
	Lower	Upper		Lower	Upper
1		≤ 5			
2	> 5	≤ 50	R28 T+		≤ 25
3	> 50	≤ 300	R25 T	> 25	≤ 200
4	> 300	≤ 2000	R22 Xn	> 200	≤ 2000
5	~~> 2000~~	~~≤ 5000*~~			

Acute Toxicity: Translation Issue

Substance LD_{50} 275 mg/kg

- 67/548/EEC = Xn R22
- CLP Annex VI = Acute Tox 4 according to Translation Tables in Annex VII
- Actual CLP should be Acute Tox 3 and should be applied according to Annex VI 1.2.1

"the manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied."

Acute Toxicity - Mixtures Hierarchy (Tiered Approach) (e.g. ore concentrates)

Use **test data for the mixture**, when available

↓

Use **Bridging Principles**, if applicable

↓

Calculation

- Additivity (Acute Toxicity)
- Summation (Skin and Eye Irritation, Aquatic)
- Thresholds (Sensitisation, CMRs, STOT)

Acute Toxicity – Conversion to ATE

Conversion of Acute Oral Toxicity Data from a Range or Limited Dose study or from the Classification Category in the absence of actual data

	Classification category or experimentally obtained acute toxicity range estimate	**Converted Acute Toxicity Point Estimate ATE**
Oral (mg/kg bw)	**0 < Category 1 ≤ 5**	**0.5**
	5 < Category 2 ≤ 50	**5**
	50 < Category 3 ≤ 300	**100**
	300 < Category 4 ≤ 2000	**500**
	2000 < Category 5 ≤ 5000	**2500**

Acute Oral Toxicity – Hazard Communication

	1272/2008 (CLP)	67/548/EEC
Cat. 1 **Cat. 2**	 **Danger** Fatal if swallowed	 T+ Very Toxic If Swallowed
Cat. 3	 **Danger** Toxic if swallowed	 T Toxic If Swallowed
Cat. 4	 **Warning** Harmful if swallowed	 Xn Harmful If Swallowed

Mixture examples given at the end of the presentation

2. Skin and Eye Corrosion and Irritation

Skin and Eye Corrosion and Irritation : Major or Key differences from the EU System

- Corrosive Cat 1 divided in to Cat 1A/1B/1C
- Criteria Differences for skin and eye irritation – mild eye irritation classified more severely
- Hazard communication more severe

Skin Corrosion/Irritation Substances Criteria – (1)

Category 1 (EU R34/R35)	Criteria: Corrosive to skin in ≥ 1 (EU 2) of 3 animals	
	Exposure	Observation
1A*	≤ 3 minutes	≤ 1 hour
1B*	> 3 minutes -- ≤ 1 hour	≤ 14 days
1C*	> 1 hour -- ≤ 4 hours	≤ 14 days

CLP Hazard Statement - *Causes Severe skin burns and eye damage*

Skin Corrosion/Irritation Substances – Criteria (2)

Category	Criteria for Skin Irritancy
Irritant Category 2 (EU R38)	(1) Mean value of ≥ 2.3 - < 4.0 (EU > 2) (2) for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of dermal reactions, or (3) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling, or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Irritant Category 3* (Applies only to some Authorities) NOT EU	Mean value of ≥ 1.5 - < 2.3 for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of dermal reactions (when not included in the irritant category above).

Skin Corrosion/Irritation - Mixtures

Sum of ingredients classified as:	Concentration triggering classification as: Skin	
	Corrosive Category 1	Irritant Category 2
Skin Category 1	≥5%	≥1% but < 5%
Skin Category 2		≥10%
(10 x Skin Category 1) + Skin Category 2		≥10%

Skin Corrosion/Irritation Mixtures for which Additivity does not apply

Ingredient	Concentration	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1 %	Category 1
Base with pH ≥11.5	≥ 1 %	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1 %	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3 %	Category 2

Skin Corrosion/Irritation– Label Elements

Category 1	Category 2
	
DANGER Causes severe skin burns and eye damage	**WARNING** Causes skin irritation

Serious Eye Damage/Eye Irritation Substances – Criteria

Category 1 (irreversible effects on the eye)

- **at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or**
- **at least in 2 of 3 tested animals, a positive response of:**
  corneal opacity ≥ 3 and/or
  iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Category 2 (irritating to eyes)

