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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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Item 2 (b) of the provisional agenda

UPDATING OF THE SECOND REVISED EDITION OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Health hazards

Revision of Chapter 3.4 with respect to strong versus weak sensitizers

Note by the secretariat

At the request of the Sub-Committee (ST/SG/AC.10/C.4/30, para. 33) the secretariat reproduces hereafter the proposal for amendment to Chapter 3.4 of the GHS, initially submitted by the Organization for the Economic Co-operation and Development (OECD) as information document UN/SECGHS/15/INF.13, and provisionally adopted by the Sub-Committee (with some editorial corrections) at its fifteenth session.

Proposal

Chapter 3.4

3.4.2.1.1 Amend to read as follows:

"3.4.2.1.1 *Hazard categories*

3.4.2.1.1.1 Respiratory sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.1.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation allows the allocation of respiratory sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other respiratory sensitizers.

3.4.2.1.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances are allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in figure 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

Figure 3.4.1: Hazard category and sub-categories for respiratory sensitizers

CATEGORY 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer - if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or - if there are positive results from an appropriate animal test[2].
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[2]. 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[2]. Severity of reaction may also be considered."

Add the following footnote 2:

"[2] At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances data from animal studies may provide valuable information in a weight of evidence assessment."

3.4.2.1.2.1 In the first sentence, replace “induce” with “lead to”.

3.4.2.1.3 Amend the text of related footnote 2 to read as follows:

“At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances data from animal studies may provide valuable information in a weight of evidence assessment.”

3.4.2.2.1 Amend to read as follows:

“3.4.2.2.1 *Hazard categories*

3.4.2.2.1.1 Skin sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.2.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation according to 3.4.2.2.1.3 allows the allocation of skin sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other skin sensitizers.

3.4.2.2.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitizers as described in 3.4.2.2.2. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in figure 3.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in 3.4.2.2.1.4 for sub-category 1A and in 3.4.2.2.1.5 for sub-category 1B.

Figure 3.4.2: Hazard category and sub-categories for skin sensitizers

CATEGORY 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer - if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or - if there are positive results from an appropriate animal test.
Sub-category 1A:	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 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.

3.4.2.2.1.4 Human evidence for sub-category 1A can include:

(a) positive responses at ≤ 500 μg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

(c) other epidemiology evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

Animal test results for sub-category 1A can include data with values indicated in Table 3.4.1 below:

Table 3.4.1: Animal test results for sub-category 1A

Assay	**Criteria**
Local lymph node assay	EC3 value ≤ 2%
Guinea pig maximisation test	≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose
Buehler assay	≥15% responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose

3.4.2.2.1.5 Human evidence for sub-category 1B can include:

(a) positive responses at > 500 μg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;

(c) other epidemiology evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

Animal test results for sub-category 1B can include data with values indicated in Table 3.4.2 below:

Table 3.4.2: Animal test results for sub-category 1B

Assay	**Criteria**
Local lymph node assay	EC3 value > 2%
Guinea pig maximisation test	≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose
Buehler assay	≥15% to < 60% responding at > 0.2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose

3.4.2.2.2.1 Insert "using a weight of evidence approach" after "any or all of the following";
Add: "(f) Severity of reaction may also be considered" at the end of the paragraph.

3.4.2.2.2.2 Delete the first sentence.

Add the following sentence at the end of the paragraph:
"For both animal and human data, consideration should be given to the impact of vehicle."

3.4.2.2.2.3 Add a comma after "met" and replace "contact sensitizer" with "skin sensitizer" twice, in the second and third line.

3.4.2.2.3 Replace "contact sensitizer" with "skin sensitizer" twice, in the third and last line.

3.4.2.2.4.1 In the first line, replace "When an adjuvant type test method" with "For Category 1, when an adjuvant type test method";

After the second sentence, insert the following sentence:
"For Category 1, a stimulation index of 3 or more is considered a positive response in the local lymph node assay.".

Delete the last sentence.

3.4.2.2.4.2 Delete.

3.4.2.2.4.3 Delete.

3.4.3.1 Replace the last sentence with the following:
"(For special labelling required by some competent authorities, see Note 1 to Table 3.4.3 of this chapter and 3.4.4.2).

3.4.3.2.3 and 3.4.3.2.4 Insert the following paragraphs as new 3.4.3.2.3 and 3.4.3.2.4:

"3.4.3.2.3 Concentration of mixtures of the highest sensitizing category/sub-category

If a mixture is classified in Category 1 or sub-category 1A, and the concentration of ingredients of the mixture that are in Category 1 and sub-category 1A is increased, the new mixture should be classified in Category 1 or sub-category 1A without additional testing.

3.4.3.2.4 Interpolation within one category/sub-category

For three mixtures with identical ingredients, where A and B are in the same category/sub-category and mixture C has the same sensitizing ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same category/sub-category as A and B."

Current paragraphs 3.4.3.2.3, 3.4.3.2.4 and 3.4.2.3.5 become new paragraphs 3.4.3.2.5, 3.4.3.2.6 and 3.4.3.2.7 respectively.

3.4.3.2.5 In the first sentence, replace "sensitization of the batch" with "sensitizing properties of the batch". In the last sentence, add "a" before "new classification".

