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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

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DEVELOPMENT OF GUIDANCE ON THE APPLICATION OF GHS CRITERIA

Transmitted by the expert from the United States of America on behalf of the informal correspondence group on classification of mixtures[1]

Purpose

1. By way of this document, the informal correspondence working group on the classification of mixtures is providing recommendations to clarify the classification criteria for mixtures in the GHS. This work was undertaken by the correspondence group to determine if the GHS criteria are uniformly understood and to develop recommendations for clarifying the criteria where inconsistency was observed.

[1] In accordance with the programme of work of the Sub-Committee for 2007-2008 approved by the Committee at its third session (refer to ST/SG/AC.10/C.4/24, Annex 2 and ST/SG/AC.10/34, para. 14).

Background

2. The project to test the classification criteria for mixtures was an outcome of the work initiated in 2005 to test the application of the GHS criteria to substances (UN/SCEGHS/10/INF.5). The work on substances resulted in extending the project to mixtures, as described in two previous documents submitted to the Sub-Committee (UN/SCEGHS/13/INF.6 and UN/SCEGHS/15/INF.27).

3. This document is the culmination of the work on mixtures that has been conducted over the past two years, beginning at the twelfth session of the Sub-Committee in December 2006. During the course of this two-year period, two sets of exercises were provided to correspondence group members who were asked to apply the GHS criteria to hypothetical mixtures. This was in an effort to determine if the criteria for mixtures were uniformly understood and applied.

4. Results showed that there was some inconsistency in application of the criteria. The correspondence group focused on these issues, and through the process of three face-to-face meetings, several rounds of e-mail correspondence, and two teleconferences, we have come to consensus on the solutions provided in annexes 1, 2 and 3 to this document.

5. The solutions that the correspondence group is proposing fall into three categories:

(a) Editorial revisions of the GHS text (see annex 1);

(b) Examples demonstrating the application of the mixtures rules (see annex 2); and

(c) Issues that are being referred to the Sub-Committee for follow-up (see annex 3).

Conclusion

6. The correspondence group requests:

(a) That the Sub-Committee approve the recommended editorial changes to the GHS text. These approved changes would be incorporated into the third revised edition of the GHS;

(b) That the Sub-Committee approve the worked examples demonstrating application of the GHS criteria for mixtures. These worked examples would then be proposed for inclusion in the UNITAR training document;

(c) That the Sub-Committee address the three remaining issues the correspondence group deemed outside our scope of work or current capacity. These issues may need to be reassigned to address any remaining needed work.

7. This document and these recommendations are put before the Sub-Committee for consideration and approval.

Annex 1

Proposed editorial amendments to the GHS text

Section 1: Editorial amendments to the bridging principles *(see UN/SCEGHS/15/INF.27, addendum 1, item 1 and addendum 2)*

Editorial revisions to the bridging principles (dilution, batching, concentration of highly toxic mixtures, interpolation within one toxicity category and substantially similar mixtures) in Chapters 3.1 to 3.10 and 4.1 are proposed hereafter[2]. These changes are to provide consistency and clarity to the text of the GHS.

3.1.3.5.1, 3.2.3.2.1, 3.3.3.2.1, 3.4.3.2.1,
3.5.3.2.1, 3.6.3.2.1, 3.7.3.2.1, 3.8.3.3.1,
3.9.3.3.1 and 3.10.3.2.1: In the first sentence, insert "both" before "the individual ingredients".

Dilution

3.1.3.5.2 Delete the second paragraph ("If a mixture….bodyweight.").

3.1.3.5.2, 3.2.3.2.2, 3.3.3.2.2, 3.4.3.2.2,
3.5.3.2.2, 3.6.3.2.2, 3.7.3.2.2, 3.8.3.3.2, 3.9.3.3.2 and 3.10.3.2.2:

In the first sentence:

- amend the beginning to read "If a tested mixture";
- replace "the new mixture may" with "the new diluted mixture may"; and
- insert "tested" after "original" at the end of the sentence.

4.1.3.4.2 In the first paragraph:

- amend the beginning to read "Where a new mixture is formed by diluting a tested mixture or";
- replace "the mixture may" with "the resulting mixture may";
- insert "tested" after "original"; and
- add the following new sentence at the end of the paragraph: "Alternatively, the method explained in 4.1.3.5 could be applied".

Delete the second paragraph.