- **at least in 2 of 3 tested animals a positive response of:**
  corneal opacity ≥ 1 and/or (EU 2-3)
  iritis ≥ 1, and/or
  conjunctival redness≥ 2 (EU 2.5)
  conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and

- **which fully reverses within an observation period of normally 21 days**

Within this category an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.**

** Optional Category but not taken up in the EU

Serious Eye Irritation/eye irritation - Mixtures

Sum of ingredients classified as:	Concentration triggering classification as	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye or Skin Category 1	≥ 3 %	≥1 % but < 3 %
Eye Category 2 / 2A		≥10 %
(10 x Eye Category 1) + Eye Category 2 / 2A		≥10 %
Skin Category 1 + Eye Category 1	≥ 3 %	≥1 % but < 3 %
10 x (Skin Category 1 + Eye Category 1) + Eye Category 2A / 2B		≥10 %

Eye Irritation - Mixtures for which Additivity does not apply

Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1 %	Category 1
Base with pH ≥11.5	≥ 1 %	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1 %	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3 %	Category 2

Serious Eye Damage/Eye Irritation – Label Elements

Category 1	Category 2
	
DANGER Causes Serious Eye Damage	**WARNING** Causes Serious Eye Irritation **Note: 67/548/EEC – *Irritating to eyes***

Mixture examples given at the end of the presentation

3. Sensitisation

Sensitisation: Classification Criteria - Current

Category 1

Respiratory Sensitisers

- **If there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or**
- **If there are positive results from an appropriate animal test.**

Skin Sensitisers

- **If there is evidence in humans that the substance can induce sensitisation by skin contact in a substantial number of persons, or**
- **If there are positive results from an appropriate animal test.**

Note - No human patch testing allowed

Sensitisation: Classification Criteria – In Rev 3 of UN GHS (2009) Strong and Weak Sensitisers

	Respiratory sensitizer	Skin sensitizer
Sub-category 1A	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered.	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

Sensitisation - Mixtures

Ingredient classified as	Cut-off/concentration limits triggering classification of a mixture as a Respiratory or Skin Sensitiser		
	Skin sensitiser	Respiratory sensitiser	
	All Physical States	Solid/Liquid	Gas
Skin sensitiser	≥ 0.1% w/w* ≥ 1.0% w/w		
Respiratory Sensitiser		≥0.1% w/w* ≥ 1.0% w/w	≥ 0.1% w/w* ≥ 0.2 % w/w

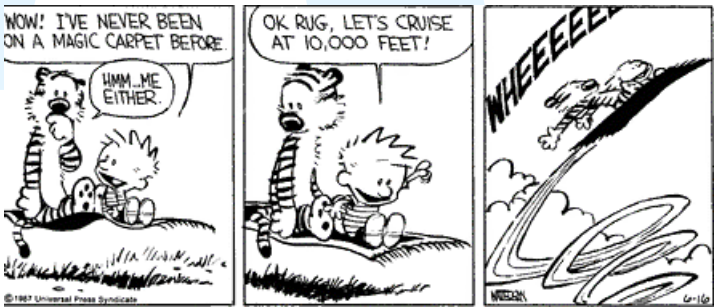
* Must be mentioned on the Safety Data Sheet

Sensitisation - Label Elements

Skin Sensitiser	Respiratory Sensitiser
	
WARNING May cause an allergic skin reaction	**DANGER** May cause allergy or asthma symptoms or breathing difficulties if inhaled

4. Aspiration Hazards – criteria slides at the end of the presentation

5. Mutagenicity, Carcinogenicity, Reproductive Toxicity



Major or key differences from the EU System

- CMR Category Numbering Changes
- Significant Changes to Reproductive Toxicity
- Possibility of Route Specific Labelling for CMRs
- No testing for CMR effects on mixtures in the EU, however, no such restriction in other territories

Germ Cell Mutagenicity

Mutation: a permanent change in the amount or structure of the genetic material in a cell.

Substances

Category 1A: (EU Cat 1) Chemicals known to induce heritable mutations in germ cells of humans

Category 1B: (EU Cat 2) Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans.

