PART 3

HEALTH HAZARDS

CHAPTER 3.1

ACUTE TOXICITY

3.1.1 Definition

Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

3.1.2 Classification criteria for substances

3.1.2.1 Chemicals 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 the table below. 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 hazard categories and acute toxicity estimate (ATE) values defining the respective categories

Exposure route	**Category 1**	**Category 2**	**Category 3**	**Category 4**	**Category 5**
Oral (mg/kg bodyweight) *see: Note (a)*	5	50	300	2000	5000
Dermal (mg/kg bodyweight) *see: Note (a)*	50	200	1000	2000	
Gases (ppmV) *see: Note (a)* *Note (b)*	100	500	2500	20000	*See detailed criteria in Note (f)*
Vapours (mg/l) *see: Note (a)* *Note (b)* *Note (c)* *Note (d)*	0.5	2.0	10	20	
Dusts and Mists (mg/l) *see: Note (a)* *Note (b)* *Note (e)*	0.05	0.5	1.0	5	

***Note**: Gases concentration 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 or ingredient in a mixture is derived using:

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

(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;

(b) 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;

(c) 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);

(d) For some chemicals the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other chemicals 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) Dust: solid particles of a substance or mixture suspended in a gas (usually air);

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

(iii) Vapour: 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 < 1 to about 100 μm;

(e) 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;

(f) 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.

3.1.2.2 The harmonized classification system for acute toxicity has been developed in such a way as to accommodate the needs of existing systems. A basic principle set by the IOMC Coordinating Group/Harmonization of Chemical Classification Systems (CG/HCCS) is that "harmonization means establishing a common and coherent basis for chemical hazard classification and communication from which the appropriate elements relevant to means of transport, consumer, worker and environment protection can be selected". To that end, five categories have been included in the acute toxicity scheme.

3.1.2.3 The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. Test data already generated for the classification of chemicals under existing systems should be accepted when reclassifying these chemicals under the harmonized system. When experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.

3.1.2.4 Category 1, the highest toxicity category, has cut-off values (see Table 3.1.1) currently used primarily by the transport sector for classification for packing groups.

3.1.2.5 Category 5 is for chemicals which are of relatively low acute toxicity but which, under certain circumstances, may pose a hazard to vulnerable populations. Criteria for identifying substances in Category 5 are provided in addition to the table. These substances are anticipated to have an oral or dermal LD_{50} value in the range 2000 - 5000 mg/kg bodyweight and equivalent doses for inhalation exposure[1]. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance to the protection of human health.

3.1.2.6 ***Specific considerations for inhalation toxicity***

3.1.2.6.1 Values for *inhalation toxicity* are based on 4 hours tests in laboratory animals. When experimental values are taken from tests using a 1 hour exposure, they can be converted to a 4 hour equivalent by dividing the 1 hour value by a factor of 2 for gases and vapours and 4 for dusts and mists.

3.1.2.6.2 Units for inhalation toxicity are a function of the form of the inhaled material. Values for dusts and mists are expressed in mg/l. Values for gases are expressed in ppmV. Acknowledging the difficulties in testing vapours, some of which consist of mixtures of liquid and vapour phases, the table provides values in units of mg/l. However, for those vapours which are near the gaseous phase, classification should be based on ppmV. As inhalation test methods are updated, the OECD and other test guideline programs will need to define vapours in relation to mists for greater clarity.

3.1.2.6.3 Vapour inhalation values are intended for use in classification of acute toxicity for all sectors. It is also recognized that the saturated vapour concentration of a chemical is used by the transport sector as an additional element in classifying chemicals for packing groups.

3.1.2.6.4 Of particular importance is the use of well articulated values in the high toxicity categories for dusts and mists. Inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/l. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats. The cut-off values in the table for dusts and mists allow clear distinctions to be made for materials with a wide range of toxicities measured under varying test conditions. The values for dusts and mists should be reviewed in the future to adapt to any future changes in OECD or other test guidelines with respect to technical limitations in generating, maintaining, and measuring dust and mist concentrations in respirable form.

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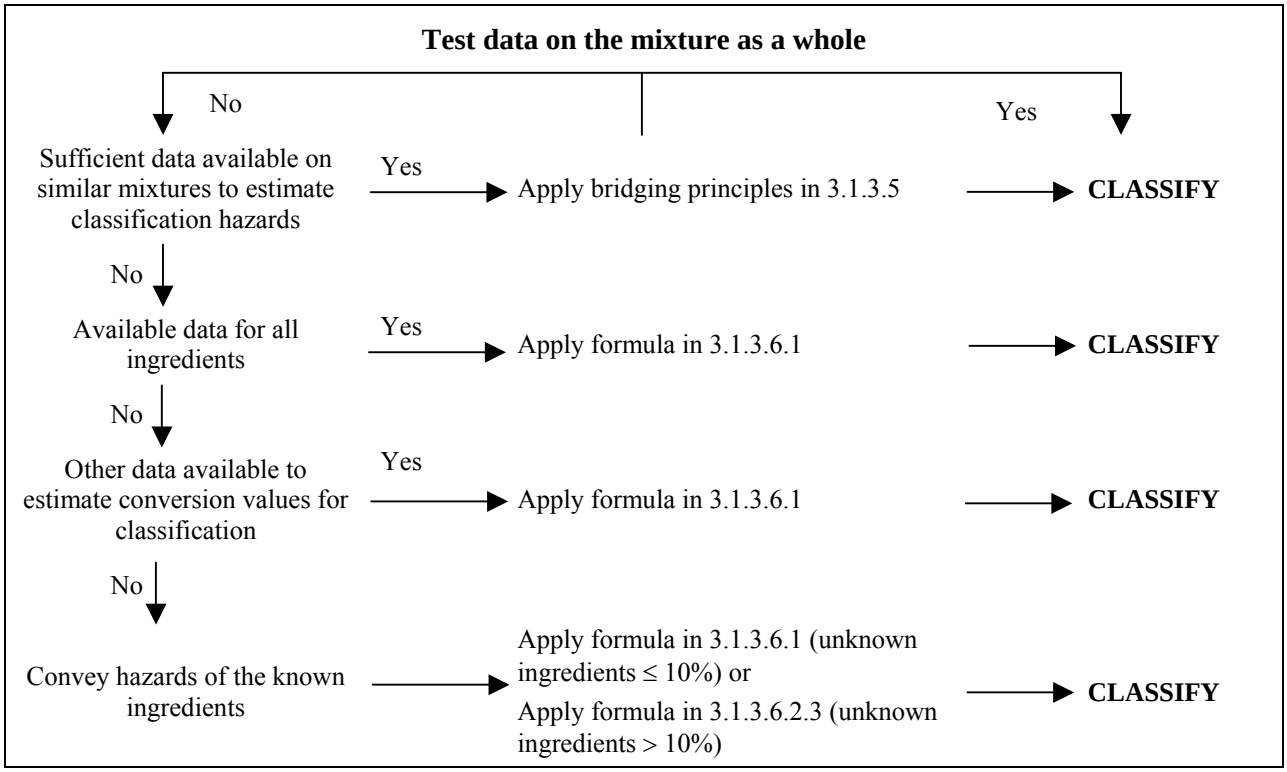
[1] *Guidance on Category 5 inhalation values: The OECD Task Force on Harmonization of Classification and Labelling (HCL) did not include numerical values in Table 3.1.1 above for acute inhalation toxicity Category 5 but instead specified doses "equivalent" to the range of 2000-5000 mg/kg bodyweight by the oral or dermal route (see Note (f) to Table 3.1.1). In some systems, the competent authority may prescribe values.*

3.1.2.6.5 In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity was corrosivity of the substance or mixture, certain authorities may also choose to label it as *corrosive to the respiratory tract.* Corrosion of the respiratory tract is defined by destruction of the respiratory tract tissue after a single, limited period of exposure analogous to skin corrosion; this includes destruction of the mucosa. The corrosivity evaluation could be based on expert judgment using such evidence as: human and animal experience, existing (*in vitro)* data, pH values, information from similar substances or any other pertinent data.

3.1.3 Classification criteria for mixtures

3.1.3.1 The criteria for substances classify acute toxicity by use of lethal dose data (tested or derived). For mixtures, it is necessary to obtain or derive information that allows the criteria to be applied to the mixture for the purpose of classification. 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. The flow chart of Figure 3.1.1 below outlines the process to be followed:

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



3.1.3.2 Classification of mixtures for acute toxicity can be carried out for each route of exposure, but is only needed for one route of exposure as long as this route is followed (estimated or tested) for all ingredients. If the acute toxicity is determined for more than one route of exposure, the more severe hazard category will be used for classification. All available information should be considered and all relevant routes of exposure should be identified for hazard communication.

3.1.3.3 In order to make use of all available data for purposes of classifying the hazards of mixtures, certain assumptions have been made and are applied where appropriate in the tiered approach:

(a) The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a reason to suspect that an ingredient present at a concentration < 1% is still relevant for classifying the mixture for acute toxicity. This point is particularly

relevant when classifying untested mixtures which contain ingredients that are classified in Category 1 and Category 2;

(b) Where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used when calculating the classification of the new mixture using the formulas in 3.1.3.6.1 and 3.1.3.6.2.3.

Table 3.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for classification for the respective routes of exposure

Exposure routes	**Classification category or experimentally obtained acute toxicity range estimate** (*see Note 1*)	**Converted Acute Toxicity point estimate** (*see Note 2*)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5 5 < Category 2 ≤ 50 50 < Category 3 ≤ 300 300 < Category 4 ≤ 2000 *2000 < Category 5 ≤ 5000*	0.5 5 100 500 2500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1000 1000 < Category 4 ≤ 2000 *2000 < Category 5 ≤ 5000*	5 50 300 1100 2500
Gases (ppmV)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2500 2500 < Category 4 ≤ 20000 *Category 5 - See footnote to 3.1.2.5.*	10 100 700 4500
Vapours (mg/l)	0 < Category 1 ≤ 0.5 0.5 < Category 2 ≤ 2.0 2.0 < Category 3 ≤ 10.0 10.0 < Category 4 ≤ 20.0 *Category 5 - See footnote to 3.1.2.5.*	0.05 0.5 3 11
Dust/mist (mg/l)	0 < Category 1 ≤ 0.05 0.05 < Category 2 ≤ 0.5 0.5 < Category 3 ≤ 1.0 1.0 < Category 4 ≤ 5.0 *Category 5 - See footnote to 3.1.2.5.*	0.005 0.05 0.5 1.5

***Note**: Gases concentration are expressed in parts per million per volume (ppmV).*

***NOTE 1**: Category 5 is for mixtures which are of relatively low acute toxicity but which under certain circumstances may pose a hazard to vulnerable populations. These mixtures are anticipated to have an oral or dermal LD_{50} value in the range of 2000-5000 mg/kg bodyweight or equivalent dose for other routes of exposure. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance for protecting human health.*

***NOTE 2**: These values are designed to be used in the calculation of the ATE for classification of a mixture based on its ingredients and do not represent test results. The values are conservatively set at the lower end of the range of Categories 1 and 2, and at a point approximately 1/10th from the lower end of the range for Categories 3 – 5.*

3.1.3.4 ***Classification of mixtures where acute toxicity test data are available for the complete mixture***

Where the mixture itself has been tested to determine its acute toxicity, it will be classified according to the same criteria as those used for substances, presented in Table 3.1.1. If test data for the mixture are not available, the procedures presented below should be followed.

3.1.3.5 ***Classification of mixtures where acute toxicity test data are not available for the complete mixture: bridging principles***

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

3.1.3.5.2 *Dilution*

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

If a mixture is diluted with water or other totally non-toxic material, the toxicity of the mixture can be calculated from test data on the undiluted mixture. For example, if a mixture with an LD_{50} of 1000 mg/kg bodyweight were diluted with an equal volume of water, the LD_{50} of the diluted mixture would be 2000 mg/kg bodyweight.

3.1.3.5.3 *Batching*

The toxicity 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 toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.1.3.5.4 *Concentration of highly toxic mixtures*

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

3.1.3.5.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.1.3.5.6 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B;

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

3.1.3.5.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolized form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolized mixtures for inhalation toxicity should be considered separately.

3.1.3.6 *Classification of mixtures based on ingredients of the mixture (additivity formula)*

3.1.3.6.1 *Data available for all ingredients*

In order to ensure that classification of the mixture is accurate, and that the calculation need only be performed once for all systems, sectors, and categories, the acute toxicity estimate (ATE) of ingredients should be considered as follows:

(a) Include ingredients with a known acute toxicity, which fall into any of the GHS acute toxicity categories;

(b) Ignore ingredients that are presumed not acutely toxic (e.g. water, sugar);

(c) Ignore ingredients if the oral limit test does not show acute toxicity at 2000 mg/kg bodyweight.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE).

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for oral, dermal or inhalation toxicity:

$$\frac{100}{\text{ATEmix}} = \sum_{n} \frac{Ci}{ATE_i}$$

where:

C_i = concentration of ingredient i
n ingredients and i is running from 1 to n
ATE_i = Acute toxicity estimate of ingredient i.

3.1.3.6.2 *Data are not available for one or more ingredients of the mixture*

3.1.3.6.2.1 Where an ATE is not available for an individual ingredient of the mixture, but available information such as listed below can provide a derived conversion value, the formula in 3.1.3.6.1 may be applied.

This may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates[2]. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;

(b) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;

(c) Evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or

(d) Data from closely analogous substances using structure/activity relationships.

This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity. If such information is not available, proceed to the provisions of 3.1.3.6.2.3.

3.1.3.6.2.2 In the event that an ingredient without any useable information at all is used in a mixture at a concentration ≥ 1%, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture should be classified based on the known ingredients only, with the additional statement that × percent of the mixture consists of ingredient(s) of unknown toxicity.

3.1.3.6.2.3 If the total concentration of the ingredient(s) with unknown acute toxicity is ≤ 10% then the formula presented in 3.1.3.6.1 should be used. If the total concentration of the ingredient(s) with unknown toxicity is > 10%, the formula presented in 3.1.3.6.1 should be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

$$\frac{100 - \left(\sum C_{\text{unknown}} \text{ if} > 10\%\right)}{ATE_{mix}} = \sum_{n} \frac{Ci}{ATE_{i}}$$

[2] *For ingredients with acute toxicity estimates available for other than the most appropriate exposure route, values may be extrapolated from the available exposure route to the most relevant route. Dermal and inhalation route data are not always required for ingredients. However, in case data requirements for specific ingredients include acute toxicity estimates for the dermal and inhalation route, the values to be used in the formula need to be from the required exposure route.*

3.1.4 Hazard communication

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. The table below presents specific label elements for substances and mixtures that are classified into acute toxicity Categories 1 to 5 based on the criteria set forth in this chapter.

Table 3.1.3: Label elements for acute toxicity

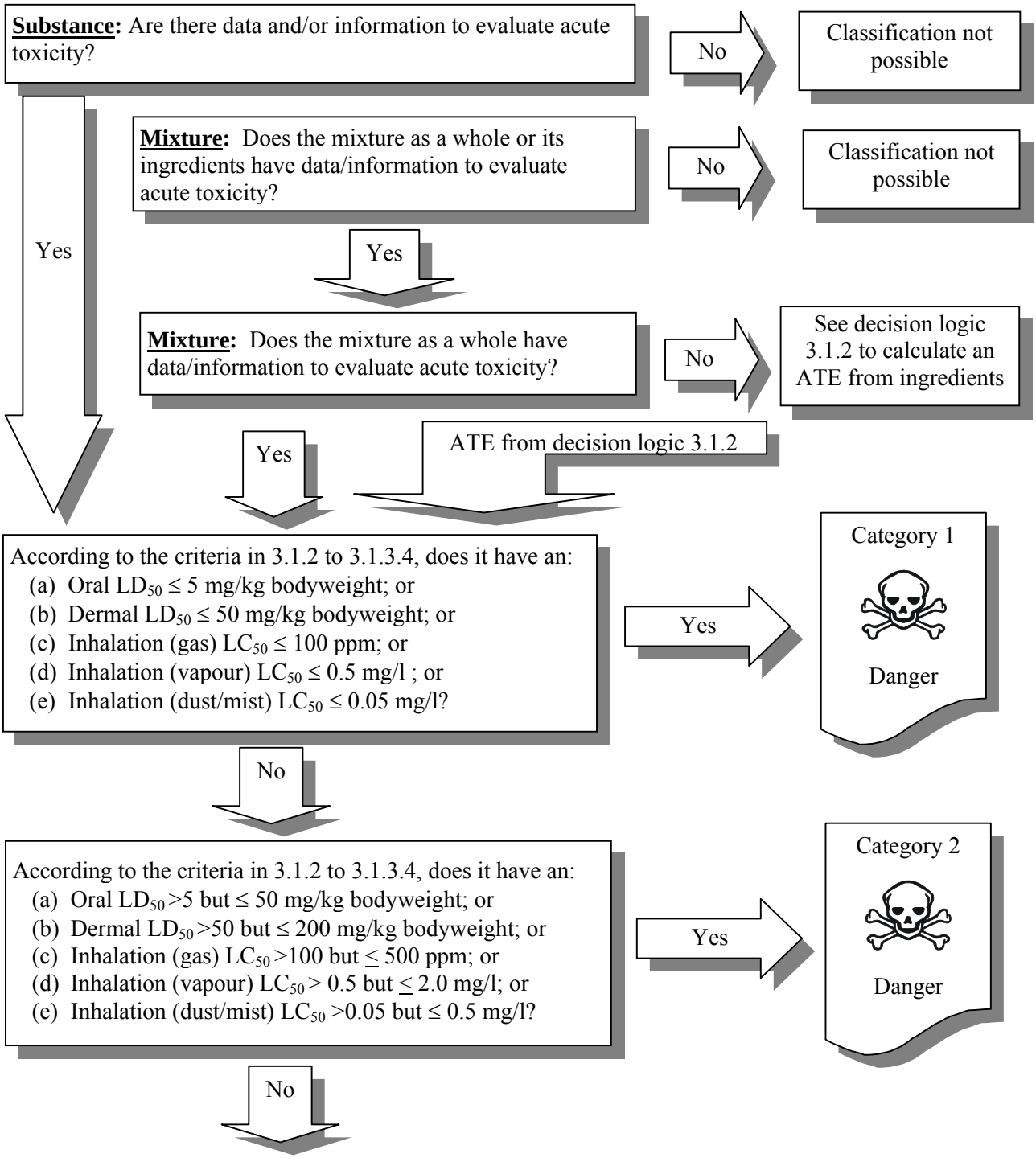
	Category 1	**Category 2**	**Category 3**	**Category 4**	**Category 5**
Symbol	Skull and crossbones	Skull and crossbones	Skull and crossbones	Exclamation mark	*No symbol*
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement: --Oral	Fatal if swallowed	Fatal if swallowed	Toxic if swallowed	Harmful if swallowed	May be harmful if swallowed
--Dermal	Fatal in contact with skin	Fatal in contact with skin	Toxic in contact with skin	Harmful in contact with skin	May be harmful in contact with skin
--Inhalation *see Note*	Fatal if inhaled	Fatal if inhaled	Toxic if inhaled	Harmful if inhaled	May be harmful if inhaled

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

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 ≤ 10.0 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 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 confirm 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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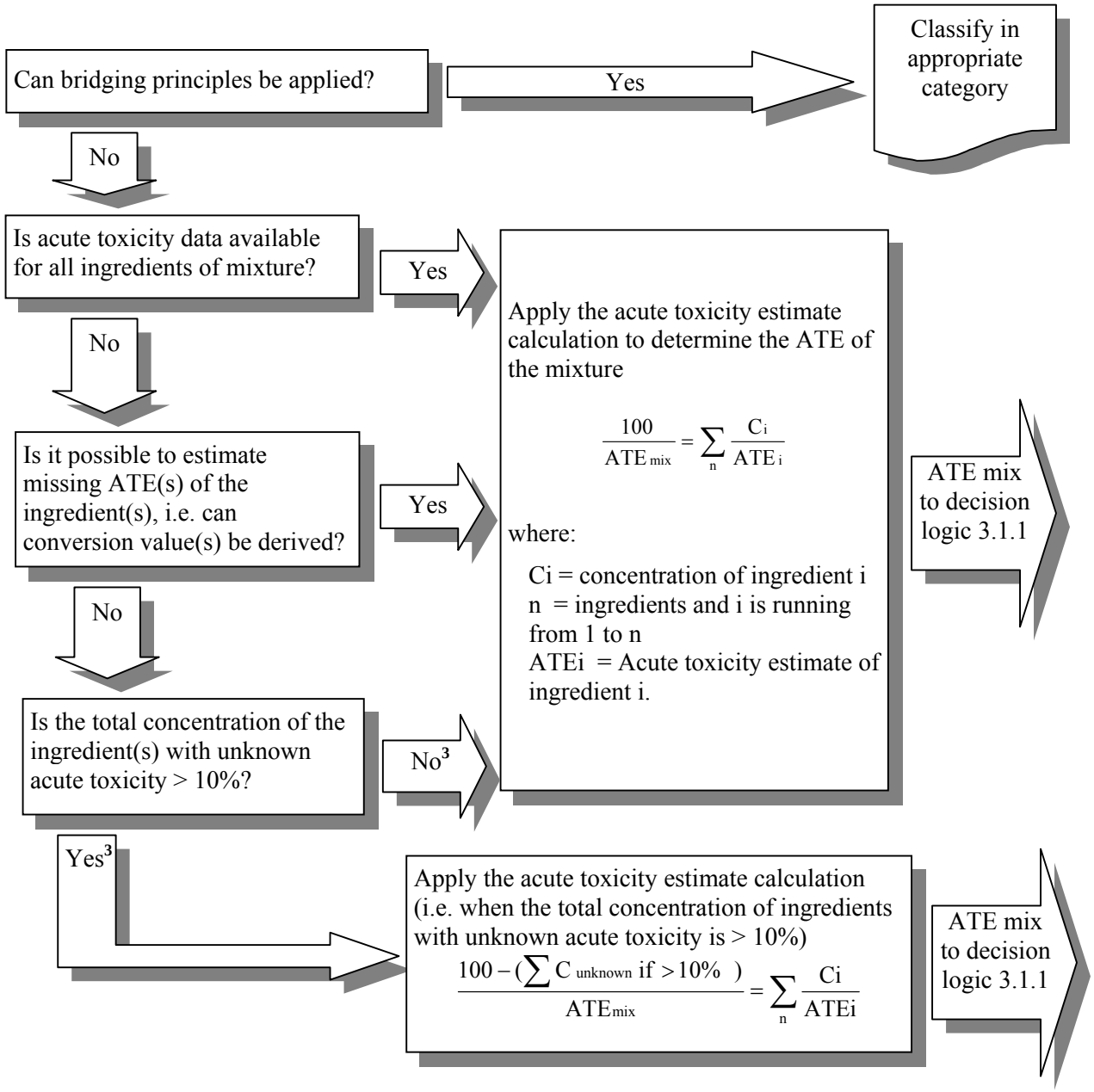
3.1.5.2 ***Decision logic 3.1.2 for acute toxicity*** *(see criteria in 3.1.3.5 and 3.1.3.6)*



[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 an additional statement on the label should identify the fact that the acute toxicity of x% of the mixture is unknown.*

CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 Definitions

Skin corrosion is the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours[1]. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to evaluate questionable lesions.

