ANNEX 1
CLASSIFICATION AND LABELLING REQUIREMENTS FOR HAZARDOUS SUBSTANCES AND MIXTURES

This annex sets out the criteria for classification in hazard classes and in their differentiations and sets out additional provisions on how the criteria may be met.

PART 1
GENERAL PRINCIPLES FOR CLASSIFICATION AND LABELLING

1.0. DEFINITIONS

Gas means a substance which:

(i) at 50°C has a vapour pressure greater than 300 kPa (absolute); or

(ii) is completely gaseous at 20°C at a standard pressure of 101,3 kPa;

Liquid means a substance or mixture which:

(i) at 50°C has a vapour pressure of not more than 300 kPa (3 bar);

(ii) is not completely gaseous at 20°C and at a standard pressure of 101,3 kPa; and

(iii) which has a melting point or initial melting point of 20°C or less at a standard pressure of 101,3 kPa;

Solid means a substance or mixture which does not meet the definitions of liquid or gas.

1.1. CLASSIFICATION OF SUBSTANCES AND MIXTURES

1.1.0. Cooperation to meet the requirements in this By-Law

Suppliers in a supply chain shall cooperate to meet the requirements for classification, labelling and packaging set out in this By-Law.

Suppliers in an industry sector may cooperate to manage the transitional arrangements in Transitional Article 1 for substances and mixtures placed on the market.

Suppliers in an industry sector may cooperate through formation of a network or by other means to share data and expertise when classifying substances and mixtures in accordance with Section III of this By-Law. In these circumstances suppliers in an industry sector shall document fully the basis on which classification decisions are made and shall make available to the competent authorities and, on request, to the relevant enforcement authorities the documentation, together with the data and information on which

classifications are based. However, where suppliers in an industry sector cooperate in this way, each supplier shall remain fully responsible for the classification, labelling and packaging of substances and mixtures he places on the market, and for meeting any other requirements of this By-Law.

The network may also be used to exchange information and best practices with a view to simplifying fulfilment of the notification obligations.

1.1.1. The role and application of expert judgement and weight of evidence determination

1.1.1.1. Where the criteria cannot be applied directly to available identified information, or where only the information referred to in Article 8(5) is available, the weight of evidence determination using expert judgment shall be applied in accordance with Article 11(3) or 11(4) respectively.

1.1.1.2. The approach to classifying mixtures may include the application of expert judgement in a number of areas in order to ensure existing information can be used for as many mixtures as possible in order to provide protection for human health and the environment. Expert judgement may also be required in interpreting data for hazard classification of substances, especially where weight of evidence determinations are needed.

1.1.1.3. A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination.

1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this

Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

1.1.1.5. For the purpose of classification for health hazards (Part 3) route of exposure, mechanistic information and metabolism studies are pertinent to determining the relevance of an effect in humans. When such information, as far as there is reassurance about the robustness and quality of the data, raises doubt about relevance in humans, a lower classification may be warranted. When there is scientific evidence that the mechanism or mode of action is not relevant to humans, the substance or mixture should not be classified.

1.1.2. Specific concentration limits, M-factors and generic cut-off values

1.1.2.1. Specific concentration limits or M-factors shall be applied in accordance with Article 12.

1.1.2.2. Cut-off values

1.1.2.2.1. Cut-off values indicate when the presence of a substance needs to be taken into account for the purposes of classification of a substance or a mixture containing that hazardous substance, whether as an identified impurity, additive, or individual constituent (see Article 13).

1.1.2.2.2. The cut-off values referred to in Article 13 shall be the following:

(a) For health and environmental hazards in Parts 3, 4 and 5 of this Annex:

(i) for substances where a specific concentration limit is set for the relevant hazard class or differentiation either in Part 3 of Annex 6 or in the classification and labelling inventory referred to in Article 40, and where the hazard class or differentiation is mentioned in Table 1.1, the lower of the specific concentration limit and the relevant generic cut-off value in Table 1.1; or

(ii) for substances where a specific concentration limit is set for the relevant hazard class or differentiation either in Part 3 of Annex 6 or in the classification and labelling inventory referred to in Article 40, and where

the hazard class or differentiation is not mentioned in Table 1.1, the specific concentration limit set either in Part 3 of Annex 6 or in the classification and labelling inventory; or

(iii) for substances where no specific concentration limit is set for the relevant hazard class or differentiation either in Part 3 of Annex 6 or in the classification and labelling inventory referred to in Article 40, and where the hazard class or differentiation is mentioned in Table 1.1, the relevant generic cut-off value set out in that table; or

(iv) for substances where no specific concentration limit is set for the relevant hazard class or differentiation either in Part 3 of Annex 6 or in the classification and labelling inventory referred to in Article 40, and where the hazard class or differentiation is not mentioned in Table 1.1, the generic concentration limit for classification in the relevant sections of Parts 3, 4 and 5 of this Annex.

(b) For aquatic environmental hazards in section 4.1 of this Annex:

(i) for substances where an M-factor has been set for the relevant hazard category either in Part 3 of Annex 6, or in the classification and labelling inventory referred to in Article 40, the generic cut-off value in Table 1.1 adjusted using the calculation set out in section 4.1 of this Annex; or

(ii) for substances where no M-factor is set for the relevant hazard category either in Part 3 of Annex 6 or in the classification and labelling inventory referred to in Article 40, the relevant generic cut-off value set out in Table 1.1.

Table 1.1

Generic cut-off values

Hazard class	Generic cut-off values to be taken into account
Acute Toxicity:	
– Category 1-3	0,1 %
– Category 4	1 %
Skin corrosion/Irritation	1 %[1]
Serious damage to eyes/eye irritation	1 %[2]
Hazardous to Aquatic Environment	
– Acute Category 1	0,1 %[3]
– Chronic Category 1	0,1 %[4]
– Chronic Category 2-4	1 %

[1] Or < 1 % where relevant, see 3.2.3.3.1.
[2] Or < 1 % where relevant, see 3.3.3.3.1.
[3] Or < 0,1 % where relevant, see 4.1.3.1.
[4] Or < 0,1 % where relevant, see 4.1.3.1.

Note:

Generic cut-off values are in weight percentages except for gaseous mixtures for those hazard classes where the generic cut-off values may be best described in volume percentage.

1.1.3. Bridging principles for the classification of mixtures where test data are not available for the complete mixture

Where the mixture itself has not been tested to determine its hazardous properties, but there are sufficient data on similar tested mixtures and individual hazardous ingredient substances to adequately characterise the hazards of the mixture, these data shall be used in accordance with the following bridging rules referred to in Article 11(4) for each individual hazard class in Part 3 and Part 4 of this Annex, subject to any specific provisions for mixtures in each hazard class.

1.1.3.1. Dilution

If a tested mixture is diluted with a substance (diluent) which has an equivalent or lower hazard category classification than the least hazardous original ingredient substance and which is not expected to affect the hazard classification of other ingredient substances, then one of the following shall be applied:

– the new mixture shall be classified as equivalent to the original mixture;

– the method explained in each section of Part 3 and in Part 4 for classification of mixtures when data are available for all components or only some components of the mixture;

– in the case of acute toxicity, the method for classification of mixtures based on ingredients of the mixture (additivity formula).

1.1.3.2. Batching

The hazard category of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product, when produced by or under the control of the same supplier, unless there is reason to believe there is significant variation such that the hazard classification of the untested batch has changed. If the latter occurs, a new evaluation is necessary.

1.1.3.3. Concentration of highly hazardous mixtures

In the case of the classification of mixtures covered by sections 3.1, 3.2, 3.3, 3.8, 3.9, 3.10 and 4.1, if a mixture is classified in the highest hazard category or sub-category, and the concentration of the componentes of the tested mixture that are in that category or sub-category is increased, the resulting untested mixture shall be classified in that category or sub-category without additional testing.

1.1.3.4. Interpolation within one toxicity category

In the case of the classification of mixtures covered by sections 3.1, 3.2, 3.3, 3.8, 3.9, 3.10 and 4.1, for three mixtures (A, B and C) with identical components, where mixtures A and B have been tested and are in the same hazard category and where untested mixture C has the same active hazardous components as mixture A and B but has concentrations of those hazardous components intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B.

1.1.3.5. Substantially similar mixtures

Given the following:

(a) two mixtures each containing two ingredients:

(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) hazard data 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 hazard classification of B.

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

1.1.3.6. Review of classification where the composition of a mixture has changed

The following variations in initial concentration are defined for the application of Article 17(2)(a):

Table 1.2

Bridging Principle for changes in the composition of a mixture

Initial concentration range of the constituent	Permitted variation in initial concentration of the constituent
≤ 2,5 %	± 30 %
2,5 < C ≤ 10 %	± 20 %
10 < C ≤ 25 %	± 10 %
25 < C ≤ 100 %	± 5 %

1.1.3.7. Aerosols

In the case of the classification of mixtures covered by sections 3.1, 3.2, 3.3, 3.4, 3.8 and 3.9, an aerosol form of a mixture shall be classified in the same hazard category as the non-aerosolised form of the mixture, provided that the added propellant does not affect the hazardous properties of the mixture upon spraying and scientific evidence is available

demonstrating that the aerosolised form is not more hazardous than the nonaerosolised form.

1.2. LABELLING

1.2.1. General rules for the application of labels required by Article 33

1.2.1.1. Hazard pictograms shall be in the shape of a square set at a point.

1.2.1.2. Hazard pictograms as laid down in Annex 5 shall have a black symbol on a white background with a red frame sufficiently wide to be clearly visible.

1.2.1.3. Each hazard pictogram shall cover at least one fifteenth of the minimum surface area of the label dedicated to the information required by Article 19. The minimum area of each hazard pictogram shall not be less than 1 cm^2.

1.2.1.4. The dimensions of the label shall be as follows:

Table 1.3

Minimum dimension of labels and pictograms

Capacity of the package	Dimensions (in millimetres) for the information required by Article 19	Dimensions of each pictogram (in millimetres)
Not exceeding 3 litres:	If possible, at least 52 x 74	Not smaller than 10 x 10 If possible, at least 16 x 16
Greater than 3 litres but, not exceeding 50 litres:	At least 74 x 105	At least 23 x 23
Greater than 50 litres but not exceeding 500 litres:	At least 105 x 148	At least 32 x 32
Greater than 500 litres:	At least 148 x 210	At least 46 x 46’

1.3. DEROGATIONS FROM LABELLING REQUIREMENTS FOR SPECIAL CASES

In accordance with Article 25 the following derogations shall apply:

1.3.1. Transportable gas cylinders

For transportable gas cylinders, one of the following shall be permitted to be used for gas cylinders with a water capacity of less than or equal to 150 litres:

(a) A format and dimensions following the prescriptions of the current edition of Standard ISO 7225 relating to "Gas cylinders – Precautionary labels". In this case, the label can bear the generic name or industrial or commercial name of the substance or mixture provided that the hazardous substances in a mixture are shown on the body of the gas cylinder in a clear and indelible way.

(b) The information specified in Article 19 provided on a durable information disc or label held captive on the cylinder.

1.3.2. Gas containers intended for propane, butane or liquefied petroleum gas (LPG)

1.3.2.1. If propane, butane and liquefied petroleum gas or a mixture containing these substances classified in accordance with the criteria of this Annex, is placed on the market in closed refillable cylinders or in non-refillable cartridges within the scope of EN 417 as fuel gases which are only released for combustion (current edition of EN 417, relating to "Non-refillable metallic gas cartridges for liquefied petroleum gases, with or without a valve, for use with portable appliances; construction, inspection, testing and marking"), these cylinders or cartridges shall only be labelled with the appropriate pictogram and the hazard and precautionary statements concerning flammability.

1.3.2.2. No information concerning the effects on human health and the environment is required on the label. Instead the supplier shall provide the information concerning effects on human health and the environment to downstream users or distributors by means of the safety data sheet (SDS).

1.3.2.3. For consumers, sufficient information shall be transmitted to enable them to take all necessary measures for health and safety.

1.3.3. Aerosols and containers fitted with a sealed spray attachment and containing substances or mixtures classified as presenting an aspiration hazard

With regard to the application of section 3.10.4, substances or mixtures classified in accordance with the criteria of sections 3.10.2 and 3.10.3 need not be labelled for this

hazard when placed on the market in aerosol containers or in containers fitted with a sealed spray attachment.

1.3.4. Metals in massive form, alloys, mixtures containing polymers, mixtures containing elastomers

1.3.4.1. Metals in massive form, alloys, mixtures containing polymers and mixtures containing elastomers do not require a label according to this Annex, if they do not present a hazard to human health by inhalation, ingestion or contact with skin or to the aquatic environment in the form in which they are placed on the market, although classified as hazardous in accordance with the criteria of this Annex.

1.3.4.2. Instead, the supplier shall provide the information to downstream users or distributors by means of the SDS.

1.3.5. Explosives placed on the market with a view to obtaining an explosive or pyrotechnic effect

Explosives, as referred to in section 2.1, placed on the market with a view to obtaining an explosive or pyrotechnic effect shall be labelled and packaged in accordance with the requirements for explosives only.

1.4. REQUEST FOR USE OF AN ALTERNATIVE CHEMICAL NAME

1.4.1. Requests for use of an alternative chemical name under Article 26 may be granted only where

(I) the substance has not been assigned a Community workplace exposure limit; and

(II) the manufacturer, importer or downstream user can demonstrate that the use of the alternative chemical name meets the need to provide enough information for necessary health and safety precautions to be taken in the workplace and the need to ensure that risks from handling the mixture can be controlled; and

(III) the substance is classified exclusively as one or more of the following hazard categories:

(a) any of the hazard categories referred to in Part 2 of this Annex;

(b) Acute toxicity, Category 4;

(c) Skin corrosion/irritation, Category 2;

(ç) Serious eye damage/eye irritation, Category 2;

(d) Specific target organ toxicity – Single exposure, Category 2 or 3;

(e) Specific target organ toxicity – Repeated exposure, Category 2;

(f) Hazardous to the aquatic environment – Chronic, Category 3 or 4.

1.4.2. The choice of the chemical name(s) for mixtures intended for the fragrance or perfume industry

In the case of substances occurring in nature, a chemical name or chemical names of the type "essential oil of …" or "extract of …" may be used instead of the chemical names of the components of that essential oil or extract as referred to in Article 20(3)(b).

1.5. EXEMPTIONS FROM LABELLING AND PACKAGING REQUIREMENTS

1.5.1. Exemptions from Article 33

1.5.1.1. Where Article 31(1) applies, the label elements mentioned in Article 19 may be provided in one of the following ways:

(a) in fold-out labels; or

(b) on tie-on tags; or

(c) on an outer packaging.

1.5.1.2. The label on any inner packaging shall contain at least hazard pictograms, the product identifier referred to in Article 20 and name and telephone number of the supplier of the substance or mixture.

1.5.2. Exemptions from Article 19

1.5.2.1. Labelling of packages where the contents do not exceed 125 ml

1.5.2.1.1. The hazard statements and the precautionary statements linked to the hazard categories listed below may be omitted from the label elements required by Article 19 where:

(a) the contents of the package do not exceed 125 ml; and

(b) the substance or mixture is classified in one or more of the following hazard categories:

1) Oxidising gases of category 1;

2) Gases under pressure;

3) Flammable liquids of category 2 or 3;

4) Flammable solids of category 1 or 2;

5) Self-reactive substances or mixtures Types C to F;

6) Self-heating substances or mixtures of category 2;

7) Substances and mixtures which, in contact with water, emit flammable gases of categories 1, 2 or 3;

8) Oxidising liquids of category 2 or 3;

9) Oxidising solids of category 2 or 3;

10) Organic peroxides Types C to F;

11) Acute toxicity of category 4, if the substances or mixtures are not supplied to the general public;

12) Skin irritation of category 2;

13) Eye irritation of category 2;

14) Specific target organ toxicity – single exposure of category 2 or 3, if the substance or mixture is not supplied to the general public;

15) Specific target organ toxicity – repeated exposure of category 2, if the substance or mixture is not supplied to the general public;

16) Hazardous to the aquatic environment – Acute of category 1;

17) Hazardous to the aquatic environment – Chronic of category 1 or 2.