Category 2: (EU Cat 3) Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans

Mixtures

Ingredient classified as	**Cut-off/concentration limits** triggering classification of a mixture as:	
	Category 1 mutagen	Category 2 mutagen
Category 1 Mutagen	≥ 0.1 %	
Category 2 Mutagen		≥ 1.0 %

Germ Cell Mutagenicity - Classification Criteria

Category 1A	Chemicals **known** to Induce heritable mutations in germ cells of humans. • Positive evidence from human epidemiological studies.
Category 1B	Chemicals which **should be regarded** as if they induce heritable mutations in the germ cells of humans. • Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals, or; • Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells; or • positive result(s) from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny.

Germ Cell Mutagenicity- Classification Criteria

Category 2	Chemicals which **cause concern** for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. • Positive evidence obtained from experiments in mammals; and/or in some cases • in vitro experiments obtained from: mammal somatic cell mutagenicity tests in vivo; or • other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

Germ Cell Mutagenicity- Label Elements

Category 1A	Category 1B	Category 2
 **DANGER** May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)		 **WARNING** Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

Carcinogenicity

Substances

Category 1 **Known or presumed human carcinogens**

Category 1A: KNOWN to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence.

(EU Cat 1)

Category 1B: PRESUMED to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence.

(EU Cat 2)

Category 2: SUSPECTED human carcinogens

(EU Cat 3)

Carcinogenicity - Classification Criteria

Category 1A
Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence

Carcinogenicity: Classification Criteria

Category 1B

Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:

- human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
- animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals

Carcinogenicity: Classification Criteria

Category 2
Suspected human carcinogens The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. Suspected human carcinogen including mixtures containing more than ≥ 0.1 or ≥ 1.0 % of such a substance.

Carcinogenicity: Specific Considerations IARC concepts – Sufficient and Limited

Sufficient evidence of carcinogenicity:

a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in

(a) two or more species of animals or

(b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. *A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites*;

Carcinogenicity: Specific Considerations IARC concepts – Sufficient and Limited

Limited evidence of carcinogenicity:

the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g.

(a) the evidence of carcinogenicity is restricted to a single experiment;
(b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies;
(c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or
(d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs

REQUIRES EXPERT JUDGEMENT

Carcinogenicity: Additional Considerations

a) Tumour type and background incidence;
b) Multi-site responses;
c) Progression of lesions to malignancy;
d) Reduced tumour latency;
e) Whether responses are in single or both sexes;
f) Whether responses are in a single species or several species;
g) Structural similarity to a substance(s) for which there is good evidence of carcinogenicity;
h) Routes of exposure;
i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans;
j) The possibility of a confounding effect of excessive toxicity at test doses;
k) Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

REQUIRES EXPERT JUDGEMENT

Carcinogenicity – Mixtures - 1

Ingredient classified as	Cut-off/concentration limits triggering classification of a mixture as	
	Category 1 Carcinogen	Category 2 Carcinogen
Category 1	≥ 0.1 %	
Category 2		> 0.1 %* ≥ 1.0 %

* An SDS should be available on request

Carcinogenicity – Setting Specific Concentration Limits

- CLP Article 10.1 allows use of SCLS based on potency
- **Potency** - the magnitude, with respect to dose, of the carcinogenic activity
- **T25**, the dose giving a tumour incidence of 25% in an exposed human population, or in experimental animals after correction for the spontaneous incidence (Dybing et al., 1997; EC, 1999)

	High potency	**Medium potency**	**Low potency**
	mg/kg bw/day		
T25	< 1	1 < T25 value < 100,	> 100
	Specific Concentration Limits		
Category 1	0.01%	0.1%.	1%.
Category 2	0.1%	1%,	1-5%*

*on a case by case basis.

REQUIRES EXPERT JUDGEMENT

Carcinogenicity - Label Elements

Category 1A	Category 1B	Category 2
 **DANGER** May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)		 **WARNING** Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

Reproductive Toxicity -Criteria

Category 1A (EU Cat 1): KNOWN human reproductive toxicant

Category 1B (EU Cat 2): PRESUMED human reproductive toxicant

Category 2 (EU Cat 3): SUSPECTED human reproductive toxicant

EFFECTS ON LACTATION: Additional Category for (EU No separate Category – R64)

EU (67/548): distinguishes between Effects on Fertility and Development and are separate categories e.g. Category 1: Substances Know to Impair Fertility (R60) or Substances Known to cause Developmental Effects (R61).

