Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

Health and environmental hazards

Classification criteria for substances and mixtures

Working definitions

Substance: Chemical elements and their compounds in the natural state or obtained by any production process

(The definition of substance includes any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excludes any solvent which may be separated without affecting the stability of the substance or changing its composition)

Working definitions

Mixture: Mixtures or solutions composed of two or more substances in which they do not react

Alloy: An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means.

(Alloys are considered to be mixtures for the purpose of classification under the GHS)

Classification criteria for mixtures

- Based on the classification criteria for substances
- Consider the classification of any impurities, additives or individual constituents of a substance which have been identified, if they exceed the cut-off value/concentration limit for a given hazard class.

Normally,

the harmonized cut-off value/concentration limit is to be applied in all jurisdictions and for all sectors.

However…

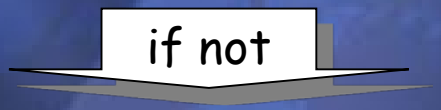
Classification criteria for mixtures

- If there is evidence that the hazard of an ingredient is present below the cut-off/concentration limit, or
- If there is conclusive data that the hazard of an ingredient will not be present at a level above the harmonized cut-off/concentration limit,

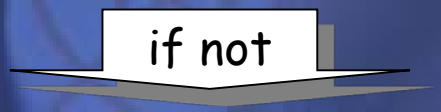
then, the mixture should be classified accordingly.

Tier approach to classification

Generally use test data for the mixture, when available



Use bridging principles, if applicable



Estimate hazards based on the known ingredient information

Classification criteria for mixtures

- Data are available for the complete mixture;
- Data are not available for the mixture itself =>apply bridging principles:
    i) Dilution;
    ii) Batching;
    iii) Concentration of mixtures of the highest category within one hazard class;
    iv) Interpolation within one toxicity category;
    v) Substancially similar mixtures;
    vi) Aerosolized mixtures;
- Classification based on ingredients: Apply additivity formula
    i) Data available for all ingredients;
    ii) Data available only for some ingredients;

Health and environmental hazards

1. Acute toxicity (Chapter 3.1)
2. Skin corrosion/irritation (Chapter 3.2)
3. Serious eye damage/eye irritation (Chapter 3.3)
4. Respiratory or skin sensitization (Chapter 3.4)
5. Germ cell mutagenicity (Chapter 3.5)
6. Carcinogenicity (Chapter 3.6)
7. Reproductive toxicity (Chapter 3.7)
8. Specific target organ toxicity-single exposure (Chapter 3.8)
9. Specific target organ toxicity-repeated exposure (Chapter 3.9)
10. Aspiration hazard (Chapter 3.10)
11. Hazardous to the aquatic environment (Chapter 4.1)
12. Hazardous to the ozone layer (Chapter 4.2)

Acute toxiticy

Acute toxicity refers to serious adverse health effects (i.e. lethality) occurring after a single or short-term oral, dermal or inhalation exposure to a substance or mixture.

Substances can be allocated to one of five toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric cut-off criteria as shown in table 3.1.1.

Acute toxicity values are expressed as (approximate) LD_{50} (oral, dermal) or LC_{50} (inhalation) values or as acute toxicity estimates (ATE). Explanatory notes are shown following Table 3.1.1.

Table 3.1.1: Acute toxicity estimate (ATE) values and criteria for acute toxicity hazard categories

Exposure route	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg bodyweight) *See notes (a) and (b)*	ATE ≤ 5	5 < ATE ≤ 50	50 < ATE ≤ 300	300 < ATE ≤ 2000	
Dermal (mg/kg bodyweight) *See notes (a) and (b)*	ATE ≤ 50	50 < ATE ≤ 200	200 < ATE ≤ 1000	1000 < ATE ≤ 2000	
Gases (ppmV) *See notes (a), (b) and (c)*	ATE ≤ 100	100 < ATE ≤ 500	500 < ATE ≤ 2500	2500 < ATE ≤ 20000	
Vapours (mg/l) *See notes (a), (b), (c), (d) and (e)*	ATE ≤ 0.5	0.5 < ATE ≤ 2.0	2.0 < ATE ≤ 10.0	10.0 < ATE ≤ 20.0	
Dusts and Mists (mg/l) *See notes (a), (b), (c) and (f)*	ATE ≤ 0.05	0.05 < ATE ≤ 0.5	0.5 < ATE ≤ 1.0	1.0 < ATE ≤ 5.0	

***Note**: Gas concentrations are expressed in parts per million per volume (ppmV).*

Notes to Table 3.1.1:

(a) The acute toxicity estimate (ATE) for the classification of a substance is derived using the LD_{50}/LC_{50} where available;

(b) The acute toxicity estimate (ATE) for a substance in a mixture is derived using:

(i) the LD_{50}/LC_{50} where available; otherwise,

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

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

(c) Inhalation cut-off values in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which has been generated according to 1 hour exposures should be by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists;

(d) It is recognized that saturated vapour concentration may be used as an additional element by some regulatory systems to provide for specific health and safety protection (e.g. UN Recommendations for the Transport of Dangerous Goods);

(e) For some substances the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other substances the test atmosphere may consist of a vapour which is near the gaseous phase. In these latter cases, classification should be based on ppmV as follows: Category 1 (100 ppmV), Category 2 (500 ppmV), Category 3 (2500 ppmV), Category 4 (20000 ppmV).

The terms "dust", "mist" and "vapour" are defined as follows:

(i) <u>Dust</u>: solid particles of a substance or mixture suspended in a gas (usually air);

(ii <u>Mist</u>: liquid droplets of a substance or mixture suspended in a gas (usually air);

(iii) <u>Vapour</u>: the gaseous form of a substance or mixture released from its liquid or solid state.

Dust is generally formed by mechanical processes. Mist is generally formed by condensation of supersatured vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from less than 1 to about 100 µm;

(f) The values for dusts and mists should be reviewed to adapt to any future changes to OECD Test Guidelines with respect to technical limitation in generating, maintaining and measuring dust and mist concentrations in respirable form;

(g) Criteria for Category 5 are intended to enable the identification of substances which are of relatively low acute toxicity hazard but which under certain circumstances may present a danger to vulnerable populations. These substances are anticipated to have an oral or dermal LD_{50} in the range of 2000-5000 mg/kg bodyweight and equivalent doses for inhalation. The specific criteria for Category 5 are:

(i) The substance is classified in this category if reliable evidence is already available that indicates the LD_{50} (or LC_{50}) to be in the range of Category 5 values or other animal studies or toxic effects in humans indicate a concern for human health of an acute nature.

(ii) The substance is classified in this category, through extrapolation, estimation or measurement of data, if assignment to a more hazardous category is not warranted, and:

- *reliable information is available indicating significant toxic effects in humans; or*

- *any mortality is observed when tested up to Category 4 values by the oral, inhalation, or dermal routes; or*

- *where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance; or*

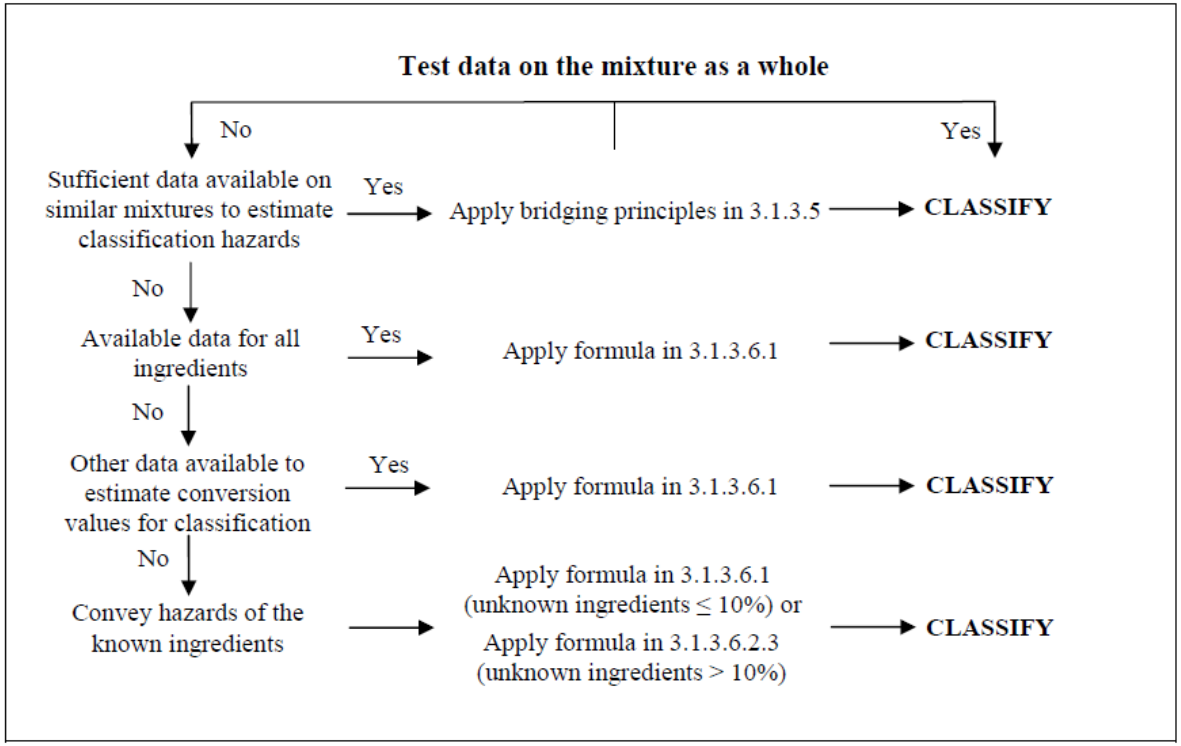
- *where expert judgement confirms reliable information indicating the potential for significant acute effects from other animal studies.*

Recognizing the need to protect animal welfare, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such a test would have a direct relevance for protecting human health.

Acute toxicity

For mixtures, the approach to classification for acute toxicity is tiered, and is dependent upon the amount of information available for the mixture itself and for its ingredients (See flow chart below)

Figure 3.1.1: Tiered approach to classification of mixtures for acute toxicity



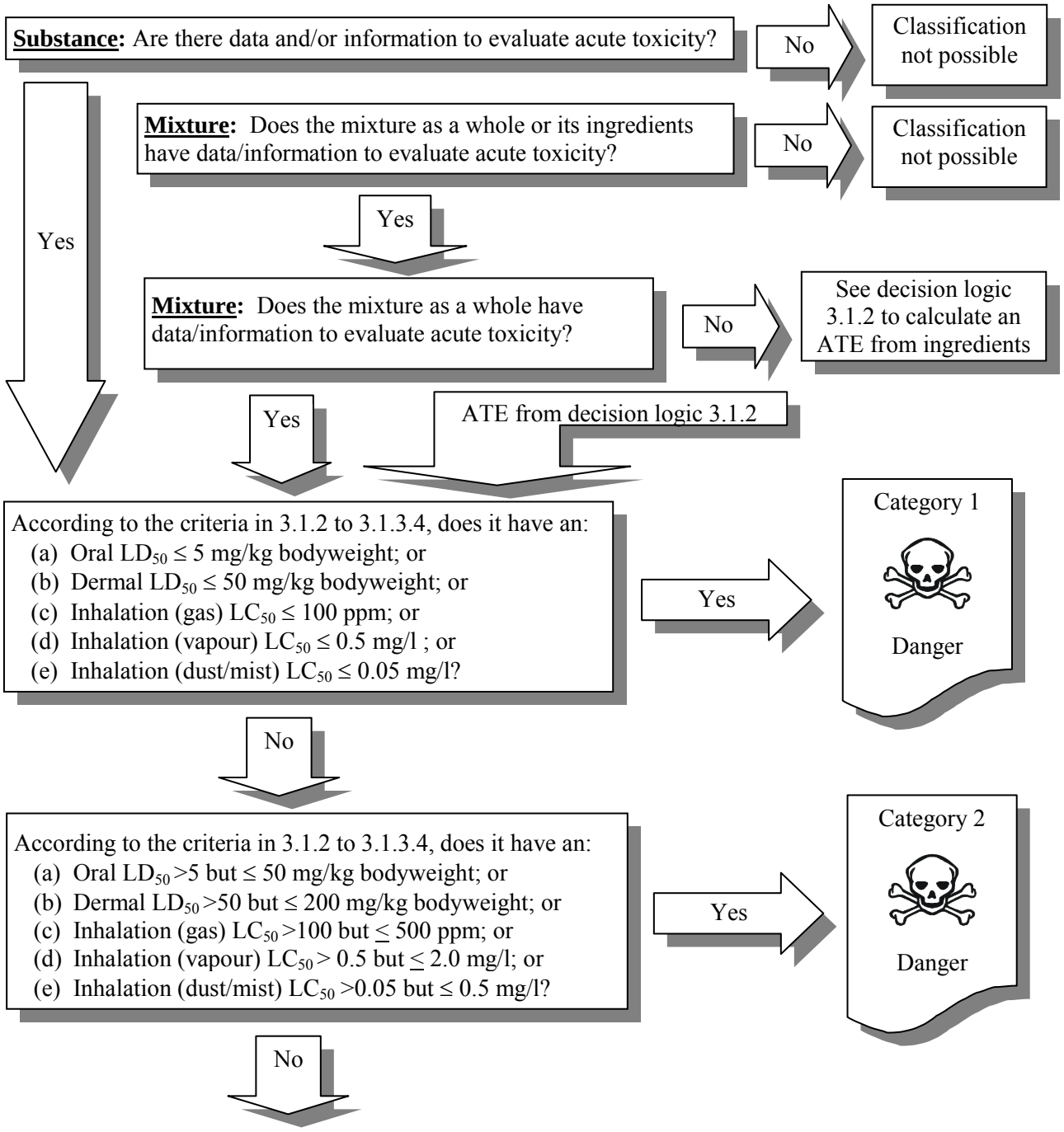
Acute toxicity

The procedure for classification of substances and mixtures is summarized in decision logics 3.1.1 and 3.1.2

3.1.5 Decision logic

The decision logic which follows, is not part of the harmonized classification system but is 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 logic.

3.1.5.1 *Decision logic 3.1.1 for acute toxicity*



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No

According to the criteria in 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >50 but ≤ 300 mg/kg bodyweight; or
(b) Dermal LD_{50} > 200 but ≤ 1000 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} >500 but ≤ 2500 ppm; or
(d) Inhalation (vapour) LC_{50} >2 but ≤ 10 mg/l; or
(e) Inhalation (dust/mist) LC_{50} >0.5 but ≤ 1.0 mg/l?

Yes → Category 3

Danger

No

According to the criteria in 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >300 but ≤ 2000 mg/kg bodyweight; or
(b) Dermal LD_{50} >1000 but ≤ 2000 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} >2500 but ≤ 20000 ppm; or
(d) Inhalation (vapour) LC_{50} >10 but ≤ 20 mg/l; or
(e) Inhalation (dust/mist) LC_{50} >1.0 but ≤ 5 mg/l?

Yes → Category 4

Warning

No

According to the criteria in 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >2000 but ≤ 5000 mg/kg bodyweight; or
(b) Dermal LD_{50} >2000 but ≤ 5000 mg/kg bodyweight; or
(c) Inhalation (gas, vapour and/or dust/mist) LC_{50} in the equivalent range of the oral and dermal LD_{50} (i.e., 2000-5000 mg/kg bodyweight)?

Yes → Category 5

No symbol

Warning

No

(a) Is there reliable information available indicating significant toxicity effects in humans?; or
(b) Was any mortality observed when tested up to Category 4 values by the oral, inhalation or dermal routes?; or
(c) Is there expert judgement that confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance?; or
(d) Is there expert judgement that confirms reliable information indicating the potential for significant acute effects from other animals?

Yes → Classify in Category 5

No symbol

(Warning)

if assignment to a more hazardous class is not warranted

No → Not classified

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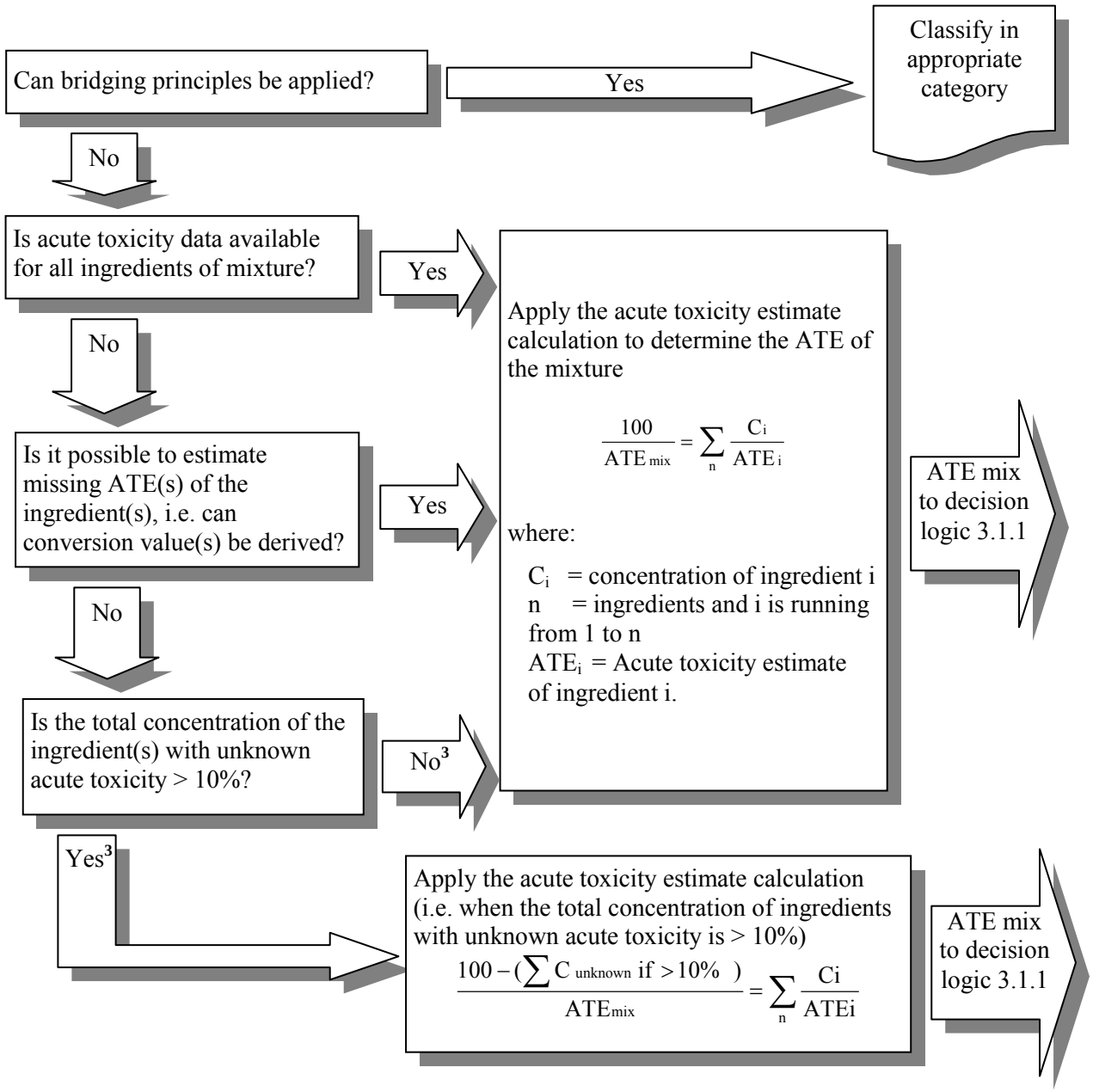
3.1.5.2 ***Decision logic 3.1.2 for acute toxicity*** *(see criteria in 3.1.3.5 and 3.1.3.6)*



[3] *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 additional statement(s) should identify the fact that x % of the mixture consists of ingredient(s) of unknown acute (oral/dermal/inhalation) toxicity. The competent authority can decide to specify that the additional statement(s) 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.*

Skin corrosion/irritation

Skin corrosion refers to the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, occurring after exposure to a substance or mixture

Skin irritation refers to the production of reversible damage to the skin occurring after exposure to a substance or mixture

Skin corrosion/irritation

Skin corrosion category and sub-categories

	Criteria
Category 1	Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure ≤ 4 h
Sub-category 1A	Corrosive responses in at least one animal following exposure ≤ 3 min during an observation period ≤ 1 h
Sub-category 1B	Corrosive responses in at least one animal following exposure > 3 min and ≤ 1 h and observations ≤ 14 days
Sub-category 1C	Corrosive responses in at least one animal after exposures > 1 h and ≤ 4 h and observations ≤ 14 days

Skin corrosion/irritation

Table 3.2.2: Skin irritation categories [a,b,c]

Categories	Criteria
Irritation (Category 2) (applies to all authorities)	(1) Mean score of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritation (Category 3) (applies to only some authorities)	Mean score of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant category above).

[a] *The use of human data is addressed in 3.2.2.2 and in chapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. 1.3.2.4.7).*

[b] *Grading criteria are understood as described in OECD Test Guideline 404.*

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.2.5.3.*

Skin corrosion/irritation

Table 3.2.3: Concentration of ingredients of a mixture classified as skin Category 1, 2 or 3 that would trigger classification of the mixture as hazardous to skin (Category 1, 2 or 3)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:		
	Skin corrosive	Skin irritant	
	Category 1 (see note below)	Category 2	Category 3
Skin Category 1	≥ 5%	≥ 1% but < 5%	
Skin Category 2		≥ 10%	≥ 1% but < 10%
Skin Category 3			≥ 10%
(10 × Skin Category 1) + Skin Category 2		≥ 10%	≥ 1% but < 10%
(10 × Skin Category 1) + Skin Category 2 + Skin Category 3			≥ 10%

NOTE: Where the sub-categories of skin Category 1 (corrosive) are used, the sum of all ingredients of a mixture classified as sub-category 1A, 1B or 1C respectively, should each be ≥5% in order to classify the mixture as either skin sub-category 1A, 1B or 1C. Where the sum of 1A ingredients is <5% but the sum of 1A+1B ingredients is ≥5%, the mixture should be classified as sub-category 1B. Similarly, where the sum of 1A + 1B ingredients is <5% but the sum of 1A + 1B + 1C ingredients is ≥ 5% the mixture should be classified as sub-category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-categorisation, the mixture should be classified as Category 1 without sub-categorisation if the sum of all ingredients corrosive to skin is ≥5%.

