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 **18 June 2010**

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Item 4 (a) of the provisional agenda
Implementation of the GHS

Implementation issues

Transmitted by the expert from the United States of America on behalf of the informal correspondence group on practical classification issues

A. Purpose

1. The purpose of this document is to provide an update on the work undertaken by the practical classification issues informal correspondence group.

2. The agreed scope of work for this informal correspondence group is to clarify application of the GHS criteria through, for example, development of proposals for changes to the GHS document or development of examples illustrating application of criteria and any related hazard communication issues, as needed.

B. Background

3. During the 17th session of the UNSCEGHS, the Subcommittee approved the program of work to be undertaken by the practical classification issues informal correspondence group for the current biennium (UN/SCEGHS/17/INF.5). Many of the work items were drawn from the document submitted by the Implementation Working Group in December 2008 (ST/SG/AC.10/C.4/2008/22).

4. The informal correspondence group met during the Subcommittee meeting in December 2009 and via a teleconference in June 2010 for discussion of proposals to modify GHS text and worked examples outlined in the agreed program of work. Based on the discussions in these meetings, the group has reached a consensus path forward for proposed editorial changes to the GHS text and worked examples on applying GHS criteria.

C. Proposed recommendations

5. The proposed recommendations in this paper are provided as an update of the activities of the correspondence groups efforts for information and consideration by the Subcommittee. These recommendations are presented in three annexes:

- Annex 1: Proposed editorial amendments to the GHS text;
- Annex 2: Worked examples illustrating the application of bridging principles; and

- Annex 3: Worked examples illustrating the application of mixture classification criteria for hazardous to the aquatic environment.

D. Next steps

6. The informal correspondence group will meet during the GHS Subcommittee's 19th session to address any remaining issues.

7. The informal correspondence group plans to submit a formal paper for the 20th session of the UNSCEGHS. This paper will recommend editorial clarifications to the text of the GHS and will suggest worked examples as guidance for inclusion in the UNITAR training documents.

Annex 1

Proposed editorial amendments to the GHS text

1. PCI Correspondence group item:

Provide clarification of paragraph 1.3.2.3 as related to a hierarchy for carcinogens, mutagens, and reproductive toxins. (Issue 3.15 of Implementation Working Group document)

Background: The current description of the recommended tiered approach to the classification of mixtures described in paragraph 1.3.2.3 does not accurately reflect the process described in paragraphs 3.5.3.1, 3.6.3.1, and 3.7.3.1 for the Germ Cell Mutagenicity, Carcinogenicity and Reproductive Toxicity hazard classes, respectively.

Proposed recommendation: To request that the SCEGHS approve a clarifying modification to the text in paragraph 1.3.2.3.1 and to include a new paragraph which specifically addresses the tiered approach for the Germ Cell Mutagenicity, Carcinogenicity and Reproductive Toxicity hazard classes.

Proposed amendments to Chapter 1.3: Classification of hazardous substances and mixtures

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

"The classification criteria for substances and mixtures are presented in Parts 2, 3 and 4 of this document, each of which is for a specific hazard class or a group of closely related hazard classes. For most hazard classes, the recommended process of classification of mixtures is based on the following sequence:

(a) Where test data are available for the complete mixture, the classification of the mixture will always be based on that data;

(b) Where test data are not available for the mixture itself, then bridging principles included and explained in each specific chapter should be considered to see whether they permit classification of the mixture;

In addition, for health and environmental hazards,

(c) If (i) test data are not available for the mixture itself, and (ii) the available information is not sufficient to allow application of the above mentioned bridging principles, then the agreed method(s) described in each chapter for estimating the hazards based on the information known will be applied to classify the mixture.

1.3.2.3.2 Insert a new paragraph 1.3.2.3.2 as follows:

"1.3.2.3.2 In most cases, it is not anticipated that reliable data for complete mixtures will be available for the Germ Cell Mutagenicity, Carcinogenicity, and Reproductive Toxicity hazard classes. Therefore, for these hazard classes, mixtures will generally be classified based on the available test data for the individual ingredients of the mixtures, using the cut-off values/concentration limit methods in each chapter. The classification may be modified on a case-by-base basis based on available test data for the complete mixture, if such data are conclusive as described in each chapter.".

2. PCI correspondence group item:

Provide clarification regarding the communication of classification information for substances or mixtures that fall into two separate categories within the same hazard class. This is a possible outcome for acute toxicity. For example: If a chemical is classified as both an oral acute toxicity Category 1 and a dermal acute toxicity Category 4. Is the chemical classified for the most severe hazard (Category 1 acute toxicity) or for both routes of exposure (oral acute toxicity Category 1 and a dermal acute toxicity Category 4)? (Issue 3.16 of Implementation Working Group document).

Proposed recommendation:

To request that the SCEGHS approve:

- New text in section 3.1.4 (Hazard communication), which clarifies that the route of exposure should be communicated as part of the classification and the statement "X percent of the mixture consists of ingredients of unknown toxicity".
- Editorial revisions to the SDS guidance provided in paragraph A4.3.2.1.2, which also clarifies that the route of exposure should be communicated as part of the classification.

Proposed amendments to Chapter 3.1: Acute toxicity

3.1.4 Insert "3.1.4.1" before the current paragraph.

3.1.4.2 Insert a new paragraph 3.1.4.2 after the Note to Table 3.1.3 as follows:

"3.1.4.2 The acute toxicity hazard statements differentiate the hazard based on the route of exposure. Communication of Acute Toxicity classification should reflect this differentiation, for example, acute oral toxicity Category 1, acute dermal toxicity Category 1 and acute inhalation toxicity Category 1. If a substance or mixture is classified for more than one route of exposure then all relevant classifications should be communicated on the safety data sheet. Similarly, if the statement "x percent of the mixture consists of ingredients of unknown toxicity" is communicated, as prescribed in paragraph 3.1.3.6.2.2, then it should also be differentiated based on the route of exposure. For example, "x percent of the mixture consists of ingredient(s) of unknown oral toxicity"."

