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**COMMITTEE OF EXPERTS ON THE TRANSPORT OF
DANGEROUS GOODS AND ON THE GLOBALLY
HARMONIZED SYSTEM OF CLASSIFICATION
AND LABELLING OF CHEMICALS**

**Sub-Committee of Experts on the
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and Labelling of Chemicals**
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**GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION
AND LABELLING OF CHEMICALS (GHS)**

DRAFT GHS

Submitted by the GHS Editorial Group

Part 3

HEALTH AND ENVIRONMENTAL HAZARDS

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CHAPTER 3.1

ACUTE TOXICITY

3.1.1 Definition

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

3.1.2 Classification criteria for substances

3.1.2.1 Chemicals can be allocated to one of five toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric 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 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	*See detailed criteria in Note (e)*
Gases (ppmV) see: *Note (a)*	100	500	2500	5000	
Vapours (mg/l) see: *Note (a)* *Note (b)* *Note (c)*	0.5	2.0	10	20	
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 LD_{50} in the range of 2000-5000 mg/kg bodyweight and equivalent doses for inhalation. The specific criteria for Category 5 are:*

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

    (ii) *The substance is classified in this Category, through extrapolation, estimation or measurement of data, if assignment to a more hazardous category is not warranted, and:*
   - *reliable information is available indicating significant toxic effects in humans; or*
   - *any mortality is observed when tested up to Category 4 values by the oral, inhalation, or dermal routes; or*
   - *where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance; or*
   - *where expert judgement confirms reliable information indicating the potential for significant acute effects from other animal studies.*

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.

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

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

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

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

3.1.2.6   *Specific considerations for inhalation toxicity*

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

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

3.1.2.6.3   Vapour inhalation values are intended for use in classification of acute toxicity for all sectors. It is also 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.

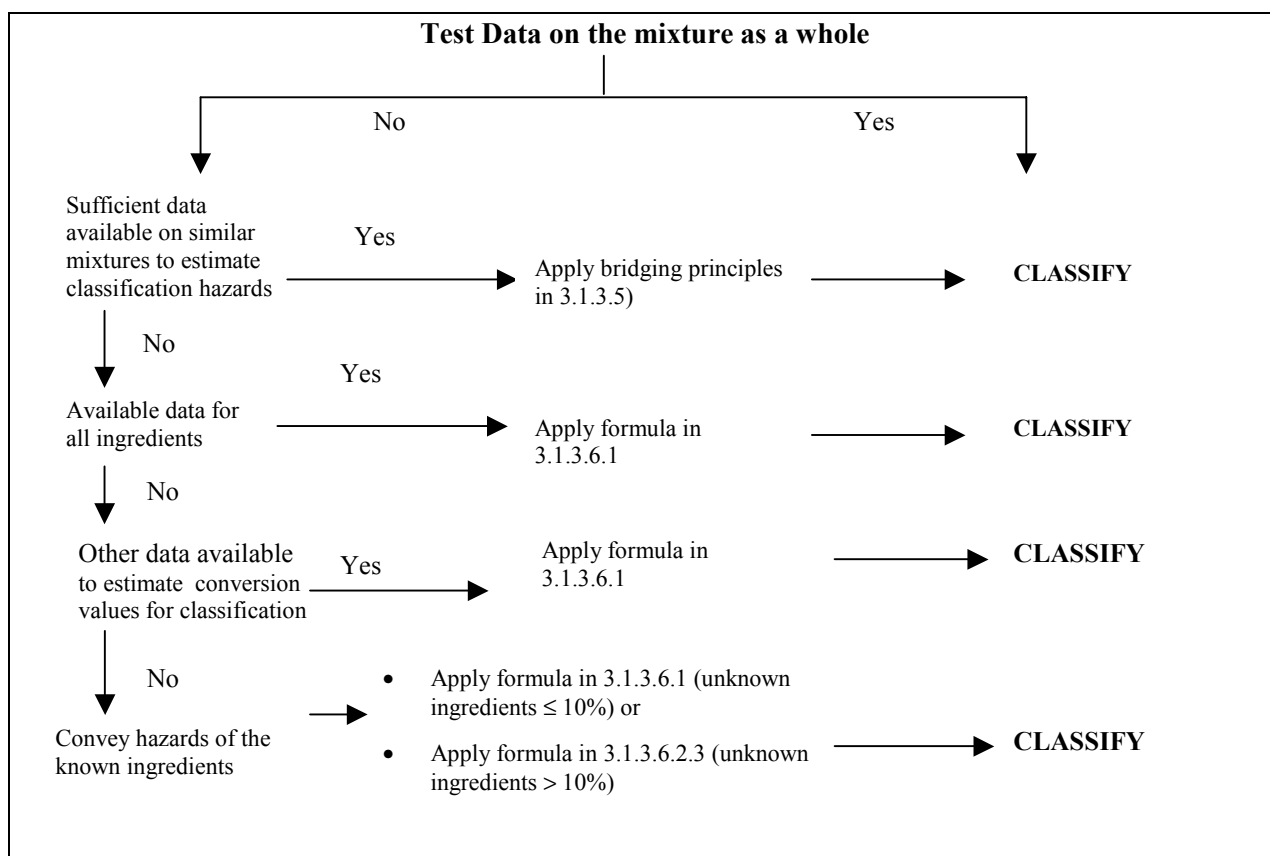[1]   *Guidance on Category 5 Inhalation Values: The OECD Task Force on Harmonisation of Classification and Labelling (HCL) did not include numerical values in Table 3.1.1 above for acute inhalation toxicity class 5 but instead specified doses "equivalent" to the range of 2000-5000 mg/kg bodyweight by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

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

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

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

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

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

(a)　　The "relevant ingredients" of a mixture are those which are present in concentrations 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 3.1.2 that relates to the results of a range test for an ingredient, or
- The appropriate conversion value from Table 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 3.1.3.6.1 and 3.1.3.6.2.3.

Table 3.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for 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 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 3.1.2.5.*	0.05 0.5 3 11
Dust/mist (mg/l)	0 < Category 1 ≤ 0.05 0.05 < Category 2 ≤ 0.5 0.5 < Category 3 ≤ 1.0 1.0 < Category 4 ≤ 5.0 *Category 5 - See footnote to 3.1.2.5.*	0.005 0.05 0.5 1.5

NOTE: gases concentration are expressed in parts per million per volume (ppmV)

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

Note 2: *These values are designed to be used in the calculation of the ATE for 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*

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

3.1.3.5.1.   *Classification of mixtures where acute toxicity test data are not available for the complete mixture: Bridging principles*

3.1.3.5.1   Where the mixture itself has not been tested to determine its acute toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately 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*

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 3.1.3.6.1 could be applied.

If a mixture is diluted with water or other totally non-toxic material, the toxicity of the mixture can be calculated from test data on the undiluted mixture. For example, if a mixture with an 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*

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

3.1.3.5.4   *Concentration of highly toxic mixtures*

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

3.1.3.5.5   *Interpolation within one toxicity category*

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

3.1.3.5.6   *Substantially similar mixtures*

Given the following:

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

(b)   The concentration of ingredient B is essentially the same in both mixtures;
(c)   The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d)   Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B;

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

3.1.3.5.7   *Aerosols*

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

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.

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

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for Oral, Dermal or Inhalation Toxicity:

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

where:
C_i =   concentration of ingredient i
n ingredients and i is running from 1 to n
ATE_i =   Acute Toxicity Estimate of ingredient i.

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

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

This may include evaluation of:

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

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

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

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

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

3.1.3.6.2.2   In the event that an ingredient without any useable information at all is used in a mixture at a concentration 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.

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

$$\frac{100 - (\sum C \, unknown \, if > 10\% \,)}{ATEmix} = \sum_{n} \frac{Ci}{ATEi}$$

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

3.1.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified into acute toxicity Categories 1-5 based on the criteria set forth in this chapter.

Table 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 Decision logics for classification of acute toxicity

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 3.1.1 for acute toxicity

Substance: Are there data and/or information to evaluate acute toxicity? — No → Classification not possible

Yes

Mixture: Does the mixture as a whole or its ingredients have data/information to evaluate acute toxicity? — No → Classification not possible

Yes

Does the mixture as a whole have data/information to evaluate acute toxicity? — No → See Decision Logic 3.1.2 to calculate an ATE from ingredients

Yes

ATE from Decision Logic 3.1.2

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:
- Oral $LD_{50} \leq 5$ mg/kg bodyweight, **or**
- Dermal $LD_{50} \leq 50$ mg/kg bodyweight, **or**
- Inhalation (gas) $LC_{50} \leq 100$ ppm, **or**
- Inhalation (vapour) $LC_{50} \leq 0.5$ mg/l, **or**
- Inhalation (dust/mist) $LC_{50} \leq 0.05$ mg/l?

Yes → Category 1 — Danger

No

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:
- Oral $LD_{50} > 5$ but ≤ 50 mg/kg bodyweight, **or**
- Dermal $LD_{50} > 50$ but ≤ 200 mg/kg bodyweight, **or**
- Inhalation (gas) $LC_{50} > 100$ but ≤ 500 ppm, **or**
- Inhalation (vapour) $LC_{50} > 0.5$ but ≤ 2.0 mg/l, **or**
- Inhalation (dust/mist) $LC_{50} > 0.05$ but ≤ 0.5 mg/l?

Yes → Category 2 — Danger

Continued on next page

No

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >50 but $\leq$ 300 mg/kg bodyweight, **or**
- Dermal LD_{50} > 200 but $\leq$ 1000 mg/kg bodyweight, **or**
- Inhalation (gas) LC_{50} >500 but $\leq$ 2500 ppm, **or**
- Inhalation (vapour) LC_{50} >2 but $\leq$ 10.0 mg/l**, or**
- Inhalation (dust/mist) LC_{50} >0.5 but < 1.0 mg/l?

Yes → Category 3 / Danger

No

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >300 but $\leq$ 2000 mg/kg bodyweight**, or**
- Dermal LD_{50} >1000 but $\leq$ 2000 mg/kg bodyweight, **or**
- Inhalation (gas) LC_{50} >2500 but $\leq$ 5000 ppm, **or**
- Inhalation (vapour) LC_{50} >10 but $\leq$ 20 mg/l, **or**
- Inhalation (dust/mist) LC_{50} >1 but < 5 mg/l?

Yes → Category 4 / Warning

No

According to the criteria in paragraphs3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >2000 but $\leq$ 5000 mg/kg bodyweight, **or**
- Dermal LD_{50} >2000 but $\leq$ 5000 mg/kg bodyweight, **or**
- Inhalation (gas, vapour and/or dust/mist) LC_{50} in the equivalent range of the oral and dermal LD_{50} (i.e., 2000-5000 mg/kg body weight)

Yes → Category 5 / Warning

No

- 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

Yes →

Classify in Category 5 (Warning)

if assignment to a more hazardous class is not warranted

No →

Not classified

Decision Logic 3.1.2 for acute toxicity

(See criteria in 3.1.3.5 and 3.1.3.6)

Can bridging principles be applied? → **Yes** → Classify in appropriate category

No ↓

Is acute toxicity data available for all ingredients of mixture? → **Yes** →

Apply the Acute Toxicity Estimate Calculation to determine the ATE of the mixture

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

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.

→ ATE mix to Decision Logic 3.1.1

No ↓

Is it possible to estimate missing ATE(s) of the ingredient(s), i.e. can conversion value(s) be derived? → **Yes** →

No ↓

Is the total concentration of the ingredient(s) with unknown acute toxicity > 10 %? → **No[1]** →

Yes[1] →

Apply the Acute Toxicity Estimate Calculation (i.e. when the total concentration of ingredients with unknown acute toxicity is above 10%)

$$\frac{100 - (\sum C_{unknown} \text{ if} > 10\%)}{\text{ATE}_{mix}} = \sum_{n} \frac{C_i}{\text{ATE}_i}$$

→ ATE mix to Decision Logic 3.1.1

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[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

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

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

3.2.2   Classification criteria for substances

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

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

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

3.2.2.3   A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 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.*

**Figure 3.2.1: Tiered testing and evaluation of 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 ≤ 2 or ≥11.5	Classify as corrosive [a]
	Not pH extreme or no data		
4	Existing skin data in animals indicate no need for animal testing [d]	Yes	Possibly no further testing may be deemed corrosive/ irritant
	No indication or no data		
5	Valid and accepted in vitro skin corrosion test [e]	Positive response	Classify as corrosive [a]
	Negative response or no data		

Figure 3.2.1 *(cont'd):* **Tiered testing and evaluation of 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
6	Valid and accepted in vitro skin irritation test [f]	Positive response	Classify as irritant [a]
	Negative response or no data		
7	*In vivo* skin corrosion test (1 animal)	Corrosive response	Classify as corrosive [a]
	Negative response		
8	*In vivo* 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 harmonized category, as shown in Table 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 skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any skin irritation in an acute skin toxicity test at the limit dose, or produces very toxic effects in an acute skin toxicity test. In the latter case, the material would be classified as being very hazardous by the dermal route for acute toxicity; it is moot whether the material is also irritating or corrosive on the skin. It should be kept in mind in evaluating acute skin toxicity information that the reporting of skin lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;

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

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

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

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

3.2.2.4 *Corrosion*

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

3.2.2.4.2   For those authorities wanting more than one designation for corrosivity, up to three subcategories are provided within the corrosive category (Category 1, see Table 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 3.2.1 Skin corrosive category and subcategories [a]

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

[a]   The use of human data is discussed in 3.2.2.1 and in *Classification of Hazardous Substances and Mixtures* (para. 1.3.2.4.7.1).

3.2.2.5 *Irritation*

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

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

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

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

3.2.2.5.4   A single irritant category (Category 2) is presented in the table using the results of animal testing. Authorities (e.g. pesticides) also have available a less severe mild irritant category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of $\geq 2.3 - \leq 4.0$. For the mild irritant category, the mean score cut-off 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 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 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 skin reactions (when not included in the irritant category above).

[a]   The use of human data is discussed in 3.2.2.1 and in the *Classification of Hazardous Substances and Mixtures* (1.3.2.4.7.1).

3.2.3   Classification criteria for mixtures

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

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

3.2.3.1.2   Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered corrosive (Skin Category 1) if it has a pH 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*

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*

        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 section 3.2.3.3 could be applied.

3.2.3.2.3   *Batching*

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

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

        If a tested mixture classified in the highest 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*

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

3.2.3.2.6   *Substantially similar mixtures*

Given the following:

(a)   Two mixtures
        (i)   A +B
        (ii)   C + B;
(b)   The concentration of ingredient B is essentially the same in both mixtures;
(c)   The concentration of ingredient A in mixture(i) equals that of ingredient C in
        mixture (ii);
(d)   Data on irritation/corrosion for A and C are available and substantially equivalent, i.e.
        they are in the same hazard category and are not expected to affect the toxicity of B.

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

3.2.3.2.7   *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-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*

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.

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 cut-off value/concentration limit.

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

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

3.2.3.3.5   On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off 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 (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 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as described in 3.2.3.1.4 and illustrated in Figure 3.2.1.

3.2.3.3.6   If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also *Classification of Hazardous Substances and Mixtures – The Use of Cut-Off Values/Concentration Limits* (1.3.2.3.1.2)).

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

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:		
	Skin corrosive	Skin irritant	
	Category 1 (see note below)	Category 2	Category 3
Skin Category 1	≥5%	≥1% but < 5%	
Skin Category 2		≥10%	≥1% but < 10%
Skin Category 3			≥10%
(10 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 3.2.3: 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.

Table3.2.4: 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

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

Table 3.2.5: Label elements for skin corrosion/irritation.

	Catégorie 1			Catégorie 2	Catégorie 3
	1 A	**1 B**	**1 C**		
Symbole	Corrosion	Corrosion	Corrosion	Exclamation mark	No symbol is used
Mention d'avertis - sement	Danger	Danger	Danger	Warning	Warning
Mention de danger	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 Decision Logic for skin corrosion/irritation

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 3.2.1 **for skin corrosion/irritation:**

Substance: Are there data/information to evaluate skin corrosion/irritation?	No → Classification not possible
Mixture: Does the mixture as whole or its ingredients have data/information to evaluate skin corrosion/irritation?	No → Classification not possible
Mixture: Does the mixture as a whole have data/information to evaluate skin corrosion/irritation?	No → See Decision Logic 3.2.2 for use with ingredients

Yes ↓

Yes ↓

Is the **substance or mixture corrosive** (see paragraphs 3.2.1.1, 3.2.2.2-3.2.2.4 and 3.2.3.1.2) considering[1]:

• Existing human experience showing irreversible damage to skin,

• Existing animal observations indicating skin corrosion after single or repeated exposure,

• In vitro data,

• Information available from structurally related compounds,

• pH extremes of ≤ 2 or ≥ 11.5[2]

• Destruction of skin in 1 or more test animals. (see paragraph 3.2.2.4.2 Table 3.2.1 for criteria and sub-categorisation)?