[2] *Note by the secretariat: The text of the relevant sections of Chapters 3.1 to 3.10 and 4.1, to which the amendments listed in section 1 of this annex apply, is reproduced (as amended) in information document UN/SCEGHS/16/INF.5.*

Batching

3.1.3.5.3, 3.2.3.2.3, 3.3.3.2.3, 3.8.3.3.3 and 3.9.3.3.3:

In the first sentence:

- replace “one production batch” with “a tested production batch”;
- delete “complex”;
- replace “another production batch” with “another untested production batch”;
- replace “and produced by” with “when produced by”, and
- replace “toxicity of the batch” with “toxicity of the untested batch”

3.4.3.2.3 In the first sentence:

- replace “one production batch” with “a tested production batch”;
- delete “complex”;
- replace “another production batch” with “another untested production batch”;
- replace “and produced by” with “when produced by”, and
- replace “sensitization of the batch” with “sensitization potential of the untested batch”

3.5.3.2.3, 3.6.3.2.3 and 3.7.3.2.3:

In the first sentence:

- replace “one production batch” with “a tested production batch”;
- delete “complex”;
- replace “another production batch” with “another untested production batch”;
- replace “commercial product produced by and under the control” with “commercial product, when produced by or under the control”; and
- replace “potential of the batch” with “potential of the untested batch”

3.10.3.2.3 In the first sentence:

- replace “one production batch” with “a tested production batch”;
- delete “complex”;
- replace “another production batch” with “another untested production batch”;
- replace “and produced by” with “when produced by”, and
- replace “of the batch has changed” with “of the untested batch has changed”

4.1.3.4.3 In the first sentence:

- replace “one production batch” with “a tested production batch”;
- delete “complex”;
- replace “another production batch” with “another untested production batch”;
- replace “and produced by” with “when produced by”, and
- insert “untested” before “batch” at the end.

Concentration of highly toxic mixtures

3.1.3.5.4 and 3.10.3.2.4:

Insert “tested” before “mixture” (twice) at the beginning of the sentence and replace, at the end, “new mixture” with “resulting untested mixture” at the end.

3.2.3.2.4 and 3.3.3.2.4:

Replace (twice) “a more concentrated mixture” with “the more concentrated untested mixture”.

3.8.3.3.4 and 3.9.3.3.4:

Amend the beginning of the paragraph to read “If in a tested mixture” and insert “resulting” before “concentrated”.

4.1.3.4.4 Amend the beginning to read: “If a tested mixture”;
Insert “the” before “ingredients”;
Replace “more concentrated mixture” with “more concentrated untested mixture” and
Insert “tested” after “original”.

Interpolation within one toxicity category

3.1.3.5.5, 3.8.3.3.5, 3.9.3.3.5, 3.10.3.2.5 and 4.1.3.4.5: Amend to read as follows:

“For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.”.

3.2.3.2.5 Amend to read as follows:

“For three mixtures (A, B, and C) with identical ingredients, where mixtures A and B have been tested and are in the same irritation/corrosion toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same irritation/corrosion category as A and B.”.

3.3.3.2.5 Amend to read as follows:

“For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same irritation/serious eye damage toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same irritation/serious eye damage category as A and B.”.

Substantially similar mixtures

3.1.3.5.6, 3.4.3.2.4
and 3.10.3.2.6 In the sentence after the sub-paragraphs:

- amend the beginning of the sentence to read: "If mixture (i) or (ii)"; and
- replace "mixture (ii)" with "the other mixture" at the end of the sentence.

3.2.3.2.6, 3.3.3.2.6, 3.5.3.2.4, 3.6.3.2.4, 3.7.3.2.4, 3.8.3.3.6
and 3.9.3.3.6 In the last sentence after the sub-paragraphs:

- amend the beginning of the sentence to read "If mixture (i) or (ii)";
- replace "mixture (ii)" with "the other mixture"; and
- insert "hazard" before "category".

4.1.3.4.6 In sub-paragraph (b), insert "essentially" before "the same".

In sub-paragraph (d), replace "Classification" with "Data on aquatic toxicity" and replace "are the same" with "substantially equivalent".

Amend the last sentence after the sub-paragraphs to read as follows:
"If mixture (i) or (ii) is already classified based on test data, then the other mixture can be assigned the same hazard category.".

Section 2: Amendments to the criteria for the classification of mixtures

Chapter 3.1: Acute toxicity *(see UN/SCEGHS/15/INF.27, addendum 1, items 2, 5 and 7):*

Note (a) to table 3.1.1: Amend to read as follows *(new text is underlined):*

"(a) The acute toxicity estimate (ATE) for the classification of a substance or ingredient in a mixture is derived using:

(i) the LD_{50}/LC_{50} where available. Otherwise,

(ii) the appropriate conversion value from Table 3.1.2 that relates to the results of a range test, or

(iii) the appropriate conversion value from Table 3.1.2 that relates to a classification category;".