Proposed amendments to Annex 4: Guidance on the preparation of Safety Data Sheets (SDS)

A4.3.2.1.2 Amend as follows (changes are indicated):

"If the substance or mixture is classified in accordance with Parts 2, 3 and/or 4 of the GHS generally the classification is communicated by providing the appropriate hazard class and category to indicate the hazard. For example, flammable liquid Category 1. However, when classification is differentiated within a hazard class and results in unique hazard statements then the classification should also reflect that differentiation. For example, the route of exposure differentiates the Acute Toxicity classification as follows: acute oral toxicity Category 1, acute dermal toxicity Category 1 and acute inhalation toxicity Category 1. If a substance or mixture is classified into more than one category in a hazard class that is differentiated, then all classifications should be communicated."

3. PCI Correspondence group item:

Discuss GHS coverage of simple asphyxiation.

Background: An asphyxiant is a vapor or gas that can cause unconsciousness or death by suffocation due to lack of oxygen. Simple asphyxiants are inert gases or vapors, which are harmful to the body when they become so concentrated that they reduce oxygen in the air (normally about 21 percent) to dangerous levels (19.5 percent or less). Simple asphyxiants frequently contribute to industrial accidents involving loss of life and are of particular concern for those who work in confined spaces.

Proposed recommendation: To request that the SCEGHS approve:

- New text in the acute toxicity chapter, which provides a definition for simple asphyxiants and the option to communicate that information on a label.
- An update to the gases under pressure chapter which alerts the reader that criteria for simple asphyxiants are provided in the acute toxicity chapter.

Proposed amendments to Chapter 3.1: Acute toxicity

3.1.2.6.6 Insert a new paragraph 3.1.2.6.6 as follows:

"In addition to classification for inhalation toxicity, if data are available that indicate that a substance or mixture may result in simple asphyxiation, the hazard may be communicated on the label as indicated in the footnote to Table 3.1.3. Simple asphyxiants are defined as substances or mixtures that displace oxygen in the ambient atmosphere, and can thus cause oxygen depravation in those who are exposed, that leads to unconsciousness and death. They are of particular concern in confined spaces. Examples of simple asphyxiants include: nitrogen, helium, argon, propane, neon, carbon dioxide and methane. Evaluation of simple asphyxiants could be based on expert judgment using such evidence as human experience, information from similar substances or any other pertinent data."

Insert a new note under Table 3.1.3 as follows *(changes are indicated)*:

***"NOTE**: If a substance/mixture is also determined to be corrosive (based on data such as skin or eye data), corrosivity hazard may also be communicated by some authorities as symbol and/or hazard statement. That is, in addition to an appropriate acute toxicity symbol, a corrosivity symbol (used for skin and eye corrosivity) may be added along with a corrosivity hazard statement such as "corrosive" or "corrosive to the respiratory tract".*

If a substance/mixture is determined to be a simple asphyxiant, this hazard may be communicated by indicating a signal word of "warning" and a hazard statement, such as "May displace oxygen and cause suffocation".

Proposed amendments to Chapter 2.5: Gases under pressure

2.5.3 Insert a note under Table 2.5.2 as follows:

*"**NOTE**: If a substance/mixture is determined to be a simple asphyxiant as described in the criteria in 3.1.2.6.6, some authorities may choose to communicate the asphyxiation hazard by indicating a signal word of "warning' and a hazard statement, such as "May displace oxygen and cause suffocation".*

4. PCI Correspondence group item:

Provide clarification in Chapters 3.1 and 4.1 regarding the location of an additional statement when a mixture contains ingredients without any usable information at a concentration ≥ 1%.

Proposed recommendation: To request that the SCEGHS approve:

- Editorial revisions to the text in paragraph 3.1.3.6 and 4.1.3.6 to clarify that the competent authority may decide where to communicate the information (i.e. SDS or label or both) or to leave the decision to the manufacturer/supplier.
- Editorial revisions to the decision logic footnote text in paragraphs 3.1.5.2 and 4.1.5.1.1 to clarify that the competent authority may decide where to communicate the information (i.e. SDS or label or both) or to leave the decision to the manufacturer/supplier.

Proposed amendments to Chapter 3.1: Acute toxicity

3.1.3.6 Amend 3.1.3.6.2.2 as follows *(changes are indicated)*:

"In the event that an ingredient without any useable information for classification is used in a mixture at a concentration ≥1%, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture should be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredients of unknown toxicity. The competent authority may decide to specify that the additional statement should be communicated on the label or on the SDS or both, or to leave the choice of where to place the statement to the manufacturer/supplier."

3.1.5.2 In the footnote to the decision logic amend as follows *(changes are indicated):*

"In the event that an ingredient without any useable information is used in a mixture at a concentration ≥1%, the classification should be based on the ingredients with the known acute toxicity only, and an additional statement should identify the fact that the acute toxicity of x % of the mixture is unknown. The competent authority may decide to specify that the additional statement should be communicated on the label or on the SDS or both, or to leave the choice of where to place the statement to the manufacturer/supplier."

Proposed amendments to Chapter 4.1: Hazardous to the aquatic environment

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

"In the event that no useable information on acute and/or chronic aquatic toxicity is available for one or more relevant ingredients, it is concluded that the mixture cannot be attributed (a) definitive hazard category(ies). In this situation the mixture should be classified based on the known ingredients only with the additional statement that: "x" % of the mixture consists of ingredient(s) of unknown hazards to the aquatic environment. The competent authority may decide to specify that the additional statement should be communicated on the label or on the SDS or both, or to leave the choice of where to place the statement to the manufacturer/supplier."