The exemptions for labelling of small packages of aerosols as flammable laid down in Directive 75/324/EEC shall apply to aerosol dispensers.

1.5.2.1.2. The precautionary statements linked to the hazard categories listed below may be omitted from the label elements required by Article 19 where:

(a) the contents of the package do not exceed 125 ml; and

(b) the substance or mixture is classified in one or more of the following hazard categories:

1) Flammable gases of category 2;

2) Reproductive toxicity: effects on or via lactation;

3) Hazardous to the aquatic environment – Chronic of category 3 or 4.

1.5.2.1.3. The pictogram, the signal word, the hazard statement and the precautionary statement linked to the hazard categories listed below may be omitted from the label elements required by Article 19 where:

(a) the contents of the package do not exceed 125 ml; and

(b) the substance or mixture is classified in one or more of the following hazard categories:

1) Corrosive to metals.

1.5.2.2. Labelling of soluble packaging for single use

The label elements required by Article 19 may be omitted from soluble packaging intended for single use where:

(a) The content of each soluble packaging does not exceed a volume of 25 ml;

(b) The classification of the contents of the soluble packaging is exclusively one or more of the hazard categories in 1.5.2.1.1 (b), 1.5.2.1.2 (b) or 1.5.2.1.3 (b); and'

(c) The soluble packaging is contained within outer packaging that fully meets the requirements of Article 19.

1.5.2.3. Section 1.5.2.2 shall not apply to substances or mixtures within the scope of By-Law on the Classification, Packaging and Labelling of Plant Protection Products published in the Official Gazette dated 25/03/2011 and numbered 27885 and Biocidal Products By-Law published in the Official Gazette dated 31/12/2009 and numbered 27449.

PART 2

PHYSICAL HAZARDS

2.1. EXPLOSIVES

2.1.1. Definitions

2.1.1.1. The class of explosives comprises

(a) explosive substances and mixtures;

(b) explosive articles, except devices containing explosive substances or mixtures in such quantity or of such a character that their inadvertent or accidental ignition or initiation shall not cause any effect external to the device either by projection, fire, smoke, heat or loud noise; and

(c) substances, mixtures and articles not mentioned in points (a) and (b) which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.

2.1.1.2. For the purposes of this By-Law the following definitions shall apply:

An explosive substance or mixture is a solid or liquid substance or mixture of substances which is in itself capable by chemical reaction of producing gas at such a temperature and pressure and at such a speed as to cause damage to the surroundings. Pyrotechnic substances are included even when they do not evolve gases.

A pyrotechnic substance or mixture is a substance or mixture of substances designed to produce an effect by heat, light, sound, gas or smoke or a combination of these as the result of non-detonative self-sustaining exothermic chemical reactions.

An unstable explosive is an explosive substance or mixture which is thermally unstable and/or too sensitive for normal handling, transport and use.

An explosive article is an article containing one or more explosive substances or mixtures.

A pyrotechnic article is an article containing one or more pyrotechnic substances or mixtures.

An intentional explosive is a substance, mixture or article which is manufactured with a view to producing a practical, explosive or pyrotechnic effect.

2.1.2. Classification criteria

2.1.2.1. Substances, mixtures and articles of this class are classified as an unstable explosive on the basis of the flowchart in Figure 2.1.2. The test methods are described in Part I of the UN RTDG, Manual of Tests and Criteria.

2.1.2.2. Substances, mixtures and articles of this class, which are not classified as an unstable explosive, shall be assigned to one of the following six divisions depending on the type of hazard they present:

(a) Division 1.1 Substances, mixtures and articles which have a mass explosion hazard (a mass explosion is one which affects almost the entire quantity present virtually instantaneously);

(b) Division 1.2 Substances, mixtures and articles which have a projection hazard but not a mass explosion hazard;

(c) Division 1.3 Substances, mixtures and articles which have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but not a mass explosion hazard:

(i) combustion of which gives rise to considerable radiant heat; or

(ii) which burn one after another, producing minor blast or projection effects or both;

(ç) Division 1.4 Substances, mixtures and articles which present no significant hazard:

– substances, mixtures and articles which present only a small hazard in the event of ignition or initiation. The effects are largely confined to the package and no projection of fragments of appreciable size or range is to be expected. An external fire shall not cause virtually instantaneous explosion of almost the entire contents of the package;

(d) Division 1.5 Very insensitive substances or mixtures which have a mass explosion hazard:

– substances and mixtures which have a mass explosion hazard but are so insensitive that there is very little probability of initiation or of transition from burning to detonation under normal conditions;

(e) Division 1.6 Extremely insensitive articles which do not have a mass explosion hazard:

– articles which contain only extremely insensitive detonating substances or mixtures and which demonstrate a negligible probability of accidental initiation or propagation.

2.1.2.3. Explosives, which are not classified as an unstable explosive, shall be classified in one of the six divisions referred to in paragraph 2.1.2.2 of this Annex based on Test Series 2 to 8 in Part I of the UN RTDG, Manual of Tests and Criteria according to the results of the tests laid down in Table 2.1.1:

Table 2.1.1

Criteria for explosives

Category	Criteria
Unstable explosives or explosives of Divisions 1.1 to 1.6	For explosives of Divisions 1.1 to 1.6, the following are the core set of tests that need to be performed: Explosibility: according to UN Test Series 2 (section 12 of the UN RTDG, Manual of Tests and Criteria). Intentional explosives[1] shall not be subject to UN Test Series 2. Sensitiveness: according to UN Test Series 3 (section 13 of the UN RTDG, Manual of Tests and Criteria). Thermal stability: according to UN Test 3(c) (sub-section 13.6.1 of the UN RTDG, Manual of Tests and Criteria). Further tests are necessary to allocate the correct Division.

[1] This comprises substances, mixtures and articles which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.

2.1.2.4. If explosives are unpackaged or repacked in packaging other than the original or similar packaging, they shall be retested.

2.1.3. Hazard Communication

Label elements shall be used for substances, mixtures or articles meeting the criteria for classification in this hazard class in accordance with Table 2.1.2.

NOTE to Table 2.1.2: Unpackaged explosives or explosives repacked in packaging other than the original or similar packaging shall include all of the following label elements:

(a) the pictogram: exploding bomb;

(b) the signal word: "Danger"; and

(c) the hazard statement: "explosive; mass explosion hazard"

unless the hazard is shown to correspond to one of the hazard categories in Table 2.1.2, in which case the corresponding symbol, the signal word and/or the hazard statement shall be assigned.

Table 2.1.2: Label elements for explosives

Classification	Unstable Explosive	Division 1.1	Division 1.2	Division 1.3	Division 1.4	Division 1.5	Division 1.6
GHS Pictograms							
Signal Word	Danger	Danger	Danger	Danger	Warning	Danger	No signal word
Hazard Statement	H200: Unstable Explosive	H201: Explosive; mass explosion hazard	H202: Explosive; severe projection hazard	H203: Explosive; fire, blast or projection hazard	H204: Fire or projection hazard	H205: May mass explode in fire	No hazard statement
Precautionary Statement Prevention	P201 P202 P281	P210 P230 P240 P250 P280	P210 P230 P240 P250 P280	P210 P230 P240 P250 P280	P210 P240 P250 P280	P210 P230 P240 P250 P280	No precautionary statement
Precautionary Statement Response	P372 P373 P380	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	No precautionary statement
Precautionary Statement Storage	P401	P401	P401	P401	P401	P401	No precautionary statement
Precautionary Statement Disposal	P501	P501	P501	P501	P501	P501	No precautionary statement

2.1.4. Additional Classification Considerations

2.1.4.1. The classification of substances, mixtures and articles in the explosives hazard class and further allocation to a division is a very complex, three step procedure. Reference to Part I of the UN RTDG, Manual of Tests and Criteria is necessary.

The first step is to ascertain whether the substance or mixture has explosive effects (Test Series 1). The second step is the acceptance procedure (Test Series 2 to 4) and the third step is the assignment to a hazard division (Test Series 5 to 7). The assessment whether a candidate for "ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE)" is insensitive enough for inclusion as an oxidising liquid or an oxidising solid is answered by Test Series 8 tests.

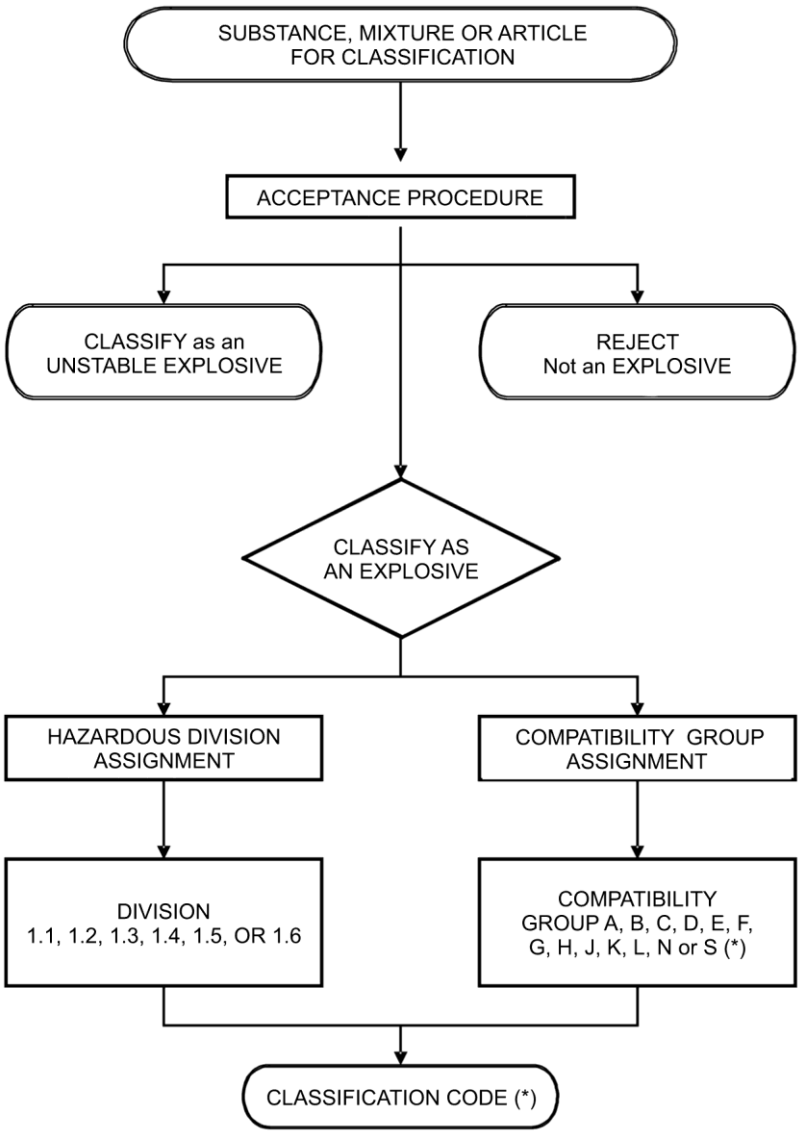
Explosive substances and mixtures wetted with water or alcohols, or diluted with other substances to suppress their explosive properties, may be treated differently in terms of classification and other hazard classes may apply, according to their physical properties (see also Annex 2 section 1.1.).

Certain physical hazards (due to explosive properties) are altered by dilution, as is the case for desensitised explosives, by inclusion in a mixture or article, packaging or other factors.

The classification procedure is set out in the following decision logic (see Figures 2.1.1 to 2.1.4).

Figure 2.1.1

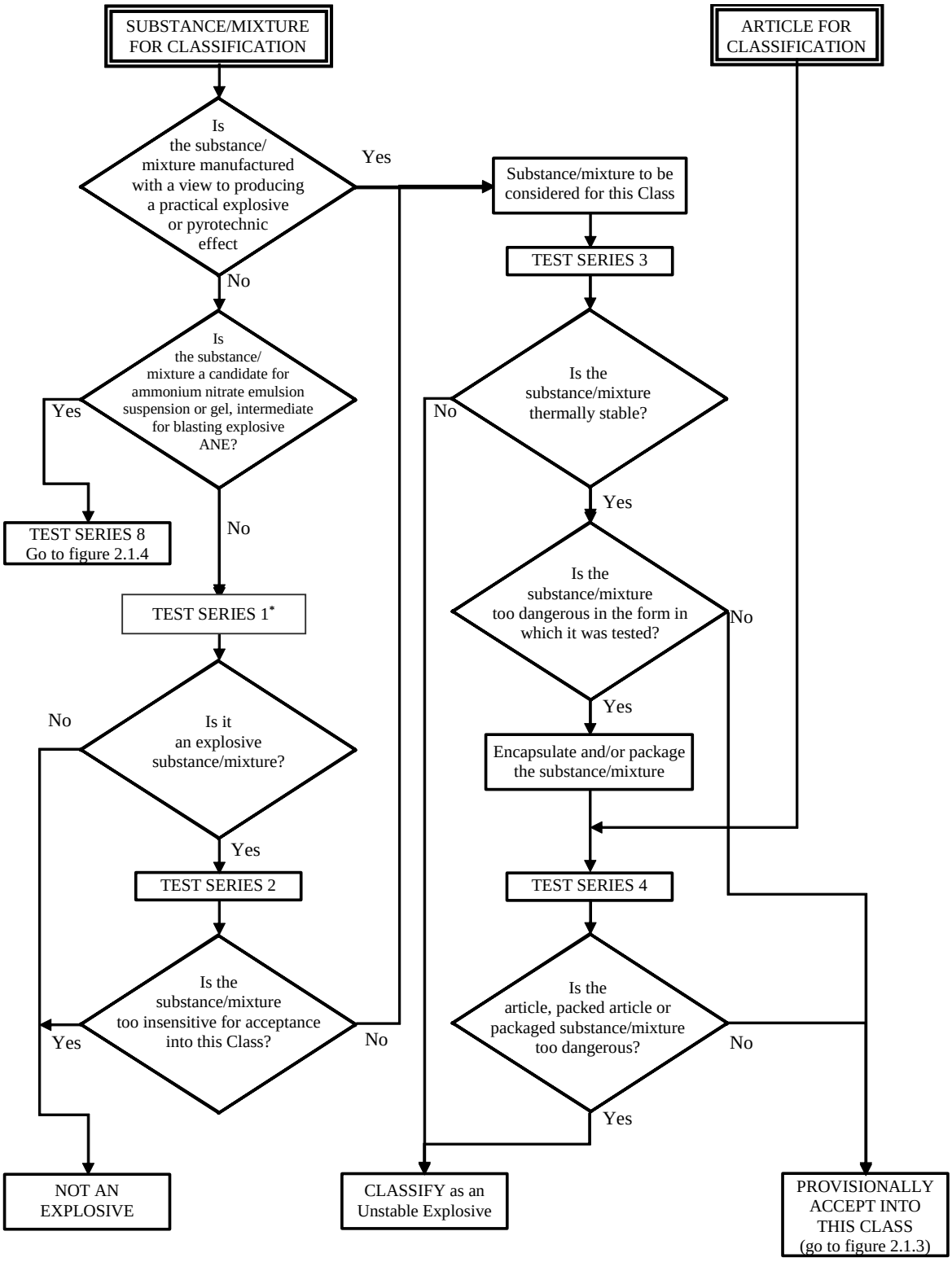
Overall scheme of the procedure for classifying a substance, mixture or article in the class of explosives (Class 1 for transport)



(*) see UN Recommendations on the Transport of Dangerous Goods, Model Regulations, 15th rev. ed, sub-section 2.1.2.