Background: see UN/SCEGHS/15/INF.27, addendum 1, item 2;

Rationale: The purpose of this minor change is to clarify that when LD_{50} data are available, application of the known LD_{50} data for acute toxicity takes precedence over acute toxicity range values in the mixtures' formulae in paragraphs 3.1.3.6.1 and 3.1.3.6.2.3.

3.1.3.2 Amend as follows *(changes are indicated):*

"3.1.3.2 Classification of mixtures for acute toxicity can be carried out for each route of exposure, but is only needed for one route of exposure as long as this route is followed (estimated or tested) for all ingredients and there is no relevant evidence to suggest acute toxicity by multiple routes. ~~If acute toxicity is determined for more than one route of exposure, the more severe hazard category will be used for classification.~~ When there is relevant evidence of toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. All available information should be considered. The pictogram and signal word used should reflect the most severe hazard category; and all relevant ~~routes of exposure~~ hazard statements should be ~~identified for hazard communication~~ used."

Background: see UN/SCEGHS/15/INF.27, addendum 1, item 7;

Rationale: The purpose of editing this paragraph is to clarify that all available information on acute toxicity must be considered in classification of a mixture. Expert judgement plays a role in determining the application of the data and relevant evidence of toxicity. The changes also clarify hazard communication elements.

3.1.3.3 (d) Insert a new sub-paragraph (d) to read as follows:

"(d) When only range data (or acute toxicity hazard category information) are available for ingredients in a mixture, they may be converted to point estimates in accordance with Table 3.1.2 when calculating the classification of the new mixture using the formulas in 3.1.3.6.1 and 3.1.3.6.2.3."

Background: see UN/SCEGHS/15/INF.27, addendum 1, item 2 and text of new sub-paragraph (c) in ST/SG/AC.10/C.4/30, Annex 1.

Rationale: The purpose of adding sub-paragraph (d) is to reinforce the instruction that when LD_{50} data are available for an ingredient in a mixture, this known information is to be used in the mixtures' formulae in paragraphs 3.1.3.6.1 and 3.1.3.6.2.3. When only range data are available, it is converted to an acute toxicity point estimate.

Table 3.1.2 Amend the heading to read as follows (the table remains unchanged):

"Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for use in the formulas for the classification of mixtures."

Background: see UN/SCEGHS/15/INF.27, addendum 1, item 2.

Rationale: The purpose of editing the heading for Table 3.1.2 is the same as that for adding sub-paragraph (d), above. That is, to reinforce the instruction that when LD_{50} data are available for an ingredient in a mixture, it is to be used. When only range data are available, it is converted to an acute toxicity point estimated.

3.1.3.6.1 Amend sub-paragraph (c) and the first sentence after it to read as follows (changes are indicated):

"(c) Ignore ingredients if ~~the oral~~ the data available are from a limit dose test (at the upper threshold for Category 4 for the appropriate route of exposure as provided in Table 3.1.1) ~~does~~ and do not show acute toxicity ~~at 2000 mg/kg bodyweight~~.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE). See note (a) to Table 3.1.1 and paragraph 3.1.3.3 for appropriate application of available data to the equation below and paragraph 3.1.3.6.2.3."

The remainder of the paragraph (introductory sentence, sub-paragraphs (a) and (b) as well as the formula and the sentence immediately before it) remains unchanged.

Background: see UN/SCEGHS/15/INF.27, addendum 1, items 2 and 5.

Rationale: The purpose of the proposed changes is twofold:

(a) refer classifiers to the instruction in note (a) to Table 3.1.1 clarifying that when LD_{50} data are available, they are applied in the mixtures' formulae; and

(b) to include the two other routes of exposure and consideration of gases, vapours, and dusts for limit dose tests above the specified threshold.

3.1.3.6.2.1 (a) Amend the text of footnote 2 related to this sub-paragraph to read as follows:

"[2] When mixtures contain ingredients that do not have acute toxicity data for each route of exposure, acute toxicity estimates may be extrapolated from the available data and applied to the appropriate routes (see 3.1.3.2). However, competent authorities may require testing for a specific route. In those cases, classification should be performed for that route based upon the competent authority's requirement."

Background: Clarification of the footnote and its relationship to paragraph 3.1.3.2 was requested. This issue was raised by a correspondence group member subsequent to the submission of UN/SCEGHS/15/INF.27 and is related to item 7 in that document).