Skin corrosion/irritation

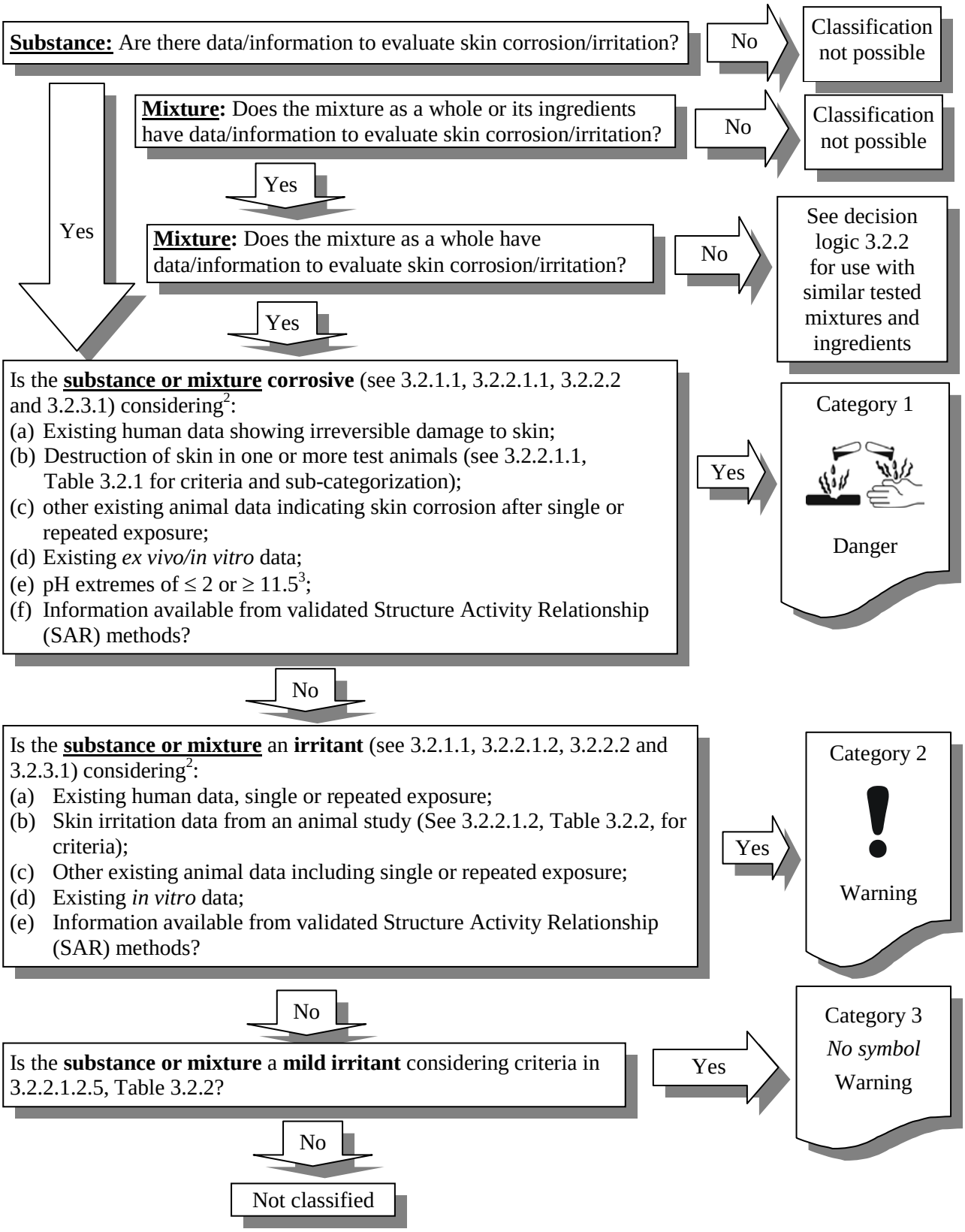
Table 3.2.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin

Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2/3) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

Skin corrosion/irritation

The procedure for classification of substances and mixtures is summarized in decision logics 3.2.1 and 3.2.2

3.2.5.1 *Decision logic 3.2.1 for skin corrosion/irritation*

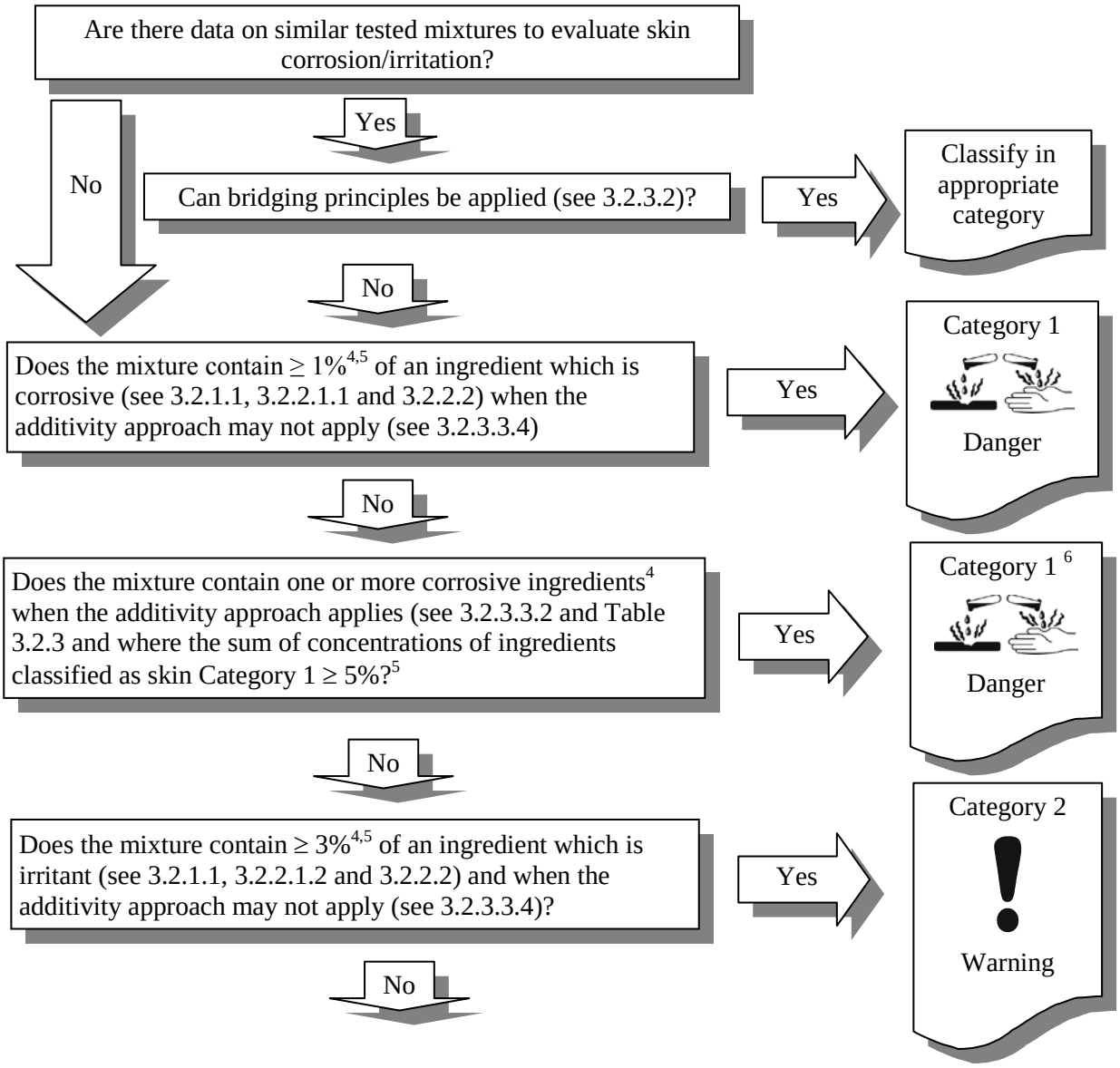


[2] *Taking into account consideration of the total weight of evidence as needed.*

[3] *Not applicable if consideration of pH and acid/alkaline reserve indicates substance or mixture may not be corrosive and confirmed by other data, preferably by data from an appropriate validated in vitro test.*

3.2.5.2 Decision logic 3.2.2 for skin corrosion/irritation

Classification of mixtures on the basis of information/data on similar tested mixtures and/or ingredients



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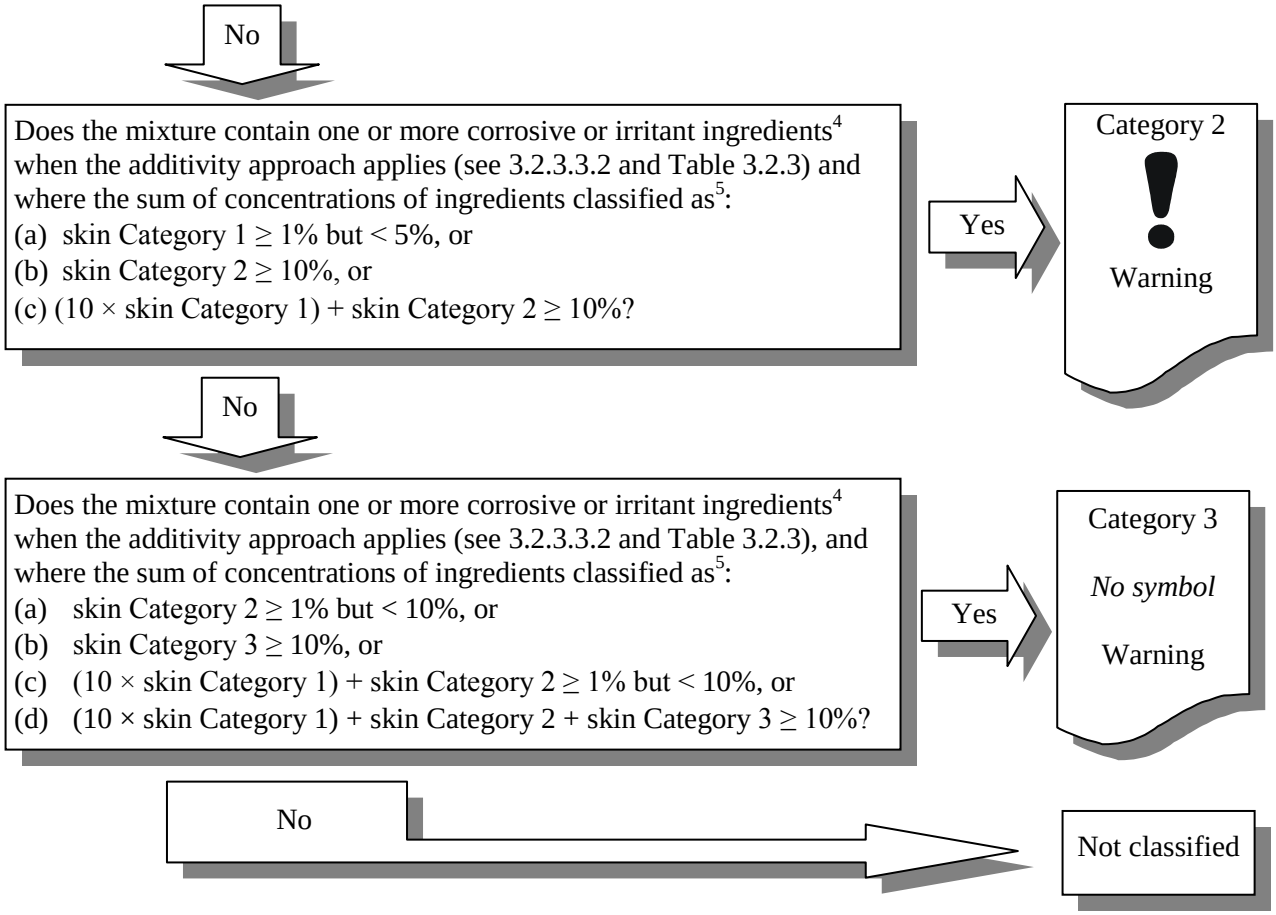
[4] *Where relevant < 1%, see 3.2.3.3.1.*

[5] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".*

[6] *See note to Table 3.2.3 for details on use of Category 1 sub-categories.*



[4] *Where relevant < 1%, see 3.2.3.3.1.*

[5] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".*

Serious eye damage/eye irritation

Serious eye damage refers to the production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible, occurring after exposure of the eye to a substance or mixture

Eye irritation refers to the production of changes in the eye, which are fully reversible, occurring after exposure of the eye to a substance or mixture

Serious eye damage/eye irritation

Category 1 (serious eye damage/irreversible effects on the eye)

Table 3.3.1: Serious eye damage/Irreversible effects on the eye category[a, b, c]

	Criteria
Category 1: **Serious eye damage/Irreversible effects on the eye**	A substance that produces: (a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.

[a] *The use of human data is addressed in 3.3.2.2 and in chapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. 1.3.2.4.7).*

[b] *Grading criteria are understood as described in OECD Test Guideline 405.*

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.3.5.3.*

Serious eye damage/eye irritation

Category 2

Table 3.3.2: Reversible effects on the eye categories [a, b, c]

	Criteria
	Substances that have the potential to induce reversible eye irritation
Category 2/2A	Substances that produce in at least 2 of 3 tested animals a positive response of: (a) corneal opacity ≥ 1; and/or (b) iritis ≥ 1; and/or (c) conjunctival redness ≥ 2; and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material, and which fully reverses within an observation period of normally 21 days.
Category 2B	Within Category 2A an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.

[a] *The use of human data is addressed in 3.3.2.2 and in chapters 1.1 (para. 1.1.2.5(c)), and 1.3 (para. 1.3.2.4.7).*

[b] *Grading criteria are understood as described in OECD Test Guideline 405.*

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.3.5.3.*

Serious eye damage/eye irritation

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixture as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as	Concentration triggering classification of a mixture as	
	Serious eye damage	Eye irritation
	Category 1	Category 2/2A
Skin Category 1 + Eye Category 1[a]	≥ 3%	≥ 1% but < 3%
Eye Category 2		≥ 10% [b]
10 × (skin Category 1 + eye Category 1)[a] + eye Category 2		≥ 10%

[a] *If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation;*

[b] *A mixture may be classified as eye Category 2B when all relevant ingredients are classified as eye Category 2B.*

Table 3.3.4: Concentration of ingredients of a mixture when the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (eye Category 1) ingredient	≥ 1%	Category 1
Other eye irritant (eye Category 2) ingredient	≥ 3%	Category 2

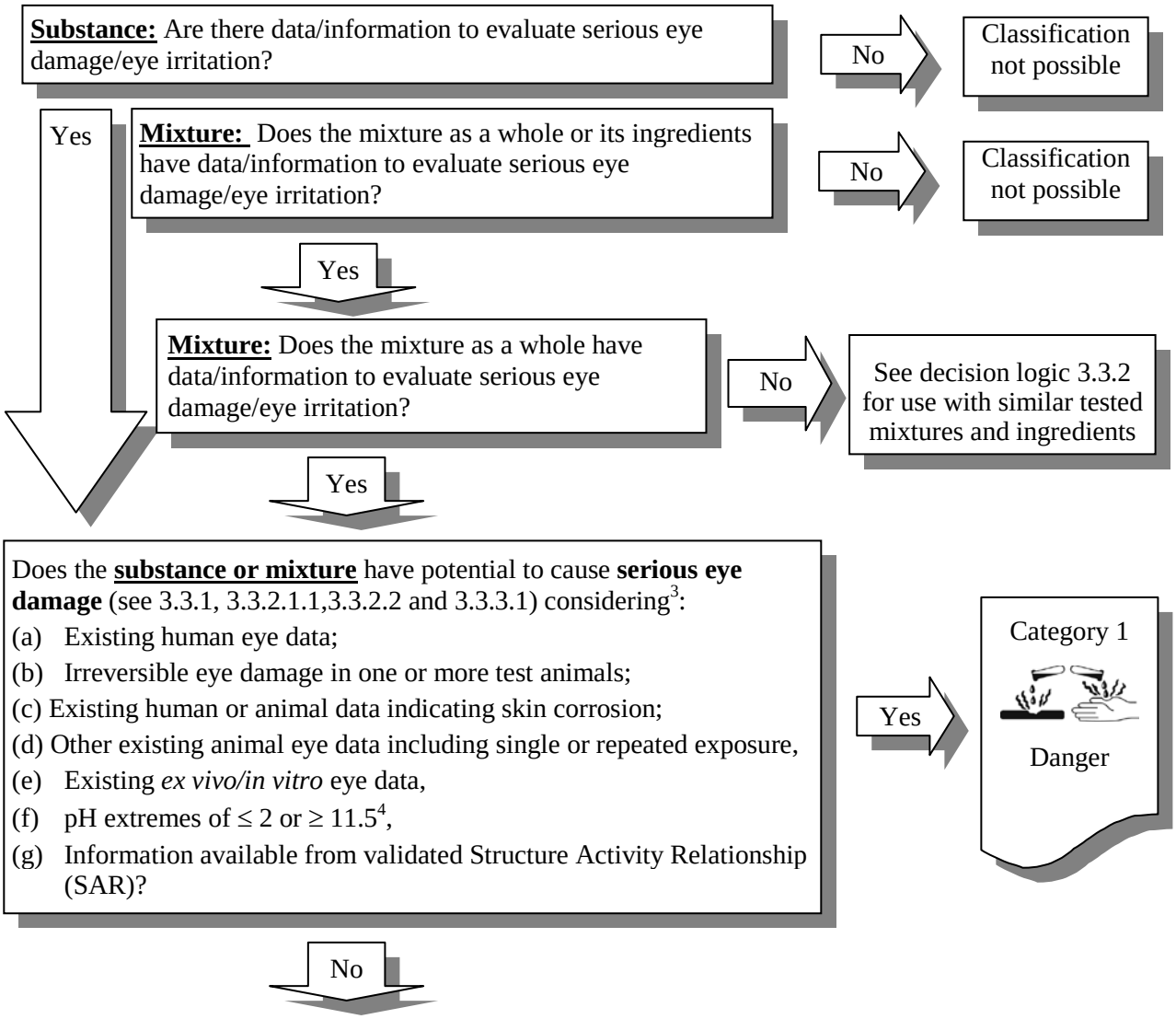
Serious eye damage/eye irritation

The procedure for classification of substances and mixtures is summarized in decision logics 3.3.1 and 3.3.2

3.3.5 Decision logics and guidance

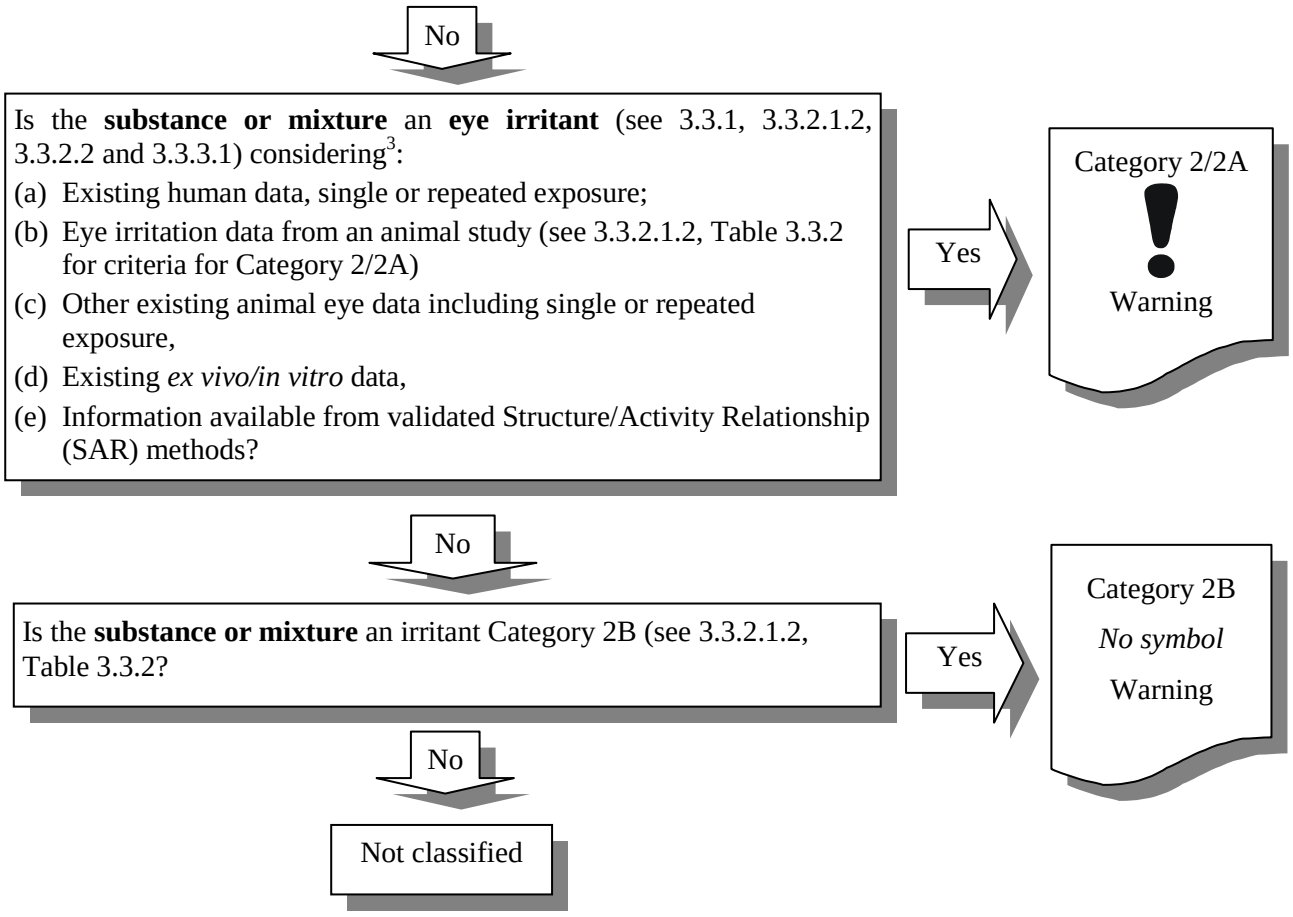
The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*



