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Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals
(Third session, 10-12 July 2002)

DRAFT GHS/MASTER/Part 3/Chapters 3.1 to 3.4

Note by the secretariat:

This document contains Part 3, Chapters 3.1 to 3.4, of the draft GHS with, in a visible mode, all amendments incorporated after the 3rd session of the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (July 2002). The corresponding consolidated document is submitted under reference SG/ST/AC.10/C.4/2002/16/Add.3 (Page 1 to 56) to the fourth session of the Sub-Committee.

PART 3

Chapters 3.1 to 3.4

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PART 3

HEALTH AND ENVIRONMENTAL HAZARDS

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CHAPTER 3.1

ACUTE TOXICITY

3.1.1 Definition ~~and general considerations~~

~~1.~~ 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

~~2.~~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 criteria expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values as shown in the table below. Explanatory notes are shown following the table.

Table ~~1~~3.1.1: Acute toxicity hazard categories and (approximate) LD50/LC50 values defining the respective categories

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

(b) *It is recognised 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);*

(c) *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 (5000 ppmV). Work in the OECD Test Guidelines Programme should be undertaken to better define the terms "dusts", "mists" and "vapours" in relation to inhalation toxicity testing;*

(d) *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;*

(e) *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 LD50 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 LD50 (or ~~(~~LC50) 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.*

Recognising 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.

~~**Specific considerations**~~

~~3.~~3.1.2.2 The harmoniz~~s~~ed 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 "harmoniz~~s~~ation 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.

~~4.~~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 harmoniz~~s~~ed system. When experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD50 value from among valid, well-performed tests.

~~5.~~3.1.2.4 Category 1, the highest toxicity category, has cut-off values ~~of 5 mg/kg bodyweight by the oral route, 50 mg/kg bodyweight by the dermal route, 100 ppm for gases or gaseous vapours, 0.5 mg/l for vapours, and 0.05 mg/l for dusts and mists. These toxicity values are~~ (see Table 3.1.1) currently used primarily by the transport sector for classification for packing groups.

~~6.~~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 LD50 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***

~~7.~~3.1.2.6.1 Values for *inhalation toxicity* are based on 4 hour 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.

~~8.~~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~~s~~ 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.

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

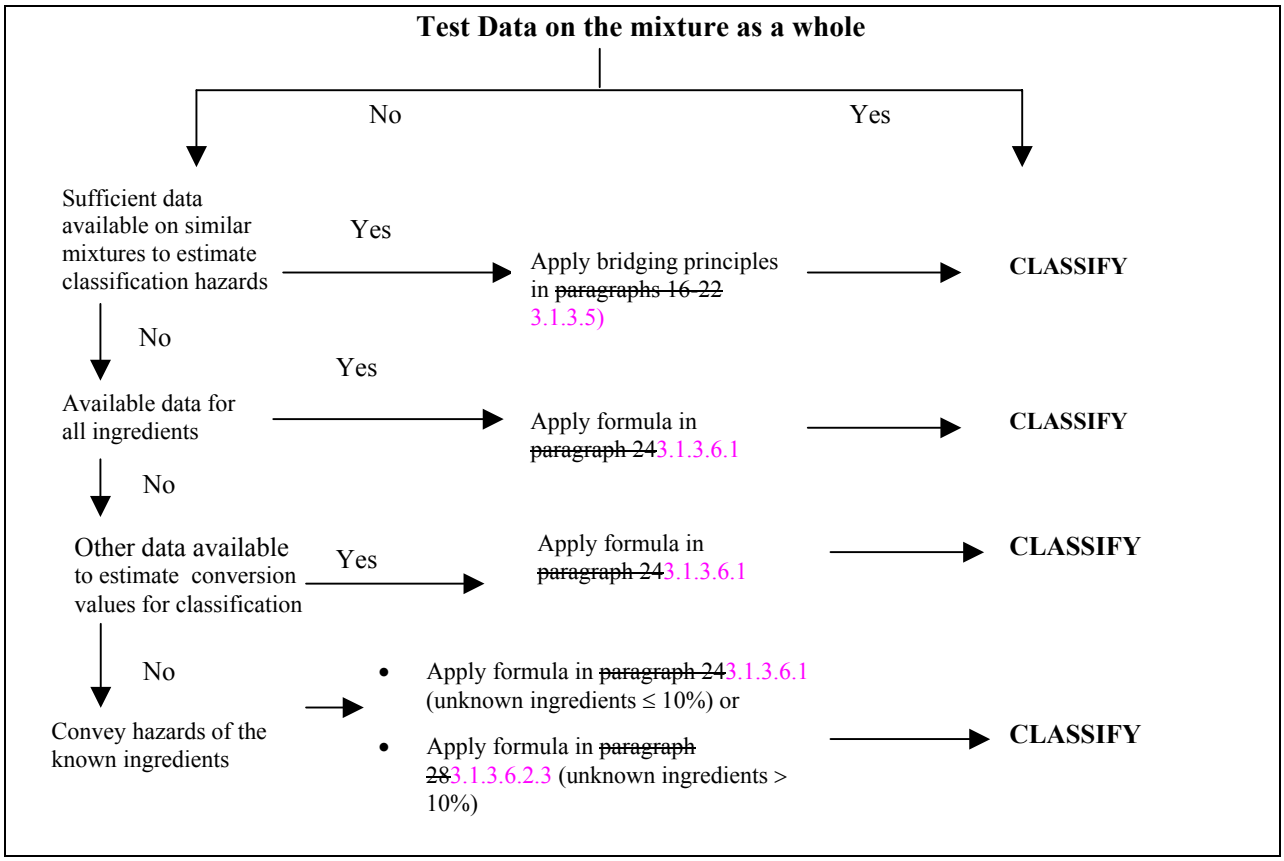
~~9.~~3.1.2.6.3 Vapour inhalation values are intended for use in classification of acute toxicity for all sectors. It is also recognised that the saturated vapour concentration of a chemical is used by the transport sector as an additional element in classifying chemicals for packing groups.

~~10.~~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.

3.1.3 Classification criteria for mixtures

~~11.~~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 ~~1~~3.1.1 below outlines the process to be followed:

Figure ~~1~~3.1.1: Tiered approach to classification of mixtures for acute toxicity



~~12.~~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.

~~13.~~3.1.3.3 In order to make use of all available data for purposes of classifying the hazards of ~~the~~ 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 of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 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) The acute toxicity estimate (ATE) for an ingredient in a mixture is derived using:

- The LD_{50}/LC_{50} where available,
- The appropriate conversion value from Table ~~2~~ 3.1.2 that relates to the results of a range test for an ingredient, or
- The appropriate conversion value from Table ~~2~~ 3.1.2 that relates to a classification category of the ingredient;

(c) 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 ~~paragraphs 24 – 29subsections~~ 3.1.3.6.1 and 3.1.3.6.2.3.

Table ~~2~~3.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for the respective routes of exposure

Exposure routes	Classification [category] or experimentally obtained acute toxicity range estimate (*see Note 1*)	[Conversion value] [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 ≤ 5000 *Category 5 - See footnote to ~~paragraph 6~~3.1.2.5.*	10 100 700 3000
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 ~~paragraph 6~~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 ~~paragraph 6~~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 a mixture based on its components 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*

~~14.~~ 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 ~~1~~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*

~~15.~~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 characterise 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 characterising the hazards of the mixture without the necessity for additional testing in animals.

3.1.3.5.2 *Dilution*

~~16.~~ If a mixture is diluted with a substance 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 paragraph ~~24~~ 3.1.3.6.1 could be applied.

~~17.~~ 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 LD50 of 1000 mg/kg bodyweight were diluted with an equal volume of water, the LD50 of the diluted mixture would be 2000 mg/kg bodyweight.

3.1.3.5.3 *Batching*

~~18.~~ 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*

~~19.~~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*

~~21.~~ 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*

~~22.~~ An aerosol form of a mixture may be classified in the same hazard category as the tested, non aerosolised 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 aerosolised 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*

~~23.~~ 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:

- Include ingredients with a known acute toxicity, which fall into any of the GHS acute toxicity categories;
- Ignore ingredients that are presumed not acutely toxic (e.g. water, sugar);
- Ignore ingredients if the oral limit test does not show acute toxicity at 2000 mg/kg bodyweight~~/body weight~~.

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

~~24.~~ 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:

$$\frac{100}{\mathrm{ATE}_{mix}} = \sum_{n} \frac{C_i}{\mathrm{ATE}_i}$$

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*

~~25.~~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 ~~paragraph 24~~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.

~~26.~~ 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 ~~paragraph 28~~3.1.3.6.2.3.

~~27.~~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 of 1% or greater, 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 x percent of the mixture consists of ingredient(s) of unknown toxicity.

~~28.~~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 ~~paragraph 24~~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 ~~paragraph 24~~3.1.3.6.1 should be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

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

[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

~~**Allocation of label elements**~~

~~29.~~ 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 ~~4~~ 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 1-5 based on the criteria set forth in this chapter.