Figure 2.1.2

Procedure for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1 for transport)



For classification purposes, start with Test Series 2.

Figure 2.1.3

Procedure for assignment to a division in the class of explosives (Class 1 for transport)

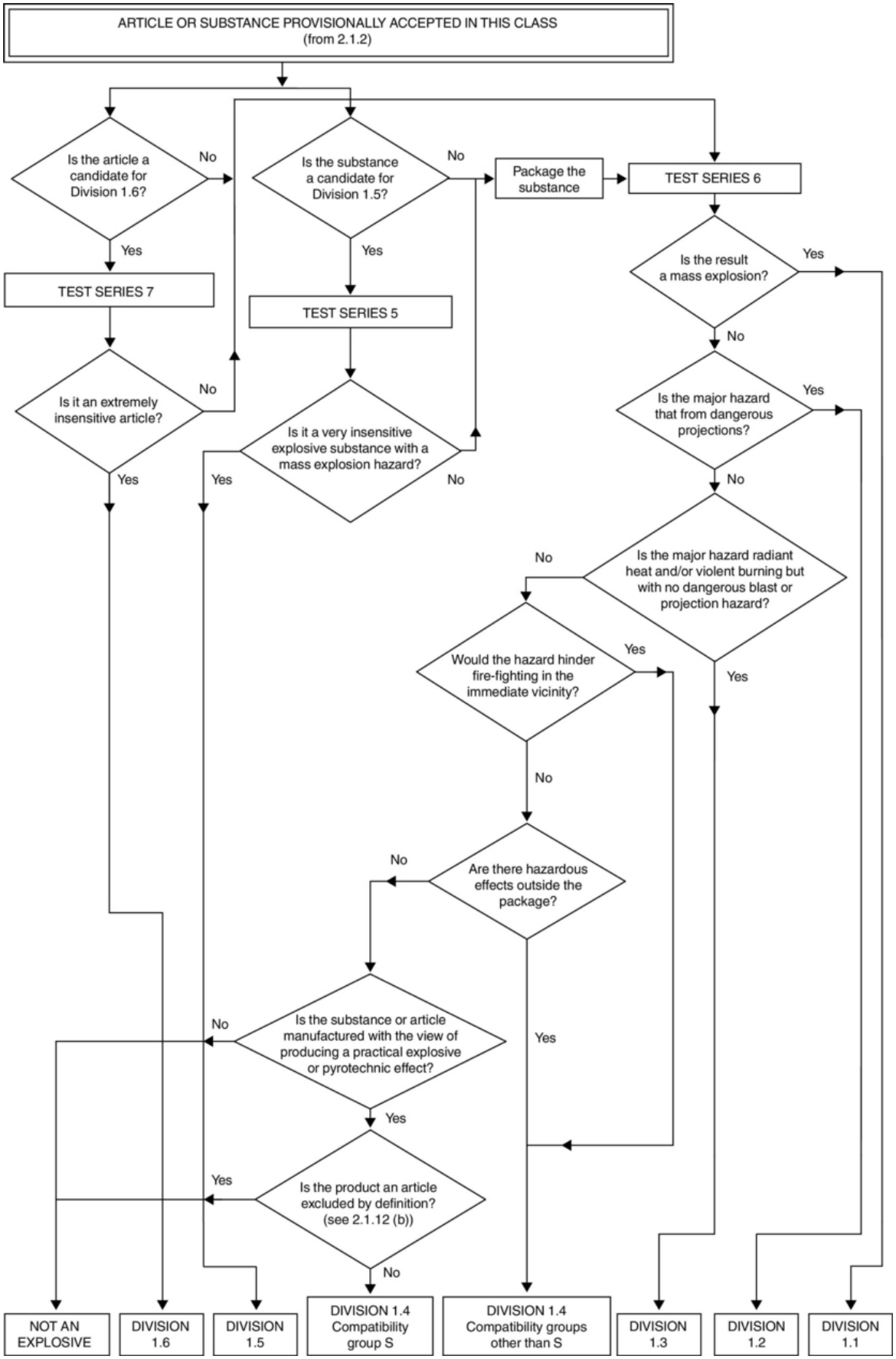
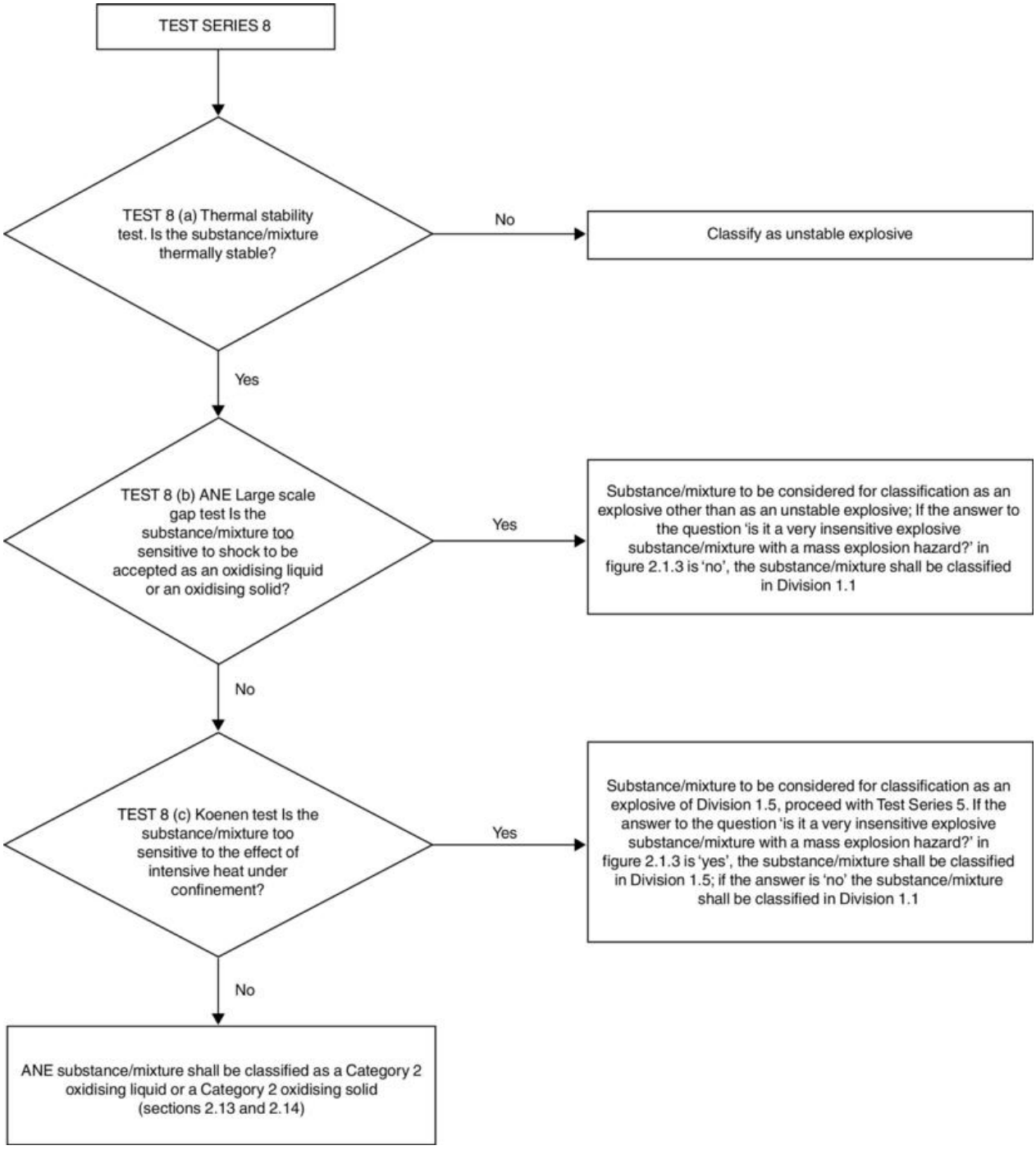


Figure 2.1.4

Procedure for classification of ammonium nitrate emulsions, suspensions or gel (ANE)



2.1.4.2. Screening procedure

Explosive properties are associated with the presence of certain chemical groups in a molecule which can react to produce very rapid increases in temperature or pressure. The screening procedure is aimed at identifying the presence of such reactive groups and the potential for rapid energy release. If the screening procedure identifies the substance or mixture to be a potential explosive, the acceptance procedure (see section 10.3 of the UN RTDG, Manual of Tests and Criteria) has to be performed.

Note:

Neither a Series 1 type (a) propagation of detonation test nor a Series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g. For organicsubstances and mixtures of organic substances with a decomposition energy of 800 J/g or more, tests 1 (a)and 2 (a) need not be performed if the outcome of the ballistic mortar Mk.IIId test (F.1), or the ballistic mortar test(F.2) or the BAM Trauzl test (F.3) with initiation by a standard No 8 detonator (see Appendix 1 to the UN RTDG,Manual of Tests and Criteria) is “no”. In this case, the results of test 1 (a) and 2 (a) are deemed to be “-”.

2.1.4.3. A substance or mixture shall not be classified as explosive if:

(a) There are no chemical groups associated with explosive properties present in the molecule. Examples of groups which may indicate explosive properties are given in Table A6.1 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria; or

(b) The substance contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200;

The oxygen balance is calculated for the chemical reaction:

$$C_xH_yO_z + [x + (y/4) - (z/2)]\ O_2 \rightarrow x\ CO_2 + (y/2)\ H_2O$$

Using the formula:

Oxygen balance = $-1600\ [2x + (y/2) - z]$/molecular weight;

(c) When the organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500°C. The exothermic decomposition energy can be determined using a suitable calorimetric technique; or,

(ç) For mixtures of inorganic oxidising substances with organic material(s), the concentration of the inorganic oxidising substance is:

– less than 15 % by mass, if the oxidising substance is assigned to Categories 1 or 2;

– less than 30 % by mass, if the oxidising substance is assigned to Category 3.

2.1.4.4. In the case of mixtures containing any known explosives, the acceptance procedure has to be performed.

2.2. FLAMMABLE GASES

2.2.1. Definition

Flammable gas means a gas or gas mixture having a flammable range with air at 20°C and a standard pressure of 101,3 kPa.

2.2.2. Classification criteria

2.2.2.1. A flammable gas shall be classified in this class in accordance with Table 2.2.1:

Table 2.2.1

Criteria for flammable gases

Category	Criteria
1	Gases, which at 20°C and a standard pressure of 101,3 kPa: (a) are ignitable when in a mixture of 13 % or less by volume in air; or (b) have a flammable range with air of at least 12 percentage points regardless of the lower flammable limit.
2	Gases, other than those of Category 1, which, at 20°C and a standard pressure of 101,3 kPa, have a flammable range while mixed in air.

Note:

Aerosols shall not be classified as flammable gases; see section 2.3.

2.2.3. Hazard Communication

Label elements shall be used for substances and mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.2.2.

Table 2.2.2

Label elements for flammable gases

Classification	Category 1	Category 2
GHS Pictogram		No pictogram
Signal Word	Danger	Warning
Hazard Statement	H220: Extremely flammable gas	H221: Flammable gas
Precautionary Statement Prevention	P210	P210
Precautionary Statement Response	P377 P381	P377 P381
Precautionary Statement Storage	P403	P403
Precautionary Statement Disposal		

2.2.4. Additional Classification Considerations

2.2.4.1. Flammability shall be determined by tests or, for mixtures where there are sufficient data available, by calculation in accordance with the methods adopted by ISO (see ISO 10156 as amended, Gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valve outlet). Where insufficient data are available to use these methods, test method EN 1839 as amended (Determination of explosion limits of gases and vapours) can be used.

2.3. FLAMMABLE AEROSOLS

2.3.1. Definitions

Aerosols, this means aerosol dispensers, are any non-refillable receptacles made of metal, glass or plastics and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state or in a gaseous state.

2.3.2. Classification criteria

2.3.2.1. Aerosols shall be considered for classification as flammable in accordance with 2.3.2.2 if they contain any component which is classified as flammable according to the criteria contained in this Part, i.e.:

– Liquids with a flash point ≤ 93°C, which includes Flammable Liquids according to section 2.6;

– Flammable gases (see 2.2);

– Flammable solids (see 2.7).

Note 1:
Flammable components do not cover pyrophoric, self-heating or water-reactive substances and mixtures because such components are never used as aerosol contents.

Note 2:
Flammable aerosols do not fall additionally within the scope of sections 2.2 (flammable gases), 2.6 (flammable liquids) or 2.7 (flammable solids).

2.3.2.2. A flammable aerosol shall be classified in one of the two categories for this Class on the basis of its components, of its chemical heat of combustion and, if applicable, of the results

of the foam test (for foam aerosols) and of the ignition distance test and enclosed space test (for spray aerosols) in accordance with Figure 2.3.1 and the UN RTDG, Manual of Tests and Criteria, Part III, sub-sections 31.4, 31.5 and 31.6.

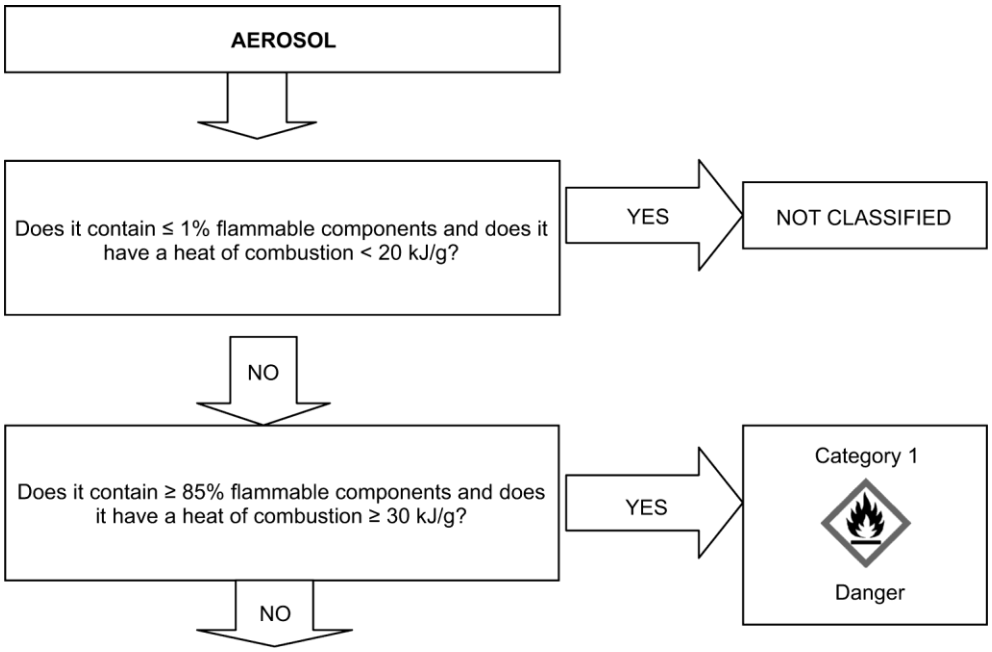
Note:

Aerosols not submitted to the flammability classification procedures in this section shall be classified as flammable aerosols, Category 1.

Figure 2.3.1

for flammable aerosols

Figure 2.3.1(a) for flammable aerosols



For spray aerosols, go to decision logic 2.3.1 (b);

For foam aerosols, got to decision logic 2.3.1 (c).