[3] *Taking into account consideration of the total weight of evidence as needed*

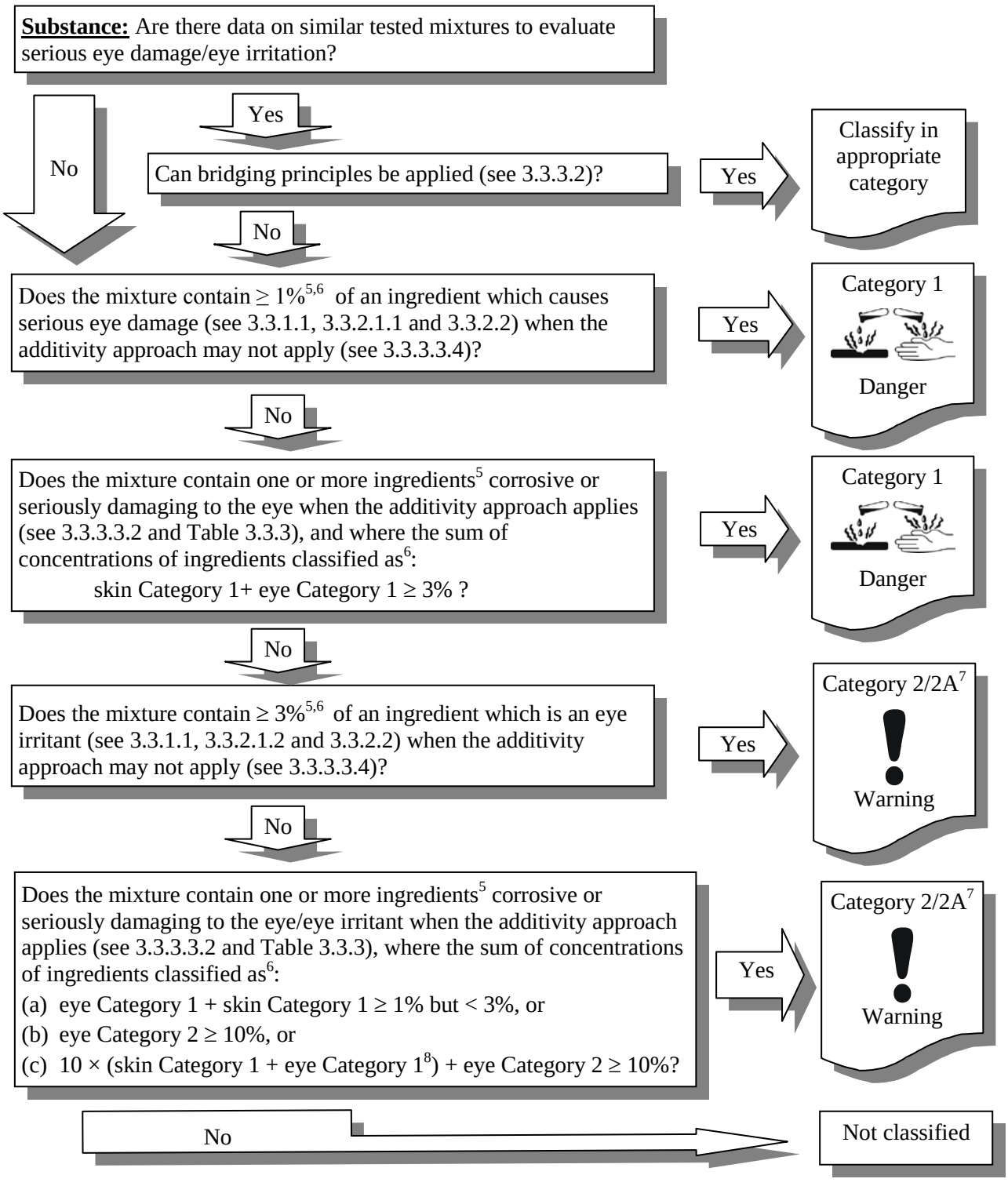
[4] *Not applicable if consideration of pH and acid/alkaline reserve indicates the substance or mixture many not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated in vitro test.*



[3] *Taking into account consideration of the total weight of evidence as needed.*

3.3.5.2 Decision logic 3.3.2 for serious eye damage/eye irritation

Classification of mixtures on the basis of information/data on similar tested mixtures and ingredients



[5] *Where relevant < 1%, see 3.3.3.3.1.*

[6] *For specific concentration limits, see 3.3.3.3.5 and 3.3.3.3.6. See also Chapter 1.3, para. 1.3.3.2 "Use of cut-off values/concentration limits".*

[7] *A mixture may be classified as eye Category 2B in case all relevant ingredients are classified as eye Category 2B.*

[8] *If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation.*

Respiratory/skin sensitization

Respiratory sensitization refers to hypersensitivity of the airways occurring after inhalation of a substance or mixture

Skin sensitization refers to an allergic response occurring after skin contact with a substance or mixture

Respiratory/skin sensitization

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.

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

CATEGORY 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer: (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[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.

Respiratory/skin sensitization

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.

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

CATEGORY 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer: (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.
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.

Respiratory/skin sensitization

Table 3.4.5: Cut-off values/concentration limits of ingredients of a mixture classified as either respiratory sensitizers or skin sensitizers that would trigger classification of the mixture

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

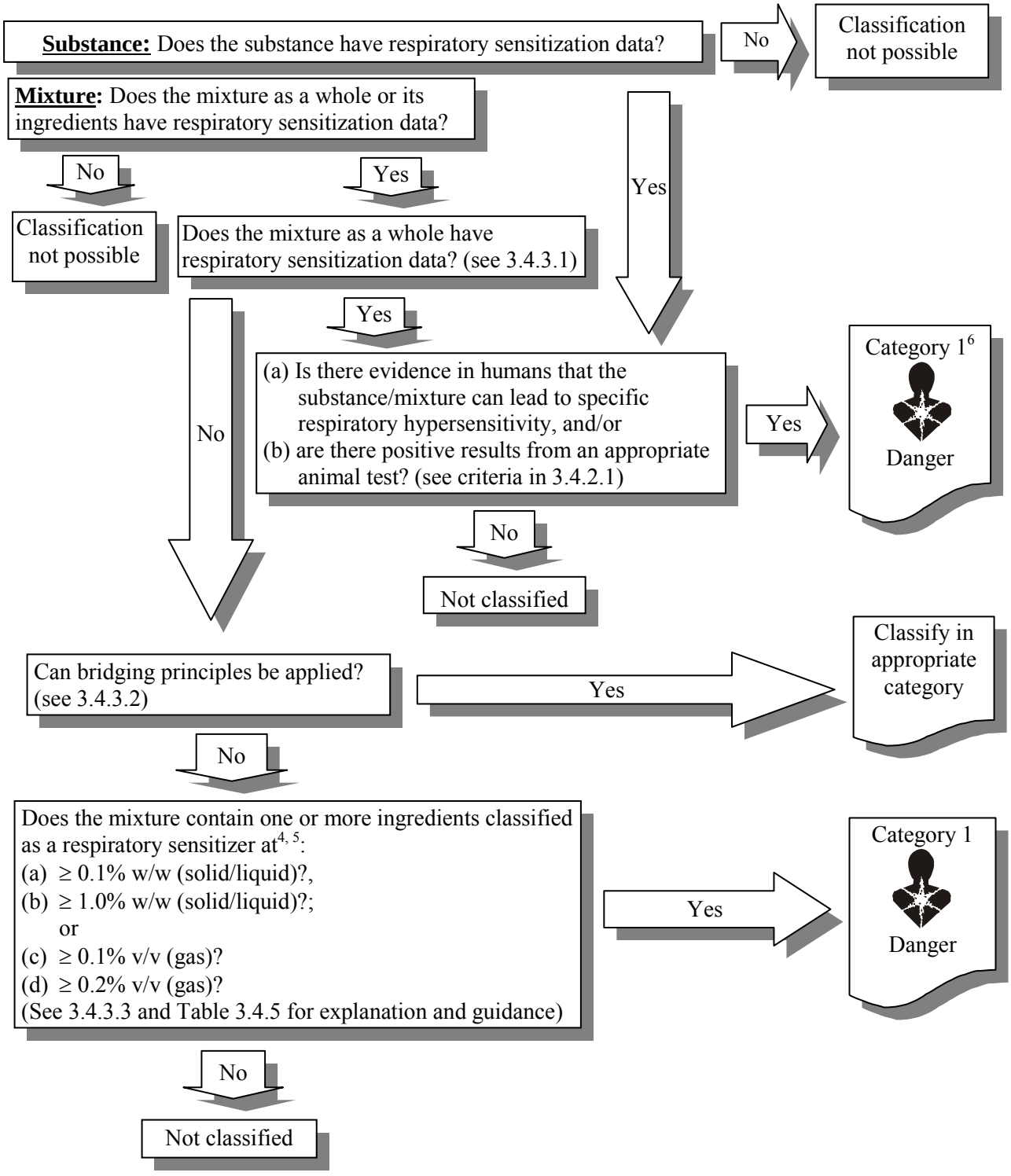
Respiratory/skin sensitization

The procedure for classification of substances and mixtures is summarized in decision logics 3.4.1 and 3.4.2

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*

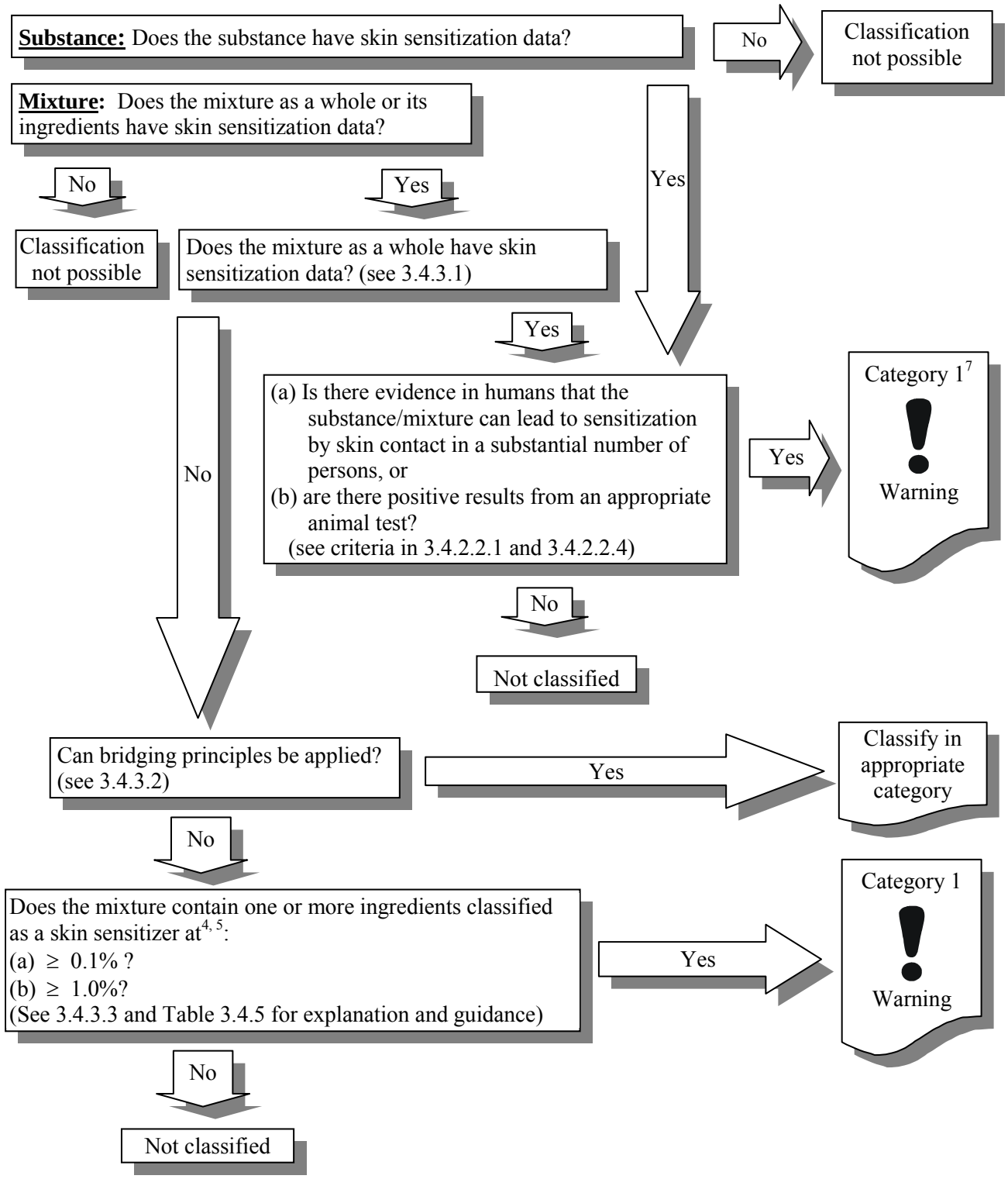


[4] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[5] *See 3.4.4.2.*

[6] *See 3.4.2.1.1 for details on use of Category 1 sub-categories.*

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.*

[7] *See 3.4.2.2.1 for details on use of Category 1 sub-categories.*

Germ cell mutagenicity

Germ cell mutagenicity refers to heritable gene mutations, including heritable structural and numerical chromosome aberrations in germ cells occurring after exposure to a substance or mixture

This hazard class is primarily concerned with chemicals that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, mutagenicity/genotoxicity tests *in vitro* and in mammalian somatic cells *in vivo* are also considered in classifying substances and mixtures within this hazard class.

A *mutation* is defined as a permanent change in the amount or structure of the genetic material in a cell. The term *mutation* applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including, for example, specific base pair changes and chromosomal translocations). The term *mutagenic* and *mutagen* will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

Germ cell mutagenicity

The more general terms *genotoxic* and *genotoxicity* apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects

Germ cell mutagenicity

2 different categories of germ cell mutagens: Cat.1 and Cat.2

CATEGORY 1: **Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans**

Category 1A: **Substances known to induce heritable mutations in germ cells of humans**

Positive evidence from human epidemiological studies.

Category 1B: **Substances which should be regarded as if they induce heritable mutations in the germ cells of humans**

(a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or

(b) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or

(c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

Germ cell mutagenicity

CATEGORY 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans

Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:

(a) Somatic cell mutagenicity tests *in vivo*, in mammals; or

(b) Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

NOTE: *Substances which are positive in in vitro mammalian mutagenicity assays, and which also show structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.*

Germ cell mutagenicity

Table 3.5.1: Cut-off values/concentration limits of ingredients of a mixture classified as germ cell mutagens that would trigger classification of the mixture

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%

Note: *The cut-off values/concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).*

Germ cell mutagenicity

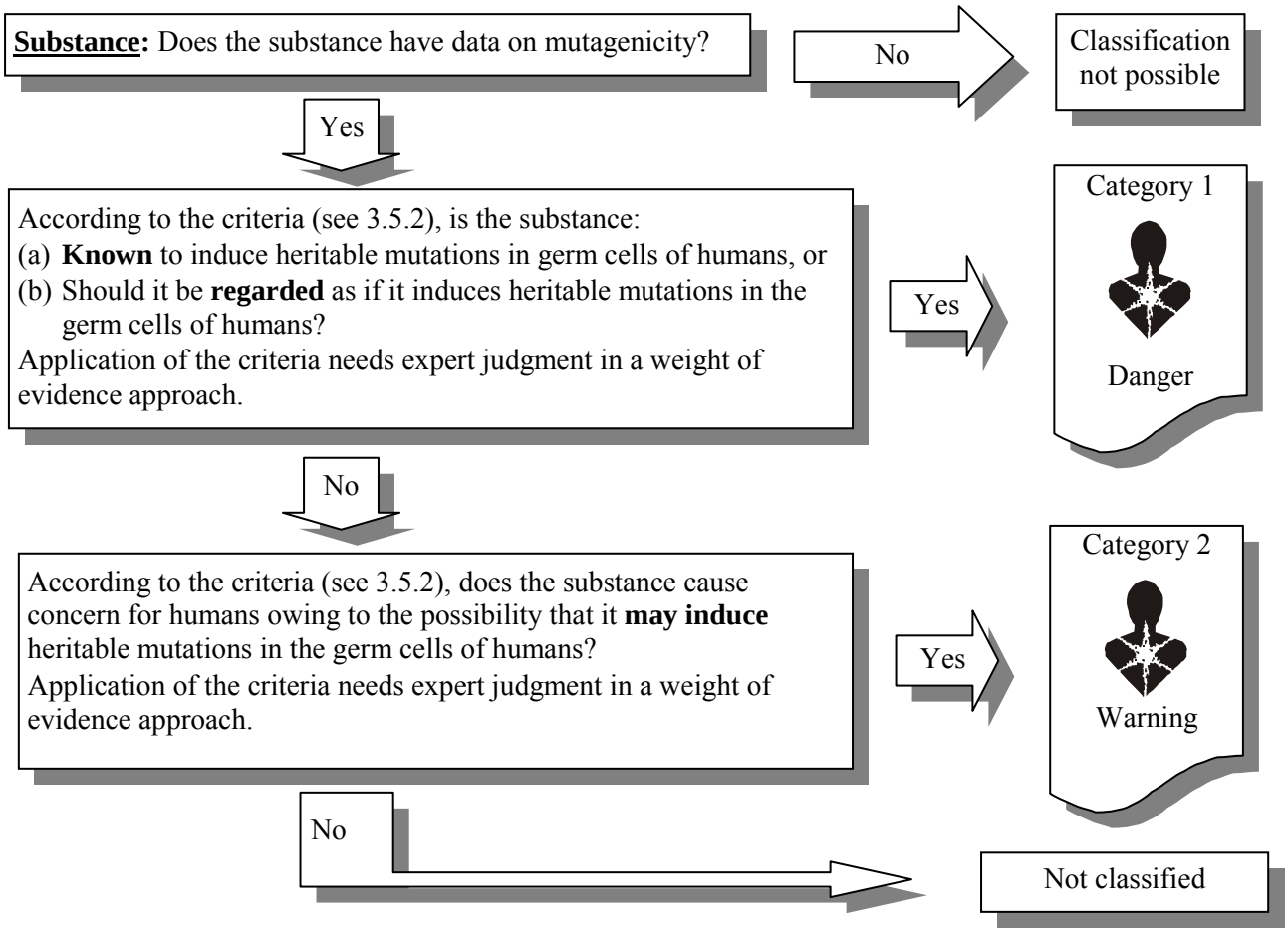
The procedure for classification of substances and mixtures is summarized in decision logics 3.5.1 and 3.5.2

3.5.5 Decision logic and guidance

3.5.5.1 *Decision logic for germ cell mutagenicity*

The decision logic which follows is not part of the harmonized classification system but is 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 logic.