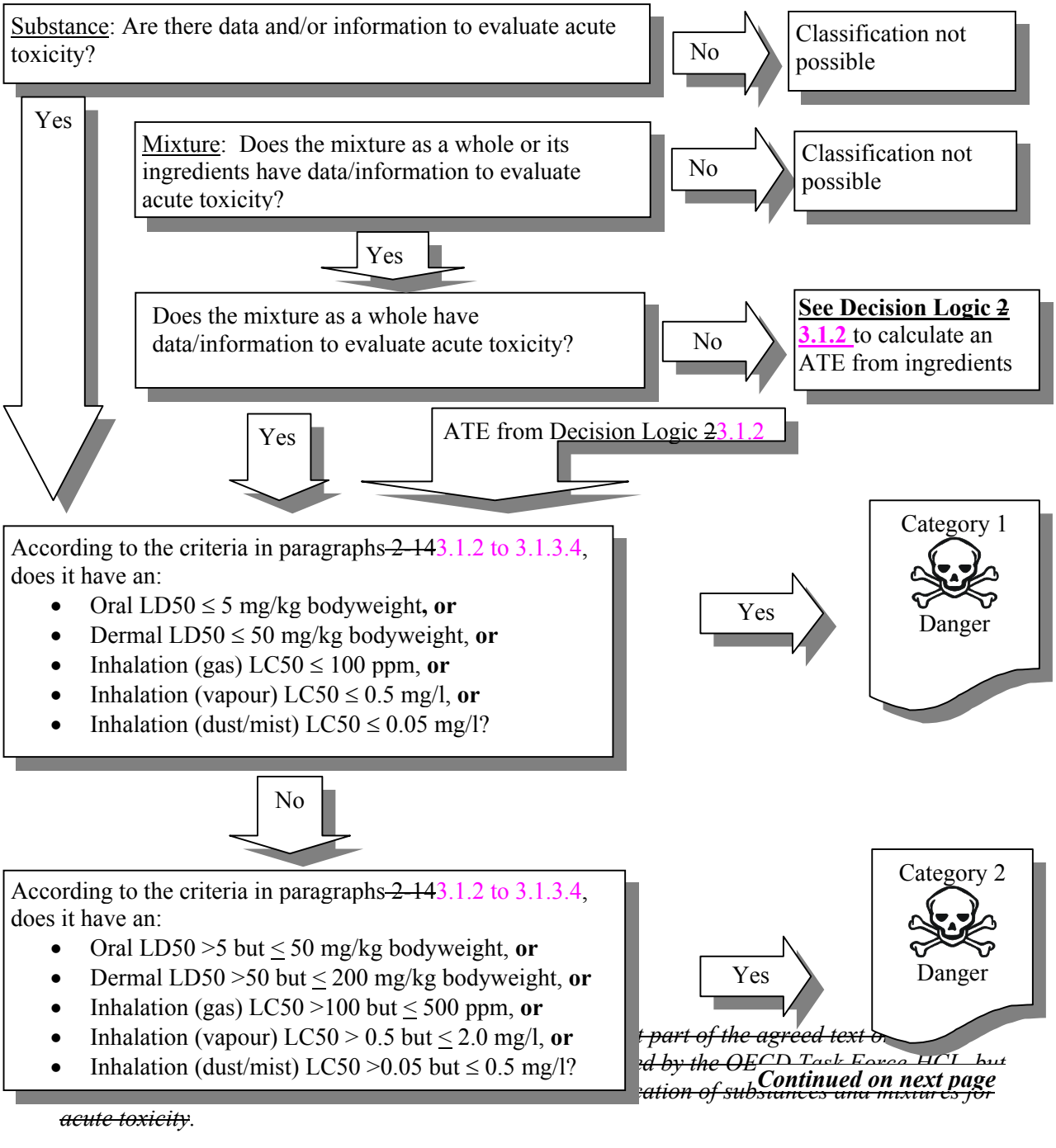
Table ~~3~~3.1.3: Acute toxicity label elements

	Category 1	Category 2	Category 3	Category 4	Category 5
Symbol	Skull and crossbones	Skull and crossbones	Skull and crossbones	Exclamation mark	No symbol is used
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	Fatal if inhaled	Fatal if inhaled	Toxic if inhaled	Harmful if inhaled	May be harmful if inhaled

3.1.5~~30.~~ Decision logics for classification of acute toxicity [3]

The decision logic 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.

Decision logic ~~1~~ 3.1.1 for acute toxicity



~~*t part of the agreed text o*~~
~~*d by the OECD Task Force HCL but*~~
~~*cation of substances and mixtures for acute toxicity*~~.

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No

According to the criteria in paragraphs ~~2-14~~3.1.2 to 3.1.3.4, does it have an:

- Oral LD50 >50 but ≤ 300 mg/kg bodyweight, **or**
- Dermal LD50 > 200 but ≤ 1000 mg/kg bodyweight, **or**
- Inhalation (gas) LC50 >500 but ≤ 2500 ppm, **or**
- Inhalation (vapour) LC50 >2 but ≤ 10.0 mg/l**, or**
- Inhalation (dust/mist) LC50 >0.5 but ≤ 1.0 mg/l?

Yes → Category 3

Danger

No

According to the criteria in paragraphs ~~2-14~~3.1.2 to 3.1.3.4, does it have an:

- Oral LD50 >300 but ≤ 2000 mg/kg bodyweight**, or**
- Dermal LD50 >1000 but ≤ 2000 mg/kg bodyweight, **or**
- Inhalation (gas) LC50 >2500 but ≤ 5000 ppm, **or**
- Inhalation (vapour) LC50 >10 but ≤ 20 mg/l, **or**
- Inhalation (dust/mist) LC50 >1 but ≤ 5 mg/l?

Yes → Category 4

Warning

No

According to the criteria in paragraphs ~~2-14~~3.1.2 to 3.1.3.4, does it have an:

- Oral LD50 >2000 but ≤ 5000 mg/kg bodyweight, **or**
- Dermal LD50 >2000 but ≤ 5000 mg/kg bodyweight, **or**
- Inhalation (gas, vapour and/or dust/mist) LC50 in the equivalent range of the oral and dermal LD50 (i.e., 2000-5000 mg/kg body weight)

Yes → Category 5

Warning

No

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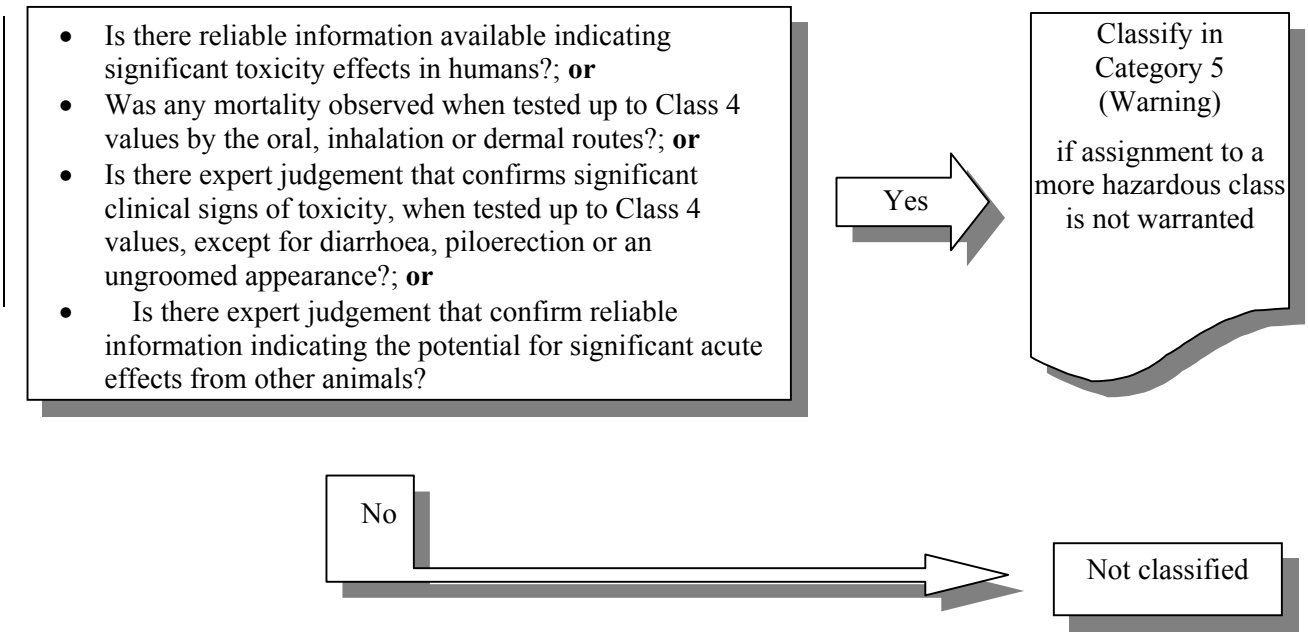
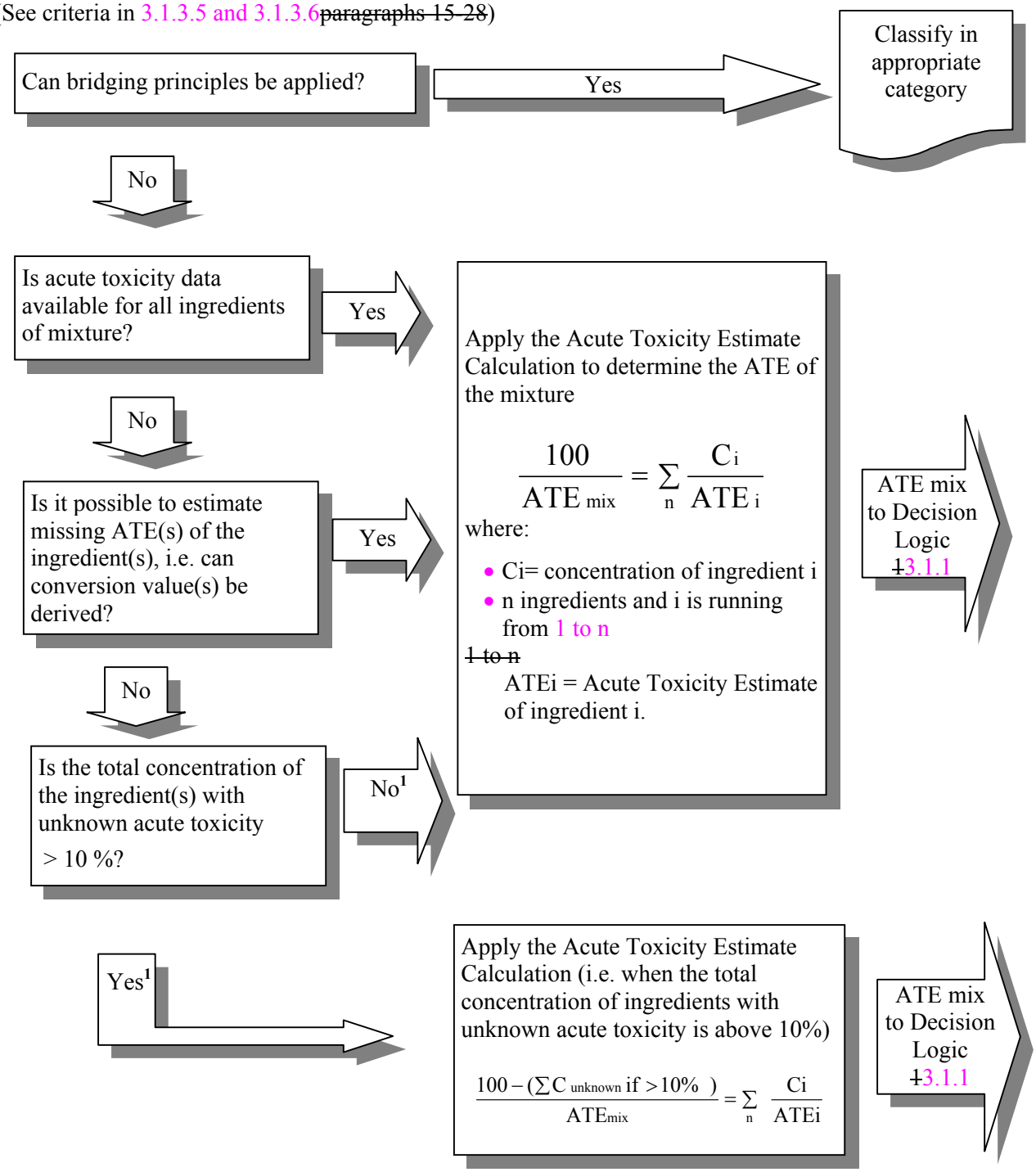

• Is there reliable information available indicating significant toxicity effects in humans?; **or**
• Was any mortality observed when tested up to Class 4 values by the oral, inhalation or dermal routes?; **or**
• Is there expert judgement that confirms significant clinical signs of toxicity, when tested up to Class 4 values, except for diarrhoea, piloerection or an ungroomed appearance?; **or**
• Is there expert judgement that confirm reliable information indicating the potential for significant acute effects from other animals?
Yes
Classify in Category 5 (Warning)
if assignment to a more hazardous class is not warranted
No
Not classified

Decision Logic ~~2~~3.1.2 for acute toxicity

(See criteria in 3.1.3.5 and 3.1.3.6~~paragraphs 15-28~~)



[1] *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 percent of the mixture is unknown*

CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 ~~———~~ Definitions ~~and general considerations~~

~~1.~~ ~~————~~ *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.