Yes →

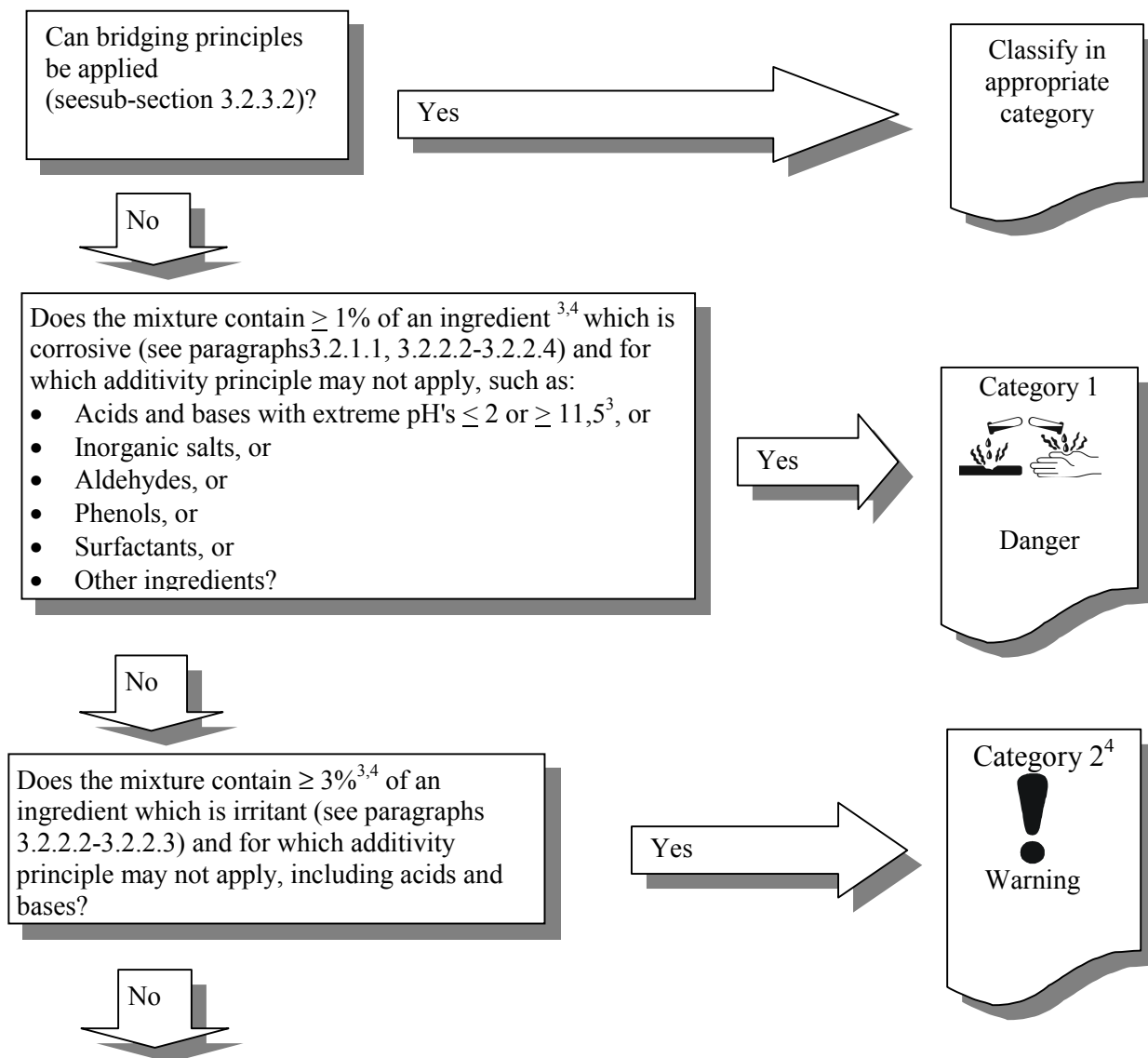Category 1

Danger

Continued on next page

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

.

No

Is the **substance or mixture** an **irritant** (see
paragraphs 3.2.1.2, 3.2.2.2-3.2.2.4 and 3.2.2.5)
considering[1].
- Existing human experience and data, single or
  repeated exposure
- Existing animal observations including single or
  repeated exposure,
- In vitro data,
- Information available from structurally related
  compounds,
- Skin irritation data from an animal study (See
  3.2.2.5.4 Table 3.2.2 for criteria)?

Yes

Category 2

!

Warning

No

Is the **substance or mixture** a **mild irritant**
considering criteria in 3.2.2.5.4 Table 3.2.2?

Yes

Category 3

Warning

No

Not Classified
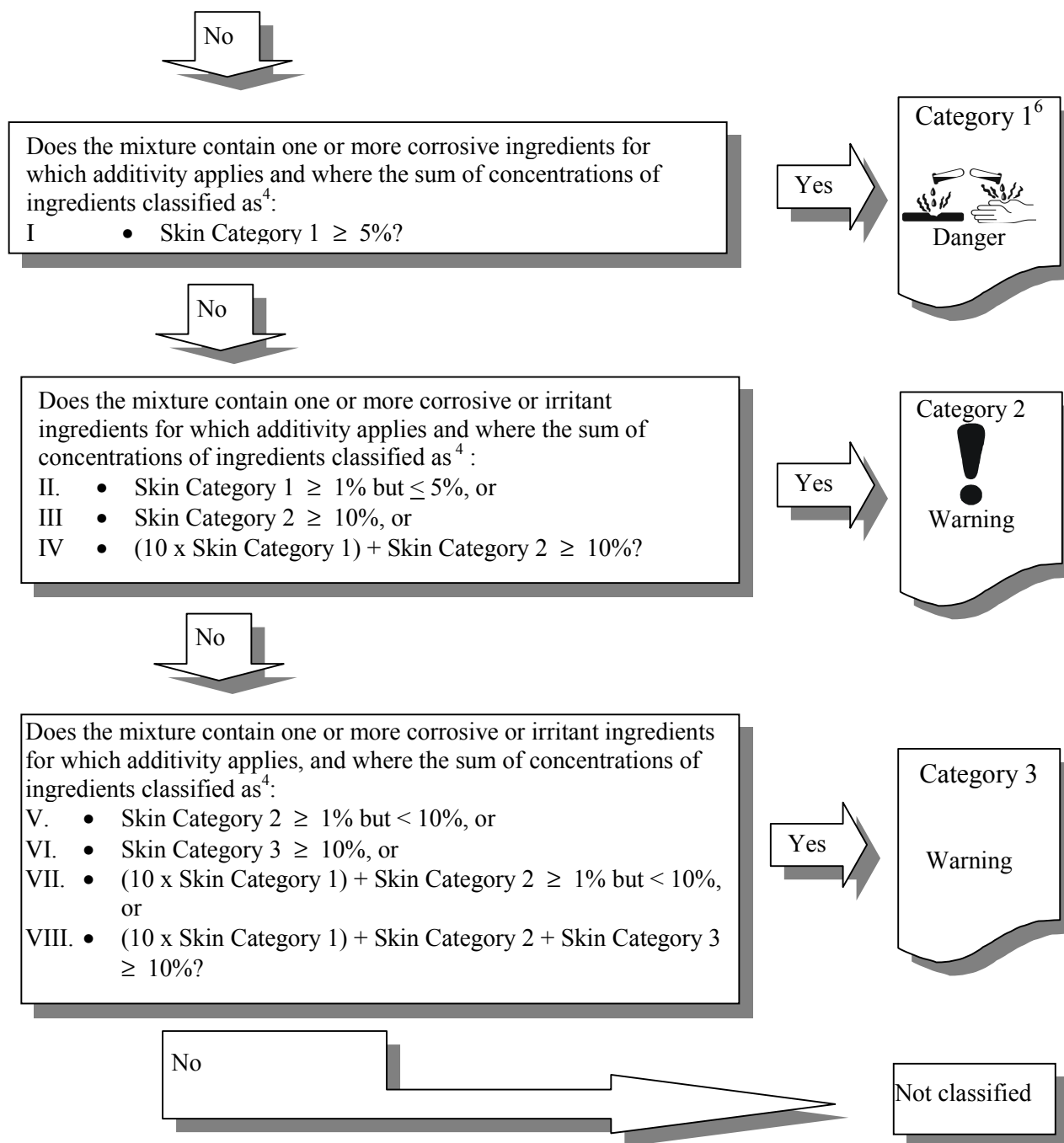
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[1] *Figure 3.2.1 contains details for testing and evaluation.*

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

Can bridging principles be applied (seesub-section 3.2.3.2)?

Yes ⟶ Classify in appropriate category

No ⬇

Does the mixture contain ≥ 1% of an ingredient [3,4] which is corrosive (see paragraphs 3.2.1.1, 3.2.2.2-3.2.2.4) and for which additivity principle may not apply, such as:

- Acids and bases with extreme pH's ≤ 2 or ≥ 11,5[3], or
- Inorganic salts, or
- Aldehydes, or
- Phenols, or
- Surfactants, or
- Other ingredients?

Yes ⟶ Category 1

Danger

No ⬇

Does the mixture contain ≥ 3%[3,4] of an ingredient which is irritant (see paragraphs 3.2.2.2-3.2.2.3) and for which additivity principle may not apply, including acids and bases?

Yes ⟶ Category 2[4]

Warning

No ⬇

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[3]   Or where relevant < 1 %, see paragraph 3.2.3.3.1.
[4]   For specific concentration limits, see paragraph 3.2.3.3.6 of this chapter. See also Chapter 1.3, para. 1.3.3.2 for "The use of Cut-off Values/Concentration Limits".
[2]   including consideration of acid/alkali reserve capacity, if appropriate.
[5]   If the mixture also contains corrosive or irritant ingredient(s) for which additivity applies, move to the box below.

No

Does the mixture contain one or more corrosive ingredients for which additivity applies and where the sum of concentrations of ingredients classified as[4]:

I • Skin Category 1 $\geq$ 5%?

Yes → Category 1[6]

Danger

No

Does the mixture contain one or more corrosive or irritant ingredients for which additivity applies and where the sum of concentrations of ingredients classified as[4]:

II. • Skin Category 1 $\geq$ 1% but $\leq$ 5%, or
III • Skin Category 2 $\geq$ 10%, or
IV • (10 x Skin Category 1) + Skin Category 2 $\geq$ 10%?

Yes → Category 2

Warning

No

Does the mixture contain one or more corrosive or irritant ingredients for which additivity applies, and where the sum of concentrations of ingredients classified as[4]:

V. • Skin Category 2 $\geq$ 1% but < 10%, or
VI. • Skin Category 3 $\geq$ 10%, or
VII. • (10 x Skin Category 1) + Skin Category 2 $\geq$ 1% but < 10%, or
VIII. • (10 x Skin Category 1) + Skin Category 2 + Skin Category 3 $\geq$ 10%?

Yes → Category 3

Warning

No → Not classified

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[4] *For specific concentration limits, see paragraph 3.2.3.3.6 of this chapter. See also Chapter 1.3, para. 1.3.3.2, for "The Use of Cut-off Values/Concentration Limits".*

[6] *See note to Table 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

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

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

3.3.2   Classification criteria for substances

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

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

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

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

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

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

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.

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 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[2].

3.3.2.7   Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to 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 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 -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, Figure3.2.1")

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	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 $\geq$ 11.5 or pH $\leq$ 2 (considering acid or alkaline reserve)	Category 1
3b	2 < pH < 11.5 (no buffering potential)		
4	Other information indicating the material is a skin corrosive	Yes	No evaluation of effects on eyes; deemed to be Category 1
	↓ No		

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

Step	Parameter	Findings	Conclusions
	No ↓		
5	Is a valid *in vitro* test available to assess severe damage to eyes ↓	→ No	→ Go to step 6
5a	*In vitro* test for severe eye irritation ↓	→ Severe damage to eyes	→ Category 1
	Not a severe eye irritant ↓		
6	Is a valid *in vitro* test for eye irritation available ➜No ↓	→ - But *in vitro* test for severe eye irritancy was negative	→ Go to step 8
		- In the absence of any *in vitro* test	→ Go to Step 7
	Yes ↓		
6a	*In vitro* eye irritation test ↓	→ Eye irritant	→ Category 2
	No indication of eye irritant properties ↓		
7	Experimentally assess skin corrosion potential (see Testing Strategy for Skin Irritation/Corrosion) ↓	→ Skin corrosive	→ No evaluation of effects on eyes, deemed to be category 1
	Not corrosive ↓	→ 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

Notes to Figure 3.3.1:

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

> (i)   Step 1a - reliable determination of eye irritancy basing on human or animal experience - depends on expert judgement: in most cases human experience is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data;
>
> (ii)   Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

Step 2a/b: SAR (Structure Activity Relationships) / SPR (Structure Property Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches. The SAR/SPR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects: i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to agents with very well known properties. ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

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

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

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

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

Step 7: In the absence of any other relevant information, it is essential to obtain this via an internationally 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)*

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

Table 3.3.1: Irreversible eye effects categories

> **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 testmaterial.

The use of human data is discussed in *Purpose, Scope and Application* (Chapter 1.1, paragraph 1.1.2.6) and *Classification of Hazardous Substances and Mixtures* (Chapter 1.3, paragraph 1.3.2.4.7).

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

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

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

Table 3.3.2: Reversible eye effects categories

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

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

3.3.3 Classification criteria for mixtures

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

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

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH 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*

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*

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

3.3.3.2.3   *Batching*

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

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

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*

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

3.3.3.2.6   *Substantially similar mixtures*

Given the following:

(a)   Two mixtures   (i)   A +B
                       (ii)   C + B;
(b)   The concentration of ingredient B is essentially the same in both mixtures;
(c)   The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d)   Data on irritation/serious eye damage for A and C are available and substantially equivalent, i.e. If mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

3.3.3.2.7   *Aerosols*

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

---

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*

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.

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.

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

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

3.3.3.3.5   On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to 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, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6   If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also Hazard Communication: Labelling – Use of Cut-Off Values/Concentration Limits (Chapter 1.3 , subsection 1.3.3.2)).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as <u>hazardous to the eye</u> (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 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

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

3.3.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

Table 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

3.3.5 Decision Logic

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

Decision Logic 3.3.1 for serious eye damage / eye irritation

Substance: Are there data/information to evaluate serious eye damage/eye irritation?

No → Classification not possible

Yes ↓

Mixture: Does the mixture as a whole or its ingredients have data/information to evaluate serious eye damage/eye irritation?

No → Classification not possible

Yes ↓

Mixture: Does the mixture as a whole have data/information to evaluate serious eye damage/eye irritation?

No → See Decision Logic 3.3.2 for use with ingredients

Yes ↓

Does the **substance or mixture** have potential to cause **irreversible eye damage (serious eye damage**, see paragraphs 3.3.1 and –3.3.2.2-3.3.2.5**)** considering[4]:

- Existing human experience,
- Existing animal observations including single or repeated exposure,
- In vitro data,
- Information available from structurally related compounds,
- pH extremes of ≤ 2 or ≥ 11.5[5]
- Irreversible eye damage in 1 or more test animals.

(see paragraph 3.3.2.5 and Table 3.3.1 for criteria and sub-categorization)

Yes → Category 1

Danger

---

[4]   *Figure 3.3.1 contains details for testing and evaluation.*
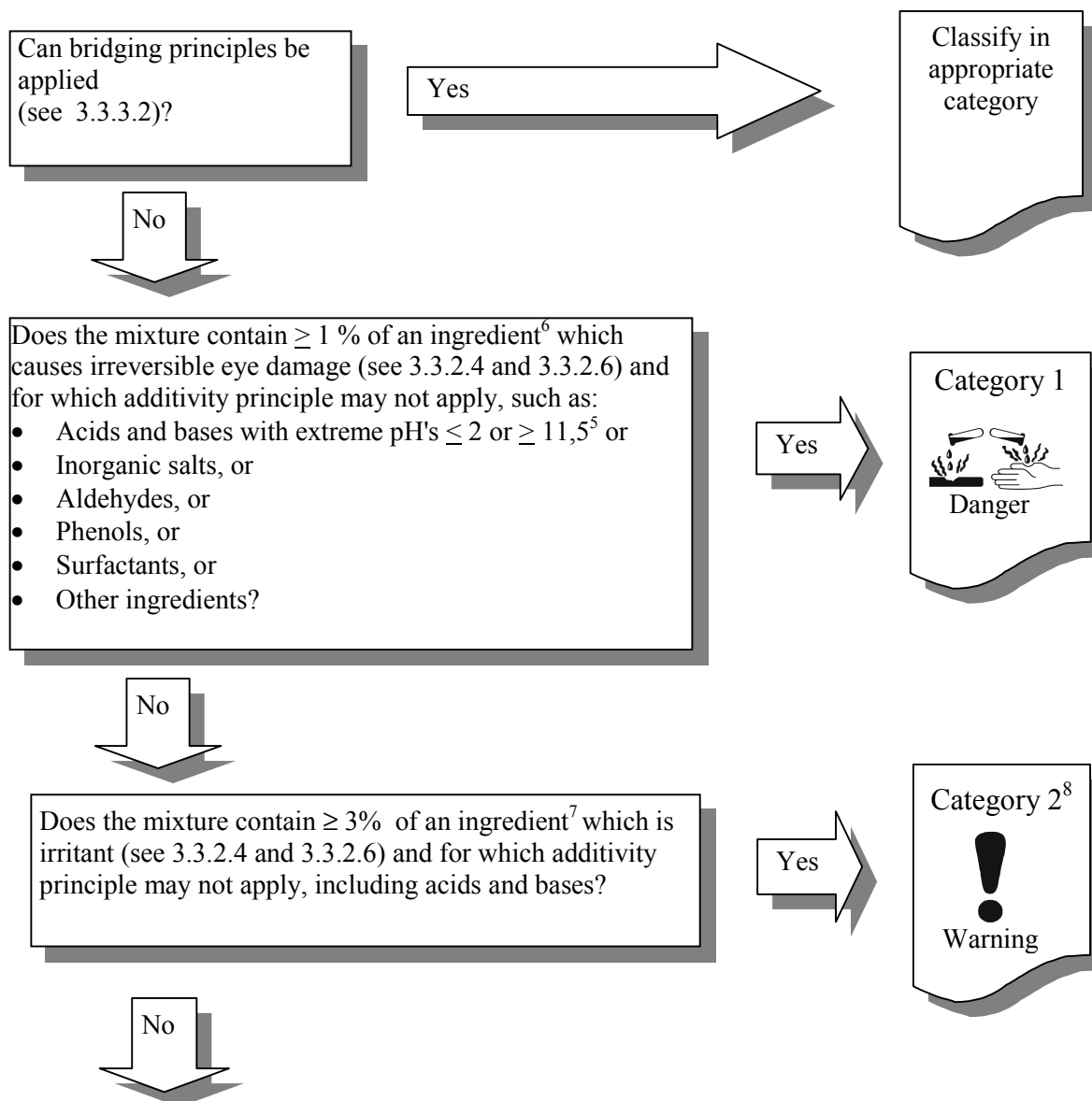[5]   *Including consideration of acid/alkali reserve capacity, if appropriate.*

No

Is the **substance or mixture** an **eye irritant** (see paragraphs 3.3.1, 3.3.2.2-3.3.2.4 and 3.3.2.6) considering[1]:
- Existing human experience and data, single or repeated exposure
- Existing animal observations including single or repeated exposure,
- In vitro data,
- Information available from structurally related compounds,
- Eye irritation data from an animal study (See paragraph 3.3.2.6 Table 3.3.2 for criteria for category 2A)?

Yes

Category 2A

!

Warning

No

Is the **substance or mixture** a mild irritant (see 3.3.2.6), category 2B, considering criteria in paragraph 3.3.2.6, Table 3.3.2?

Yes

Category 2B

Warning

No

Not Classified

---

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

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

Can bridging principles be applied (see 3.3.3.2)?

Yes →

Classify in appropriate category

No ↓

Does the mixture contain ≥ 1 % of an ingredient[6] which causes irreversible eye damage (see 3.3.2.4 and 3.3.2.6) and for which additivity principle may not apply, such as:
- Acids and bases with extreme pH's ≤ 2 or $\geq 11,5$[5] or
- Inorganic salts, or
- Aldehydes, or
- Phenols, or
- Surfactants, or
- Other ingredients?

Yes →

Category 1

Danger

No ↓

Does the mixture contain ≥ 3% of an ingredient[7] which is irritant (see 3.3.2.4 and 3.3.2.6) and for which additivity principle may not apply, including acids and bases?