3.5.5.1.1 *Decision logic 3.5.1 for substances*



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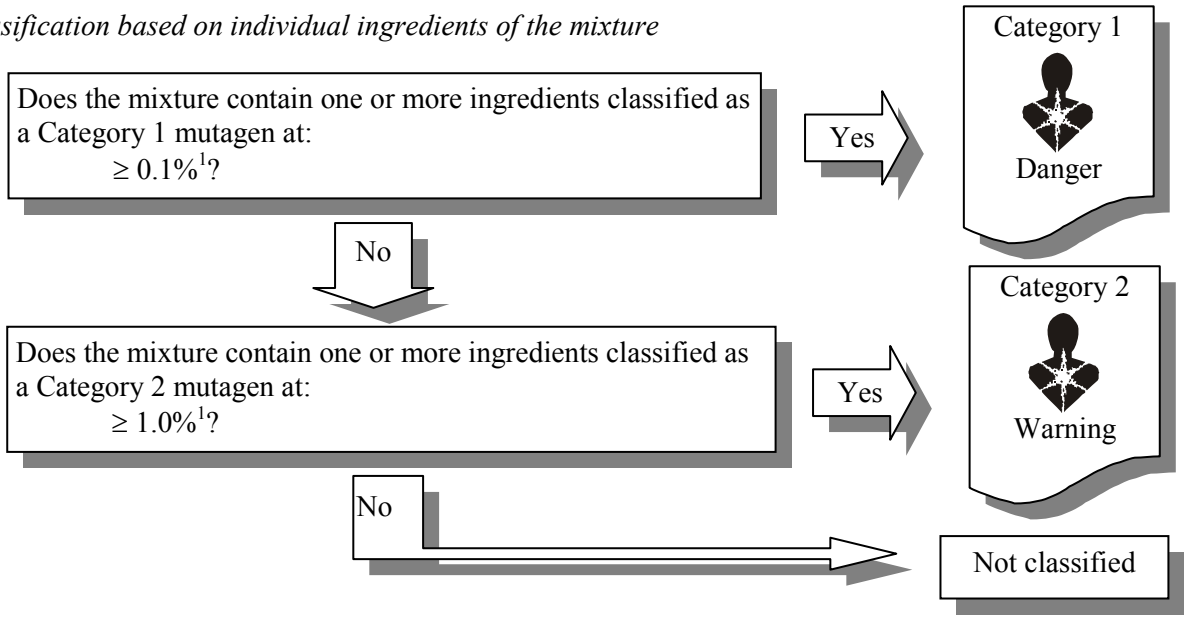
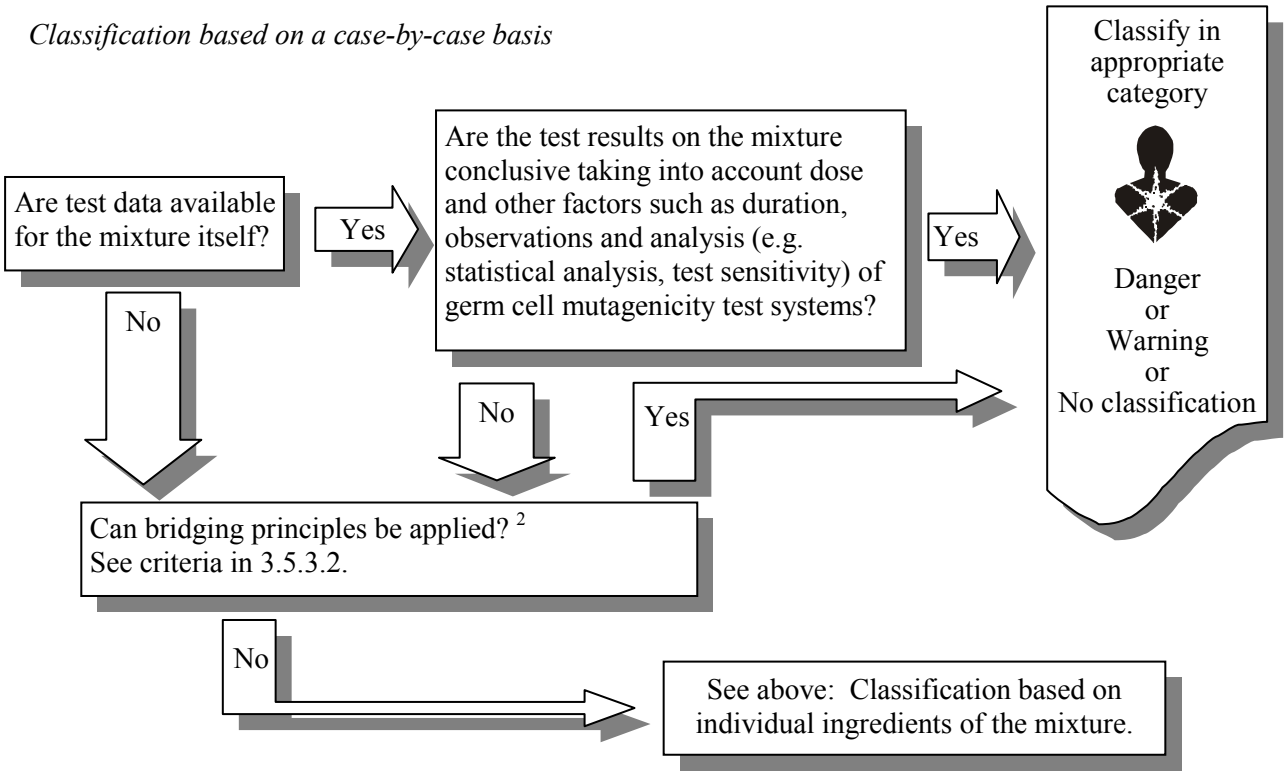
3.5.5.1.2 *Decision logic 3.5.2 for mixtures*

Mixture:
Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may **be modified on a case-by-case basis** based on the available test data for the mixture itself or based on bridging principles. See modified classification on a case-by-case basis below. For further details see criteria in 3.5.3.

Classification based on individual ingredients of the mixture



Classification based on a case-by-case basis



[1] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2 and Table 3.5.1 of this Chapter.*

[2] *If data on another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with 3.5.3.2.*

Carcinogenicity

Carcinogenicity refers to the induction of cancer or an increase in the incidence of cancer occurring after exposure to a substance or mixture. Substances and mixtures which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

Classification of a substance or mixture as posing a carcinogenic hazard is based on its inherent properties and does not provide information on the level of the human cancer risk which the use of the substance or mixture may represent.

Carcinogenicity

For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route specific classification may be warranted.

Carcinogenicity

Hazard categories for carcinogens

CATEGORY 1:	**Known or presumed human carcinogens**
	The placing of a substance in Category 1 is done on the basis of epidemiological and/or animal data. An individual substance may be further distinguished:
Category 1A:	**Known to have carcinogenic potential for humans; the placing of a substance is largely based on human evidence.**
Category 1B:	**Presumed to have carcinogenic potential for humans; the placing of a substance is largely based on animal evidence.**
	Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
	Classification: Category 1 (A and B) Carcinogen

Carcinogenicity

CATEGORY 2:	**Suspected human carcinogens** The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. **Classification**: Category 2 Carcinogen

Carcinogenicity

Table 3.6.1: Cut-off values/concentration limits of ingredients of a mixture classified as carcinogen that would trigger classification of the mixture [a]

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% (note 2)

[a] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonized approach.*

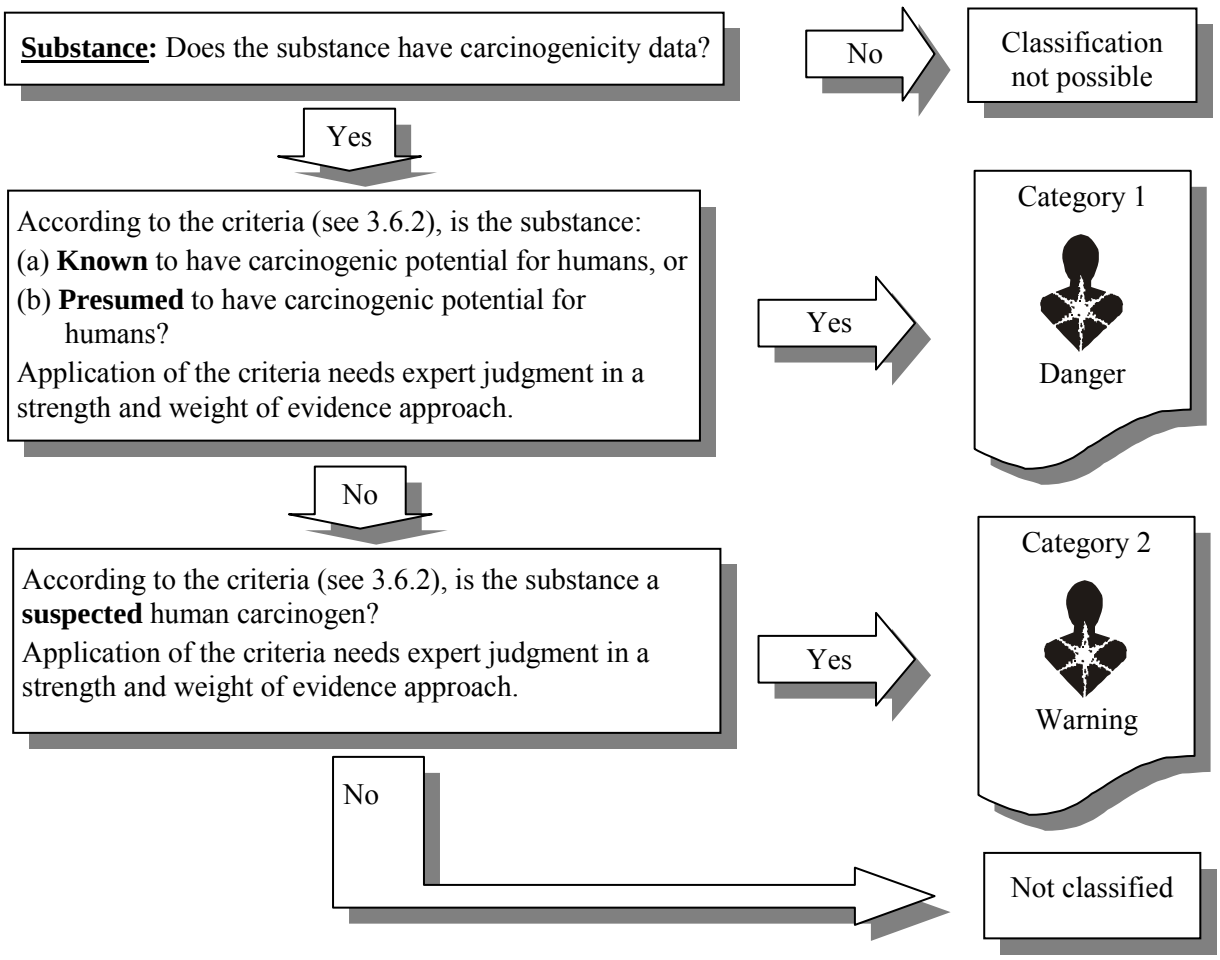
Carcinogenicity

The procedure for classification of substances and mixtures is summarized in decision logics 3.6.1 and 3.6.2

3.6.5 Decision logic and guidance

The decision logics which follow is not part of the harmonized classification system but is 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 logic.

3.6.5.1 *Decision logic 3.6.1 for substances*



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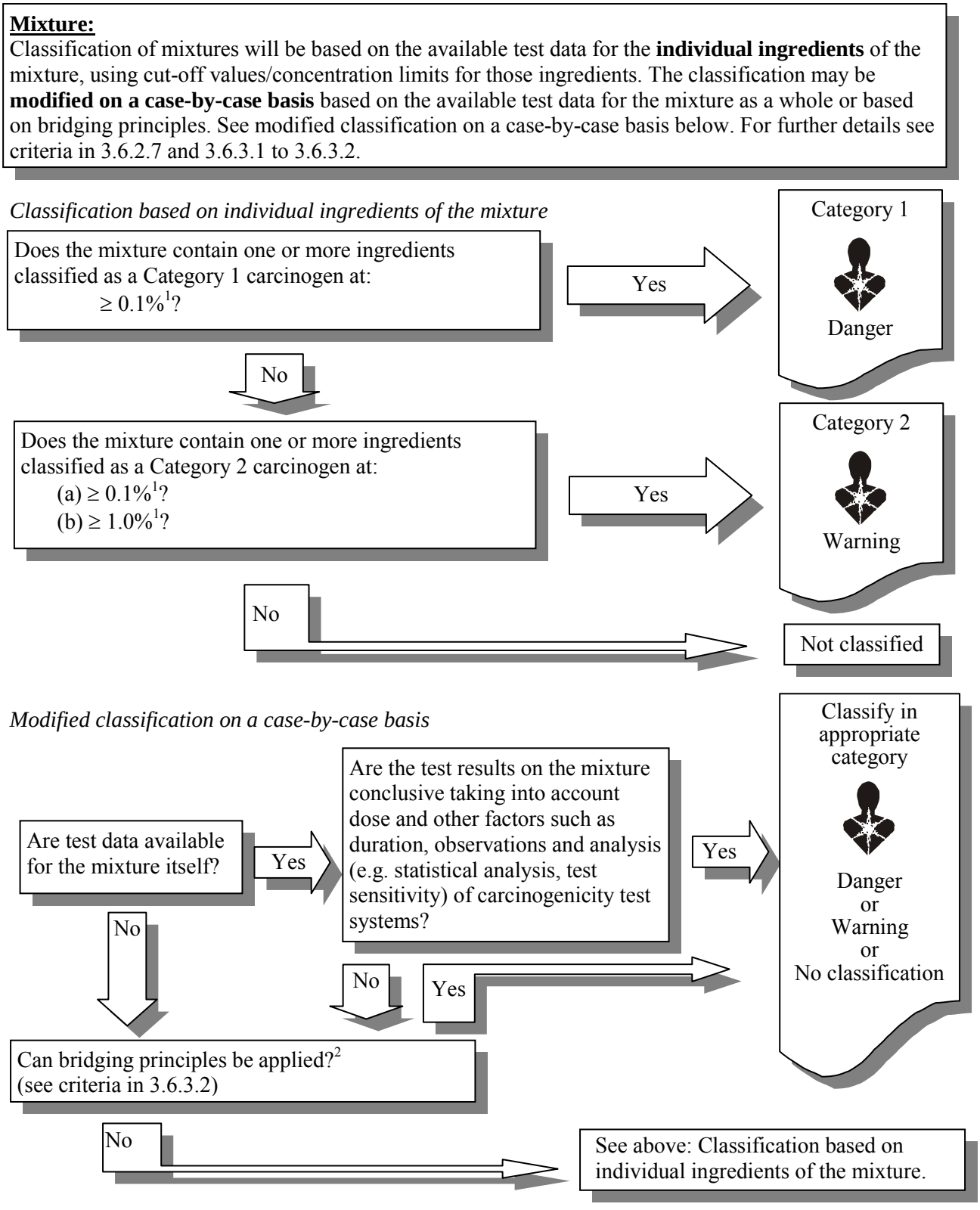
3.6.5.2 *Decision logic 3.6.2 for mixtures*



[1] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2 and in Table 3.6.1 of this Chapter.*

[2] *If data of another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with 3.6.3.2.*

Reproductive toxicity

Reproductive toxicity refers to adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring, occurring after exposure to a substance or mixture.

For classification purposes, the known induction of genetically based inheritable effects in the offspring is addressed in *Germ cell mutagenicity* (Chapter 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

Reproductive toxicity

For the purpose of classification for reproductive toxicity, substances are allocated to:

- Category 1; or
- Category 2

Effects on sexual function and fertility, and on development, are considered.

Effects on lactation are allocated to a separate hazard category.

Reproductive toxicity

Figure 3.7.1 (a): Hazard categories for reproductive toxicants

CATEGORY 1:	**Known or presumed human reproductive toxicant** This category includes substances which are known to have produced an adverse effect on sexual function and fertility or on development in humans or for which there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. For regulatory purposes, a substance can be further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
CATEGORY 1A:	**Known human reproductive toxicant** The placing of the substance in this category is largely based on evidence from humans.
CATEGORY 1B:	**Presumed human reproductive toxicant** The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Reproductive toxicity

CATEGORY 2:	**Suspected human reproductive toxicant** This category includes substances for which there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 could be the more appropriate classification.

Reproductive toxicity

Figure 3.7.1 (b): Hazard category for effects on or via lactation

EFFECTS ON OR VIA LACTATION

Effects on or via lactation are allocated to a separate single category. It is appreciated that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, should be classified to indicate this property hazardous to breastfed babies. This classification can be assigned on the basis of:

(a) absorption, metabolism, distribution and excretion studies that would indicate the likelihood the substance would be present in potentially toxic levels in breast milk; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) human evidence indicating a hazard to babies during the lactation period.

Reproductive toxicity

Table 3.7.1: Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants or for effects on or via lactation that would trigger classification of the mixtures[a]

	Cut-off/concentration limits triggering classification of a mixture as:			
Ingredients classified 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)

[a] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonized approach.*

Reproductive toxicity

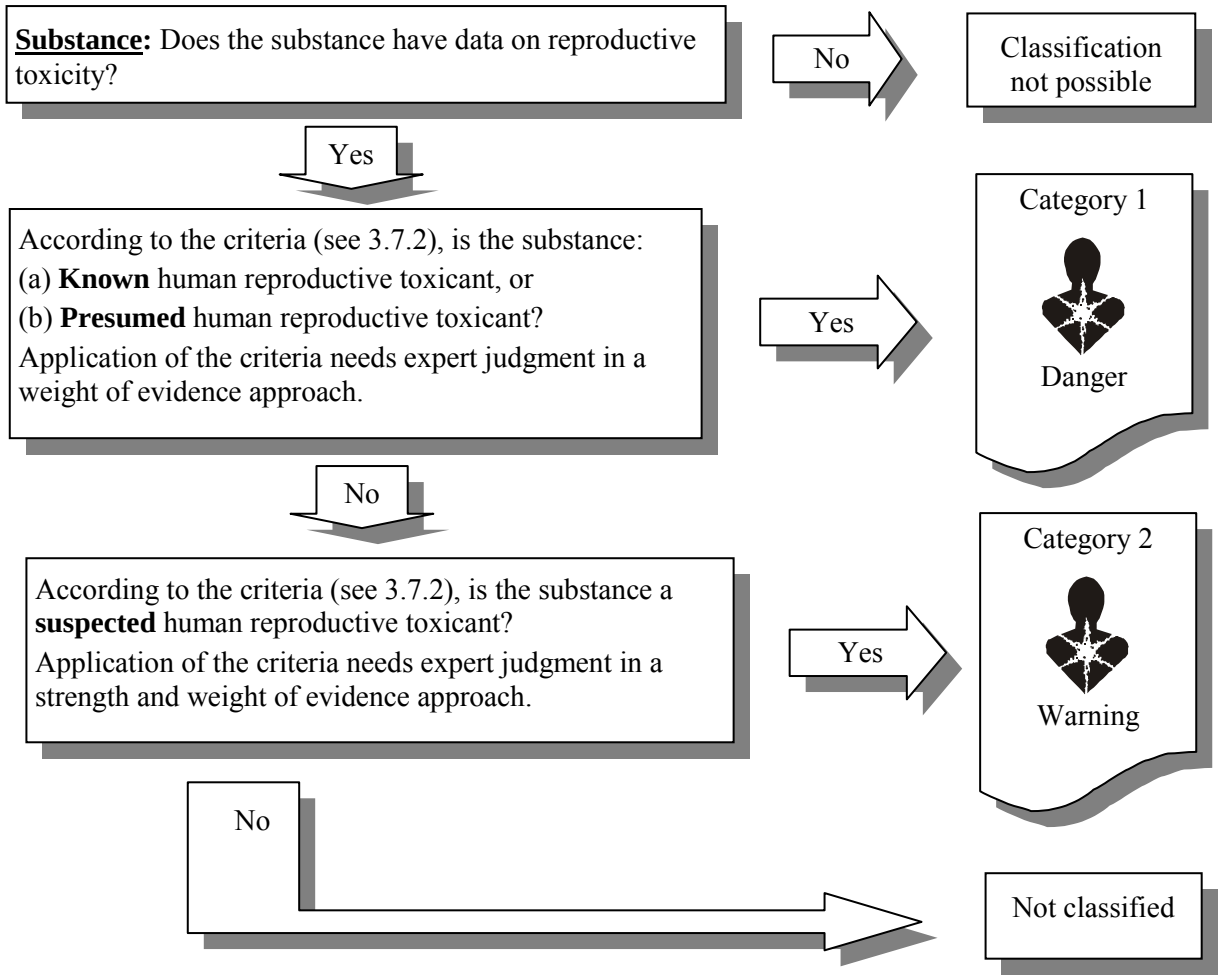
The procedure for classification of substances and mixtures is summarized in decision logics 3.7.1 to 3.7.4

3.7.5 Decision logics for classification

3.7.5.1 *Decision logic for reproductive toxicity*

The decision logic which follows is not part of the harmonized classification system but is 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 logic.

3.7.5.1.1 *Decision logic 3.7.1 for substances*



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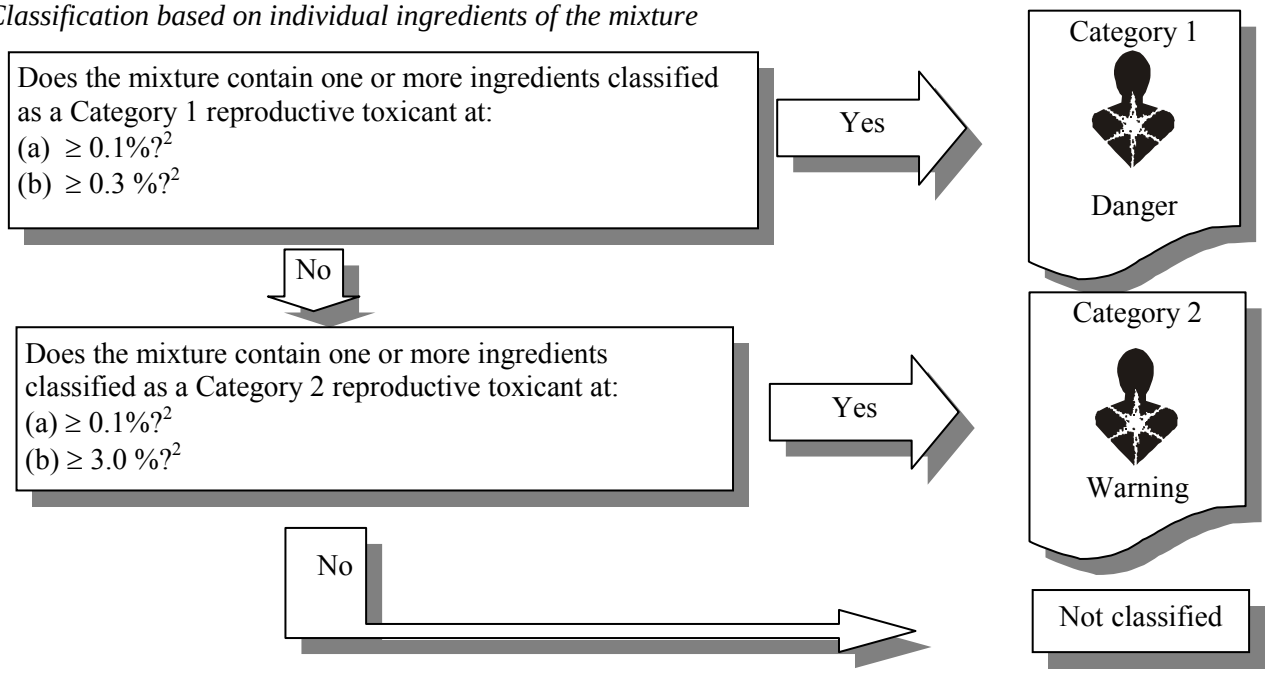
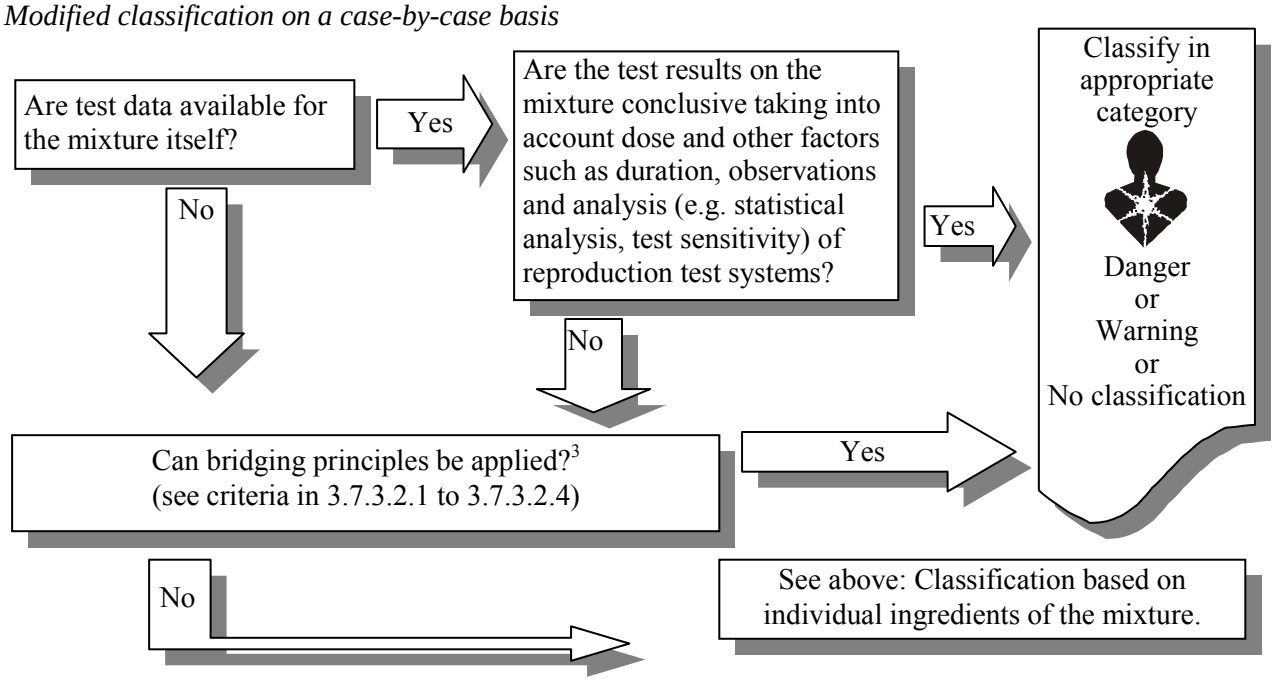
3.7.5.1.2 *Decision logic 3.7.2 for mixtures*

Mixture: Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may be **modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See modified classification on a case-by-case basis below. For further details see criteria in 3.7.3.1, 3.7.3.2 and 3.7.3.3.

