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

Health hazards

Proposal for revising Chapter 3.4 with respect to strong versus weak sensitizers: Explanatory notes and revised chapter with visible changes

Transmitted by the Organisation for Economic Co-operation and Development (OECD)

This document includes explanatory notes to the proposal for revising Chapter 3.4 of the GHS and the proposed revised Chapter 3.4 with visible changes (Annex).

Explanatory notes

1. In December 2002, the UN Sub-Committee of Experts on the GHS (UN SCEGHS) requested that the OECD examine the available information concerning strong versus weak sensitizers and, if appropriate, propose revisions to the classification criteria for respiratory and/or dermal sensitization.

2. The proposal includes two new subcategories 1A and 1B for respiratory sensitization and two subcategories 1A and 1B for skin sensitization. New sections 3.4.2.1.1 (for respiratory sensitization) and 3.4.2.2.1 (for skin sensitization) describe the subcategories.

3. Sentences are added at the beginning of the new paragraph 3.4.2.1.1.3 for respiratory sensitization, and at the beginning of the new paragraph 3.4.2.2.1.3 for skin sensitization to strengthen the weight of evidence approach.

4. On the basis of an impact analysis, the proposed guidance value for skin sensitization Subcategory 1A is: $\leq 2\%$ for the LLNA (Table 3.4.1) and: $\leq 500\ \mu g/cm^2$ for human data (3.4.2.2.1.4).

5. The subcategories 1A and 1B may be used for substances and for mixtures that are not classified on the basis of data available for all or some ingredients, when data are sufficient and when required by a competent authority (Sections 3.4.2.1.1 for respiratory sensitization and 3.4.2.2.1 for skin sensitization). For mixtures that are classified on the basis of data available for all or some ingredients, specific cut-off values are provided for the subcategories 1A and 1B (Table 3.4.3); subcategories 1A and IB cannot be used for such mixtures that can be classified as Category 1 only.

6. Whatever the category or subcategory, the label remains the same as it is in the current GHS for respiratory and skin sensitization.

7. The six notes to the table of Section 3.4.3.3 are replaced with a single Note 1; the six notes were confusing (repeating what is the normal consequence of classification: an SDS and a label would normally be expected), and the same text was repeated in several notes.

8. Given the inclusion of two subcategories, two paragraphs that apply for more than one category only are inserted in Section 3.4.3.2, under the bridging principles (new Paragraphs 3.4.3.2.3 and 3.4.3.2.4), and the existing Paragraph 3.4.3.2.2 on dilution is slightly revised.

9. The proposal includes a few additional changes: in 3.4.2.2.2.2, the first sentence is deleted as it is now in the new paragraph 3.4.2.2.1.3, and a sentence is added to note the possible impact of vehicles; the footnote 2 is revised to delete the example that is not considered relevant; in 3.4.2.2.4.1, the criteria for a positive response with the LLNA is inserted and the last sentence is deleted as it is considered to include too specific information. Paragraphs 3.4.2.2.4.2 and 3.4.2.2.4.3 are deleted as they are no longer relevant; the subcategories 1A and 1B are mentioned in the table of Section 3.4.4; Paragraph 3.4.4.2 is slightly revised to extend its application to classified mixtures; slight change to the Decision Logic (new footnote 6).

Annex

PROPOSED REVISED CHAPTER 3.4 (WITH VISIBLE CHANGES)

"RESPIRATORY OR SKIN SENSITIZATION

3.4.1 Definitions and general considerations

3.4.1.1 A *respiratory sensitizer* is a substance that will lead to hypersensitivity of the airways following inhalation of the substance[1].

A *skin sensitizer* is a substance that will lead to an allergic response following skin contact[1].

3.4.1.2 For the purpose of this chapter, sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen.

3.4.1.3 For respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization. For skin sensitization, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

3.4.1.4 Usually, for both skin and respiratory sensitization, lower levels are necessary for elicitation than are required for induction. Provisions for alerting sensitized individuals to the presence of a particular sensitizer in a mixture can be found at section 3.4.4.

