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 Transport of Dangerous Goods

Tenth session
Geneva, 7-9 December 2005
Item 2 (b) of the provisional agenda

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

Chapter 3.4

Respiratory or skin sensitization

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

"CHAPTER 3.4

RESPIRATORY OR SKIN SENSITIZATION

3.4.1 Definitions and general considerations

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

A *skin sensitizer* is a substance that will ~~induce~~ 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.

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

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*

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

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

3.4.2.1.2 *Human evidence*

3.4.2.1.2.1 Evidence that a substance can 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.

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.

3.4.2.2 *Skin sensitizers*

3.4.2.2.1 *Hazard category*

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

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

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:

(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);

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[2] *At present recognized 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.*

[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.*

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

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.

3.4.2.2.2.3 If none of the above mentioned conditions are met the substance need not be classified as a contact sensitizer. However, a combination of two or more indicators of 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 contact sensitizers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers should also be considered for classification as 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 When 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. 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 Notes 1, 3 and 5 to Table 3.4.1 of this chapter.)

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 rules. 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 *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 of the batch has changed. If the latter occurs, new classification is necessary.

3.4.3.2.4 *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 *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 components or only for some components 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 for solid/liquid and gas respectively.

Table 3.4.1: 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/concentration limits triggering classification of a mixture as:**		
	Skin Sensitizer	**Respiratory Sensitizer**	
	All physical states	Solid/Liquid	Gas
Skin Sensitizer	≥ 0.1% (Note 1)	-	-
	≥ 1.0% (Note 2)	-	-
Respiratory Sensitizer	-	≥ 0.1% (Note 3)	≥ 0.1% (Note 5)
	-	≥ 1.0 % (Note 4)	≥ 0.2% (Note 6)

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 competent authorities may require supplemental labelling for mixtures containing a sensitizing ingredient at concentrations above 0.1%. The label warning for skin sensitizers between 0.1% and 1.0% may differ from the label warning for skin 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 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 a gaseous respiratory sensitizer is 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 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: Respiratory or skin sensitization label elements.

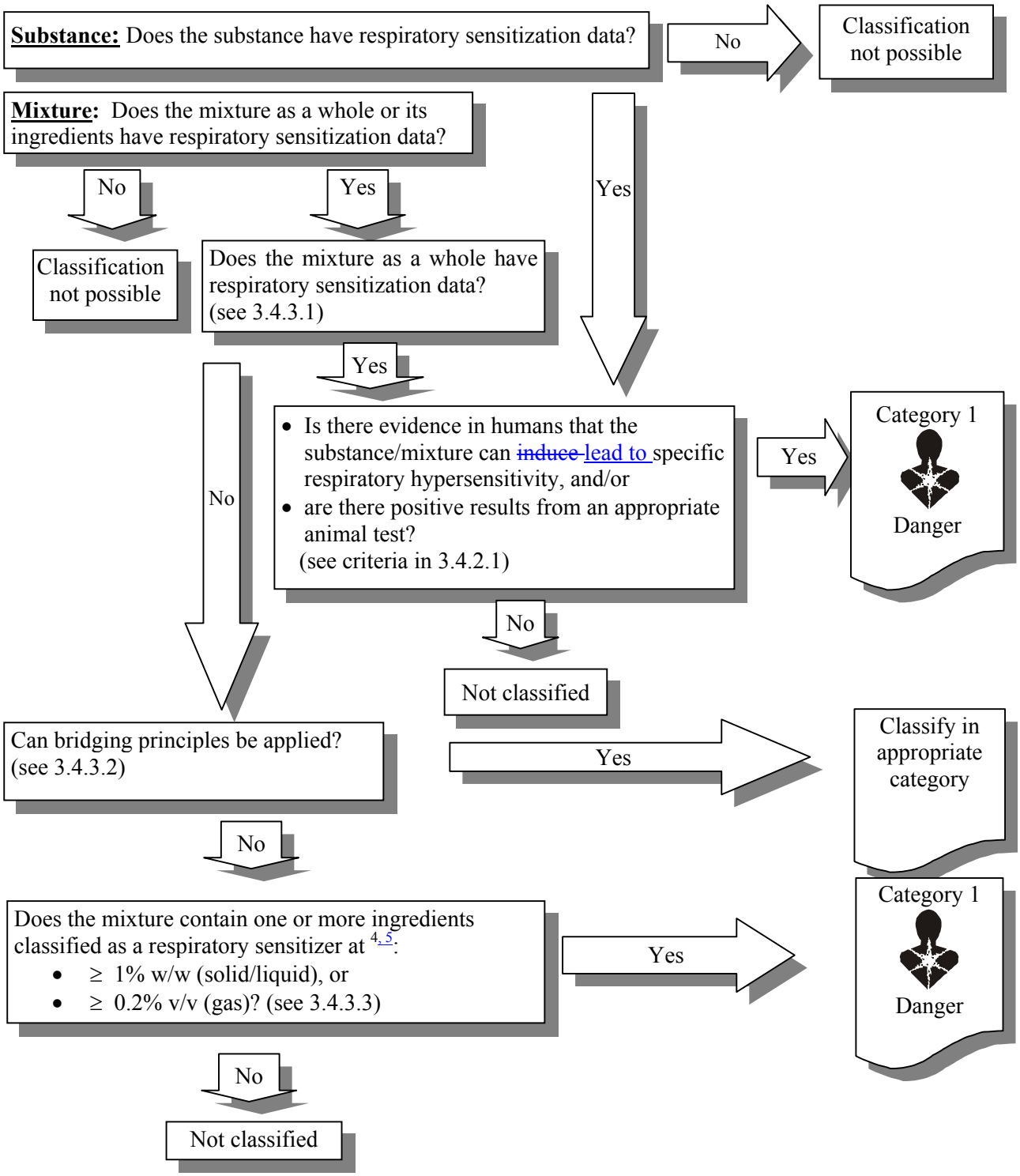
	Respiratory sensitization Category 1	**Skin sensitization Category 1**
Symbol	Health hazard	Exclamation mark
Signal Word	Danger	Warning
Hazard Statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