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis



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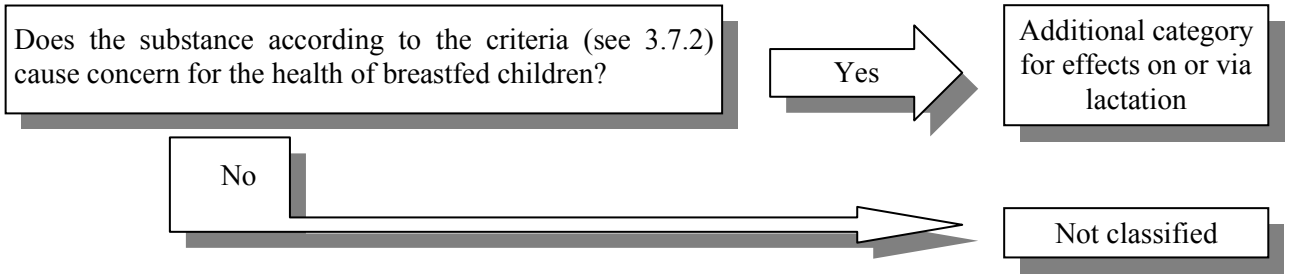
[2] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2, and in Table 3.7.1 of this Chapter.*

[3] *If data on another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with 3.7.3.2.*

3.7.5.2 *Decision logic for effects on or via lactation*

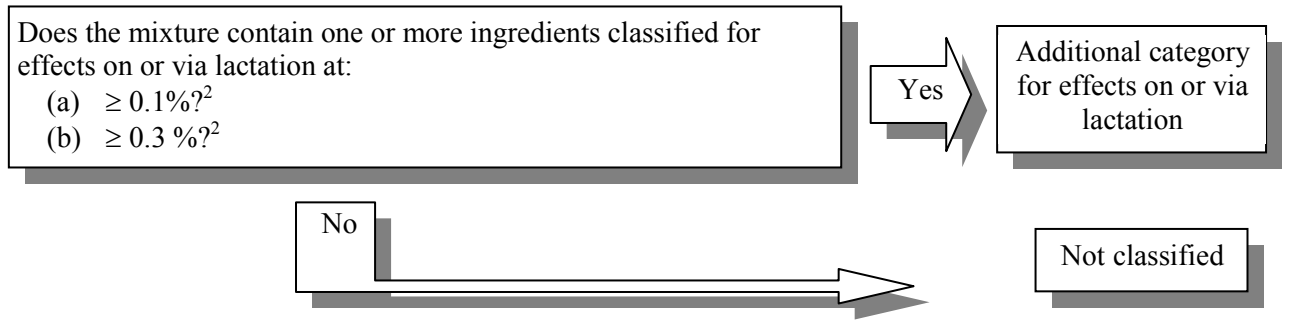
3.7.5.2.1 *Decision logic 3.7.3 for substances*



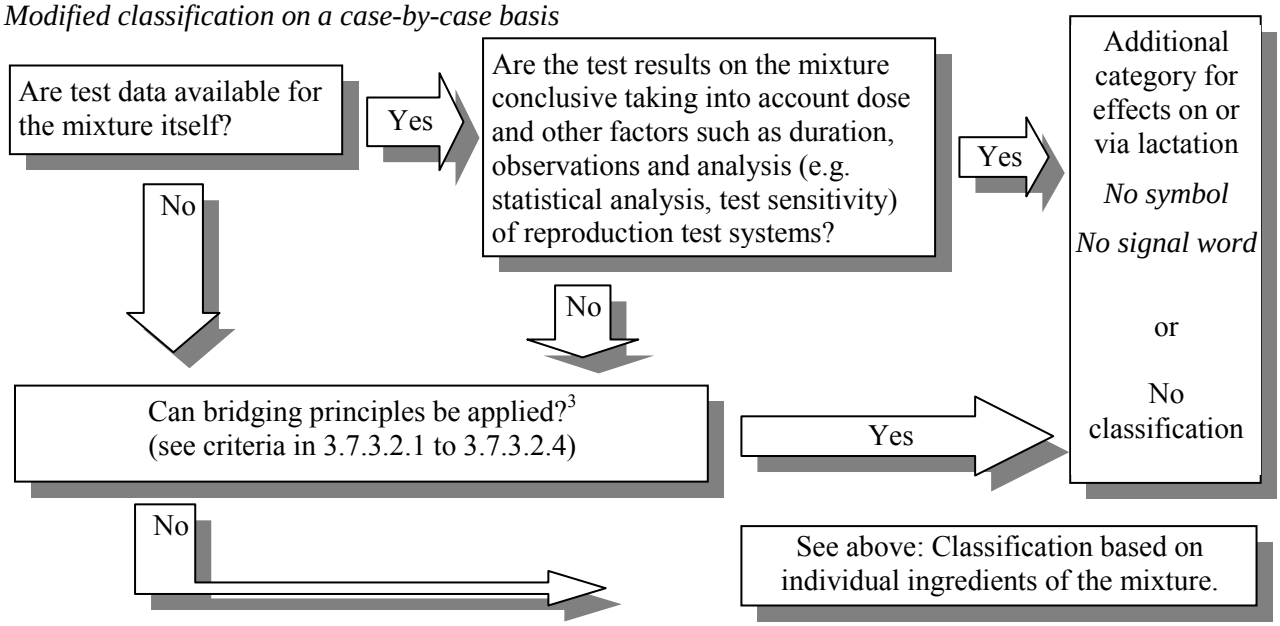
3.7.5.2.2 *Decision logic 3.7.4 for mixtures*

Mixture: Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may be **modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See modified classification on a case-by-case basis below. For further details see criteria in 3.7.3.1, 3.7.3.2 and 3.7.3.3.

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis



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[2] *For specific concentration limits, see "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2, and in Table 3.7.1 of this Chapter.*

[3] *If data on another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with 3.7.3.2.*

STOT-Single exposure

Specific target organ toxicity – single exposure (STOT) refers to specific, non lethal target organ effects occurring after a single exposure to a substance or a mixture.

Classification depends upon the availability of reliable evidence that a single exposure to the substance or mixture has produced a consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or has produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health. It is recognized that human data will be the primary source of evidence for this hazard class.

STOT-Single exposure

Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1.9).

Then substances are placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Figure 3.8.1), or in Category 3.

STOT-Single exposure

CATEGORY 1: **Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure**

Placing a substance in Category 1 is done on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or

(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure**

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification.

In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.9).

STOT-Single exposure

CATEGORY 3: **Transient target organ effects**

There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances/mixtures may be classified specifically for these effects as discussed in 3.8.2.2.

STOT-Single exposure

Table 3.8.1: Guidance value ranges for single-dose exposures[a]

		Guidance value ranges for:		
Route of exposure	**Units**	**Category 1**	**Category 2**	**Category 3**
Oral (rat)	mg/kg body weight	$C \leq 300$	$2000 \geq C > 300$	Guidance values do not apply[b]
Dermal (rat or rabbit)	mg/kg body weight	$C \leq 1000$	$2000 \geq C > 1000$	
Inhalation (rat) gas	ppmV/4h	$C \leq 2500$	$20000 \geq C > 2500$	
Inhalation (rat) vapour	mg/1/4h	$C \leq 10$	$20 \geq C > 10$	
Inhalation (rat) dust/mist/fume	mg/l/4h	$C \leq 1.0$	$5.0 \geq C > 1.0$	

[a] *The guidance values and ranges mentioned in Table 3.8.1. above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.*

[b] *Guidance values are not provided since this classification is primarily based on human data. Animal data may be included in the weight of evidence evaluation.*

STOT-Single exposure

Table 3.8.2: Cut-off values/concentration limits of ingredients of a mixture classified as a specific target organ toxicant that would trigger classification of the mixture as Category 1 or 2[a]

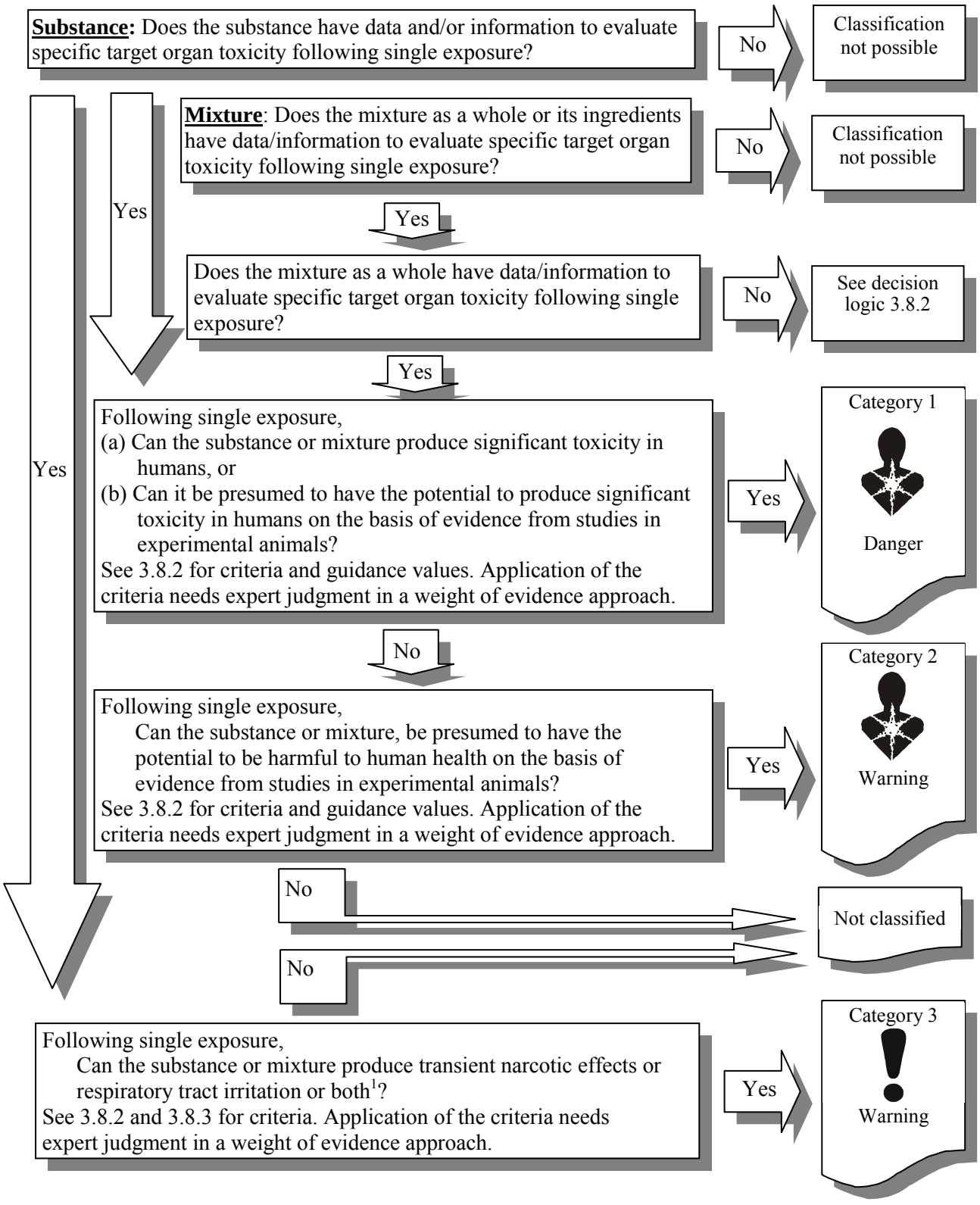
Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1	**Category 2**
Category 1 Target organ toxicant	≥ 1.0% (note 1)	1.0 ≤ ingredient < 10% (note 3)
	≥ 10% (note 2)	
Category 2 Target organ toxicant	--	≥ 1.0% (note 4)
		≥ 10% (note 5)

[a] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonized approach.*

STOT-Single exposure

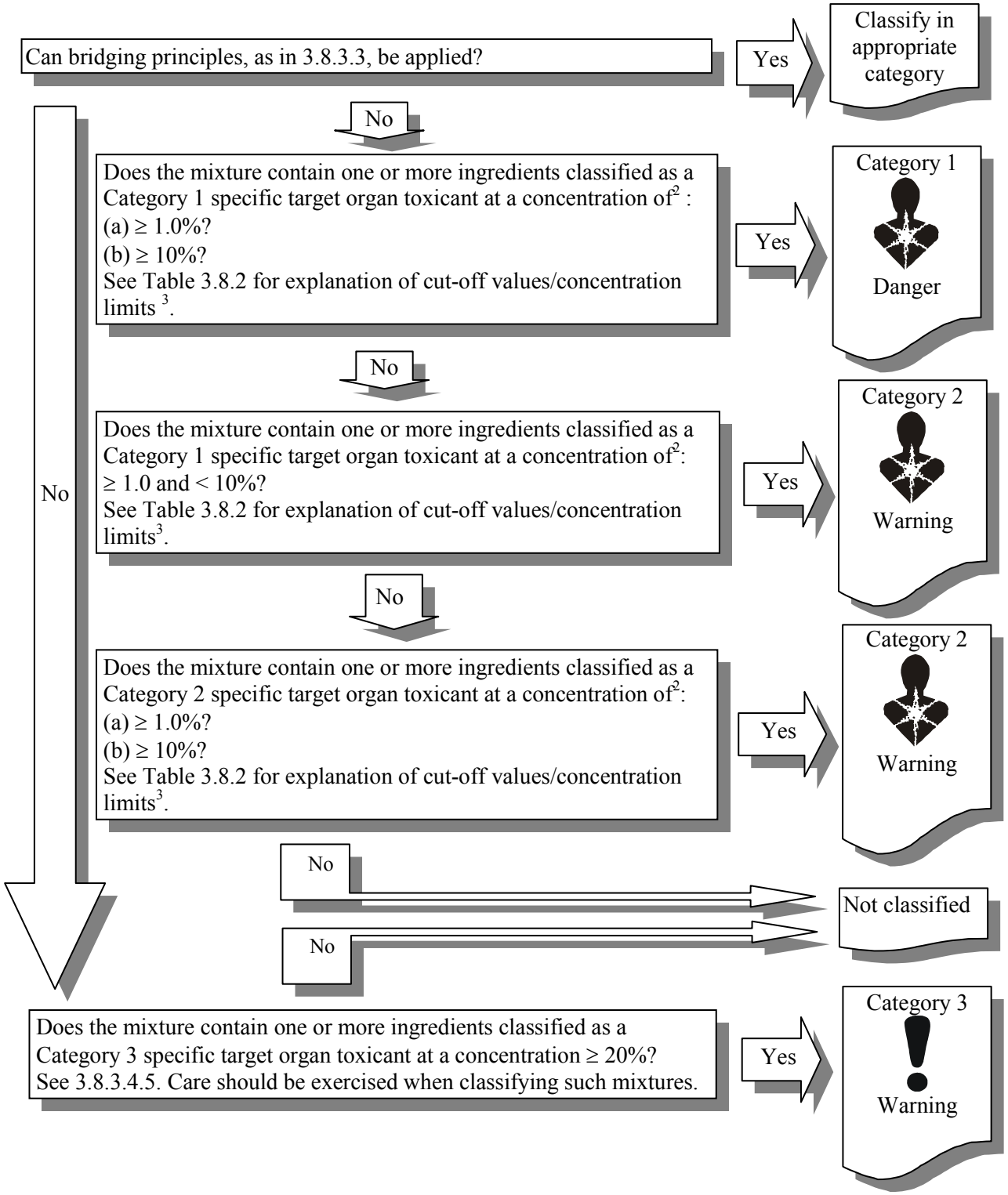
The procedure for classification of substances and mixtures is summarized in decision logics 3.8.1 and 3.8.2

3.8.5.1 ***Decision logic 3.8.1***



[1] *Classification in Category 3 would only occur when classification into Category 1 or Category 2 (based on more severe respiratory effects or narcotic effects that are not transient) is not warranted. See 3.8.2.2.1 (e) (respiratory effects) and 3.8.2.2.2 (b) (narcotic effects).*

3.8.5.2 ***Decision logic 3.8.2***



[2] *See 3.8.2 of this chapter and "The use of cut-off values/concentration limits" in Chapter 1.3, para. 1.3.3.2.*

[3] *See 3.8.3.4 and Table 3.8.2 for explanation and guidance.*

STOT-Repeated exposure

Specific target organ toxicity - repeated exposure (STOT) refers to specific toxic effects on target organs occurring after aspiration of a substance or mixture repeated exposure.

Classification depends upon the availability of reliable evidence that a repeated exposure to the substance or mixture has produced a consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or has produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health. It is recognized that human data will be the primary source of evidence for this hazard class.

STOT-Repeated exposure

Substances are classified as specific target organ toxicant by expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

For both categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.