3.4.2 Classification criteria for substances

3.4.2.1 *Respiratory sensitizers*

3.4.2.1.1 *Hazard ~~category~~ categories*

~~Substances shall be classified as respiratory sensitizers (Category 1) in accordance with the criteria given below:~~

~~(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.~~

1. *This is a working definition for the purpose of this document*

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

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 subcategory 1A, strong sensitizers, or subcategory 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 subcategories 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 subcategories 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].
Subcategory 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based upon animal or other tests[2]. Severity of reaction may also be considered.
Subcategory 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 upon animal or other tests[2]. Severity of reaction may also be considered.

3.4.2.1.2 *Human evidence*

3.4.2.1.2.1 Evidence that a substance can ~~induce~~ lead to induce specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

3.4.2.1.2.2 When considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases:

(a) the size of the population exposed;

(b) the extent of exposure.

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[2] *At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, ~~animal testing may be used, e.g. a modification of the guinea pig maximization test for determination of relative allergenicity of proteins. However, these tests still need further validation.~~ data from animal studies may provide valuable information in a weight of evidence assessment.*

3.4.2.1.2.3 The evidence referred to above could be:

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) *in vivo* immunological test (e.g. skin prick test);

(ii) *in vitro* immunological test (e.g. serological analysis);

(iii) studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

3.4.2.1.2.4 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

3.4.2.1.2.5 The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognized that in practice many of the examinations listed above will already have been carried out.

3.4.2.1.3 *Animal studies*

Data from appropriate animal studies[2] which may be indicative of the potential of a substance to cause sensitization by inhalation in humans[3] may include:

(a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;

(b) specific pulmonary responses in guinea pigs.

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[2] *At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances~~, animal testing may be used, e.g. a modification of the guinea pig maximization test for determination of relative allergenicity of proteins. However, these tests still need further validation~~.data from animal studies may provide valuable information in a weight of evidence assessment..*

[3] *The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitizers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperreactivity, they should not be considered as respiratory sensitizers.*

3.4.2.2 *Skin sensitizers*

3.4.2.2.1 *Hazard ~~category~~ categories*

~~Substances shall be classified as contact sensitizers (Category 1) in accordance with the criteria below:~~

~~(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.~~

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

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 subcategory 1A, strong sensitizers, or subcategory 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 subcategories 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 Subcategory 1A and in 3.4.2.2.1.5 for Subcategory 1B.

Figure 3.4.2: Hazard category and subcategories 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.
Subcategory 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.
Subcategory 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 Subcategory 1A can include positive responses at $\leq$ 500 µg/cm^2 (HRIPT, HMT – induction threshold); 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 then that is indicative of a strong sensitizer; other epidemiology evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure then that is indicative of a strong sensitizer.

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

Table 3.4.1: Animal test results for Subcategory 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 subcategory 1B can include any positive response at > 500 µg/cm2 (HRIPT, HMT – induction threshold); 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 then that is indicative of a skin sensitizer of subcategory 1B; other epidemiology evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure then that is indicative of a skin sensitizer of subcategory 1B.

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

Table 3.4.2: Animal test results for Subcategory 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 *Specific considerations*

3.4.2.2.2.1 For classification of a substance, evidence should include any or all of the following using a weight of evidence approach:

(a) Positive data from patch testing, normally obtained in more than one dermatology clinic;

(b) Epidemiological studies showing allergic contact dermatitis caused by the substance; Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;

(c) Positive data from appropriate animal studies;

(d) Positive data from experimental studies in man (see Chapter 1.3, para. 1.3.2.4.7);

(e) Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

(f) Severity of reaction may also be considered.

3.4.2.2.2.2 ~~Positive effects seen in either humans or animals will normally justify classification.~~ Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on contact sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should also be given to the impact of vehicle.