~~2.~~ *Skin Irritation* is the production of reversible damage to the skin following the application of a test substance for up to 4 hours[2].

3.2.2 Classification criteria for substances

~~3.~~3.2.2.1 ~~——~~ The harmoniz~~s~~ed system includes guidance on the use of data elements that are evaluated before animal testing for ~~dermal~~skin corrosion and irritation is undertaken. It also includes hazard classes for corrosion and irritation.

~~4.~~3.2.2.2 Several factors should be considered in determining the corrosion and irritation potential of chemicals before testing is undertaken. 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 ~~dermal~~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 ~~dermal~~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 ~~dermal~~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.

~~5.~~ All the above information that is available on a chemical should be used in determining the need for in vivo ~~dermal~~skin irritation testing. Although information might be gained from the evaluation of single parameters within a tier (see ~~paragraph 6~~3.2.2.3), e.g. caustic alkalis with extreme pH should be considered as ~~dermal~~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.

~~6.~~3.2.2.3 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 1), recognising that all elements may not be relevant in certain cases.

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

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

Figure ~~1~~3.2.1: Tiered testing and evaluation of ~~dermal~~skin corrosion and irritation potential (see also the "Testing and evaluation strategy for serious eye damage/ eye irritation/Figure 3.3.1")

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 $\leq$ 2 or $\geq$11.5 →	Classify as corrosive [(a)]
	↓ Not pH extreme or no data		
4	Existing ~~dermal~~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 ~~dermal~~skin corrosion test [(e)]	Positive response →	Classify as corrosive [(a)]
	↓ Negative response or no data		

Continued on next page

Figure 3.2.1~~1~~ *(cont'd):* Tiered testing and evaluation of ~~dermal~~skin corrosion and irritation potential (see also the "Testing and evaluation strategy for serious eye damage/ eye irritation/Figure ~~1~~3.3.1")

Step	Parameter		Finding		Conclusion
6	Valid and accepted in vitro ~~dermal~~skin irritation test [(f)]	→	Positive response	→	Classify as irritant [(a)]
	↓				
	Negative response or no data				
	↓				
7	*In vivo* ~~dermal~~skin corrosion test (1 animal)	→	Corrosive response	→	Classify as corrosive [(a)]
	↓				
	Negative response				
	↓				
8	*In vivo* ~~dermal~~skin irritation test (3 animals total) [(h)]	→	Non-irritant 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)]	→	Irritant response	→	Classify as irritant [(a)]
	↓				
	Not as above	→	Non-irritant response	→	No further testing, not classified

(a) Classify in the appropriate harmonis~~z~~ed category, as shown in Table ~~1~~ 3.2.1 below;

(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 ~~dermal~~skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any ~~dermal~~skin irritation in an acute ~~dermal~~skin toxicity test at the limit dose, or produces very toxic effects in an acute ~~dermal~~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 ~~dermal~~skin toxicity information that the reporting of ~~dermal~~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) ~~[~~E~~An e~~xamples of ~~an~~ internationally accepted validated in vitro test methods for ~~dermal~~skin corrosion are~~is~~ OECD Test Guidelines 430 and~~or~~ 431~~]~~;

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

(g) This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human ~~dermal~~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*

~~7.~~3.2.2.4.1 A single harmoniz~~s~~ed *corrosion category* ~~-~~is provided in Table ~~1~~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.

~~8.~~3.2.2.4.2 For those authorities wanting more than one designation for corrosivity, up to three subcategories are provided within the corrosive category (Category 1, see Table ~~1~~3.2.1): subcategory 1A - where responses are noted following up to 3 minutes exposure and up to 1 hour observation; subcategory 1B - where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and subcategory 1C - where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

Table ~~1~~3.2.1 Skin corrosive category and subcategories [a]

Category 1: Corrosive	**Corrosive subcategories**	**Corrosive in ≥ 1 of 3 animals**	
(applies to authorities not using subcategories)	(only applies to some authorities)	**Exposure**	**Observation**
corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes -- ≤ 1 hour	≤ 14 days
	1C	> 1 hour -- ≤ 4 hours	≤ 14 days

[a] The use of human data is discussed in ~~paragraphs 4 and 5 of this chapter~~3.2.2.1 and in *Classification of Hazardous Substances and Mixtures* (~~Chapter 1.2, paragraph 17~~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 ~~2~~ 3.2.2 that

(a) is centrist in sensitivity among existing classifications;
(b) recognises 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 ~~dermal~~skin irritant category.

~~10.~~3.2.2.5.2 Reversibility of ~~dermal~~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.

~~11.~~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 ~~2~~3.2.2). They mainly differ in the severity of ~~dermal~~skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of $\geq$ 2.3 - $\leq$ 4.0. For the mild irritant category, the mean score cut-offs~~~~ values are $\geq$ 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 ~~2~~3.2.2 Skin irritation categories[a]

Categories	**Criteria**
Irritant **(Category 2)** (applies to all authorities)	(1) Mean value of $\geq$ 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 ~~dermal~~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 $\geq$ 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 ~~dermal~~skin reactions (when not included in the irritant category above).

[a] The use of human data is discussed in ~~paragraphs 4 and 5 of this chapter~~3.2.2.1 and in the *Classification of Hazardous Substances and Mixtures* (~~Chapter 1.2, paragraph 17~~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*

~~13.~~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.

~~14.~~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 of 2 or less or a pH of 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation 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*

~~15.~~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 characterise 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 characterising the hazards of the mixture without the necessity for additional testing in animals.

3.2.3.2.2 *Dilution*

~~16.~~ 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 ~~paragraphs 22-27~~ section 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

~~17.~~ 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*

~~18.~~ If a tested mixture classified in the highest subcategory for corrosion is concentrated, a more concentrated mixture should be classified in the highest corrosion subcategory 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*

~~19.~~ 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*

~~20.~~ 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*

~~21.~~ An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised 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 components or only for some components of the mixture*

~~22.~~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 of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

~~23.~~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 components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component 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 components 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 components exceeds a ~~threshold~~ cut-off value/concentration limit.

~~24.~~3.2.3.3.3 Table ~~3~~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.

~~25.~~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 ~~paragraphs 22 and 23~~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 ~~paragraph 14~~3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits of Table ~~3~~3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table ~~3~~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~~3.2.3 does not apply is summarised in Table ~~4~~3.2.4 below.

~~26.~~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 levels mentioned in Tables 3.2.3 ~~–~~ 3.2.4. In these cases the mixture could be classified according to that data (see also *Classification of Hazardous Substances and Mixtures* – Use of Cut-Off Values/Concentration Limits (~~Chapter 1.2, paragraphs 28-31~~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 levels mentioned in Tables ~~3 – 4~~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 ~~paragraph 14~~3.2.3.1.4 and illustrated in Figure ~~1~~3.2.1.

~~27.~~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 – The Use of Cut-Off Values/Concentration Limits* (~~Chapter 1.2, paragraphs 28-31~~1.3.2.3.1.2).

Table ~~3~~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~~		
	Skin ~~C~~corrosive	Skin ~~I~~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 x Skin Category 1) + Skin Category 2		≥10%	≥1% but <10%
(10 x Skin Category 1) + Skin Category 2 + Skin Category 3			≥10%

***Note to Table ~~3~~ 3.2.3**: Only some authorities will use the subcategories 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 ~~4~~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) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.2.4 Hazard communication

~~**Allocation of label elements**~~

~~28.~~ General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.~~3~~4). Annex 2 contains summary tables about classification and labelling. Annex ~~4~~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.