Figure 2.3.1(b) for spray aerosols

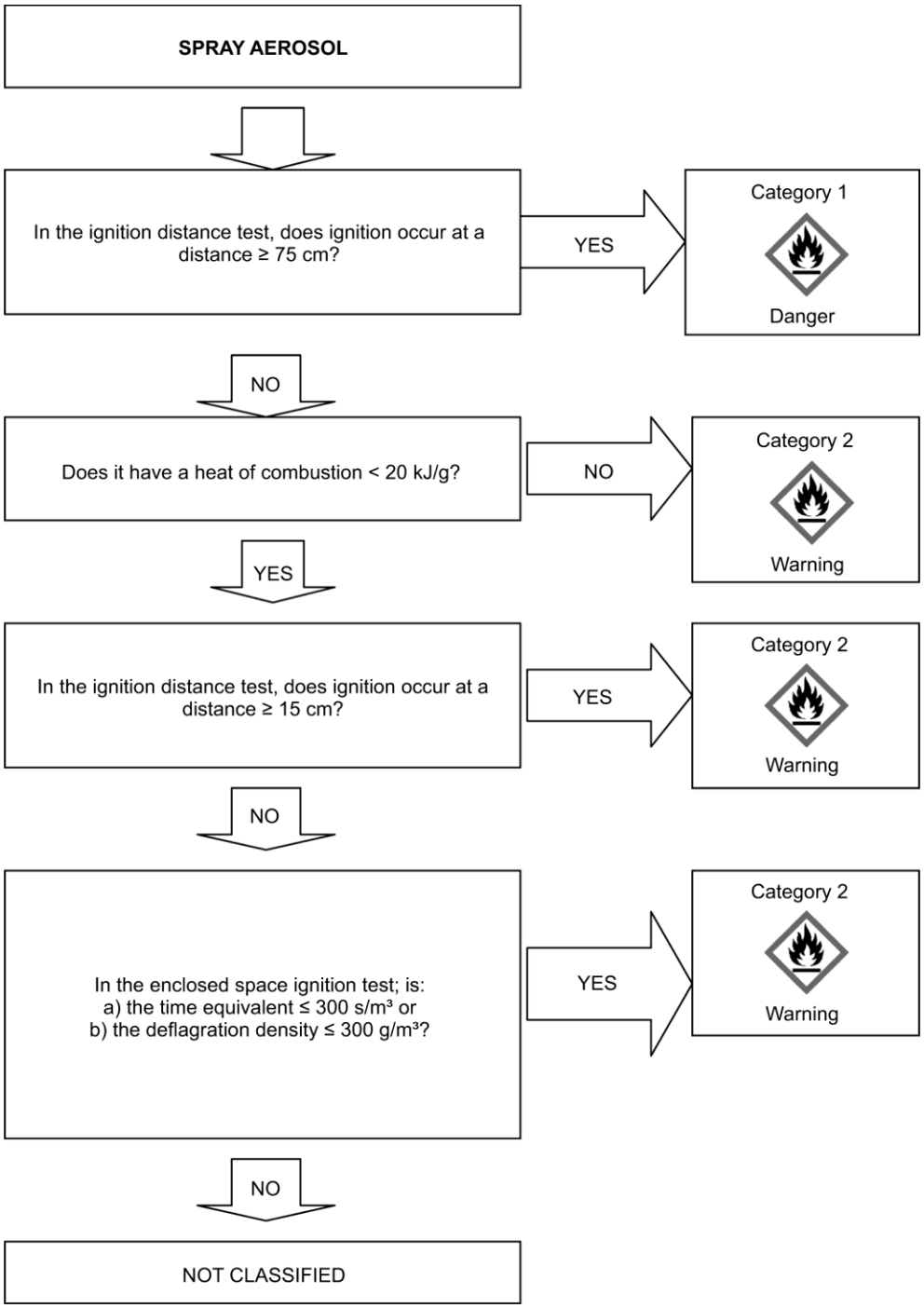
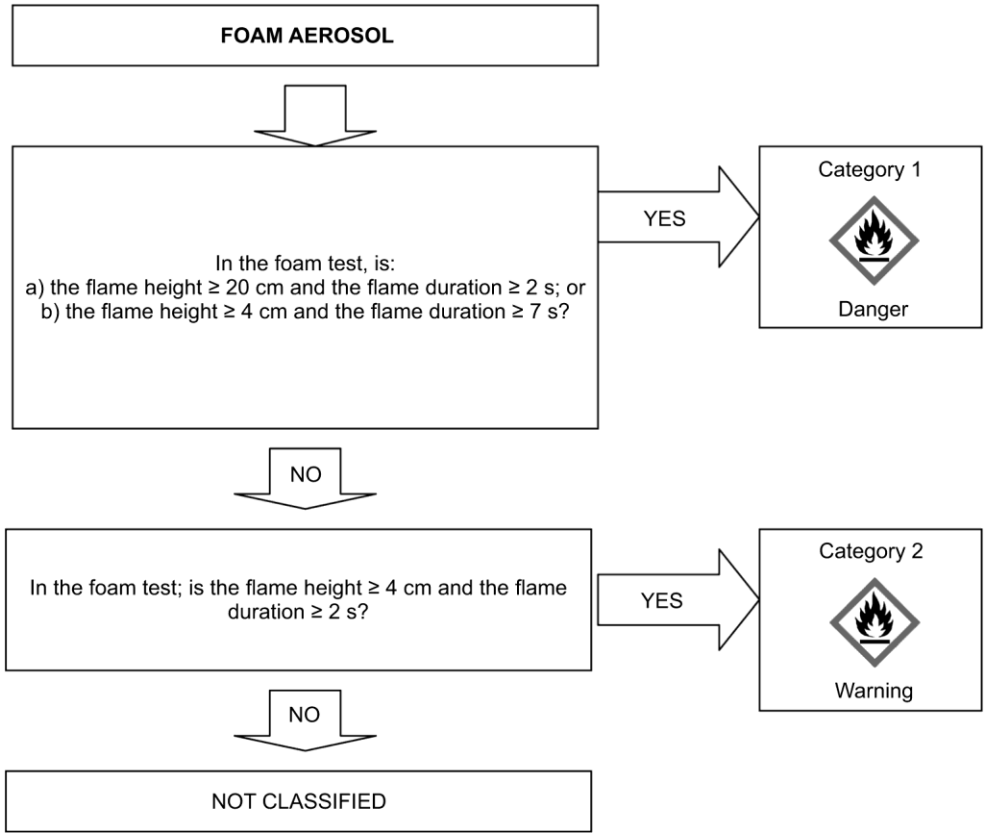


Figure 2.3.1(c) for foam aerosols



2.3.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.3.2.

Table 2.3.2

Label elements for flammable aerosols

Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H222: Extremely flammable aerosol	H223: Flammable aerosol
Precautionary Statement Prevention	P210 P211 P251	P210 P211 P251
Precautionary Statement Response		
Precautionary Statement Storage	P410 + P412	P410 + P412
Precautionary Statement Disposal		

2.3.4. Additional Classification Considerations

2.3.4.1. The chemical heat of combustion (ΔH_c), in kilojoules per gram (kJ/g), is the product of the theoretical heat of combustion (ΔH_{comb}), and a combustion efficiency, usually less than 1,0 (a typical combustion efficiency is 0,95 or 95 %).

For a composite aerosol formulation, the chemical heat of combustion is the summation of the weighted heats of combustion for the individual components, as follows:

$$\Delta H_{c\ (product)} = \sum_{i}^{n} \left[w_i\ \% \times \Delta H_{c(i)} \right]$$

where:

ΔH_c = chemical heat of combustion (kJ/g);

w_i % = mass fraction of component i in the product;

$\Delta H_{c(i)}$ = specific heat of combustion (kJ/g)of component i in the product.

The chemical heats of combustion can be found in the literature, calculated or determined by tests (see ASTM D 240 as amended – Standard Test Methods for Heat of Combustion of Liquid Hydrocarbon Fuels by Bomb Calorimeter, EN/ISO 13943 as amended, 86.l to 86.3 – Fire safety – Vocabulary, and NFPA 30B as amended – Code for the Manufacture and Storage of Aerosol Products).

2.4. OXIDISING GASES

2.4.1. Definitions

Oxidising gas means any gas or gas mixture which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

2.4.2. Classification criteria

2.4.2.1. An oxidising gas shall be classified in a single category for this class in accordance with Table 2.4.1.:

Table 2.4.1

Criteria for oxidising gases

Category	Criteria
1	Any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

NOTE:

"Gases which cause or contribute to the combustion of other material more than air does" mean pure gases or gas mixtures with an oxidising power greater than 23,5 % as determined by a method specified in ISO 10156 as amended or 10156-2 as amended.

2.4.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.4.2.

Table 2.4.2

Label elements for oxidising gases

Classification	Category 1
GHS Pictogram	
Signal word	Danger
Hazard statement	H270: May cause or intensify fire; oxidiser
Precautionary statement prevention	P220 P244
Precautionary statement response	P370 + P376
Precautionary statement storage	P403
Precautionary statement disposal	

2.4.4. Additional Classification Considerations

To classify an oxidising gas, tests or calculation methods as described in ISO 10156 as amended, gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valve outlet and ISO 10156-2 as amended, gas cylinders – gases and gas mixtures – Determination of oxidising ability of toxic and corrosive gases and gas mixtures – shall be performed.

2.5. GASES UNDER PRESSURE

2.5.1. Definition

2.5.1.1. Gases under pressure are gases which are contained in a receptacle at a pressure of 200 kPa (gauge) or more, or which are liquefied or liquefied and refrigerated.

They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.

2.5.1.2. The critical temperature is the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression.

2.5.2. Classification criteria

Gases shall be classified, according to their physical state when packaged, in one of four groups in accordance with Table 2.5.1:

Table 2.5.1

Criteria for gases under pressure

Group	Criteria
Compressed gas	A gas which when packaged under pressure is entirely gaseous at -50°C; including all gases with a critical temperature ≤ -50°C.
Liquefied gas	A gas which, when packaged under pressure, is partially liquid at temperatures above -50°C. A distinction is made between: (i) high pressure liquefied gas: a gas with a critical temperature between -50°C and +65°C; and (ii) low pressure liquefied gas: a gas with a critical temperature above +65°C.
Refrigerated liquefied gas	A gas which when packaged is made partially liquid because of its low temperature.
Dissolved gas	A gas which when packaged under pressure is dissolved in a liquid phase solvent.

2.5.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.5.2.

Table 2.5.2

Label elements for gases under pressure

Classification	Compressed gas	Liquefied gas	Refrigerated liquefied gas	Dissolved gas
GHS Pictograms				
Signal Word	Warning	Warning	Warning	Warning
Hazard Statement	H280: Contains gas under pressure; may explode if heated	H280: Contains gas under pressure; may explode if heated	H281: Contains refrigerated gas; may cause cryogenic burns or injury	H280: Contains gas under pressure; may explode if heated
Precautionary Statement Prevention			P282	
Precautionary Statement Response			P336 P315	
Precautionary Statement Storage	P410 + P403	P410 + P403	P403	P410 + P403
Precautionary Statement Disposal				

Note:

Pictogram GHS04 is not required for gases under pressure where pictogram GHS02 or pictogram GHS06 appears.

2.5.4. Additional Classification Considerations

For this group of gases, the following information is required to be known:

– the vapour pressure at 50°C;

– the physical state at 20°C at standard ambient pressure;

– the critical temperature.

Data can be found in the literature, calculated or determined by testing. Most pure gases are already classified in the UN RTDG, Model Regulations.

2.6. FLAMMABLE LIQUIDS

2.6.1. Definition

Flammable liquid means a liquid having a flash point of not more than 60°C.

2.6.2. Classification criteria

2.6.2.1. A flammable liquid shall be classified in one of the three categories for this class in accordance with Table 2.6.1:

Table 2.6.1

Criteria for flammable liquids

Category	Criteria
1	Flash point < 23°C and initial boiling point ≤ 35°C
2	Flash point < 23°C and initial boiling point > 35°C
3	Flash point ≥ 23°C and ≤ 60°C[1]

[1] For the purpose of this By-Law gas oils, diesel and light heating oils having a flash point between ≥ 55°C and ≤ 75°C may be regarded as Category 3.

Note: Aerosols shall not be classified as flammable liquids; see section 2.3.

2.6.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.6.2.

Table 2.6.2

Label elements for flammable liquids

Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal Word	Danger	Danger	Warning
Hazard Statement	H224: Extremely flammable liquid and vapour	H225: Highly flammable liquid and vapour	H226: Flammable liquid and vapour
Precautionary Statement Prevention	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280
Precautionary Statement Response	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378
Precautionary Statement Storage	P403 + P235	P403 + P235	P403 + P235
Precautionary Statement Disposal	P501	P501	P501

2.6.4. Additional Classification Considerations

2.6.4.1. For the classification of flammable liquids data on flash point and initial boiling point are needed. Data can be determined by testing, found in literature or calculated. If data are not available, the flash point and the initial boiling point shall be determined through testing. For flash point determination a closed-cup method shall be used.

2.6.4.2. In the case of mixtures[1] containing known flammable liquids in defined concentrations, although they may contain non-volatile components e.g. polymers, additives, the flash point need not be determined experimentally if the calculated flash point of the mixture, using the method given in 2.6.4.3, is at least 5°C[2] greater than the relevant classification criterion and provided that:

(a) the composition of the mixture is accurately known (if the material has a specified range of composition, the composition with the lowest calculated flash point shall be selected for assessment);

(b) the lower explosion limit of each component of the mixture is known (an appropriate correlation has to be applied when these data are extrapolated to other temperatures than test conditions) as well as a method for calculating the lower explosion limit;

(c) the temperature dependence of the saturated vapour pressure and of the activity coefficient is known for each component as present in the mixture;

(ç) the liquid phase is homogeneous.

2.6.4.3. One suitable method is described in Gmehling and Rasmussen (Ind. Eng. Fundament, 21, 186, (1982)). For a mixture containing non-volatile components the flash point is calculated from the volatile components. It is considered that a non-volatile component only slightly decreases the partial pressure of the solvents and the calculated flash point is only slightly below the measured value.

2.6.4.4. Possible test methods for determining the flash point of flammable liquids are listed in Table 2.6.3.

Table 2.6.3

Methods for determining the flash point of flammable liquids

European standards:	EN ISO 1516 as amended Determination of flash/no flash – Closed cup equilibrium method

[1] To date, the calculation method has been validated for mixtures containing up to 6 volatile components. These components may be flammable liquids like hydrocarbons, ethers, alcohols, esters (except acrylates), and water. It is however not yet validated for mixtures containing halogenated sulphurous, and/or phosphoric compounds as well as reactive acrylates.

[2] If the calculated flash point is less than 5°C greater than the relevant classification criterion, the calculation method may not be used and the flash point should be determined experimentally.

	EN ISO 1523 as amended Determination of flash point – Closed cup equilibrium method
	EN ISO 2719 as amended Determination of flash point – Pensky-Martens closed cup method
	EN ISO 3679 as amended Determination of flash point – Rapid equilibrium closed cup method
	EN ISO 3680 as amended Determination of flash/no flash – Rapid equilibrium closed cup method
	EN ISO 13736 as amended Petroleum products and other liquids – Determination of flash point – Abel closed cup method
National standards:	
Association française de normalisation, AFNOR:	NF M07-036 as amended Détermination du point d'éclair – Vase clos Abel-Pensky (identical to DIN 51755)
British Standards Institution	BS 2000 Standard Part 170 as amended (similar to EN ISO 13736)
Deutsches Institut für Normung	DIN 51755 (flash points below 65 C) as amended Prüfung von Mineralölen und anderen brennbaren Flüssigkeiten; Bestimmung des Flammpunktes im geschlossenen Tiegel, nach Abel-Pensky (identical to NF M07-036)

2.6.4.5. Liquids with a flash point of more than 35°C and not more than 60°C need not be classified in Category 3 if negative results have been obtained in the sustained combustibility test L.2, Part III, section 32 of the UN RTDG, Manual of Tests and Criteria.