Skin irritation is the production of reversible damage to the skin following the application of a test substance for up to 4 hours[1].

3.2.2 Classification criteria for substances

3.2.2.1 The harmonized system includes guidance on the use of data elements that are evaluated before animal testing for skin corrosion and irritation is undertaken. It also includes hazard categories for corrosion and irritation.

3.2.2.2 Several factors should be considered in determining the corrosion and irritation potential of chemicals before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. Existing human experience and data including from single or repeated exposure and animal observations and data should be the first line of analysis, as they give information directly relevant to effects on the skin. In some cases enough information may be available from structurally related compounds to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when buffering capacity is known, although the correlation is not perfect. Generally, such agents are expected to produce significant effects on the skin. It also stands to reason that if a chemical is highly toxic by the dermal route, a skin irritation/corrosion study may not be practicable since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations are made of skin irritation/corrosion in acute toxicity studies and are observed up through the limit dose, additional testing would not be needed, provided that the dilutions used and species tested are equivalent. *In vitro* alternatives that have been validated and accepted may also be used to help make classification decisions.

All the above information that is available on a chemical should be used in determining the need for *in vivo* skin irritation testing. Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.3), e.g. caustic alkalis with extreme pH should be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

3.2.2.3 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognizing that all elements may not be relevant in certain cases.

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

Figure 3.2.1: Tiered testing and evaluation of skin corrosion and irritation potential

Step	Parameter	Finding	Conclusion
1a	Existing human or animal experience [(g)]	→ Corrosive	→ Classify as corrosive [(a)]
	↓ Not corrosive or no data		
1b	Existing human or animal experience [(g)]	→ Irritant	→ Classify as irritant [(a)]
	↓ Not irritant or no data		
1c	Existing human or animal experience	→ Not corrosive or irritant	→ No further testing, not classified
	↓ No data		
2a	Structure-activity relationships or structure-property relationships [(b)]	→ Corrosive	→ Classify as corrosive [(a)]
	↓ Not corrosive or no data		
2b	Structure-activity relationships or structure-property relationships [(b)]	→ Irritant	→ Classify as irritant [(a)]
	↓ Not irritating or no data		
3	pH with buffering [(c)]	→ pH ≤ 2 or ≥ 11.5	→ Classify as corrosive [(a)]
	↓ Not pH extreme or no data		
4	Existing skin data in animals indicate no need for animal testing [(d)]	→ Yes	→ Possibly no further testing may be deemed corrosive/ irritant
	↓ No indication or no data		
5	Valid and accepted *in vitro* skin corrosion test [(e)]	→ Positive response	→ Classify as corrosive [(a)]
	↓ Negative response or no data		
	↓		

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Figure 3.2.1 *(cont'd)*: **Tiered testing and evaluation of skin corrosion and irritation potential**

Step	Parameter		Finding		Conclusion
6	Valid and accepted *in vitro* skin irritation test [(f)]	→	Positive response	→	Classify as irritant [(a)]
	↓				
	Negative response or no data				
	↓				
7	*In vivo* skin corrosion test (1 animal)	→	Positive response	→	Classify as corrosive [(a)]
	↓				
	Negative response				
	↓				
8	*In vivo* skin irritation test (3 animals total) [(h)]	→	Positive response	→	Classify as irritant [(a)]
	↓				
	Negative response	→	No further testing	→	No further testing, not classified
	↓				
9	When it is ethical to perform human patch testing [(g)]	→	Positive response	→	Classify as irritant [(a)]
	↓				
	Not as above	→	Negative response	→	No further testing, not classified

(a) Classify in the appropriate harmonized category, as shown in Table 3.2.1;

(b) Structure-activity and structure-property relationships are presented separately but would be conducted in parallel;

(c) Measurement of pH alone may be adequate, but assessment of acid or alkali reserve is preferable; methods are needed to assess buffering capacity;

(d) Pre-existing animal data should be carefully reviewed to determine if in vivo skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any skin irritation in an acute skin toxicity test at the limit dose, or produces very toxic effects in an acute skin toxicity test. In the latter case, the material would be classified as being very hazardous by the dermal route for acute toxicity; it is moot whether the material is also irritating or corrosive on the skin. It should be kept in mind in evaluating acute skin toxicity information that the reporting of skin lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;

(e) Examples of internationally accepted validated in vitro test methods for skin corrosion are OECD Test Guidelines 430 and 431;

(f) Presently there are no validated and internationally accepted in vitro test methods for skin irritation;

(g) This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human skin irritation testing, but an OECD guideline has been proposed;

(h) Testing is usually conducted in 3 animals, one coming from the negative corrosion test.

3.2.2.4 *Corrosion*

3.2.2.4.1 A single harmonized corrosion category is provided in Table 3.2.1, using the results of animal testing. A corrosive is a test material that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 of 3 tested animals after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology should be considered to discern questionable lesions.

3.2.2.4.2 For those authorities wanting more than one designation for corrosivity, up to three sub-categories are provided within the corrosive category (Category 1, see Table 3.2.1): sub-category 1A, where responses are noted following up to 3 minutes exposure and up to 1 hour observation; sub-category 1B, where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and sub-category 1C, where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

Table 3.2.1: Skin corrosion category and sub-categories [a]

Category 1: Corrosive	**Corrosive sub-categories**	**Corrosive in ≥ 1 of 3 animals**	
(applies to authorities not using sub-categories)	(only applies to some authorities)	**Exposure**	**Observation**
corrosive	1A	≤ 3 min	≤ 1 h
	1B	> 3 min ≤ 1 h	≤ 14 days
	1C	> 1 h ≤ 4 h	≤ 14 days

[a] *The use of human data is discussed in 3.2.2.1 and in "Classification of hazardous substances and mixtures" (para. 1.3.2.4.7.1).*

3.2.2.5 *Irritation*

3.2.2.5.1 A single *irritant category* is provided in Table 3.2.2 that:

(a) is centrist in sensitivity among existing classifications;

(b) recognizes that some test materials may lead to effects which persist throughout the length of the test; and

(c) acknowledges that animal responses in a test may be quite variable. An additional mild irritant category is available for those authorities that want to have more than one skin irritant category.

3.2.2.5.2 Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material should be considered to be an irritant.

3.2.2.5.3 Animal irritant responses within a test can be quite variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

3.2.2.5.4 A single irritant category (Category 2) is presented in the table using the results of animal testing. Authorities (e.g. pesticides) also have available a less severe mild irritant category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of ≥ 2.3 ≤ 4.0. For the mild irritant category, the mean score cut-off values are ≥ 1.5 < 2.3 for at least 2 tested animals. Test materials in the irritant category would be excluded from being placed in the mild irritant category.

Table 3.2.2 Skin irritation categories [a]

Categories	Criteria
Irritant (Category 2) (applies to all authorities)	(1) Mean value of ≥ 2.3 ≤ 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 irritant (Category 3) (applies to only some authorities)	Mean value of ≥ 1.5 < 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 discussed in 3.2.2.1 and in the "Classification of hazardous substances and mixtures" (para. 1.3.2.4.7.1).*

3.2.3 Classification criteria for mixtures

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

3.2.3.1.1 The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

3.2.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

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

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

3.2.3.2.2 *Dilution*

If a mixture is diluted with a diluent which has an equivalent or lower corrosivity/irritancy classification than the least corrosive/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

The irritation/corrosion potential 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 toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.2.3.2.4 *Concentration of mixtures of the highest corrosion/ irritation category*

If a tested mixture classified in the highest sub-category for corrosion is concentrated, a more concentrated mixture should be classified in the highest corrosion sub-category without additional testing. If a tested mixture classified in the highest category for skin irritation is concentrated and does not contain corrosive ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

3.2.3.2.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same irritation/ corrosion toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same irritation/corrosion category as A and B.

3.2.3.2.6 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Data on irritation/corrosion for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

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

3.2.3.2.7 *Aerosols*

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

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

3.2.3.3.1 In order to make use of all available data for purposes of classifying the skin irritation/corrosion hazards of mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

3.2.3.3.2 In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such ingredients exceeds a cut-off value/concentration limit.

3.2.3.3.3 Table 3.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

3.2.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.2.3.3.1 and 3.2.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits of Table 3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.2.3, due to chemical characteristics that make this approach unworkable, should be classified as skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as skin Category 2/3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarized in Table 3.2.4 below.

3.2.3.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture could be classified according to those data (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)). On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as described in 3.2.3 and illustrated in Figure 3.2.1.

3.2.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)).

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**: Only some authorities will use the sub-categories of skin Category 1 (corrosive). In these cases, the sum of all ingredients of a mixture classified as skin Category 1A, 1B or 1C respectively, should each be ≥ 5% in order to classify the mixture as either skin Category 1A, 1B or 1C. In case the sum of the skin Category 1A ingredients is < 5% but the sum of skin Category ingredients 1A+1B is ≥ 5%, the mixture should be classified as skin Category 1B. Similarly, in case the sum of skin Category 1A + 1B is < 5% but the sum of Category 1A + 1B + 1C is ≥ 5% the mixture would be classified as Category 1C.*

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

3.2.4 Hazard communication

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. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

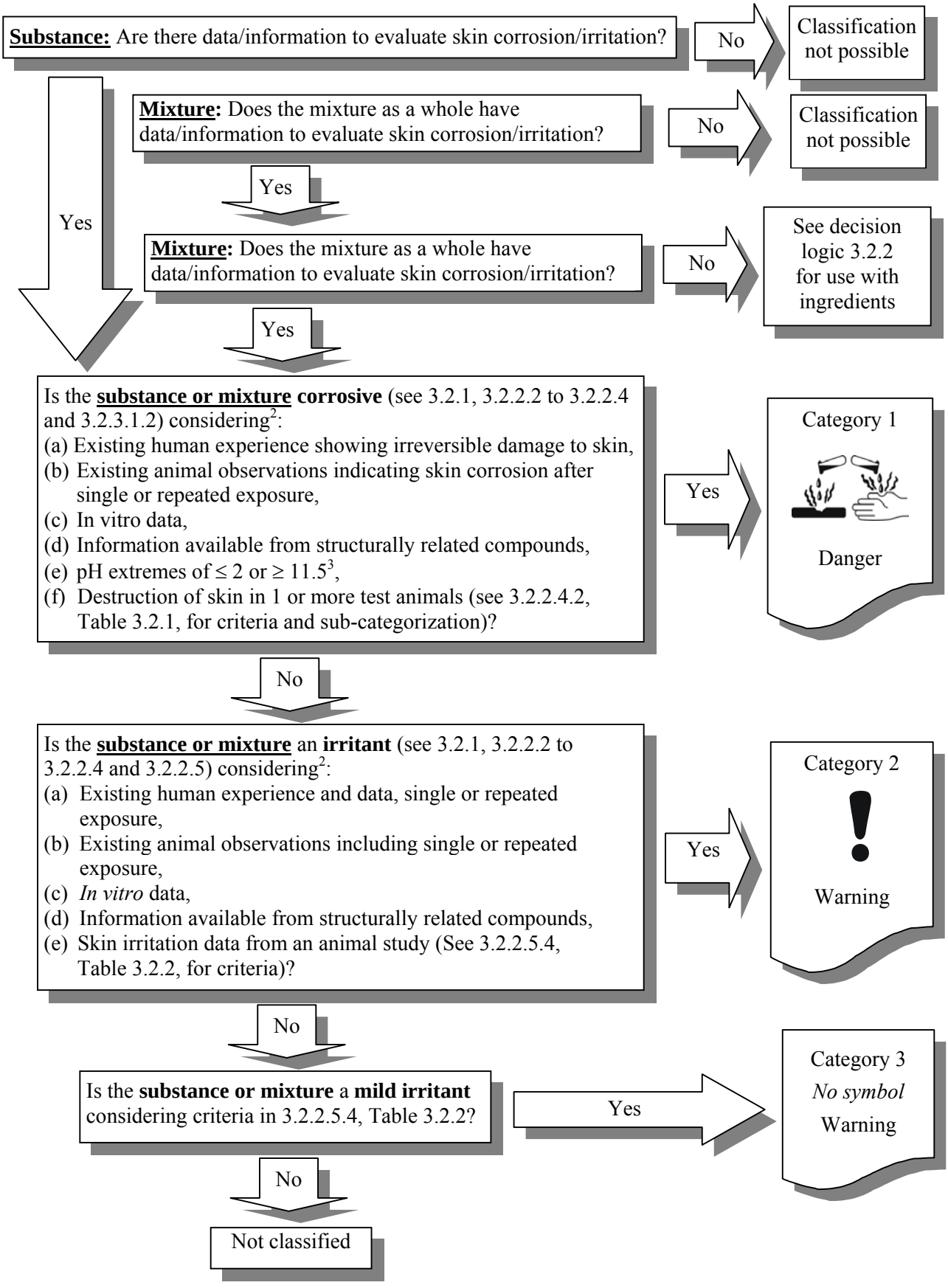
Table 3.2.5: Label elements for skin corrosion/irritation

	Category 1			**Category 2**	**Category 3**
	1 A	**1 B**	**1 C**		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 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.

3.2.5.1 *Decision logic 3.2.1 for skin corrosion/irritation*

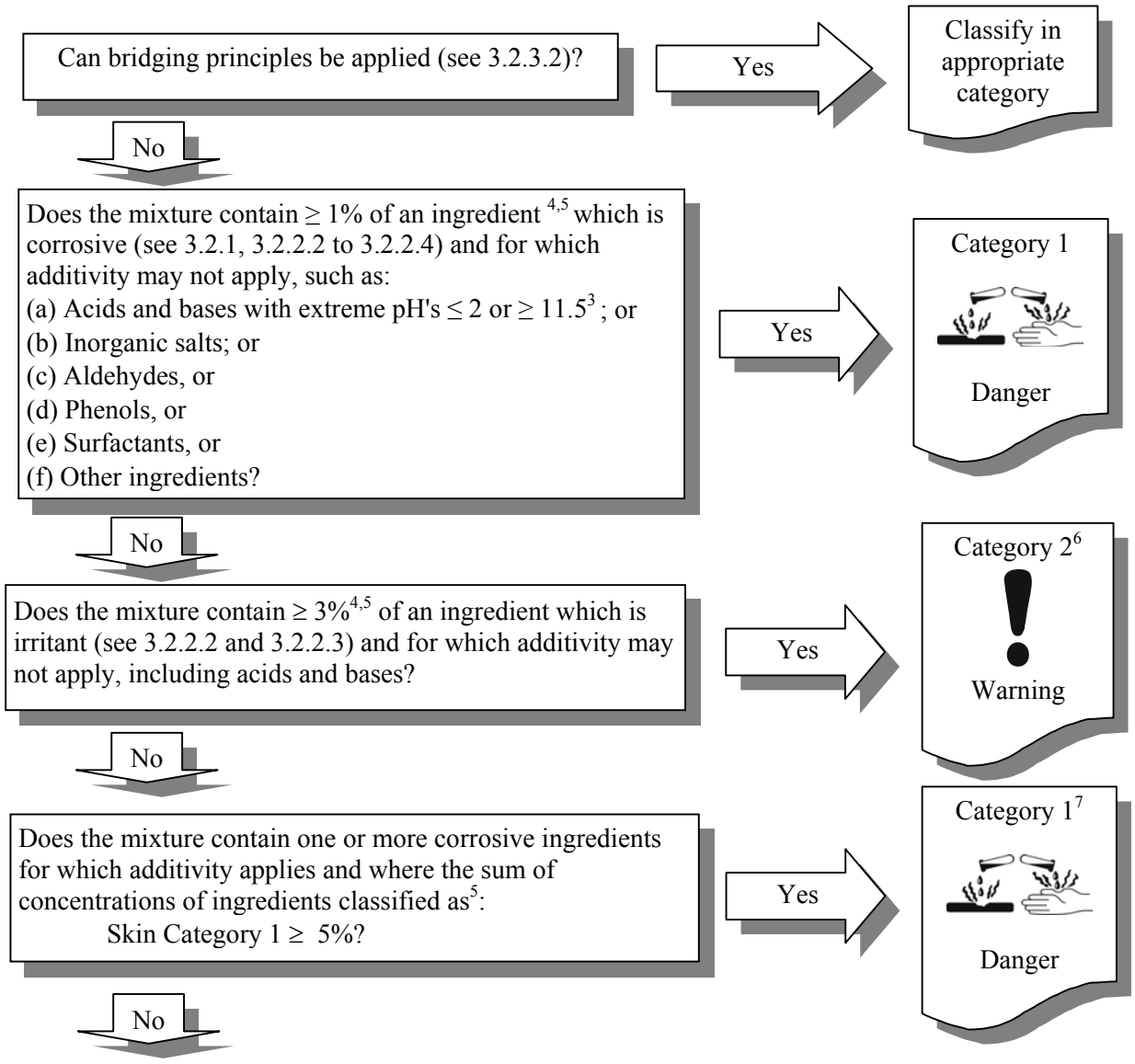


[2] *Figure 3.2.1 contains details for testing and evaluation.*

[3] *Including consideration of acid/alkali reserve capacity, if appropriate.*

3.2.5.2 *Decision logic 3.2.2 for skin corrosion/irritation*

Classification of mixtures on the basis of information/data on ingredients



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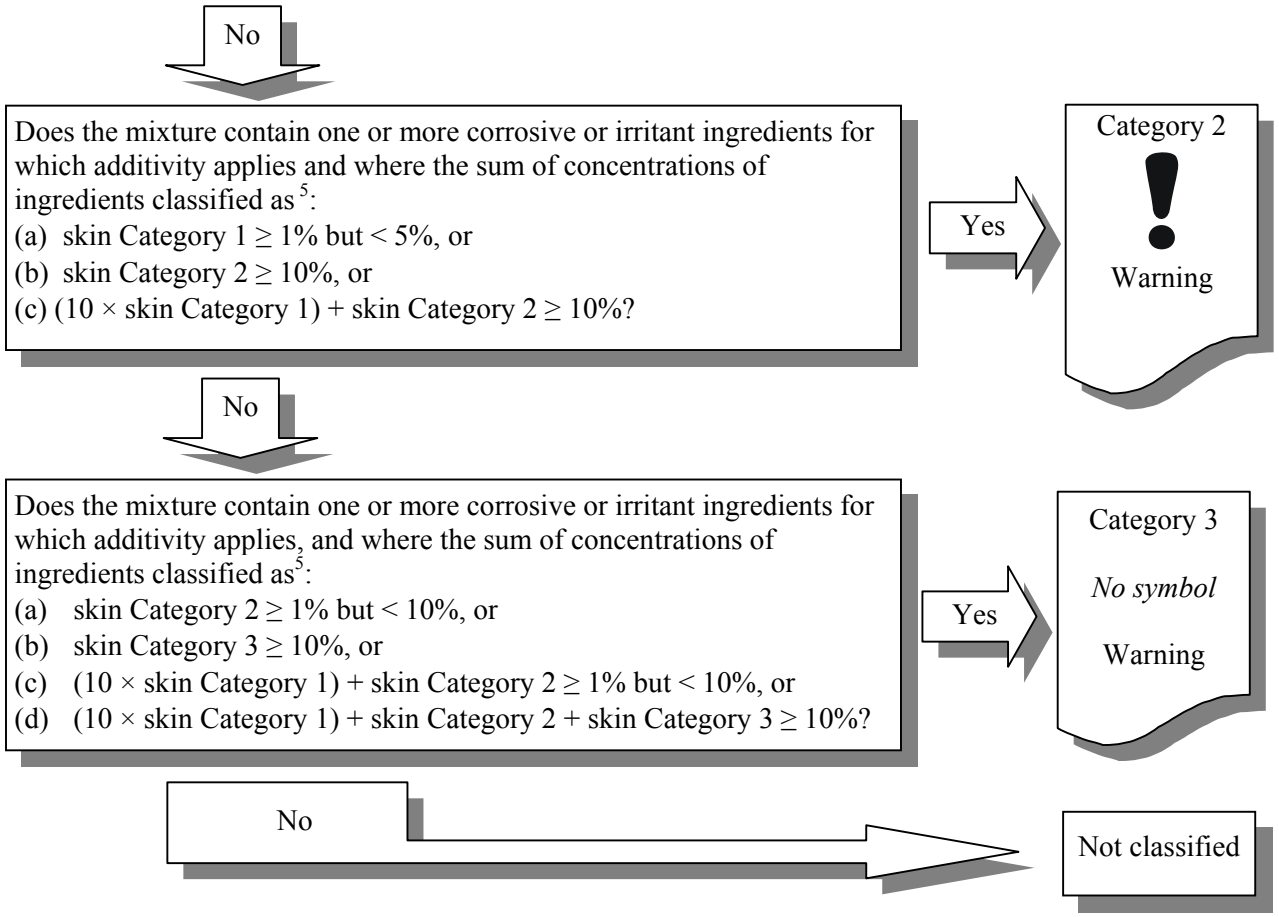
[3] *Including consideration of acid/alkali reserve capacity, if appropriate.*

[4] *Or 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 "The use of cut-off values/concentration limits".*

[6] *If the mixture also contains corrosive or irritant ingredient(s) for which additivity applies, move to the box below.*

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



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

CHAPTER 3.3

SERIOUS EYE DAMAGE /EYE IRRITATION

3.3.1 Definitions

Serious eye damage is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application[1] .

Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application[1].

3.3.2 Classification criteria for substances

3.3.2.1 A tiered testing and evaluation scheme is presented that combines pre-existing information on serious ocular tissue damage and on eye irritation (including data relating to historical human or animal experience) as well as considerations on structure-activity relationships (SAR) or structure-property relationships (SPR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.

3.3.2.2 The proposals for classification of eye irritation and serious damage to the eye include elements that are harmonized and will be used by all authorities as well as optional sub-categories that will be applied by only some authorities (e.g. authorities classifying pesticides).

The harmonized system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard categories for local lesions on the eyes.

3.3.2.3 Before there is any *in vivo* testing for serious eye damage/eye irritation, all existing information on a test material should be reviewed. Preliminary decisions can often be made from existing data as to whether an agent causes serious (i.e. irreversible) damage to the eyes. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilize a tiered testing strategy for serious eye damage and eye irritation.

3.3.2.4 Several factors should be considered in determining the serious eye damage or irritation potential of chemicals before testing is undertaken. Accumulated human and animal experience should be the first line of analysis, as it gives information directly relevant to effects on the eye. In some cases enough information may be available from structurally related compounds to make hazard decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may produce serious eye damage, especially when associated with significant buffering capacity. Such agents are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted may be used to make classification decisions.

3.3.2.5 All the above information that is available on a chemical should be used in determining the need for *in vivo* eye irritation testing. Although information might be gained from the evaluation of single parameters within a tier (e.g. caustic alkalis with extreme pH should be considered as local corrosives), there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon expert judgement, considering human experience with

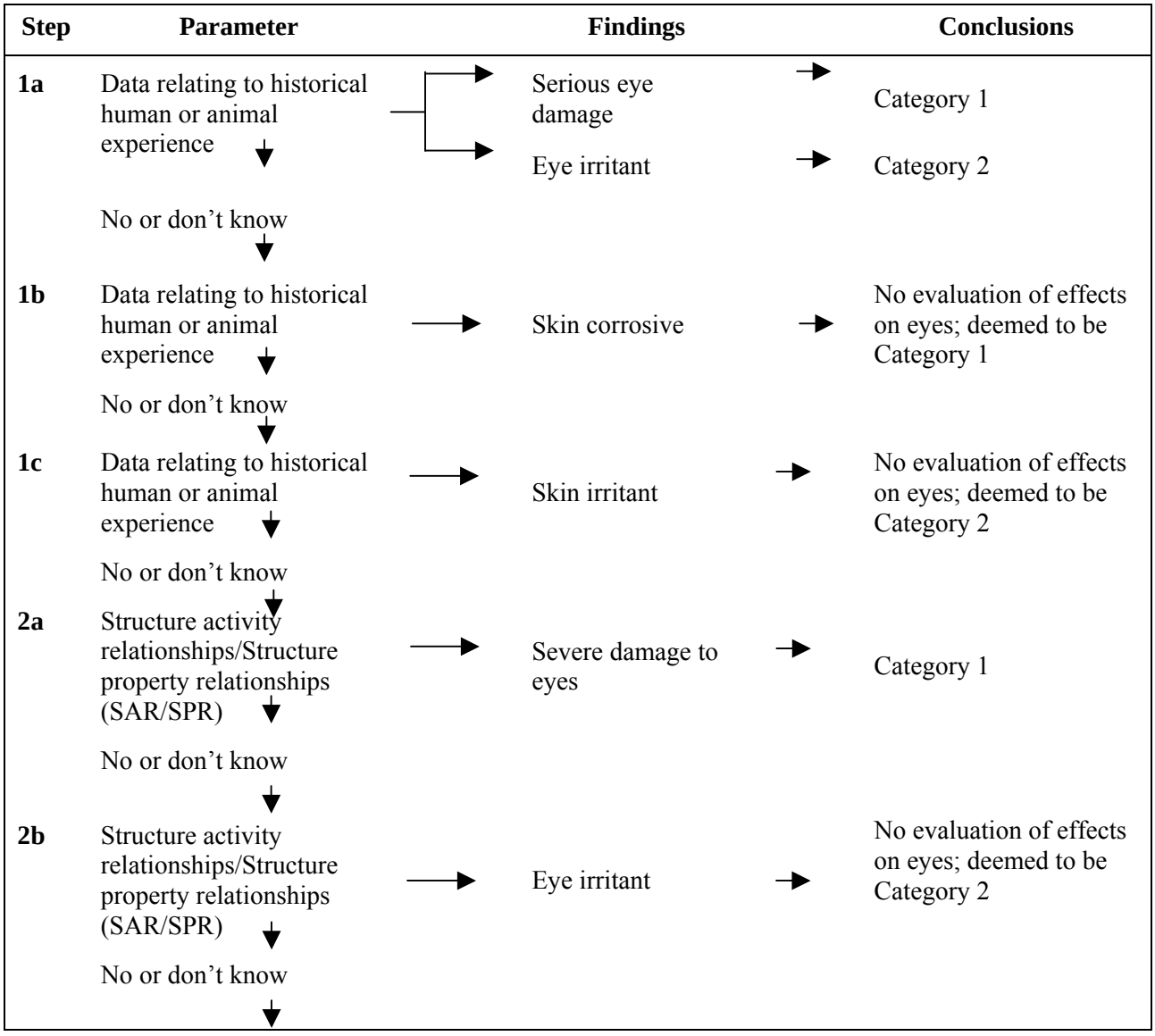
[1] *This is a working definition for the purpose of this document.*

the substance, followed by the outcome of skin irritation testing and of well validated alternative methods. Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable, recognizing that all elements may not be relevant in certain cases. The tiered approach explained in Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[2].

3.3.2.7 Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to organize existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).

Figure 3.3.1: Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)



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[2] *OECD (1996). Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods. Document ENV/MC/TG(96)9 (http://www.oecd.org/ehs/test/background.htm).*

Figure 3.3.1 *(cont'd)*: **Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)**

Step	Parameter	Findings	Conclusions
2c	Structure activity relationships/Structure property relationships (SAR/SPR) →	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No or don't know		
3a	pH/acid or alkaline reserve →	pH ≥ 11.5 or pH ≤ 2 (considering acid or alkaline reserve) →	Category 1
	↓		
3b	2 < pH < 11.5 (no buffering potential)		
	↓		
4	Other information indicating the material is a skin corrosive →	Yes →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No		
5	Is a valid *in vitro* test available to assess severe damage to eyes →	No →	Go to step 6
	↓		
5a	*In vitro* test for severe eye irritation →	Severe damage to eyes →	Category 1
	↓ Not a severe eye irritant		
6	Is a valid *in vitro* test for eye irritation available → No	- But *in vitro* test for severe eye irritancy was negative →	Go to step 8
		- In the absence of any *in vitro* test →	Go to Step 7
	↓ Yes		
6a	*In vitro* eye irritation test →	Eye irritant →	Category 2
	↓ No indication of eye irritant properties		
	↓		
7	Experimentally assess skin corrosion potential (see Testing Strategy for Skin Irritation/Corrosion) →	Skin corrosive →	No evaluation of effects on eyes, deemed to be Category 1
	↓ Not corrosive		
	↓		

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Figure 3.3.1 *(cont'd)*: **Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)**

Step	Parameter	Findings	Conclusions
8	1 rabbit eye test →	Serious damage to eyes →	Category 1
	↓ No serious damage ↓		
9	1 or 2 further rabbits →	Eye irritant →	Category 2
	↓ →	Not an eye irritant →	Not classified

NOTES to Figure 3.3.1:

Step 1a/b: *Data relating to historical human or animal experience: pre-existing information on eye irritation and skin corrosion are shown separately because evaluation of skin corrosion has to be considered if there is no information on local effects on eyes. Analysis of pre-existing experience with the chemical may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

(i) Step 1a - reliable determination of eye irritancy basing on human or animal experience - depends on expert judgement: in most cases human experience is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data;

(ii) Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

Step 2a/b/c: *SAR (Structure Activity Relationships)/SPR (Structure Property Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches. The SAR/SPR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

(i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to agents with very well known properties;

(ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

Step 3: *pH extremes like ≤ 2 and ≥ 11.5 may indicate strong local effects, especially in combination with assessment of acid or alkaline reserve, substances exhibiting such physico-chemical properties should be considered as leading to serious damage to eyes (Category 1).*

Step 4: *All attainable information should be used, including human experience. But this information should be restricted to that which pre-exists (e.g. the results of a skin LD_{50} test or historical information on skin corrosion).*

Step 5: *These must be alternative methods for the assessment of eye irritation/ or serious damage to eyes (e.g. irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see section 1.3.2 in Chapter 1.3).*

Step 6: *At present this step seems not to be achievable in the near future. Validated alternative methods for the reliable assessment of (reversible) eye irritation need to be developed.*

Step 7: *In the absence of any other relevant information, it is essential to obtain this via an internationally recognized corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted in vitro skin corrosivity assay. If this is not available, then the assessment should be completed using animal tests (see the skin irritation/ corrosion strategy, section 3.2.2).*

Step 8: *Staged assessment of eye irritation in vivo. If in a limit test with one rabbit serious damage to eyes is detected no further testing is needed.*

Step 9: *Only two animals may be employed for irritation testing (including the one used for evaluation of possible serious effects) if these two animals give concordant clearly irritant or clearly non-irritant responses. In the case of different or borderline responses a third animal is needed. Depending on the result of this three-animal test, classification may be required or not.*

3.3.2.8 *Irreversible effects on the eye/serious damage to eyes (Category 1)*

A single harmonized hazard category is adopted for substances that have the potential to seriously damage the eyes. This hazard category - Category 1 (irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 3.3.1: Irreversible eye effects categories [a]

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:
(a) at least in 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) at least in 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 installation of the test material.

[a] *The use of human data is discussed in "Purpose, scope and application" (para. 1.1.2.5 (c)) and "Classification of hazardous substances and mixtures" (para. 1.3.2.4.7).*

3.3.2.9 *Reversible effects on the eye (Category 2)*

A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonized Category 2 (irritating to eyes); others may want to distinguish between Category 2A (irritating to eyes) and Category 2B (mildly irritating to eyes).

Table 3.3.2: Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes) is a test material that produces:
(a) at least in 2 of 3 tested animals a positive response of: (i) corneal opacity ≥ 1; and/or (ii) iritis ≥ 1; and/or (iii) conjunctival redness ≥ 2; and/or (iv) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of normally 21 days.
Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

For those chemicals where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

3.3.3 Classification criteria for mixtures

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

The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies used to develop data for these hazard classes.

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

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

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

3.3.3.2.2 *Dilution*

If a mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/irritancy classification than the least damaging/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The irritation/serious eye damage potential 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 toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/ irritation category*

If a tested mixture classified in the highest category for serious eye damage is concentrated, a more concentrated mixture should be classified in the highest serious eye damage category without additional testing. If a tested mixture classified in the highest sub-category for skin/eye irritation is concentrated and does not contain serious eye damage ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

3.3.3.2.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same irritation/ serious eye damage toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same irritation/serious eye damage category as A and B.

3.3.3.2.6 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Data on irritation/serious eye damage for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[3].

[3] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognized.*

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

3.3.3.3.1 In order to make use of all available data for purposes of classifying the eye irritation/serious eye damaging properties of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for eye irritation/serious eye damage.

3.3.3.3.2 In general, the approach to classification of mixtures as eye irritant or seriously damaging to the eye when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified an irritant or a seriously damaging to the eye.

3.3.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.3.3.3.1 and 3.3.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1 %. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table 3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarized in Table 3.3.4.

3.3.3.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also 1.3.3.2 *"Use of cut-off values/Concentration limits"*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy should be applied as referred to in section 3.3.3, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also 1.3.3.2 *"Use of cut-off values/concentration limits"*).

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 mixtures as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as	Concentration triggering classification of a mixture as	
	Irreversible eye effects	Reversible eye effects
	Category 1	Category 2
Eye or skin Category 1	≥ 3%	≥ 1% but < 3%
Eye Category 2/2A		≥ 10%
(10 × eye Category 1) + eye Category 2/2A		≥ 10%
Skin Category 1 + eye Category 1	≥ 3%	≥ 1% but < 3%
10 × (skin Category 1 + eye Category 1) + eye Category 2A/2B		≥ 10%

Table 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to 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 (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.3.4 Hazard communication

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.

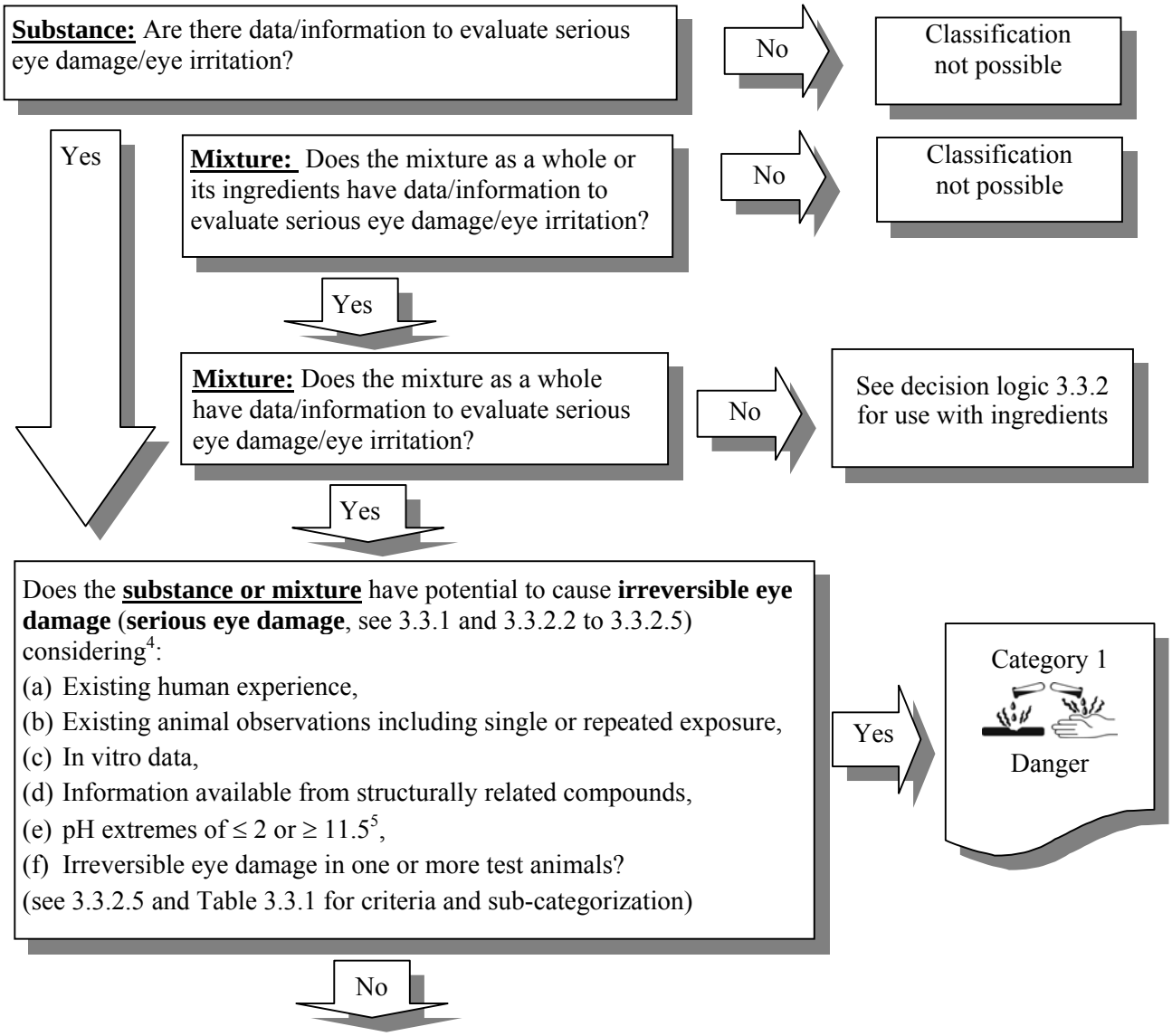
Table 3.3.5: Label elements for serious eye damage/eye irritation

	Category 1	Category 2A	Category 2B
Symbol	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

3.3.5 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.