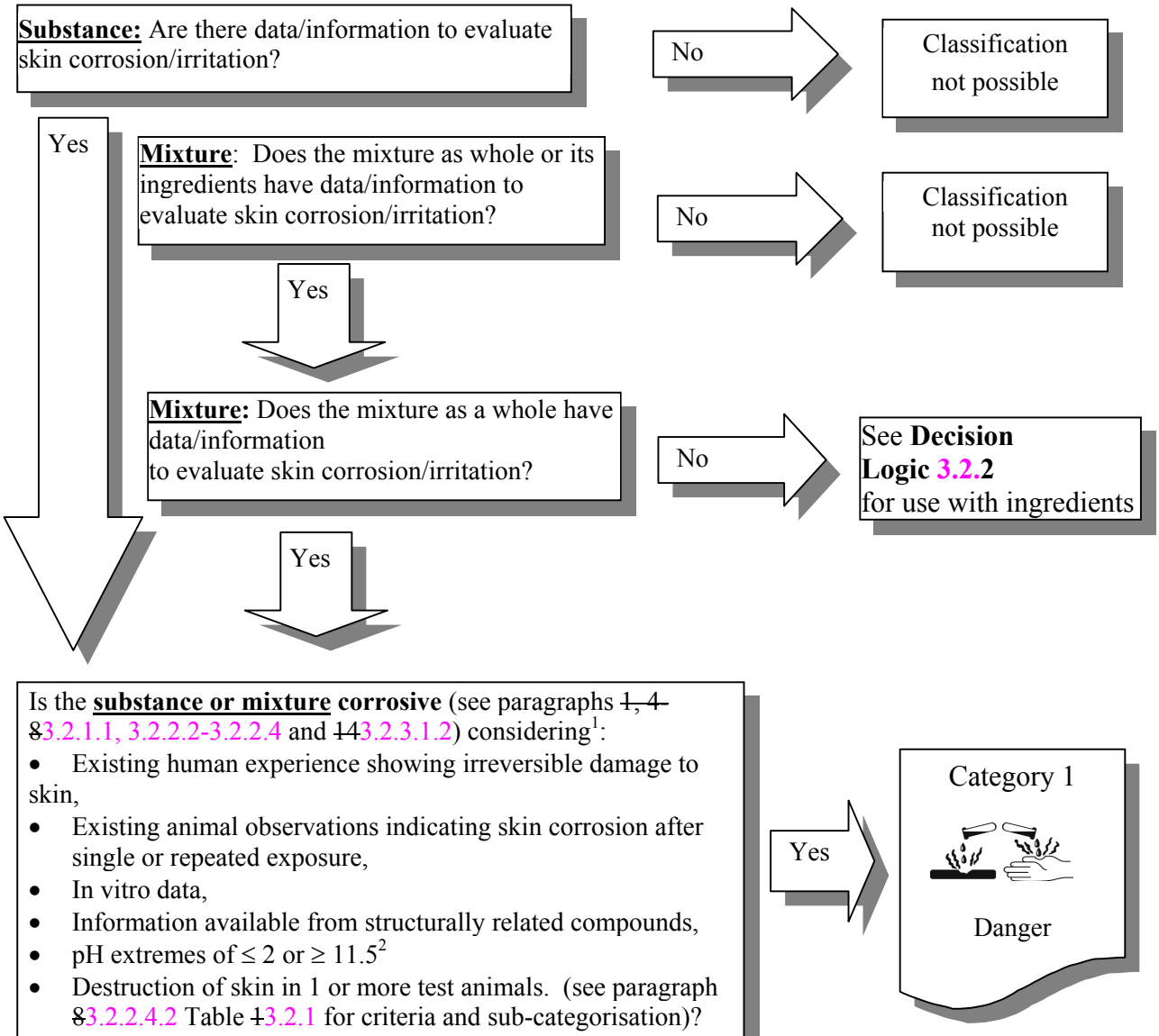
Table ~~5~~3.2.5: Label elements for skin corrosion/irritation.

	Category 1			Category 2	Category 3
	1A	**1B**	**1C**		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	No symbol is used
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

~~29.~~3.2.5 Decision Logic for skin corrosion/irritation[3]:

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

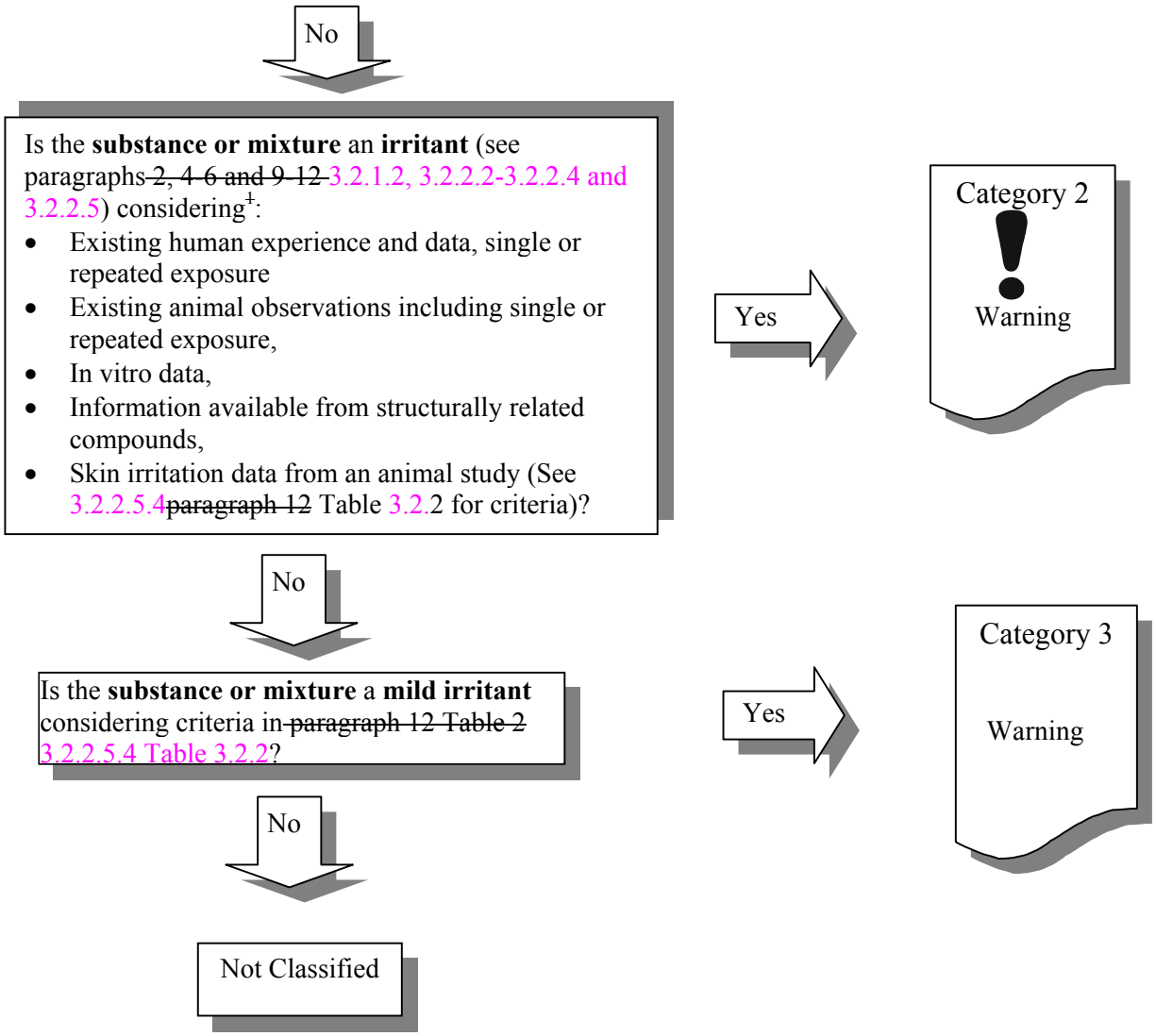
Decision Logic ~~1~~3.2.1



[3] ~~*The decision logic that followsin 3.2.5 is not part of the agreed text on the harmonization of classification for skin corrosion/irritation developed by the OECD Task Force – HCL, but has been provided here as additional guidance.*~~

Continued on next page

[1] *Figure ~~1~~ 3.2.1 contains details for testing and evaluation.*
[2] *Including consideration of acid/alkali reserve capacity, if appropriate.*



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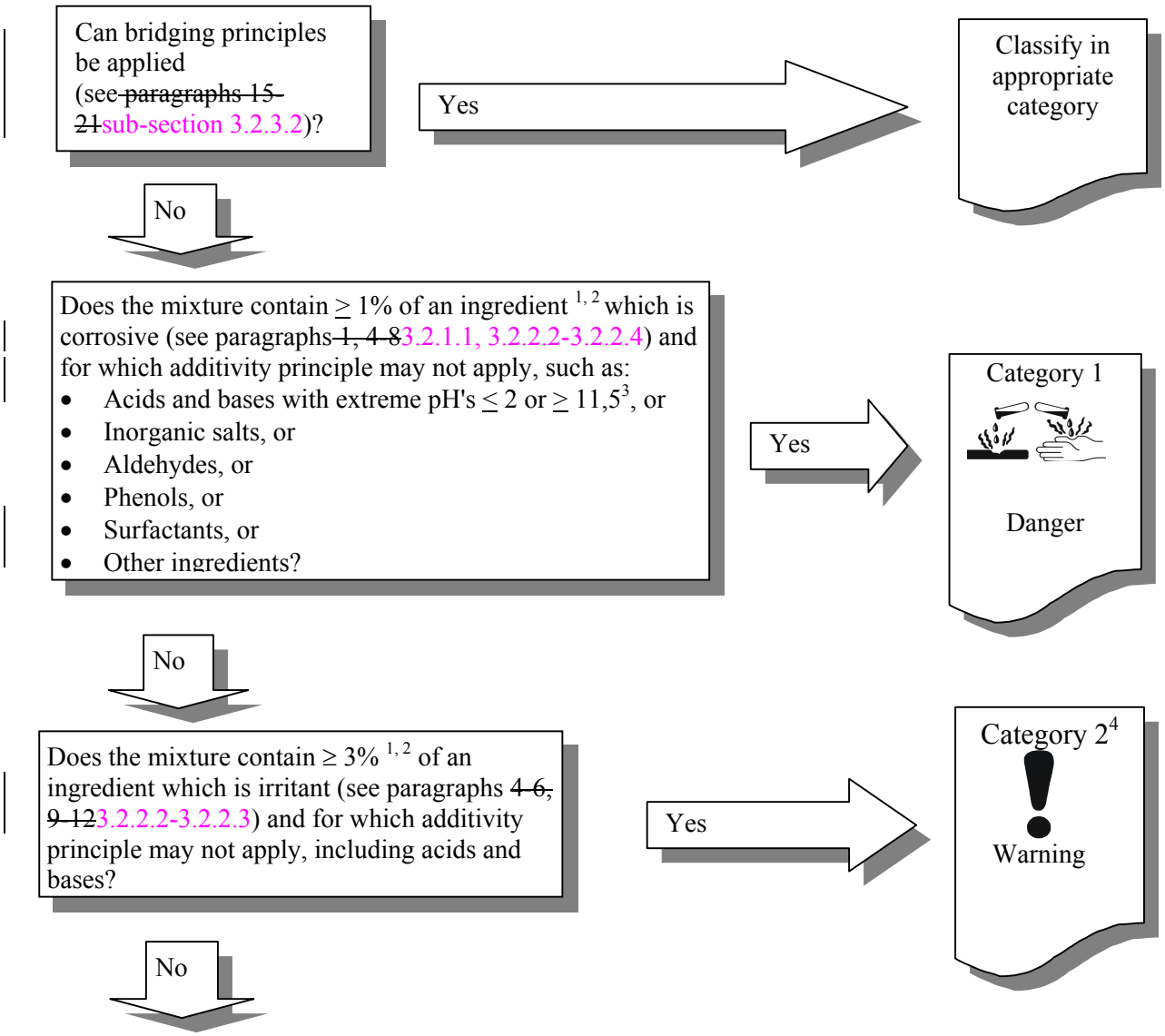
[1] *Figure 3.2.1 contains details for testing and evaluation.*