4.1.5.1.1 In the footnote to the decision logic amend as follows *(changes are indicated):*

"If not all ingredients have information, include the statement "x" % of the mixture consists of ingredients of unknown hazards to the aquatic environment. The competent authority may decide to specify that the additional statement should be communicated on the label or on the SDS or both, or to leave the choice of where to place the statement to the manufacturer/supplier. Alternatively, in the case of a mixture with highly toxic ingredients, if toxicity values are available for these highly toxic ingredients and all other ingredients do not significantly contribute to the hazard of the mixture, then the additivity formula may be applied (see 4.1.3.5.5.5). In this case and other cases where toxicity values are available for all ingredients, the acute classification may be made solely on the basis of the additivity formula."

5. PCI correspondence group item:

Review the description of the categories of hazard (e.g., Categories 1 and 2) and sub-categories (e.g., Categories 1A or 1B) to address inconsistencies between the tables, figures, and decision logics within the chapters. This applies to Chapters 3.5 (Germ cell mutagenicity), 3.6 (Carcinogenicity) and 3.7 (Reproductive toxicity) (Issue 3.14 of the Implementation Working Group document)

Proposed recommendation: To request that the SCEGHS approve:

- Updates to Tables 3.5.1, 3.6.1, 3.7.1 which are modified by adding an extra column to distinguish that mixtures are classified into either Category 1A or Category 1B. An additional row has also been added to the tables to distinguish how Category 1A versus Category 1B ingredients impact the mixture classification.
- Updates to Tables 3.5.2, 3.6.2, 3.7.2 which are modified by consolidating the columns for Categories 1A and 1B into a single column which is relabeled to indicate that the symbol, signal word and hazard statement are the same for both Category 1A and 1B.

Proposed amendments to Chapter 3.5: Germ cell mutagenicity

3.5.3.3 Amend Table 3.5.1 as follows:

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

3.5.4 Amend Table 3.5.2 as follows:

	Category 1 (Category 1A, 1B)	**Category 2**
Symbol	Health hazard	Health hazard
Signal word	Danger	Warning
Hazard statement	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

Proposed amendments to Chapter 3.6: Carcinogenicity

3.6.3.3 Amend Table 3.6.1 as follows:

Ingredient classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**		
	Category 1 carcinogen		**Category 2 carcinogen**
	Category 1A	**Category 1B**	
Category 1A carcinogen	≥ 0.1%	--	--
Category 1B carcinogen	--	≥ 0.1%	--
Category 2 carcinogen	--	--	≥ 0.1% (note 1)
			≥ 1.0% (note2)

3.6.4 Amend Table 3.6.2 as follows:

	Category 1 (Category 1A, 1B)	**Category 2**
Symbol	Health hazard	Health hazard
Signal word	Danger	Warning
Hazard statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

Proposed amendments to Chapter 3.7: Reproductive toxicity

3.7.3.3.2 Amend Table 3.7.1 as follows:

Ingredient classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**			
	Category 1 reproductive toxicant		**Category 2 reproductive toxicant**	**Additional category for effects on or via lactation**
	Category 1A	**Category 1B**		
Category 1A reproductive toxicant	≥ 0.1% (note 1) ≥ 0.3% (note 2)	--	--	--
Category 1B reproductive toxicant	--	≥ 0.1% (note 1) ≥ 0.3% (note 2)	--	--
Category 2 reproductive toxicant	--	--	≥ 0.1% (note 3) ≥ 3.0% (note 4)	--
Additional category for effects on or via lactation	--	--	--	≥ 0.1% (note 1) ≥ 0.3% (note 2)

3.7.4 Amend Table 3.7.2 as follows:

	Category 1 (Category 1A, 1B)	**Category 2**	**Additional category for effects on or via lactation**
Symbol	Health hazard	Health hazard	*No symbol*
Signal word	Danger	Warning	*No signal word*
Hazard statement	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)	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)	May cause harm to breast-fed children.

Annex 2

Bridging principles examples

PCI correspondence group item: Provide clarity for the conditions necessary for the use of bridging principles through the provision of agreed examples (Issue 2.2 of Implementation Working Group document)

Proposed recommendation: The following examples of the application of Bridging Principles, below, will be suggested for inclusion in UNITAR's advance training document, which is under development.

1. Dilution bridging principle example

The following example uses acute toxicity data to demonstrate the application of the dilution bridging principle, however, it is intended to illustrate how the dilution bridging principle might apply across all hazard classes that allow the use of dilution.

Dilution

If a tested mixture is diluted with a diluent that has an equivalent or lower toxicity classification than the least toxic original ingredient, and which is not expected to affect the toxicity of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the formula explained in 3.1.3.6.1 could be applied.

Tested mixture information:

Acute toxicity Classification and Test Data		
Oral	**Dermal**	**Inhalation Vapours**
Category 4 (LD_{50}: 310 mg/kg)	**Category 4** (LD_{50}: 1,250 mg/kg)	**Category 2** (LC_{50}: 1.97 mg/l)

Information on ingredients in the tested mixture:

Ingredient	**Wt%**	**Acute toxicity Classification and Test Data**		
		Oral	**Dermal**	**Inhalation Vapours**
Ingredient 1	26	**Category 5** (LD_{50}: 2,737 mg/kg)	**Category 4** (LD_{50}: 1,500 mg/kg)	**Category 4** (LC_{50}: 11 mg/l)
Ingredient 2	40	**Category 3** (LD_{50}: 118 mg/kg)	**Category 4** (LD_{50}: 1,250 mg/kg)	**Category 3** (LC_{50}: 4 mg/l)
Ingredient 3	34	**Category 4** (LD_{50}: 1950 mg/kg)	**Category 4** (LD_{50}: 1,100 mg/kg)	**Category 2** (LC_{50}: 1.5 mg/l)