Yes →

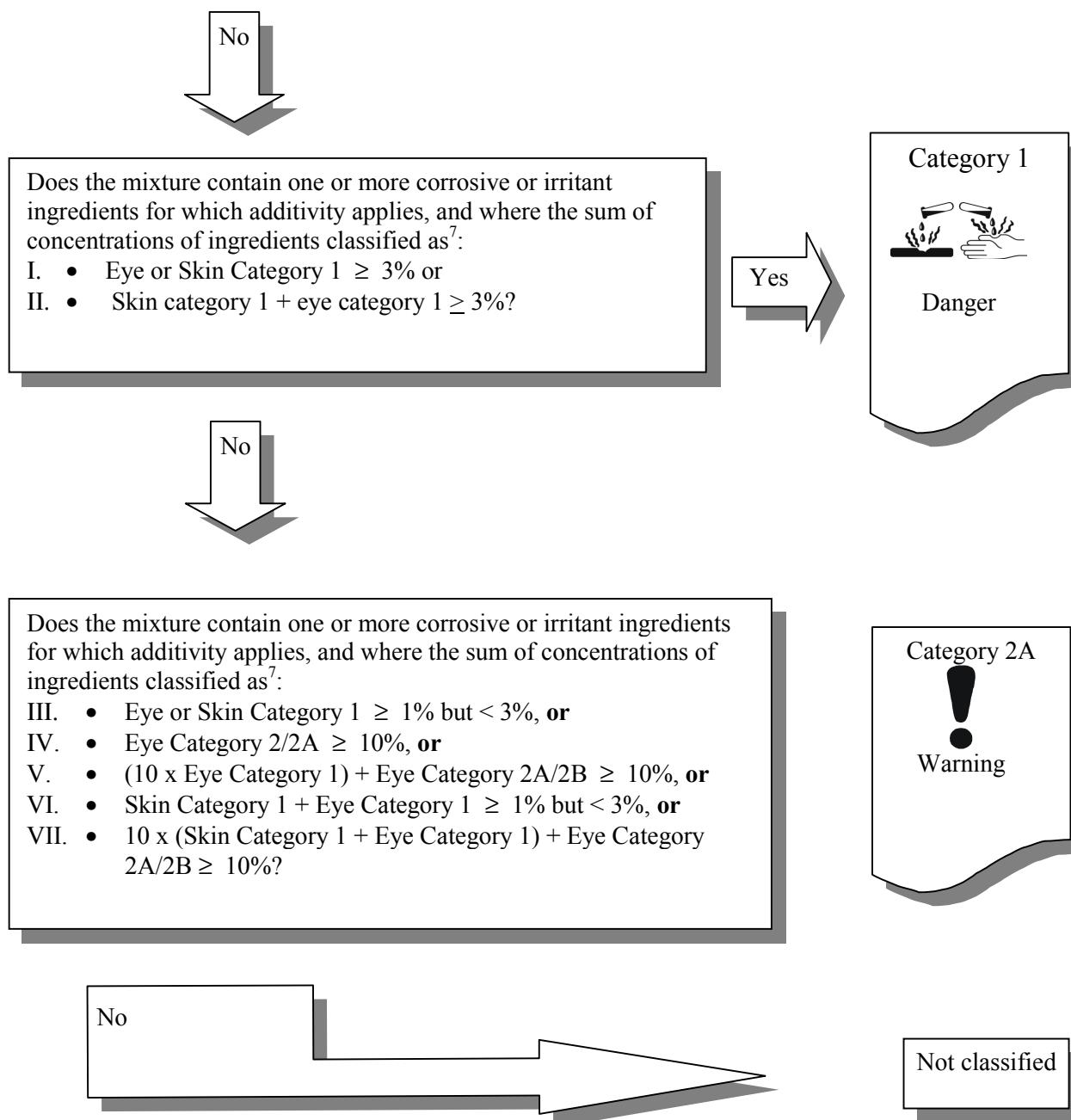Category 2[8]

!

Warning

No ↓

---

[6]   *Or where relevant < 1 %, see paragraph 3.3.3.3.1.*
[5]   *Including consideration of acid/alkali reserve capacity, if appropriate.*
[7]   *For specific concentration limits, see paragraph 3.3.3.3.4 of this chapter. See also Chapter 1.3, para. 1.3.3.2 for "The Use of Cut-Off Values/Concentration Limits.*
[8]   *If the mixture also contains corrosive ingredient(s) for which additivity applies move to the box below.*

No

Does the mixture contain one or more corrosive or irritant ingredients for which additivity applies, and where the sum of concentrations of ingredients classified as[7]:
I. • Eye or Skin Category 1 $\geq$ 3% or
II. • Skin category 1 + eye category 1 $\geq$ 3%?

Yes

Category 1

Danger

No

Does the mixture contain one or more corrosive or irritant ingredients for which additivity applies, and where the sum of concentrations of ingredients classified as[7]:
III. • Eye or Skin Category 1 $\geq$ 1% but < 3%, **or**
IV. • Eye Category 2/2A $\geq$ 10%, **or**
V. • (10 x Eye Category 1) + Eye Category 2A/2B $\geq$ 10%, **or**
VI. • Skin Category 1 + Eye Category 1 $\geq$ 1% but < 3%, **or**
VII. • 10 x (Skin Category 1 + Eye Category 1) + Eye Category 2A/2B $\geq$ 10%?

Category 2A

Warning

No

Not classified

---

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

CHAPTER 3.4

RESPIRATORY OR SKIN SENSITIZATION

3.4.1   Definitions

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

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*

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.

3.4.2.1.2   *Human evidence*

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

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

-        the size of the population exposed

-        the extent of exposure.

---

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

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.

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

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

3.4.2.1.3   *Animal studies*

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

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

3.4.2.2   *Skin sensitizers*

3.4.2.2.1   *Hazard category*

---

[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.*

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 sensitization by skin contact in a substantial number of persons, or
>
> - If there are positive results from an appropriate animal test.

3.4.2.2.2   *Specific considerations*

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

- 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 1.3, paragraph 1.3.2.4.7);
- Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

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

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

- 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 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*

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

There is no 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 sensitization.

3.4.2.2.4   *Animal studies*

3.4.2.2.4.1   When an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant test method a response of at least 15% of the animals is considered positive. Test methods for skin sensitization are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are well-validated and scientific justification is given. The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used as a first stage in the assessment of skin sensitization potential. In case of a positive result in this latter test it may not be necessary to conduct a further guinea pig test.

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

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

3.4.3   Classification criteria for mixtures

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

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of these data. Care should be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive. [For special labelling required by some competent authorities, see Notes 1, 3 and 5 to Table 3.4.1 of this chapter.]

3.4.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.4.3.2.1   Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately 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*

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

3.4.3.2.3   *Batching*

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

3.4.3.2.4   *Substantially similar mixtures*

Given the following:

(a)   Two mixtures: (i)   A + B
                                     (ii)   C + B;
(b)   The concentration of ingredient B is essentially the same in both mixtures;
(c)   The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d)   Ingredient B is a sensitizer and ingredients A and C are not sensitizers;
(e)   A and C are not expected to affect the sensitizing properties of B.

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

3.4.3.2.5   *Aerosols*

An aerosol form of the mixture may be classified in the same hazard category as the tested non-aerosolised form of the mixture provided that the added propellant does not affect the sensitizing 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   *Classification of mixtures when data are available for all components or only for some components of the mixture*

The mixture should be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value / concentration limit for the specific endpoint as shown in Table 3.4.1 for solid/liquid and gas respectively.

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

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

NOTE 1: If a skin sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. 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 sensitizers 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 sensitizers 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

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.   Table 3.4.2 below presents specific label elements for substances and mixtures that are classified as respiratory and skin sensitizers based on the criteria in this chapter.

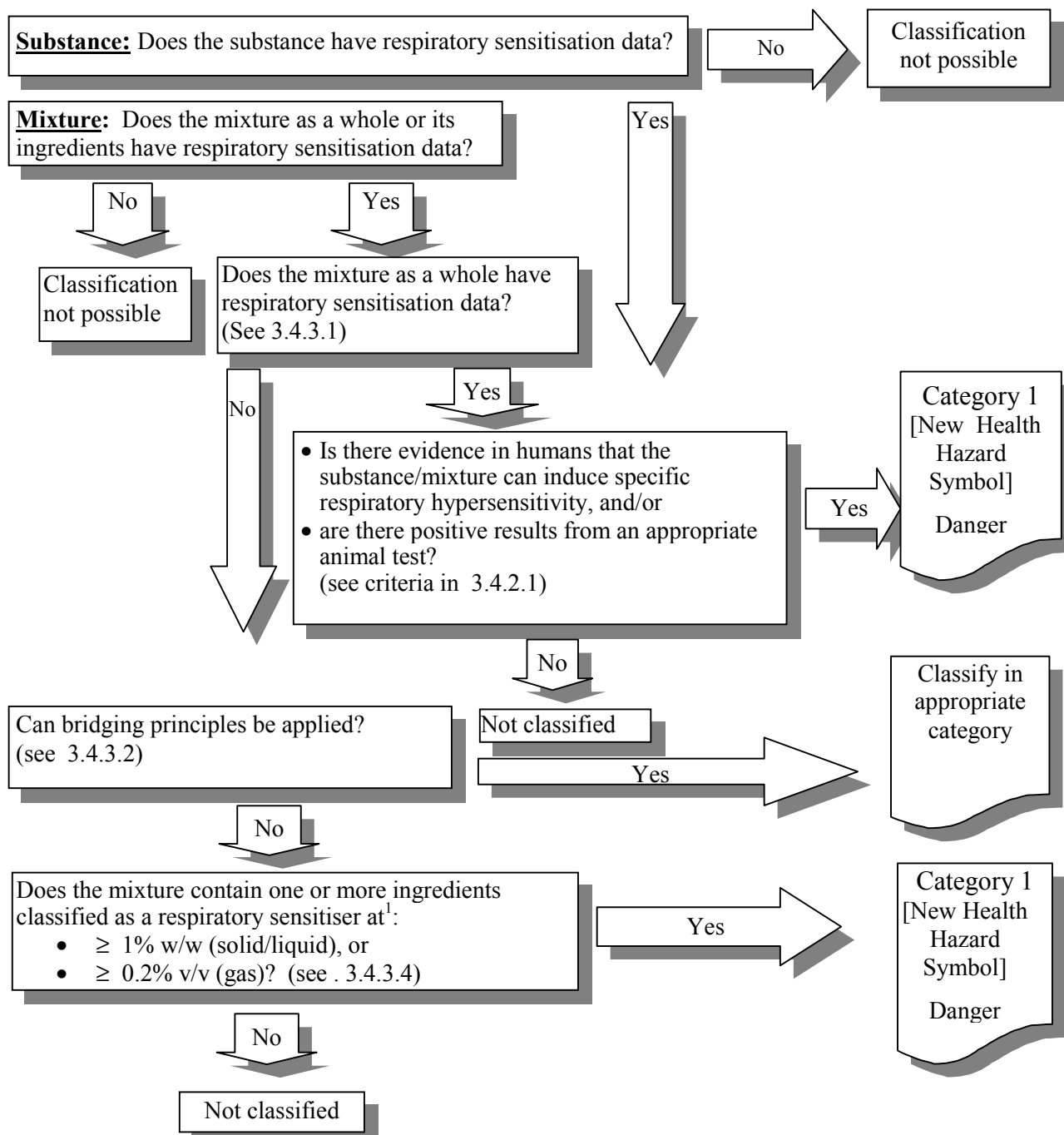**Table 3.4.2: Respiratory or skin sensitization label elements.**

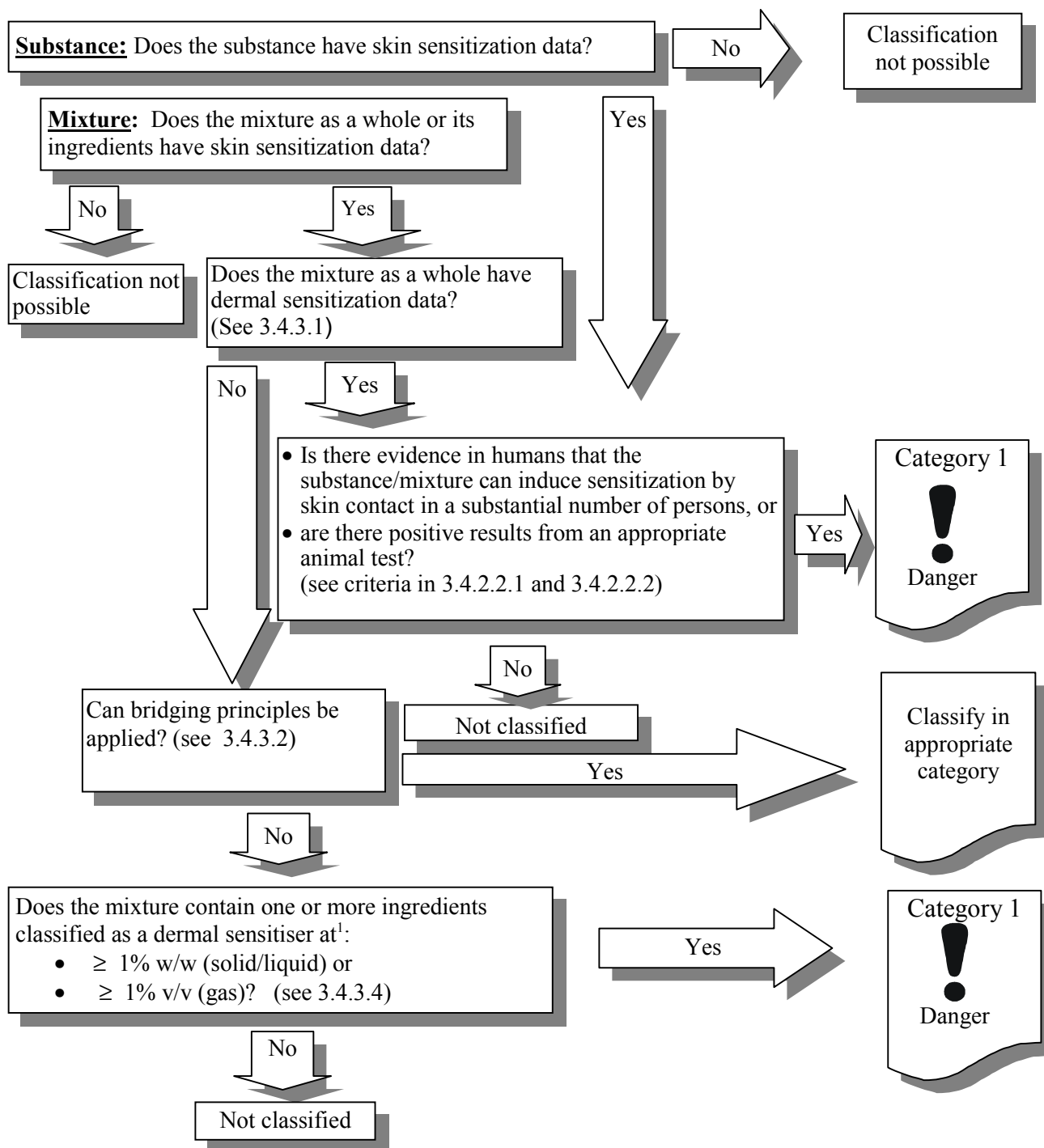|	Respiratory Sensitization Category 1	Skin Sensitization Category 1
Symbol	New health hazard symbol	Exclamation Mark
Signal Word	Danger	Warning
Hazard Statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

3.4.5 Decision logic

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

3.4.5.1 Decision Logic 3.4.1 for Respiratory Sensitization

Substance: Does the substance have respiratory sensitisation data? — No → Classification not possible

Yes

Mixture: Does the mixture as a whole or its ingredients have respiratory sensitisation data?

No → Classification not possible

Yes → Does the mixture as a whole have respiratory sensitisation data? (See 3.4.3.1)

No

Yes →

- Is there evidence in humans that the substance/mixture can induce specific respiratory hypersensitivity, and/or
- are there positive results from an appropriate animal test? (see criteria in 3.4.2.1)

Yes → Category 1 [New Health Hazard Symbol] Danger

No → Not classified

Can bridging principles be applied? (see 3.4.3.2)

Yes → Classify in appropriate category

No

Does the mixture contain one or more ingredients classified as a respiratory sensitiser at[1]:
- ≥ 1% w/w (solid/liquid), or
- ≥ 0.2% v/v (gas)? (see . 3.4.3.4)

Yes → Category 1 [New Health Hazard Symbol] Danger

No → Not classified

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

3.4.5.2 _Decision logic 3.4.2 for Skin Sensitization_

Substance: Does the substance have skin sensitization data? → No → Classification not possible

→ Yes

Mixture: Does the mixture as a whole or its ingredients have skin sensitization data?

No → Classification not possible

Yes → Does the mixture as a whole have dermal sensitization data? (See 3.4.3.1)

No

Yes →

- Is there evidence in humans that the substance/mixture can induce sensitization by skin contact in a substantial number of persons, or
- are there positive results from an appropriate animal test? (see criteria in 3.4.2.2.1 and 3.4.2.2.2)

Yes → Category 1 **!** Danger

No → Not classified

Can bridging principles be applied? (see 3.4.3.2)

Yes → Classify in appropriate category

No

Does the mixture contain one or more ingredients classified as a dermal sensitiser at[1]:
- $\geq$ 1% w/w (solid/liquid) or
- $\geq$ 1% v/v (gas)? (see 3.4.3.4)

Yes → Category 1 **!** Danger

No → Not classified

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

CHAPTER 3.5

GERM CELL MUTAGENICITY

3.5.1 Definitions and general considerations

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

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

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

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

3.5.2 Classification criteria for substances

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

Figure 3.5.1 – Hazard categories for germ cell mutagens

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

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

<u>Criterion:</u>   Positive evidence from human epidemiological studies**.**

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

<u>Criteria:</u>

- Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
- Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
- Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

<u>**CATEGORY 2:**</u>**Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans**

<u>Criteria:</u>
Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:
- Somatic cell mutagenicity tests *in vivo*, in mammals; or
- Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

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

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

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

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

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

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

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

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

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

(a)   Mutagenicity tests:
>   Mammalian spermatogonial chromosome aberration test (OECD 483)
>   Spermatid micronucleus assay

(b)   Genotoxicity tests:
>   Sister chromatid exchange analysis in spermatogonia
>   Unscheduled DNA synthesis test (UDS) in testicular cells

3.5.2.8   Examples of genotoxicity tests in somatic cells are:

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

3.5.2.9   Examples of *in vitro* mutagenicity tests are:

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

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

3.5.3 Classification criteria for mixtures

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

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

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

3.5.3.2.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately 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.

3.5.3.2.2 *Dilution*

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

3.5.3.2.3 *Batching*

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

3.5.3.2.4 *Substantially similar mixtures*

Given the following:

(a)   Two mixtures: (i)   A + B
                                          (ii)   C + B;
(b)   The concentration of mutagen ingredient B is the same in both mixtures;
(c)   The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d)   Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the germ cell mutagenicity of B.