STOT-Repeated exposure

CATEGORY 1: **Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure**

Placing a substance in Category 1 is done on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or,

(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure**

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

STOT-Repeated exposure

Table 3.9.1: Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg bw/d	≤ 10
Dermal (rat or rabbit)	mg/kg bw/d	≤ 20
Inhalation (rat) gas	ppmV/6h/d	≤ 50
Inhalation (rat) vapour	mg/litre/6h/d	≤ 0.2
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	≤ 0.02

Table 3.9.2: Guidance values to assist in Category 2 classification

Route of exposure	Units	Guidance value range (dose/concentration)
Oral (rat)	mg/kg bw/d	$10 < C \leq 100$
Dermal (rat or rabbit)	mg/kg bw/d	$20 < C \leq 200$
Inhalation (rat) gas	ppmV/6h/d	$50 < C \leq 250$
Inhalation (rat) vapour	mg/litre/6h/d	$0.2 < C \leq 1.0$
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	$0.02 < C \leq 0.2$

***Note**: "bw" is for body weight, "h" for" hour" and "d" for "day".*

STOT-Repeated exposure

Table 3.9.3: Cut-off values/concentration limits of ingredients of a mixture classified as a specific target organ toxicant that would trigger classification of the mixture[a]

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1	**Category 2**
Category 1 Target organ toxicant	≥ 1.0% (note 1)	1.0 ≤ ingredient < 10% (note 3)
	≥ 10% (note 2)	1.0 ≤ ingredient < 10% (note 3)
Category 2 Target organ toxicant		≥ 1.0% (note 4)
		≥ 10% (note 5)

[a] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonized approach.*

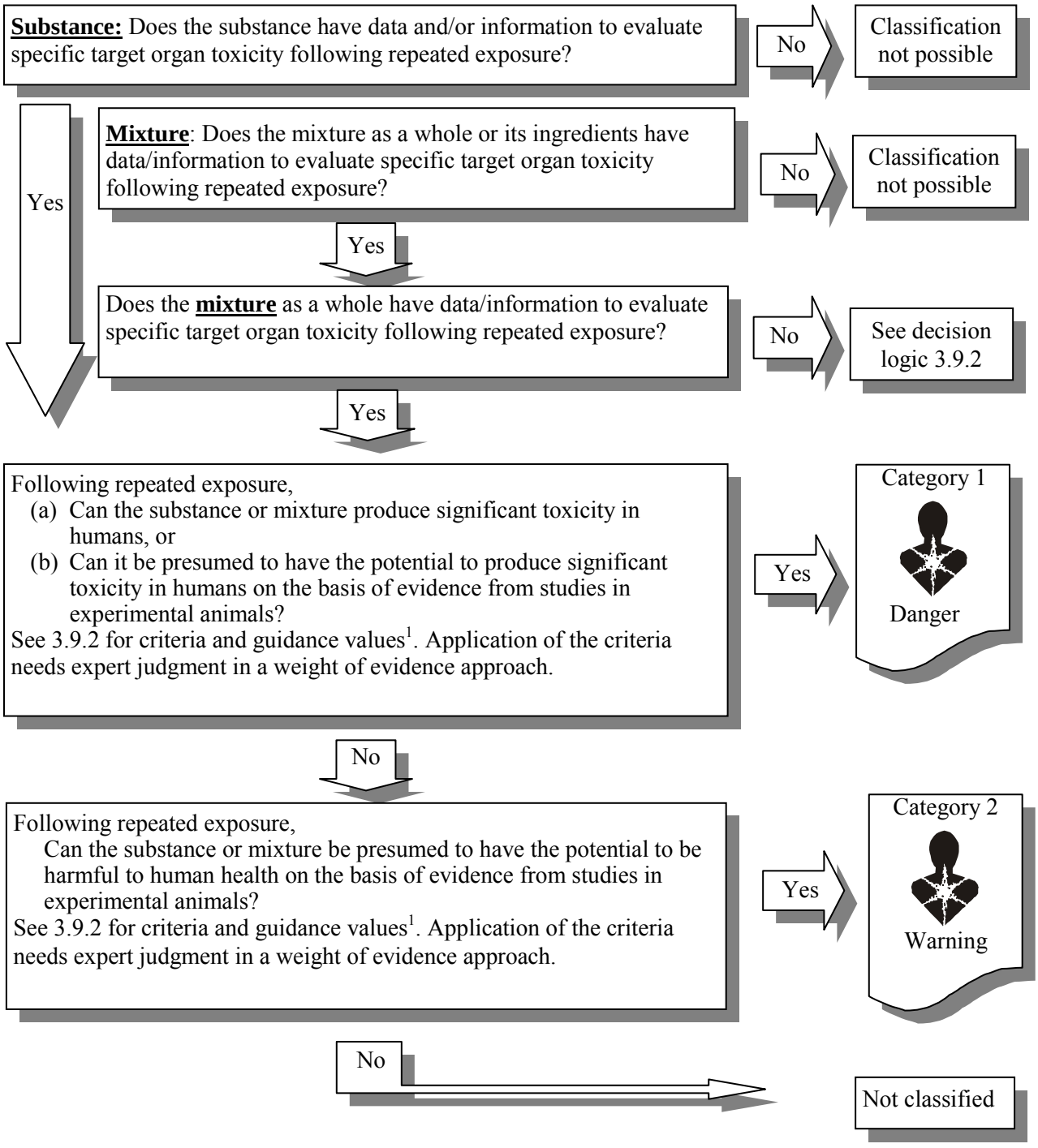
STOT-Repeated exposure

The procedure for classification of substances and mixtures is summarized in decision logics 3.9.1 and 3.9.2

3.9.5 Decision logic for specific target organ toxicity following repeated exposure

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

3.9.5.1 *Decision logic 3.9.1*



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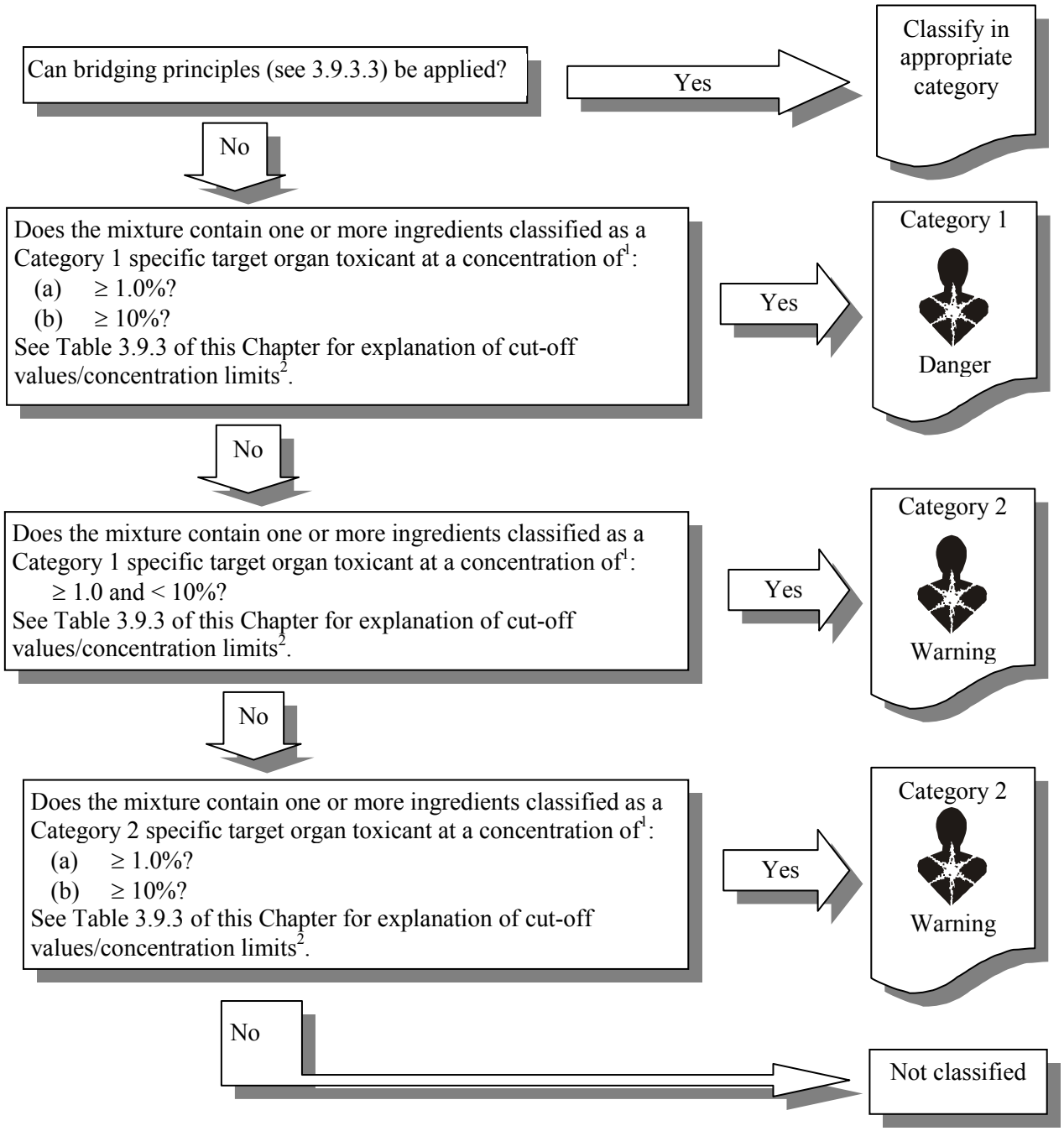
[1] *See 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2 "The use of cut-off values/concentration limits".*

3.9.5.2 ***Decision logic 3.9.2***



[1] *See 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2 "The use of cut-off values/concentration limits".*

[2] *See 3.9.3.4 and 3.9.4 and Table 3.9.3 for explanation and guidance.*

Aspiration hazard

Aspiration hazard refers to severe acute effects such as chemical pneumonia, pulmonary injury or death occurring after aspiration of a substance or mixture.

Aspiration of a substance or mixture can occur as it is vomited following ingestion. This may have consequences for labelling, particularly where, due to acute toxicity, a recommendation may be considered to induce vomiting after ingestion. However, if the substance/mixture also presents an aspiration toxicity hazard, the recommendation to induce vomiting may need to be modified.

Aspiration hazard

Table 3.10.1: Hazard categories for aspiration toxicity

Categories	Criteria
Category 1: Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard	A substance is classified in Category 1: (a) Based on reliable and good quality human evidence (see note 1); or (b) If it is a hydrocarbon and has a kinematic viscosity $\leq$ 20.5 mm^2/s, measured at 40° C.
Category 2: Chemicals which cause concern owing to the presumption that they cause human aspiration toxicity hazard	On the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point, and volatility, substances, other than those classified in Category 1, which have a kinematic viscosity $\leq$ 14 mm^2/s, measured at 40° C (see note 2).

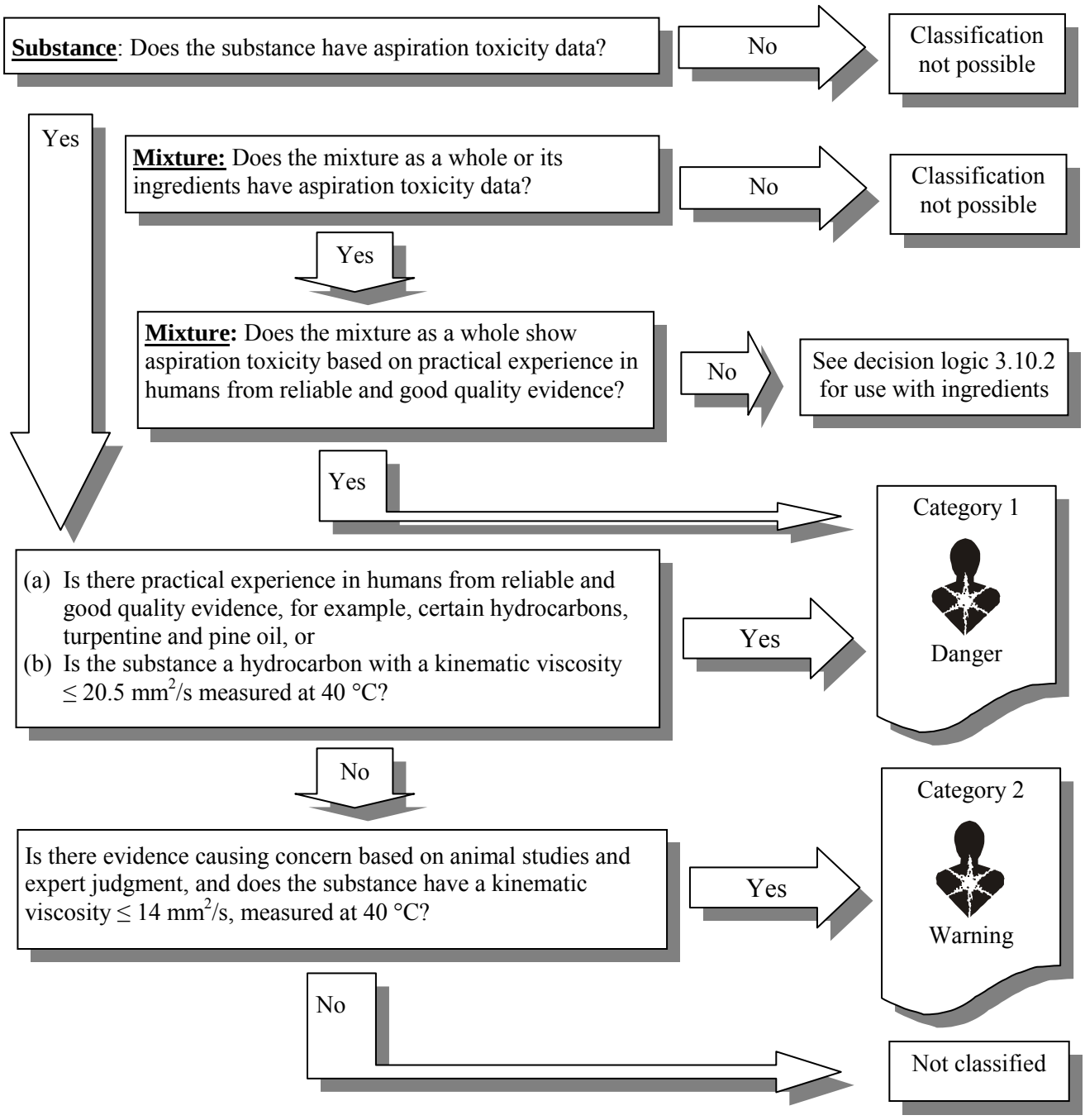
NOTE 1: *Examples of substances included in Category 1 are certain hydrocarbons, turpentine and pine oil.*

NOTE 2: *Taking this into account, some authorities would consider the following to be included in this Category: n-primary alcohols with a composition of at least 3 carbon atoms but not more than 13; isobutyl alcohol, and ketones with a composition of no more than 13 carbon atoms.*

Aspiration hazard

The procedure for classification of substances and mixtures is summarized in decision logics 3.10.1 and 3.10.2

3.10.5.1 ***Decision logic 3.10.1***



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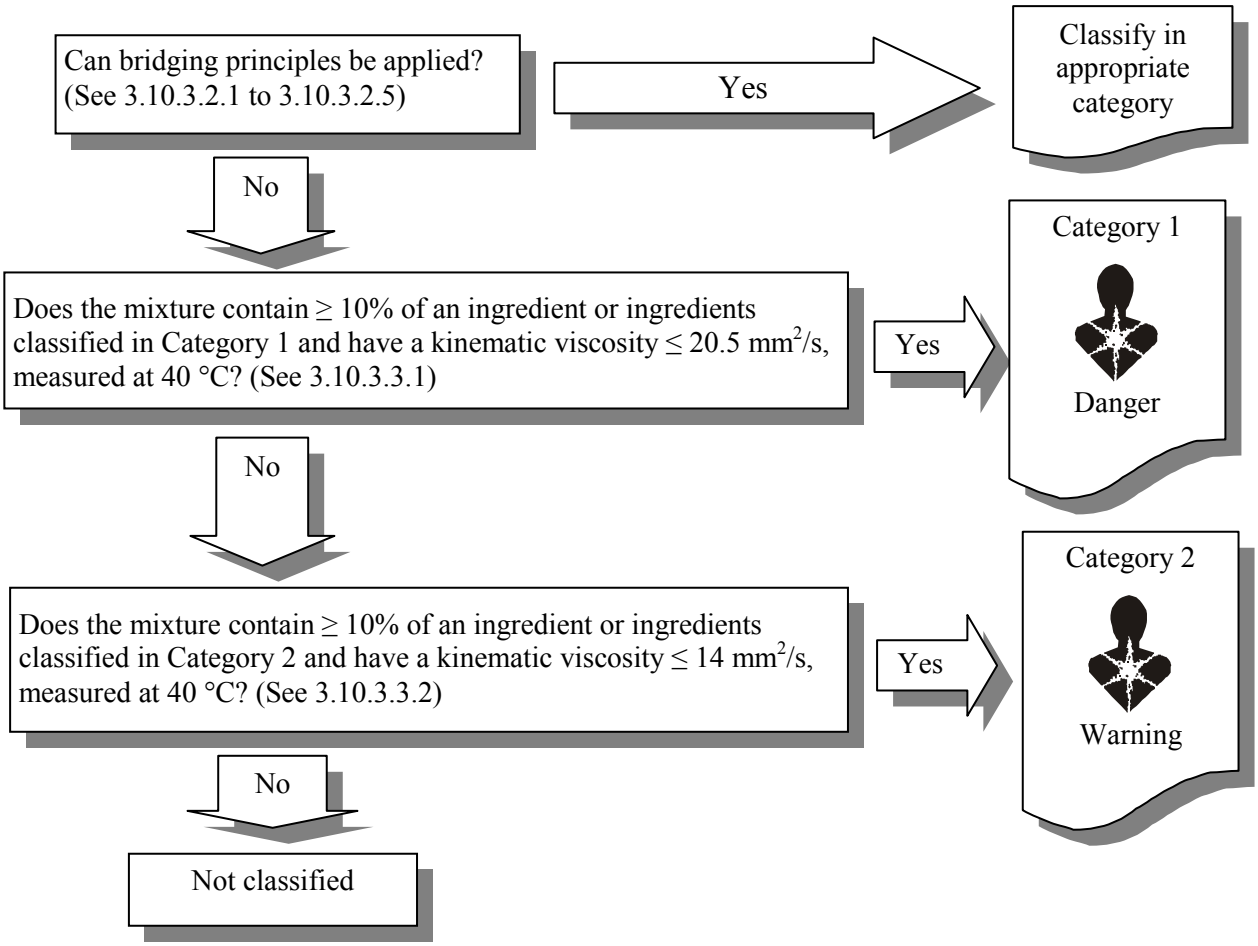
3.10.5.2 ***Decision logic 3.10.2***



Hazardous to the aquatic environment

The basic elements for use within the harmonized system are:

(a) acute aquatic toxicity;

(b) chronic aquatic toxicity;

(c) potential for or actual bioaccumulation; and

(d) degradation (biotic or abiotic) for organic chemicals.

While data from internationally harmonized test methods are preferred, in practice, data from national methods may also be used where they are considered as equivalent.

In general, it has been agreed that freshwater and marine species toxicity data can be considered as equivalent data and are preferably to be derived using OECD Test Guidelines or equivalent according to the principles of Good Laboratory Practices. Where such data are not available classification should be based on the best available data.

Hazardous to the aquatic environment

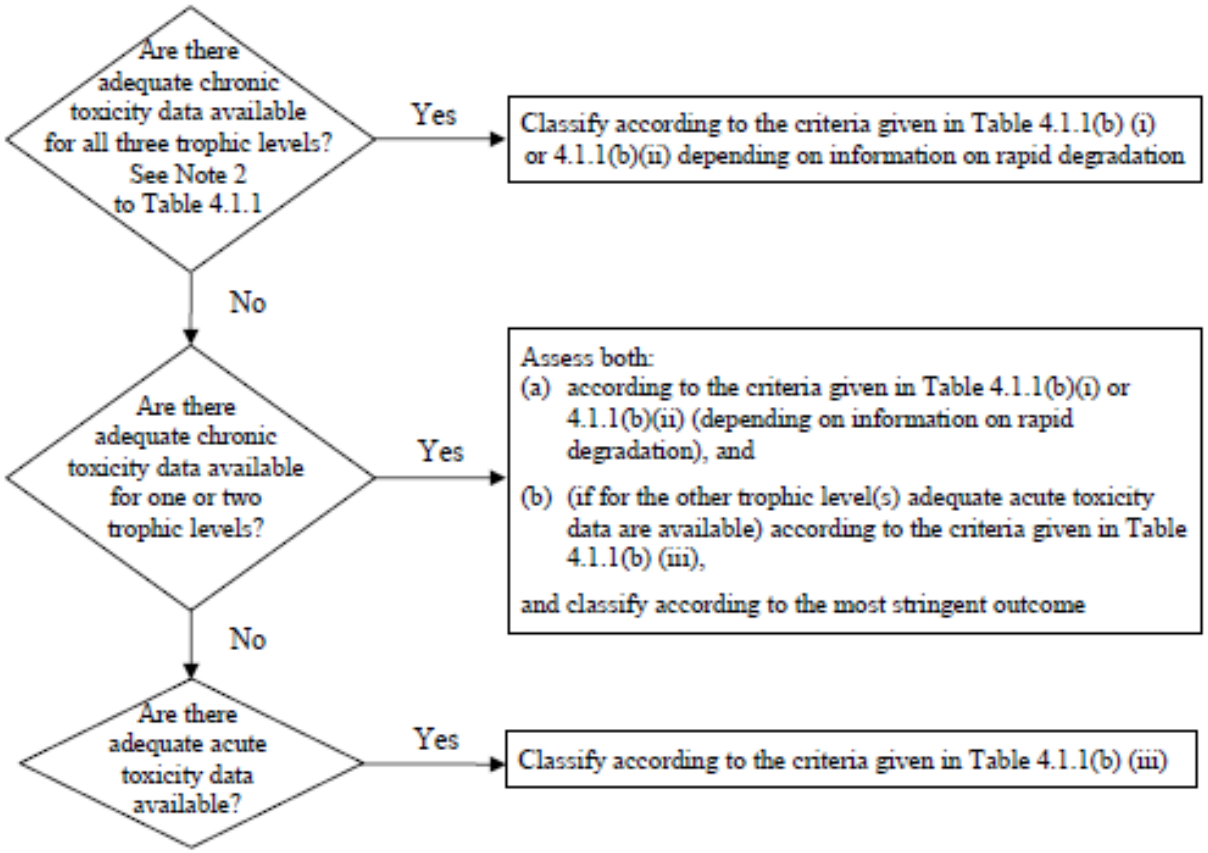
The core part of the harmonized classification system for substances consists of three acute classification categories and three chronic classification categories (see Table 4.1.1 (a) and (b)).

The acute and the chronic classification categories are applied independently. The criteria for classification of a substance in categories Acute 1 to 3 are defined on the basis of the acute toxicity data only (EC_{50} or LC_{50}).

The criteria for classification of a substance into categories Chronic 1 to 3 follow a tiered approach where the first step is to see if available information on chronic toxicity merits long-term hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute toxicity data and environmental fate data (degradability and bioaccumulation data) (see Fig.4.1.1).

Hazardous to the aquatic environment

Figure 4.1.1: Categories for substances long-term (chronic) hazardous to the aquatic environment



Hazardous to the aquatic environment

Table 4.1.1: Categories for substances hazardous to the aquatic environment *(Note 1)*

(a) Short-term (acute) aquatic hazard

Category Acute 1: *(Note 2)*

96 hr LC_{50} (for fish)	≤ 1 mg/l and/or
48 hr EC_{50} (for crustacea)	≤ 1 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤ 1 mg/l *(Note 3)*

Category Acute 1 may be subdivided for some regulatory systems to include a lower band at $L(E)C_{50} \leq 0.1$ mg/l

Category Acute 2:

96 hr LC_{50} (for fish)	>1 but ≤ 10 mg/l and/or
48 hr EC_{50} (for crustacea)	>1 but ≤ 10 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 but ≤ 10 mg/l *(Note 3)*

Category Acute 3:

96 hr LC_{50} (for fish)	>10 but ≤ 100 mg/l and/or
48 hr EC_{50} (for crustacea)	>10 but ≤ 100 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 but ≤ 100 mg/l *(Note 3)*

Some regulatory systems may extend this range beyond an $L(E)C_{50}$ of 100 mg/l through the introduction of another category.