CLP: distinguishes by Hazard Communication

Reproductive Toxicity -Criteria

Category 1A
The classification of a substance in this Category 1A is largely based on evidence from humans

Reproductive Toxicity - Criteria

Category 1B
Presumed human reproductive toxicant The classification of a substance in this Category 1B is largely based on data from *animal* studies. Such data shall provide clear evidence of an adverse effect on sexual function and *fertility or on development* in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Reproductive Toxicity -Criteria

Category 2
Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Reproductive Toxicity - Criteria

Effects on or via lactation
Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts *sufficient* to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the: (a) human evidence indicating a hazard to babies during the lactation period; and/or (b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or (c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

Reproductive Toxicity – Mixtures

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as		
	Category 1 Repro. Tox.	Category 2 Repro. Tox.	Additional category for effects on or via lactation
Category 1	> 0.1 % ≥ 0.3 % EU ≥ 0.5 %		
Category 2		≥ 0.1 % * ≥ 3.0 % EU ≥ 5.0 %	
Category for effects on or via lactation			≥ 0.1 % * ≥ 0.3 % New to CLP

* An SDS should be available on request

Reproductive Toxicity – Setting Specific Concentration Limits

- EU have used the concept that 1000 mg/kg bw of a preparation should contain amounts of the reproductive toxic substance which correspond at maximum to the NOAEL of a valid study.
- The concentration limit in % in preparations was calculated by dividing the NOAEL by the limit-dose (1000) followed by multiplication with 100
- Used for setting SCLs for N,N-dimethyl acetamide, dimethyl formamide (DMF) and borates
- HOWEVER - not accepted at UN level but currently setting of SCLs under discussion in EU expert group under ECHA

Reproductive Toxicity: Label Elements

Reproductive Toxicity: includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.

Category 1	Category 2	Effects on or via lactation
		***No Pictogram***
DANGER **May damage fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)**	**WARNING** **Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)**	***No Signal Word*** **May cause harm to breast-fed children.**

6. STOT

What is STOT? (1)

Specific target organ toxicity is defined as specific, non-lethal target organ/systemic toxicity arising from a single or repeated exposure to a substance or mixture.

All significant health effects that can impair function, both reversible and irreversible, immediate or delayed are included.

By any route of exposure relevant to humans

- Examples:
- changes affecting the function or morphology of a tissue/organ
- Serious changes to biochemistry/haematology, relevant for human health

What is STOT? (2)

SINGLE OR REPEATED EXPOSURE

Categories: 1, 2 or 3

Substances are classified by the use of expert judgment on the basis of the weight of all evidence available (human incidents, epidemiology, animal studies), including the use of recommended guidance values

Substances are placed in categories depending upon the nature and severity of the effect(s) observed

Guideline values

Labelling

What is STOT (3)?

	SINGLE Exposure	REPEATED Exposure
Category 1	**Substances that have produced significant toxicity in humans, or that, on the basis of evidence from animal studies, can be presumed to have the potential to produce significant toxicity in humans following single exposure**	**(EU Toxic): Substances that have produced significant toxicity in humans, or that, on the basis of evidence from animal studies can be presumed to have the potential to produce significant toxicity in humans following repeated exposure**
Category 2	**Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure**	**(EU Harmful): Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure.**
Category 3	**Transient Target organ effects (Only Narcotic Effects and Respiratory Tract Irritation)**	

A. Single Exposure STOT (1): guideline values

Route of exposure	Units	Guidance value ranges for		
		Category 1	Category 2	Category 3
Oral (rat)	mg/kg bw	C ≤ 300	2000 ≥ C > 300	Guidance Values do not apply
Dermal (rat or rabbit)	mg/kg bw	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	ppm	C ≤ 2500	5000 ≥ C > 2500	
Inhalation (rat) vapour	mg/l	C ≤ 10	20 > C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1.0	5.0 > C > 1.0	

A. Single Exposure STOT(2): Label Elements

Category 1	Category 2	Category 3
		
DANGER **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)*	**DANGER** **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)*	**WARNING** **May cause Respiratory Irritation** *Or* **May cause Drowsiness and dizziness**