Rationale: It is proposed that the current text in the footnote be deleted and replaced with the proposed text. This footnote explains that where a competent

authority requires evaluation by a specific route of exposure, acute toxicity data may not be extrapolated from route to route.

Chapter 3.8: Specific target organ toxicity

3.8.3.4.5 In the first sentence, replace "extrapolating toxicity" with "extrapolating the toxicity" and add the following sentence at the end of the paragraph:

"Respiratory tract irritation and narcotic effects are to be evaluated separately based upon the criteria in 3.8.2.2. When conducting classifications for these hazards, the contribution of each ingredient should be considered additive, unless there is evidence that the effects are not additive.".

Background: see UN/SCEGHS/15/INF.27, addendum 1, items 13.

Rationale: The correspondence group proposes that the text in the paragraph be edited to clarify that respiratory tract irritation and narcotic effects are distinct effects to be evaluated separately, and that for each, effects should be considered additive unless evidence exists to suggest otherwise.

Annex 2

Examples of the application of the classification criteria for mixtures

Example 1:

The following example demonstrates the application of data when the available range data spans more than one acute toxicity range estimate in Table 3.1.2.

This will be proposed for inclusion in UNITAR training document (see UN/SCEGHS/15/INF.27, addendum 1, item 2):

Ingredient information:

Ingredient	Wt%	Test Data
Ingredient 1	16	LD_{50}: 1,600 mg/kg
Ingredient 2	4	Acute toxicity range estimate: 200 < LD_{50} < 2,000
Ingredient 3	80	LD_{50}: 3,450 mg/kg

Answer:

Apply the equation in paragraph 3.1.3.6.1:

$$\frac{100}{ATE_{mixture}} = \sum_{n} \frac{Ci}{ATEi}$$

$$\frac{100}{ATE_{mixture}} = \frac{16}{1,600} + \frac{4}{200} + \frac{80}{3,450}$$

Therefore: $ATE_{mixture}$ = 1,880 mg/kg, Category 4

Rationale:

(a) Classification via application of substance criteria is not possible since acute toxicity test data was not provided for the mixture (paragraph 3.1.3.4);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.1.3.5.1);

(c) Classification of the mixture based on ingredient data can be considered (paragraph 3.1.3.6);

(d) Applying the "relevant ingredients" concept from paragraph 3.1.3.3(a) means that all ingredients will be considered when applying criteria in paragraph 3.1.3.6;

(e) Data is available for all ingredients so criteria in paragraph 3.1.3.6.1 apply;

(f) Ingredients 1, 2 and 3 are all included in the $ATE_{mixture}$ calculation because they have data that fall within a GHS acute toxicity category [paragraph 3.1.3.6.1 (a)].

(g) Applying the guidance in Note (a) to Table 3.1.1:

(i) The LD_{50} data for ingredients 1 and 3 are used in the $ATE_{mixture}$ calculation since data are available;

(ii) The use of expert judgment is needed to determine what value to use in the $ATE_{mixture}$ calculation for ingredient 2. Since the experimentally obtained acute toxicity range estimate of $200 < LD_{50} < 2{,}000$ for ingredient 2 is existing data developed prior to development of the GHS criteria it does not match up with the ranges provided in Table 3.1.2. The lower end of the range falls within the Category 3 range of 50 – 300 mg/kg and the converted acute toxicity point estimate for an Oral Category 3 ingredient is 100. Given that the converted point estimate is lower than the experimentally determined value of > 200 mg/kg it does not make sense to use the converted point estimate. In this case, one should apply the known information, and 200 mg/kg should be used in the $ATE_{mixture}$ calculation.

(End of example 1)

Example 2:

The following example demonstrates the application of the "relevant ingredients" criteria in paragraph 3.1.3.3.

This will be proposed for inclusion in UNITAR training document (UN/SCEGHS/15/INF.27, addendum 1, item 3):

Acute toxicity – Oral

Ingredient information:

Ingredient	Wt%	Classification	Test Data
Ingredient 1	4	Oral Category 3	LD_{50}: 125 mg/kg
Ingredient 2	92	-	No data available
Ingredient 3	3	Oral Category 4	$LD_{50:}$ 1500 mg/kg
Ingredient 4	0.9	-	No data available
Ingredient 5	0.1	Oral Category 2	LD_{50}: 10 mg/kg

Answer:

Apply the equation in paragraph 3.1.3.6.2.3:

$$\frac{100-\left(\sum C_{unknown}\, if\ >10\%\right)}{ATE_{mixture}}=\sum_{n}\frac{C_i}{ATE_i}$$

$$\frac{100-(92)}{ATE_{mixture}}=\frac{4}{125}+\frac{3}{1500}$$

Therefore: $ATE_{mixture}$ = 235 mg/kg, Category 3, and
"92% of the mixture consists of an ingredient of unknown toxicity."