Hazardous to the aquatic environment

(b) **Long-term (chronic) aquatic hazard** *(see also figure 4.1.1)*

(i) **Non-rapidly degradable substances (Note 4) for which there are adequate chronic toxicity data available**

Category Chronic 1: *(Note 2)*	
Chronic NOEC or EC_x (for fish)	≤ 0.1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.1 mg/l
Category Chronic 2:	
Chronic NOEC or EC_x (for fish)	≤ 1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤ 1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 1 mg/l

(ii) **Rapidly degradable substances for which there are adequate chronic toxicity data available**

Category Chronic 1: *(Note 2)*	
Chronic NOEC or EC_x (for fish)	≤ 0.01 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.01 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.01 mg/l
Category Chronic 2:	
Chronic NOEC or EC_x (for fish)	≤ 0.1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.1 mg/l
Category Chronic 3:	
Chronic NOEC or EC_x (for fish)	≤ 1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤ 1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 1 mg/l

Hazardous to the aquatic environment

(iii) Substances for which adequate chronic toxicity data are not available

Category Chronic 1: *(Note 2)*

96 hr LC_{50} (for fish)	≤ 1 mg/l and/or
48 hr EC_{50} (for crustacea)	≤ 1 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤ 1 mg/l *(Note 3)*

and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log K_{ow} ≥ 4). *(Notes 4 and 5)*

Category Chronic 2:

96 hr LC_{50} (for fish)	> 1 but ≤ 10 mg/l and/or
48 hr EC_{50} (for crustacea)	> 1 but ≤ 10 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	> 1 but ≤ 10 mg/l *(Note 3)*

and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log K_{ow} ≥ 4). *(Notes 4 and 5)*

Category Chronic 3:

96 hr LC_{50} (for fish)	> 10 but ≤ 100 mg/l and/or
48 hr EC_{50} (for crustacea)	> 10 but ≤ 100 mg/l and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	> 10 but ≤ 100 mg/l *(Note 3)*

and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log K_{ow} ≥ 4). *(Notes 4 and 5).*

Hazardous to the aquatic environment

NOTE 1: *The organisms fish, crustacea and algae are tested as surrogate species covering a range of trophic levels and taxa, and the test methods are highly standardized. Data on other organisms may also be considered, however, provided they represent equivalent species and test endpoints.*

NOTE 2: *When classifying substances as Acute 1 and/or Chronic 1 it is necessary at the same time to indicate an appropriate M factor (see 4.1.3.5.5.5) to apply the summation method.*

NOTE 3: *Where the algal toxicity ErC_{50} [= EC_{50} (growth rate)] falls more than 100 times below the next most sensitive species and results in a classification based solely on this effect, consideration should be given to whether this toxicity is representative of the toxicity to aquatic plants. Where it can be shown that this is not the case, professional judgment should be used in deciding if classification should be applied. Classification should be based on the ErC_{50}. In circumstances where the basis of the EC_{50} is not specified and no ErC_{50} is recorded, classification should be based on the lowest EC_{50} available.*

NOTE 4: *Lack of rapid degradability is based on either a lack of ready biodegradability or other evidence of lack of rapid degradation. When no useful data on degradability are available, either experimentally determined or estimated data, the substance should be regarded as not rapidly degradable.*

NOTE 5: *Potential to bioaccumulate, based on an experimentally derived BCF $\geq$ 500 or, if absent, a log $K_{ow} \geq 4$, provided log K_{ow} is an appropriate descriptor for the bioaccumulation potential of the substance. Measured log K_{ow} values take precedence over estimated values and measured BCF values take precedence over log K_{ow} values.*

Hazardous to the aquatic environment

(c) **"Safety net" classification**

Category Chronic 4:

Poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have a log $K_{ow} \geq 4$, indicating a potential to bioaccumulate, will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence would include an experimentally determined BCF < 500, or a chronic toxicity NOECs > 1 mg/l, or evidence of rapid degradation in the environment.

Hazardous to the aquatic environment

Table 4.1.2: Classification scheme for substances hazardous to the aquatic environment

Classification categories			
Short-term (acute) hazard (*Note 1*)	**Long-term (chronic) hazard** (*Note 2*)		
	Adequate chronic toxicity data available		**Adequate chronic toxicity data not available** (*Note 1*)
	Non-rapidly degradable substances (*Note 3*)	**Rapidly degradable substances** (*Note 3*)	
Category: Acute 1 $L(E)C_{50} \leq 1.00$	**Category: Chronic 1** NOEC or $EC_x \leq 0.1$	**Category: Chronic 1** NOEC or $EC_x \leq 0.01$	**Category: Chronic 1** $L(E)C_{50} \leq 1.00$ and lack of rapid degradability and/or BCF ≥ 500 or, if absent log $K_{ow} \geq 4$
Category: Acute 2 $1.00 < L(E)C_{50} \leq 10.0$	**Category: Chronic 2** $0.1 <$ NOEC or $EC_x \leq 1$	**Category: Chronic 2** $0.01 <$ NOEC or $EC_x \leq 0.1$	**Category: Chronic 2** $1.00 < L(E)C_{50} \leq 10.0$ and lack of rapid degradability and/or BCF ≥ 500 or, if absent log $K_{ow} \geq 4$
Category: Acute 3 $10.0 < L(E)C_{50} \leq 100$		**Category: Chronic 3** $0.1 <$ NOEC or $EC_x \leq 1$	**Category: Chronic 3** $10.0 < L(E)C_{50} \leq 100$ and lack of rapid degradability and/or BCF ≥ 500 or, if absent log $K_{ow} \geq 4$
	Category: Chronic 4 (*Note 4*) Example: (*Note 5*) No acute toxicity and lack of rapid degradability and BCF ≥ 500 or, if absent log Kow ≥ 4, unless NOECs > 1 mg/l		

Hazardous to the aquatic environment

NOTE 1: *Acute toxicity band based on L(E)C_{50} values in mg/l for fish, crustacea and/or algae or other aquatic plants (or QSAR estimation if no experimental data).*

NOTE 2: *Substances are classified in the various chronic categories unless there are adequate chronic toxicity data available for all three trophic levels above the water solubility or above 1 mg/l. ("Adequate" means that the data sufficiently cover the endpoint of concern. Generally this would mean measured test data, but in order to avoid unnecessary testing it can, on a case-by-case basis, also be estimated data, e.g. (Q)SAR, or for obvious cases expert judgment).*

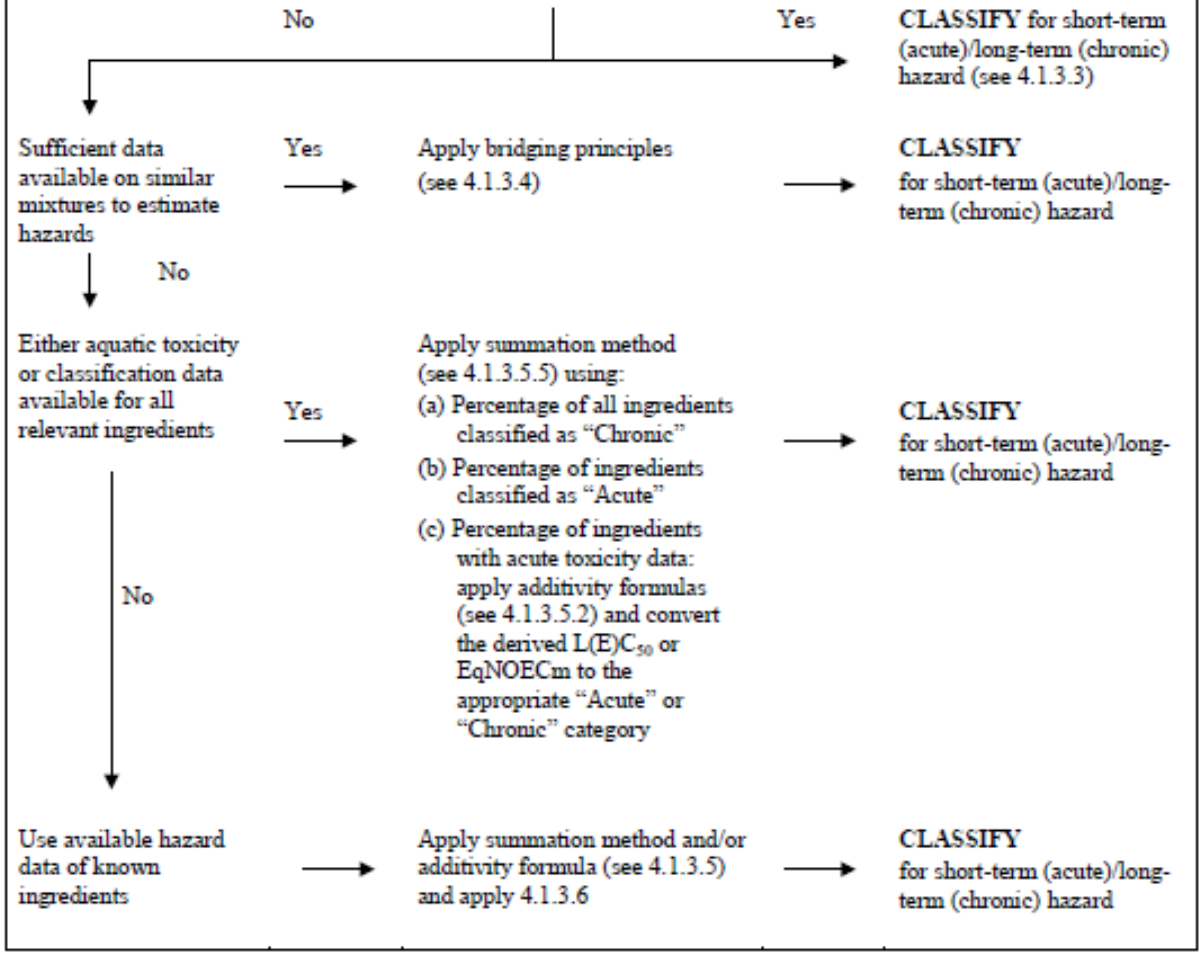
NOTE 3: *Chronic toxicity band based on NOEC or equivalent EC_x values in mg/l for fish or crustacea or other recognized measures for chronic toxicity.*

NOTE 4: *The system also introduces a "safety net" classification (referred to as category Chronic 4) for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern.*

NOTE 5: *For poorly soluble substances for which no acute toxicity has been demonstrated at the solubility limit, and are both not rapidly degraded and have a potential to bioaccumulate, this category should apply unless it can be demonstrated that the substance does not require classification for aquatic long-term (chronic) hazards.*

Hazardous to the aquatic environment

Figure 4.1.2: Tiered approach to classification of mixtures for short-term (acute) and long-term (chronic) aquatic environmental hazards



Hazardous to the aquatic environment

Table 4.1.3: Classification of a mixture for short-term (acute) hazards based on summation of the concentrations of classified ingredients

Sum of the concentrations (in %) of ingredients classified as:		Mixture is classified as:
Acute 1 × M[a]	≥ 25%	Acute 1
(M × 10 × Acute 1) + Acute 2	≥ 25%	Acute 2
(M × 100 × Acute 1) + (10 × Acute 2) + Acute 3	≥ 25%	Acute 3

[a] *For explanation of the M factor, see 4.1.3.5.5.5.*

Table 4.1.4: Classification of a mixture for long-term (chronic) hazards based on summation of the concentrations of classified ingredients

Sum of the concentrations (in %) of ingredients classified as:		Mixture is classified as:
Chronic 1 × M[a]	≥ 25%	Chronic 1
(M × 10 × Chronic 1) + Chronic 2	≥ 25%	Chronic 2
(M × 100 × Chronic 1) + (10 × Chronic 2)+ Chronic 3	≥ 25%	Chronic 3
Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4	≥ 25%	Chronic 4

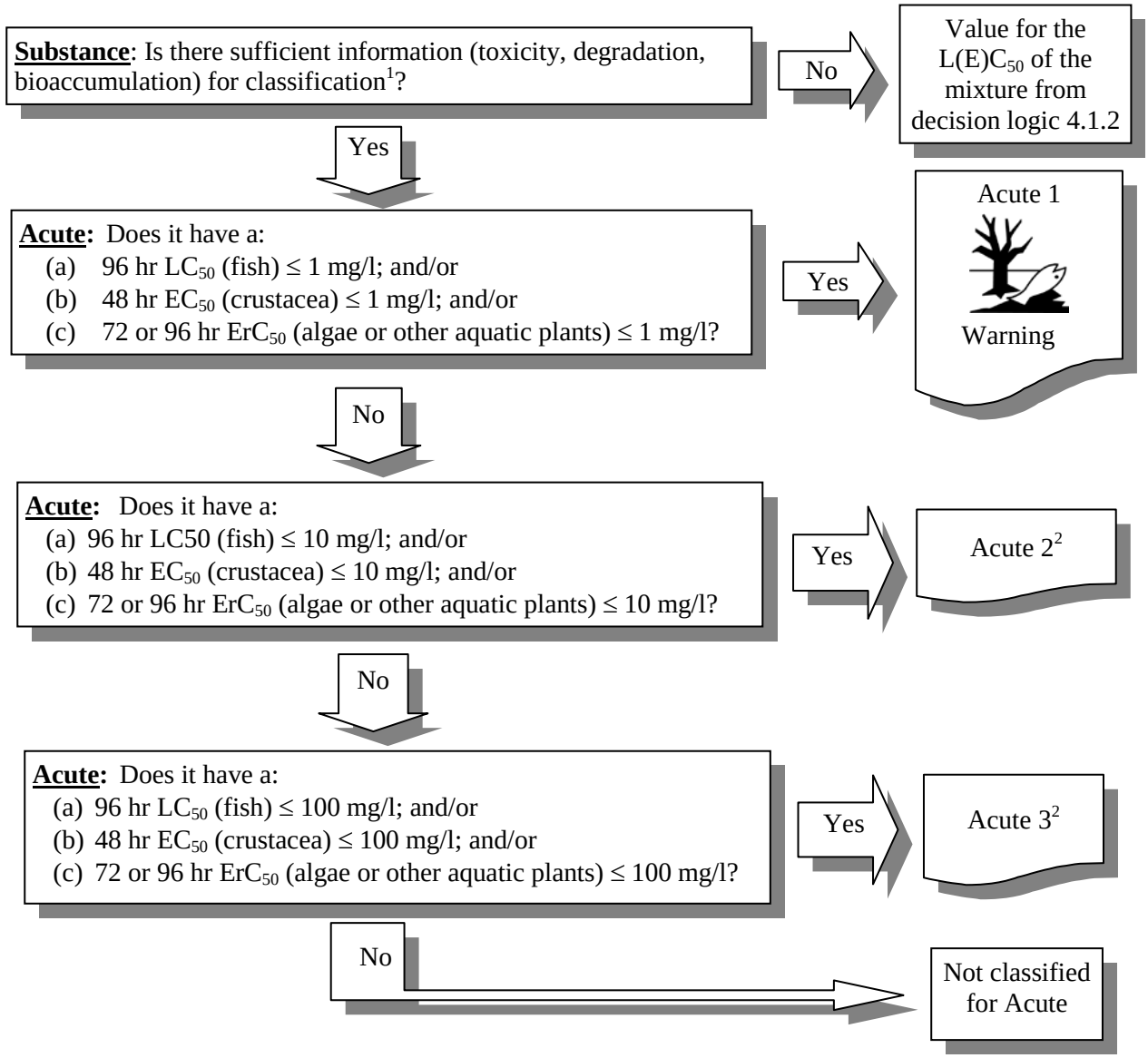
[a] *For explanation of the M factor, see 4.1.3.5.5.5.*

Hazardous to the aquatic environment

The procedure for classification of substances and mixtures is summarized in decision logics 4.1.1 to 4.1.4

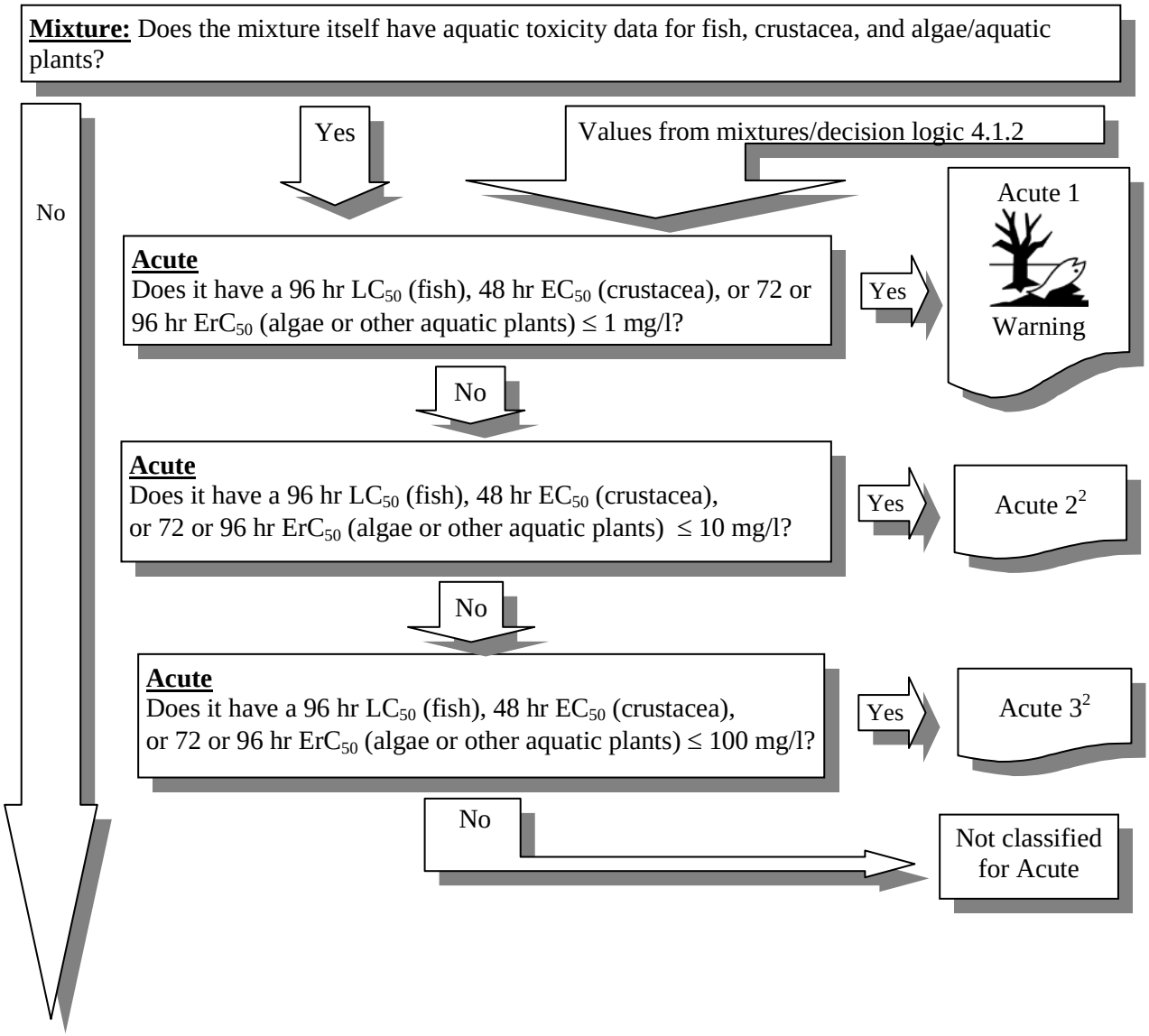
4.1.5.1 *Short-term (acute) aquatic hazard classification*

4.1.5.1.1 *Decision logic 4.1.1 for substances and mixtures hazardous to the aquatic environment*

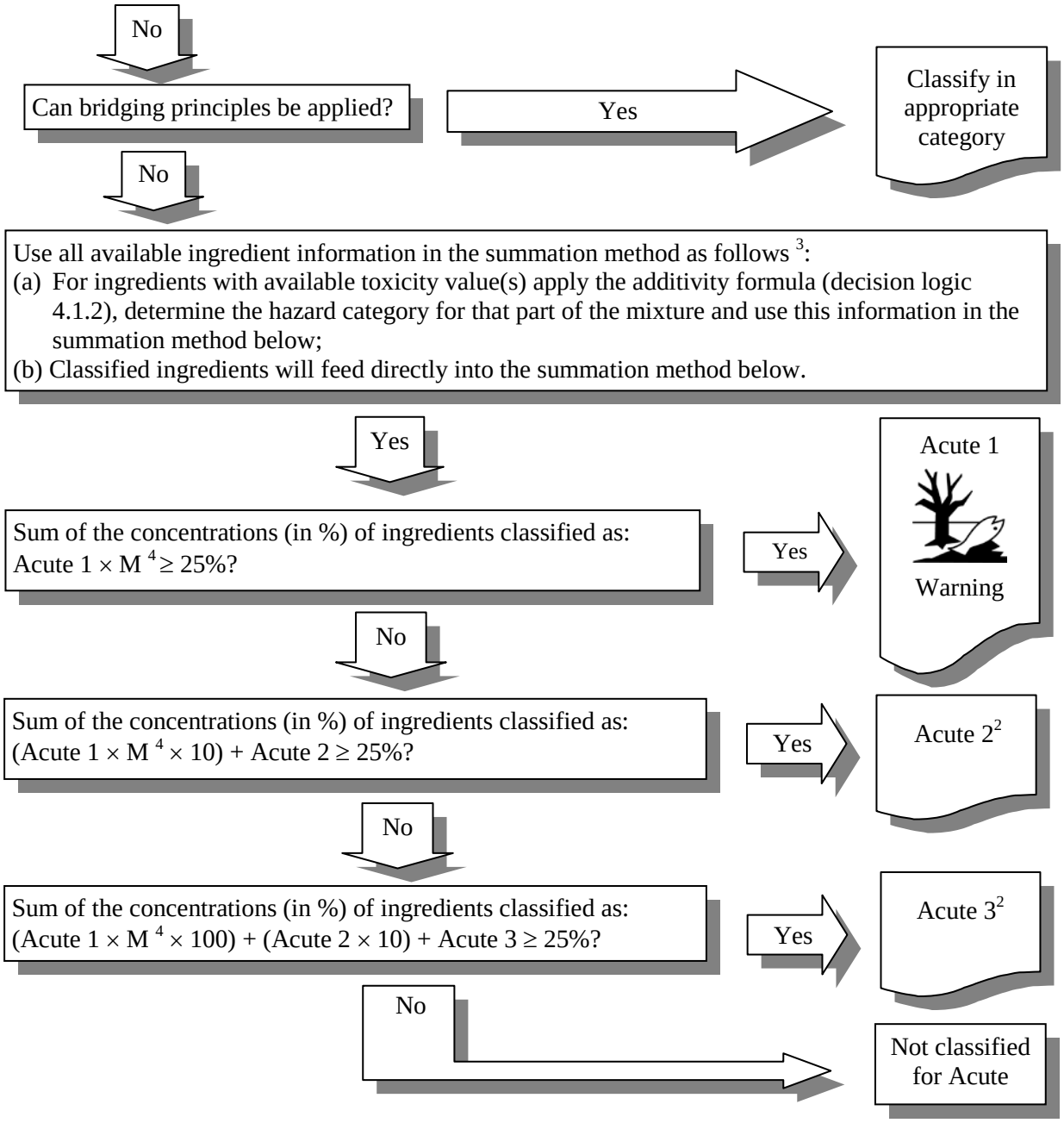


[1] *Classification can be based on either measured data and/or calculated data (see 4.1.2.13 and Annex 9) and/or analogy decisions (see A9.6.4.5 in Annex 9).*