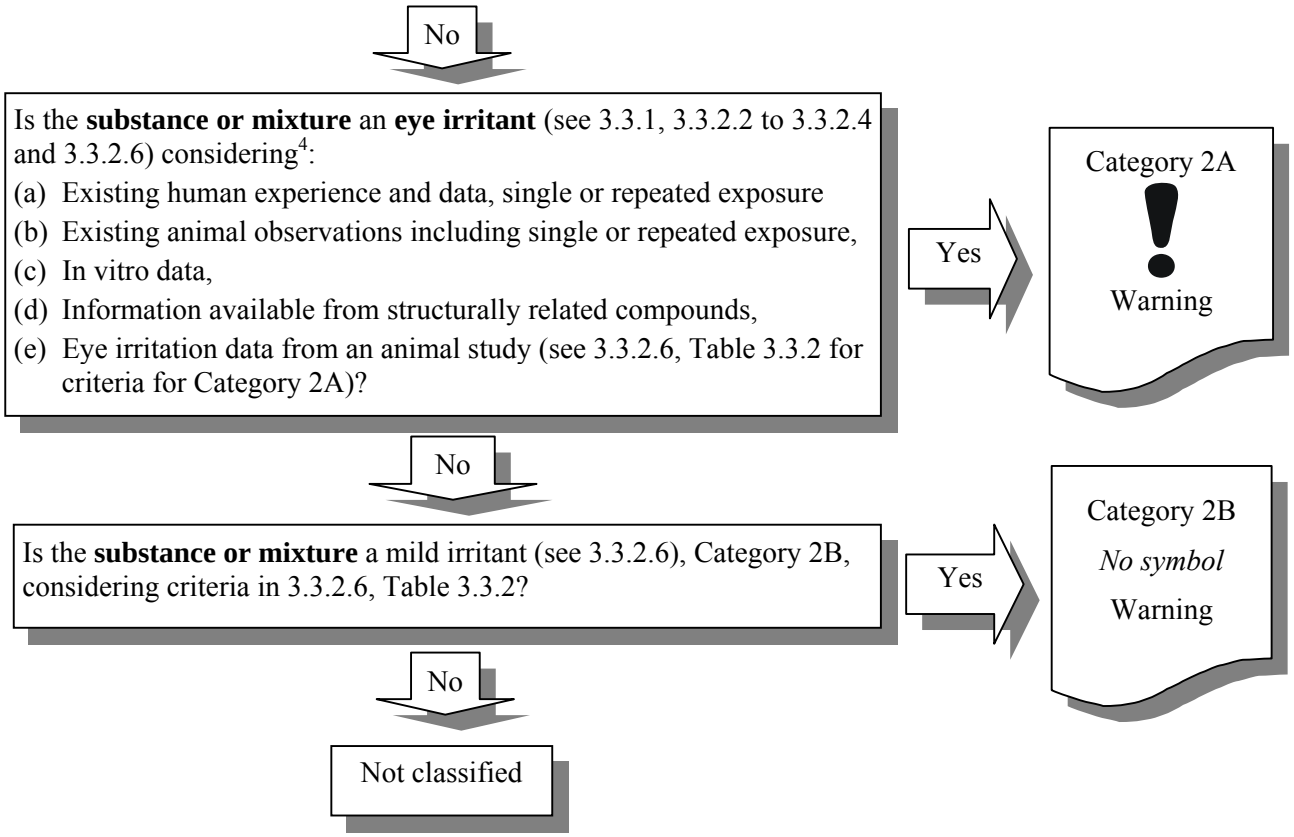
3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*



(Cont'd on next page)

[4] *Figure 3.3.1 contains details for testing and evaluation.*

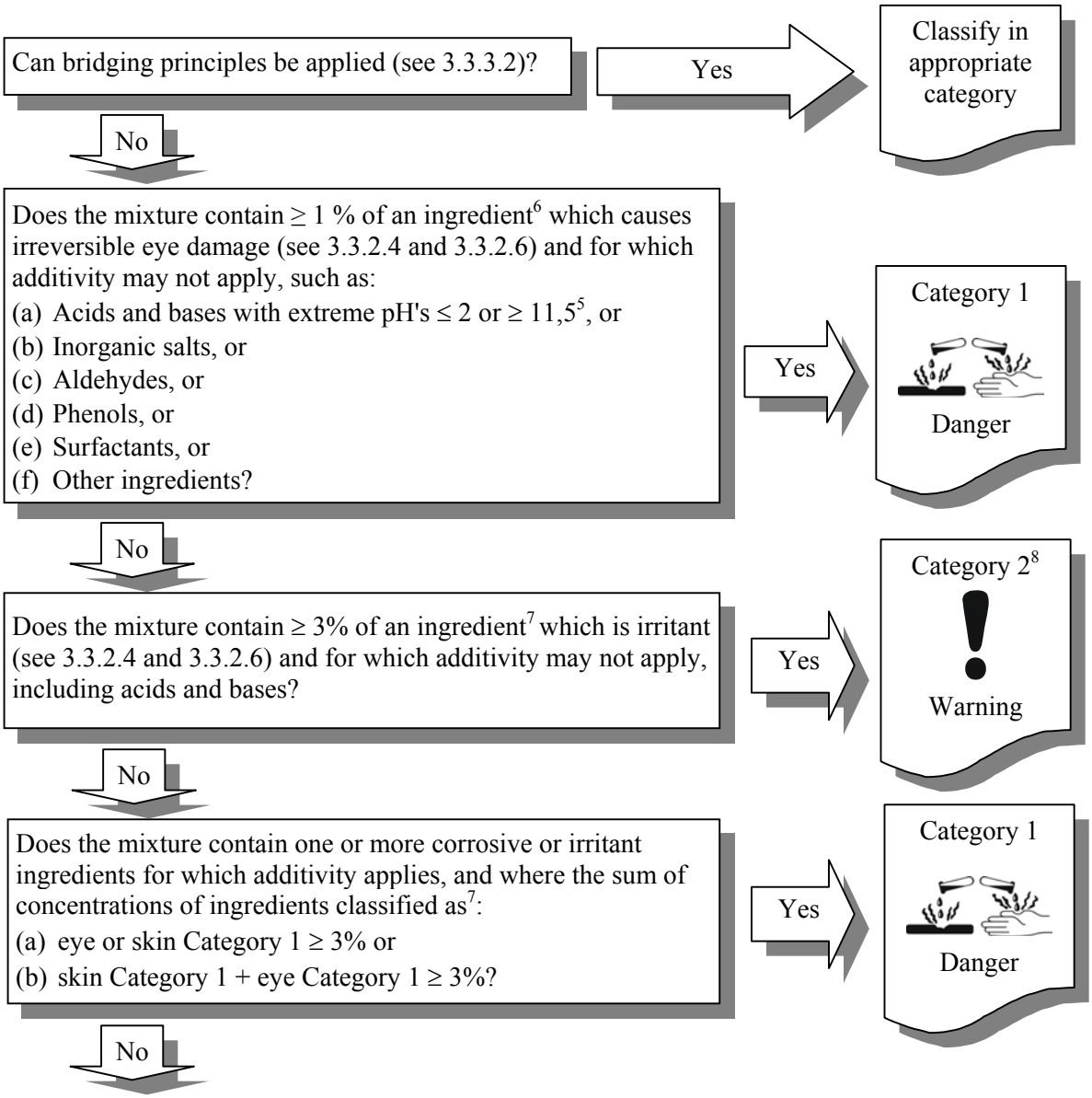
[5] *Including consideration of acid/alkali reserve capacity, if appropriate.*



[4] *Figure 3.3.1 contains details for testing and evaluation.*

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 ingredients



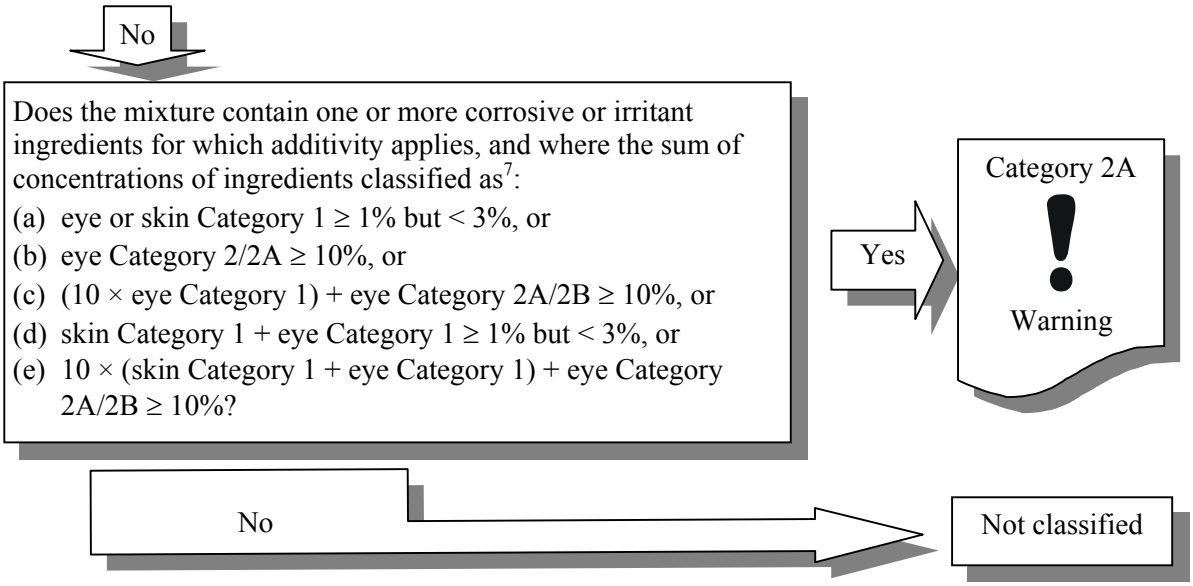
(Cont'd on next page)

[5] *Including consideration of acid/alkali reserve capacity, if appropriate.*

[6] *Or where relevant < 1 %, see 3.3.3.3.1.*

[7] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

[8] *If the mixture also contains other corrosive or irritant ingredient(s) for which additivity applies move to the box below.*



[7] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

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 lead to hypersensitivity of the airways following inhalation of the substance[1].

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

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

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

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

3.4.2 Classification criteria for substances

3.4.2.1 *Respiratory sensitizers*

3.4.2.1.1 *Hazard category*

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

(a)	If there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or
(b)	If there are positive results from an appropriate animal test.

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.

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

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.

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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.*

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:

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

3.4.2.2.2 *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);

(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 sub-categorize 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 principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.4.3.2.2 *Dilution*

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

3.4.3.2.3 *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 ingredients or only for some ingredients of the mixture*

The mixture should be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value/concentration limit for the specific endpoint as shown in Table 3.4.1 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 values/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 ≥ 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 ≥ 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 ≥ 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: Label elements for respiratory or skin sensitization

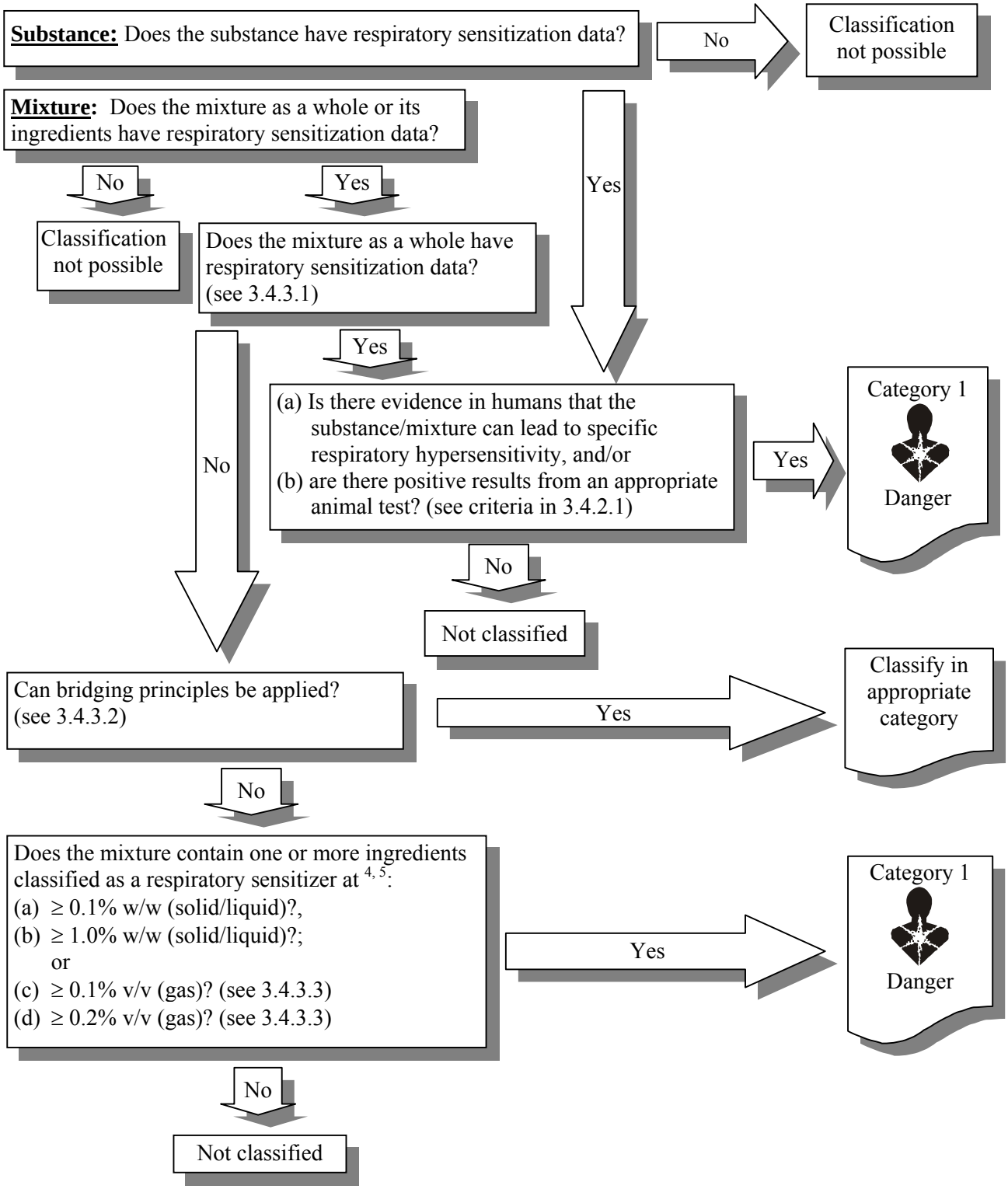
	Respiratory sensitization Category 1	**Skin sensitization Category 1**
Symbol	Health hazard	Exclamation mark
Signal word	Danger	Warning
Hazard statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

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-offs 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 a supplemental label element 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.

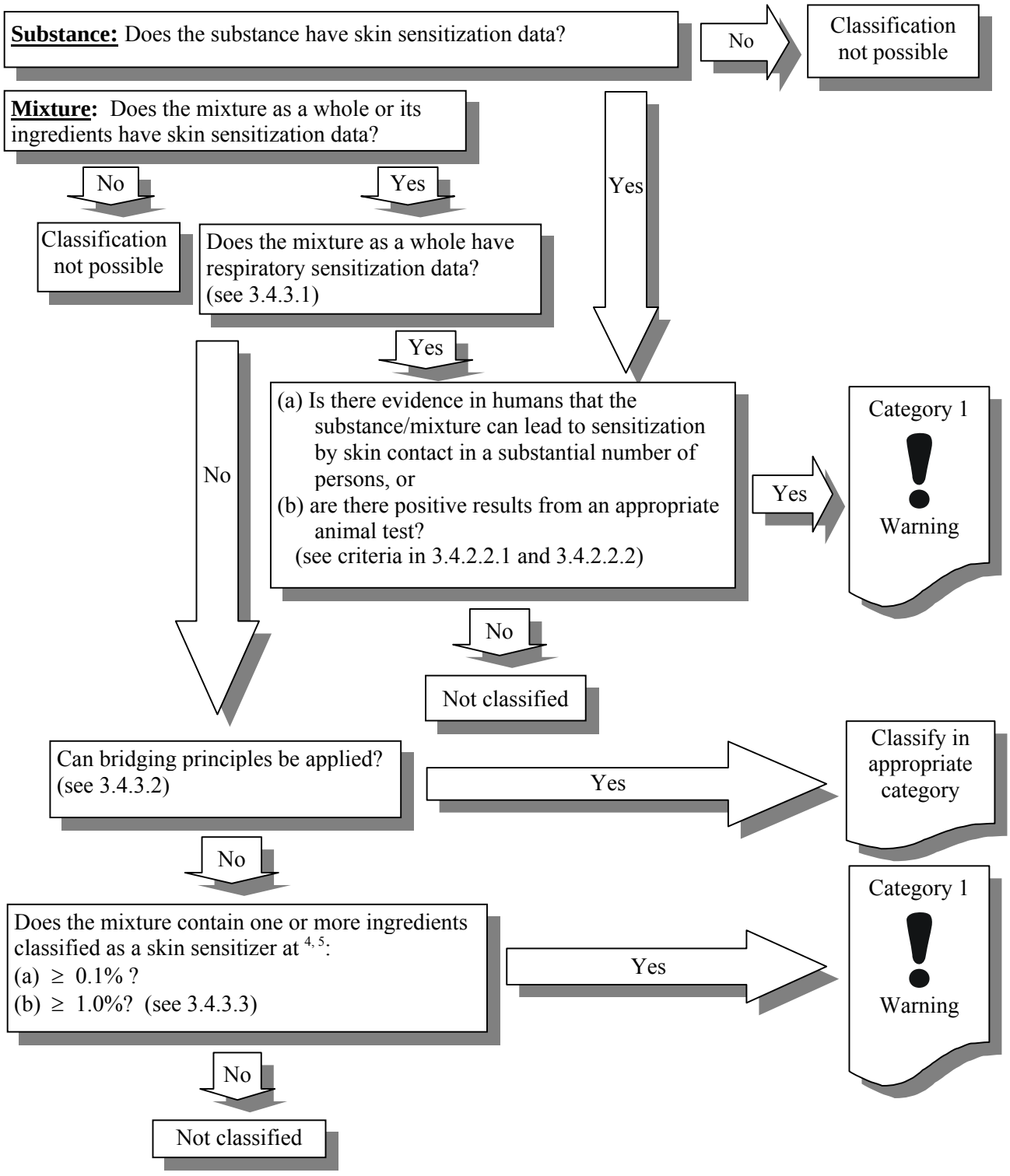
3.4.5.1 *Decision logic 3.4.1 for respiratory sensitization*



[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.*

CHAPTER 3.5

GERM CELL MUTAGENICITY

3.5.1 Definitions and general considerations

3.5.1.1 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.

3.5.1.2 In the present context, commonly found definitions of the terms mutagenic, mutagen, mutations and genotoxic are used. A *mutation* is defined as a permanent change in the amount or structure of the genetic material in a cell.

3.5.1.3 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.

3.5.1.4 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.

3.5.2 Classification criteria for substances

3.5.2.1 The classification system provides for two different categories of germ cell mutagens to accommodate the weight of evidence available. The two-category system is described in the following.

3.5.2.2 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in *in vitro* tests may also be considered.

3.5.2.3 The system is hazard based, classifying chemicals on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of chemical substances.

3.5.2.4 Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in OECD Test Guidelines. Evaluation of the test results should be done using expert judgement and all the available evidence should be weighed for classification.

3.5.2.5 Examples of *in vivo* heritable germ cell mutagenicity tests are:

Rodent dominant lethal mutation test (OECD 478)
Mouse heritable translocation assay (OECD 485)
Mouse specific locus test

3.5.2.6 Examples of *in vivo* somatic cell mutagenicity tests are:

Mammalian bone marrow chromosome aberration test (OECD 475)
Mouse spot test (OECD 484)
Mammalian erythrocyte micronucleus test (OECD 474)

Figure 3.5.1: Hazard categories for germ cell mutagens

<u>CATEGORY 1:</u> Chemicals known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans

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

Positive evidence from human epidemiological studies.

Category 1B: Chemicals 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.

<u>CATEGORY 2</u>: Chemicals 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*:** *Chemicals which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.*

3.5.2.7 Examples of mutagenicity/genotoxicity tests in germ cells are:

(a) Mutagenicity tests:

Mammalian spermatogonial chromosome aberration test (OECD 483)
Spermatid micronucleus assay

(b) Genotoxicity tests:

Sister chromatid exchange analysis in spermatogonia
Unscheduled DNA synthesis test (UDS) in testicular cells

3.5.2.8 Examples of genotoxicity tests in somatic cells are:

Liver Unscheduled DNA Synthesis (UDS) *in vivo* (OECD 486)
Mammalian bone marrow Sister Chromatid Exchanges (SCE)

3.5.2.9 Examples of *in vitro* mutagenicity tests are:

In vitro mammalian chromosome aberration test (OECD 473)
In vitro mammalian cell gene mutation test (OECD 476)
Bacterial reverse mutation tests (OECD 471)

3.5.2.10 The classification of individual substances should be based on the total weight of evidence available, using expert judgement. In those instances where a single well-conducted test is used for classification, it should provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the chemical compared to the route of human exposure should also be taken into account.

3.5.3 Classification criteria for mixtures

3.5.3.1 *Classification of mixtures when data are available for the mixture itself*

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 the ingredients classified as germ cell mutagens. The classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

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

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

3.5.3.2.2 *Dilution*

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

3.5.3.2.3 *Batching*

The germ cell mutagenic potential 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 produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the germ cell mutagenic potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.5.3.2.4 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the germ cell mutagenicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be classified in the same category.

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

The mixture will be classified as a mutagen when at least one ingredient has been classified as a Category 1 or Category 2 mutagen and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.5.1 below for Category 1 and 2 respectively.

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 1 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).*

3.5.4 Hazard communication

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. The table below presents specific label elements for substances and mixtures classified as germ cell mutagens based on the criteria in this chapter.