Rationale:

(a) Classification via application of substance criteria is not possible since acute toxicity test data was not provided for the mixture (paragraph 3.1.3.4);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.1.3.5.1);

(c) Classification of the mixture based on ingredient data can be considered (paragraph 3.1.3.6);

(d) Applying the "relevant ingredients" concept from paragraph 3.1.3.3 (a) means that ingredient 4 could be excluded from both the $ATE_{mixture}$ calculations. This is true for the calculation in either paragraph 3.1.3.6.1 or 3.1.3.6.2.3. This same reasoning could

also apply to ingredient 5, as it is below the "relevant ingredients" threshold; however, the use of expert judgment is necessary to make this decision for ingredient 5 as it is classified in Category 2. For this example, it was decided that since the percentage of this ingredient is well below the threshold (i.e. 0.1%) and the ingredient is classified in Category 2, it would be excluded from the ATE calculation;

(e) The total concentration of ingredients with unknown acute toxicity (i.e. ingredient 2) is 92%, therefore, the $ATE_{mixture}$ equation in paragraph 3.1.3.6.2.3 must be used. This calculation corrects for ingredients with unknown acute toxicity above 10% of the mixture;

(f) Ingredients 1 and 3 are included in the $ATE_{mixture}$ calculation because they have data that fall within a GHS acute toxicity category [Paragraph 3.1.3.6.1 (a)];

(g) Applying the guidance in Note (a) to Table 3.1.1 results in using the LD_{50} data for Ingredients 1 and 3 in the $ATE_{mixture}$ calculation since data are available;

(h) Ingredient 2 does not have any useable information for the oral route $ATE_{mixture}$ calculation and is in the mixture at a concentration ≥ 1% so an additional statement is included (paragraph 3.1.3.6.2.2.);

(End of example 2)

Example 3:

The following example demonstrates the application of the criteria found in paragraph 3.1.3.6.1 (c).

This will be proposed for inclusion in UNITAR training document (UN/SCEGHS/15/INF.27, addendum 1, item 4):

Acute toxicity – Oral

Ingredient information:

Ingredient	Wt%	Classification	Test data
Ingredient 1	4	Oral Category 4	LD_{50}: 1,737 mg/kg
Ingredient 2	5	-	LD_{50}: > 5,000 mg/kg
Ingredient 3	5	-	LD_{50}: 5,400 mg/kg
Ingredient 4	86	-	Oral limit dose > 2,000 mg/kg (No signs of toxicity)

Answer:

Apply the equation in paragraph 3.1.3.6.1:

$$\frac{100}{ATE_{mixture}} = \sum_{n} \frac{Ci}{ATEi}$$

$$\frac{100}{ATE_{mixture}} = \frac{4}{1{,}737}$$

Therefore: $ATE_{mixture}$ = 43,425 mg/kg, Not Classified

Rationale:

(a) Classification via application of substance criteria is not possible since acute toxicity test data was not provide for the mixture (paragraph 3.1.3.4).

(b) Classification via the application of bridging principles is not possible since data on a similar mixture (paragraph 3.1.3.5.1) was not provided.

(c) Classification of mixture based ingredient data can be considered (paragraph 3.1.3.6).

(d) Applying the “relevant ingredients” concept from paragraph 3.1.3.3(a) means that all ingredients will be considered when applying criteria in paragraph 3.1.3.6.

(e) Data is available for all ingredients so criteria in paragraph 3.1.3.6.1 apply.

(f) Applying sub-paragraph 3.1.3.6.1 (a):

(i) Ingredient 1 is included in the $ATE_{mixture}$ calculation because it falls into a GHS acute toxicity category;

(ii) Ingredients 2 and 3 can be ignored in the $ATE_{mixture}$ calculation because they do not fall within a GHS acute toxicity category.

(g) Applying paragraph 3.1.3.6.1 (c):

Ingredient 4 can be ignored in the $ATE_{mixture}$ calculation because it has oral limit dose test data that does not show acute toxicity at 2,000 mg/kg.

(End of example 3)

Example 4:

The following example demonstrates the application of the criteria found in paragraph 3.1.3.2.