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

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

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

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

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 mutagen	**Category 2 mutagen**
Category 1 mutagen	≥ 0.1 %	-
Category 2 mutagen	-	≥ 1.0%

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

3.5.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.   The table below presents specific label elements for substances and mixtures classified as germ cell mutagens based on the criteria in this chapter.

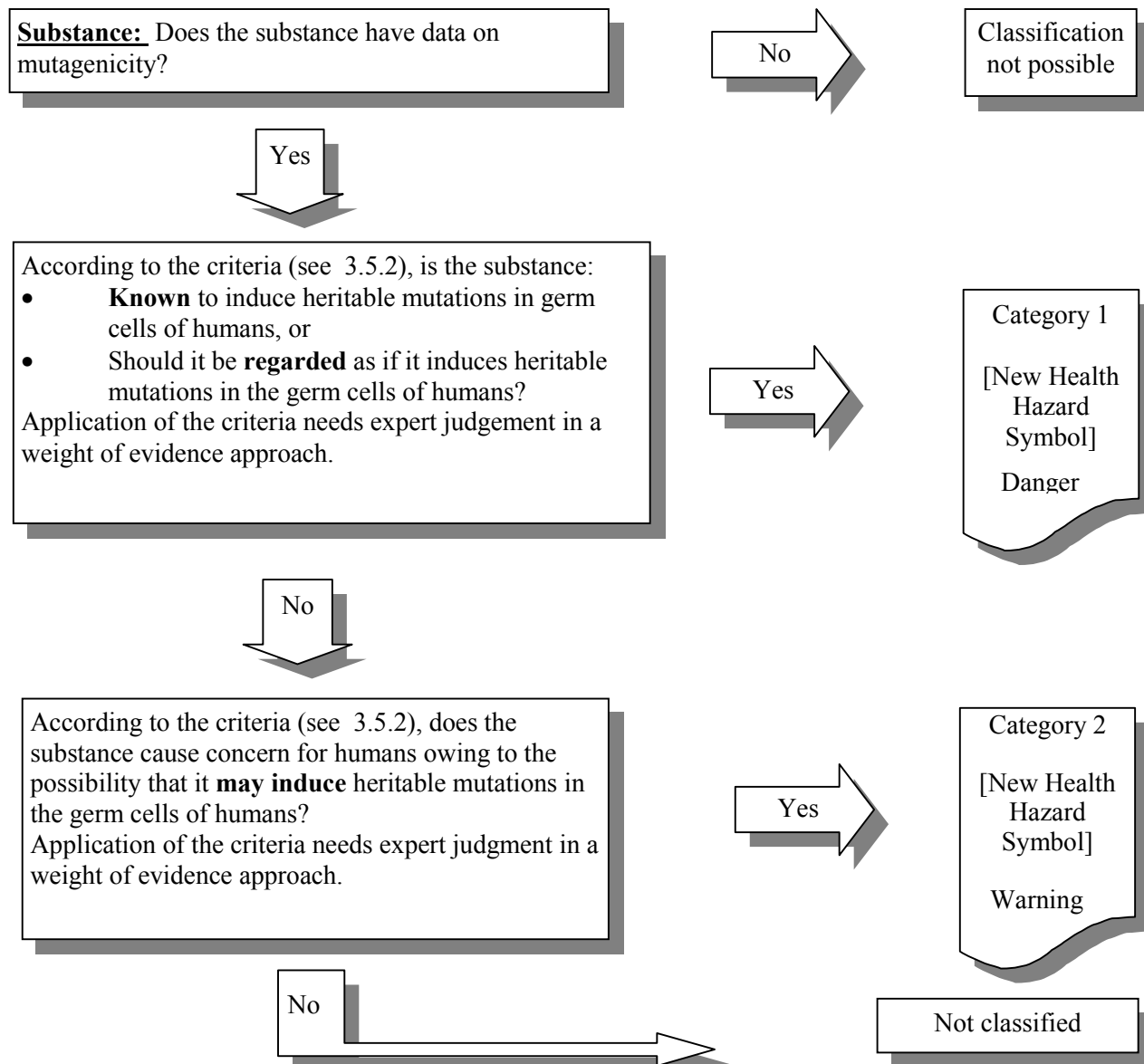**Table 3.5.2: Label elements of germ cell mutagenicity**

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

3.5.5   Decision logic and guidance

3.5.5.1   Decision Logic for Germ Cell Mutagenicity

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.
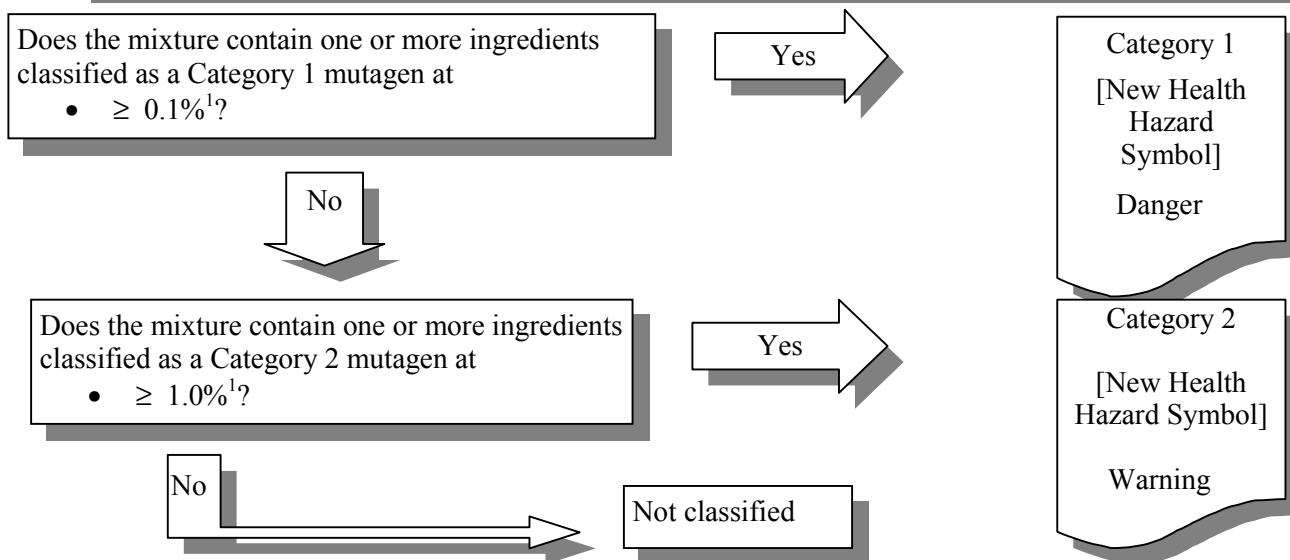
Decision logic 3.5.1 for substances

Substance: Does the substance have data on mutagenicity?	No →	Classification not possible

Yes ↓

According to the criteria (see 3.5.2), is the substance: • **Known** to induce heritable mutations in germ cells of humans, or • Should it be **regarded** as if it induces heritable mutations in the germ cells of humans? Application of the criteria needs expert judgement in a weight of evidence approach.	Yes →	Category 1 [New Health Hazard Symbol] Danger

No ↓

According to the criteria (see 3.5.2), does the substance cause concern for humans owing to the possibility that it **may induce** heritable mutations in the germ cells of humans? Application of the criteria needs expert judgment in a weight of evidence approach.	Yes →	Category 2 [New Health Hazard Symbol] Warning

No →

Not classified
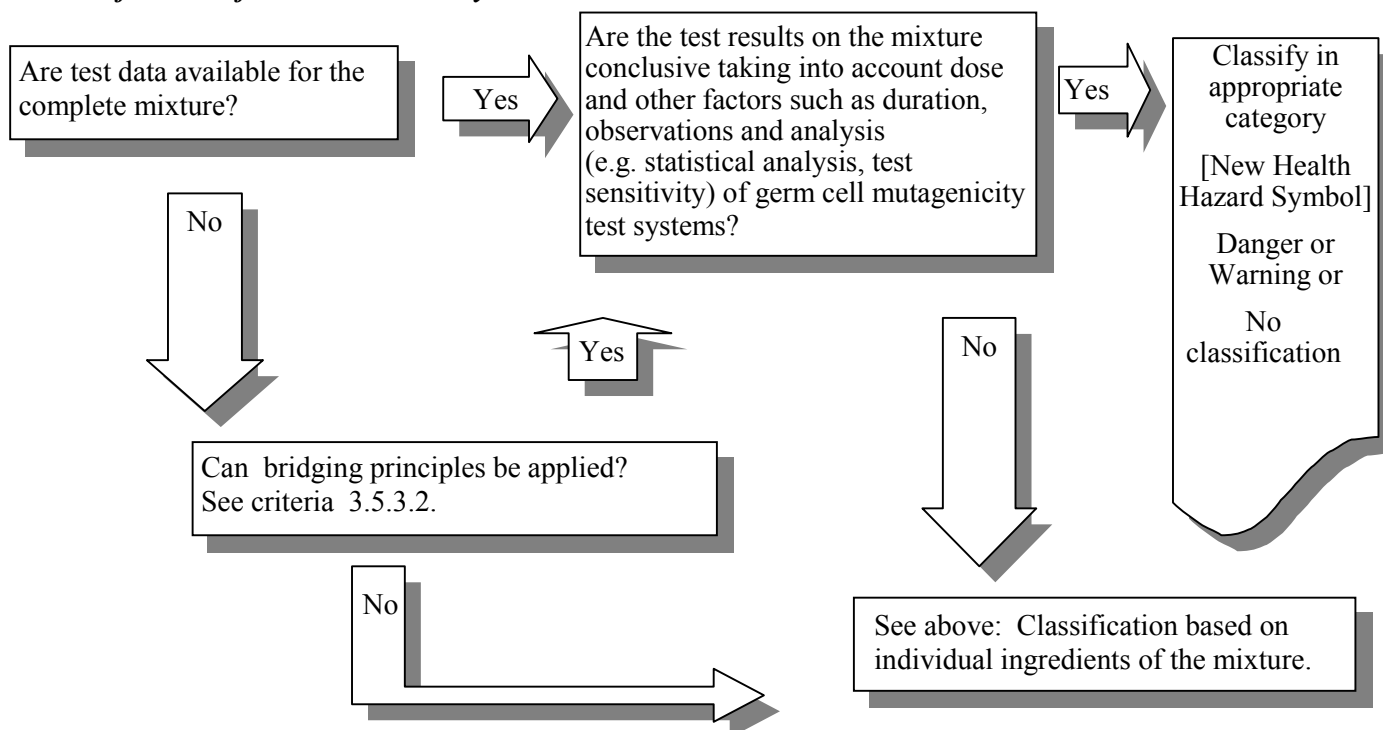
Continued on next page

Decision logic 3.5.2 for mixtures

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

Does the mixture contain one or more ingredients classified as a Category 1 mutagen at
- ≥ 0.1%[1]?

Yes →

Category 1

[New Health Hazard Symbol]

Danger

No ↓

Does the mixture contain one or more ingredients classified as a Category 2 mutagen at
- ≥ 1.0%[1]?

Yes →

Category 2

[New Health Hazard Symbol]

Warning

No →

Not classified

Modified classification on a case-by-case basis

Are test data available for the complete mixture?

Yes →

Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems?

Yes →

Classify in appropriate category

[New Health Hazard Symbol]

Danger or Warning or

No classification

No ↓

Yes ↑

No ↓

Can bridging principles be applied? See criteria 3.5.3.2.

No →

See above: Classification based on individual ingredients of the mixture.

1 For specific concentration limits, see " The use of Cut-Off Valves / Concentration limits in Chapter 1.3, para.1.3.3.2 and Table 3.5.1 of this Chapter

3.5.5.2 Guidance

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

CHAPTER 3.6

CARCINOGENICITY

3.6.1   Definitions

The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

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

3.6.2   Classification criteria for substances

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

Figure 3.6.1 : Hazard categories for carcinogens

CATEGORY 1:   Known or presumed human carcinogens

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

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

Category 1B: Presumed to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence.

Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

Classification: Category 1 (A and B) Carcinogen

CATEGORY 2: **Suspected human carcinogens**

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

Classification: Category 2 Carcinogen

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

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

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

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

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

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

- Tumour type and background incidence.
- Multisite responses.
- Progression of lesions to malignancy.
- Reduced tumour latency.

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

- Whether responses are in single or both sexes.
- Whether responses are in a single species or several species.
- Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity.
- Routes of exposure.
- Comparison of absorption, distribution, metabolism and excretion between test animals and humans.
- The possibility of a confounding effect of excessive toxicity at test doses.
- Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

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

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

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

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

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

3.6.2.7   The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation Carcinogenic potency as used here does not preclude risk assessment. The proceedings of a WHO/IPCS workshop on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, on Developing a Conceptual Framework for Cancer Risk Assessment (1999, Lyon, France)*, points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens.

3.6.3   Classification criteria for mixtures

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

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

3.6.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.6.3.2.1   Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately 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.

3.6.3.2.2   *Dilution*

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

3.6.3.2.3   *Batching*

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

3.6.3.2.4   *Substantially similar mixtures*

Given the following:

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

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

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

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

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

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

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

Table 3.6.1: Cut-off values/concentration limits of ingredients of a mixture classified as carcinogen that would trigger classification of the mixture[1].

Ingredient Classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 carcinogen	Category 2 carcinogen
Category 1 carcinogen	≥ 0.1 %	
Category 2 carcinogen	-	≥ 0.1% (note1)
		≥ 1.0% (note 2)

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

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

3.6.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 3.6.2 below presents specific label elements for substances and mixtures that are classified as carcinogenic based on the criteria set forth in this chapter.
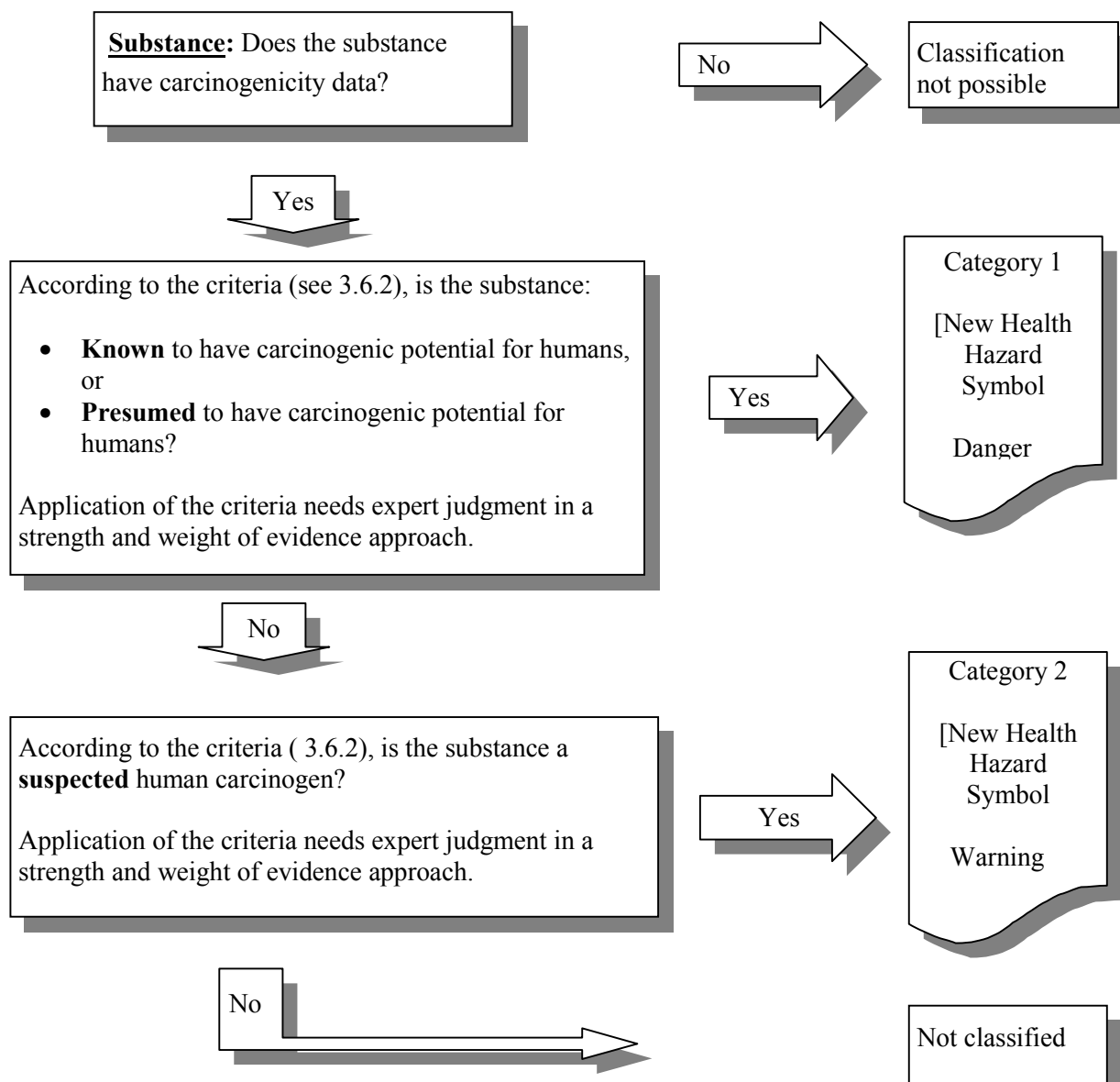
TABLE 3.6.2: Label elements for carcinogenicity

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

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

3.6.5   Decision logic and guidance for Carcinogenicity

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

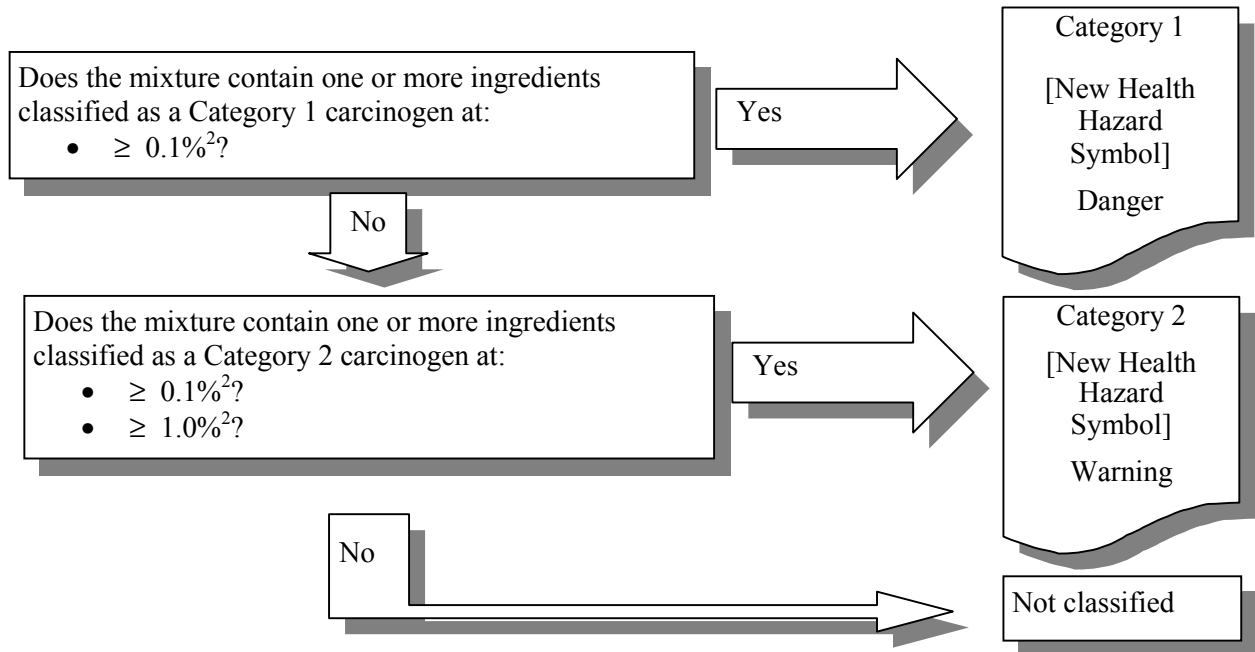**3.6.5.1   *Decision logic 3.6.1 for substances***

Substance: Does the substance have carcinogenicity data?