Table 3.5.2: Label elements for germ cell mutagenicity

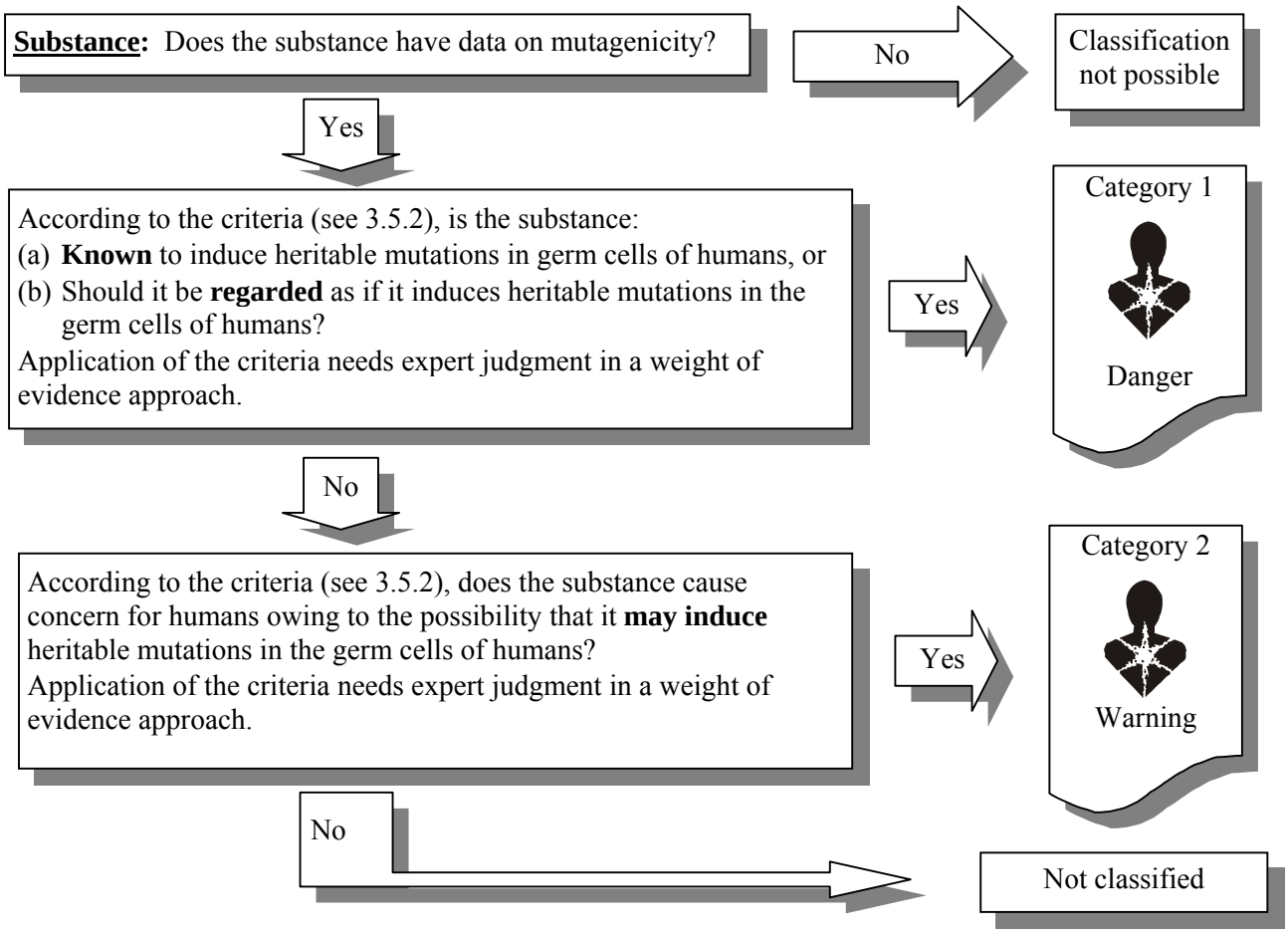
	Category 1A	**Category 1B**	**Category 2**
Symbol	Health hazard	Health hazard	Health hazard
Signal word	Danger	Danger	Warning
Hazard statement	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause genetic defects (state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

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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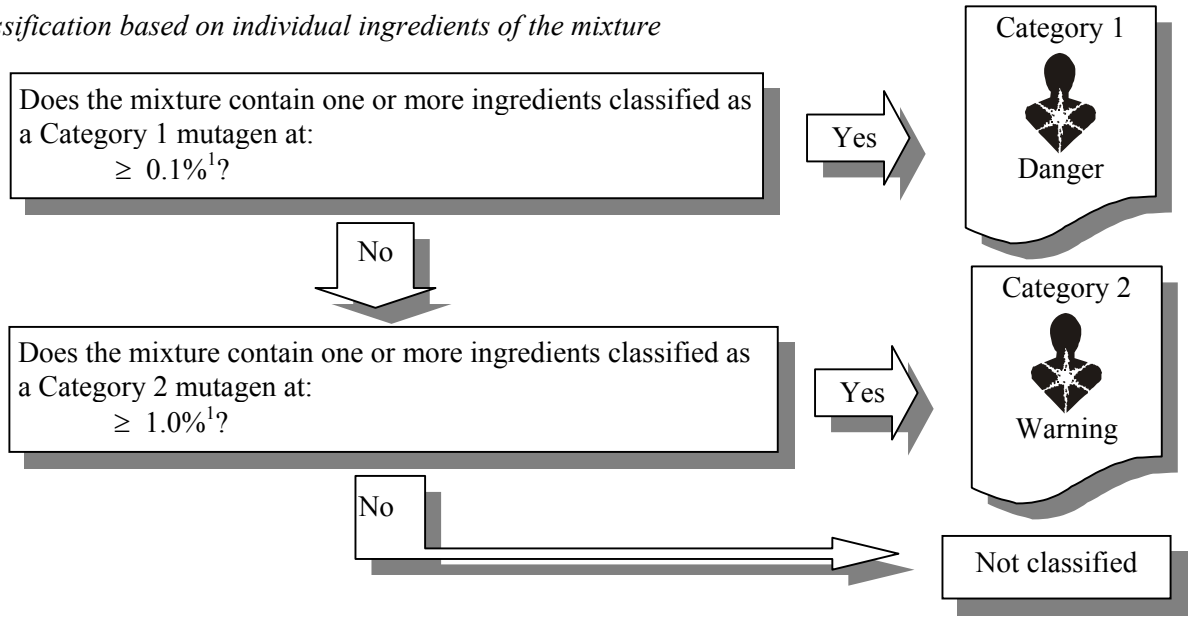
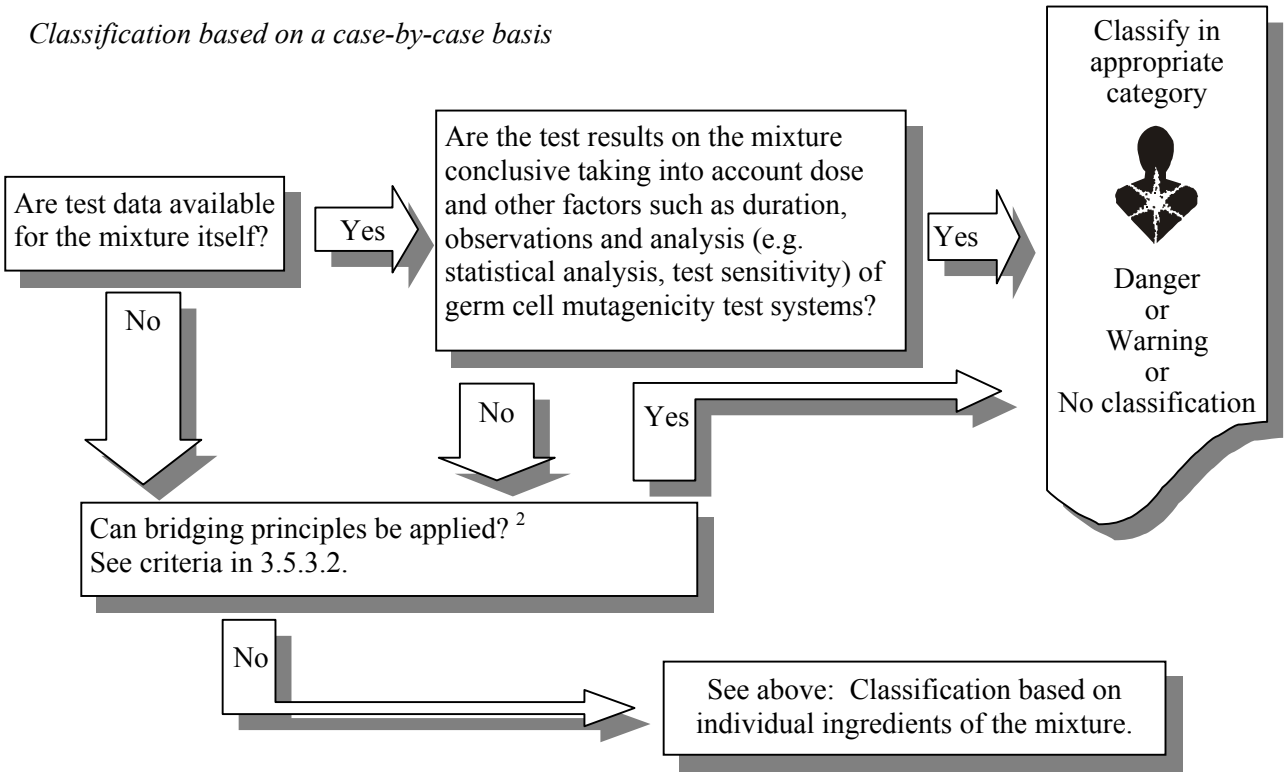
3.5.5.1.2 ***Decision logic 3.5.2 for mixtures***

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.*

3.5.5.2 ***Guidance***

It is increasingly accepted that the process of chemical-induced tumorigenesis in man and animals involves genetic changes in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of chemicals in somatic and/or germ cells of mammals *in vivo* may have implications for the potential classification of these chemicals as carcinogens (see also Carcinogenicity, Chapter 3.6, para. 3.6.2.5.3).

CHAPTER 3.6

CARCINOGENICITY

3.6.1 Definitions

The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence. Substances 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 chemical as posing a carcinogenic hazard is based on the inherent properties of the substance and does not provide information on the level of the human cancer risk which the use of the chemical may represent.

3.6.2 Classification criteria for substances

3.6.2.1 For the purpose of classification for carcinogenicity, chemical 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.

Figure 3.6.1: Hazard categories for carcinogens

CATEGORY 1: Known or presumed human carcinogens

The placing of a chemical in Category 1 is done on the basis of epidemiological and/or animal data. An individual chemical may be further distinguished:

Category 1A: Known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence.

Category 1B: **Presumed to have carcinogenic potential for humans; the placing of a chemical 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 chemical 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

CATEGORY 2: **Suspected human carcinogens**

The placing of a chemical 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 chemical 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

3.6.2.2 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for chemicals which have an intrinsic property to produce such toxic effects. The evaluations should be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

3.6.2.3 *Carcinogen classification* is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place chemicals with human cancer potential into hazard categories.

3.6.2.4 *Strength of evidence* involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms "sufficient" and "limited" are used here as they have been defined by the International Agency for Research on Cancer (IARC) and are outlined in 3.6.5.3.1.

3.6.2.5 *Additional considerations (weight of evidence)*: Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

3.6.2.5.1 The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.5.2 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) Tumour type and background incidence;

(b) Multisite responses;

(c) Progression of lesions to malignancy;

(d) Reduced tumour latency;

Additional factors which may increase or decrease the level of concern include:

(e) Whether responses are in single or both sexes;

(f) Whether responses are in a single species or several species;

(g) Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity;

(h) Routes of exposure;

(i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(j) The possibility of a confounding effect of excessive toxicity at test doses;

(k) Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

Guidance on how to consider important factors in classification of carcinogenicity is included in 3.6.5.3

3.6.2.5.3 *Mutagenicity:* It is recognized that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a chemical has a potential for carcinogenic effects.

3.6.2.5.4 The following additional considerations apply to classification of chemicals into either Category 1 or Category 2. A chemical that has not been tested for carcinogenicity may in certain instances be classified in Category 1 or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

3.6.2.5.5 The classification should also take into consideration whether or not the chemical is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

3.6.2.5.6 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

3.6.2.6 It is realized that some regulatory authorities may need flexibility beyond that developed in the hazard classification scheme. For inclusion into Safety Data Sheets, positive results in any carcinogenicity study performed according to good scientific principles with statistically significant results may be considered.

3.6.2.7 The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation Carcinogenic potency as used here does not preclude risk assessment. The proceedings of a WHO/IPCS workshop on the *Harmonization of Risk Assessment for Carcinogenicity and Mutagenicity (Germ cells)-A Scoping Meeting (1995, Carshalton, UK)*, points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens.

3.6.3 Classification criteria for mixtures

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

Classification of mixtures will be based on the available test data of 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. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of carcinogenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

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

3.6.3.2.1 Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles.

This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.6.3.2.2 *Dilution*

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

3.6.3.2.3 *Batching*

The carcinogenic potential 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 produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the carcinogenic potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.6.3.2.4 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the carcinogenicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

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

The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.6.1 for Category 1 and 2 respectively.

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 1 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.*

NOTE 1: *If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 1%, whereas others would normally not require a label in this case.*

NOTE 2: *If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an SDS and a label would generally be expected.*

3.6.4 Hazard communication

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 3.6.2 below presents specific label elements for substances and mixtures that are classified as carcinogenic based on the criteria set forth in this chapter.

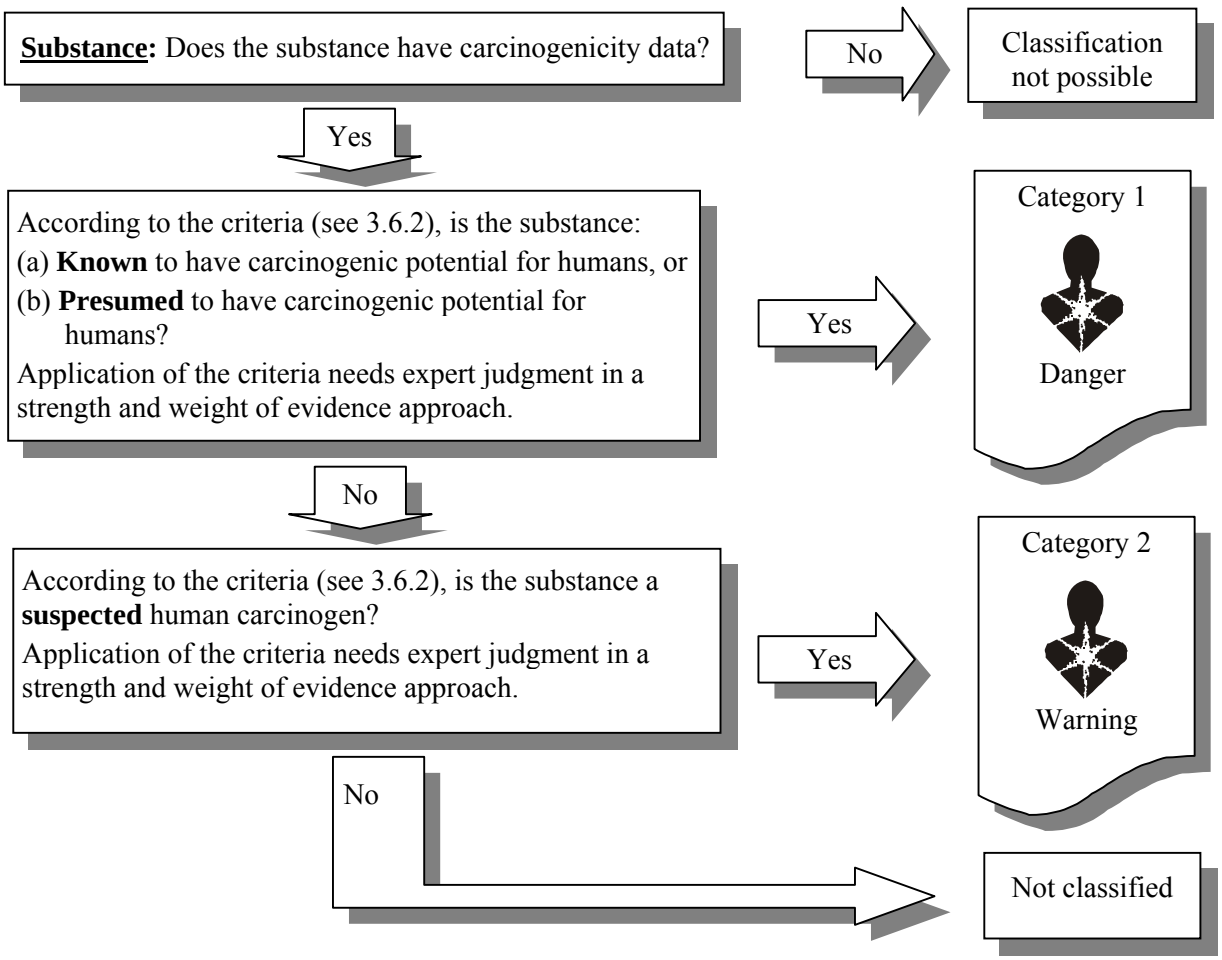
Table 3.6.2: Label elements for carcinogenicity

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

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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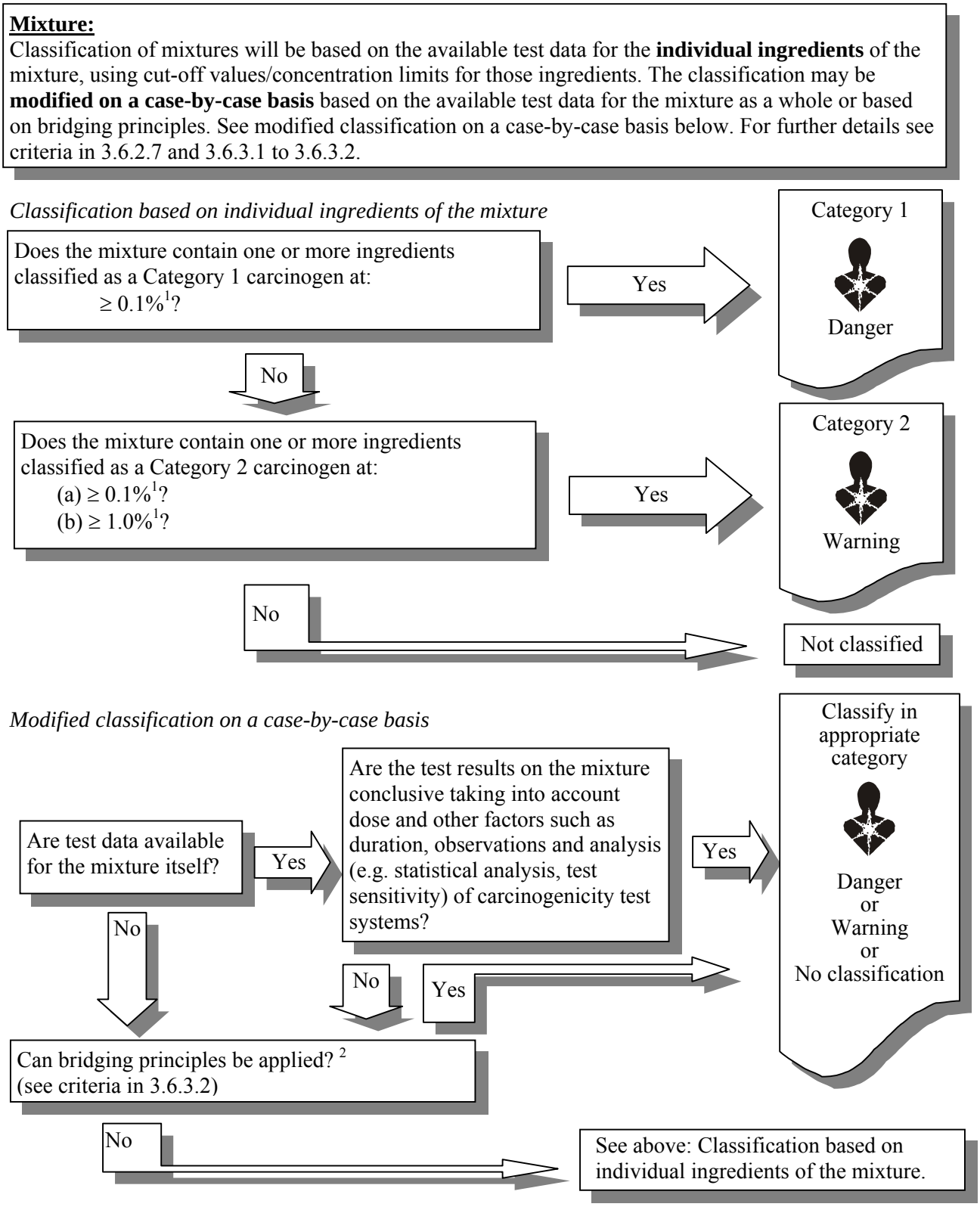
3.6.5.2 ***Decision logic 3.6.2 for mixtures***



[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.*

3.6.5.3 ***Background guidance***

3.6.5.3.1 Excerpts[3] from monographs of the International Agency for Research on Cancer (IARC) *Monographs programme on the evaluation of the strength of evidence of carcinogenic risks to humans* follow as in 3.6.5.3.1.1 and 3.6.5.3.1.2[4].

3.6.5.3.1.1 *Carcinogenicity in humans*

3.6.5.3.1.1.1 The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

(a) Sufficient evidence of carcinogenicity: the working group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;

(b) Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

3.6.5.3.1.1.2 In some instances the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

3.6.5.3.1.2 *Carcinogenicity in experimental animals*

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

(a) Sufficient evidence of carcinogenicity: The working group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (i) two or more species of animals or (ii) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols;

(b) Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset;

(c) Limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (i) the evidence of carcinogenicity is restricted to a single experiment; or (ii) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (iii) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

[3] *The excerpts from IARC Monographs, which follow, are taken from the OECD Integrated Document on Harmonization of Classification and Labelling. They are not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL, but are provided here as additional guidance.*

[4] *See 3.6.2.4.*

3.6.5.3.2 *Guidance on how to consider important factors in classification of carcinogenicity**

The guidance provides an approach to analysis rather than hard and fast rules. This section provides some considerations. The weight of evidence analysis called for in GHS is an integrative approach which considers important factors in determining carcinogenic potential along with the strength of evidence analysis. The IPCS "*Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis*" (2001), the International Life Sciences Institute (ILSI) "*Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action*" (Meek et al., 2003; Cohen et al., 2003, 2004) and the IARC (Preamble section 12(b)) provide a basis for systematic assessments which may be performed in a consistent fashion internationally; the IPCS also convened a panel in 2004 to further develop and clarify the human relevance framework. However, the internationally available documents are not intended to dictate answers, nor provide lists of criteria to be checked off.