3.4.2.2.2.3 If none of the above mentioned conditions are met, the substance need not be classified as a skin ~~contact~~ sensitizer. However, a combination of two or more indicators of skin ~~contact~~ sensitization as listed below may alter the decision. This shall be considered on a case-by-case basis.

(a) Isolated episodes of allergic contact dermatitis;

(b) Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;

(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in 3.4.2.2.4.1, but which are sufficiently close to the limit to be considered significant;

(d) Positive data from non-standard methods;

(e) Positive results from close structural analogues.

3.4.2.2.3 *Immunological contact urticaria*

Substances meeting the criteria for classification as respiratory sensitizers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as skin ~~contact~~ sensitizers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers should also be considered for classification as skin ~~contact~~ sensitizers.

There is no recognized animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence which will be similar to that for skin sensitization.

3.4.2.2.4 *Animal studies*

3.4.2.2.4.1 For Category 1, w~~W~~hen an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test

method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of 3 or more is considered a positive response in the Local Lymph Node Assay. Test methods for skin sensitization are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are well-validated and scientific justification is given. ~~The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used as a first stage in the assessment of skin sensitization potential. In case of a positive result in this latter test it may not be necessary to conduct a further guinea pig test.~~

~~3.4.2.2.4.2 When evaluating animal data, produced by testing according to the OECD or equivalent Guidelines for skin sensitization, the rate of sensitized animals may be considered. This rate reflects the sensitizing capacity of a substance in relation to its mildly irritating dose. This dose may vary between substances. A more appropriate evaluation of the sensitizing capacity of a substance could be carried out if the dose response relationship was known for the substance. This is an area that needs further development.~~

~~3.4.2.2.4.3 There are substances that are extremely sensitizing at low doses where others require high doses and long time of exposure for sensitization. For the purpose of hazard classification it may be preferable to distinguish between strong and moderate sensitizers. However, at present animal or other test systems to subcategorize sensitizers have not been validated and accepted. Therefore, sub-categorization should not yet be considered as part of the harmonized classification system.~~

3.4.3 Classification criteria for mixtures

3.4.3.1 *Classification of mixtures when data are available for the complete mixture*

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of these data. Care should be exercised in evaluating data on mixtures that the dose used does not render the results inconclusive. (For special labelling required by some competent authorities, see Note~~s~~ 1~~, 3 and 5~~ to Table 3.4.3~~.4.1~~ of this chapter~~.~~)and 3.4.4.2).

3.4.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

3.4.3.2.1 Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.4.3.2.2 *Dilution*

If a mixture is diluted with a diluent which is not a sensitizer and which is not expected to affect the sensitization of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.4.3.2.3 *Concentration of mixtures of the highest sensitizing Category/subcategory*

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

3.4.3.2.4 *Interpolation within one category/subcategory*

For three mixtures with identical ingredients, where A and B are in the same category/subcategory 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/subcategory as A and B.

3.4.3.2.~~3~~5 *Batching*

The sensitizing properties of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the ~~sensitization~~ sensitizing properties of the batch has changed. If the latter occurs, a new classification is necessary.

3.4.3.2.~~4~~6 *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) is already classified by testing, then mixture (ii) can be assigned the same hazard category.

3.4.3.2.~~5~~7 *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.

3.4.3.3 ***Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture***

The mixture should be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value/concentration limit for the specific endpoint as shown in Table 3.4.~~1~~3 for solid/liquid and gas respectively.