Information on diluent:

Ingredient	Acute toxicity test data		
	Oral	**Dermal**	**Inhalation Vapours**
Diluent	**Category 5** (LD_{50}: 2,500 mg/kg)	**Category 3** (LD_{50}: 950 mg/kg)	**Category 5** (LC_{50}: 19 mg/l)

Information on an untested mixture:

The tested mixture is diluted 50% with an ingredient that is not expected to affect the toxicity of the other ingredients resulting in the following untested mixture:

Ingredient	Wt%
Ingredient 1	13
Ingredient 2	20
Ingredient 3	17
Diluent	50

Answer:

(a) Oral route – Classification: Acute Oral Toxicity; Category 4

(b) Dermal route – The Dilution bridging principle cannot be applied.

(c) Inhalation route – Classification: Acute Inhalation Toxicity; Category 2

Rationale:

(a) Since acute toxicity test data was not provided for the untested mixture classification via application of substance criteria is not possible;

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;

(c) Classification of the mixture based on ingredient information should be considered if the classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;

Oral route

(c) The dilution bridging principle can be applied because the diluent's classification (i.e., Category 5) is an equivalent toxicity classification category as the least toxic original ingredients (i.e., Ingredient 1 which is also classified in Category 5);

Dermal route

(d) The dilution bridging principle can not be applied because the diluent's classification (i.e., Category 3) is in a higher toxicity classification category than the least toxic original ingredients (i.e., Ingredients 1, 2, and 3 are all classified in Category 4);

(e) Classification of the mixture based on ingredient data should be considered;

Inhalation route

(f) The dilution bridging principle can be applied because the diluent's classification (i.e., Category 5) is in a lower toxicity classification category as the least toxic original ingredients (i.e., Ingredient 1 is classified in Category 4).

2. Batching Bridging Principle Example

The following example uses Specific Target Organ Toxicity – Single Dose data to demonstrate the application of the Batching Bridging Principle, however, it is intended to illustrate how the Batching bridging principle might apply across all hazard classes that allow the use of Batching.

Batching

The toxicity of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the untested batch has changed. If the latter occurs, a new classification is necessary.

Background

1. Ingredient A is a complex substance that in commercial batches contains a mixture of isomers. Specific Target Organ Toxicity – Single Exposure effects have been well documented for the ortho-isomers contained in Ingredient A.

2. Accidental ingestion of mixtures containing Ingredient A in humans due to contamination of drink and food has been reported which resulted in paralysis of the lower extremities.

3. Mixtures containing various concentrations of Ingredient A have been tested over the course of many years in animal studies. The results of these studies show a direct correlation of Ingredient A's ortho-isomers concentration in the mixture to statically significant effects in the animal studies. A guideline is established that any mixture containing greater than or equal to 0.5% of the ortho-isomers of Ingredient A must be classified as Specific Target Organ Toxicity – Single Exposure; Category 2. Mixtures contain less than 0.5% of the ortho-isomers of Ingredient A are not classified.

Untested mixture information:

Manufacturing batch	Wt% of ortho-isomer of Ingredient A
Batch 1	0.42
Batch 2	0.52

Answer:

(a) Batch 1: Applying the Batching bridging principle the Untested Batch 1 mixture does not require classification.

(b) Batch 2: Applying the Batching bridging principle the Untested Batch 2 mixture is classified as Specific Target Organ Toxicity – Single Exposure; Category 2.

Rationale:

(a) Classification via application of substance criteria is not possible since Specific Target Organ Toxicity – Single Exposure test data was not provided for each batch of the mixture;

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and similar tested mixtures;

(c) The batching bridging principle can be applied since there is a reason to believe that a significant variation in toxicity can occur based on the concentration of Ingredient A's ortho-isomers concentration in each batch.

3. Concentration of highly toxic mixtures bridging principle example

The following example uses Acute Toxicity data to demonstrate the application of the concentration of highly toxic mixtures bridging principle, however, it is intended to illustrate how the concentration of highly toxic mixtures bridging principle might apply across all hazard classes that allow the use of concentration of highly toxic mixtures.

Concentration of highly toxic mixtures

If a tested mixture is classified in Category 1, and the concentration of the ingredients of the tested mixture that are in Category 1 is increased, the resulting untested mixture should be classified in Category 1 without additional testing.

Tested mixture information:

Acute toxicity Classification and Test Data	
Oral	**Dermal**
Category 1 (LD_{50}: 3 mg/kg)	**Category 2** (LD_{50}: 85 mg/kg)

Information on ingredients in the tested mixture:

Ingredient	**Wt%**	**Acute toxicity Classification and Test Data**	
		Oral	**Dermal**
Ingredient 1	75	**Category 1** (LD_{50}: 1 mg/kg)	**Category 2** (LD_{50}: 195 mg/kg)
Ingredient 2	25	**Category 2** (LD_{50}: 6 mg/kg)	**Category 1** (LD_{50}: 40 mg/kg)

Information on an untested mixture:

Ingredient	**Wt%**
Ingredient 1	80
Ingredient 2	20

Answer:

(a) Oral route – Applying the concentration of highly toxic mixtures bridging principle, the untested mixture can be classified as Oral Acute Toxicity; Category 1 without additional testing

(b) Dermal route – Concentration of highly toxic mixtures bridging principle cannot be applied.

Rationale:

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

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;

(c) Classification of the mixture based on ingredient information should be considered if the classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;

Oral route

(c) The concentration of highly toxic mixtures bridging principle can be applied because the tested mixture is classified in Category 1 and the concentration of Ingredient 1 (i.e., a Category 1 ingredient) has increased in the untested mixture.