3.4.3.3 In the paragraph, replace "Table 3.4.1" with "Table 3.4.3";

Replace the entire table and its six notes with a new table and a single note 1, as follows:

"Table 3.4.3: Cut-off values/concentration limits of ingredients of a mixture classified as either skin sensitizers or respiratory sensitizers that would trigger classification of the mixture

Ingredient classified as:	**Cut-off values/concentration limits triggering classification of a mixture as:**		
	Skin sensitizer Category 1	**Respiratory sensitizer Category 1**	
	All physical states	Solid/Liquid	Gas
Skin sensitizer Category 1	≥ 0.1% (Note 1)		
	≥ 1.0%		
Skin sensitizer Sub-category 1A	≥ 0.1%		
Skin sensitizer Sub-category 1B	≥ 1.0%		
Respiratory sensitizer Category 1		≥ 0.1% (Note 1)	≥ 0.1% (Note 1)
		≥ 1.0 %	≥ 0.2%
Respiratory sensitizer Sub-category 1A		≥ 0.1%	≥ 0.1%
Respiratory sensitizer Sub-category 1B		≥ 1.0 %	≥ 0.2%

***NOTE 1**: Some competent authorities may require SDS and/or supplemental labelling only, as described in 3.4.4.2 for mixtures containing a sensitizing ingredient at concentrations between 0.1 and 1% (or between 0.1 and 0.2% for a gaseous respiratory sensitizer). While the current cut-off values reflect existing systems, all recognize that special cases may require information to be conveyed below that level."*

3.4.4.1 In the last sentence, replace "Table 3.4.2" with "Table "3.4.4".

In the new Table 3.4.4, add "and Sub-categories 1A and 1B" after "Category 1" in the first row of the two last columns.

3.4.4.2 In the first sentence, replace "Table 3.4.1" with "Table 3.4.3".

Amend the second sentence to read as follows:
"To protect these individuals, certain authorities may choose to require the name of the ingredients as a supplemental label element whether or not the mixture as a whole is classified as sensitizer."

Delete the last sentence.

3.4.5.1 Add a footnote 6 to "Category 1" above the first exclamation mark, as follows:

"[6] *See 3.4.2.1.1 for details on use of Category 1 subcategories*"

In the last but one box on the left, delete the two references into brackets and insert at the bottom of the box: "(See 3.4.3.3 and Table 3.4.3 for explanation and guidance)".

3.4.5.2 Add a footnote 6 to "Category 1" above the first exclamation mark, as follows:

"[6] *See 3.4.2.2.1 for details on use of Category 1 subcategories*"

In the last but one box on the left, delete the reference into brackets and insert at the bottom of the box: "(See 3.4.3.3 and Table 3.4.3 for explanation and guidance)".

Consequential amendments to Annexes 1 and 2

Annex 1

Amend the tables for respiratory and skin sensitization (page 254 of the English version to read as follows:

For respiratory sensitization, add two columns similar to the first one, but replace "Category 1" with "Category 1A" in the second column and with "Category 1B" in the third column.

For skin sensitization, add two columns similar to the first one, but replace "Category 1" with "Category 1A" in the second column and with "Category 1B" in the third column.

Annex 2

A2.20 Replace the text under "1. *For substances and tested mixtures*" with:

"(a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and /or

(b) if there are positive results from an appropriate animal test."

Add the following columns and rows:

Hazard sub-category	**Criteria**	**Hazard communication elements**	
1A (where data are sufficient and where required by a competent authority)	1. *For substances and tested mixtures* 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. 2. *If data for the complete mixture are not available*, apply bridging principles (see 3.4.3.2). 3. *If bridging principles do not apply*, classify the mixture as respiratory sensitizer if it contains at least one ingredient classified as sub-category 1A at the following concentrations: (a) Solids or liquids: ≥ 0.1% w/w (b) Gases: ≥ 0.1% v/v	Symbol	
		Signal word	Danger
		Hazard statement	May cause allergic or asthma symptoms or breathing difficulties if inhaled
1B (where data are sufficient and where required by a competent authority)	1. *For substances and tested mixtures* 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. 2. I*f data for the complete mixture are not available*, apply bridging principles (see 3.4.3.2). 3. *If bridging principles do not apply*, classify the mixture as respiratory sensitizer if it contains at least one ingredient classified as sub-category 1B at the following concentrations: (a) Solids or liquids: ≥ 1% w/w (b) Gases: ≥ 0.2% v/v	Symbol	
		Signal word	Danger
		Hazard statement	May cause allergic or asthma symptoms or breathing difficulties if inhaled

A2.21 Replace the text under "1. *For substances and tested mixtures*" with:

(a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or

(b) if there are positive results from an appropriate animal test.

Add the following columns and rows:

Hazard category	**Criteria**	**Hazard communication elements**	
1A (where data are sufficient and where required by a competent authority)	1. *For substances and tested mixtures* showing a high frequency of occurrence in humans and/or a high potency in animals, which can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered. 2. *If data for the complete mixture are not available*, apply bridging principles (see 3.4.3.2) 3. *If bridging principles do not apply*, classify the mixture as skin sensitizer if it contains at least one ingredient classified as sub-category 1A at a concentration ≥ 0.1%.	Symbol	
		Signal word	Warning
		Hazard statement	May cause allergic skin reaction
1B (where data are sufficient and where required by a competent authority)	1. *For substances and tested mixtures* showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals, which can be presumed to have the potential to produce sensitization in humans. 2. *If data for the complete mixture are not available*, apply bridging principles (see 3.4.3.2) 3. *If bridging principles do not apply*, classify the mixture as skin sensitizer if it contains at least one ingredient classified as sub-category 1B at a concentration ≥ 1.0%.	Symbol	
		Signal word	Warning
		Hazard statement	May cause allergic skin reaction