Table 3.4.~~1~~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% ~~(Note 2)~~		
Skin sensitizer Subcategory 1A	≥ 0.1%		
Skin sensitizer Subcategory 1B	≥ 1.0%		
Respiratory sensitizer Category 1		≥ 0.1% (Note ~~3~~1)	≥ 0.1% (Note ~~5~~1)
		≥ 1.0 % ~~(Note 4)~~	≥ 0.2% ~~(Note 6)~~
Respiratory sensitizer Subcategory 1A		≥ 0.1%	≥ 0.1%
Respiratory sensitizer Subcategory 1B		≥ 1.0 %	≥ 0.2%

NOTE 1*: ~~If a skin sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. In addition, some~~ 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 ~~above 0.1%. The label warning for skin sensitizers~~ between 0.1% and 1.0% (or between 0.1% ~~may differ from the label warning for skin sensitizers ≥ 1.0%,~~ and 0.2% for a gaseous respiratory sensitizer ~~depending on competent authority requirements. While the~~ current cut-off values reflect existing systems, all recognize that special cases may require information to be conveyed below that level.*

~~***NOTE 2****: If a skin sensitizer is present in the mixture as an ingredient at a concentration of ≥ 1.0%, both an SDS and a label would generally be expected.~~*

~~***NOTE 3****: If a solid or liquid respiratory sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. In addition, some competent authorities may require supplemental labelling for mixtures containing a sensitizing ingredient at concentrations above 0.1%. The label warning for solid or liquid respiratory~~*

~~*sensitizers between 0.1% and 1.0% may differ from the label warning for solid or liquid respiratory sensitizers ≥1.0%, depending on competent authority requirements. While the current cut off values reflect existing systems, all recognize that special cases may require information to be conveyed below that level.*~~

~~***NOTE 4**: If a solid or liquid respiratory sensitizer is present in the mixture as an ingredient at a concentration of ≥1.0%, both an SDS and a label would generally be expected.*~~

~~***NOTE 5**: If and 0.2% for a gaseous respiratory sensitizeris present in the mixture as an ingredient at a concentration between 0.1% and 0.2%, both an SDS and a label would generally be expected. In addition, some competent authorities may require supplemental labelling for mixtures containing a sensitizing ingredient at concentrations above 0.1%. The label warning for gaseous respiratory sensitizers between 0.1% and 0.2% may differ from the label warning for gaseous respiratory sensitizers ≥0.2%, depending on competent authority requirements. While the current cut off values reflect existing systems, all recognize that special cases may require information to be conveyed below that level.*~~

~~***NOTE 6**: If a gaseous respiratory sensitizer is present in the mixture as an ingredient at a concentration of ≥0.2%, both an SDS and a label would generally be expected.*~~

3.4.4 Hazard communication

3.4.4.1 General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 3.4.~~2~~4 below presents specific label elements for substances and mixtures that are classified as respiratory and skin sensitizers based on the criteria in this chapter.