B. Repeated Exposure STOT (1): guideline values

Route of exposure	Units	Guidance value (dose/concentration)	
		Category 1	Category 2
Oral (rat)	mg/kg/bw/day	C ≤ 10	10 ≥ C > 100
Dermal (rat or rabbit)	mg/kg/bw/day	C ≤ 20	20 ≥ C > 200
Inhalation (rat) gas	ppm/6h/day	C ≤ 50	50 ≥ C > 250
Inhalation (rat) vapour	mg/l/6h/day	C ≤ 0.2	0.2 > C > 1
Inhalation (rat) dust/mist/fume	mg/l/6h/day	C ≤ 0.02	0.02 > C > 0.2

B. STOT Repeated Exposure (2): Label Elements

Category 1	Category 2
 **DANGER** **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***)**	 **WARNING** **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***)**

STOT – Mixtures

Ingredient Classified as Target Organ Systemic Toxicant:	Cut-off/concentration limits triggering classification of a mixture as:		
	Category 1	Category 2	Category 3 (Single Exposure only)
Category 1	≥ 10.0 %	1.0≤ ingredient < 10 %	
Category 2		≥ 1.0 % *	
		≥ 10.0 %	
Category 3 (single exposure only)			≥ 20 % **

* An SDS should be available on request

≥ 20 %**might not always be appropriate. Expert judgment should be exercised. *Note that under current EU rules the equivalent to Cat 3 (R37 and R67) are subject to the Addtivity rules, but not under GHS*

Issues metals/minerals industry (1)

- Proposed cut-offs for classification as STOT after repeated exposure 1 or 2 in the UN GHS & EU CLP are so low that virtually each and every poorly soluble particulate would be classified

Route of exposure	Units	Guidance value (dose/concentration)	
		Category 1	Category 2
Oral (rat)	mg/kg/bw/day	C ≤ 10	10 ≥ C > 100
Dermal (rat or rabbit)	mg/kg/bw/day	C ≤ 20	20 ≥ C > 200
Inhalation (rat) gas	ppm/6h/day	C ≤ 50	50 ≥ C > 250
Inhalation (rat) vapour	mg/l/6h/day	C ≤ 0.2	0.2 > C > 1
Inhalation (rat) dust/mist/fume	mg/l/6h/day	C ≤ 0.02	0.02 > C > 0.2

Issues metals/minerals industry (2)

- To be addressed at UN GHS level

- Ongoing work with metals industry + consultant to submit an INF paper before UN-GHS meeting July. The aim is to trigger a discussion at UN level with a view to having some reflections/work launched on the criteria and their application (e.g. differences rat model vs. humans, species sensitivity etc.)

4. Aspiration Hazards

Aspiration Hazard - Substances

Category 1

Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard.
A substance is classified in Category 1:
(a) Based on reliable and good quality human evidence; or
(b) If it is a hydrocarbon and has a kinematic viscosity of 20.5mm2/s or less, measured at 40° C.
Substances in Category 1 include but not limited to hydrocarbons, turpentine and pine oil

Category 2 (GHS UN but not EU)

Chemicals which cause concern owing to the presumption that they cause human aspiration toxicity hazard
On the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point, and volatility, substances of 14 mm^2/s or less, measured at 40°C.

Note: Taking this into account, some authorities would consider the following to be included in this Category: n-primary alcohols with a composition of at least 3 carbon atoms but not more that 13; isobutyl alcohol, and ketones with a composition of no more than 13 carbon atoms.

Aspiration Hazard - Mixtures

Category 1

A mixture which contains a total of 10% or more of a substance classified in Category 1, and has a kinematic viscosity of 20.5 mm2/s or less, measured at 40°C.

In the case of a mixture which separates into two or more distinct layers, one of which contains 10% or more of a substance classified in category 1, and has a kinematic viscosity of 20.5 mm2/s or less, measured at 40°C.

Category 2 UN GHS but not in EU

A mixture which contains a total of 10% or more of a substance classified in Category 2, and has a kinematic viscosity of 14 mm2/s or less, measured at 40°C.

In classifying mixtures in this category, the use of expert judgment that considers surface tension, water solubility, boiling point, volatility is critical and especially when Category 2 are mixed with water.

In the case of a mixture which separates into two or more distinct layers, one of which contains 10% or more of a substance classified in Category 2, and has a kinematic viscosity of 14mm^2/s or less measured at 40°C.