2.6.4.6 Possible test methods for determining the initial boiling point of flammable liquids are listed in Table 2.6.4.

Table 2.6.4

Methods for determining the initial boiling point of flammable liquids

European standards:	EN ISO 3405 as amended Petroleum products — Determination of distillation characteristics at atmospheric pressure
	EN ISO 3924 as amended Petroleum products — Determination of boiling range distribution— Gas chromatography method

	EN ISO 4626 as amended Volatile organic liquids — Determination of boiling range of organic solvents used as raw materials
By-Law on Test Methods	Method A.2 of the By-Law on Test Methods

2.7. FLAMMABLE SOLIDS

2.7.1. Definition

2.7.1.1. A flammable solid means a solid which is readily combustible, or may cause or contribute to fire through friction.

Readily combustible solids are powdered, granular, or pasty substances or mixtures which are dangerous if they can be easily ignited by brief contact with an ignition source, such as a burning match, and if the flame spreads rapidly.

2.7.2. Classification criteria

2.7.2.1. Powdered, granular or pasty substances or mixtures (except powders of metals or metal alloys – see 2.7.2.2) shall be classified as readily combustible solids when the time of burning of one or more of the test runs, performed in accordance with the test method described in Part III, sub-section 33.2.1, of the UN RTDG, Manual of Tests and Criteria, is less than 45 seconds or the rate of burning is more than 2,2 mm/s.

2.7.2.2. Powders of metals or metal alloys shall be classified as flammable solids when they can be ignited and the reaction spreads over the whole length of the sample in 10 minutes or less.

2.7.2.3. A flammable solid shall be classified in one of the two categories for this class using Method N.1 as described in 33.2.1 of the UN RTDG, Manual of Tests and Criteria in accordance with Table 2.7.1:

Table 2.7.1

Criteria for flammable solids

Category	Criteria
1	Burning rate test Substances and mixtures other than metal powders: (a) wetted zone does not stop fire and (b) burning time < 45 seconds or burning rate > 2,2 mm/s Metal powders burning time ≤ 5 minutes

2	Burning rate test Substances and mixtures other than metal powders: (a) wetted zone stops the fire for at least 4 minutes and (b) burning time < 45 seconds or burning rate > 2,2 mm/s Metal powders burning time > 5 minutes and ≤ 10 minutes

Note 1:

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

Note 2:

Aerosols shall not be classified as flammable solids; see section 2.3.

2.7.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.7.2.

Table 2.7.2

Label elements for flammable solids

Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H228: Flammable Solid	H228: Flammable Solid
Precautionary Statement Prevention	P210 P240 P241 P280	P210 P240 P241 P280
Precautionary Statement Response	P370 + P378	P370 + P378
Precautionary Statement Storage		

Precautionary Statement Disposal		

2.8. SELF-REACTIVE SUBSTANCES AND MIXTURES

2.8.1. Definition

2.8.1.1. Self-reactive substances or mixtures are thermally unstable liquid or solid substances or mixtures liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). This definition excludes substances and mixtures classified according to this Part as explosives, organic peroxides or as oxidising.

2.8.1.2. A self-reactive substance or mixture is regarded as possessing explosive properties when in laboratory testing the formulation is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

2.8.2. Classification criteria

2.8.2.1. Any self-reactive substance or mixture shall be considered for classification in this class as a self-reactive substance or mixture unless:

(a) they are explosives, according to the criteria given in 2.1;

(b) they are oxidising liquids or solids, according to the criteria given in 2.13 or 2.14, except that mixtures of oxidising substances, which contain 5 % or more of combustible organic substances shall be classified as self-reactive substances according to the procedure defined in 2.8.2.2;

(c) they are organic peroxides, according to the criteria given in 2.15;

(ç) their heat of decomposition is less than 300 J/g; or

(d) their self-accelerating decomposition temperature (SADT) is greater than 75°C for a 50 kg package[1].

2.8.2.2. Mixtures of oxidising substances, meeting the criteria for classification as oxidising substances, which contain 5 % or more of combustible organic substances and which do not meet the criteria mentioned in (a), (c), (d) or (e) in 2.8.2.1, shall be subjected to the self-reactive substances classification procedure;

Such a mixture showing the properties of a self-reactive substance type B to F (see 2.8.2.3) shall be classified as a self-reactive substance.

---

[1] See UN RTDG, Manual of Tests and Criteria, sub-sections 28.1, 28.2, 28.3 and Table 28.3.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

2.8.2.3. Self-reactive substances and mixtures shall be classified in one of the seven categories of "types A to G" for this class, according to the following principles:

(a) any self-reactive substance or mixture which can detonate or deflagrate rapidly, as packaged, shall be defined as self-reactive substance TYPE A;

(b) any self-reactive substance or mixture possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package shall be defined as self-reactive substance TYPE B;

(c) any self-reactive substance or mixture possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion shall be defined as self-reactive substance TYPE C;

(ç) any self-reactive substance or mixture which in laboratory testing:

(i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or

(ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or

(iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

shall be defined as self-reactive substance TYPE D;

(d) any self-reactive substance or mixture which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement shall be defined as self-reactive substance TYPE E;

(e) any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power shall be defined **as** self-reactive substance TYPE F;

(f) any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable (SADT is 60°C to 75°C for a 50 kg package), and, for liquid mixtures, a diluent having a

boiling point not less than 150°C is used for desensitisation shall be defined as self-reactive substance TYPE G. If the mixture is not thermally stable or a diluent having a boiling point less than 150°C is used for desensitisation, the mixture shall be defined as self-reactive substance TYPE F.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

2.8.2.4. Criteria for temperature control

Self-reactive substances need to be subjected to temperature control if their SADT is less than or equal to 55°C. Test methods for determining the SADT as well as the derivation of control and emergency temperatures are given in, Part II, section 28 of the UN RTDG, Manual of Tests and Criteria. The test selected shall be conducted in a manner which is representative, both in size and material, of the package.

2.8.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.8.1.

Table 2.8.1

Label elements for self-reactive substances and mixtures

Classification	Type A	Type B	Type C & D	Type E & F	Type G
GHS Pictograms					There are no label elements allocated to this hazard category
Signal Word	Danger	Danger	Danger	Warning	
Hazard Statement	H240: Heating may cause an explosion	H241: Heating may cause a fire or explosion	H242: Heating may cause a fire	H242: Heating may cause a fire	
Precautionary Statement Prevention	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	

Precautionary Statement Response	P370 + P378 P370 + P380 + P375	P370 + P378 P370 + P380 + P375	P370 + P378	P370 + P378	
Precautionary Statement Storage	P403 + P235 P411 P420	P403 + P235 P411 P420	P403 + P235 P411 P420	P403 + P235 P411 P420	
Precautionary Statement Disposal	P501	P501	P501	P501	

Type G has no hazard communication elements assigned but shall be considered for properties belonging to other hazard classes.

2.8.4. Additional Classification Considerations

2.8.4.1. The properties of self-reactive substances or mixtures which are decisive for their classification shall be determined experimentally. The classification of a self reactive substance or mixture shall be performed in accordance with test series A to H as described in Part II of the UN RTDG, Manual of Tests and Criteria. The procedure for classification is described in Figure 2.8.1.

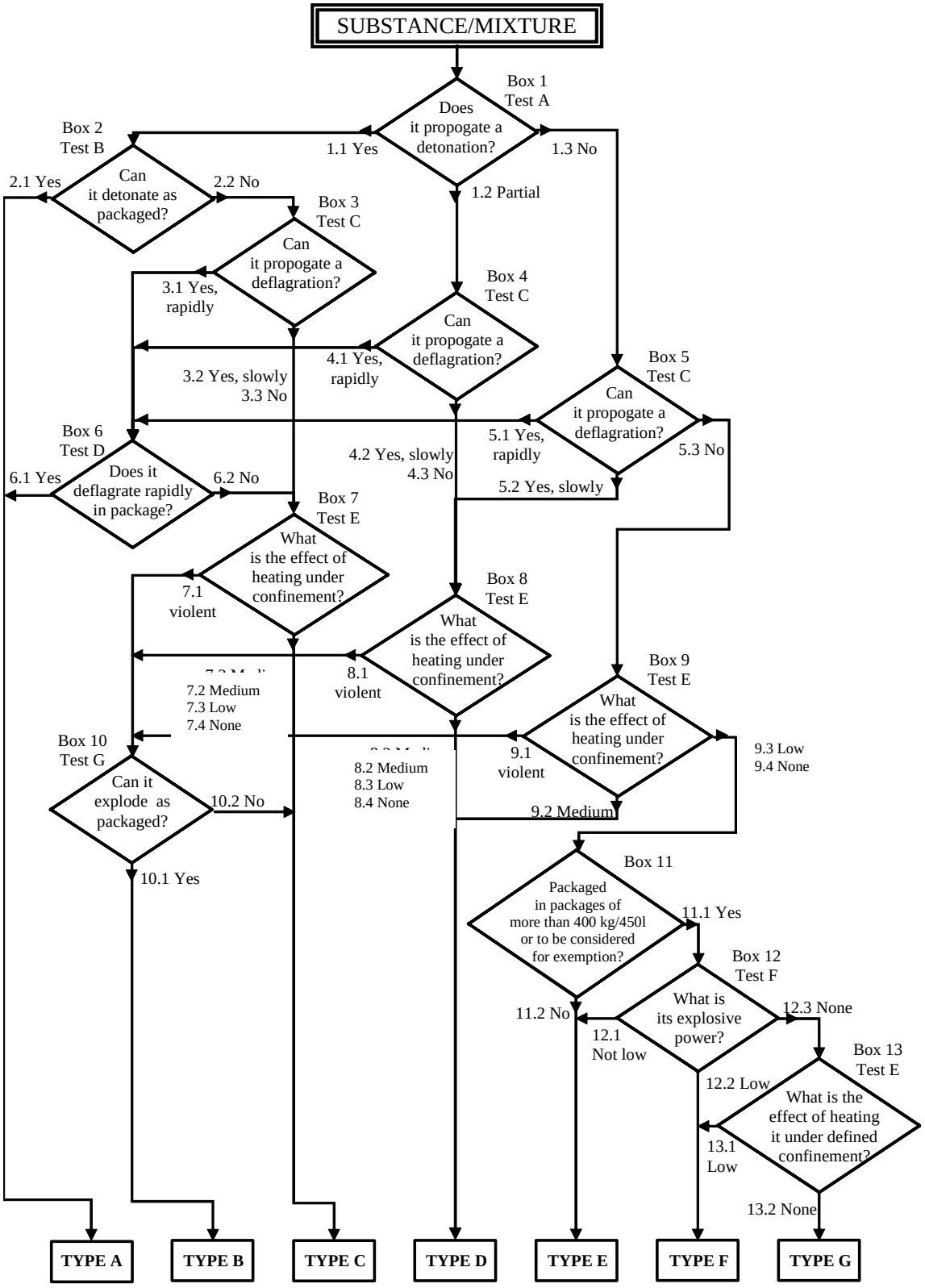
2.8.4.2. The classification procedures for self-reactive substances and mixtures need not be applied if:

(a) There are no chemical groups present in the molecule associated with explosive or self reactive properties. Examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria; or

(b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT for a 50 kg package is greater than 75°C or the exothermic decomposition energy is less than 300J/g. The onset temperature and decomposition energy can be estimated using a suitable calorimetric technique (see Part II, sub-section 20.3.3.3 of the UN RTDG, Manual of Tests and Criteria).

Figure 2.8.1

Self-reactive substances and mixtures



2.9. PYROPHORIC LIQUIDS

2.9.1. Definition

Pyrophoric liquid means a liquid substance or mixture which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

2.9.2. Classification criteria

2.9.2.1. A pyrophoric liquid shall be classified in a single category for this class using test N.3 in Part III, sub-section 33.3.1.5 of the UN RTDG, Manual of Tests and Criteria according to Table 2.9.1:

Table 2.9.1

Criteria for pyrophoric liquids

Category	Criteria
1	The liquid ignites within 5 min when added to an inert carrier and exposed to air, or it ignites or chars a filter paper on contact with air within 5 min.

2.9.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.9.2.

Table 2.9.2

Label elements for pyrophoric liquids

Classification	Category 1
GHS Pictogram	
Signal Word	Danger
Hazard Statement	H250: Catches fire spontaneously if exposed to air
Precautionary Statement Prevention	P210 P222 P280
Precautionary Statement Response	P302 + P334 P370 + P378

Precautionary Statement Storage	P422
Precautionary Statement Disposal	

2.9.4. Additional Classification Considerations

2.9.4.1. The classification procedure for pyrophoric liquids need not be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

2.10. PYROPHORIC SOLIDS

2.10.1. Definition

Pyrophoric solid means a solid substance or mixture which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

2.10.2. Classification criteria

2.10.2.1. A pyrophoric solid shall be classified in a single category for this class using test N.2 in Part III, sub-section 33.3.1.4 of the UN RTDG, Manual of Tests and Criteria in accordance with Table 2.10.1:

Table 2.10.1

Criteria for pyrophoric solids

Category	Criteria
1	The solid ignites within 5 minutes of coming into contact with air.

Note:

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.10.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.10.2.

Table 2.10.2

Label elements for pyrophoric solids

Classification	Category 1
GHS Pictogram	
Signal Word	Danger
Hazard Statement	H250: Catches fire spontaneously if exposed to air
Precautionary Statement Prevention	P210 P222 P280
Precautionary Statement Response	P335 + P334 P370 +P378
Precautionary Statement Storage	P422
Precautionary Statement Disposal	

2.10.4. Additional Classification Considerations

2.10.4.1. The classification procedure for pyrophoric solids need not be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

2.11. SELF-HEATING SUBSTANCES AND MIXTURES

2.11.1. Definition

2.11.1.1. A self-heating substance or mixture is a liquid or solid substance or mixture, other than a pyrophoric liquid or solid, which, by reaction with air and without energy supply, is liable to self-heat; this substance or mixture differs from a pyrophoric liquid or solid in that it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days).

2.11.1.2. Self-heating of a substance or a mixture is a process where the gradual reaction of that substance or mixture with oxygen (in the air) generates heat. If the rate of heat production exceeds the rate of heat loss, then the temperature of the substance or mixture will rise which, after an induction time, may lead to self-ignition and combustion.

2.11.2. Classification criteria

2.11.2.1. A substance or mixture shall be classified as a self-heating substance or mixture of this class, if in the tests performed in accordance with the test method given in the UN RTDG, Manual of Tests and Criteria, Part III, sub-section 33.3.1.6:

(a) a positive result is obtained using a 25 mm cube sample at 140°C;

(b) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 100 mm cube sample at 120°C and the substance or mixture is to be packed in packages with a volume of more than 3 m^3;

(c) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 100 mm cube sample at 100°C and the substance or mixture is to be packed in packages with a volume of more than 450 litres;

(d) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a positive result is obtained in a test using a 100 mm cube sample at 100°C.

2.11.2.2. A self-heating substance or mixture shall be classified in one of the two categories for this class if, in a test performed in accordance with test method N.4 in Part III, sub-section 33.3.1.6 of the UN RTDG, Manual of Tests and Criteria, the result meets the criteria according to Table 2.11.1:

Table 2.11.1

Criteria for self-heating substances and mixtures

Category	Criteria
1	A positive result is obtained in a test using a 25 mm sample cube at 140°C

2	(a)	a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C and the substance or mixture is to be packed in packages with a volume of more than 3 m^3; or
	(b)	a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C, a positive result is obtained in a test using a 100 mm cube sample at 120°C and the substance or mixture is to be packed in packages with a volume of more than 450 litres; or
	(c)	a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C and a positive result is obtained in a test using a 100 mm cube sample at 100°C.

Note:

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.11.2.3. Substances and mixtures with a temperature of spontaneous combustion higher than 50°C for a volume of 27 m³ shall not be classified as a self-heating substance or mixture.