Dermal route

(d) The concentration of highly toxic mixtures bridging principle cannot be applied because the tested mixture is not classified into Category 1.

4. Interpolation within one toxicity category bridging principle example

The following example uses Skin Corrosion/Irritation data to demonstrate the application of the Interpolation within one toxicity category bridging principle, however, it is intended to illustrate how the Interpolation within one toxicity category bridging principle might apply across all hazard classes that allow the use of interpolation within one toxicity category.

Interpolation within one toxicity category

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.

Tested mixture information:

Skin Corrosion/Irritation Classification and Test Data	
Mixture A	**Mixture B**
Skin Irritation; Category 2 Animal 1: Mean Erythema/eschar: 2.5 Mean Oedema: 1.5 Animal 2: Mean Erythema/eschar: 2.3 Mean Oedema: 1.3 Animal 3: Mean Erythema/eschar: 2.2 Mean Oedema: 1	**Skin Irritation; Category 2** Animal 1: Mean Erythema/eschar: 3.8 Mean Oedema: 2.5 Animal 2: Mean Erythema/eschar: 3.5 Mean Oedema: 2.9 Animal 3: Mean Erythema/eschar: 4.0 Mean Oedema: 3.2

Information on ingredients in the tested mixture:

Ingredient	**Ingredient classification**	**Weight %**	
		Mixture A	**Mixture B**
Ingredient 1	Skin Corrosive; Category 1C	1	5
Ingredient 2	Skin Irritant Category 2	15	30
Water	Not Classified	84	65

Untested mixture information:

Ingredient	Weight %		
	Mixture A	Mixture C	Mixture B
Ingredient 1	1	4	5
Ingredient 2	15	20	30
Water	84	76	65

Answer:

Applying the interpolation within one toxicity category bridging principle the untested Mixture C can be classified as Skin Irritant; Category 2 without additional animal testing.

Rationale:

(a) Classification via application of substance criteria is not possible since skin corrosion/irritation test data was not provided for the untested mixture;

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;

(c) Classification of the mixture based on ingredient information should be considered if the classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;

(d) The interpolation within one toxicity category bridging principle can be applied because:

(i) Mixtures A and B have both been tested and are in the same irritation/corrosion toxicity category (i.e., Skin Irritant; Category 2); AND
(ii) Untested Mixture C has the same toxicologically active ingredients (i.e., Ingredients 1 and 2) as tested Mixtures A and B; AND
(iii) The concentrations of Ingredients 1 and 2 in Mixture C are both intermediate to the concentrations of Ingredients 1 and 2 in Mixtures A and B.

5. Substantially similar mixtures bridging principle example

The following example uses Skin Sensitization data to demonstrate the application of the substantially similar mixtures bridging principle, however, it is intended to illustrate how the Substantially similar mixtures bridging principle might apply across all hazard classes that allow the use of substantially similar mixtures.

Substantially similar mixtures

Given the following:

(a) Two mixtures: (i) A + B;

(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Ingredient B is a sensitizer and ingredients A and C are not sensitizers;

(e) A and C are not expected to affect the sensitizing properties of B.

If mixture (i) or (ii) is already classified based on test data, then the other mixture can be assigned the same hazard category.

Background information:

1. Ingredient 1 has been used in products ranging from 1.2 to 6.0 weight percent for years without reports of sensitization.

2. Existing animal test data on Ingredient 1 indicates that it is a Category 1 skin sensitizer.

3. Ingredients 2(a) and 2(b) are analogous lubricant materials with slightly different viscosities. Ingredients 2(a) and 2(b) have both been tested in animal studies and are not skin sensitizers. They are not expected to affect the sensitization potential of Ingredient 1.

4. There are no data to suggest that the other ingredients are skin sensitizers or that they will affect the sensitization potential of Ingredient 1.

5. Products containing Ingredient 1 were then tested in animal studies, which were all negative. Subsequently, clinical study data were gather and are summarized below:

Tested mixture information:

Product Name	Wt% of Ingredient 1 in Product	Repeated insult patch tests # of positive cases/# Tested
Product 1	5.0	0/298
Product 2	6.0	0/198
Product 3	6.0	0/307
Product 4	5.0	0/197
Product 5	2.5	0/103
		Total: 0/1,103

Detailed composition of Tested Mixture & substantially similar untested mixture:

Tested Mixture (Product 1)	
Ingredient	**Wt%**
Ingredient 1	5.0
Ingredient 2(a)	91.0
Ingredient 3	3.0
Ingredient 4	0.9
Ingredient 5	0.1

Untested Mixture (Product 6)	
Ingredient	**Wt%**
Ingredient 1	4.8
Ingredient 2(b)	91.2
Ingredient 3	3.0
Ingredient 4	0.9
Ingredient 5	0.1

Answer:

The Untested Mixture (Product 6) is not classified based on the test data available for the similar tested mixture (Product 1).