Decision Logic ~~2~~ 3.2.2: Classification of mixtures on the basis of information/data on ingredients



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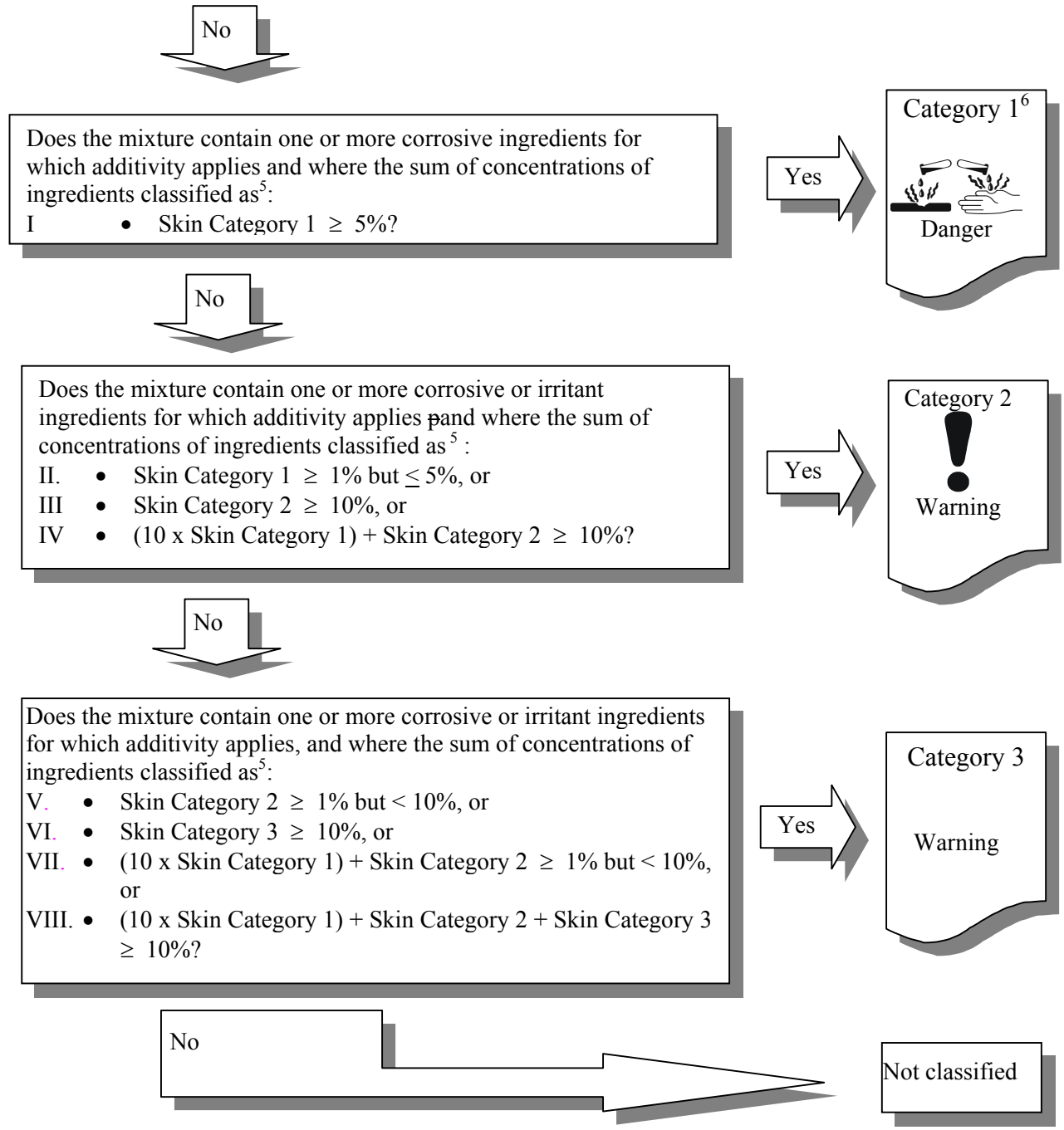
1 ~~or~~ *Or where relevant < 1 %, see paragraph ~~22~~3.2.3.3.1.*

2 *For specific concentration limits, see paragraph ~~27~~3.2.3.3.6 of this chapter. See also Chapter 1.~~2~~3, para. 1.3.3.2 for "The use of Cut-off Values/Concentration Limits".*

3 ~~i~~*ncluding consideration of acid/alkali reserve capacity, if appropriate.*

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



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[5] *For specific concentration limits, s~~S~~ee paragraph ~~27~~ 3.2.3.3.6 of this chapter. See also Chapter 1.2~~3~~, para. 1.3.3.2, for "The Use of Cut-off Values/Concentration Limits". ~~as well as paragraph 273.2.3.3.6 of this chapter.~~*

[6] *See note to Table ~~3~~ 3.2.3 for details on use of Category 1 subcategories.*

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CHAPTER 3.3

SERIOUS EYE DAMAGE /EYE IRRITATION

3.3.1 Definitions ~~and general considerations~~

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]

~~2.~~ 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.~~3.3.2.1 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.

~~4.~~3.3.2.2 The proposals for classification of eye irritation and serious damage to the eye include elements that are harmoniz~~s~~ed and will be used by all authorities as well as optional subcategories that will be applied by only some authorities (e.g. authorities classifying pesticides).

~~5.~~ The harmoniz~~s~~ed system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard classes for local lesions on the eyes.

~~6.~~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 utilise a tiered testing strategy for serious eye damage and eye irritation.

~~7.~~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 ~~is known~~. 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.

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

~~8.~~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 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.

~~9.~~3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable, recognising that all elements may not be relevant in certain cases. The tiered approach explained in Figure ~~1~~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].

~~10.~~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 organise 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 ~~1~~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")

Step	Parameter	Findings	Conclusions
1a	Data relating to historical human or animal experience ↓	→ Serious eye damage	→ Category 1
		→ Eye irritant	→ Category 2
	No or don't know ↓		
1b	Data relating to historical human or animal experience ↓	→ Skin corrosive	→ No evaluation of effects on eyes; deemed to be Category 1
	No or don't know ↓		

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[2] *OECD (1996). Final Report of the OECD Workshop on Harmonisation 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 ~~1~~ 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~~1~~3.2.1")

Step	Parameter	Findings	Conclusions
1c	Data relating to historical human or animal experience →	Skin irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓ No or don't know		
2a	~~SAR/SPR~~Structure activity relationships/Structure property relationships (SAR/SPR) →	Severe damage to eyes →	Category 1
	↓ No or don't know		
2b	Structure activity relationships/Structure property relationships (SAR/SPR) →	Eye irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓ No or don't know		
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 ~~dermal~~skin corrosive →	Yes →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No		

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 3.2.11")

Step	Parameter	Findings	Conclusions
	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	→ - But *in vitro* test for severe eye irritancy was negative	→ Go to step 8
	No ↓	- 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 ↓	→ Serious damage to eyes	→ Category 1
8	1 rabbit eye test		
	↓ No serious damage ↓	→ Eye irritant	→ Category 2
9	1 or 2 further rabbits	→ Not an eye irritant	→ Not classified
	~~Not an eye irritant~~		

Notes to Figure ~~1~~3.3.1:

Step 1a/b: Data relating to historical human or animal experience: ~~Pre~~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 ~~dermal~~skin and eye~~ocular~~ effects:

(i) Step 1a - reliable determination of eye irritancy basing on human or animal experience - depends on expert judgement: ~~In~~ 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: 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 ~~dermal~~skin and eye~~ocular~~ 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 ~~dermal~~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 ~~"General Considerations" of~~para. 1.3.2 in Chapter 1.~~2~~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 recognised 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, para 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)*

~~11.~~ 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 ~~1~~3.3.1: Irreversible eye effects categories

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:

- 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
- at least in 2 of 3 tested animals, a positive response of:
  corneal opacity ≥ 3 and/or
  iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test-material.

The use of human data is discussed in *Purpose, Scope and Application* (Chapter 1.1, paragraph ~~18~~1.1.2.6) and *Classification of Hazardous Substances* and Mixtures (Chapter 1.~~2~~3, paragraph ~~17~~1.3.2.4.7).

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

~~12.~~ 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.

~~13.~~ 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 the eyes) and Category 2B (mildly irritating to eyes).

Table ~~2~~3.3.2: Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes) is a test material that produces:

- at least in 2 of 3 tested animals a positive response of:
  corneal opacity ≥ 1 and/or
  iritis ≥ 1, and/or
  conjunctival redness≥ 2
  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.

~~14.~~ 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*

~~15.~~ 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.

~~16.~~ 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 of 2 or less or 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation 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*

~~17.~~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 characterise 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 characterising the hazards of the mixture without the necessity for additional testing in animals.

3.3.3.2.2 *Dilution*

~~18.~~ 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 ~~paragraphs 24-29~~3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

~~19.~~ 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 class*

~~20.~~ If a tested mixture classified in the highest subcategory for serious eye damage is concentrated, a more concentrated mixture should be classified in the highest serious eye damage subcategory without additional testing. If a tested mixture classified in the highest 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*

~~21.~~ 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*

~~22.~~ 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. If mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

3.3.3.2.7 *Aerosols*

~~23.~~ An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[3].

3.3.3.3 *Classification of mixtures when data are available for all components or only for some components 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 of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for eye irritation/serious eye damage.

~~25.~~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 components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component 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 components 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 components exceeds a threshold cut-off value/concentration limit.

~~26.~~3.3.3.3.3 Table ~~3~~ 3.3.3~~below~~ 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.

~~27.~~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 paragraphs ~~24 and 25~~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 paragraph ~~15~~3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table ~~3~~3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table ~~3~~ 3.3.3 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~~ 3.3.3 does not apply is summarised in Table ~~4~~ 3.3.4. ~~below.~~

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[3] *Bridging rules 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 recognised*

~~28.~~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 and 4~~3.3.3 and 3.3.4. In these cases the mixture could be classified according to that data (see also Chapter 1.2 – "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 paragraph 3.3.2~~16~~, Figure 3.3.~~-~~1 and explained in detail in this chapter.