2.11.2.4. Substances and mixtures with a spontaneous ignition temperature higher than 50°C for a volume of 450 litres shall not be assigned to Category 1 of this class.

2.11.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.11.2.

Table 2.11.2

Label elements for self-heating substances and mixtures

Classification	Category 1	Category 2

GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H251: Self-heating; may catch fire	H252: Self-heating in large quantities; may catch fire
Precautionary Statement Prevention	P235 + P410 P280	P235 + P410 P280
Precautionary Statement Response		
Precautionary Statement Storage	P407 P413 P420	P407 P413 P420
Precautionary Statement Disposal		

2.11.4. Additional Classification Considerations

2.11.4.1. For detailed schemes for the decision logic for classification and the tests to be carried out for ascertaining the different categories, see Figure 2.11.1.

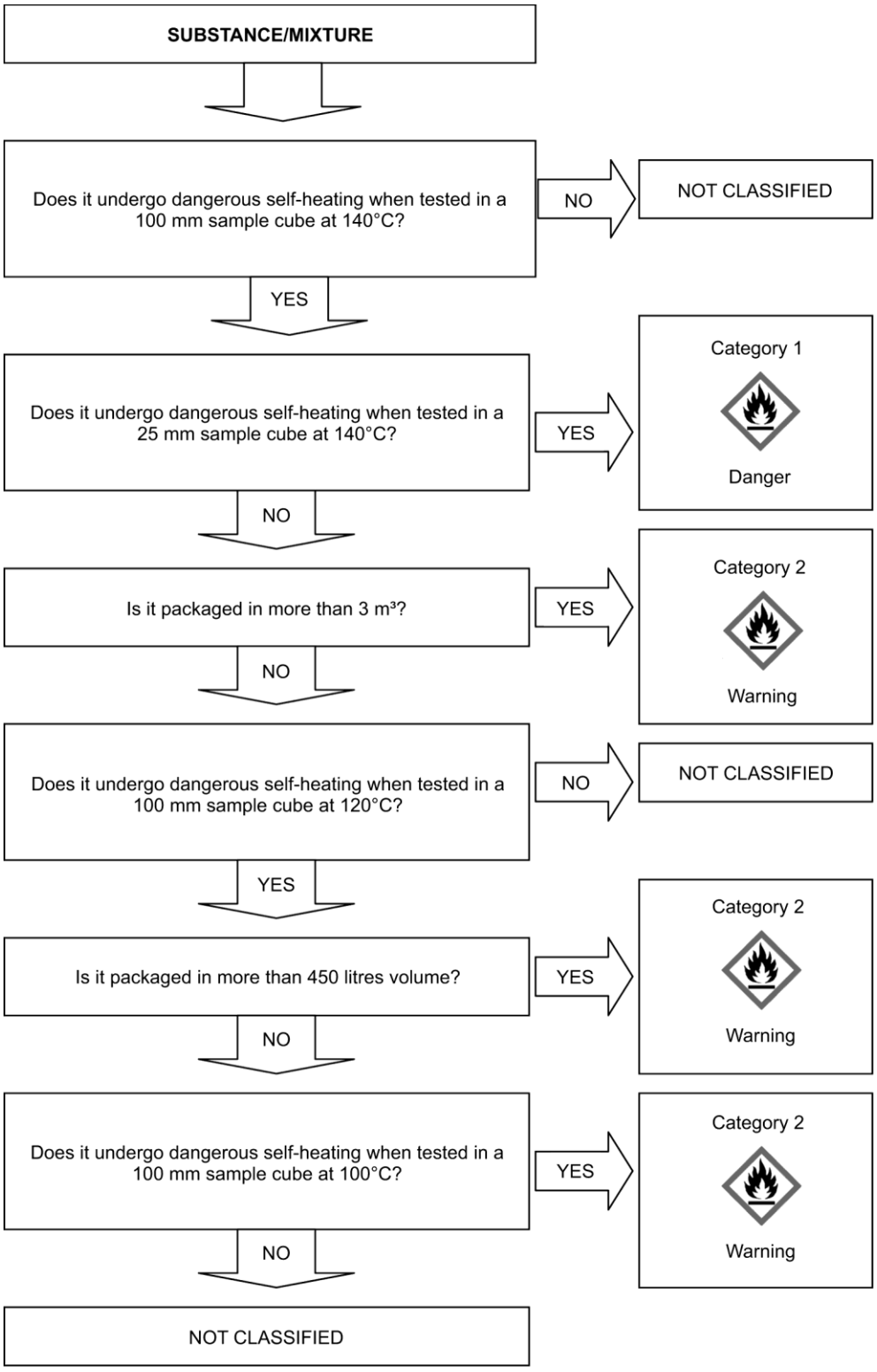
2.11.4.2. The classification procedure for self-heating substances or mixtures need not be applied if the results of a screening test can be adequately correlated with the classification test and an appropriate safety margin is applied. Examples of screening tests are:

(a) The Grewer Oven test (VDI guideline 2263, Part 1, 1990, Test methods for the Determination of the Safety Characteristics of Dusts) with an onset temperature 80 K above the reference temperature for a volume of 1 l;

(b) The Bulk Powder Screening Test (Gibson, N. Harper, D.J. Rogers, R.Evaluation of the fire and explosion risks in drying powders, Plant Operations Progress, 4 (3), 181-189, 1985) with an onset temperature 60 K above the reference temperature for a volume of 1 l.

Figure 2.11.1.

Self-heating substances and mixtures



2.12. SUBSTANCES AND MIXTURES WHICH IN CONTACT WITH WATER EMIT FLAMMABLE GASES

2.12.1. Definition

Substances or mixtures which, in contact with water, emit flammable gases means solid or liquid substances or mixtures which, by interaction with water, are liable to become spontaneously flammable or to give off flammable gases in dangerous quantities.

2.12.2. Classification criteria

2.12.2.1. A substance or mixture which, in contact with water, emits flammable gases shall be classified in one of the three categories for this class, using test N.5 in Part III, sub-section 33.4.1.4 of the UN RTDG, Manual of Tests and Criteria, in accordance with Table 2.12.1:

Table 2.12.1

Criteria for substances or mixtures which in contact with water emit flammable gases

Category	Criteria
1	Any substance or mixture which reacts vigorously with water at ambient temperatures and demonstrates generally a tendency for the gas produced to ignite spontaneously, or which reacts readily with water at ambient temperatures such that the rate of evolution of flammable gas is equal to or greater than 10 litres per kilogram of substance over any one minute.
2	Any substance or mixture which reacts readily with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 20 litres per kilogram of substance per hour, and which does not meet the criteria for Category 1.
3	Any substance or mixture which reacts slowly with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 1 litre per kilogram of substance per hour, and which does not meet the criteria for Categories 1 and 2.

Note:

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance must also be tested in the new form.

2.12.2.2. A substance or mixture shall be classified as a substance or mixture which in contact with water emits flammable gases if spontaneous ignition takes place in any step of the test procedure.

2.12.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.12.2.

Table 2.12.2

Label elements for substances or mixtures which in contact with water emit flammable gases

Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal Word	Danger	Danger	Warning
Hazard Statement	H260: In contact with water releases flammable gases which may ignite spontaneously	H261: In contact with water releases flammable gases	H261: In contact with water releases flammable gases
Precautionary Statement Prevention	P223 P231 + P232 P280	P223 P231 + P232 P280	P231 + P232 P280
Precautionary Statement Response	P335 + P334 P370 + P378	P335 + P334 P370 + P378	P370 + P378
Precautionary Statement Storage	P402 + P404	P402 + P404	P402 + P404
Precautionary Statement Disposal	P501	P501	P501

2.12.4. Additional Classification Considerations

2.12.4.1. The classification procedure for this class need not be applied if:

(a) the chemical structure of the substance or mixture does not contain metals or metalloids; or

(b) experience in production or handling shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water; or

(c) the substance or mixture is known to be soluble in water to form a stable mixture.

2.13. OXIDISING LIQUIDS

2.13.1. Definition

Oxidising liquid means a liquid substance or mixture which, while in itself not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material.

2.13.2. Classification criteria

2.13.2.1. An oxidising liquid shall be classified in one of the three categories for this class using test O.2 in Part III, sub-section 34.4.2 of the UN RTDG, Manual of Tests and Criteria in accordance with Table 2.13.1:

Table 2.13.1

Criteria for oxidising liquids

Category	Criteria
1	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, spontaneously ignites; or the mean pressure rise time of a 1:1 mixture, by mass, of substance (or mixture) and cellulose is less than that of a 1:1 mixture, by mass, of 50 % perchloric acid and cellulose.
2	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 40 % aqueous sodium chlorate solution and cellulose; and the criteria for Category 1 are not met.
3	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 65 % aqueous nitric acid and cellulose; and the criteria for Category 1 and 2 are not met.

2.13.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.13.2.

Table 2.13.2

Label elements for oxidising liquids

Classification	Category 1	Category 2	Category 3

GHS Pictograms			
Signal Word	Danger	Danger	Warning
Hazard Statement	H271:May cause fire or explosion; strong oxidiser	H272: May intensify fire; oxidiser	H272: May intensify fire; oxidiser
Precautionary Statement Prevention	P210 P220 P221 P280 P283	P210 P220 P221 P280	P210 P220 P221 P280
Precautionary Statement Response	P306 + P360 P371 + P380 + P375 P370 + P378	P370 + P378	P370 + P378
Precautionary Statement Storage			
Precautionary Statement Disposal	P501	P501	P501

2.13.4. Additional Classification Considerations

2.13.4.1. For organic substances or mixtures the classification procedure for this class shall not apply if:

(a) the substance or mixture does not contain oxygen, fluorine or chlorine; or

(b) the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

2.13.4.2. For inorganic substances or mixtures the classification procedure for this class shall not apply if they do not contain oxygen or halogen atoms.

2.13.4.3. In the event of divergence between test results and known experience in the handling and use of substances or mixtures which shows them to be oxidising, judgments based on known experience shall take precedence over test results.

2.13.4.4. In cases where substances or mixtures generate a pressure rise (too high or too low), caused by chemical reactions not characterising the oxidising properties of the substance or mixture, the test described in Part III, sub-section 34.4.2 of the UN RTDG, Manual of Tests and Criteria shall be repeated with an inert substance, e.g. diatomite (kieselguhr), in place of the cellulose in order to clarify the nature of the reaction and to check for a false positive result.

2.14. OXIDISING SOLIDS

2.14.1. Definition

Oxidising solid means a solid substance or mixture which, while in itself is not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material.

2.14.2. Classification criteria

2.14.2.1. An oxidising solid shall be classified in one of the three categories for this class using test O.1 in Part III, sub-section 34.4.1 of the UN RTDG, Manual of Tests and Criteria in accordance with Table 2.14.1:

Table 2.14.1

Criteria for oxidising solids

Category	Criteria
1	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time less than the mean burning time of a 3:2 mixture, by mass, of potassium bromate and cellulose.
2	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 2:3 mixture (by mass) of potassium bromate and cellulose and the criteria for Category 1 are not met.
3	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose and the criteria for Categories 1 and 2 are not met.

Note 1:

Some oxidising solids also present explosion hazards under certain conditions (when stored in large quantities). Some types of ammonium nitrate may give rise to an explosion hazard under extreme conditions and the "Resistance to detonation test" (BC Code, Annex 3, Test 5) can be used to assess this hazard. Appropriate information shall be made in the SDS.

Note 2:

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.14.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.14.2.

Table 2.14.2

Label elements for oxidising solids

	Category 1	Category 2	Category 3
GHS Pictograms			
Signal Word	Danger	Danger	Warning
Hazard Statement	H271: May cause fire or explosion; strong oxidiser	H272: May intensify fire; oxidiser	H272: May intensify fire; oxidiser
Precautionary Statement Prevention	P210 P220 P221 P280 P283	P210 P220 P221 P280	P210 P220 P221 P280
Precautionary Statement Response	P306 + P360 P371 + P380 + P375 P370 + P378	P370 + P378	P370 + P378
Precautionary Statement Storage			
Precautionary Statement Disposal	P501	P501	P501

2.14.4. Additional Classification Considerations

2.14.4.1. For organic substances or mixtures the classification procedure for this class shall not apply if:

(a) the substance or mixture does not contain oxygen, fluorine or chlorine; or

(b) the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

2.14.4.2. For inorganic substances or mixtures the classification procedure for this class shall not apply if they do not contain oxygen or halogen atoms.

2.14.4.3. In the event of divergence between test results and known experience in the handling and use of substances or mixtures which shows them to be oxidising, judgments based on known experience shall take precedence over test results.

2.15. ORGANIC PEROXIDES

2.15.1. Definition

2.15.1.1. Organic peroxides means liquid or solid organic substances which contain the bivalent -O-O- structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals. The term organic peroxide includes organic peroxide mixtures (formulations) containing at least one organic peroxide. Organic peroxides are thermally unstable substances or mixtures, which can undergo exothermic self-accelerating decomposition. In addition, they can have one or more of the following properties:

(i) be liable to explosive decomposition;

(ii) burn rapidly;

(iii) be sensitive to impact or friction;

(iv) react dangerously with other substances.

2.15.1.2. An organic peroxide is regarded as possessing explosive properties when in laboratory testing the mixture (formulation) is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

2.15.2. Classification criteria

2.15.2.1. Any organic peroxide shall be considered for classification in this class, unless it contains:

(a) not more than 1,0 % available oxygen from the organic peroxides when containing not more than 1,0 % hydrogen peroxide; or

(b) not more than 0,5 % available oxygen from the organic peroxides when containing more than 1,0 % but not more than 7,0 % hydrogen peroxide.

NOTE:

The available oxygen content (%) of an organic peroxide mixture is given by the formula:

$$16 \times \sum_{i}^{n} \left(\frac{n_i \times c_i}{m_i} \right)$$

where:

n_i = number of peroxygen groups per molecule of organic peroxide i;

c_i = concentration (mass %) of organic peroxide i;

m_i = molecular mass of organic peroxide i.

2.15.2.2. Organic peroxides shall be classified in one of the seven categories of "Types A to G" for this class, according to the following principles:

(a) any organic peroxide which, as packaged, can detonate or deflagrate rapidly shall be defined as organic peroxide TYPE A;

(b) any organic peroxide possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package shall be defined as organic peroxide TYPE B;

(c) any organic peroxide possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion shall be defined as organic peroxide TYPE C;

(ç) any organic peroxide which in laboratory testing:

(i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or

(ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or

(iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

shall be defined as organic peroxide TYPE D;

(d) any organic peroxide which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement shall be defined as organic peroxide TYPE E;

(e) any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power shall be defined as organic peroxide TYPE F;

(f) any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable, i.e. the SADT is 60°C or

higher for a 50 kg package[1], and, for liquid mixtures, a diluent having a boiling point of not less than 150°C is used for desensitisation, shall be defined as organic peroxide TYPE G. If the organic peroxide is not thermally stable or a diluent having a boiling point less than 150°C is used for desensitisation, the organic peroxide shall be defined as organic peroxide TYPE F.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

2.15.2.3. Criteria for temperature control

The following organic peroxides need to be subjected to temperature control:

(a) Organic peroxide types B and C with an SADT ≤ 50 C;

(b) Organic peroxide type D showing a medium effect when heated under confinement[2] with an SADT ≤ 50°C or showing a low or no effect when heated under confinement with an SADT ≤ 45°C; and

(c) Organic peroxide types E and F with an SADT ≤ 45°C.

Test methods for determining the SADT as well as the derivation of control and emergency temperatures are given in the UN RTDG, Manual of Tests and Criteria, Part II, section 28. The test selected shall be conducted in a manner which is representative, both in size and material, of the package.

2.15.3. Hazard Communication

Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.15.1.