This will be proposed for inclusion in UNITAR training document (This example was requested subsequent to the submission of document UN/SCEGHS/15/INF.27 to the Sub-Committee. It is related UN/SCEGHS/15/INF.27, addendum 1, item 7):

Ingredient information:

Ingredient	**Wt%**	**Acute toxicity test data**		
		Oral	**Dermal**	**Inhalation Vapours**
Ingredient 1	26	LD_{50}: 2,737 mg/kg	LD_{50}: 6,480 mg/kg	LC_{50}: 11 mg/l
Ingredient 2	23	LD_{50}: 4,500 mg/kg	LD_{50}:> 6,000 mg/kg	LC_{50}: 19 mg/l
Ingredient 3	11	$LD_{50:}$ > 5,000 mg/kg	No data available	No data available
Ingredient 4	40	LD_{50}: 400 mg/kg	Dermal limit dose > 2,000 mg/kg (No signs of toxicity)	LC_{50}: 4 mg/l

Answer:

(a) Oral route - Apply the equation in paragraph 3.1.3.6.1:

$$\frac{100}{ATE_{mixture}} = \sum_{n} \frac{Ci}{ATEi}$$

$$\frac{100}{ATE_{mixture}} = \frac{26}{2{,}737} + \frac{23}{4{,}500} + \frac{40}{400}$$

$ATE_{mixture}$ = 873 mg/kg, Acute Oral Toxicity; Category 4

(b) Inhalation route - Apply the equation in paragraph 3.1.3.6.2.3:

$$\frac{100 - \left(\sum C_{unknown} \text{ if } > 10\%\right)}{ATE_{mixture}} = \sum_{n} \frac{C_i}{ATE_i}$$

$$\frac{100 - (11)}{ATE_{mixture}} = \frac{26}{11} + \frac{23}{19} + \frac{40}{4}$$

$ATE_{mixture}$ = 6.6 mg/l, Acute inhalation toxicity; Category 3 and "11% of the mixture consists of an ingredient of unknown inhalation toxicity"

Pictogram:	
Signal word:	Danger
Hazard statements:	Toxic if inhaled. Harmful if swallowed.

Rationale:

(a) Classification via application of substance criteria is not possible since acute toxicity test data was not provided for the mixture (paragraph 3.1.3.4);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.1.3.5.1);

(c) Classification based on ingredient data for the mixture can be considered (paragraph 3.1.3.6);

(d) Applying the "relevant ingredients" concept from paragraph 3.1.3.3 (a) means that all ingredients will be considered when applying criteria in paragraphs 3.1.3.6.1 and 3.1.3.6.2.3;

(e) Review of the ingredient test data show there is relevant evidence to suggest acute toxicity via the oral and inhalation routes so the $ATE_{mixture}$ calculation was applied to the oral and inhalation routes (paragraph 3.1.3.2). Review of the ingredient test data via the dermal route show that the data are not applicable to the dermal $ATE_{mixture}$ calculation (paragraph 3.1.3.6.1(c));

Oral route

(f) Data is available for all ingredients via the oral route so criteria in paragraph 3.1.3.6.1 apply;

(g) Ingredients 1, 2 and 4 are included in the $ATE_{mixture}$ calculation because they have data that fall within a GHS acute toxicity category [Paragraph 3.1.3.6.1 (a)].

(h) Applying the guidance in Note (a) to Table 3.1.1 results in using the LD_{50} data for ingredients 1, 2 and 4 in the $ATE_{mixture}$ calculation since data is available.

Inhalation route

(i) The total concentration of ingredients with unknown inhalation acute toxicity (i.e., ingredient 3) is 11%, therefore, the $ATE_{mixture}$ equation in paragraph 3.1.3.6.2.3 must be used for the inhalation route. This calculation corrects for ingredients with unknown acute toxicity above 10% of the mixture.

(j) Ingredients 1, 2 and 4 are included in the $ATE_{mixture}$ calculation because they have data that fall within a GHS acute toxicity category [Paragraph 3.1.3.6.1 (a)];

(k) Applying the guidance in Note (a) to Table 3.1.1 results in using the LD_{50} data for ingredients 1, 2 and 4 in the $ATE_{mixture}$ calculation since data is available;

(l) Ingredient 3 does not have any useable information for the inhalation route $ATE_{mixture}$ calculation and is in the mixture at a concentration ≥ 1% so an additional statement is included (paragraph 3.1.3.6.2.2).

(End of example 4)]

Example 5

The following two examples demonstrate application of data for mixtures when additivity may not apply (paragraphs 3.2.3.3.4 and 3.3.3.3.4). The first example is for skin corrosion/irritation. The second example is for serious eye damage/irritation.