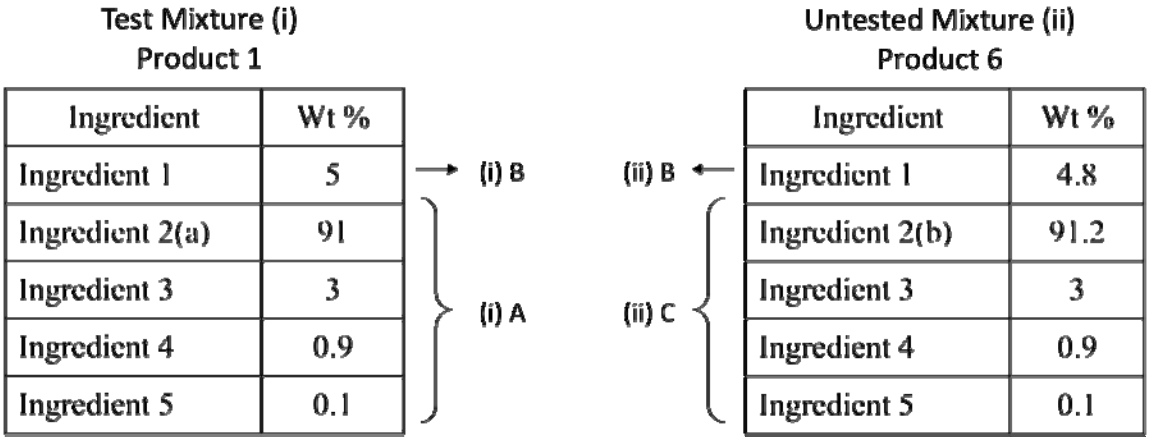
Rationale:

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

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;

(c) Classification of the mixture based on ingredient information should be considered if the classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;

(d) As illustrated using the figure below, the Substantially similar mixtures bridging principle can be applied because:



(i) The concentration of Ingredient B (i.e., Ingredient 1 in both mixtures) is essentially the same in both mixtures

(ii) Ingredient B is a sensitizer and Ingredients A (i.e., Ingredients 2(a), 3, 4, 5) in mixture (i) & C (i.e., Ingredients 2(b), 3, 4, 5) in mixture (ii) are not sensitizers

(iii) Ingredients A & C are not expected to affect the sensitizing properties of ingredient B.

(iv) Since Product 1 was already not classified based on test data, then Product 7 is also not classified based on the test data.

6. Aerosols bridging principle example

The following example uses Skin Irritation data to demonstrate the application of the Aerosols Bridging Principle, however, it is intended to illustrate how the Aerosols bridging principle might apply across all hazard classes that allow the use of Aerosols.

Aerosols

An aerosol form of the mixture may be classified in the same hazard category as the tested non-aerosolized form of the mixture provided that the added propellant does not affect the sensitizing properties of the mixture upon spraying.

Tested mixture information:

Skin Corrosion/Irritation test data
Animal 1: Mean Erythema/eschar: 3.8 Mean Oedema: 2.5 Animal 2: Mean Erythema/eschar: 3.5 Mean Oedema: 2.9 Animal 3: Mean Erythema/eschar: 4.0 Mean Oedema: 3.2

Based on the test data the mixture is classified: Skin Corrosion/Irritation; Category 2

The tested mixture is aerosolized using a 50/50 mixture of propane/butane as the propellant.

Aerosolized untested mixture information:

Ingredient	Weight %
Tested Mixture	50
Liquefied Propane	25
Liquefied Butane	25

Answer:

Applying the Aerosols bridging principle the aerosolized untested mixture can be classified as Skin Irritant; Category 2 without additional animal testing.

Rationale:

(a) Classification via application of substance criteria is not possible since skin corrosion/irritation test data was not provided for the aerosolized untested mixture;

(b) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;

(c) The aerosols bridging principle can be applied because:

(i) The non-aerosolized mixture has been tested, and

(ii) The propellant (i.e. 50/50 mixture of liquefied propane/butane) is not corrosive or an irritant, and

(iii) The propellant will not affect the irritation properties of the mixture upon spraying.

Annex 3

Examples of application of mixture classification criteria for hazardous to the aquatic environment

PCI Correspondence Group Item: Provide examples of the application of the classification criteria for the aquatic toxicity of mixtures.

Proposed recommendation: The following examples of the application of mixture classification criteria for aquatic toxicity will be suggested for inclusion in UNITAR's advance training document, which is under development.

Example 1

The following example demonstrates application of the acute additivity methods when toxicity data are available for all of the components of a mixture.

Ingredient information:

Ingredient	Wt%	Acute toxicity data	$L(E)C_{50}$
Ingredient 1	20	Fish (96 hr LC_{50})	0.15
		Crustacea (48 hr EC_{50})	11
		Algae /aquatic plants (72 or 96 hr ErC_{50})	33
Ingredient 2	20	Fish (96 hr LC_{50})	12
		Crustacea (48 hr EC_{50})	1.2
		Algae /aquatic plants (72 or 96 hr ErC_{50})	43
Ingredient 3	60	Fish (96 hr LC_{50})	>100
		Crustacea (48 hr EC_{50})	>100
		Algae /aquatic plants (72 or 96 hr ErC_{50})	>100

Answer:

Mixture is Category 1, M-Factor 1

Applying the acute additivity formula from 4.1.3.5.2 (a):

$$\frac{\sum Ci}{L(E)C_{50_m}} = \sum_n \frac{Ci}{L(E)C_{50_i}}$$

where:

C_i = concentration of ingredient i (weight percentage);

$L(E)C_{50_i}$ = LC_{50} or EC_{50} for ingredient i, in (mg/l);

n = number of ingredients, and i is running from 1 to n;

$L(E)C_{50_m}$ = $L(E)C_{50}$ of the part of the mixture with test data;

Fish $LC_{50Mixture}$ = 100/(20/0.15 + 20/12 + 60/100) = **0.74** mg/l

Crustacea $EC_{50Mixture}$ = 100/(20/11 + 20/1.2 + 60/100) = 5.24 mg/l

Algae $ErC_{50Mixture}$ = 100/(20/33 + 20/43 = 60/100) = 59.8 mg/l

Rationale:

(a) Classification via application of substance criteria is not possible since acute aquatic toxicity test data was not provided for the mixture (paragraph 4.1.3.3);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 4.1.3.4);

(c) Classification based on ingredient data for the mixture can be considered (paragraph 4.1.3.5);

(d) Adequate toxicity data is available for more than one ingredient so the additivity formulas can be considered (paragraph 4.1.3.5.2);

(e) Classification of the mixture based on the acute summation method should be considered (paragraph 4.1.3.5.5) if the Additivity Formula is not applied;

(f) Applying the "relevant ingredients" concept from paragraph 4.1.3.1 means that ingredients 1, 2, and 3 will be considered when applying the acute additivity formula (paragraph 4.1.3.5.2 (a)).