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-off values/concentration limits established in Table 3.4.1, 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 supplementary information on the label even though 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.

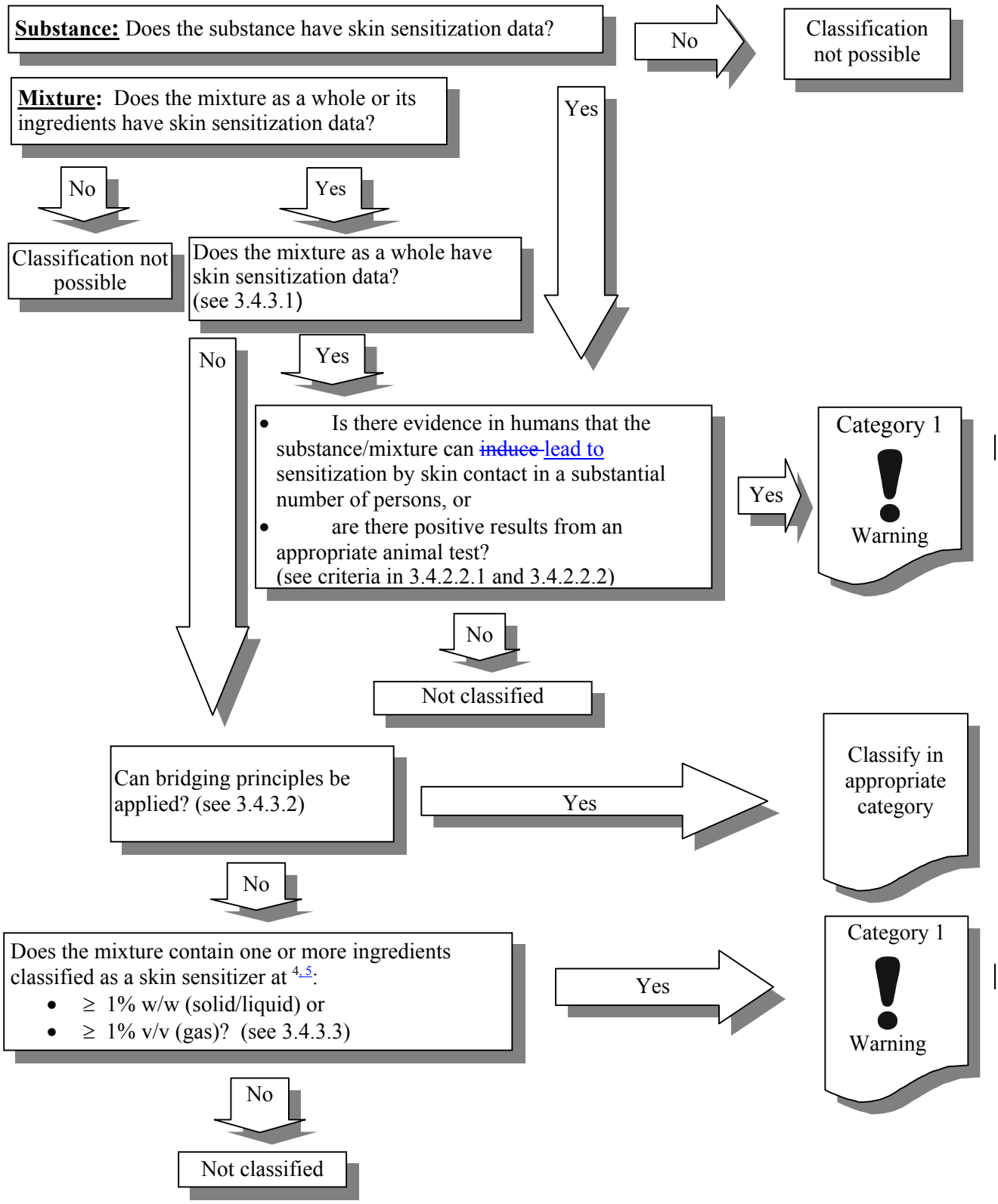
3.4.5.1 *Decision logic 3.4.1 for respiratory sensitization*



[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.*

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.*