Both examples will be proposed for inclusion in the UNITAR training document (UN/SCEGHS/15/INF.27, addendum 1, item 9):

(a) Skin corrosion/irritation

Ingredient information:

Ingredient	Wt%	Classification	Ingredient information
Ingredient 1	4	Skin Category 1	pH = 1.8
Ingredient 2	5	Skin Category 2	-
Ingredient 3	5	Skin Category 3	-
Ingredient 4	86	-	No data available

Mixture information: Mixture pH = 4.0

Answer:

For this mixture, the classification was assigned as a Category 1 because ingredient 1 (Category 1) is in the mixture at ≥ 1%

Rationale:

(a) Classification via application of substance criteria is not possible since test data (other than a pH) was not provided for the mixture (paragraph 3.2.3.1.1);

(b) The overall mixture pH of 4.0 does not result in classification in Category 1 since this does not fall within the criteria of pH ≤ 2 or pH ≥ 11.5 (paragraph 3.2.3.1.2);

(c) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.2.3.2.1);

(d) Classification of the mixture based on ingredient data can be considered (paragraph 3.2.3.3);

(e) Ingredient 1 with a pH = 1.8 is an ingredient for which additivity might not apply as described in paragraph 3.2.3.3.4 and summarized in Table 3.2.4. Expert judgment would be needed to determine whether or not additivity applies. Knowledge of the components is important. Given the limited information in this example, the classifier of this mixture chose to apply non-additivity for a conservative approach. Without information on the mode of action of Ingredient 1, the mixture could be corrosive regardless of the overall pH. Therefore, the criteria described in paragraph 3.2.3.3.4 were applied (i.e. “A mixture containing corrosive or irritant ingredients that

cannot be classified based on the additivity approach shown in Table 3.2.3, due to chemical characteristics that make this approach unworkable, should be classified as skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as skin Category 2/3 when it contains ≥ 3% of an irritant ingredient").

(b) Serious eye damage/eye irritation

Ingredient information:

Ingredient	Wt%	Classification	Ingredient information
Ingredient 1	0.5	Eye Category 1	-
Ingredient 2	3.5	Eye Category 2	Surfactant
Ingredient 3	15	-	-
Ingredient 4	15	-	-
Ingredient 5	66	-	No data available

Answer: Mixture is Category 2 because:

(a) Mixture contains 0.5% of an Eye Category 1 which is not ≥ 1% so the mixture is not Category 1;

(b) Mixture contains 3.5% of an Eye Category 2 which is ≥ 3.0% so the mixture is Category 2

Rationale:

(a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.3.3.1).

(b) Classification considering the pH of the mixture is not possible as the pH was not provided (paragraph 3.3.3.1).

(c) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.3.3.2.1).

(d) Classification of the mixture based on ingredient data can be considered (paragraph 3.3.3.3).

(e) Ingredient 2 (Surfactant) is an ingredient for which additivity might not apply as described in paragraph 3.3.3.3.4 and summarized in Table 3.3.4. Expert judgment would be needed to determine whether or not additivity applies. Knowledge of the components is important. Given the limited information in this example, the classifier of this mixture chose to apply non-additivity for a conservative approach. Therefore, the criteria described in paragraph 3.3.3.3.4 apply (i.e., "A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.3.3, due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2/3 when it contains ≥ 3% of an irritant ingredient").

(End of example 5)

Example 6:

The following example demonstrates application of the relevant ingredients concept for mixtures in the Skin/Eye chapters.

This will be proposed for inclusion in the UNITAR training document (UN/SCEGHS/15/INF.27, addendum 1, item 10):

Serious eye damage/Eye irritation

Ingredient information:

Ingredient	Wt%	Classification	Ingredient information
Ingredient 1	91	-	-
Ingredient 2	5	Eye Category 2A	-
Ingredient 3	3	-	-
Ingredient 4	0.9	Eye Category 1	-
Ingredient 5	0.1	-	-

Answer:

Mixture is Category 2 because:

Equations from Table 3.3.3

Category 1 calculations:

(a) ∑%Eye Category 1 = 0.9 which is not ≥ 3%
(b) ∑%Skin Category 1 = 0.0 which is not ≥ 3%
(c) ∑%Skin Category 1 + ∑%Eye Cat 1 = 0.9 which is not ≥ 3%

Category 2 calculations:

(d) ∑%Eye Category 1= 0.9 which is not ≥ 1% but < 3%
(e) ∑% Skin Category 1 = 0 which is not ≥ 1% but < 3%
(f) ∑%Eye Category 2/2A = 5 which is not ≥ 10%
(g) (10× ∑%Eye Category 1) + ∑%Eye Category 2/2A = (10 × 0.9) + 5 = 14% which is ≥ 10%