~~29.~~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 Hazard Communication: Labelling – Use of Cut-Off Values/Concentration Limits (Chapter 1.3~~2~~ , subsection 1.3.3.2~~paragraphs 28-31~~)).

Table ~~3~~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 x Eye Category 1) + Eye Category 2/2A		≥10%
Skin Category 1 + Eye Category 1	≥ 3%	≥1% but <3%
10 x (Skin Category 1 + Eye Category 1) + Eye Category 2A/2B		≥10%

Table ~~4~~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

~~**Allocation of label elements**~~

~~30.~~ General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.~~3~~4). Annex 2 contains summary tables about classification and labelling. Annex ~~4~~3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

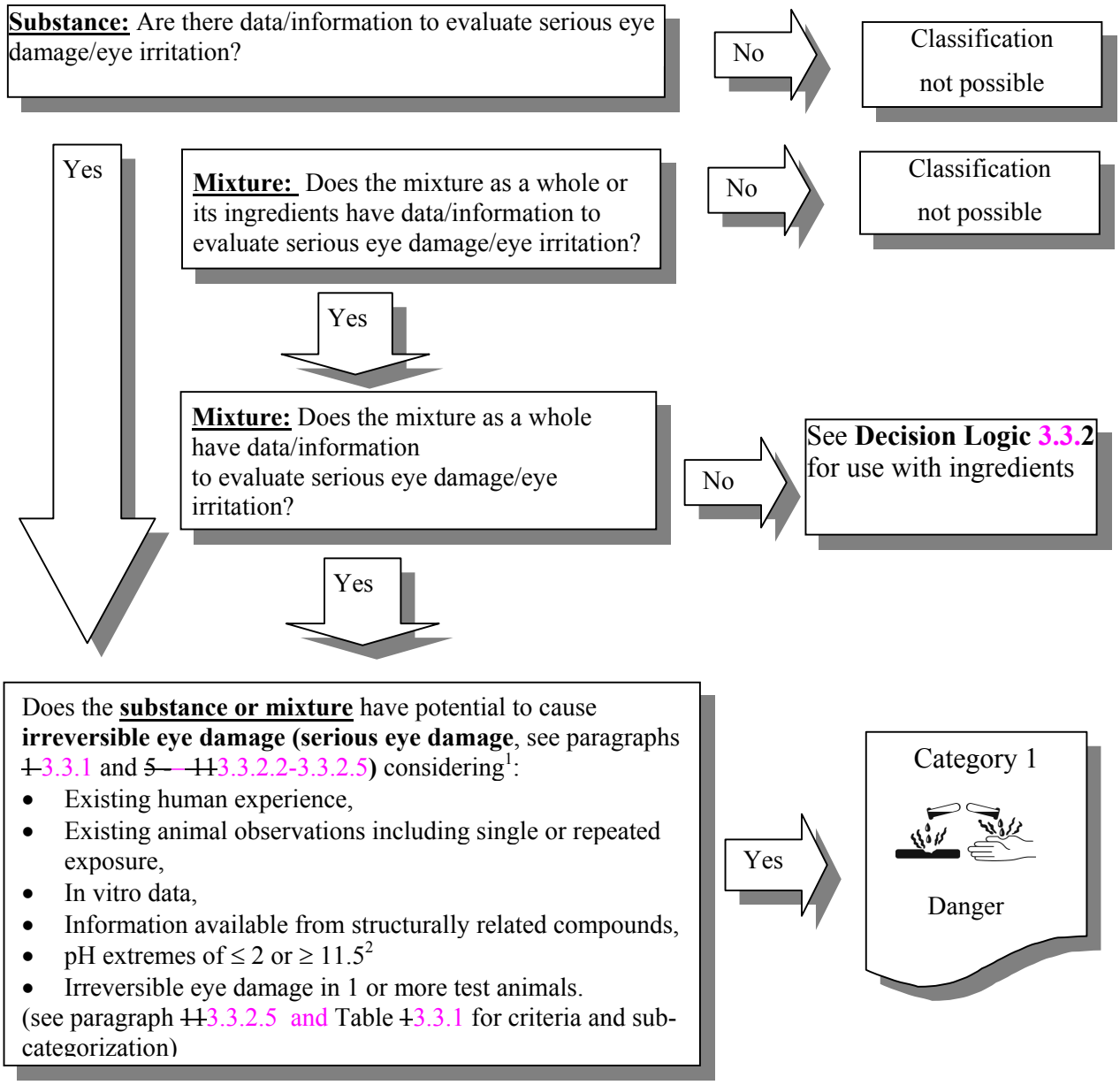
Table ~~5~~3.3.5: Label elements for serious eye damage/eye irritation

	Category 1	Category 2A	Category 2B
Symbol	Corrosive symbol	Exclamation mark	No symbol is used
Signal word	Danger	Warning	Warning
Hazard statement	Causes severe eye damage	Causes severe eye irritation	Causes eye irritation

~~31.~~3.3.5 Decision Logic for serious eye damage/ eye irritation[4]:

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

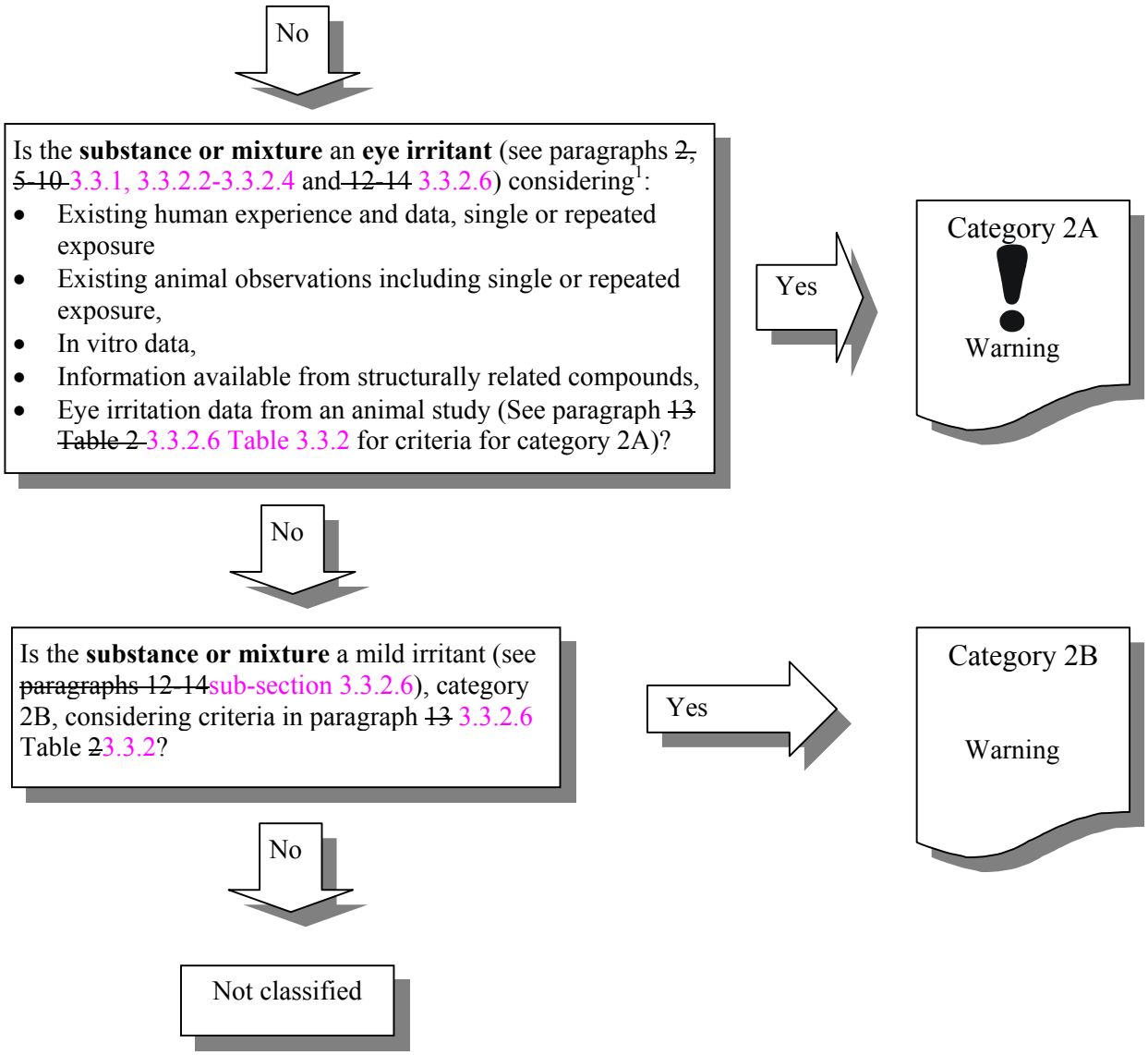
Decision Logic ~~1~~3.3.1



[1] *Figure ~~1~~3.3.1 contains details for testing and evaluation.*

[2] *~~1~~Including consideration of acid/alkali reserve capacity, if appropriate.-*