3.6.5.3.2.1 Mode of action

The various international documents on carcinogen assessment all note that mode of action in and of itself, or consideration of comparative metabolism, should be evaluated on a case-by-case basis and are part of an analytic evaluative approach. One must look closely at any mode of action in animal experiments taking into consideration comparative toxicokinetics/toxicodynamics between the animal test species and humans to determine the relevance of the results to humans. This may lead to the possibility of discounting very specific effects of certain types of chemicals. Life stage-dependent effects on cellular differentiation may also lead to qualitative differences between animals and humans. Only if a mode of action of tumour development is conclusively determined not to be operative in humans may the carcinogenic evidence for that tumour be discounted. However, a weight of evidence evaluation for a substance calls for any other tumorigenic activity to be evaluated as well.

3.6.5.3.2.2 Responses in multiple animal experiments

Positive responses in several species add to the weight of evidence, that a chemical is a carcinogen. Taking into account all of the factors listed in 3.6.2.5.2 and more, such chemicals with positive outcomes in two or more species would be provisionally considered to be classified in GHS Category 1B until human relevance of animal results are assessed in their entirety. It should be noted, however, that positive results for one species in at least two independent studies, or a single positive study showing unusually strong evidence of malignancy may also lead to Category 1B.

3.6.5.3.2.3 Responses are in one sex or both sexes

Any case of gender-specific tumours should be evaluated in light of the total tumorigenic response to the substance observed at other sites (multi-site responses or incidence above background) in determining the carcinogenic potential of the substance.

If tumours are seen only in one sex of an animal species, the mode of action should be carefully evaluated to see if the response is consistent with the postulated mode of action. Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response.

3.6.5.3.2.4 Confounding effects of excessive toxicity or localized effects

Tumours occurring only at excessive doses associated with severe toxicity generally have doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard. For example, forestomach tumours, following administration by gavage of an irritating or corrosive, non-mutagenic chemical, may be of questionable relevance. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered.

3.6.5.3.2.5 Tumour type, reduced tumour latency

Unusual tumour types or tumours occurring with reduced latency may add to the weight of evidence for the carcinogenic potential of a substance, even if the tumours are not statistically significant.

Toxicokinetic behaviour is normally assumed to be similar in animals and humans, at least from a qualitative perspective. On the other hand, certain tumour types in animals may be associated with toxicokinetics or toxicodynamics that are unique to the animal species tested and may not be predictive of carcinogenicity in humans. Very few such examples have been agreed internationally. However, one example is the lack of human relevance of kidney tumours in male rats associated with compounds causing α2u-globulin nephropathy (IARC, Scientific Publication N° 147). Even when a particular tumour type may be discounted, expert judgment must be used in assessing the total tumour profile in any animal experiment.

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CHAPTER 3.7

REPRODUCTIVE TOXICITY

3.7.1 Definitions and general considerations

3.7.1.1 *Reproductive toxicity*

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document N°225 Principles for evaluating health risks to reproduction associated with exposure to chemicals. 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.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) Adverse effects on sexual function and fertility;

(b) Adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, chemicals with these effects would be classified as reproductive toxicants with a general hazard statement.

3.7.1.2 *Adverse effects on sexual function and fertility*

Any effect of chemicals that would interfere with sexual function and fertility. This may include, but not be limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (see 3.7.2.1). This is because it is desirable to be able to classify chemicals specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

3.7.1.3 *Adverse effects on development of the offspring*

Taken in its widest sense, developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women and men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth and functional deficiency.

3.7.2 *Classification criteria for substances*

3.7.2.1 *Hazard categories*

For the purpose of classification for reproductive toxicity, chemical substances are allocated to one of two categories. Effects on sexual function and fertility, and on development, are considered. In addition, effects on lactation are allocated to a separate hazard category.

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.
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.

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.

3.7.2.2 *Basis of classification*

3.7.2.2.1 Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence. Classification as a reproductive toxicant is intended to be used for chemicals which have an intrinsic, specific property to produce an adverse effect on reproduction and chemicals should not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

3.7.2.2.2 In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity.

3.7.2.2.3 For human evidence to provide the primary basis for a Category 1A classification there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification should ideally be from well conducted epidemiological studies which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans should be supplemented with adequate data from studies in experimental animals and classification in Category 1B should be considered.

3.7.2.3 *Weight of evidence*

3.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also 3.7.2.2.3).

3.7.2.3.2 Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information, which could reduce or increase concerns about the hazard to human health. If it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.3.3 In some reproductive toxicity studies in experimental animals the only effects recorded may be considered of low or minimal toxicological significance and classification may not necessarily be the outcome. These include for example small changes in semen parameters or in the incidence of spontaneous defects in the foetus, small changes in the proportions of common foetal variants such as are observed in skeletal examinations, or in foetal weights, or small differences in postnatal developmental assessments.

3.7.2.3.4 Data from animal studies ideally should provide clear evidence of specific reproductive toxicity in the absence of other, systemic, toxic effects. However, if developmental toxicity occurs together with other toxic effects in the dam, the potential influence of the generalized adverse effects should be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/foetus first, and then evaluate maternal toxicity, along with any other factors, which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses should not be automatically discounted. Discounting developmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

3.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity should not be used to negate findings of embryo/foetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, e.g. irreversible effects such as structural malformations. In some situations it is reasonable to assume that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, for example if the chemical is so toxic that dams fail to thrive and there is severe inanition; they are incapable of nursing pups; or they are prostrate or dying.

3.7.2.4 *Maternal toxicity*

3.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. So, in the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, should be used to determine the degree of influence that should be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus should be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2 Based on pragmatic observation, it is believed that maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited numbers of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification

should be considered where there is significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.

3.7.2.4.3 Classification should not automatically be discounted for chemicals that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a chemical is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it may be reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification may not necessarily be the outcome in the case of minor developmental changes e.g. small reduction in foetal/pup body weight, retardation of ossification when seen in association with maternal toxicity.

3.7.2.4.4 Some of the end-points used to assess maternal toxicity are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

(a) Maternal mortality: an increased incidence of mortality among the treated dams over the controls should be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10% is considered excessive and the data for that dose level should not normally be considered for further evaluation.

(b) Mating index (No. animals with seminal plugs or sperm/No. mated × 100) [1]

(c) Fertility index (No. animals with implants/No. of matings × 100) [1]

(d) Gestation length (if allowed to deliver)

(e) Body weight and body weight change: consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight should be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

(f) Food and water consumption (if relevant): the observation of a significant decrease in the average food or water consumption in treated dams compared to the control group may be useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption should be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

(g) Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies): The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group may be useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs should be reported in the study. Examples of frank clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

[1] *It is recognized that this index can also be affected by the male.*

(h) Post-mortem data: increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, e.g. absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

3.7.2.5 ***Animal and experimental data***

3.7.2.5.1 A number of internationally accepted test methods are available; these include methods for developmental toxicity testing (e.g. OECD Test Guideline 414, ICH Guideline S5A, 1993), methods for peri- and post-natal toxicity testing (e.g. ICH S5B, 1995) and methods for one or two-generation toxicity testing (e.g. OECD Test Guidelines 415, 416).

3.7.2.5.2 Results obtained from Screening Tests (e.g. OECD Guidelines 421 - Reproduction/ Developmental Toxicity Screening Test, and 422 - Combined Repeated Dose Toxicity Study with Reproduction/Development Toxicity Screening Test) can also be used to justify classification, although it is recognized that the quality of this evidence is less reliable than that obtained through full studies.

3.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive function and which occur in the absence of significant generalized toxicity, may be used as a basis for classification, e.g. histopathological changes in the gonads.

3.7.2.5.4 Evidence from *in vitro* assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgement must be used to assess the adequacy of the data. Inadequate data should not be used as a primary support for classification.

3.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.5.6 Studies involving routes of administration such as intravenous or intraperitoneal injection, which may result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, e.g. by irritation, must be interpreted with extreme caution and on their own would not normally be the basis for classification.

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification. However, there was no agreement within the OECD Task Force regarding the inclusion within the criteria of a specified dose as a limit dose. Some Test Guidelines specify a limit dose, other Test Guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

3.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information

indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on Maternal Toxicity for further guidance in this area.

3.7.2.5.9 However, specification of the actual "limit dose" will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg unless expected human response indicates the need for a higher dose level, has been recommended as a limit dose.

3.7.2.5.10 Further discussions are needed on the inclusion within the criteria of a specified dose as a limit dose.

3.7.3 Classification criteria for mixtures

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

Classification of mixtures will be based on the available test data of the individual constituents of the mixture using cut-off values/concentration limits for the ingredients of the mixture. The classification may be modified on a case-by case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of reproduction test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

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

3.7.3.2.1 Where the mixture itself has not been tested to determine its reproductive toxicity, 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.

3.7.3.2.2 *Dilution*

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

3.7.3.2.3 *Batching*

The reproductive toxicity potential 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 produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the reproductive toxicity potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.7.3.2.4 *Substantially similar mixtures*

Given the following:

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

(b) The concentration of Ingredient B, toxic to reproduction, is the same in both mixtures;

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the reproductive toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

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

3.7.3.3.1 The mixture will be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1 or Category 2 reproductive toxicant and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.7.1 below for Category 1 and 2 respectively.

3.7.3.3.2 The mixture will be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.7.1 for the additional category for effects on or via lactation.

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]

Ingredients classified as:	Cut-off/concentration limits triggering classification of a mixture as:		
	Category 1 reproductive toxicant	**Category 2 reproductive toxicant**	**Additional category for effects on or via lactation**
Category 1 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.*

NOTE 1*: If a Category 1 reproductive toxicant or substance classified in the additional category for effects on or via lactation is present in the mixture as an ingredient at a concentration between 0.1% and 0.3%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 0.3%, whereas others would normally not require a label in this case.*

NOTE 2*: If a Category 1 reproductive toxicant or substance classified in the additional category for effects on or via lactation is present in the mixture as an ingredient at a concentration of ≥ 0.3%, both an SDS and a label would generally be expected.*

NOTE 3*: If a Category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration between 0.1% and 3.0%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 3.0%, whereas others would normally not require a label in this case.*

NOTE 4*: If a Category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration of ≥ 3.0%, both an SDS and a label would generally be expected.*

3.7.4 Hazard communication

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 3.7.2: Label elements for reproductive toxicity

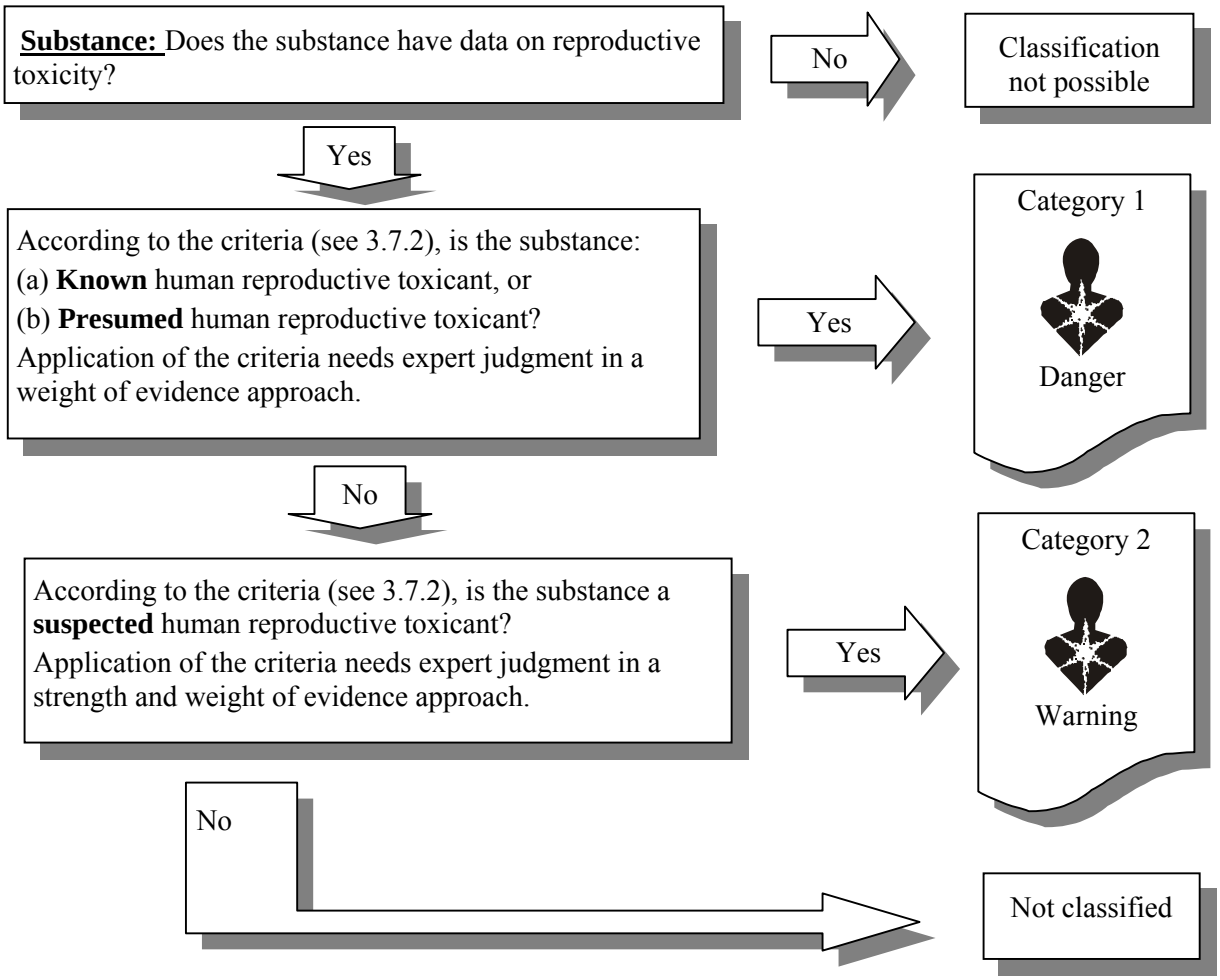
	Category 1A	**Category 1B**	**Category 2**	**Additional category for effects on or via lactation**
Symbol	Health hazard	Health hazard	Health hazard	*No symbol*
Signal word	Danger	Danger	Warning	*No signal word*
Hazard statement	May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May damage fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause harm to breast-fed children.

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*

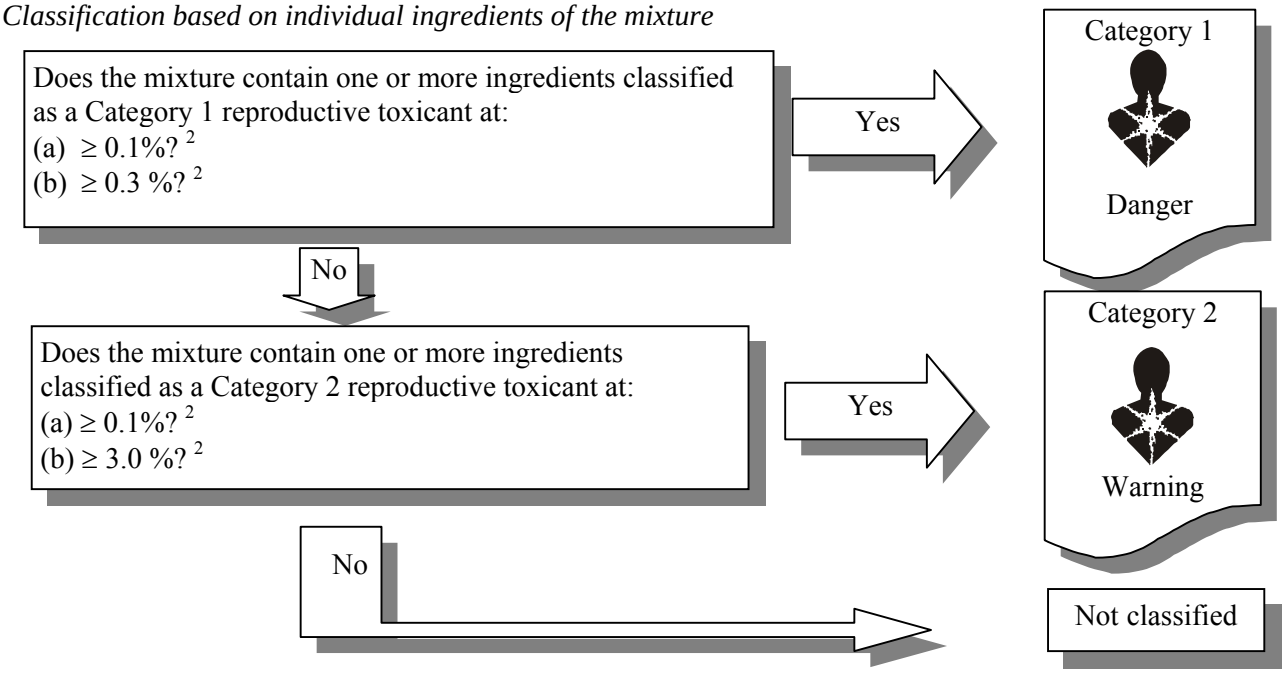


(Cont'd on next page)

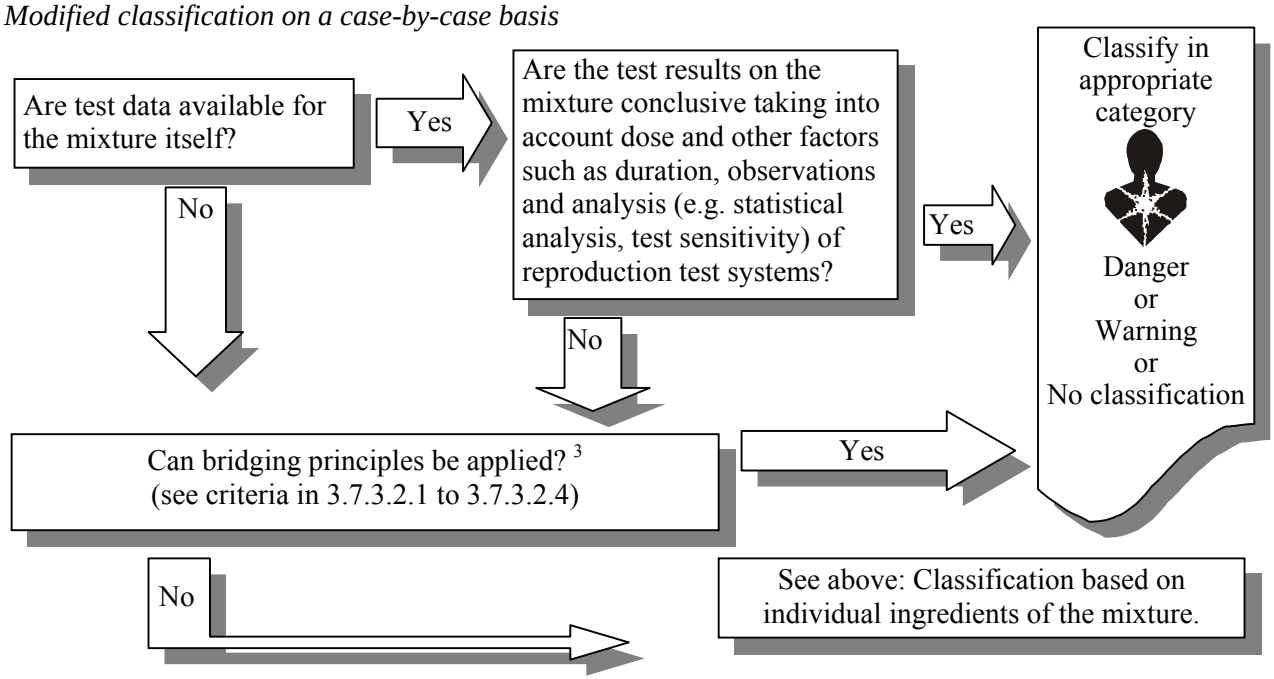
3.7.5.1.2 ***Decision logic 3.7.2 for mixtures***

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



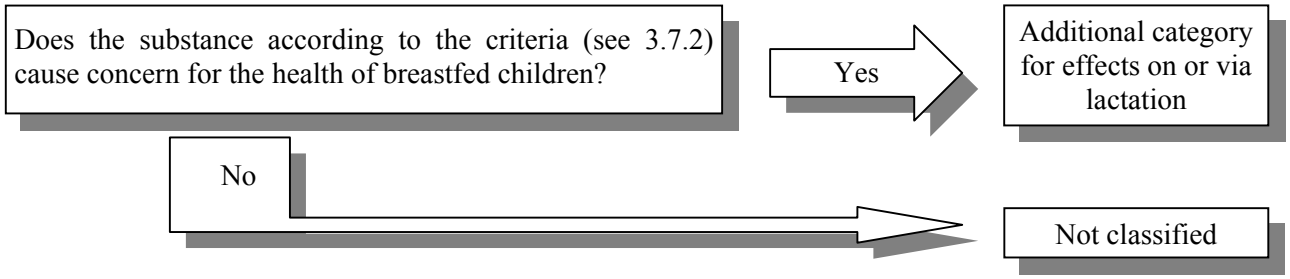
(*Cont'd on next page*)