Table 3.4.~~2~~4: Label elements for respiratory or skin sensitization

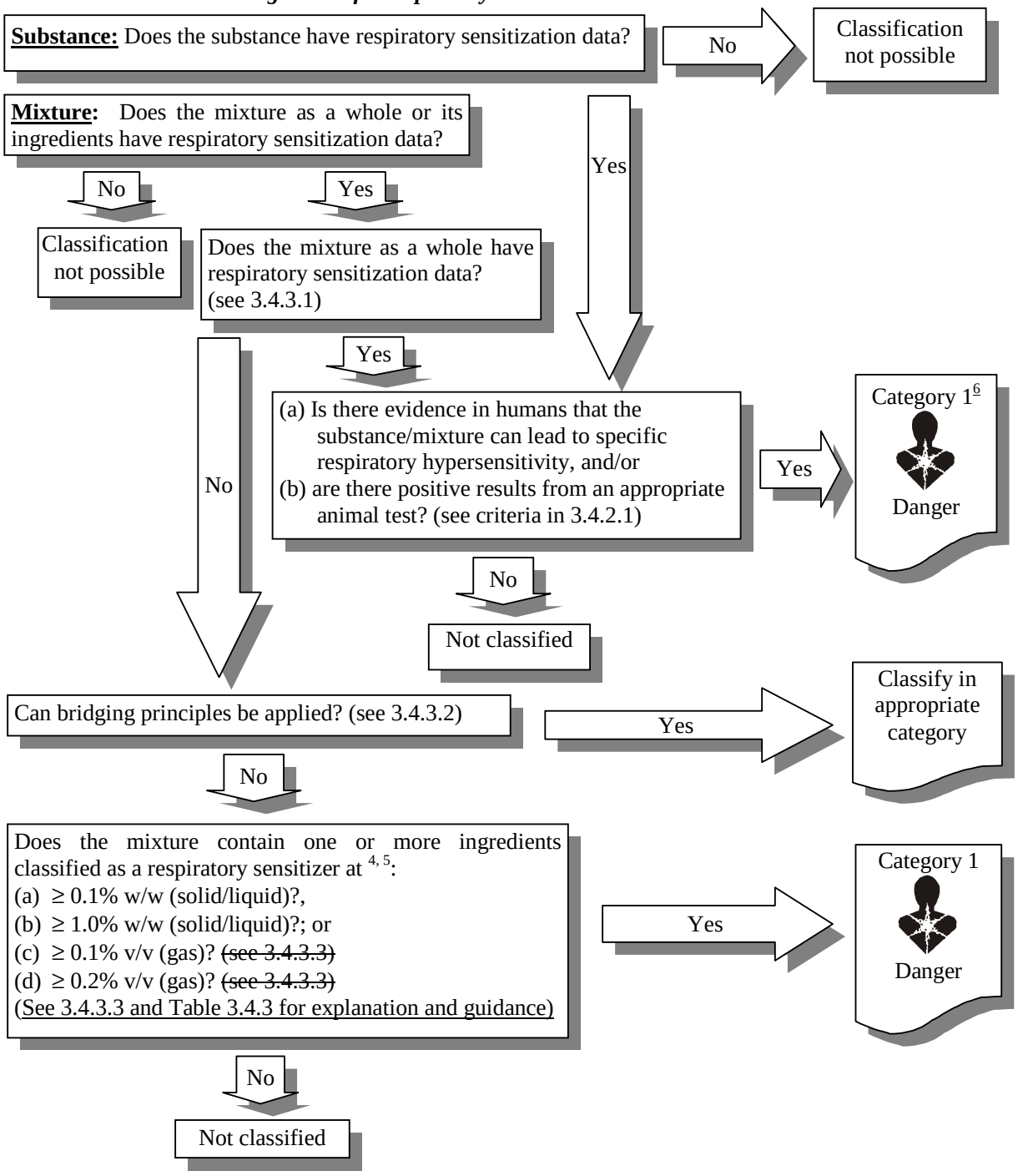
	Respiratory sensitization Category 1 and subcategories 1A and 1B	**Skin sensitization Category 1 and Subcategories 1A and 1B**
Symbol	Health hazard	Exclamation mark
Signal word	Danger	Warning
Hazard statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

3.4.4.2 Some chemicals that are classified as sensitizers may elicit a response, when present in a mixture in quantities below the cut-offs established in Table 3.4.~~1~~3, in individuals who are already sensitized to the chemicals. To protect these individuals, certain authorities may choose to require the name of the ingredient as a supplemental label element ~~even though~~ whether or not the mixture as a whole is ~~not~~ classified as sensitizer. ~~Others may choose to classify and label the mixture as a sensitizer in accordance with notes 1, 3 and 5 to Table 3.4.1.~~

3.4.5 Decision logic

The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.4.5.1 ***Decision logic 3.4.1 for respiratory sensitization***