(g) All ingredients have acute aquatic toxicity data available for all taxonomic groups (i.e. fish, crustacean and algae) so the toxicity was calculated for each taxonomic group and the lowest value (i.e. Fish) was used to determine the classification (paragraph 4.1.3.5.3);

Example 2

The following example demonstrates application of the acute and chronic summation methods when classification data is available for some or all of the components of a mixture.

Ingredient information:

Ingredient	Wt%	Acute classification (M-factor)	Chronic classification (M-factor)
Ingredient 1	0.14	Acute 1 (M-factor: 1)	Chronic 1 (M-factor: 1)
Ingredient 2	0.1	Acute 1 (M-factor: 10)	Not classified
Ingredient 3	1.0	Acute 2	Chronic 2
Ingredient 4	5.0	Acute 3	Not classified
Ingredient 5	25.0	Not classified	Chronic 4
Ingredient 6	68.76	Not classified	Not classified

Answer:

Acute Classification - Category 3 because:

Acute 1: (Acute 1) x M ≥ 25%

using data from ingredients of the mixture:

(0.14% x 1) + (0.1% x 10) = 1.14% (Not classified)

Acute 2: (M x 10 x Acute 1) + Acute 2 ≥ 25%

using data from ingredients of the mixture:

(1 x 10 x 0.14%) + (10 x 10 x 0.1%) + 1.0% = 12.4% (Not classified)

Acute 3: (M x 100 x Acute 1) + (10 x Acute 2) + Acute 3 ≥ 25%

using data from ingredients of the mixture:

(1 x 100 x 0.14)+ (10 x 100 x 0.1%) + (10 x 1.0) + 5% = 129% (Classified)

Chronic Classification - Category 4 because:

Chronic 1: (Chronic 1) x M ≥ 25%

using data from ingredients of the mixture:

0.14% x 1 = 0.14% (Not classified)

Chronic 2: (M x 10 x Chronic 1) + Chronic 2 ≥ 25%

using data from ingredients of the mixture:

(1 x 10 x 0.14%) + 1.0% = 2.4% (Not classified)

Chronic 3: (M x 100 x Chronic 1) + (10 x Chronic 2) + Chronic 3 ≥ 25%

using data from ingredients of the mixture:

(1 x 100 x 0.14%) + (10 x 1.0) = 24% (Not classified)

Chronic 4: Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25%

using data from ingredients of the mixture:

0.14% + 1.0% + 25.0 = 26.14% (Classified)

Rationale:

(a) Classification via application of substance criteria is not possible since aquatic toxicity test data was not provided for the mixture (paragraph 4.1.3.3);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 4.1.3.4);

(c) Classification based on ingredient data for the mixture can be considered (paragraph 4.1.3.5);

(d) Adequate toxicity data is not available for more than one ingredient so the Additivity Formulas cannot be considered (paragraph 4.1.3.5.2);

(e) Acute and Chronic classification data is available for some of the ingredients of the mixture so the Summation Method can be considered (paragraph 4.1.3.5.5);

Acute classification:

(f) Applying the "relevant ingredients" concept from paragraph 4.1.3.1 means that Ingredients 1, 2, 3, and 4 will be considered when applying criteria in paragraph 4.1.3.5.5;

(g) The Acute summation method approach described in paragraph 4.1.3.5.5.3 applies and the cut-off value/concentration limits provided in Table 4.1.3 are used for classification.

Chronic classification:

(h) Applying the "relevant ingredients" concept from paragraph 4.1.3.1 means that Ingredients 1, 3, and 5 will be considered when applying criteria in paragraph 4.1.3.5.5;

(i) The chronic summation method approach described in paragraph 4.1.3.5.5.4 applies and the cut-off value/concentration limits provided in Table 4.1.4 are used for classification.

Example 3

The following example demonstrates application of a stepped approach where the additivity formula is used for the part of the mixture that has chronic toxicity data and passing that result into the chronic summation method.

Ingredient information:

Ingredient	Wt%	Chronic toxicity data	NOEC or EC_x	Rapidly Degradable	Classification
Ingredient 1	15	NOEC (for fish)	4.1	Yes	Chronic 2
		NOEC (for crustacea)	0.13		
Ingredient 2	5	NOEC (for algae)	.8	No	Chronic 2
Ingredient 3	80	Data not provided by supplier			Chronic 3

Answer:

Mixture is Chronic Category 3

Applying the Chronic additivity formula from 4.1.3.5.2 (b):

$$\frac{\sum Ci + \sum Cj}{EqNOEC_m} = \sum_n \frac{Ci}{NOECi} + \sum_n \frac{Cj}{0.1 \times NOECj}$$

where:

C_i = concentration of ingredient i (weight percentage) covering the rapidly degradable ingredients;

Cj = concentration of ingredient j (weight percentage) covering the non- rapidly degradable ingredients;

$NOEC_i$ = NOEC (or other recognized measures for chronic toxicity) for ingredient i covering the rapidly degradable ingredients, in mg/l;

NOECj = NOEC (or other recognized measures for chronic toxicity) for ingredient j covering the non-rapidly degradable ingredients, in mg/l;

n = number of ingredients, and i and j are running from 1 to n;

$EqNOEC_m$ = Equivalent NOEC of the part of the mixture with test data;

$NOEC_{Mixture}$ = 20/(15/0.13) + 5/(0.1x 0.8) = 0.11 mg/l

The part of the mixture (i.e., 20%) with Chronic Toxicity data (i.e., Ingredients 1 & 2) has an $NOEC_M$ of 0.11 mg/l resulting in a classification of Chronic 2.