[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***

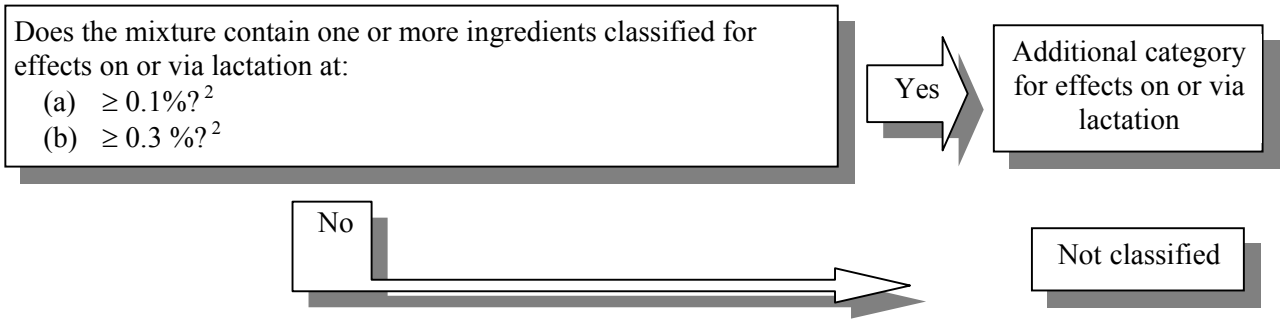
3.7.5.2.1 *Decision logic 3.7.3 for substances*



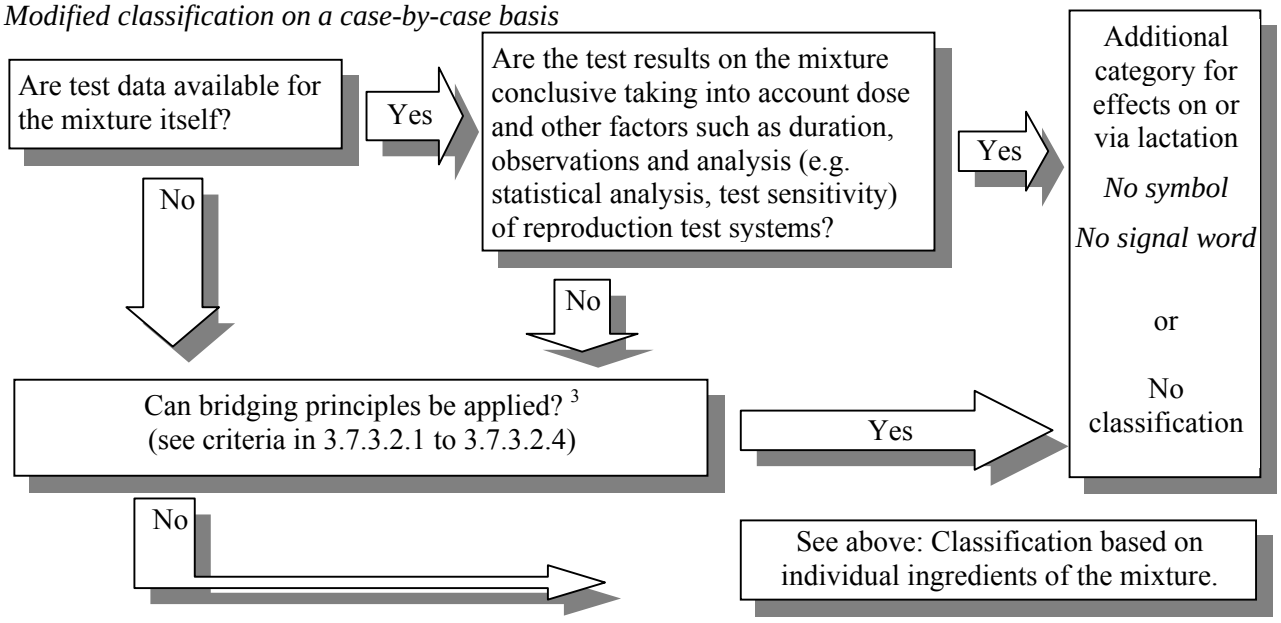
3.7.5.2.2 *Decision logic 3.7.4 for mixtures*

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



[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.*

CHAPTER 3.8

SPECIFIC TARGET ORGAN TOXICITY SINGLE EXPOSURE

3.8.1 Definitions and general considerations

3.8.1.1 The purpose of this chapter is to provide a means of classifying substances and mixtures that produce specific, non lethal target organ toxicity arising from a single exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in chapters 3.1 to 3.7 and 3.10 are included (see also para. 3.8.1.6).

3.8.1.2 Classification identifies the substance or mixture as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

3.8.1.3 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.

3.8.1.4 Assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

3.8.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.8.1.6 Specific target organ toxicity following a repeated exposure is classified in the GHS as described in *Specific target organ toxicity – Repeated exposure* (Chapter 3.9) and is therefore excluded from the present chapter. Other specific toxic effects, listed below are assessed separately in the GHS and consequently are not included here:

(a) acute toxicity (Chapter 3.1);

(b) skin corrosion/irritation (Chapter 3.2);

(c) serious eye damage/eye irritation (Chapter 3.3);

(b) respiratory or skin sensitization (Chapter 3.4);

(e) germ cell mutagenicity (Chapter 3.5);

(f) carcinogenicity (Chapter 3.6);

(g) reproductive toxicity (Chapter 3.7); and

(h) aspiration toxicity (Chapter 3.10).

3.8.1.7 The classification criteria in this chapter are organized as criteria for substances Categories 1 and 2 (see 3.8.2.1), criteria for substances Category 3 (see 3.8.2.2) and criteria for mixtures (see 3.8.3). See also Figure 3.8.1.

3.8.2 Classification criteria for substances

3.8.2.1 *Substances of Category 1 and Category 2*

3.8.2.1.1 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).

Figure 3.8.1: Hazard categories for specific target organ toxicity following 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).

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.

NOTE: *For these 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 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*.

3.8.2.1.2 The relevant route of exposure by which the classified substance produces damage should be identified.

3.8.2.1.3 Classification is determined by expert judgement, on the basis of the weight of all evidence available including the guidance presented below.

3.8.2.1.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification.

3.8.2.1.5 The information required to evaluate specific target organ toxicity comes either from single exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

3.8.2.1.6 In exceptional cases, based on expert judgement, it may be appropriate to place certain substances with human evidence of target organ toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans should not be considered in the classification and any available evidence from animal studies should be consistent with the Category 2 classification. In other words, if there are also animal data available on the chemical that warrant Category 1 classification, the chemical should be classified as Category 1.

3.8.2.1.7 *Effects considered to support classification for Category 1 and 2*

3.8.2.1.7.1 Evidence associating single exposure to the substance with a consistent and identifiable toxic effect demonstrates support for classification.

3.8.2.1.7.2 It is recognized that evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

3.8.2.1.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, and macroscopic and microscopic pathological examination and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process.

Examples of relevant toxic effects in humans and/or animals are provided below:

(a) Morbidity resulting from single exposure;

(b) Significant functional changes, more than transient in nature, in the respiratory system, central or peripheral nervous systems, other organs or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);

(c) Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

(d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;

(g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

3.8.2.1.8 *Effects considered not to support classification for Category 1 and 2*

It is recognized that effects may be seen that would not justify classification.

Examples of such effects in humans and/or animals are provided below:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;

(b) Small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

(c) Changes in organ weights with no evidence of organ dysfunction;

(d) Adaptive responses that are not considered toxicologically relevant;

(e) Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification.

3.8.2.1.9 *Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals for Category 1 and 2*

3.8.2.1.9.1 In order to help reach a decision about whether a substance should be classified or not, and to what degree it would be classified (Category 1 vs. Category 2), dose/concentration "guidance values" are provided for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged.

3.8.2.1.9.2 Thus, in animal studies, when significant toxic effects are observed, that would indicate classification, consideration of the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the dose/concentration).

3.8.2.1.9.3 The guidance value ranges proposed for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.1.

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 ≤ 300	2000 ≥ C > 300	Guidance values do not apply[b]
Dermal (rat or rabbit)	mg/kg body weight	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	ppm	C ≤ 2500	5000 ≥ C > 2500	
Inhalation (rat) vapour	mg/1	C ≤ 10	20 ≥ C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1.0	5.0 ≥ 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.*

3.8.2.1.9.4 Thus it is feasible that a specific profile of toxicity is seen to occur at a dose/concentration below the guidance value, e.g. < 2000 mg/kg body weight by the oral route, however the nature of the effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, e.g. ≥ 2000 mg/kg body weight by the oral route, and in addition there is supplementary information from other sources, e.g. other single dose studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification would be the prudent action to take.

3.8.2.1.10 *Other considerations*

3.8.2.1.10.1 When a chemical is characterized only by use of animal data (typical of new chemicals, but also true for many existing chemicals), the classification process would include reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

3.8.2.1.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to single exposure to a chemical substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a chemical is unclassified because specific target organ toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ toxic effect, the substance should be classified.

3.8.2.1.10.3 A chemical that has not been tested for specific target organ toxicity may in certain instances, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

3.8.2.1.10.4 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.

3.8.2.2 *Substances of Category 3*

3.8.2.2.1 *Criteria for respiratory tract irritation*

The criteria for respiratory tract irritation as Category 3 are:

(a) Respiratory irritant effects (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data;

(b) Subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (e.g. electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids;

(c) The symptoms observed in humans should also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of this classification endpoint;

(d) There are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation;

(e) This special classification would occur only when more severe organ effects including in the respiratory system are not observed.

3.8.2.2.2 *Criteria for narcotic effects*

The criteria for narcotic effects as Category 3 are:

(a) Central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness;

(b) Narcotic effects observed in animal studies may include lethargy, lack of coordination righting reflex, narcosis, and ataxia. If these effects are not transient in nature, then they should be considered for classification as Category 1 or 2.

3.8.3 Classification criteria for mixtures

3.8.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

3.8.3.2 *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 this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

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

3.8.3.3.2 *Dilution*

If a mixture is diluted with a diluent which has the same or a lower toxicity classification as the least toxic original ingredient and which is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.8.3.3.3 *Batching*

The toxicity 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 toxicity of the batch has changed. If the latter occurs, a new classification is necessary.

3.8.3.3.4 *Concentration of highly toxic mixtures*

If in a mixture of Category 1, the concentration of a toxic ingredient is increased, the concentrated mixture should be classified in Category 1 without additional testing.

3.8.3.3.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.8.3.3.6 Substantially similar mixtures

Given the following:

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

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

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

3.8.3.3.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolized form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolized mixtures for inhalation toxicity should be considered separately.

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

3.8.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.8.2 below for Category 1 and 2 respectively.

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) ≥ 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.*

***NOTE 1**: If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

***NOTE 2**: If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

***NOTE 3**: If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, some authorities classify this mixture as a Category 2 specific target organ toxicant, whereas others would not.*

***NOTE 4**: If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the*

ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.

NOTE 5: *If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

3.8.3.4.2 These cut-off values and consequent classifications should be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

3.8.3.4.3 Mixtures should be classified for either or both single and repeated dose toxicity independently.

3.8.3.4.4 Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

3.8.3.4.5 Care should be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A cut-off value/concentration limit of 20% has been suggested; however, it should be recognized that this cut-off value concentration limit may be higher or less depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgment should be exercised.

3.8.4 Hazard communication

3.8.4.1 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.

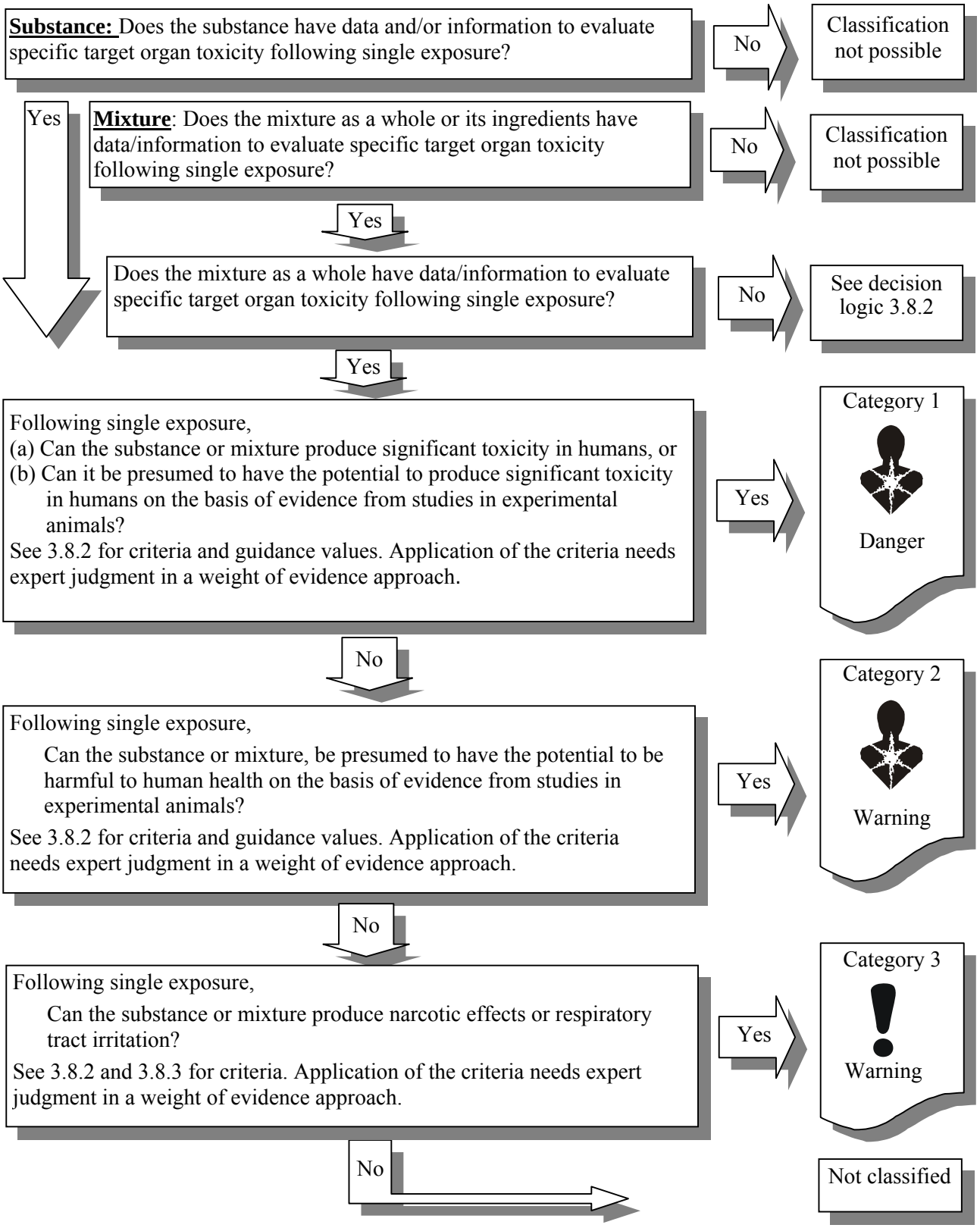
Table 3.8.3: Label elements for specific target organ toxicity after single exposure

	Category 1	**Category 2**	**Category 3**
Symbol	Health hazard	Health hazard	Exclamation mark
Signal word	Danger	Warning	Warning
Hazard statement	Causes damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause respiratory irritation; or May cause drowsiness or dizziness

3.8.5 Decision logic for specific target organ toxicity following single 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 study the criteria before and during use of the decision logic.

3.8.5.1 *Decision logic 3.8.1*



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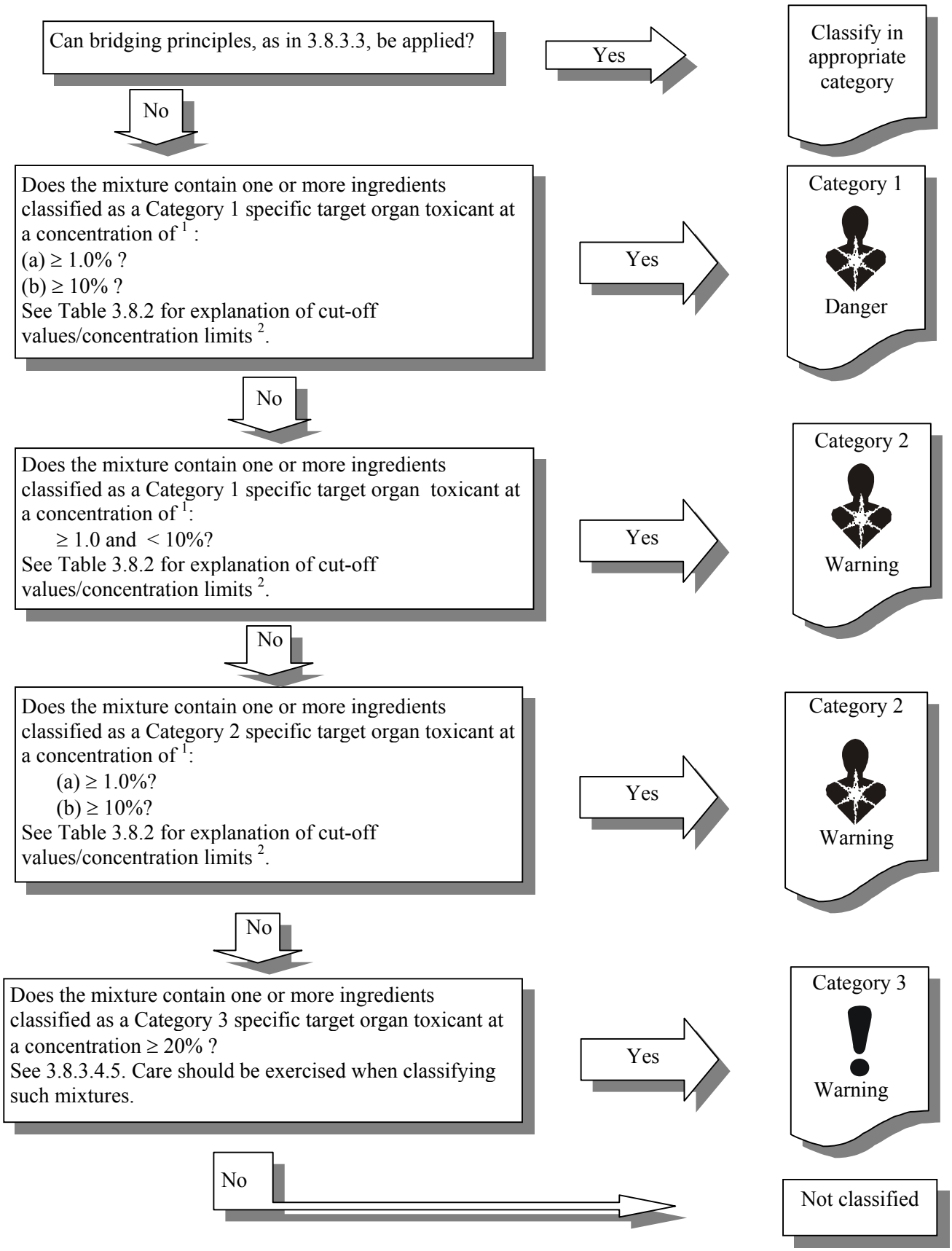
3.8.5.2 ***Decision logic 3.8.2***



[1] *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.*

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

CHAPTER 3.9

SPECIFIC TARGET ORGAN TOXICITY REPEATED EXPOSURE

3.9.1 Definitions and general considerations

3.9.1.1 The purpose of this document is to provide a means of classifying substances that produce specific target organ toxicity arising from a repeated exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

3.9.1.2 Classification identifies the chemical substance as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

3.9.1.3 Classification depends upon the availability of reliable evidence that a repeated exposure to the substance 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.

3.9.1.4 Assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

3.9.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.9.1.6 Non-lethal toxic effects observed after a single-event exposure are classified in the GHS as described in *Specific target organ toxicity – Single exposure* (Chapter 3.8) and are therefore excluded from the present chapter. Other specific toxic effects, such as acute /toxicity, serious eye damage/eye irritation, skin corrosion/irritation, respiratory or skin sensitization, carcinogenicity, germ cell mutagenicity, reproductive toxicity and aspiration toxicity are assessed separately in the GHS and consequently are not included here.

3.9.2 Classification criteria for substances

3.9.2.1 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.

Figure 3.9.1: Hazard categories for specific target organ toxicity following 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).

NOTE: *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.*

3.9.2.2 The relevant route of exposure by which the classified substance produces damage should be identified.

3.9.2.3 Classification is determined by expert judgement, on the basis of the weight of all evidence available including the guidance presented below.

3.9.2.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification. This taps the considerable body of industrial toxicology data collected over the years. Evaluation should be based on all existing data, including peer-reviewed published studies and additional data acceptable to regulatory agencies.

3.9.2.5 The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include haematological, clinico-chemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species may also be used. Other long-term exposure studies, e.g. for carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

3.9.2.6 In exceptional cases, based on expert judgement, it may be appropriate to place certain substances with human evidence of specific target organ toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans should not be considered in the classification and any available evidence from animal studies should be consistent with the Category 2 classification. In other words, if there are also animal data available on the chemical that warrant Category 1 classification, the chemical should be classified as Category 1.

3.9.2.7 ***Effects considered to support classification***

3.9.2.7.1 Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for classification.