No → Classification not possible

Yes ↓

According to the criteria (see 3.6.2), is the substance:

- **Known** to have carcinogenic potential for humans, or
- **Presumed** to have carcinogenic potential for humans?

Application of the criteria needs expert judgment in a strength and weight of evidence approach.

Yes → Category 1

[New Health Hazard Symbol

Danger

No ↓

According to the criteria (3.6.2), is the substance a **suspected** human carcinogen?

Application of the criteria needs expert judgment in a strength and weight of evidence approach.

Yes → Category 2

[New Health Hazard Symbol

Warning

No →

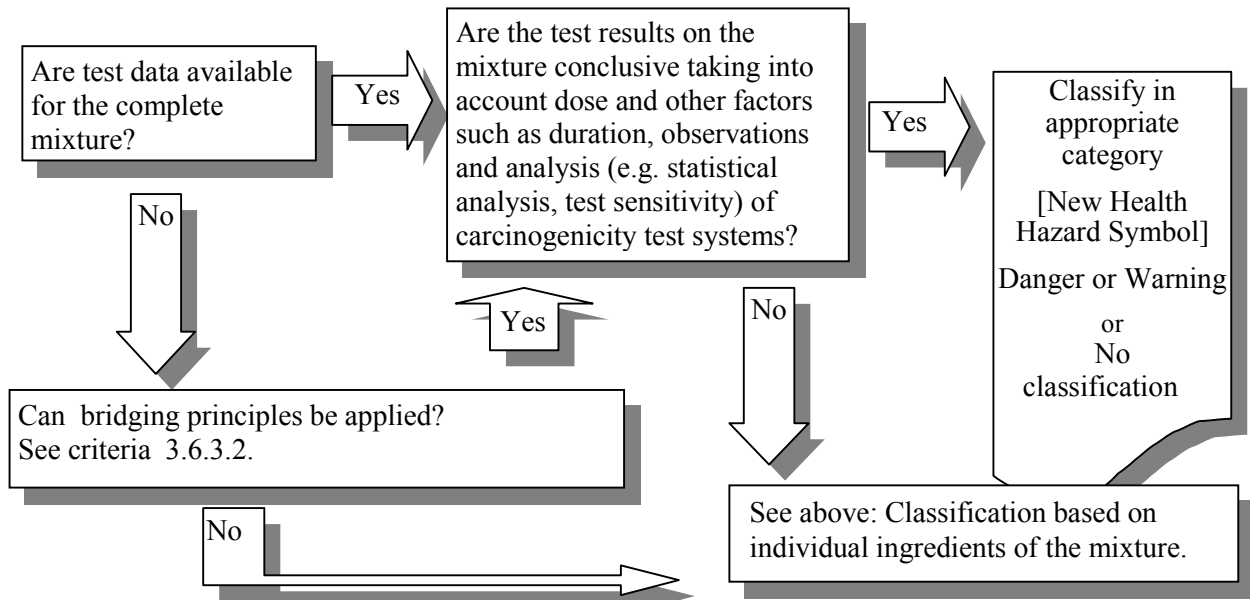Not classified

Continued on next page

3.6.5.2 *Decision logic 3.6.2 for mixtures*

Mixture:
Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may be **modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See Modified classification on a case-by-case basis below. For further details see criteria (paragraphs 3.6.2.7, 3.6.3.1-3.6.3.2).

Does the mixture contain one or more ingredients classified as a Category 1 carcinogen at:
- $\geq 0.1\%^{2}$?

Yes →

Category 1

[New Health Hazard Symbol]

Danger

No ↓

Does the mixture contain one or more ingredients classified as a Category 2 carcinogen at:
- $\geq 0.1\%^{2}$?
- $\geq 1.0\%^{2}$?

Yes →

Category 2

[New Health Hazard Symbol]

Warning

No →

Not classified

Modified classification on a case-by-case basis

Are test data available for the complete mixture?

Yes →

Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of carcinogenicity test systems?

Yes →

Classify in appropriate category

[New Health Hazard Symbol]

Danger or Warning

or
No classification

No ↓

Can bridging principles be applied? See criteria 3.6.3.2.

Yes ↑

No ↓

See above: Classification based on individual ingredients of the mixture.

No →

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[2] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2 and in Table 3.6.1 of this Chapter.*

3.6.5.2 *Background Guidance* [3]

Excerpts from monographs of the International Agency for Research on Cancer (IARC) Monographs Programme on the Evaluation of the Strength of Evidence of Carcinogenic Risks to Humans follow as in 3.6.5.2.1 and 3.6.5.2.2[4] .

3.6.5.2.1 *Carcinogenicity in humans*

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

(a) Sufficient evidence of carcinogenicity: the Working Group on Carcinogenicity of the OECD Task Force on Harmonization of Classification and Labelling considered that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;

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

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

3.6.5.2.2 Carcinogenicity in experimental animals

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

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

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

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

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[3]   *The information and guidance which follows is taken from the OECD Integrated Document on Harmonisation of Classification and Labelling. It is not part of the agreed text on the harmonised classification system developed by the OECD Task Force-HCL, but has been provided here as additional.*

[4]   *See para 3.6.2.4 of this Chapter.*

CHAPTER 3.7

REPRODUCTIVE TOXICITY

3.7.1   Definitions and general considerations

3.7.1.1   *Reproductive toxicity*

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed at the IPCS/OECD Workshop for the Harmonization of Risk Assessment for Reproductive and Developmental Toxicity, Carshalton, UK, 17-21 October, 1994[1]. For classification purposes, the known induction of genetically based inheritable effects in the offspring is addressed in *Germ Cell Mutagenicity* (Chapter 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ-cell mutagenicity.

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

- Adverse effects on reproductive ability or capacity;
- Adverse effects on development of the offspring.

3.7.1.2   *Adverse effects on reproductive ability or capacity*

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

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

3.7.1.3   *Adverse effects on development of the offspring*

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

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[1]   *OECD Monograph Series on Testing and Assessment No. 17, 1998.*

3.7.2   Classification criteria for substances

3.7.2.1   *Hazard categories*

For the purpose of classification for reproductive toxicity, chemical substances are allocated to one of two categories. Effects on reproductive ability or capacity, and on development, are considered as separate issues. In addition, effects on lactation are allocated to a separate hazard category.

Figure 3.7.1 (a): Hazard categories for reproductive toxicants

<u>CATEGORY 1</u>: **Known or presumed human reproductive or developmental toxicant**

This Category includes substances which are known to have produced an adverse effect on reproductive ability or capacity or on development in humans or for which there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. For regulatory purposes, a substance can be further distinguished on the basis of whether the evidence for classification is primarily from human data (<u>Category 1A</u>) or from animal data (<u>Category 1B</u>).

<u>CATEGORY 1A</u>: **Known to have produced an adverse effect on reproductive ability or capacity or on development in humans.**

The placing of the substance in this category is largely based on evidence from humans.

<u>CATEGORY 1B</u>: **Presumed to produce an adverse effect on reproductive ability or capacity or on development in humans.**

The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of specific reproductive toxicity in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

<u>CATEGORY 2</u>: **Suspected human reproductive or developmental toxicant**

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

Figure 3.7.1 (b): Hazard category for lactation effects

<u>**EFFECTS ON OR VIA LACTATION**</u>

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

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

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

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

3.7.2.2 *Basis of classification*

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

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

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

3.7.2.3 *Weight of evidence*

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

are assembled together into a weight of evidence determination. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also paragraph 3.7.2.2.3).

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

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

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

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

3.7.2.4   *Maternal toxicity*

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

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

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

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

> Maternal mortality: an increased incidence of mortality among the treated dams over the controls should be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material.   Maternal mortality greater than 10% is considered excessive and the data for that dose level should not normally be considered for further evaluation.
>
> Mating index (no. animals with seminal plugs or sperm/no. mated x 100)[2]
>
> Fertility index (no. animals with implants/no. of matings x 100) **[2]**
>
> Gestation length (if allowed to deliver)
>
> Body weight and body weight change: consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight should be included in the evaluation of maternal toxicity whenever such data are available.   The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine.   In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

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

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

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

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

3.7.2.5   Animal and experimental data

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

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

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

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

3.7.2.5.5   It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property

will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

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

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

3.7.2.5.8   In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on Maternal Toxicity for further guidance in this area.

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

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

3.7.3   Classification criteria for mixtures

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

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

3.7.3.2   *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.7.3.2.1   Where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately 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.

3.7.3.2.2   *Dilution*

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

3.7.3.2.3   *Batching*

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

3.7.3.2.4   *Substantially similar mixtures*

Given the following:

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

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

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

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

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

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

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

Table 3.7.1: Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants that would trigger classification of the mixture.[3]

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 reproductive toxicant	Category 2 reproductive toxicant
Category 1 reproductive toxicant	≥ 0.1 % (note 1)	
	≥ 0.3 % (note 2)	
Category 2 reproductive toxicant		≥ 0.1 % (note 3)
		≥ 3.0 % (note 4)

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

Note 2: If a Category 1 reproductive toxicant is present in the mixture as an ingredient at a concentration of ≥ 0.3%, both an SDS and a label would generally be expected.

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

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

3.7.3.4 *Criteria for the classification of mixtures containing substances which have effects on lactation[4].*

Harmonized criteria for the classification of mixtures containing substances which have effects on lactation have to date not been developed. The data base for this hazard category is extremely limited, and experience will have to be gained in using the category in the harmonized system before the issue of classification of mixtures containing components which can contaminate breast milk can be addressed. This issue should be considered in the future.

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

[4]   *This text has been provided here to draw attention to this issue, and is not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL.*

3.7.4   **Hazard communication**

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.7.2: Label elements for reproductive toxicity

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

3.7.5   **Decision logic for classification of reproductive toxicity**

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

3.7.5.1 *Decision logic 3.7.1 for substances*

Substance: Does the substance have data on reproductive toxicity?	No →	Classification not possible

Yes ↓

According to the criteria (3.7.2), is the substance: • **Known** to have produced an adverse effect on reproductive ability or capacity, or on development, in humans, **or** • **Presumed** to produce an adverse effect on reproductive ability or capacity, or on development, in humans ? Application of the criteria needs expert judgment in a weight of evidence approach.	Yes →	Category 1 [New Health Hazard Symbol] Danger

No ↓

According to the criteria (see 3.7.2), is the substance **suspected** to produce an adverse effect on reproductive ability or capacity, or on development, in humans? Application of the criteria needs expert judgment in a weight of evidence approach.	Yes →	Category 2 [New Health Hazard Symbol] Warning

No →

Not classified as reproductive toxicant

Continued on next page

3.7.5.2 Decision logic 3.7.2 for mixtures

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

Classification based on individual ingredients of the mixture

Does the mixture contain one or more ingredients classified as a Category 1 reproductive toxicant at:
- $\geq 0.1\%^{5}$?
- $\geq 0.3\%^{5}$?

Yes → Category 1 [New Health Hazard Symbol] Danger

No

Does the mixture contain one or more ingredients classified as a Category 2 reproductive toxicant at:
- $\geq 0.1\%^{5}$?
- $\geq 3.0\%^{5}$?

Yes → Category 2 [New Health Hazard Symbol] Warning

No

Not classified

Modified classification on a case-by-case basis

Are test data available for the complete mixture?

Yes → Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of reproduction test systems?

No

Yes → Classify in appropriate category [New Health Hazard Symbol] Danger or Warning or No classification

No

Can bridging principles be applied? See criteria in 3.7.3.2.1-3.7.3.2.4.

Yes

No

See above: Classification based on individual ingredients of the mixture.

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[5]   *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2, and in Table 3.7. of this Chapter.*

3.7.6   Decision logic for classification of effects on or via lactation:

Decision logic 3.7.3

Does the substance according to the criteria (see 3.7.2) cause concern for the health of breastfed children ?	Yes →	Additional category for effects on or via lactation
No →		Not classified in additional category

CHAPTER 3.8

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY
- SINGLE EXPOSURE

3.8.1   Definitions and general considerations

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

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

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

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

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

3.8.1.6   Specific target organ/systemic toxicity following a repeated exposure is classified in the GHS as described in *Target Organ Systemic Toxicity – Repeated Exposure* (Chapter 3.9) and is therefore excluded from the present chapter. Other specific toxic effects, such as acute lethality/toxicity, serious damage to eyes/irritation and skin corrosivity/irritation, skin and respiratory sensitization, carcinogenicity, mutagenicity and reproductive toxicity are assessed separately in the GHS and consequently are not included here.

3.8.2   Classification criteria for substances

3.8.2.1   Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.9). Then substances are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

Figure 3.8.1: Categories for specific target organ systemic toxicity/single exposure

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

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

- reliable and good quality evidence from human cases or epidemiological studies; or,
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.9) to be used as part of weight-of-evidence evaluation.

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

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see.8.2.9) in order to help in classification.
In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.6).

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

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

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

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

3.8.2.5   The information required to evaluate specific target organ/systemic toxicity comes either from single exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and

microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

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

3.8.2.7 *Effects considered to support classification*

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

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

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

- Morbidity resulting from single exposure;

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

- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

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

- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;

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

3.8.2.8 *Effects considered not to support classification*

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

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

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

- Changes in organ weights with no evidence of organ dysfunction;

- Adaptive responses that are not considered toxicologically relevant;

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

- Where there are only local effects, at the site of administration for the routes tested, and especially when adequate testing by other principal routes show lack of specific target organ/systemic toxicity.

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

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

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

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

Table 3.8.1: Guidance value ranges for single-dose exposures

		Guidance value ranges for :	
Route of exposure	Units	Category 1	Category 2
Oral (rat)	mg/kg body weight	$C \le 300$	$2000 \ge C > 300$
Dermal (rat or rabbit)	mg/kg body weight	$C \le 1000$	$2000 \ge C > 1000$
Inhalation (rat) gas	ppm	$C \le 2500$	$5000 \ge C > 2500$
Inhalation (rat) vapour	mg/1	$C \le 10$	$20 \quad > C > 10$
Inhalation (rat) dust/mist/fume	mg/l/4h	$C \le 1.0$	$5.0 \quad > C > 1.0$

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

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

3.8.2.10   *Other considerations*

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

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

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

3.8.2.10.4   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.

3.8.3 Classification criteria for mixtures

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

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

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

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

3.8.3.3.2 *Dilution*

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

3.8.3.3.3 *Batching*

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

3.8.3.3.4 *Concentration of highly toxic mixtures*

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

3.8.3.3.5 *Interpolation within one toxicity category*

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

3.8.3.3.6 *Substantially similar mixtures*

Given the following:

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

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

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

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

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

3.8.3.3.7   *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-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.

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

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

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

Ingredient Classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1 **Target Organ Systemic Toxicant**	$\geq$ 1.0 % (note 1) $\geq$ 10 % (note 2)	1.0$\leq$ ingredient < 10% (note 3)
Category 2 **Target Organ Systemic Toxicant**		$\geq$ 1.0 % (note 4) $\geq$ 10 % (note 5)

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

Note 2:   *If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of $\geq$ 10%, both an SDS and a label would generally be expected.*

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

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

Note 5:   *If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of $\geq$ 10%, both an SDS and a label would generally be expected.*

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

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

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

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

3.8.4   Hazard communication

3.8.4.1   General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

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

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

3.8.5   Decision Logic for Target Organ Systemic Toxicity from single exposure

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

Decision logic 3.8.1

Substance: Does the substance have data and/or information to evaluate target organ systemic toxicity following single exposure?	No →	Classification not possible
Mixture: Does the mixture as a whole or its ingredients have data/information to evaluate target organ systemic toxicity following single exposure?	No →	Classification not possible

Yes ↓ (Substance)

Yes ↓ (Mixture)

Does the mixture as a whole have data/information to evaluate target organ systemic toxicity following single exposure?	No →	See Decision Logic 3.8.2

Yes ↓

Following single exposure, • Can the substance or mixture produce significant toxicity in humans, or • Can it be presumed to have the potential to produce significant toxicity in humans on the basis of evidence from studies in experimental animals? See 3.8.2 for criteria and guidance values. Application of the criteria needs expert judgment in a weight of evidence approach.	Yes →	Category 1 [New Health Hazard Symbol] Danger

No ↓

Following single exposure, • Can the substance or mixture, be presumed to have the potential to be harmful to human health on the basis of evidence from studies in experimental animals? See 3.8.2 for criteria and guidance values. Application of the criteria needs expert judgment in a weight of evidence approach.	Yes →	Category 2 [New Health Hazard Symbol] Warning

No →

Not classified

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Decision logic 3.8.2

Can bridging principles, as in 3.8.3.3 , be applied?	**Yes** →	Classify in appropriate category

↓ **No**

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of[2] : • ≥ 1.0% ? • ≥ 10% ? See Table 3.8.2 for explanation of cut-off values/concentration limits[2].	**Yes** →	Category 1 [New Health Hazard Symbol] Danger

↓ **No**

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of [4]: • ≥ 1.0 and < 10%? See Table 3.8.2 for explanation of cut-off values/concentration limits[2].	**Yes** →	Category 2 [New Health Hazard Symbol] Warning

↓ **No**

Does the mixture contain one or more ingredients classified as a Category 2 target organ systemic toxicant at a concentration of [2]: • ≥ 1.0%? • ≥ 10%? See Table 3.8.2 for explanation of cut-off values/concentration limits[3].	**Yes** →	Category 2 [New Health Hazard Symbol] Warning

No → Not classified

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[2]   *See 3.8.2 of this Chapter and "The Use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2.*

[3]   *See 3.8.3.4 and Table3.8.2 for explanation and guidance.*

CHAPTER 3.9

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY
- REPEATED EXPOSURE

3.9.1 Definitions and general considerations

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

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

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

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

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

3.9.1.6 Non-lethal toxic effects observed after a single-event exposure are classified in the GHS as described in *Specific* Target *Organ Systemic Toxicity – Single Exposure* (Chapter 3.8) and are therefore excluded from the present chapter. Other specific toxic effects, such as acute lethality/toxicity, serious damage to eyes/eye irritation and skin corrosivity/irritation, skin and respiratory sensitization, carcinogenicity, mutagenicity and reproductive toxicity are assessed separately in the GHS and consequently are not included here.