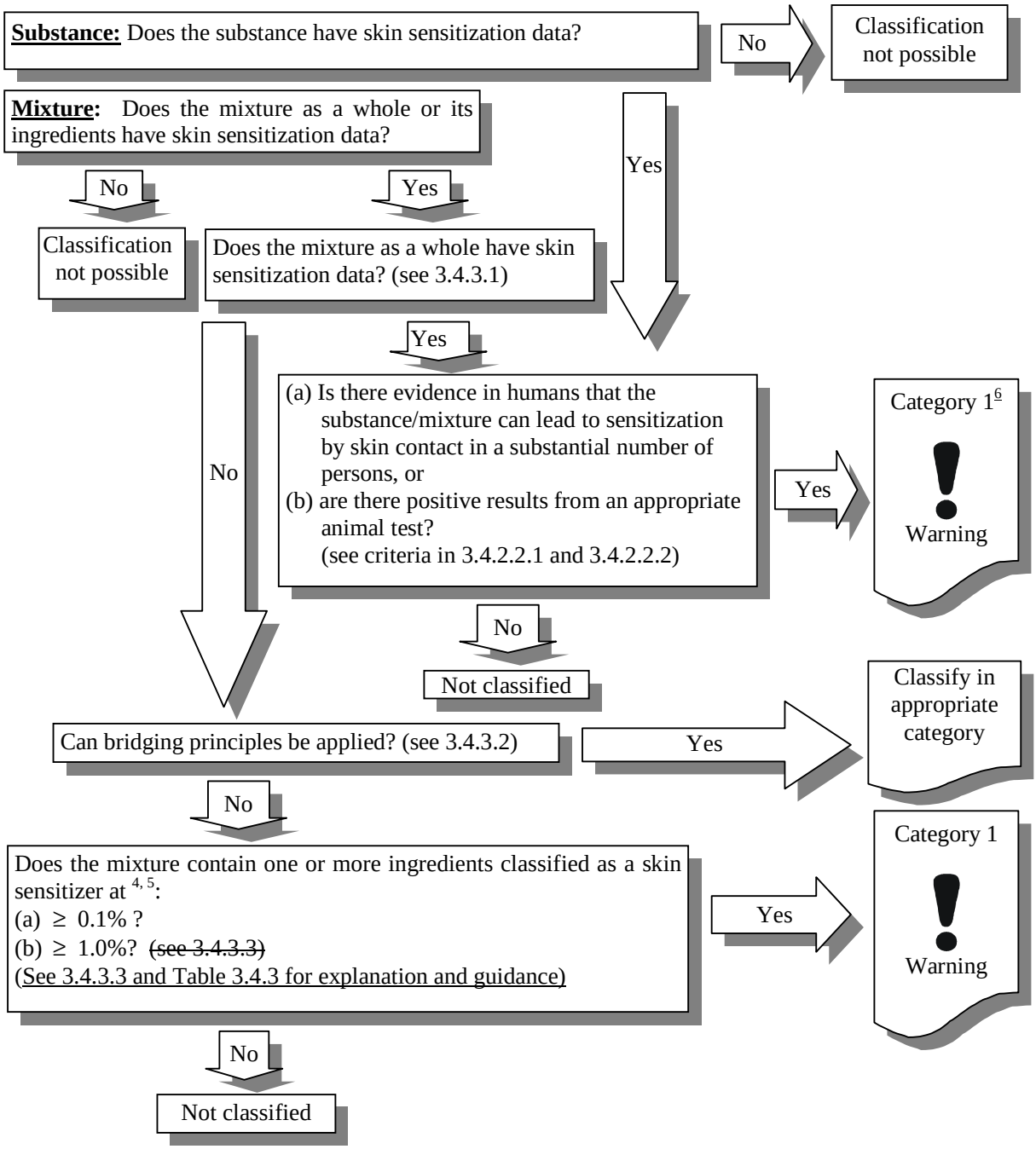


[4] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[5] *See 3.4.4.2.*

[6] *See 3.4.2.1.1 for details on use of Category 2 subcategories.*

3.4.5.2 ***Decision logic 3.4.2 for skin sensitization***



[4] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[5] *See 3.4.4.2.*

[6] *See 3.4.2.1.1 for details on use of Category 2 subcategories.*