[2] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*



[2] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*



[2] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*

[3] *If not all ingredients have information, include the statement "x % of the mixture consists of ingredients(s) of unknown hazards to the aquatic environment" on the label. The competent authority can decide to specify that the additional statement 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 short-term (acute) classification may be made solely on the basis of the additivity formula.*

[4] *For explanation of M factor see 4.1.3.5.5.5.*

4.1.5.1.2 *Decision logic 4.1.2 for mixtures (additivity formula)*

Apply the additivity formula:

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

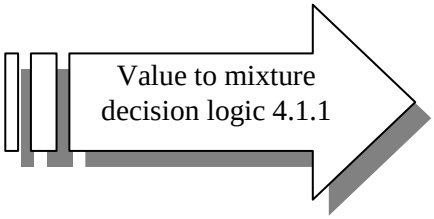
where:

C_i = concentration of ingredient i (weight percentage)

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

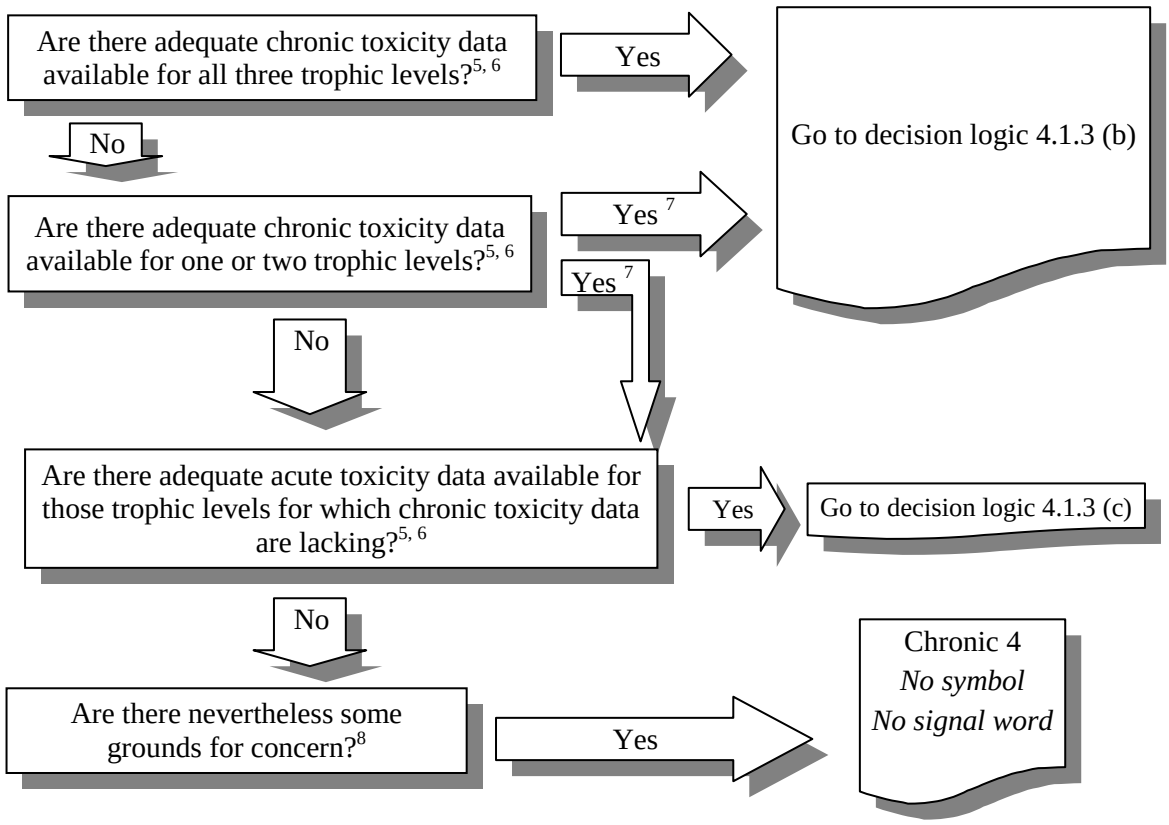
n = number of ingredients, and i is running from 1 to n

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



4.1.5.2 *Long-term (chronic) aquatic hazard classification*

4.1.5.2.1 *Decision logic 4.1.3 (a) for substances*



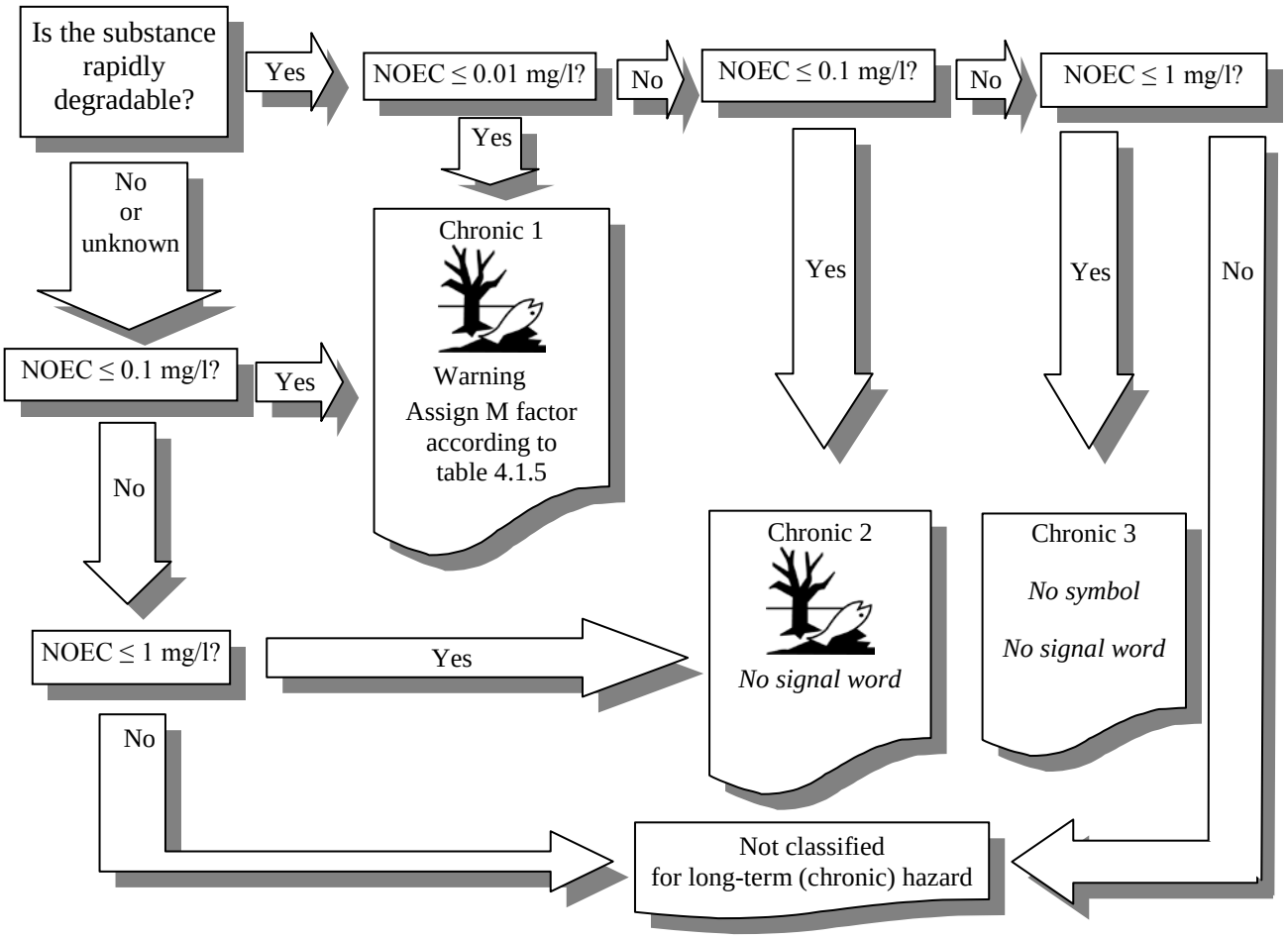
[5] *Data are preferably to be derived using internationally harmonized test methods (e.g. OECD Test Guidelines or equivalent) according to the principles of good laboratory practices (GLP), but data from other test methods such as national methods may also be used where they are considered as equivalent (see 4.1.1.2.2 and A9.3.2 of Annex 9).*

[6] *See Figure 4.1.1.*

[7] *Follow the flowchart in both ways and choose the most stringent classification outcome.*

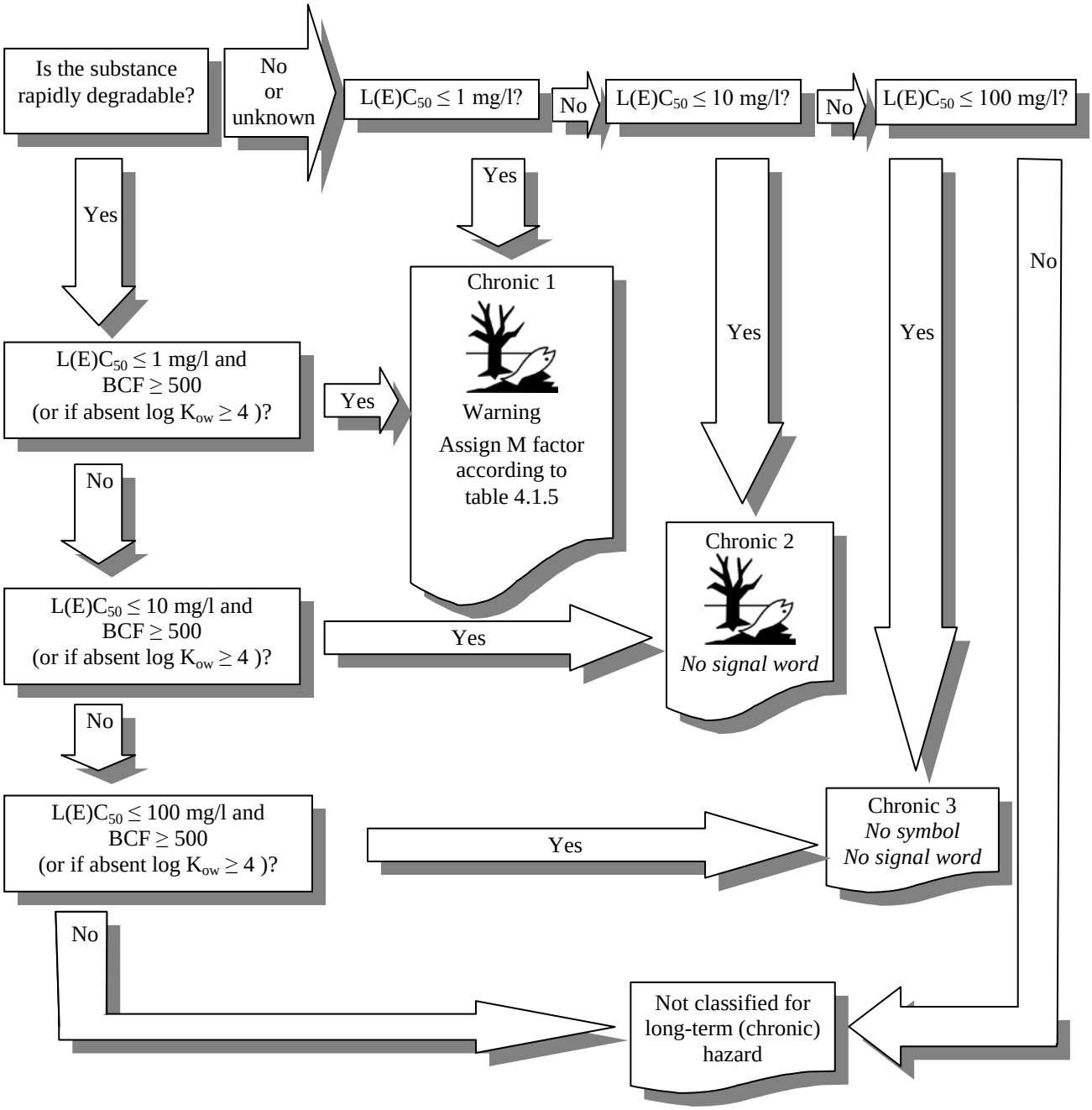
[8] *Note that the system also introduces a "safety net" classification (referred to as Category: Chronic 4) for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern.*

4.1.5.2.2 *Decision logic 4.1.3 (b) for substances (when adequate chronic toxicity data are available for all three trophic levels)*[5]



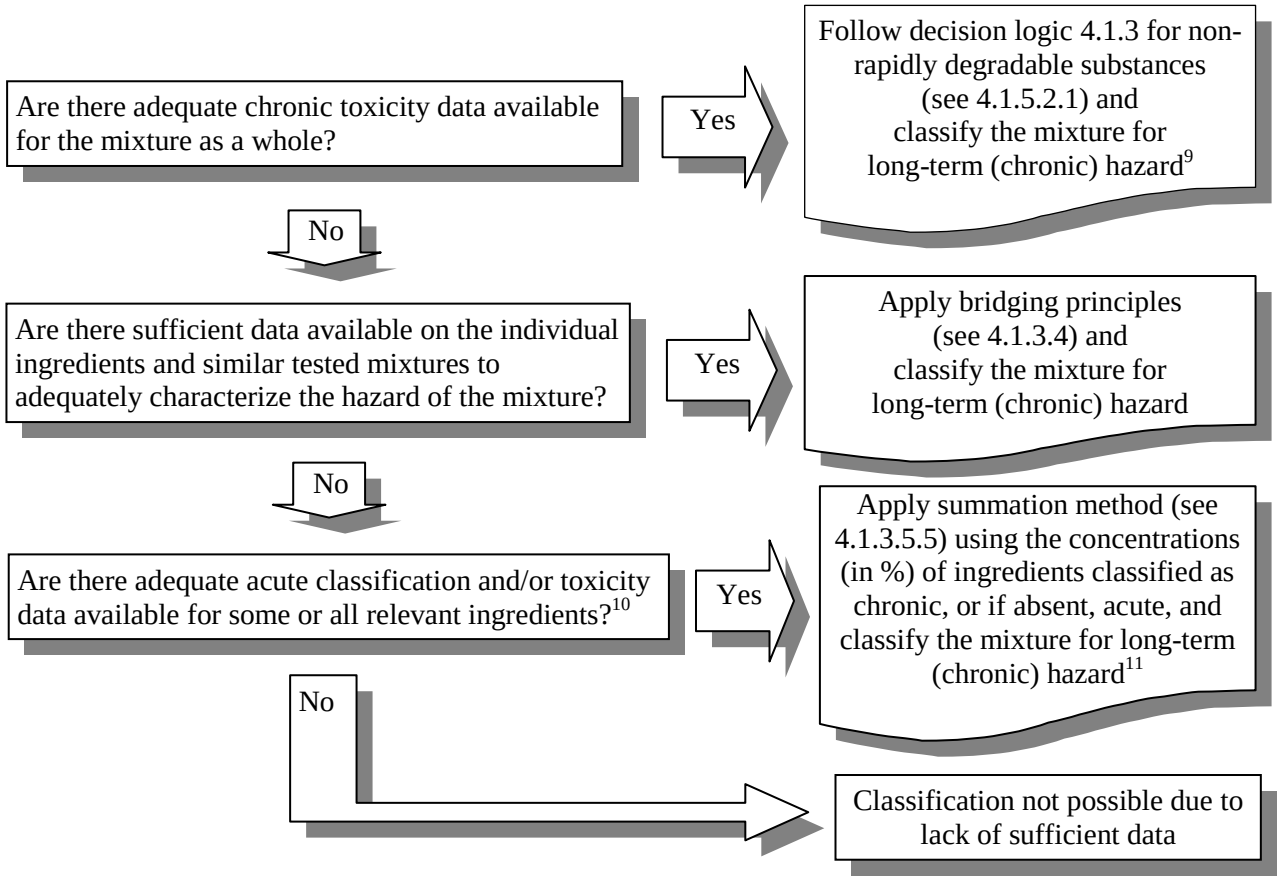
[5] *Data are preferably to be derived using internationally harmonized test methods (e.g. OECD Test Guidelines or equivalent) according to the principles of good laboratory practices (GLP), but data from other test methods such as national methods may also be used where they are considered as equivalent (see 4.1.1.2.2 and A9.3.2 of Annex 9).*

4.1.5.2.3 *Decision logic 4.1.3 (c) for substances (when adequate chronic toxicity data not are available for all three trophic levels)*[5]



[5] *Data are preferably to be derived using internationally harmonized test methods (e.g. OECD Test Guidelines or equivalent) according to the principles of good laboratory practices (GLP), but data from other test methods such as national methods may also be used where they are considered as equivalent (see 4.1.1.2.2 and A9.3.2 of Annex 9).*

4.1.5.2.4 *Decision logic 4.1.4 for mixtures*



[9] *Degradability and bioaccumulation tests for mixtures are not used as they are usually difficult to interpret, and such tests may be meaningful only for single substances. The mixture is therefore by default regarded as non-rapidly degradable. However, if the available information allows the conclusion that all relevant ingredients of the mixture are rapidly degradable the mixture can, for classification purposes, be regarded as rapidly degradable.*

[10] *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: "× % of the mixture consists of ingredient(s) of unknown hazards to the aquatic environment". The competent authority can decide to specify that the additional statement 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.*

[11] *When adequate toxicity data are available for more than one ingredient in the mixture, the combined toxicity of those ingredients may be calculated using the additivity formulas (a) or (b) in 4.1.3.5.2, depending on the nature of the toxicity data. The calculated toxicity may be used to assign that portion of the mixture a short-term (acute) or long-term (chronic) hazard category which is then subsequently used in applying the summation method. (It is preferable to calculate the toxicity of this part of the mixture using for each ingredient a toxicity value that relate to the same taxonomic group (e.g. fish, crustacea or algae) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three groups) (see 4.1.3.5.3)).*

Hazardous to the ozone layer

Ozone Depleting Potential (ODP) is an integrative quantity, distinct for each halocarbon source species, that represents the extent of ozone depletion in the stratosphere expected from the halocarbon on a mass-for-mass basis relative to CFC-11.

The formal definition of ODP is the ratio of integrated perturbations to total ozone, for a differential mass emission of a particular compound relative to an equal emission of CFC-11

Hazardous to the ozone layer

Table 4.2.1: Criteria for substances and mixtures hazardous to the ozone layer

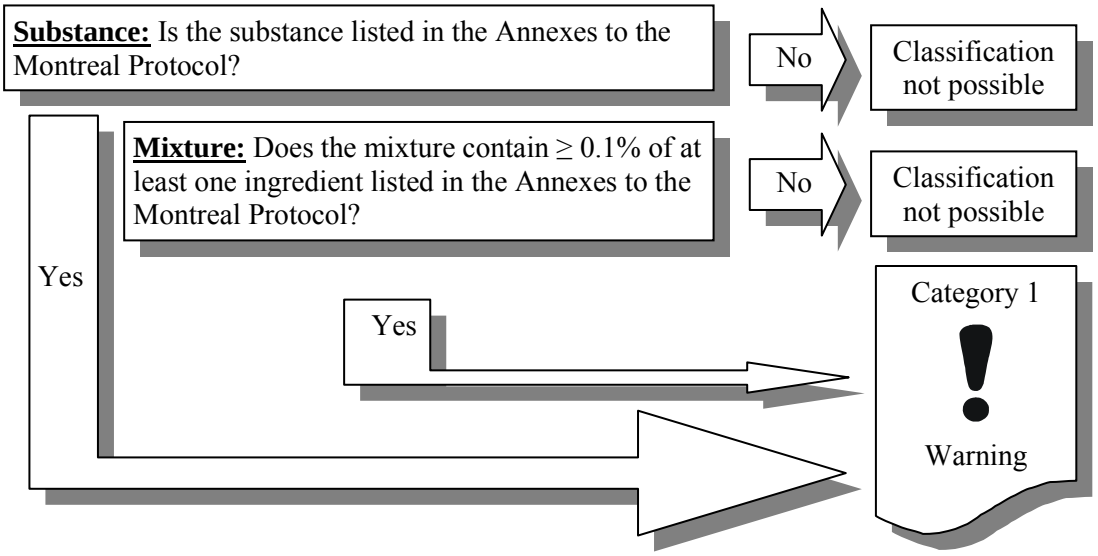
Category	Criteria
1	Any of the controlled substances listed in Annexes to the Montreal Protocol; or Any mixture containing at least one ingredient listed in the Annexes to the Montreal Protocol, at a concentration $\geq 0.1\%$

The procedure for classification of substances and mixtures is summarized in decision logic 4.2.1

4.2.4 Decision logic for substances and mixtures hazardous to the ozone layer

The decision logic which follows is not part of the harmonized classification system but is 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 logic.

Decision logic 4.2.1



Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

End of health and environmental hazards classification criteria for substances and mixtures