3.9.2.7.2 It is recognized that evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

3.9.2.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, macroscopic and microscopic pathological examination and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process. Examples of relevant toxic effects in humans and/or animals are provided below:

(a) Morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, or due to the overwhelming of the de-toxification process by repeated exposure;

(b) Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);

(c) Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

(d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver);

(g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

3.9.2.8 ***Effects considered not to support classification***

It is recognized that effects may be seen that would not justify classification. Examples of such effects in humans and/or animals are provided below:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate “significant” toxicity;

(b) Small changes in clinical biochemistry, haematology or urinalysis parameters and /or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

(c) Changes in organ weights with no evidence of organ dysfunction;

(d) Adaptive responses that are not considered toxicologically relevant;

(e) Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification.

3.9.2.9 ***Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals***

3.9.2.9.1 In studies conducted in experimental animals, reliance on observation of effects alone, without reference to the duration of experimental exposure and dose/concentration, omits a fundamental concept of toxicology, i.e. all substances are potentially toxic, and what determines the toxicity is a function of the dose/concentration and the duration of exposure. In most studies conducted in experimental animals the test guidelines use an upper limit dose value.

3.9.2.9.2 In order to help reach a decision about whether a substance should be classified or not, and to what degree it would be classified (Category 1 vs. Category 2), dose/concentration "guidance values" are provided in Table 3.9.1 for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimize the test objective and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

3.9.2.9.3 Thus, in animal studies, when significant toxic effects are observed, that would indicate classification, consideration of the duration of experimental exposure and the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the duration of exposure and the dose/concentration).

3.9.2.9.4 The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

3.9.2.9.5 The guidance values proposed refer basically to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment should be done on a case-by-case basis; e.g. for a 28-day study the guidance values below would be increased by a factor of three.

3.9.2.9.6 Thus for Category 1 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur at or below the (suggested) guidance values as indicated in Table 3.9.1 would justify classification:

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	ppm/6h/d	50
Inhalation (rat) vapour	mg/litre/6h/d	0.2
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02

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

3.9.2.9.7 For Category 2 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur within the (suggested) guidance value ranges as indicated in Table 3.9.2 would justify classification:

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 - 100
Dermal (rat or rabbit)	mg/kg bw/d	20 - 200
Inhalation (rat) gas	ppm/6h/d	50 - 250
Inhalation (rat) vapour	mg/litre/6h/d	0.2 - 1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02 - 0.2

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

3.9.2.9.8 The guidance values and ranges mentioned in 3.2.9.9.6 and 3.2.9.9.7 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

3.9.2.9.9 Thus it is feasible that a specific profile of toxicity is seen to occur in repeat-dose animal studies at a dose/concentration below the guidance value, eg. < 100 mg/kg bw/day by the oral route, however the nature of the effect, e.g. nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect, may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, eg. ≥ 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, e.g. other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification would be the prudent action to take.

3.9.2.10 *Other considerations*

3.9.2.10.1 When a chemical is characterized only by use of animal data (typical of new chemicals, but also true for many existing chemicals), the classification process would include reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

3.9.2.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a chemical substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a chemical is unclassified because no specific target organ toxicity was seen at or below the proposed

dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance should be classified.

3.9.2.10.3 A chemical that has not been tested for specific target organ toxicity may in certain instances, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

3.9.2.10.4 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.

3.9.3 Classification criteria for mixtures

3.9.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

3.9.3.2 *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 this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

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

3.9.3.3.2 *Dilution*

If a mixture is diluted with a diluent which has the same or a lower toxicity classification as the least toxic original ingredient and which is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.9.3.3.3 *Batching*

The toxicity 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 toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.9.3.3.4 *Concentration of highly toxic mixtures*

If in a mixture of Category 1, the concentration of a toxic ingredient is increased, the concentrated mixture should be classified in Category 1 without additional testing.

3.9.3.3.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.9.3.3.6 *Substantially similar mixtures*

Given the following:

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

(ii) C + B;

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

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

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

3.9.3.3.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolized form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolized mixtures for inhalation toxicity should be considered separately.

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

3.9.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.9.3 for Category 1 and 2 respectively.

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.*

NOTE 1: *If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

NOTE 2: *If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

NOTE 3: *If a Category 1 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, some authorities classify this mixture as a Category 2 target organ toxicant, whereas others would not.*

NOTE 4: *If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

NOTE 5: *If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

3.9.3.4.2 These cut-off values and consequent classifications should be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

3.9.3.4.3 Mixtures should be classified for either or both single- and repeated-dose toxicity independently.

3.9.3.4.4 Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause specific target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

3.9.4 Hazard communication

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.

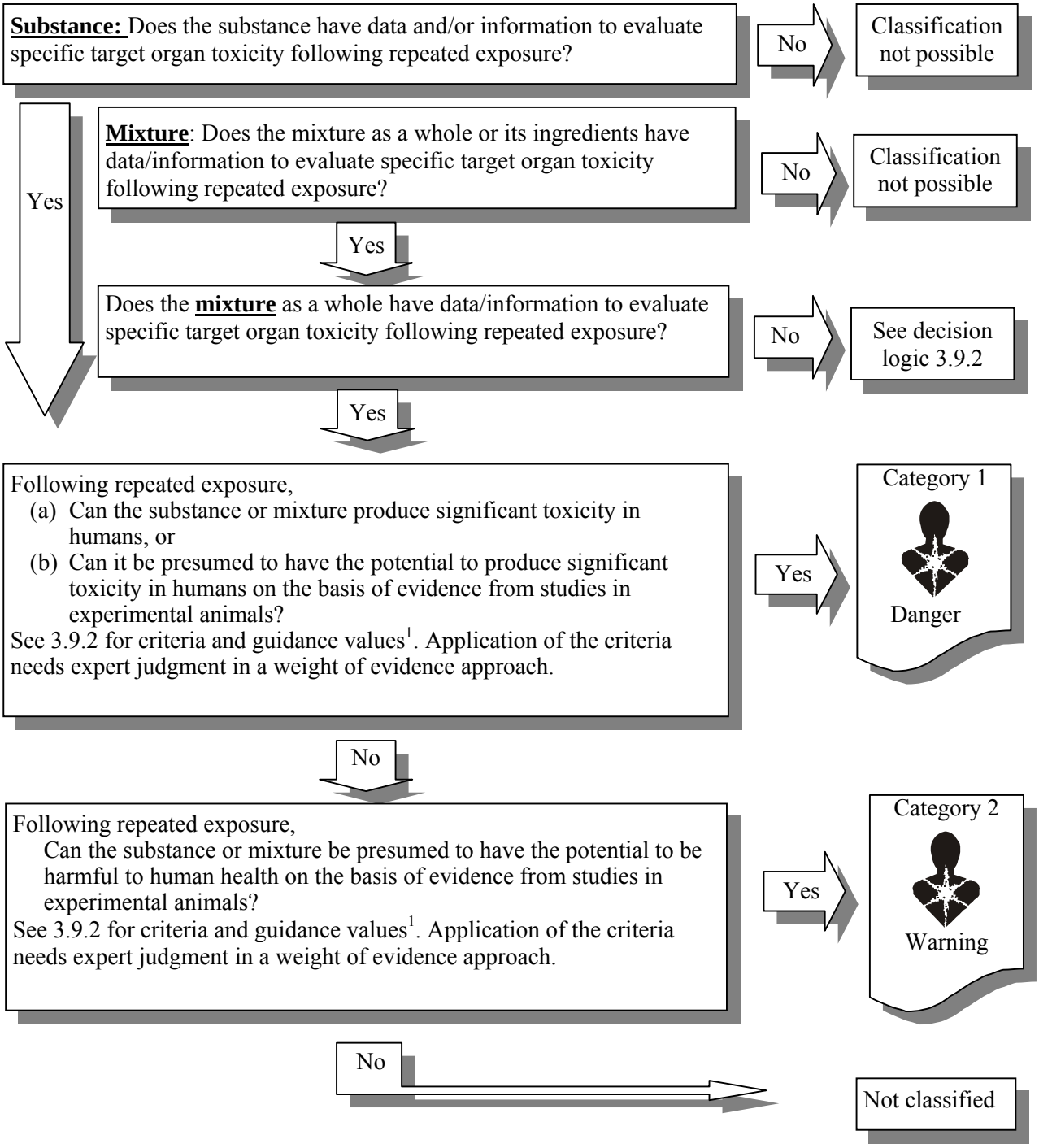
Table 3.9.4: Label elements for specific target organ toxicity following repeated exposure

	Category 1	**Category 2**
Symbol	Health hazard	Health hazard
Signal word	Danger	Warning
Hazard statement	Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

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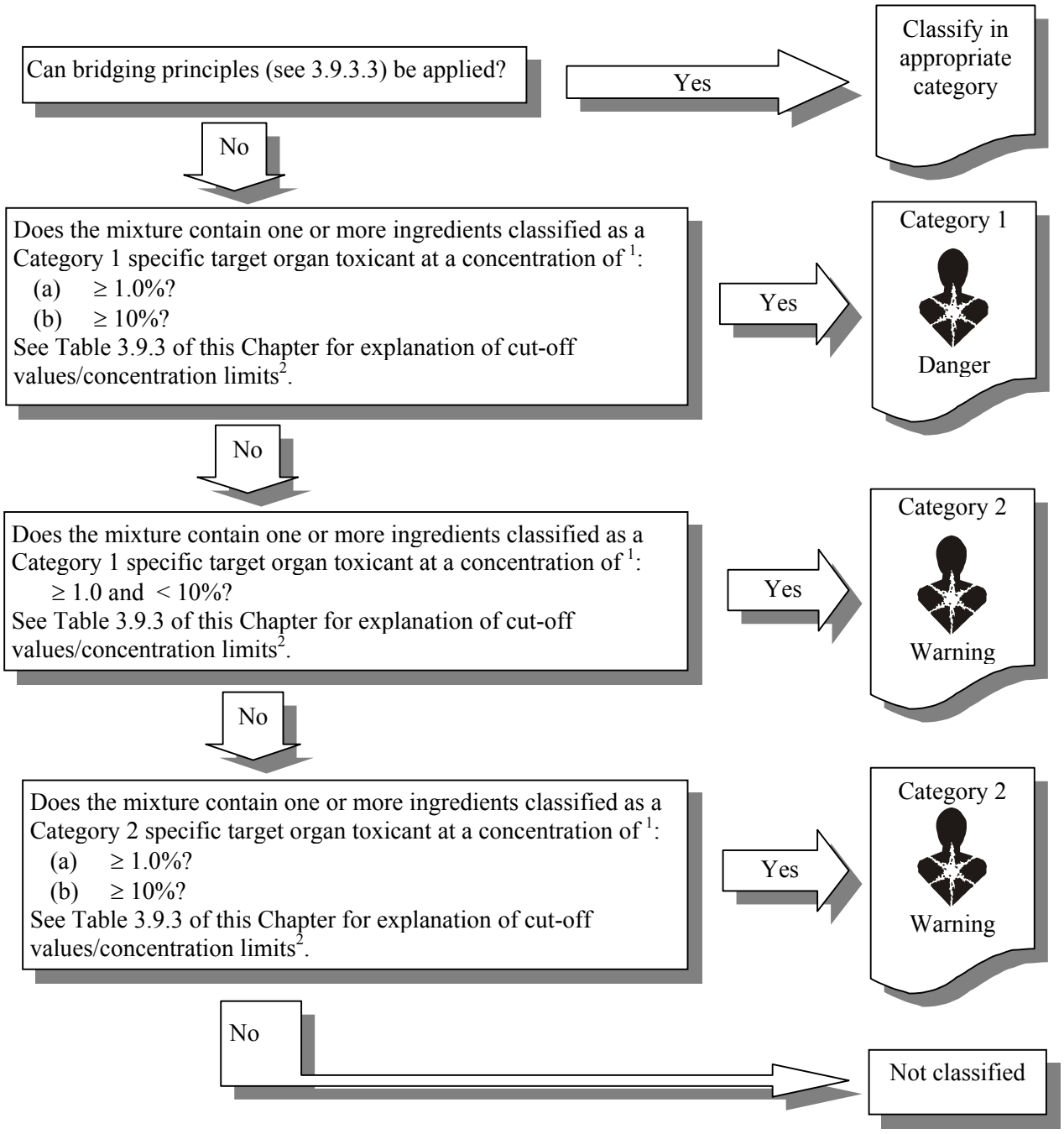
[1] *See 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2 "The use of cut-off values/concentration limits".*

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.*

CHAPTER 3.10

ASPIRATION HAZARD

3.10.1 Definitions and general and specific considerations

3.10.1.1 The purpose of this chapter is to provide a means of classifying substances or mixtures that may pose an aspiration toxicity hazard to humans.

3.10.1.2 *Aspiration* means the entry of a liquid or solid chemical product directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system.

3.10.1.3 Aspiration toxicity includes severe acute effects such as chemical pneumonia, varying degrees of pulmonary injury or death following aspiration.

3.10.1.4 Aspiration is initiated at the moment of inspiration, in the time required to take one breath, as the causative material lodges at the crossroad of the upper respiratory and digestive tracts in the laryngopharyngeal region.

3.10.1.5 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.

3.10.1.6 *Specific considerations*

3.10.1.6.1 A review of the medical literature on chemical aspiration revealed that some hydrocarbons (petroleum distillates) and certain chlorinated hydrocarbons have been shown to pose an aspiration hazard in humans. Primary alcohols, and ketones have been shown to pose an aspiration hazard only in animal studies.

3.10.1.6.2 While a methodology for determination of aspiration hazard in animals has been utilized, it has not been standardized. Positive experimental evidence with animals can only serve as a guide to possible aspiration toxicity in humans. Particular care must be taken in evaluating animal data for aspiration hazards.

3.10.1.6.3 The classification criteria refer to kinematic viscosity. The following provides the conversion between dynamic and kinematic viscosity:

$$\frac{\text{Dynamic viscosity (mPa·s)}}{\text{Density (g/cm}^3\text{)}} = \text{Kinematic viscosity (mm}^2\text{/s)}$$

3.10.1.6.4 *Classification of aerosol/mist products*

Aerosol and mist products are usually dispensed in containers such as self-pressurized containers, trigger and pump sprayers. The key to classifying these products is whether a pool of product is formed in the mouth, which then may be aspirated. If the mist or aerosol from a pressurized container is fine, a pool may not be formed. On the other hand, if a pressurized container dispenses product in a stream, a pool may be formed that may then be aspirated. Usually, the mist produced by trigger and pump sprayers is coarse and therefore, a pool may be formed that then may be aspirated. When the pump mechanism may be removed and contents are available to be swallowed then the classification of the products should be considered.

3.10.2 Classification criteria for substances

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 ≤ 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 ≤ 14 mm^2/s, measured at 40º 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.*

3.10.3 Classification criteria for mixtures

3.10.3.1 *Classification when data are available for the complete mixture*

A mixture is classified in Category 1 based on reliable and good quality human evidence.

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

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

3.10.3.2.2 *Dilution*

If a mixture is diluted with a diluent that does not pose an aspiration toxicity hazard, and which is not expected to affect the aspiration toxicity of other ingredients or the mixture, then the new mixture may be classified as equivalent to the original mixture. However, the concentration of aspiration toxicant(s) should not drop below 10%.

3.10.3.2.3 Batching

The aspiration toxicity 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 aspiration toxicity, reflected by viscosity or concentration, of the batch has changed. If the latter occurs, new classification is necessary.

3.10.3.2.4 *Concentration of Category 1 mixtures*

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

3.10.3.2.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.10.3.2.6 *Substantially similar mixtures*

Given the following:

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

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

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

(d) Aspiration toxicity for A and C is substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the aspiration toxicity of B.

If mixture (i) is already classified based on the criteria in table 3.10.1, then mixture (ii) can be assigned the same hazard category.

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

3.10.3.3.1 *Category 1*

3.10.3.3.1.1 A mixture which contains ≥ 10% of an ingredient or ingredients classified in Category 1, and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40 °C, will be classified in Category 1.

3.10.3.3.1.2 In the case of a mixture which separates into two or more distinct layers, one of which contains ≥ 10 % of an ingredient or ingredients classified in Category 1 and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40 °C, then the entire mixture is classified in Category 1.

3.10.3.3.2 *Category 2*

3.10.3.3.2.1 A mixture which contains ≥ 10% of an ingredient or ingredients classified in Category 2, and has a kinematic viscosity ≤ 14 mm^2/s, measured at 40 °C, will be classified in Category 2.

3.10.3.3.2.2 In classifying mixtures in this category, the use of expert judgment that considers surface tension, water solubility, boiling point, volatility is critical and especially when Category 2 substances are mixed with water.

3.10.3.3.2.3 In the case of classifying a mixture which separates into two or more distinct layers, one of which contains ≥ 10 % of an ingredient or ingredients classified in Category 2 and has a kinematic viscosity ≤ 14 mm^2/s, measured at 40 °C, then the entire mixture is classified in Category 2.

3.10.4 Hazard communication

3.10.4.1 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. The table below presents specific label elements for substances and mixtures which are classified as posing an aspiration toxicity hazard, Categories 1 and 2, based on the criteria set forth in this chapter.

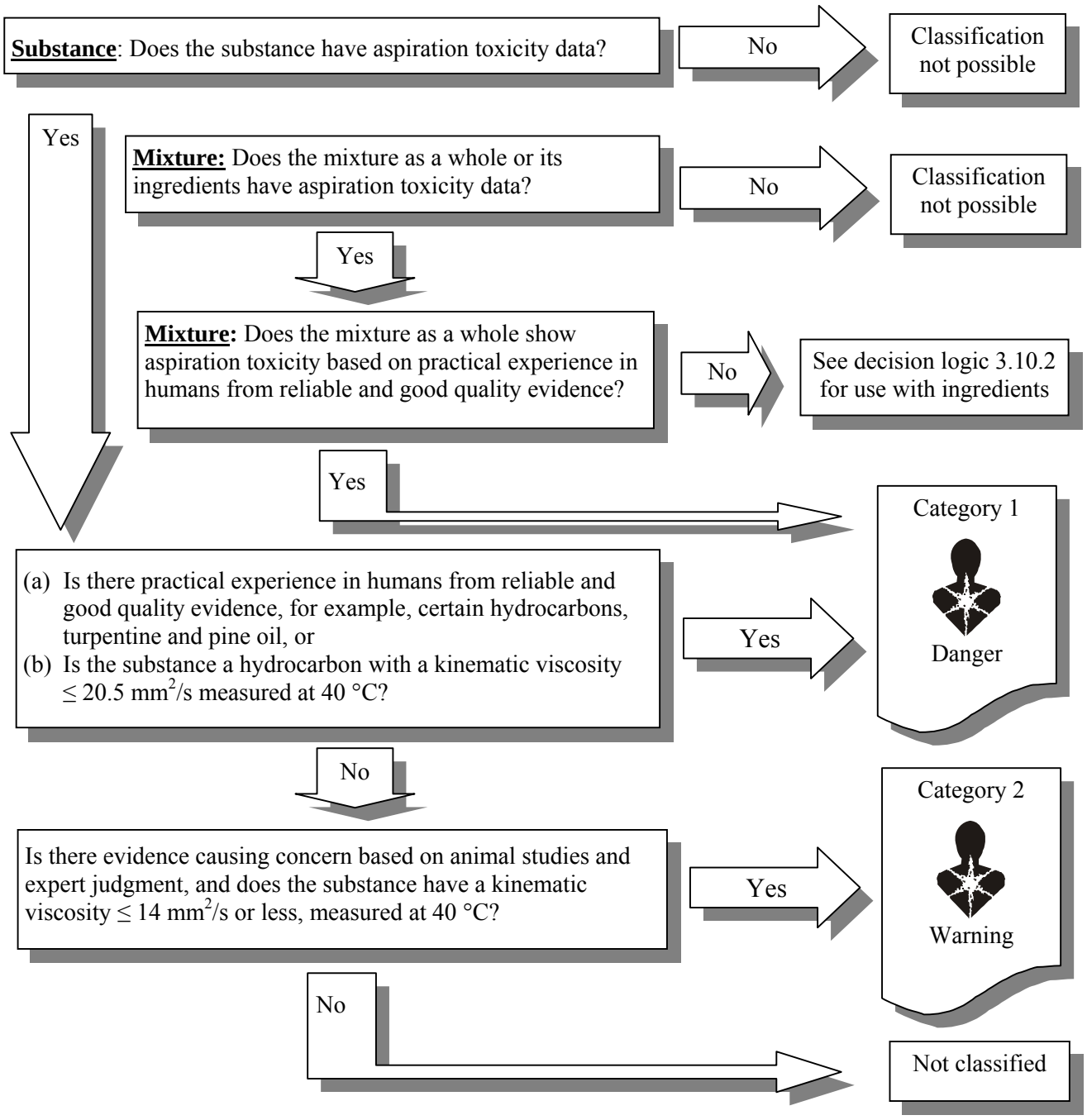
Table 3.10.2: Label elements for aspiration toxicity

	Category 1	**Category 2**
Symbol	Health hazard	Health hazard
Signal word	Danger	Warning
Hazard statement	May be fatal if swallowed and enters airways	May be harmful if swallowed and enters airways

3.10.5 Decision logic for aspiration 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.

3.10.5.1 ***Decision logic 3.10.1***



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3.10.5.2 ***Decision logic 3.10.2***