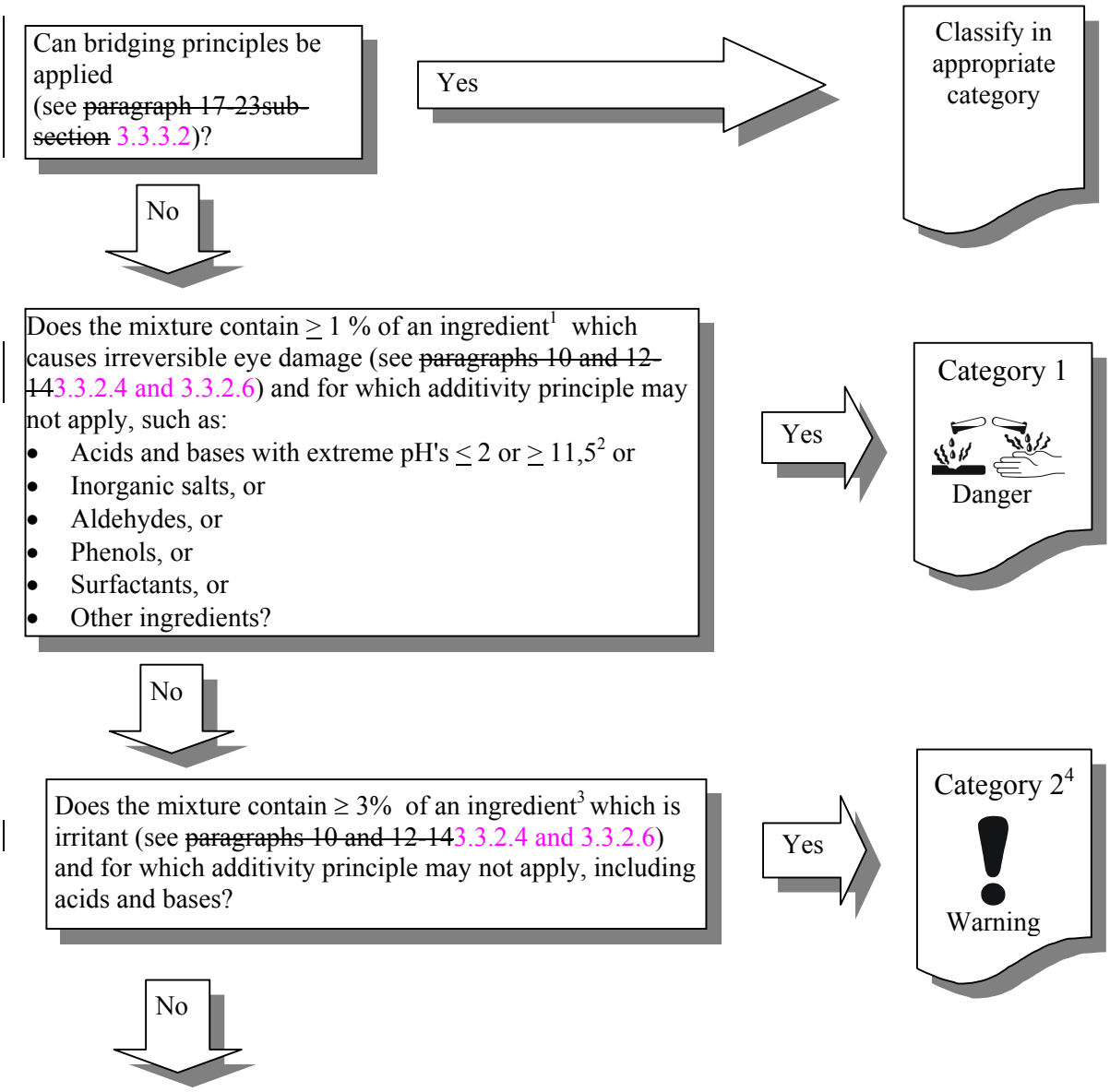
Continued on next page



Continued on next page

[1] *Figure ~~1~~3.3.1 contains details for testing and evaluation.*

Decision Logic ~~2~~3.3.2 Classification of mixtures on the basis of information/data on ingredients



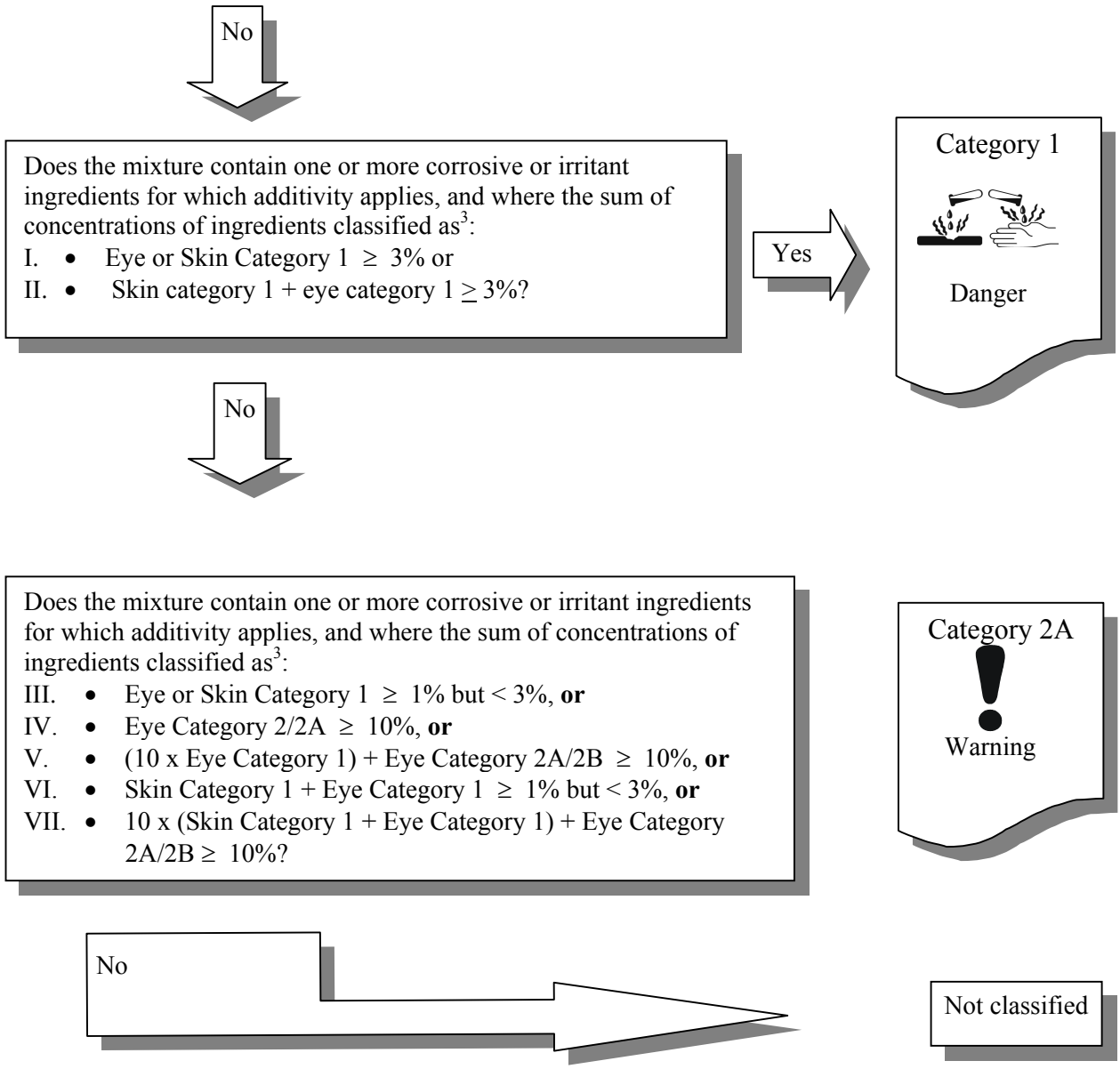
Continued on next page

[1] *Or where relevant < 1 %, see paragraph ~~24~~3.3.3.3.1.*

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

[3] *For specific concentration limits, see paragraph ~~27~~ 3.3.3.3.4 of this chapter. See also Chapter 1.3~~2~~, para. 1.3.3.2 for "The Use of Cut-Off Values/Concentration Limits.*

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



[3] *For specific concentration limits, see paragraph ~~27~~3.3.3.3.4 of this chapter. See also Chapter ~~1.2~~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~~

~~**Definitions**~~

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

~~2.~~ A *skin sensitizer* is a substance that will induce an allergic response following skin contact.[1]

3.4.2 Classification criteria for substances

3.4.2.1 *Respiratory sensitizers*

3.4.2.1.1 *Hazard category*

~~3.~~ Substances shall be classified as respiratory sensitizers (Category 1) in accordance with the criteria given below:

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

~~**Specific considerations**~~

3.4.2.1.2 *Human evidence*

~~4.~~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.

~~5.~~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:

- the size of the population exposed
- the extent of exposure.

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

~~6.~~3.4.2.1.2.3 The evidence referred to above could be:

- clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
  - in vivo immunological test (e.g. skin prick test);
  - in vitro immunological test (e.g. serological analysis);
  - 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;
  - a chemical structure related to substances known to cause respiratory hypersensitivity;
- data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

~~7.~~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.

~~8.~~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 recognised that in practice many of the examinations listed above will already have been carried out.

3.4.2.1.3 *Animal studies*

~~9.~~ Data from appropriate animal studies[2] which may be indicative of the potential of a substance to cause sensiti~~z~~sation by inhalation in humans[3] may include:

- measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;
- specific pulmonary responses in guinea pigs.

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[2] *At present recognised 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 maximisation 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*

~~10.~~ Substances shall be classified as contact sensitizers (Category 1) in accordance with the criteria given below:

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

3.4.2.2.2 *Specific considerations*

~~11.~~3.4.2.2.2.1 For classification of a substance, evidence should include any or all of the following:

- Positive data from patch testing, normally obtained in more than one dermatology clinic;
- 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;
- Positive data from appropriate animal studies;
- Positive data from experimental studies in man (See Chapter ~~1.2~~1.3, paragraph ~~17~~1.3.2.4.7);
- Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

~~12.~~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 sensitiz~~s~~ation 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.

~~13.~~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 sensitiz~~s~~ation as listed below may alter the decision. This shall be considered on a case-by-case basis.

- Isolated episodes of allergic contact dermatitis;
- Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;

- Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in paragraph ~~16~~ 3.4.2.2.4.1 of this chapter, but which are sufficiently close to the limit to be considered significant;
- Positive data from non-standard methods;
- Positive results from close structural analogues.

3.4.2.2.3 *Immunological contact urticaria*

~~14.~~ 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.

~~15.~~ There is no recognised 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 sensitizsation.

3.4.2.2.4 *Animal studies*

~~16.~~3.4.2.2.4.1 When an adjuvant type test method for skin sensitizsation is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant test method a response of at least 15% of the animals is considered positive. Test methods for skin sensitizsation 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 M~~m~~ouse E~~e~~ar S~~s~~welling T~~t~~est~~,~~ (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 sensitizsation potential. In case of a positive result in this latter test it may not be necessary to conduct a further guinea pig test.

~~17.~~3.4.2.2.4.2 When evaluating animal data, produced by testing according to the OECD or equivalent Guidelines for skin sensitizsation, the rate of sensitizsed animals may be considered. This rate reflects the sensitizsing capacity of a substance in relation to its mildly irritating dose. This dose may vary between substances. A more appropriate evaluation of the sensitizsing 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 sensitizsing at low doses where others require high doses and long time of exposure for sensitizsation. 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 subcategorise sensitizers have not been validated and accepted. Therefore, sub-categorisation should not yet be considered as part of the harmonizsed 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*

~~20.~~3.4.3.2.1 Where the mixture itself has not been tested to determine its sensitiz~~s~~ing properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise 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 characterising the hazards of the mixture without the necessity for additional testing in animals.