3.9.2 Classification criteria for substances

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

Figure 3.9.1: Categories for specific target organ systemic toxicity/repeated exposure

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

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

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

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

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

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

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

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

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

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

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

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

3.9.2.7   *Effects considered to support classification*

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

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

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

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

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

- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

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

- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

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

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

3.9.2.8 *Effects considered not to support classification*

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

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

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

- Changes in organ weights with no evidence of organ dysfunction;

- Adaptive responses that are not considered toxicologically relevant;

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

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

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

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

effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

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

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

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

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

Table 3.9.1: Guidance values to assist in Category 1 classification

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

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

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

Table 3.9.2: Guidance values to assist in Category 2 classification

Route of Exposure	Units	Guidance Value Ranges: (dose/concentration)
Oral (rat)	mg/kg bw/d	10 - 100
Dermal (rat or rabbit)	mg/kg bw/d	20 - 200
Inhalation (rat) gas	ppm/6h/d	50 - 250
Inhalation (rat)vapour	mg/litre/6h/d	0.2 - 1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02 - 0.2

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

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

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

3.9.2.10   *Other considerations*

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

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

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

3.9.2.10.4   It is recognised that saturated vapour concentration may be used as an additional element by some regulatory systems to provide for specific health and safety protection.

3.9.3   Classification criteria for mixtures

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

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

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

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

3.9.3.3.2   *Dilution*

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

3.9.3.3.3   *Batching*

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

3.9.3.3.4   *Concentration of highly toxic mixtures*

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

3.9.3.3.5   *Interpolation within one toxicity category*

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

3.9.3.3.6   *Substantially similar mixtures*

Given the following:

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

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

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

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

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

3.9.3.3.7   *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-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.

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

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

Table 3.9.3: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture.[1]

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

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

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

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

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

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

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

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

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

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

3.9.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.9.4: Label elements for target organ systemic toxicity after repeated exposure

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

3.9.5   Decision logic for target organ systemic toxicity following repeated exposure

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

Decision logic 3.9.1

Substance: Does the substance have data and/or information to evaluate target organ systemic toxicity following repeated exposure?

No → Classification not possible

Yes ↓

Mixture: Does the mixture as a whole or its ingredients have data/information to evaluate target organ systemic toxicity following repeated exposure?

No → Classification not possible

Yes ↓

Does the **mixture** as a whole have data/information to evaluate target organ systemic toxicity following repeated exposure?

No → See Decision logic 3.9.2

Yes ↓

Following repeated exposure,
- Can the substance or mixture produce significant toxicity in humans, or
- Can it be presumed to have the potential to produce significant toxicity in humans on the basis of evidence from studies in experimental animals?

See 3.9.2 for criteria and guidance values[2].Application of the criteria needs expert judgment in a weight of evidence approach.

Yes → Category 1

[New Health Hazard Symbol]

Danger

No ↓

Following repeated exposure,
- Can the substance or mixture be presumed, to have the potential on the basis of evidence from studies in experimental animals, to be harmful to human health?

See 3.9.2 for criteria and guidance values[2]. Application of the criteria needs expert judgment in a weight of evidence approach.

Yes → Category 2

[New Health Hazard Symbol]

Warning

No →

Not classified

Continued on next page

Decision Logic 3.9.2

Can bridging principles, 3.9.3.3, be applied?	Yes →	Classify in appropriate category

No ↓

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of [2]: • ≥ 1.0%? • ≥ 10%? See Table 3.9.3 of this Chapter for explanation of cut-off values/concentration limits[3].	Yes →	Category 1 [New Health Hazard Symbol] Danger

No ↓

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of [2]: • ≥ 1.0 and < 10%? See Table 3.9.3 of this Chapter for explanation of cut-off values/concentration limits[3].	Yes →	Category 2 [New Health Hazard Symbol] Warning

No ↓

Does the mixture contain one or more ingredients classified as a Category 2 target organ systemic toxicant at a concentration of [2]: • ≥ 1.0%? • ≥ 10%? See Table 3.9.3 of this Chapter for explanation of cut-off values/concentration limits[3].	Yes →	Category 2 [New Health Hazard Symbol] Warning

No → Not classified

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[2] *In this chapter, see 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2, see "The Use of Cut-off Values/Concentration Limits".*

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

CHAPTER 3.10

HAZARDOUS TO THE AQUATIC ENVIRONMENT

3.10.1 Definitions and general considerations

3.10.1.1. Definitions

Acute aquatic toxicity means the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance.

Availability of a substance means the extent to which this substance becomes a soluble or disaggregate species. For metal availability, the extent to which the metal ion portion of a metal (M°) compound can disaggregate from the rest of the compound (molecule).

Bioavailability (or biological availability) means the extent to which a substance is taken up by an organism, and distributed to an area within the organism. It is dependent upon physico-chemical properties of the substance, anatomy and physiology of the organism, pharmacokinetics, and route of exposure. Availability is not a prerequisite for bio availability.

Bioaccumulation means net result of uptake, transformation and elimination of a substance in an organism due to all routes of exposure (i.e. air, water, sediment/soil and food)

Bioconcentration means net result of uptake, transformation and elimination of a substance in an organism due to waterborne exposure.

Chronic aquatic toxicity means potential or actual properties of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life-cycle of the organism.

Complex mixtures or multi-component substances or complex substances means mixtures comprising a complex mix of individual substances with different solubilities and physico-chemical properties. In most cases, they can be characterised as a homologous series of substances with a certain range of carbon chain length/number of degree of substitution.

Degradation means the decomposition of organic molecules to smaller molecules and eventually to carbon dioxide, water and salts.

3.10.1.2 *Basic elements*

3.10.1.2.1 The basic elements for use within the harmonized system are:

- acute aquatic toxicity;
- potential for or actual bioaccumulation;
- degradation (biotic or abiotic) for organic chemicals; and
- chronic aquatic toxicity.

3.10.1.2.2   While data from internationally harmonized test methods are preferred, in practice, data from national methods may also be used where they are considered as equivalent. In general, it has been agreed that freshwater and marine species toxicity data can be considered as equivalent data and are preferably to be derived using OECD Test Guidelines or equivalent according to the principles of Good Laboratory Practices (GLP). Where such data are not available classification should be based on the best available data.

3.10.1.3   *Acute aquatic toxicity*

Acute aquatic toxicity would normally be determined using a fish 96 hour LC_{50} (OECD Test Guideline 203 or equivalent), a crustacea species 48 hour EC_{50} (OECD Test Guideline 202 or equivalent) and/or an algal species 72 or 96 hour EC_{50} (OECD Test Guideline 201 or equivalent). These species are considered as surrogate for all aquatic organisms and data on other species such as Lemna may also be considered if the test methodology is suitable.

3.10.1.4   *Bioaccumulation potential*

The potential for bioaccumulation would normally be determined by using the octanol/water partition coefficient, usually reported as a log K_{ow} determined by OECD Test Guideline 107 or 117. While this represents a potential to bioaccumulate, an experimentally determined Bioconcentration Factor (BCF) provides a better measure and should be used in preference when available. A BCF should be determined according to OECD Test Guideline 305.

3.10.1.5   *Rapid degradability*

3.10.1.5.1   Environmental degradation may be biotic or abiotic (e.g. hydrolysis) and the criteria used reflect this fact (See 3.10.2.10.3).   Ready biodegradation can most easily be defined using the OECD biodegradability tests OECD Test Guideline 301 (A - F). A pass level in these tests can be considered as indicative of rapid degradation in most environments. These are freshwater tests and thus the use of the results from OECD Test Guideline 306 which is more suitable for marine environments has also been included. Where such data are not available, a BOD(5 days)/COD ratio > 0.5 is considered as indicative of rapid degradation.

3.10.1.5.2   Abiotic degradation such as hydrolysis, primary degradation, both abiotic and biotic, degradation in non-aquatic media and proven rapid degradation in the environment may all be considered in defining rapid degradability. Special guidance on data interpretation is provided in the Guidance Document (Annex 8).

3.10.1.6   *Chronic aquatic toxicity*

Chronic toxicity data are less available than acute data and the range of testing procedures less standardised. Data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), or 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) can be accepted (See also Chapter 3.3.2 of Annex 8). Other validated and internationally accepted tests could also be used. The NOECs or other equivalent L(E)Cx should be used.

3.10.1.7   *Other considerations*

3.10.1.7.1   The harmonized system for classifying chemical substances for the hazards they present to the aquatic environment is based on a consideration of systems existing listed in3.10.1.7.4. The aquatic environment may be considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. To that extent, the proposal does not address aquatic pollutants for which there may be a need to consider effects beyond the aquatic environment such as the impacts on human health etc. The basis, therefore, of the identification of hazard is the aquatic toxicity of the substance, although this may be modified by further information on the degradation and bioaccumulation behaviour.

3.10.1.7.2   While the scheme is intended to apply to all substances and mixtures, it is recognised that for some substances, e.g. metals, poorly soluble substances, etc., special guidance will be necessary. For instance, application of the criteria to metals and metal compounds is contingent on completion of an appropriate validation exercise, as provided in OECD series on Testing and Assessment n° 29 reproduced in Annex 9 to this document.

3.10.1.7.3   Two Guidance Documents (see Annexes 8 and 9) have been prepared to cover issues such as data interpretation and the application of the criteria defined below to such groups of substances. Considering the complexity of this endpoint and the breadth of the application of the system, the Guidance Documents are considered an important element in the operation of the harmonized scheme .(As noted above, Annex 9 is subject to validation).

3.10.1.7.4   Consideration has been given to existing classification systems as currently in use, including the EU Supply and Use Scheme, the revised GESAMP hazard evaluation procedure, IMO Scheme for Marine Pollutant, the European Road and Rail Transport Scheme (RID/ADR), the Canadian and US Pesticide systems and the US Land Transport Scheme. The harmonized scheme is considered suitable for use for packaged goods in both supply and use and multimodal transport schemes, and elements of it may be used for bulk land transport and bulk marine transport under MARPOL 73/78 Annex II insofar as this uses aquatic toxicity.

3.10.2   **Classification criteria for substances**

3.10.2.1   The harmonized classification system for substances consists of three acute classification categories and four chronic classification categories (see Figure 3.10.1). The acute and the chronic classification categories are applied independently. The criteria for classification of a substance in acute categories I to III are defined on the basis of the acute toxicity data only (EC_{50} or LC_{50}). The criteria for classification of a substance into chronic categories combine two types of information, i.e. acute toxicity data and environmental fate data (degradability and bioaccumulation data). For assignment of mixtures to chronic categories, degradation and bioaccumulation properties are derived from tests on components.

3.10.2.2   Substances classified under the following criteria will be categorised as 'hazardous to the aquatic environment'. These criteria describe in detail the classification categories. They are diagrammatically summarised in Table 3.10.1.

Figure 3.10.1: categories for substances hazardous to the aquatic environment

<u>Acute toxicity</u>

<u>**Category: Acute I**</u>
      96 hr LC50 (for fish) $\leq$1 mg/L and/or
      48 hr EC50 (for crustacea) $\leq$1 mg/L and/or
      72 or 96hr ErC_{50} (for algae or other aquatic plants) $\leq$1 mg/L.
Category: Acute I may be subdivided for some regulatory systems to include a lower band at $L(E)C_{50} \leq 0$ 1 mg/L.

<u>**Category: Acute II**</u>
      96 hr LC_{50} (for fish)   >1 - $\leq$10 mg/L and/or
      48 hr EC_{50} (for crustacea)   >1 - $\leq$10 mg/L and/or
      72 or 96hr ErC_{50} (for algae or other aquatic plants) >1 - $\leq$10 mg/L.

<u>**Category: Acute III**</u>
      96 hr LC_{50} (for fish)   >10 - $\leq$100 mg/L and/or
      48 hr EC_{50} (for crustacea) >10 - $\leq$100 mg/L and/or
      72 or 96hr ErC_{50} (for algae or other aquatic plants) >10 - $\leq$100 mg/L.
Some regulatory systems may extend this range beyond an $L(E)C_{50}$ of 100 mg/L through the introduction of another category.

<u>Chronic toxicity</u>

<u>**Category: Chronic I**</u>
      96 hr LC_{50} (for fish) $\leq$1 mg/L and/or
      48 hr EC50 (for crustacea) $\leq$1 mg/L and/or
      72 or 96hr ErC50 (for algae or other aquatic plants) $\leq$1 mg/L
and the substance is not rapidly degradable and/or the log $K_{ow} \geq 4$ (unless the experimentally determined BCF <500).

<u>**Category: Chronic II**</u>
      96 hr LC_{50} (for fish)   >1 to $\leq$10 mg/L and/or
      48 hr EC_{50} (for crustacea)>1 to $\leq$10 mg/L and/or
      72 or 96hr ErC_{50} (for algae or other aquatic plants) >1 to $\leq$10 mg/L
and the substance is not rapidly degradable and/or the log $K_{ow} \geq 4$ (unless the experimentally determined BCF <500), unless the chronic toxicity NOECs are > 1 mg/L.

Figure 3.10.1: categories for substances hazardous to the aquatic environment (*cont'd*)

<u>**Category: Chronic III**</u>
      96 hr LC_{50} (for fish)   >10 to $\leq$100 mg/L and/or
      48 hr EC_{50} (for crustacea)   >10 to $\leq$100 mg/L and/or
      72 or 96hr ErC_{50} (for algae or other aquatic plants) >10 to $\leq$100 mg/L
and the substance is not rapidly degradable and/or the log $K_{ow} \geq 4$ (unless the experimentally determined BCF <500) unless the chronic toxicity NOECs are >1 mg/L.

<u>**Category: Chronic IV**</u> Poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have a log $K_{ow} \geq 4$, indicating a potential to bioaccumulate, will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence would include an experimentally determined BCF

<500, or a chronic toxicity NOECs > 1 mg/L, or evidence of rapid degradation in the environment.

Table 3.10.1: Classification scheme for substances hazardous to the aquatic environment

Classification criterion elements				Classification categories	
Toxicity		Degradability (*Note 3*)	Bioaccumulation (*Note 4*)		
Acute (*Note 1a and 1b*)	Chronic (*Note 2a and 2b*)			Acute	Chronic
Box 1: value ≤ 1.00 mg/L		**Box 5:**	**Box 6:**	**Category: Acute I Box 1**	**Category: Chronic I Boxes 1+5+6 Boxes 1+5 Boxes 1+6**
Box 2: 1.00 < value ≤ 10.0 mg/L		lack of rapid degradability	BCF ≥ 500 or, if absent log K_{ow} ≥ 4	**Category: Acute II Box 2**	**Category: Chronic II Boxes 2+5+6 Boxes 2+5 Boxes 2+6 Unless Box 7**
Box 3: 10.0 < value ≤ 100 mg/L				**Category: Acute III Box 3**	**Category: Chronic III Boxes 3+5+6 Boxes 3+5 Boxes 3+6 Unless Box 7**
Box 4: No acute toxicity (*Note 5*)	**Box 7:** value > 1.00 mg/L				**Category: Chronic IV Boxes 4+5+6 Unless Box 7**

Notes to Table 3.10.1:

Note 1a: Acute toxicity band based on L(E)C-50 values in mg/L for fish, crustacea and/or algae or other aquatic plants (or QSAR estimation if no experimental data).

Note 1b: Where the algal toxicity ErC-50 [= EC-50 (growth rate)] falls more than 100 times below the next most sensitive species and results in a classification based solely on this effect, consideration should be given to whether this toxicity is representative of the toxicity to aquatic plants. Where it can be shown that this is not the case, professional judgement should be used in deciding if classification should be applied. Classification should be based on the ErC-50. In circumstances where the basis of the EC-50 is not specified and no ErC-50 is recorded, classification should be based on the lowest EC-50 available.

Note 2a: Chronic toxicity band based on NOEC values in mg/L for fish or crustacea or other recognised measures for long-term toxicity.

Note 2b: It is the intention that the system be further developed to include chronic toxicity data.

Note 3. Lack of rapid degradability is based on either a lack of Ready Biodegradability or other evidence of lack of rapid degradation.

Note 4: Potential to bioaccumulate, based on an experimentally derived BCF ≥ 500 or, if absent, a log K_{ow} ≥ 4 provided log K_{ow} is an appropriate descriptor for the bioaccumulation potential of the substance.

Measured log K_{ow} values take precedence over estimated values and measured BCF values take precedence over log K_{ow} values.

Note 5: *"No acute toxicity" is taken to mean that the L(E)C-50 is above the water solubility. Also for poorly soluble substances, (w.s. < 1.00 mg/L), where there is evidence that the acute test would not have provided a true measure of the intrinsic toxicity.*

3.10.2.3   The system for classification recognises that the core intrinsic hazard to aquatic organisms is represented by both the acute and chronic toxicity of a substance, the relative importance of which is determined by the specific regulatory system in operation. Distinction can be made between the acute hazard and the chronic hazard and therefore separate hazard categories are defined for both properties representing a gradation in the level of hazard identified. The lowest of the available toxicity values will normally be used to define the appropriate hazard category(ies). There may be circumstances, however, when a weight of evidence approach may be used. Acute toxicity data are the most readily available and the tests used are the most standardised. For that reason, these data form the core of the classification system.

3.10.2.4   Acute toxicity represents a key property in defining the hazard where transport of large quantities of a substance may give rise to short-term dangers arising from accidents or major spillages. Hazards categories up to $L(E)C_{50}$ values of 100 mg/L are thus defined although categories up to 1000 mg/L may be used in certain regulatory frameworks. The Acute Category I may be further sub-divided to include an additional category for acute toxicity $L(E)C_{50}$ ≤0.1 mg/L in certain regulatory systems such as that defined by MARPOL 73/78 Annex II. It is anticipated that their use would be restricted to regulatory systems concerning bulk transport.