Aspiration Hazard - Label Elements

Aspiration Hazard

DANGER

May be fatal if swallowed and enters airways

Mixtures Examples

Acute Toxicity – Mixtures (1): Bridging Example

Dilution

Mixture A (Tested) + **Mixture or Substance B (Classification known)** = **Mixture of A+B (=C) (Not Tested)**

→ **If 'B' is water or is *non-toxic** (> LD50 5000 mg/kg) then classification of 'C' can be calculated**

e.g. if LD_{50} of 'A' is 50 mg/kg (Acute Cat 2), and it is diluted 2x with water, then toxicity of 'C' is estimated to be 100 mg/kg (Acute Cat 3)

Acute Toxicity – Mixtures (2): Additivity

- **LD_{50} Range Concerted to Acute Toxicity Estimate (ATE)**

Classification converted to ATE when Concentration of unknown ingredients is < 10%

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

or when Concentration of unknown ingredients is > 10%

$$\frac{100 - (\sum C_{\text{unknown}} \text{ if } > 10\%)}{\mathbf{ATE_{mix}}} = \sum_{\mathbf{n}} \frac{\mathbf{Ci}}{\mathbf{ATEi}}$$

Acute Toxicity – Mixtures (3): Additivity

Example 1: Oral LD50 data available for all ingredients

Ingredient	% w/w	Acute Toxicity Classification	Additional Data
Component A	60.00	Acute Toxicity Cat. 4 (oral)	Oral LD50: 908 mg/kg (rat)
Component B	25.00	Acute Toxicity Cat. 2 (oral)	Oral LD50: 27 mg/kg (rat)
Component C	15.00	Not Classified	Oral LD50 > 5000 mg/kg

No test data available on actual mixture or related formulations but data available for all ingredients thus need to apply formula in GHS section 3.1.3.6.1

$$\frac{100}{ATE_{mix}} = \sum_{i}^{n} \frac{C_i}{ATE_i}$$ **= 100/(60/908 + 25/27)**

ATE mix = 96 mg/kg⇒ **Acute Oral Toxicity Cat. 3**

Acute Toxicity – Mixtures (4): Additivity

Example 2: Ingredients classified for acute toxicity but actual oral LD50 data not available for all ingredients

Ingredient	% w/w	Acute Toxicity Classification	Additional Data
Component D	40.00	Acute Toxicity Cat. 4 (oral)	Oral LD50: Not Available
Component E	30.00	Acute Toxicity Cat. 3 (oral)	Oral LD50: 50 - 300 mg/kg
Component F	23.00	Acute Toxicity Cat. 2 (oral)	Oral LD50: 35 mg/kg (rat)
Component C	7.00	Not Classified	Oral LD50 > 5000 mg/kg

No test data available on actual mixture or related formulations and actual oral LD50 data not available for Components D and E thus need to identify the appropriate conversion values (so called 'Converted Acute Toxicity point estimate') in GHS Table 3.1.2 for these ingredients before applying formula in GHS section 3.1.3.6.1:

Component D **Converted Acute Toxicity point estimate ⇒ 500**
Component E **Converted Acute Toxicity point estimate ⇒ 100**

$$\frac{100}{ATE_{mix}} = \sum_{i}^{n} \frac{C_i}{ATE_i}$$ **= 100/(40/500 + 30/100 + 23/35)**

ATE mix = 101 mg/kg ⇒ **Acute Oral Toxicity Cat. 3**

Acute Toxicity – Mixtures (5): Additivity

Example 3: Formulation contains an ingredient of unknown acute toxicity

Ingredient	% w/w	Acute Toxicity Classification	Additional Data
Component H	40.00	Acute Toxicity Cat. 4 (oral)	Oral LD50: 1800 mg/kg
Component J	30.00	Acute Toxicity Cat. 4 (oral)	Oral LD50: 1500 mg/kg
Component K	20.00	Unknown	Oral LD50: No Data
Component C	10.00	Not Classified	Oral LD50 > 5000 mg/kg

If unknown ingredients ≤ 10% then apply formula in GHS section 3.1.3.6.1
If unknown ingredients > 10% then apply formula in GHS section 3.1.3.6.2.3

$$\frac{100-(\sum C_{\text{unknown}} \text{if} > 10\%)}{\mathbf{ATE_{mix}}} = \sum_{n} \frac{\mathbf{Ci}}{\mathbf{ATEi}}$$