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1 See UN RTDG, Manual of Tests and Criteria, sub-sections 28.1, 28.2, 28.3 and Table 28.3.

2 As determined by test series E as prescribed in UN RTDG, Manual of Tests and Criteria, Part II.

Table 2.15.1

Label elements for organic peroxides

Classification	Type A	Type B	Type C & D	Type E & F	Type G
GHS Pictograms					There are no label elements allocated to this hazard category
Signal Word	Danger	Danger	Danger	Warning	
Hazard Statement	H240: Heating may cause an explosion	H241: Heating may cause a fire or explosion	H242: Heating may cause a fire	H242: Heating may cause a fire	
Precautionary Statement Prevention	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	
Precautionary Statement Response					
Precautionary Statement Storage	P411 + P235 P410 P420	P411 + P235 P410 P420	P411 + P235 P410 P420	P411 + P235 P410 P420	
Precautionary Statement Disposal	P501	P501	P501	P501	

Type G has no hazard communication elements assigned but shall be considered for properties belonging to other hazard classes.

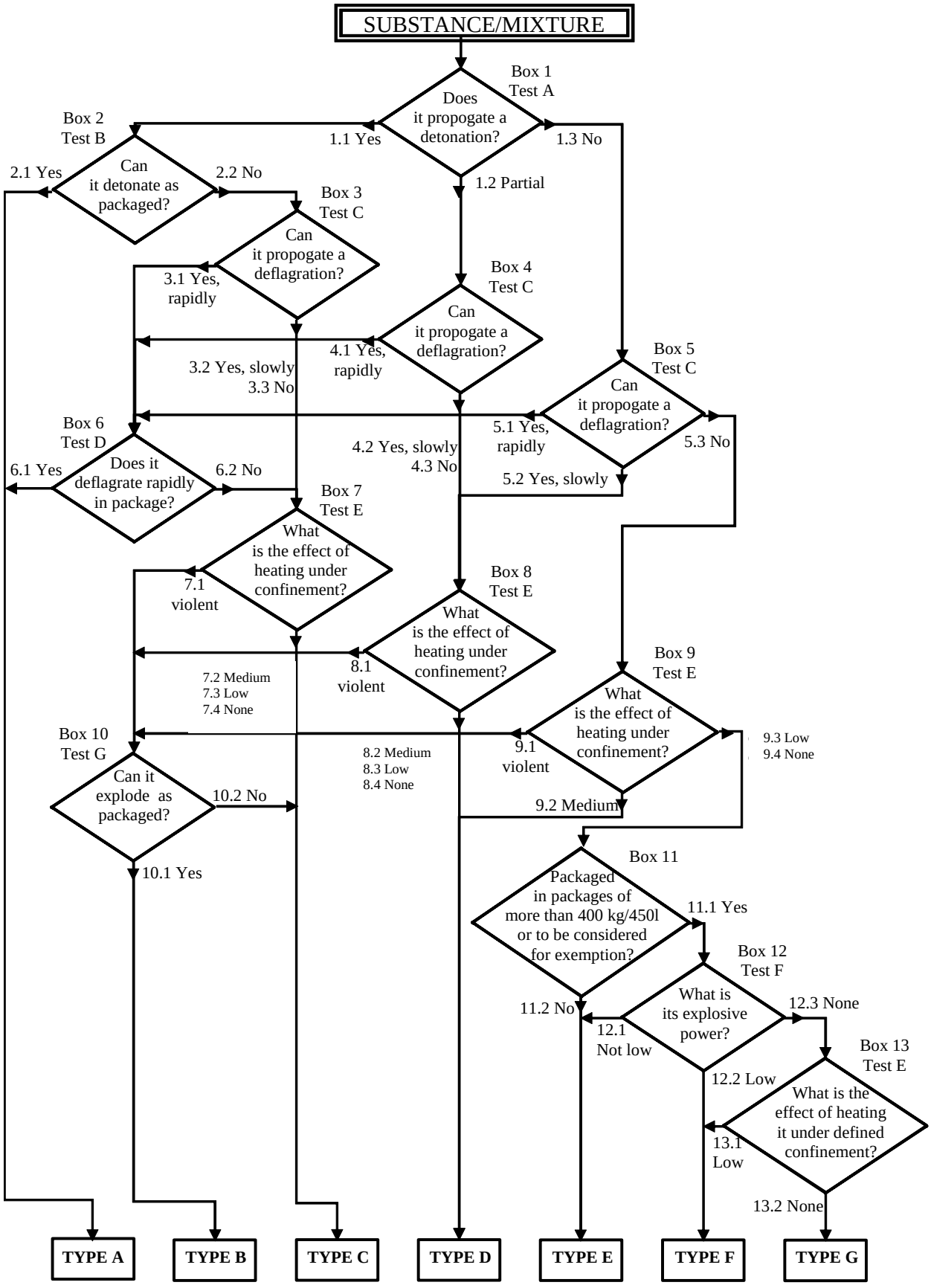
2.15.4. Additional Classification Considerations

2.15.4.1. Organic peroxides are classified by definition based on their chemical structure and on the available oxygen and hydrogen peroxide contents of the mixture (see 2.15.2.1). The properties of organic peroxides which are necessary for their classification shall be determined experimentally. The classification of organic peroxides shall be performed in accordance with test series A to H as described in Part II of the UN RTDG, Manual of Tests and Criteria. The procedure for classification is described in Figure 2.15.1.

2.15.4.2. Mixtures of already classified organic peroxides may be classified as the same type of organic peroxide as that of the most dangerous component. However, as two stable components can form a thermally less stable mixture, the SADT of the mixture shall be determined.

Note: The sum of the individual parts can be more hazardous than the individual components.

Figure 2.15.1
Organic Peroxides



2.16. CORROSIVE TO METALS

2.16.1. Definition

A substance or a mixture that is corrosive to metals means a substance or a mixture which by chemical action will materially damage, or even destroy, metals.

2.16.2. Classification criteria

2.16.2.1. A substance or a mixture which is corrosive to metals is classified in a single category for this class, using the test in Part III, sub-section 37.4 of the UN RTDG, Manual of Tests and Criteria, in accordance with Table 2.16.1:

Table 2.16.1

Criteria for substances and mixtures corrosive to metals

Category	Criteria
1	Corrosion rate on either steel or aluminium surfaces exceeding 6,25 mm per year at a test temperature of 55°C when tested on both materials.

Note:

Where an initial test on either steel or aluminium indicates the substance or mixture being tested is corrosive the follow up test on the other metal is not required.

2.16.3. Hazard Communication

Label elements shall be used for substances and mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.16.2.

Table 2.16.2

Label elements for substances and mixtures corrosive to metals

Classification	Category 1
GHS Pictogram	
Signal Word	Warning
Hazard Statement	H290: May be corrosive to metals
Precautionary Statement Prevention	P234
Precautionary Statement Response	P390

Precautionary Statement Storage	P406
Precautionary Statement Disposal	

2.16.4. Additional Classification Considerations

2.16.4.1. The corrosion rate can be measured according to the test method of Part III sub-section 37.4 of the UN RTDG, Manual of Tests and Criteria. The specimen to be used for the test shall be made of the following materials:

(a) for the purposes of testing steel, steel types

– S235JR+CR (1.0037 resp.St 37-2),

– S275J2G3+CR (1.0144 resp.St 44-3), ISO 3574 as amended, Unified Numbering System (UNS) G 10200, or SAE 1020;

(b) for the purposes of testing aluminium: non-clad types 7075-T6 or AZ5GU-T6.

PART 3

HEALTH HAZARDS

3.1. ACUTE TOXICITY

3.1.1. Definitions

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

3.1.1.2. The hazard class Acute Toxicity is differentiated into:

– Acute oral toxicity;

– Acute dermal toxicity;

– Acute inhalation toxicity.

3.1.2. Criteria for classification of substances as acutely toxic

3.1.2.1. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD_{50} (oral, dermal) or LC_{50} (inhalation) values or as acute toxicity estimates (ATE). Explanatory notes are shown following Table 3.1.1.

Table 3.1.1

Acute toxicity hazard categories and

acute toxicity estimates (ATE) defining the respective categories

Exposure Route	Category 1	Category 2	Category 3	Category 4
Oral (mg/kg bodyweight) See Note (a) Note (b)	ATE ≤ 5	5 < ATE ≤ 50	50 < ATE ≤ 300	300 < ATE ≤ 2000
Dermal (mg/kg bodyweight) See Note (a) Note (b)	ATE ≤ 50	50 < ATE ≤ 200	200 < ATE ≤ 1000	1000 < ATE ≤ 2000
Gases (ppmV[1]) see: Note (a) Note (b) Note (c)	ATE ≤ 100	100 < ATE ≤ 500	500 < ATE ≤ 2500	2500 < ATE ≤ 20000
Vapours (mg/l) see: Note (a) Note (b) Note (c) Note (d)	ATE ≤ 0,5	0,5 < ATE ≤ 2,0	2,0 < ATE ≤ 10,0	10,0 < ATE ≤ 20,0
Dusts and Mists (mg/l) see: Note (a) Note (b) Note (c)	ATE ≤ 0,05	0,05 < ATE ≤ 0,5	0,5 < ATE ≤ 1,0	1,0 < ATE ≤ 5,0

[1] Gas concentrations are expressed in parts per million per volume (ppmV)

Notes to Table 3.1.1:

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

(b) The acute toxicity estimate (ATE) for the classification of a substance 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, or
- the appropriate conversion value from Table 3.1.2 that relates to a classification category.

(c) Generic concentration limits for inhalation toxicity in the table are based on 4-hour testing exposures. Conversion of existing inhalation toxicity data which have been generated using a 1-hour exposure can be carried out by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists.

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

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

– dust: solid particles of a substance or mixture suspended in a gas (usually air);

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

– vapour: the gaseous form of a substance or mixture released from its liquid or solid state.

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

3.1.2.2. Specific considerations for classification of substances as acutely toxic

3.1.2.2.1. 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. When experimental data for acute toxicity are available in several animal species, scientific judgement shall be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.

3.1.2.3. Specific considerations for classification of substances as acutely toxic by the inhalation route

3.1.2.3.1. 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 shall be based on ppmV.

3.1.2.3.2. Of particular importance in classifying for inhalation toxicity 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.

3.1.2.3.3. In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity was corrosivity, the substance or mixture shall also be labelled as "corrosive to the respiratory tract" (see note 1 in 3.1.4.1). Corrosion of the respiratory tract is defined by destruction of the respiratory tract tissue after a single, limited period of exposure analogous to skin corrosion; this includes destruction of the mucosa. The corrosivity evaluation can be based on expert judgment using such evidence as: human and animal experience, existing (in vitro) data, pH values, information from similar substances or any other pertinent data.

3.1.3. Criteria for classification of mixtures as acutely toxic

3.1.3.1. The criteria for classification of substances for acute toxicity as outlined in section 3.1.2 are based on 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 outlines the process to be followed.

3.1.3.2. For acute toxicity each route of exposure shall be considered for the classification of mixtures, but only one route of exposure is needed as long as this route is followed (estimated or tested) for all components and there is no relevant evidence to suggest acute toxicity by multiple routes. When there is relevant evidence of toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. All available information shall be considered. The pictogram and signal word used shall reflect the most severe hazard category and all relevant hazard statements shall be used.

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

(a) the "relevant ingredients" of a mixture are those which are present in concentrations of 1 % (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1 % is still relevant for classifying the mixture for acute toxicity (see Table 1.1).

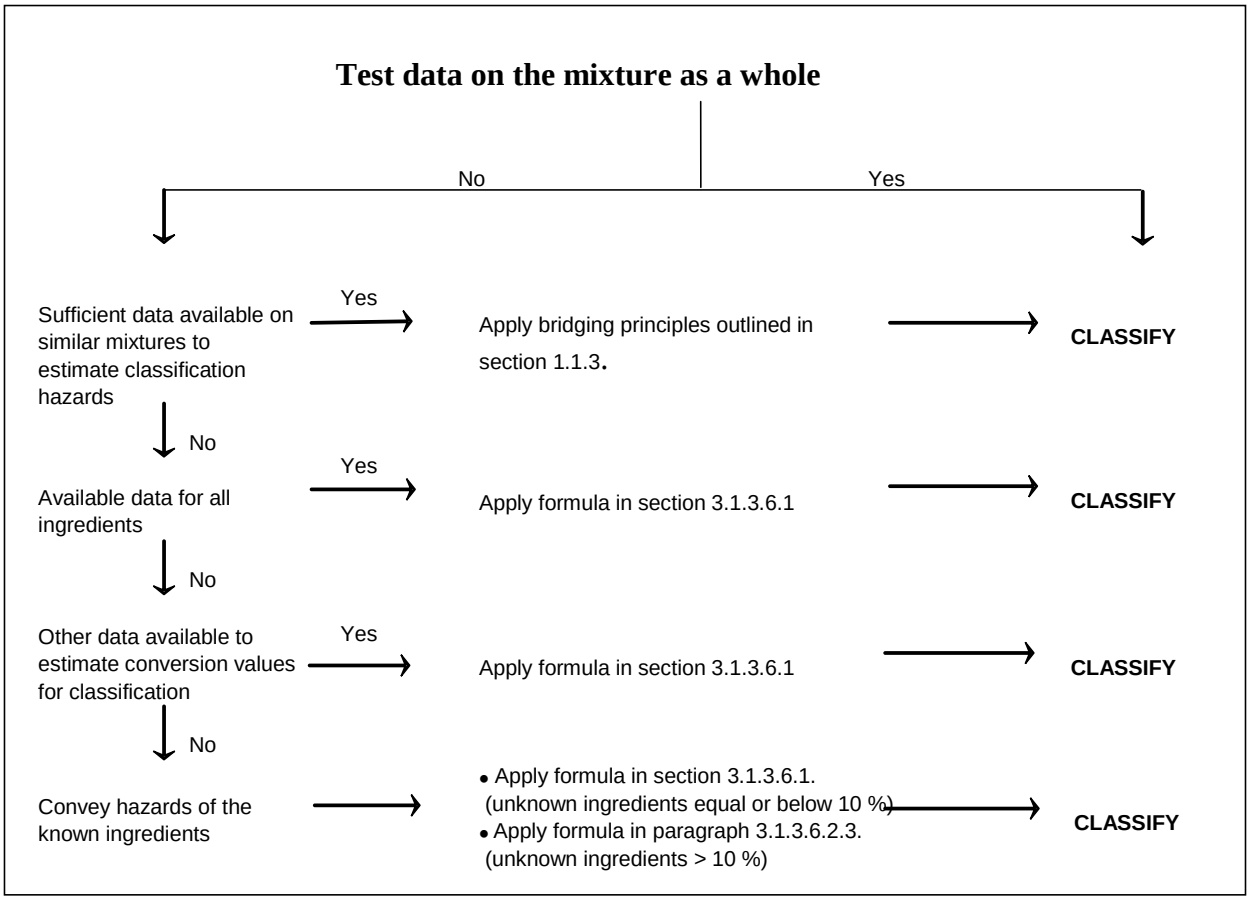
(b) where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used, when calculating the classification of the new mixture using the formulas in section 3.1.3.6.1 and paragraph 3.1.3.6.2.3.

(c) If the converted acute toxicity point estimates for all components of a mixture are within the same category, then the mixture should be classified in that category.

(d) When only range data (or acute toxicity hazard category information) are available for components in a mixture, they may be converted to point estimates in accordance with Table 3.1.2 when calculating the classification of the new mixture using the formulas in sections 3.1.3.6.1 and 3.1.3.6.2.3.

Figure 3.1.1

Tiered approach to classification of mixtures for acute toxicity



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

3.1.3.4.1. Where the mixture itself has been tested to determine its acute toxicity, it shall 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 under sections 3.1.3.5 and 3.1.3.6 shall be followed.