3.4.3.2.2 *Dilution*

~~21.~~ If a mixture is diluted with a diluent which is not a sensitizer and which is not expected to affect the sensitiz~~s~~ation of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.4.3.2.3 *Batching*

~~22.~~ The sensitiz~~s~~ing 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 sensitiz~~s~~ation of the batch has changed. If the latter occurs, new classification is necessary.

3.4.3.2.4 *Substantially similar mixtures*

~~23.~~ 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 i~~I~~ngredients A and C are not sensitizers;
(e) A and C are not expected to affect the sensitiz~~s~~ing 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-aerosolised form of the mixture provided that the added propellant does not affect the sensitizsing properties of the mixture upon spraying. [For special labelling required by some competent authorities, see Notes 1, 3 and 5 to Table 3.4.1 of this chapter.]

3.4.3.3~~4~~ *Classification of mixtures when data are available for all components or only for some components of the mixture*

~~25.~~ 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 ~~1~~ 3.4.1 ~~below~~ for solid/liquid and gas respectively.

Table 3.4.1: Cut-off values/concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitizsers that would trigger classification of the mixture

Ingredient Classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**		
	Skin Sensititi~~t~~izer	**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. 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 recognise that special cases may require information to be conveyed below that level. [In addition, some competent authorities may require a special labelling phrase for all mixtures containing sensitisers above 0.1%.].*

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

***NOTE 3**: If a solid or liquid respiratory sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. 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 recognise that special cases may require information to be conveyed below that level. [In addition, some competent authorities may require a special labelling phrase for all mixtures containing sensitizsers above 0.1%.].*

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

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

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

3.4.4 Hazard communication

~~**Allocation of label elements**~~

~~26.~~ General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter ~~1.3~~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 ~~2~~ 3.4.2 below presents specific label elements for substances and mixtures that are classified as respiratory and skin sensitizsers based on the criteria in this chapter.

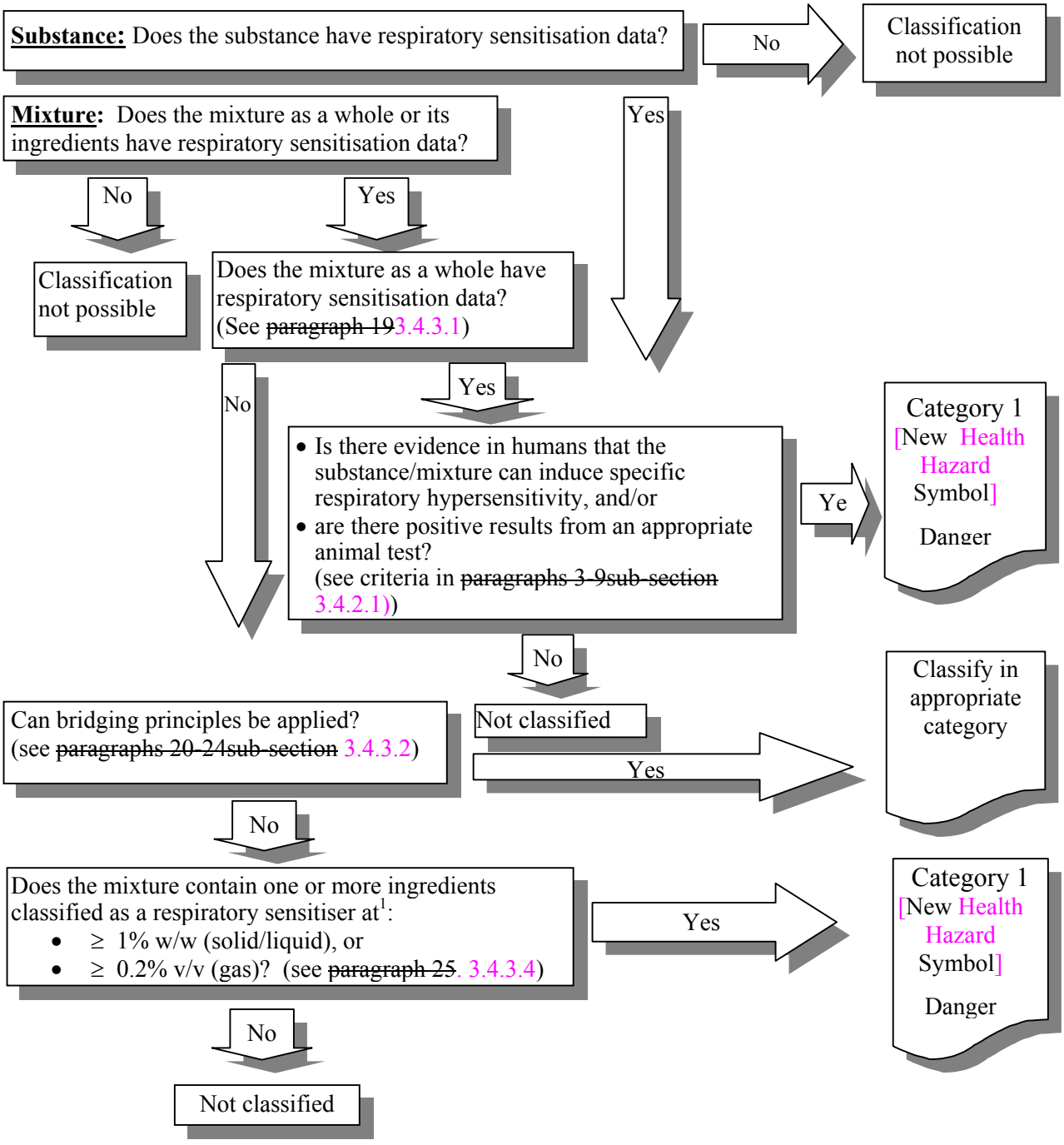
Table ~~2~~3.4.2: Respiratory or skin sensitizsation label elements.

	Respiratory Sensitizsation Category 1	**Skin Sensitizsation Category 1**
Symbol	New health hazard symbol	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

~~27.~~3.4.5 Decision logic ~~and guidance~~

3.4.5.1 Decision Logic 3.4.1 for Respiratory Sensitiz~~s~~ation

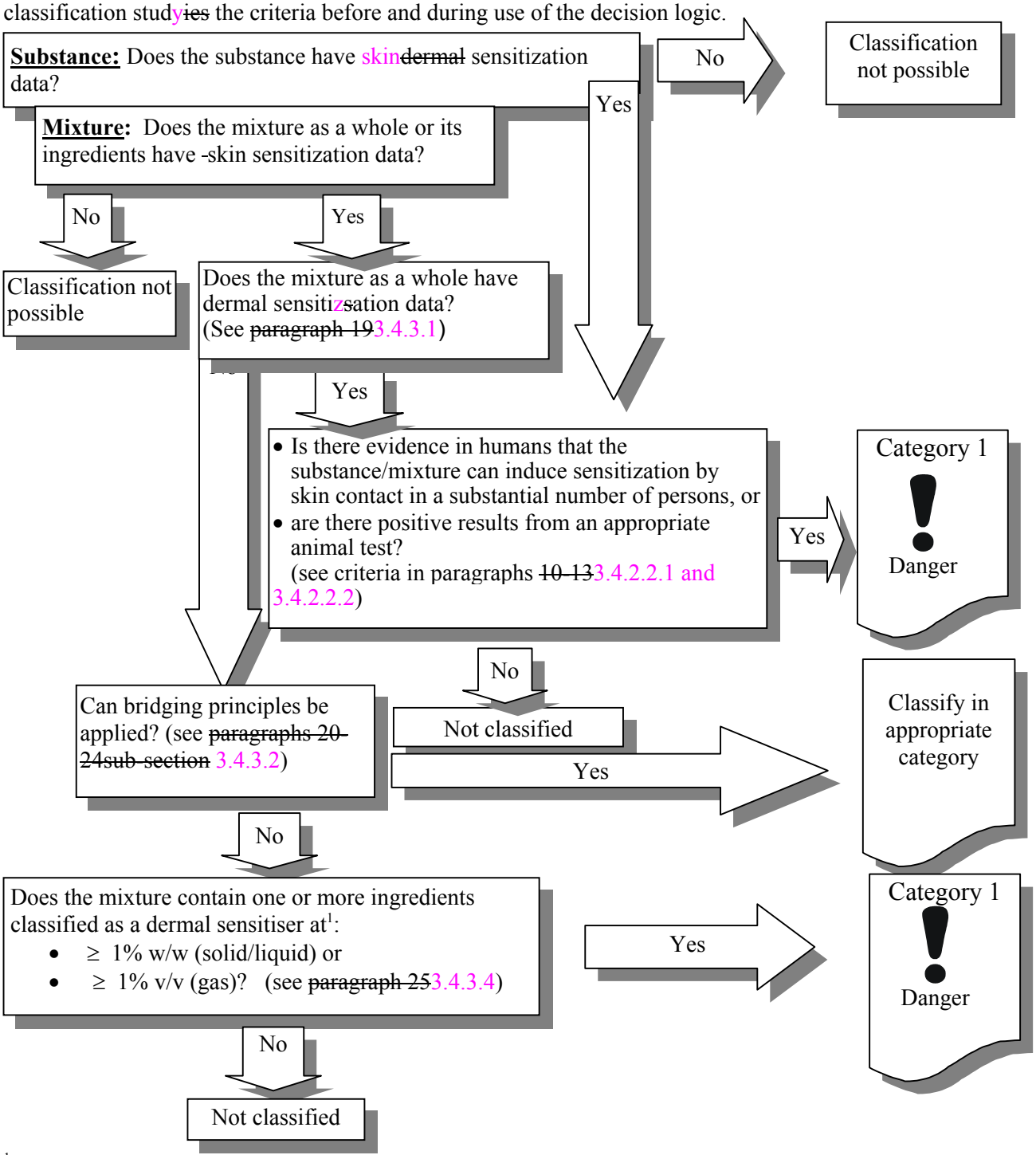
The decision logic~~,~~ which follows is not part of the harmoniz~~s~~ed classification system~~,~~ but is~~has been~~ provided here as additional guidance. It is strongly recommended that the person responsible for classification study~~ies~~ the criteria before and during use of the decision logic.



[1] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.2~~3~~, para. 1.3.3.2*

3.4.5.2 Decision logic 3.4.2 for ~~Dermal~~Skin Sensitizsation

The decision logic~~,~~ which follows is not part of the harmonizsed classification system~~,~~ but is~~has been~~ provided here as additional guidance. It is strongly recommended that the person responsible for classification studyies the criteria before and during use of the decision logic.



[1] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para 1.3.3.2.*.