Rationale:

(a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.3.3.1);

(b) Classification considering pH of the mixture is not possible as the pH was not provided (paragraph 3.3.3.1);

(c) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.3.3.2.1);

(d) Classification of the mixture based on ingredient data can be considered (paragraph 3.3.3.3);

(e) Expert judgment is necessary when applying the "relevant ingredients" concept from paragraph 3.3.3.3.1 since ingredient 4 (Eye Category 1) is below 1%. In this case the relatively high concentration of Ingredient 4 (i.e., 0.9%) and application of the additivity approach which includes a weighting factor for Category 1 ingredients weighs in favor of including ingredient 4 in the additivity calculations. In fact, for this particular example if ingredient 4 was not considered relevant and was ignored during the calculations the mixture would not be classified because the concentration of ingredient 2 (Eye Category 2A) is not high enough to cause the additivity equations in Table 3.3.3 to exceed the cut-off value/concentration limits;

(f) The additivity approach described in paragraphs 3.3.3.3.2 and 3.3.3.3.3 applies and the cut-off value/concentration limits provided in Table 3.3.3 are used for classification.

(End of example 6)

Example 7:

The following example demonstrates application of the guidance in paragraph 3.8.3.4.5, that is, whether or not additivity should be considered for Specific Target Organ Toxicity – Single Exposure (STOT-SE) Category 3 transient effects.

This will be proposed for inclusion in the UNITAR training document (UN/SCEGHS/15/INF.27, addendum 1, item 13):

Ingredient information:

Ingredient	Wt%	Classification
Ingredient 1	0.5	-
Ingredient 2	3.5	Category 3 – Respiratory Tract Irritation
Ingredient 3	15	Category 3 - Narcotic effects
Ingredient 4	15	Category 3 - Narcotic effects
Ingredient 5	66	-

Answer**:**
Mixture is Category 3 – Narcotic effects

∑%Category 3 – Narcotic effects = 15% + 15% = 30% which is > 20%%, therefore classify as Category 3 – Narcotic Effects

∑%Category 3 – Respiratory Irritation = 3.5%, which is < 20%, not classified for Respiratory Irritation

Rationale:

(a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.8.3.2);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.8.3.3.1);

(c) Application of paragraph 3.8.3.4.5 is used for classification. Expert judgement is necessary when applying this paragraph. Paragraph 3.8.3.4.5 notes that a cut-off value/concentration limit of 20% has been suggested, but that the cut-off value/concentration limit at which effects occur may be higher or less depending on the Category 3 ingredient(s). In this case, the classifiers judged that 30% is sufficient to classify.

(End of example 7)

Annex 3

Issues to be referred to the Sub-Committee for follow-up

1. Paragraph 3.1.3.6.2.1 allows for extrapolation between routes of exposure which could require substantial supplemental technical information, among other considerations. Significant effort would be needed for such guidance, as application of these criteria would be directed toward highly trained and experience experts. This may be an issue that the Sub-Committee chooses to address at a later date, however, the correspondence group on the classification of mixtures decided that further guidance on this paragraph was outside the resources and time constraints of the group.

2. Under paragraph 3.1.3.2, when more than one route of exposure is evaluated, it is possible that the classification of a mixture will fall into different GHS categories. This raises the question of the appropriate classification of the mixture. For example, if a mixture is both a dermal Category 5 and an inhalation Category 4, how should this mixture be classified? should the mixture be:

(a) Acute toxicity category 4; or

(b) Acute dermal toxicity category 5 and acute inhalation toxicity category 4?

This was not generally considered an issue about the application of the mixtures criteria but rather a hazard communication issue which would be better addressed by the Sub-Committee. This issue will be referred to the Sub-Committee for follow-up.

3. There were two issues that came up on reproductive hazards having to do with the appropriate classification and subsequent hazard communication elements for mixtures containing ingredients with different reproductive hazard endpoints:

(a) One issue had to do with a mixture containing two ingredients that are reproductive hazards, both of which are present above the cut-off concentrations. For instance, ingredient 1 is classified as Category 1A, and the test data indicate only effects on fertility. Ingredient 2 is classified as Category 2 and has data indicating only developmental effects. Is this mixture considered to be a Category 1, Category 1A or Category 1A/Category 2?

(b) The second issue is related and has to do with the correct hazard communication elements. That is, can the hazard communication statements be modified to choose either developmental or fertility endpoints?

These two issues were not considered to be about application of the criteria for mixtures, but rather hazard communication issues that would be better addressed by the Sub-Committee by referring these issues for follow-up by the appropriate correspondence group.