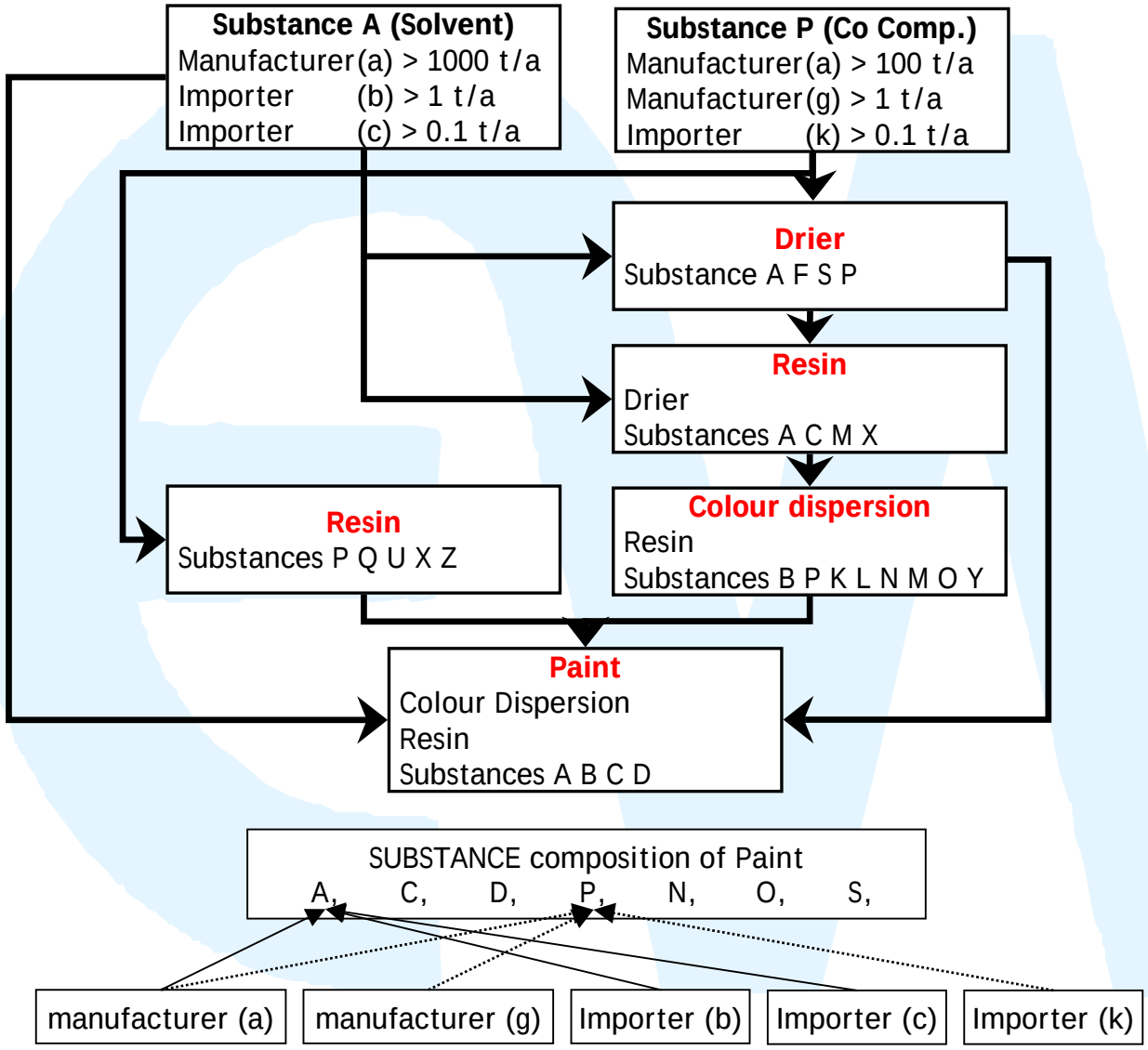
$$\frac{100-20}{ATE_{mix}} = \sum_{n} \frac{Ci}{ATEi} \quad = \quad \mathbf{80/(40/1800 + 30/1500)}$$

ATE mix = 1895 mg/kg $\Rightarrow$ **Acute Oral Toxicity Cat. 4**

If Component K subsequently found to be not classified for acute toxicity then *ATE mix* would be based on Components H and J and derived using formula in GHS section 3.1.3.6.1, that is
2368 mg/kg $\Rightarrow$ Acute Oral Toxicity Cat. 5