Ingredient information going into the chronic summation method calculations:

Ingredient	Wt %	Classification
Additivity result – part of mixture with toxicity data	20	Chronic 2
Ingredient 3	60	Chronic 3

Chronic 1: (Chronic 1) x M ≥ 25%

0% (Not classified)

Chronic 2: (M x 10 x Chronic 1) + Chronic 2 ≥ 25%

using data from the additivity result & ingredients of the mixture:

(0%) + 20% = 20% (Not classified)

Chronic 3: (M x 100 x Chronic 1) + (10 x Chronic 2) + Chronic 3 ≥ 25%

using data from the additivity result & ingredients of the mixture:

(0%) + (10 x 20) + 60 = 260% (Classified)

Rationale:

(a) Classification via application of substance criteria is not possible since acute aquatic toxicity test data was not provided for the mixture (paragraph 4.1.3.3);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 4.1.3.4);

(c) Classification based on ingredient data for the mixture can be considered (paragraph 4.1.3.5);

(d) Adequate toxicity data is available for more than one ingredient (i.e., Ingredients 1 & 2) so the Additivity Formulas can be considered for the part of the mixture with data (paragraph 4.1.3.5.2);

(e) Classification of the mixture based on the Chronic Summation Method should be considered (paragraph 4.1.3.5.5.4) if the Additivity Formula is not applied. If the mixture is classified by more than one method then the more conservative result should be used (paragraph 4.1.3.5.3);

(f) Applying the "relevant ingredients" concept from paragraph 4.1.3.1 means that Ingredients 1, 2, and 3 will be considered when applying the Chronic Additivity Formula (paragraph 4.1.3.5.2 (b));

(g) When applying the Additivity Formula the preferred method is to calculate the toxicity of this part of the mixture for each ingredient toxicity values that relate to the same taxonomic group (i.e. fish, crustacean or algae) and then to use the highest toxicity obtained (i.e., use the most sensitive of the three groups). However, when toxicity data for each ingredient are not available in the same taxonomic group the data from the most sensitive test organism should be used (paragraph 4.1.3.5.3). In this case Ingredient 1's toxicity data for Crustacea is used because it is has the lowest value (i.e. highest toxicity) and Ingredient 2's Algae data is used;

(h) Application of the Chronic Additivity Formula results in 20% of the mixture being classified at Chronic Category 2, which is used in the Chronic Summation Method with the classification information provided for Ingredient 3;

Example 4

The following example demonstrates application of the tiered approach of mixture's classification where acute toxicity data is available on the mixture as well as on the ingredients. And chronic classification data is only available on the ingredients.

Ingredient information:

Ingredient	Wt%	Acute Toxicity Data	$L(E)C_{50}$ mg/l	Chronic Classification
Ingredient 1	5	LC_{50} (for fish)	12	Not classified
		EC_{50} (for crustacea)	18	
		ErC_{50} (algae)	0.9	
Ingredient 2	1.5	LC_{50} (for fish)	40	Chronic 2
		EC_{50} (for crustacea)	25	
		ErC_{50} (algae)	9.5	
Ingredient 3	93.5	LC_{50} (for fish)	> 100	Chronic 4
		EC_{50} (for crustacea)	> 100	
		ErC_{50} (algae)	> 100	

Information on tested mixture:

Acute Toxicity Data	$L(E)C_{50}$ mg/l
LC_{50} (for fish)	68
EC_{50} (for crustacea)	90
ErC_{50} (algae)	12.5

Answer:

Acute classification - Category 3

Chronic classification - Category 4 because:

Chronic 1: (Chronic 1) x M ≥ 25%

0% (Not classified)

Chronic 2: (M x 10 x Chronic 1) + Chronic 2 ≥ 25%

using data from the ingredients of the mixture:

(0%) + 1.5% = 1.5% (Not classified)

Chronic 3: (M x 100 x Chronic 1) + (10 x Chronic 2) + Chronic 3 ≥ 25%

using data from the ingredients of the mixture:

(0%) + (10 x 1.5) + 0 = 15% (Not classified)

Chronic 4: Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25%

using data from ingredients of the mixture:

0% + 1.5% + 0% + 93.5% = 95% (Classified)

Acute classification:

(a) Classification via application of substance criteria is possible for Acute Toxicity since acute aquatic toxicity test data was provided for the mixture (paragraph 4.1.3.3);

(b) The higher toxicity value (from the most sensitive test organism) which in this case is Algae or other aquatic plants is used to classify the tested mixture (paragraph 4.1.3.3.3 (a));

Chronic classification:

(c) Classification via application of substance criteria is not possible since chronic aquatic toxicity test data was not provided for the mixture (paragraph 4.1.3.3.4 (a));

(d) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 4.1.3.4);

(e) Adequate chronic toxicity data is not available for more than one ingredient so the Chronic additivity formulas cannot be considered (paragraph 4.1.3.5.2 (b));

(f) Chronic classification data is available for some of the ingredients of the mixture so the summation method can be considered (paragraph 4.1.3.5.5);

(g) Applying the “relevant ingredients” concept from paragraph 4.1.3.1 means that Ingredients 2, and 3 will be considered when applying criteria in paragraph 4.1.3.5.5;

(h) The chronic summation method approach described in paragraph 4.1.3.5.5.4 applies and the cut-off value/concentration limits provided in Table 4.1.4 are used for classification.