3.10.2.5   For packaged substances it is considered that the principal hazard is defined by chronic toxicity, although acute toxicity at $L(E)C_{50}$ levels ≤1 mg/L are also considered hazardous. Levels of substances up to 1 mg/L are considered as possible in the aquatic environment following normal use and disposal. At toxicity levels above this, it is considered that the short-term toxicity itself does not describe the principal hazard, which arises from low concentrations causing effects over a longer time scale. Thus, a number of hazard categories are defined which are based on levels of chronic aquatic toxicity. Chronic toxicity data are not available for many substances, however, and it is necessary to use the available data on acute toxicity to estimate this property. The intrinsic properties of a lack of rapid degradability and/or a potential to bioconcentrate in combination with acute toxicity may be used to assign a substance to a chronic hazard category. Where chronic toxicity is available showing NOECs >1 mg/L, this would indicate that no classification in a chronic hazard category would be necessary. Equally, for substances with an $L(E)C_{50}$ >100 mg/L, the toxicity is considered as insufficient to warrant classification in most regulatory systems.

3.10.2.6   While the current system will continue to rely on the use of acute toxicity data in combination with a lack of rapid degradation and/or a potential to bioaccumulate as the basis for classification for assigning a chronic hazard category, it is recognised that actual chronic toxicity data would form a better basis for classification where these data are available. It is thus the intention that the scheme should be further developed to accommodate such data. It is anticipated that in such a further development, the available chronic toxicity data would be used to classify in the chronic hazard in preference to that derived from their acute toxicity in combination with a lack of rapid degradation and/or a potential to bioaccumulate.

3.10.2.7   Recognition is given to the classification goals of MARPOL 73/78 Annex II, which covers the transport of bulk quantities in ships tanks, which are aimed at regulating operational discharges from ships

and assigning of suitable ship types. They go beyond that of protecting aquatic ecosystems, although that clearly is included. Additional hazard categories may thus be used which take account of factors such as physico-chemical properties and mammalian toxicity.

3.10.2.8   *Aquatic toxicity*

3.10.2.8.1   The organisms fish, crustacea and algae are tested as surrogate species covering a range of trophic levels and taxa, and the test methods are highly standardised. Data on other organisms may also be considered, however, provided they represent equivalent species and test endpoints. The algal growth inhibition test is a chronic test but the EC_{50} is treated as an acute value for classification purposes. This EC_{50} should normally be based on growth rate inhibition. If only the EC_{50} based on reduction in biomass is available, or it is not indicated which EC_{50} is reported, this value may be used in the same way.

3.10.2.8.2   Aquatic toxicity testing, by its nature, involves the dissolution of the substance under test in the water media used and the maintenance of a stable bioavailable exposure concentration over the course of the test. Some substances are difficult to test under standard procedures and thus special guidance will be developed on data interpretation for these substances and how the data should be used when applying the classification criteria.

3.10.2.9   *Bioaccumulation*

It is the bioaccumulation of substances within the aquatic organisms that can give rise to toxic effects over longer time scales even when actual water concentrations are low. The potential to bioaccumulate is determined by the partitioning between n-octanol and water. The relationship between the partition coefficient of an organic substance and its bioconcentration as measured by the BCF in fish has considerable scientific literature support. Using a cut-off value of log $K_{ow} \geq 4$ is intended to identify only those substances with a real potential to bioconcentrate. In recognition that the log K_{ow} is only an imperfect surrogate for a measured BCF, such a measured value would always take precedence. A BCF in fish of <500 is considered as indicative of a low level of bioconcentration.

3.10.2.10   *Rapid degradability*

3.10.2.10.1 Substances that rapidly degrade can be quickly removed from the environment. While effects can occur, particularly in the event of a spillage or accident, they will be localised and of short duration. The absence of rapid degradation in the environment can mean that a substance in the water has the potential to exert toxicity over a wide temporal and spatial scale. One way of demonstrating rapid degradation utilises the biodegradation screening tests designed to determine whether a substance is 'readily biodegradable'. Thus a substance which passes this screening test is one that is likely to biodegrade 'rapidly' in the aquatic environment, and is thus unlikely to be persistent. However, a fail in the screening test does not necessarily mean that the substance will not degrade rapidly in the environment. Thus a further criterion was added which would allow the use of data to show that the substance did actually degrade biotically or abiotically in the aquatic environment by >70% in 28 days. Thus, if degradation could be demonstrated under environmentally realistic conditions, then the definition of 'rapid degradability' would have been met. Many degradation data are available in the form of degradation half-lives and these can also be used in defining rapid degradation. Details regarding the interpretation of these data are further elaborated in the Guidance Document of Annex 8. Some tests measure the ultimate biodegradation of the substance, i.e. full mineralisation is achieved. Primary biodegradation would not normally qualify in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment.

3.10.2.10.2 It must be recognised that environmental degradation may be biotic or abiotic (e.g. hydrolysis) and the criteria used reflect this fact. Equally, it must be recognised that failing the ready biodegradability criteria in the OECD tests does not mean that the substance will not be degraded rapidly in the real environment. Thus where such rapid degradation can be shown, the substance should be considered as rapidly degradable. Hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment. A specific definition of rapid degradability is shown below. Other evidence of rapid degradation in the environment may also be considered and may be of particular importance where the substances are inhibitory to microbial activity at the concentration levels used in standard testing. The range of available data and guidance on its interpretation are provided in the Guidance Document of Annex 8.

3.10.2.10.3 Substances are considered rapidly degradable in the environment if the following criteria hold true:

(a) if in 28-day ready biodegradation studies, the following levels of degradation are achieved;

- tests based on dissolved organic carbon: 70%
- tests based on oxygen depletion or carbon dioxide generation: 60% of theoretical maxima

These levels of biodegradation must be achieved within 10 days of the start of degradation which point is taken as the time when 10% of the substance has been degraded; or

(b) if, in those cases where only BOD and COD data are available, when the ratio of BOD5/COD is ≥0.5; or

(c) if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level >70% within a 28 day period.

3.10.2.11 *Inorganic compounds and metals*

3.10.2.11.1 For inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally the use of bioaccumulation data should be treated with care. Specific guidance will be provided on how these data for such materials may be used in meeting the requirements of the classification criteria.

3.10.2.11.2 Poorly soluble inorganic compounds and metals may be acutely or chronically toxic in the aquatic environment depending on the intrinsic toxicity of the bioavailable inorganic species and the rate and amount of this species which may enter solution. A protocol for testing these poorly soluble materials is included in Annex 9. This protocol is undergoing validation testing under the auspices of the OECD.

3.10.2.12 *Category Chronic IV*

The system also introduces as 'safety net' classification (Category: Chronic IV) for use when the data available do not allow classification under the formal criteria but there are nevertheless some

grounds for concern. The precise criteria are not defined with one exception. For poorly water soluble organic substances for which no toxicity has been demonstrated, classification can occur if the substance is both not rapidly degraded and has a potential to bioaccumulate. It is considered that for such poorly soluble substances, the toxicity may not have been adequately assessed in the short-term test due to the low exposure levels and potentially slow uptake into the organism. The need for this classification can be negated by demonstrating the absence of long-term effects, i.e. a long-term NOECs > water solubility or 1 mg/L, or rapid degradation in the environment.

3.10.2.13 *Use of QSARs*

While experimentally derived test data are preferred, where no experimental data are available, validated Quantitative Structure Activity Relationships (QSARs) for aquatic toxicity and log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification to the agreed criteria, if restricted to chemicals for which their mode of action and applicability are well characterised. Reliable calculated toxicity and log K_{ow} values should be valuable in the safety net context. QSARs for predicting ready biodegradation are not yet sufficiently accurate to predict rapid degradation.

3.10.3 Classification criteria for mixtures

3.10.3.1 The classification system for mixtures covers all classification categories which are used for substances meaning acute categories I to III and chronic categories I to IV. In order to make use of all available data for purposes of classifying the aquatic environmental hazards of the mixture, the following assumption has been made and is applied where appropriate.

The "relevant components" of a mixture are those which are present in a concentration of 1% (w/w) or greater, unless there is a presumption (e.g. in the case of highly toxic components) that a component present at less than 1% can still be relevant for classifying the mixture for aquatic environmental hazards.

3.10.3.2 The approach for classification of aquatic environmental hazards is tiered, and is dependent upon the type of information available for the mixture itself and for its components. Elements of the tiered approach include: (a) classification based on tested mixtures; (b) classification based on bridging principles, (c) the use of "summation of classified components" and /or an "additivity formula". Figure 3.10.2 outlines the process to be followed.

**Figure 3.10.2: Tiered approach to classification of mixtures for acute and
chronic aquatic environmental hazards**

Aquatic toxicity test data available on the mixture as a whole

No   Yes   **CLASSIFY** for acute/chronic toxicity hazard (See 3.10.3.3)

Sufficient data available on similar mixtures to estimate hazards	Yes →	Apply bridging principles (See 3.10.3.4)	→ **CLASSIFY** For acute/chronic toxicity hazard

No ↓

Either aquatic toxicity or classification data available for all relevant components	Yes →	Apply Summation Method (See 3.10.3.5.5) using: • Percentage of all components classified as "Chronic" • Percentage of components classified as "Acute" • Percentage of components with acute toxicity data: apply Additivity Formula (See3.10.3.5.2) and convert the derived L(E)C$_{50}$ to the appropriate "Acute" Category	→ **CLASSIFY** For acute/chronic toxicity hazard

No

Use available hazard data of known components	→	Apply Summation Method and/or Additivity Formula (See 3.10.3.5) and apply paragraph 3.10.3.6	→ **CLASSIFY** For acute /chronic toxicity hazard

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

3.10.3.3.1   When the mixture as a whole has been tested to determine its aquatic toxicity, it can be classified according to the criteria that have been agreed for substances, but only for acute toxicity. The classification should be based on the data for fish, crustacea and algae/plants. Classification of mixtures by using LC_{50} or EC_{50} data for the mixture as a whole is not possible for chronic categories since both toxicity data and environmental fate data are needed, and there are no degradability and bioaccumulation data for mixtures as a whole. It is not possible to apply the criteria for chronic classification because the data from degradability and bio-accumulation tests of mixtures cannot be interpreted; they are meaningful only for single substances.

3.10.3.3.2   When there is acute toxicity test data (LC_{50} or EC_{50}) available for the mixture as a whole, this data as well as information with respect to the classification of components for chronic toxicity should be used to complete the classification for tested mixtures as follows. When chronic (long-term) toxicity data (NOEC) is also available, this should be used as well.

- $L(E)C_{50}$ (LC_{50} or EC_{50}) of the tested mixture ≤ 100mg/L and NOEC of the tested mixture ≤ 1.0 mg/L or unknown:
    - → Classify mixture as Category Acute I, II or III
    - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for chronic classification (Chronic I, II, III, IV or no need of chronic classification).

- $L(E)C_{50}$ of the tested mixture ≤ 100mg/L and NOEC of the tested mixture > 1.0 mg/L:
    - → Classify mixture as Category Acute I, II or III
    - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for classification as Category Chronic I. If the mixture is not classified as Category Chronic I, then there is no need for chronic classification.

- $L(E)C_{50}$ of the tested mixture >100mg/L, or above the water solubility, and NOEC of the tested mixture ≤ 1.0mg/L or unknown:
    - → No need to classify for acute toxicity hazard
    - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for Chronic classification (Category Chronic IV or no need for chronic classification).

- $L(E)C_{50}$ of the tested mixture >100mg/L, or above the water solubility, and NOEC of the tested mixture > 1.0 mg/L:
    - → No need to classify for acute or chronic toxicity hazard

3.10.3.4 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.10.3.4.1   Where the mixture itself has not been tested to determine its aquatic environmental hazard, but there are sufficient data on the individual components and similar tested mixtures to adequately characterise the hazards of the mixture, this 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.

3.10.3.4.2   *Dilution*

If a mixture is formed by diluting another classified mixture or a substance with a diluent which has an equivalent or lower aquatic hazard classification than the least toxic original component and which is not expected to affect the aquatic hazards of other components, then the mixture may be classified as equivalent to the original mixture or substance.

If a mixture is formed by diluting another classified mixture or a substance with water or other totally non-toxic material, the toxicity of the mixture can be calculated from the original mixture or substance.

3.10.3.4.3   *Batching*

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

3.10.3.4.4   *Concentration of mixtures which are classified with the most severe classification categories*
            (Chronic I and Acute I)

If a mixture is classified as Chronic I and/or Acute I, and components of the mixture which are classified as Chronic I and/or Acute I are further concentrated, the more concentrated mixture should be classified with the same classification category as the original mixture without additional testing.

3.10.3.4.5   *Interpolation within one toxicity category*

If mixtures A and B are in the same classification category and mixture C is made in which the toxicologically active components have concentrations intermediate to those in mixtures A and B, then mixture C is assumed to be in the same category as A and B. Note that the identity of the components is the same in all three mixtures.

3.10.3.4.6   *Substantially similar mixtures*

Given the following:

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

(b)   The concentration of component B is the same in both mixtures;
(c)   The concentration of component A in mixture (i) equals that of component C in mixture (ii);
(d)   Classification for A and C are available and are the same, i.e. they are in the same hazard category and are not expected to affect the aquatic toxicity of B.

Then there is no need to test mixture (ii) if mixture (i) is already characterised by testing and both mixtures would be classified in the same category.

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

3.10.3.5.1   The classification of a mixture is based on summation of the classification of its components. The percentage of components classified as "Acute" or "Chronic" will feed straight into the summation method. Details of the summation method are described in 3.10.3.5.5.

3.10.3.5.2   Mixtures can be made of a combination of both components that are classified (as Acute I, II, III and/or Chronic I, II, III, IV) and those for which adequate test data is available. When adequate toxicity data is available for more than one component in the mixture, the combined toxicity of those components may be calculated using the following additivity formula, and the calculated toxicity may be used to assign that portion of the mixture an acute hazard category which is then subsequently used in applying the summation method.

$$\frac{\sum C_i}{L(E)C_{50m}} = \sum_n \frac{C_i}{L(E)C_{50i}}$$

where:

C_i	=	concentration of component i (weight percentage)
$L(E)C_{50i}$	=	(mg/L) LC_{50} or EC_{50} for component i
n	=	number of components, and i is running from 1 to n
$L(E)C_{50m}$	=	$L(E) C_{50}$ of the part of the mixture with test data

3.10.3.5.3   When applying the additivity formula for part of the mixture, it is preferable to calculate the toxicity of this part of the mixture using for each substance toxicity values that relate to the same species (i.e. fish, daphnia or algae) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three species). However, when toxicity data for each component are not available in the same species, the toxicity value of each component should be selected in the same manner that toxicity values are selected for the classification of substances, i.e. the higher toxicity (from the most sensitive test organism) is used. The calculated acute toxicity may then be used to classify this part of the mixture as Acute I, II or III using the same criteria described for substances.

3.10.3.5.4   If a mixture is classified in more than one way, the method yielding the more conservative result should be used.

3.10.3.5.5   *Summation method*

3.10.3.5.5.1   Rationale

3.10.3.5.5.1.1   In case of the substance classification categories Acute I/Chronic I to Acute III/Chronic III, the underlying toxicity criteria differ by a factor of 10 in moving from one category to another. Substances with a classification in a high toxicity band may therefore contribute to the classification of a mixture in a lower band. The calculation of these classification categories therefore needs to consider the contribution of all substances classified Acute I/Chronic I to Acute III/Chronic III together.

3.10.3.5.5.1.2   When a mixture contains components classified as Acute Category I, attention should be paid to the fact that such components, when their acute toxicity is well below 1 mg/L contribute to the toxicity of the mixture even at a low concentration. (See also *Classification of Hazardous Substances and Mixtures* in Chapter 1.3,1.3.3.2.1). Active ingredients in pesticides often possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application

of the normal cut-off values/concentration limits may lead to an "underclassification" of the mixture. Therefore, multiplying factors should be applied to account for highly toxic components, as described in paragraph 3.10.3.5.5.5.

3.10.3.5.5.2   Classification procedure

        In general a more severe classification for mixtures overrides a less severe classification, e.g. a classification with Chronic I overrides a classification with Chronic II. As a consequence the classification procedure is already completed if the result of the classification is Chronic I. A more severe classification than chronic I is not possible therefore it is not necessary to undergo the further classification procedure.

3.10.3.5.5.3   Classification for the Acute Categories I, II and III

3.10.3.5.5.3.1   First, all components classified as Acute I are considered. If the sum of these components is greater than 25% the whole mixture is classified as Category Acute I. If the result of the calculation is a classification of the mixture as Category Acute I, the classification process is completed.

3.10.3.5.5.3.2   In cases where the mixture is not classified as Acute I, classification of the mixture as Acute II is considered. A mixture is classified as Acute II if ten times the sum of all components classified as Acute I plus the sum of all components classified as Acute II is greater than 25%. If the result of the calculation is classification of the mixture as Category Acute II, the classification process is completed.

3.10.3.5.5.3.3   In cases where the mixture is not classified either as Acute I or Acute II, classification of the mixture as Acute III is considered. A mixture is classified as Acute III if 100 times the sum of all components classified as Acute I plus 10 times the sum of all components classified as Acute II plus the sum of all components classified as Acute III is greater than 25%.

3.10.3.5.5.3.4   The classification of mixtures for acute hazards based on this summation of classified components, is summarised in Table 3.10.2.

**Table 3.10.2: Classification of a mixture for acute hazards,
based on summation of classified components**

Sum of components classified as:		Mixture is classified as:
Acute I x M[a]	>25%	Acute I
(M x 10 x Acute I) +Acute II	>25%	Acute II
(M x 100 x Acute I)+ (10 x Acute II) + Acute III	>25%	Acute III

    [a] *For explanation of the M factor, see paragraph 3.10.3.5.5.5.*

3.10.3.5.5.4   Classification for the Chronic Categories I, II, III and IV

3.10.3.5.5.4.1   First all components classified as Chronic I are considered. If the sum of these components is greater than 25% the mixture is classified as Category Chronic I. If the result of the calculation is a classification of the mixture as Category Chronic I the classification procedure is completed.

3.10.3.5.5.4.2   In cases where the mixture is not classified as Chronic I, classification of the mixture as Chronic II is considered. A mixture is classified as Chronic II if 10 times the sum of all components classified as Chronic I plus the sum of all components classified as Chronic II is greater than 25%. If the result of the calculation is classification of the mixture as Chronic II, the classification process is completed.

3.10.3.5.5.4.3   In cases where the mixture is not classified either as Chronic I or Chronic II, classification of the mixture as Chronic III is considered. A mixture is classified as Chronic III if 100 times the sum of all components classified as Chronic I plus 10 times the sum of all components classified with Chronic II plus the sum of all components classified as Chronic III is greater than 25%.