The above same principles can to be used to determine the acute dermal or inhalation toxicity of a mixture

Acute Toxicity – Mixtures in Mixtures



Some substances are considered to be below cut-off concentration due to dilution in the manufacturing process

Skin Corrosion/Irritation Mixtures Example 1

Ingredient	Skin Effects Classification	% w/w
Component A	Skin Irritant Cat. 2	43.00
Component B	Skin Irritant Cat. 2	24.00
Component N	Skin Corrosive Cat. 1	1.50
Component C	Not classified	to 100

pH of mixture: 4 – 5 (neat liquid)
N.B. Need to consider acid/alkaline reserve when pH of the mixture is ≤ 2 or ≥ 11.5 (GHS Section 3.2.3.1.2 refers).

No test data available on actual mixture or related formulations thus need to apply summation method as detailed in GHS section 3.2.3.3 and Table 3.2.3.

➢Mixture contains Component N which is classified as Skin Corrosive Cat. 1 and present at 1.5% $\Rightarrow$ $\leq 5\%$ thus mixture itself is not classified as Skin Corrosive Cat. 1.

➢However, Component N is present {$\geq 1\%$ but $<5\%$} thus the mixture is classified as **Skin Irritant Category 2**

Skin Corrosion/Irritation Mixtures Example 2

Ingredient	Skin Effects Classification	% w/w
Component L	Skin Irritant Cat. 2	5.00
Component M	Skin Irritant Cat. 2	4.00
Component N	Skin Corrosive Cat. 1	0.50
Component C	Not classified	to 100

pH of mixture: 10 (neat liquid)
N.B. Need to consider acid/alkaline reserve when pH of the mixture is ≤ 2 or ≥ 11.5 (GHS Section 3.2.3.1.2 refers).

No test data available on actual mixture or related formulations thus need to apply summation method as detailed in GHS section 3.2.3.3 and Table 3.2.3.

- Mixture contains Component N which is classified as Skin Corrosive Cat. 1 and present at 0.5% $\Rightarrow \leq 5\%$ thus mixture itself is not classified as Skin Corrosive Cat. 1.

- However, the sum of (10 x Skin Cat. 1) + Skin Cat. 2 = (10 x 0.5) + (5 + 4) = 14% $\Rightarrow \geq 10\%$ thus the mixture is classified as **Skin Irritant Category 2**

Eye Irritation Mixtures Example 1

Ingredient	Skin/Eye Effects Classification	% w/w
Component P	Eye Irritant Cat. 2	35.00
Component Q	Eye Damage Cat. 1	2.50
Component N	Skin Corrosive Cat. 1	1.50
Component C	Not classified	to 100

pH of mixture: 3 – 4 (neat liquid)
N.B. Need to consider acid/alkaline reserve when pH of the mixture is ≤ 2 or ≥ 11.5 (GHS Section 3.3.3.1 refers).

No test data available on actual mixture or related formulations thus need to apply summation method as detailed in GHS section 3.3.3.3 and Table 3.3.3.

Mixture contains Components Q (Eye Cat. 1) and N (Skin Cat. 1) which are both are present individually at < 3%. However, the sum of these two ingredients (Skin Cat. 1 + Eye Cat. 1) is 4% $\Rightarrow$ $\geq$ 3% thus mixture is classified as **Serious Eye Damage Category 1.**

Eye Irritation Mixtures Example 2

Ingredient	Skin / Eye Effects Classification	% w / w
Component P	Eye Irritant Cat. 2	7.00
Component S	Eye Irritant Cat. 2	1.00
Component T	Eye Irritant Cat. 2	1.00
Component C	Not classified	to 100

pH of mixture: 7 - 8 (neat liquid)
N.B. Need to consider acid/alkaline reserve when pH of the mixture is ≤ 2 or ≥ 11.5 (GHS Section 3.3.3.1 refers).

No test data available on actual mixture or related formulations thus need to apply summation method as detailed in GHS section 3.3.3.3 and Table 3.3.3.

Mixture does not contain any ingredients classified as Eye Cat. 1 or Skin Cat. 1 thus mixture itself is **Not Classified** as Serious Eye Damage Category 1.

Sum of the ingredients in the mixture classified as Eye Irritant Cat. 2 is 9% ⇒ ≤ 10% thus mixture is **Not Classified** as Eye Irritant Cat. 2.