3.10.3.5.5.4.4   If the mixture is still not classified in either Category Chronic I, II or III, classification of the mixture as Chronic IV should be considered. A mixture is classified as Chronic IV if the sum of the percentages of components classified as Chronic I, II, III and IV is greater than 25%.

3.10.3.5.5.4.5   The classification of mixtures for chronic hazards, based on this summation of classified components, is summarised in Table 3.10.3.

**Table 3.10.3: Classification of a mixture for chronic hazards,
based on summation of classified components**

Sum of components classified as:	Mixture is classified as:
Chronic I x M[a] >25%	Chronic I
(M x 10 x Chronic I)+Chronic II >25%	Chronic II
(M x 100 x Chronic I)+(10x Chronic II)+Chronic III >25%	Chronic III
Chronic I + Chronic II + Chronic III +Chronic IV > 25%	Chronic IV

[a] *For explanation of the M factor, see paragraph 3.10.3.5.5.5.*

3.10.3.5.5.5 Mixtures with highly toxic components

Acute Category 1 components with toxicities well below 1 mg/L may influence the toxicity of the mixture and should be given increased weight in applying the summation of classification approach. When a mixture contains components classified as Acute or Chronic Category I, the tiered approach described in 3.10.3.5.5.3 and 3.10.3.5.5.4 should be applied using a weighted sum by multiplying the concentrations of Acute Category I components by a factor, instead of merely adding up the percentages. This means that the concentration of "Acute I" in the left column of Table 3.10.2 and the concentration of "Chronic I" in the left column of Table 3.10.3 are multiplied by the appropriate multiplying factor. The

multiplying factors to be applied to these components are defined using the toxicity value, as summarised in Table 3.10.4 below. Therefore, in order to classify a mixture containing Acute/Chronic I components, the classifier needs to be informed of the value of the M factor in order to apply the summation method. Alternatively, the additivity formula (paragraph 3.10.3.5.2) may be used when toxicity data are available for all highly toxic components in the mixture and there is convincing evidence that all other components, including those for which specific acute toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture.

Table 3.10.4: Multiplying factors for highly toxic components of mixtures

L(E)C50 value	Multiplying factor (M)
$0.1 < L(E)C_{50} \leq 1$	1
$0.01 < L(E)C_{50} \leq 0.1$	10
$0.001 < L(E)C_{50} \leq 0.01$	100
$0.0001 < L(E)C_{50} \leq 0.001$	1000
$0.00001 < L(E)C_{50} \leq 0.0001$	10000
(continue in factor 10 intervals)	

3.10.3.6 *Classification of mixtures with components without any useable information*

In the event that no useable information on acute and/or chronic aquatic hazard is available for one or more relevant components, it is concluded that the mixture cannot be attributed (a) definitive hazard category(ies). In this situation the mixture should be classified based on the known components only, with the additional statement that: "x percent of the mixture consists of components(s) of unknown hazards to the aquatic environment".

3.10.4   Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.10.5: Label elements for hazardous to the aquatic environment

ACUTE			
	Category 1	**Category 2**	**Category 3**
Symbol	Fish and tree	No symbol is used	No symbol is used
Signal word	Warning	No signal word is used	No signal word is used
Hazard Statement	Very toxic to aquatic life	Toxic to aquatic life	Harmful to aquatic life

CHRONIC				
	Category 1	**Category 2**	**Category 3**	**Category 4**
Symbol	Fish and tree	Fish and tree	No symbol is used	No symbol is used
Signal word	Warning	No signal word is used	No signal word is used	No signal word is used
Hazard statement	Very toxic to aquatic life with long lasting effects	Toxic to aquatic life with long lasting effects	Harmful to aquatic life with long lasting effects	May cause long lasting harmful effects to aquatic life

3.10.5   Decision Logic for Hazardous to the Aquatic Environment

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 3.10.1

Substance: Is there sufficient information (toxicity, degradation, bioaccumulation) for classification[1]?

No → Value for the $L(E)C_{50}$ of the mixture from Decision Logic 3.10.2

Yes ↓

Acute Does it have a:
- 96 hr LC_{50} (fish) ≤ 1 mg/L, **and/or**
- 48 hr EC_{50} (crustacea) ≤ 1 mg/L, **and/or**
- 72 or 96 hr ErC_{50} (algae or other aquatic plants) ≤ 1 mg/L?

Yes → Acute Category 1

Warning

No ↓   and ↓

Chronic
Does it lack the potential to rapidly degrade? **and/or**
Does it have the potential to bioaccumulate
   (BCF ≥ 500 or if absent, log Kow ≥ 4)? [3]

Yes → Chronic Category 1

Warning

Acute Does it have a:
- 96 hr LC_{50} (fish) ≤ 10 mg/L, **and/or**
- 48 hr EC_{50} (crustacea) ≤ 10 mg/L, **and/or**
- 72 or 96 hr ErC_{50} (algae or other aquatic plants) ≤ 10 mg/L?

Yes → Acute Category 2[2]

No ↓   and ↓

Chronic
- Does it lack the potential to rapidly degrade? **and/or**
- Does it have the potential to bioaccumulate (BCF ≥ 500 or if absent, log Kow ≥ 4)[3] ?

Yes → Chronic Category 2

Unless chronic NOEC(s) >1 mg/L

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[1]   *Classification can be based on either measured data and/or calculated data (see paragraph 3.10.2.13 of this chapter and Annex 8) and/or analogy decisions (see paragraph A8.6.4.5 of Annex 8).*
[2]   *Labelling requirements differ from on regulatory system to another, and certain classification categories may only be used in one or a few regulations*
[3]   *See Note 4 of Table 3.10.1 and Chapter A8.5 of Annex 8.*

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No

Acute Does it have a:
- 96 hr LC_{50} (fish) $\leq$ 100 mg/L, **and/or**
- 48 hr EC_{50} (crustacea) $\leq$ 100 mg/L, **and/or**
- 72 or 96 hr ErC_{50} (algae or other aquatic plants) $\leq$ 100 mg/L?

Yes → Acute Category 3[2]

No

and

Chronic
- Does it lack the potential to rapidly degrade? **and/or**
- Does it have the potential to bioaccumulate (BCF$\geq$ 500 or if absent, log $K_{ow} \geq$ 4)?[3].

Yes → Chronic Category 3

Unless chronic NOEC(s) > 1 mg/L

Chronic[5]
- Is it poorly soluble with no acute toxicity[4)]? **and**
- Does it lack the potential to rapidly degrade? **and/or**
- Does it have the potential to bioaccumulate (BCF$\geq$ 500 or if absent, log $K_{ow} \geq$ 4)?[3]

Yes → Chronic Category 4[5]

Unless chronic NOEC(s)> 1 mg/L

No

Not classified

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

[3] *See Note 4 of Table 3.10.1 and Chapter A8.5 of Annex 8.*

[4] *See Table 3.10.1, Note 5 further developed in Annex89, sub-section A8.3.5.7.*

[5] *See paragraph 3.10.2.12.*

Mixture: Does the mixture as a whole have aquatic toxicity data for fish, crustacea, and algae/aquatic plants?

No

Yes

Values from Mixtures/ Decision Logic 3.10.2

Acute
Does it have a 96 hr LC_{50} (fish), 48 hr EC_{50} (crustacea), or 72 or 96 hr ErC_{50} (algae or other aquatic plants)
- ≤ 1 mg/L?

Yes → Acute Category 1

Warning

No

and

Acute
Does it have a 96 hr LC_{50} (fish), 48 hr EC_{50} (crustacea), or 72 or 96 hr ErC_{50} (algae or other aquatic plants)
- ≤ 10 mg/L?

Yes → Acute Category 2[2]

and

No

Acute
Does it have a 96 hr LC_{50} (fish), 48 hr EC_{50} (crustacea), or 72 or 96 hr ErC_{50} (algae or other aquatic plants)
- ≤ 100 mg/L?

Yes → Acute Category 3 [2]

and

No

Not classified for acute

Chronic
See Decision Logic 3.10.3 for Chronic Classification
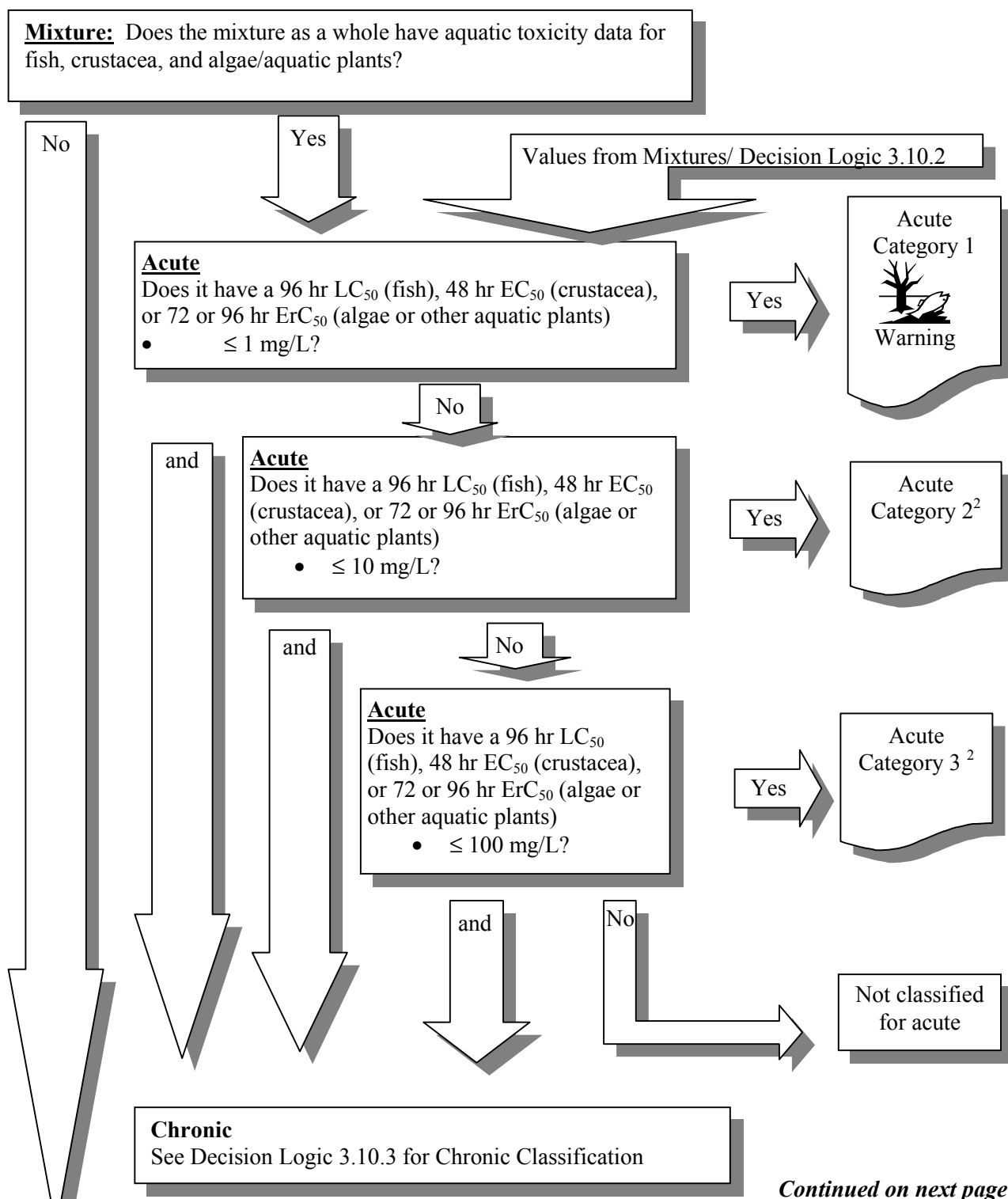
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[2] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*

| Can bridging principles be applied? | →Yes→ | Classify in appropriate category |

↓ No

Use all available ingredient information in the summation method as follows[6]:
- For ingredients with available toxicity value(s) apply the additivity formula (decision logic 3.10.2), determine the toxicity category for that part of the mixture and use this information in the summation method below,
- Classified ingredients will feed directly into the summation method below

↓ Yes

Sum of ingredients classified as:
- Acute $1 \times M^7 \geq 25\%$?

→ Yes → **Acute Category 1** — Warning

↓ No

Sum of ingredients classified as:
- $(\text{Acute } 1 \times M^7 \times 10) + \text{Acute } 2 \geq 25\%$?

→ Yes → Acute Category 2^2

↓ No

Sum of ingredients classified as:
- $(\text{Acute } 1 \times M^7 \times 100) + (\text{Acute } 2 \times 10) + \text{Acute } 3 \geq 25\%$?

→ Yes → Acute Category 3^2

↓ No → Not classified for acute

and / and / and

Chronic
See Decision Logic 3.10.3 for Chronic Classification

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

[6] *If not all components have information, include the statement "x percent of the mixture consists of ingredients(s) of unknown hazards to the aquatic environment" on the label. Alternatively, in the case of a mixture with highly toxic ingredients, if toxicity values are available for these highly toxic ingredients and all other ingredients do not significantly contribute to the hazard of the mixture, than the additivity formula may be applied. (See paragraph 3.10.3.5.5.5). In this case and other cases where toxicity values are available for all ingredients, the acute classification may be made solely on the basis of the additivity formula.*

[7] *For explanation of M factor see paragraph 3.10.3.5.5.5.*

Mixtures decision logic 3.10.2 (Additivity method)

Apply the Additivity Method:

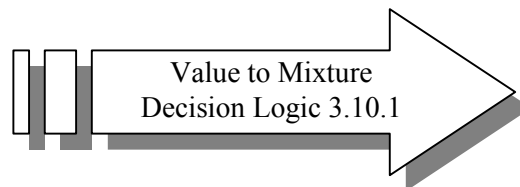$$\frac{\sum Ci}{L(E)C_{50m}} = \sum_{n} \frac{Ci}{L(E)C_{occ}}$$

where:

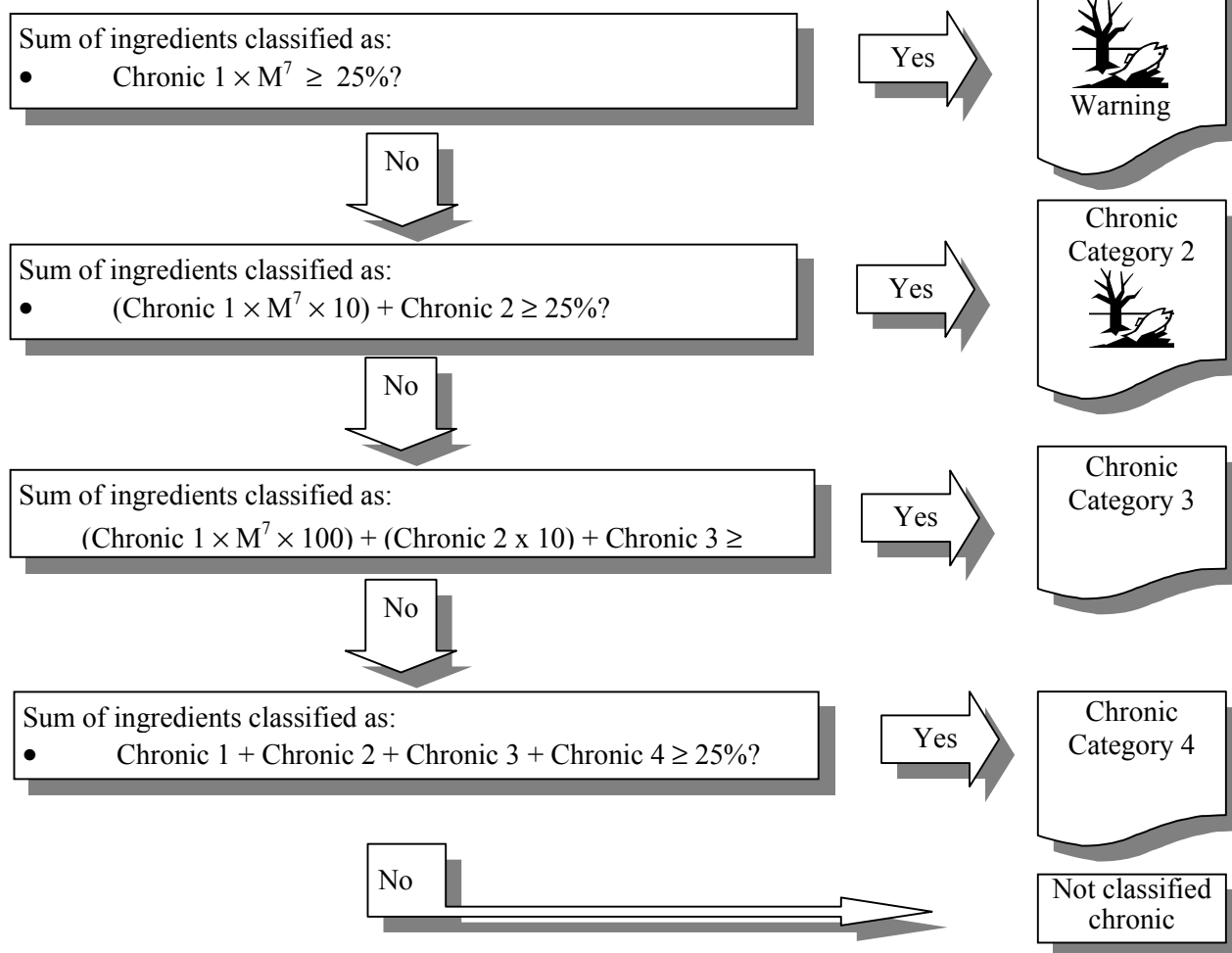|		
C_i	=	concentration of component i (weight percentage)
$L(E)C_{occ}$	=	(mg/L) LC_{50} or EC_{50} for component I
n	=	number of components
$L(E)C_{50m}$	=	$L(E)C_{50}$ of the part of the mixture with test data

Value to Mixture Decision Logic 3.10.1

Mixtures decision logic 3.10.3 (Chronic classification)

Sum of ingredients classified as:
- Chronic $1 \times M^7 \geq 25\%$?

Yes → Chronic Category 1 / Warning

No ↓

Sum of ingredients classified as:
- (Chronic $1 \times M^7 \times 10$) + Chronic $2 \geq 25\%$?

Yes → Chronic Category 2

No ↓

Sum of ingredients classified as:
 (Chronic $1 \times M^7 \times 100$) + (Chronic 2 x 10) + Chronic 3 $\geq$

Yes → Chronic Category 3

No ↓

Sum of ingredients classified as:
- Chronic 1 + Chronic 2 + Chronic 3 + Chronic $4 \geq 25\%$?

Yes → Chronic Category 4

No → Not classified chronic

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[7]   *For explanation of M factor see paragraph 3.10.3.5.5.5.*