3.1.3.5. Classification of mixtures where acute toxicity data are 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 shall be used in accordance with the bridging rules set out in section 1.1.3.

3.1.3.5.2. If a tested mixture is diluted with a diluents that has an equivalent or lower toxicity classification than the least toxic original component and which is not expected to affect the toxicity of other components, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the formula explained in section 3.1.3.6.1 can be applied.

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 shall be considered as follows:

(a) include ingredients with a known acute toxicity, which fall into any of the acute toxicity categories shown in Table 3.1.1;

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

(c) ignore components if the data available are from a limit dose test (at the upper threshold for Category 4 for the appropriate route of exposure as provided in Table 3.1.1) and do not show acute toxicity.

Components that fall within the scope of this section are considered to be components with a known acute toxicity estimate (ATE). See note (b) to Table 3.1.1 and section 3.1.3.3 for appropriate application of available data to the equation below, and section 3.1.3.6.2.3.

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

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

where:

Ci = concentration of ingredient i (% w/w or % v/v)
i = the individual ingredient from 1 to n
n = the number of ingredients
ATEi = Acute Toxicity Estimate of ingredient i.

3.1.3.6.2. Classification of mixtures when data are not available for all components

3.1.3.6.2.1. Where an ATE is not available for an individual ingredient of the mixture, but available information, such as that listed below, can provide a derived conversion value such as those laid out in Table 3.1.2, the formula in section 3.1.3.6.1 shall be applied.

This includes evaluation of:

(a) extrapolation between oral, dermal and inhalation acute toxicity estimates[1]. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;

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

(c) (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) (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 (expert judgement, see section 1.1.1), to reliably estimate acute toxicity. If such information is not available, proceed to paragraph 3.1.3.6.2.3.

3.1.3.6.2.2. In the event that a compound without any useable information for classification 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 shall be classified based on the known compounds only, with the additional statement on the label and in the SDS that: " x percent of the mixture consists of component(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 section 3.1.3.6.1 shall be used. If the total concentration of the ingredient(s) with unknown toxicity is > 10 %, the formula presented in section 3.1.3.6.1 shall be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

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[1] When mixtures contain components that do not have acute toxicity data dor each route of exposure, acute toxicity estimates may be extrapolated from the available data and applied to the appropriate routes (see section 3.1.3.2). However, specific legislation may require testing for a specific legislation may require testing for a specific route. In those cases, classification shall be performed for that route based upon the legal requirements.

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

Table 3.1.2 Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for use in the formulas for the classification of mixtures

Exposure routes	Classification Category or experimentally obtained acute toxicity range estimate	Converted acute toxicity point estimate (see Note 1)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5 5 < Category 2 ≤ 50 50 < Category 3 ≤ 300 300 < Category 4 ≤ 2000	0,5 5 100 500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1000 1000 < Category 4 ≤ 2000	5 50 300 1100
Gases (ppmV)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2500 2500 < Category 4 ≤ 20000	10 100 700 4500
Vapours (mg/l)	0 < Category 1 ≤ 0,5 0,5 < Category 2 ≤ 2,0 2,0 < Category 3 ≤ 10,0 10,0 < Category 4 ≤ 20,0	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	0,005 0,05 0,5 1,5

Note 1:

These values are designed to be used in the calculation of the ATE for classification of a mixture based on its components and do not represent test results.

3.1.4. Hazard Communication

3.1.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.1.3. Without prejudice to Article 29, Combined hazard statements may be used in accordance with Annex 3.

Table 3.1.3

Acute toxicity label elements

Classification	Category 1	Category 2	Category 3	Category 4

GHS Pictograms				
Signal Word	Danger	Danger	Danger	Warning
Hazard Statement: - Oral	H300: Fatal if swallowed	H300: Fatal if swallowed	H301: Toxic if swallowed	H302: Harmful if swallowed
- Dermal	H310:Fatal in contact with skin	H310:Fatal in contact with skin	H311: Toxic in contact with skin	H312: Harmful in contact with skin
- Inhalation (see Note 1)	H330:Fatal if inhaled	H330: Fatal if inhaled	H331: Toxic if inhaled	H332: Harmful if inhaled
Precautionary Statement Prevention (oral)	P264 P270	P264 P270	P264 P270	P264 P270

Precautionary Statement Response (oral)	P301 + P310 P321 P330	P301 + P310 P321 P330	P301 + P310 P321 P330	P301 + P312 P330
Precautionary Statement Storage (oral)	P405	P405	P405	
Precautionary Statement Disposal (oral)	P501	P501	P501	P501
Precautionary Statement Prevention (dermal)	P262 P264 P270 P280	P262 P264 P270 P280	P280	P280
Precautionary Statement Response (dermal)	P302 + P350 P310 P322 P361 P363	P302 + P350 P310 P322 P361 P363	P302 + P352 P312 P322 P361 P363	P302 + P352 P312 P322 P363
Precautionary Statement Storage (dermal)	P405	P405	P405	
Precautionary Statement Disposal (dermal)	P501	P501	P501	P501
Precautionary Statement Prevention (inhalation)	P260 P271 P284	P260 P271 P284	P261 P271	P261 P271

Precautionary Statement Response (inhalation)	P304 + P340 P310 P320	P304 + P340 P310 P320	P304 + P340 P311 P321	P304 + P340 P312
Precautionary Statement Storage (inhalation)	P403 + P233 P405	P403 + P233 P405	P403 + P233 P405	
Precautionary Statement Disposal (inhalation)	P501	P501	P501	

Note1:

In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity is corrosivity, the substance or mixture shall also be labelled as EUH071: "corrosive to the respiratory tract" – see advice at 3.1.2.3.3. In addition to an appropriate acute toxicity pictogram, a corrosivity pictogram (used for skin and eye corrosivity) may be added together with the statement "corrosive to the respiratory tract".

Note2:

In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1 % or greater, the mixture shall be labelled with the additional statement that "x percent of the mixture consists of ingredient(s) of unknown toxicity" – see advice at 3.1.3.6.2.2.

3.2. SKIN CORROSION/IRRITATION

3.2.1. Definitions

3.2.1.1. Skin Corrosion means 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. 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 shall be considered to evaluate questionable lesions.

Skin Irritation means the production of reversible damage to the skin following the application of a test substance for up to 4 hours.

3.2.2. Classification criteria for substances

3.2.2.1. Several factors need to be considered in determining the corrosion and irritation potential of substances before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. Existing human experience and animal data from single or repeated exposure shall be the first line of analysis, as they give information directly relevant to effects on the skin. In vitro alternatives that have been validated and accepted may also be used to help make classification decisions (see Article 7). In some cases enough information may be available from structurally related compounds to make classification decisions.

3.2.2.2. Likewise, pH extremes like ≤ 2 and $\geq 11,5$ may indicate the potential to cause skin effects, especially when buffering capacity is known, although the correlation is not perfect. Generally, such substances are expected to produce significant effects on the skin. If consideration of alkali/acid reserve suggests the substance may not be corrosive despite the low or high pH value, then further testing shall be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

3.2.2.3. If a substance is highly toxic by the dermal route, a skin irritation/corrosion study is not practicable since the amount of test substance to be applied considerably exceeds the toxic dose and, consequently, results 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 is not needed, provided that the dilutions used and species tested are equivalent.

3.2.2.4. All the above information that is available on a substance shall 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 paragraph 3.2.2.5), e.g. caustic alkalis with extreme pH shall 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 shall 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.

3.2.2.5. A tiered approach to the evaluation of initial information shall be considered, where applicable, recognising that all elements may not be relevant in certain cases.

3.2.2.6. Corrosion

3.2.2.6.1. On the basis of the results of animal testing a substance is classified as corrosive, as shown in Table 3.2.1. A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal 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 shall be considered to discern questionable lesions.

3.2.2.6.2. Three subcategories are provided within the corrosive category: 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.

3.2.2.6.3. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and.1.1.1.5.

Table 3.2.1

Skin Corrosive category and subcategories

		Corrosive in ≥ 1 of 3 animals	
	Corrosive subcategories	Exposure	Observation
Category 1: Corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes – ≤ 1 hour	≤ 14 days
	1C	> 1 hour – ≤ 4 hours	≤ 14 days

3.2.2.7. Irritation

3.2.2.7.1. Using the results of animal testing a single irritant category (Category 2) is presented in Table 3.2.2. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and.1.1.1.5. The major criterion for the irritant

category is that at least 2 of 3 tested animals have a mean score of ≥ 2,3 – ≤ 4,0.

Table 3.2.2

Skin irritation category

Category	Criteria
Category 2: Irritant	(1) Mean value of ≥ 2,3 – ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

3.2.2.8. Comments on responses obtained in skin irritation tests in animals

3.2.2.8.1. Animal irritant responses within a test can be quite variable, as they are with corrosion. The major criterion for classification of a substance as irritant to skin, as shown in paragraph 3.2.2.7.1, is the mean value of the scores for either erythema/eschar or oedema calculated in at least 2 of 3 tested animals. 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.

3.2.2.8.2. 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 shall be considered to be an irritant.

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 substances and mixtures 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 (paragraph 3.2.2.5), to help ensure an accurate classification as well as avoid unnecessary animal testing. A mixture is considered corrosive to skin (Skin Corrosive 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 mixture may not be corrosive despite the low or high pH value, then further testing shall 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 hazards, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

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:

Assumption: 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 generic 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 concentration limit.

3.2.3.3.3. Table 3.2.3 provides the generic concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

3.2.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.2.3.3.1 and 3.2.3.3.2 may not be applicable given that many of such substances are corrosive or irritant at concentrations < 1 %.

3.2.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as a classification criterion (see paragraph 3.2.3.1.2) since pH is a better indicator of corrosion than the concentration limits of Table 3.2.3.

3.2.3.3.4.3. A mixture containing ingredients that are corrosive or irritant to the skin and that cannot be classified on the basis of the additivity approach (Table 3.2.3), due to chemical characteristics that make this approach unworkable, shall be classified as Skin Corrosive Category 1A, 1B or 1C if it contains ≥ 1 % of an ingredient classified in Category 1A, 1B or 1C respectively or as Category 2 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.

3.2.3.3.5. On occasion, reliable data may show that the skin corrosion/irritation hazard of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture shall be classified according to that data (see also Articles 12 and 13). On other occasions, when it is expected that the skin corrosion/irritation hazard of an ingredient is not evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture shall be considered. In those

cases the tiered weight of evidence strategy shall be applied, as described in paragraph 3.2.2.5.

3.2.3.3.6. If there are data showing that (an) ingredient(s) is/are corrosive or irritant at a concentration of < 1 % (corrosive) or < 3 % (irritant), the mixture shall be classified accordingly.

Table 3.2.3

Generic concentration limits of ingredients

classified for skin corrosive/irritant hazard (Category 1 or 2)

that trigger classification of the mixture as corrosive/irritant to skin

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosive	Skin Irritant
	Category 1 (see note below)	Category 2
Skin Corrosive Categories 1A, 1B, 1C	≥ 5 %	≥ 1 % but < 5 %
Skin irritant Category 2		≥ 10 %
(10 x Skin Corrosive Category 1A, 1B, 1C) + Skin irritant Category 2		≥ 10 %

Note:

The sum of all ingredients of a mixture classified as Skin Corrosive Category 1A, 1B or 1C respectively, shall each be ≥ 5 % respectively in order to classify the mixture as either Skin Corrosive Category 1A, 1B or 1C. If the sum of the Skin Corrosive Category 1A ingredients is < 5 % but the sum of Category 1A+1B ingredients is ≥ 5 %, the mixture shall be classified as Skin Corrosive Category 1B. Similarly, if the sum of Skin Corrosive Category 1A+1B ingredients is < 5 % but the sum of Category 1A+1B+1C ingredients is ≥ 5 % the mixture shall be classified as Skin Corrosive Category 1C.

Table 3.2.4

Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that trigger classification of the mixture as corrosive/irritant 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 (Categories 1A, 1B, 1C) 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

3.2.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.2.5.

Table 3.2.5

Label elements for skin corrosion/irritation

Classification	Category 1 A/1 B/1 C	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H314: Causes severe skin burns and eye damage	H315: Causes skin irritation
Precautionary Statement Prevention	P260 P264 P280	P264 P280
Precautionary Statement Response	P301 + P330 + P331 P303 + P361 + P353 P363 P304 + P340 P310 P321 P305 + P351 + P338	P302 + P352 P321 P332 + P313 P362
Precautionary Statement Storage	P405	
Precautionary Statement Disposal	P501	

3.3. SERIOUS EYE DAMAGE/EYE IRRITATION

3.3.1. Definitions

3.3.1.1. Serious eye damage means 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.

Eye irritation means 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.

3.3.2. Classification criteria for substances

3.3.2.1. The classification system for substances involves a tiered testing and evaluation scheme, combining 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 (Q)SAR and the output of validated in vitro tests in order to avoid unnecessary animal testing.

3.3.2.2. Before any in vivo testing for serious eye damage/eye irritation is carried out, all existing information on a substance shall be reviewed. Preliminary decisions can often be made from existing data as to whether a substance causes serious (i.e. irreversible) damage to the eyes. If a substance can be classified on the basis of these data, no testing is required.

3.3.2.3. Several factors need to be considered in determining the serious eye damage or irritation potential of a substance before testing is undertaken. Accumulated human and animal experience shall 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 $\geq 11{,}5$ may produce serious eye damage, especially when associated with significant buffering capacity. Such substances 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. Skin corrosive substances shall be considered as leading to serious damage to the eyes as well (Category 1), while skin irritant substances may be considered as leading to eye irritation (Category 2). In vitro alternatives that have been validated and accepted can be used to make classification decisions (see Article 7).

3.3.2.4. All the above information that is available on a substance shall be used in determining the need for in vivo eye irritation testing. Although information may be gained from the evaluation of single parameters within a tier (e.g. caustic alkalis with extreme pH shall be considered as local corrosives), the totality of existing information shall be considered in making an overall weight of evidence determination, particularly when there is information

available on some but not all parameters. Generally, primary emphasis shall 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 or mixtures shall be avoided whenever possible.

3.3.2.5. A tiered approach to the evaluation of initial information shall be considered where applicable, while recognising that all elements may not be relevant in certain cases.

3.3.2.6. Irreversible effects on the eye/serious damage to eyes (Category 1)

3.3.2.6.1. Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). Substances are classified in this hazard category on the basis of the results of animal testing, in accordance with the criteria listed in Table 3.3.1. 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. Substances are also classified in Category 1 if they fulfil the criteria of corneal opacity ≥ 3 or iritis > 1,5 detected in a Draize eye test with rabbits, recognising that such severe lesions usually do not reverse within a 21-day observation period.

Table 3.3.1

Category for irreversible eye effects

Category	Criteria
Irreversible effects on the eye (Category 1)	If, when applied to the eye of an animal, a substance produces: – at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or – at least in 2 of 3 tested animals, a positive response of: – corneal opacity ≥ 3 and/or – iritis > 1,5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

3.3.2.6.2. The use of human data is discussed in paragraphs 3.3.2.1, 3.3.2.4, and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5.

3.3.2.7. Reversible effects on the eye (Category 2)

3.3.2.7.1. Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Table 3.3.2

Category for reversible eye effects

Category	Criteria
Irritating to eyes (Category 2)	if, when applied to the eye of an animal, a substance 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 and/or − 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 21 days

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

3.3.3.1.1. 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

3.3.3. Classification criteria for mixtures

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

classes.

3.3.3.1.2. Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of mixtures that 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 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 (Category 1) if it has a pH $\leq$ 2,0 or $\geq$ 11,5. If consideration of alkali/acid reserve suggests the mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

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

3.3.3.2.1. Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

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

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

Assumption: 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 % is still 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 generic concentration limit for classification in 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 concentration limit.

3.3.3.3.3. Table 3.3.3 provides the generic concentration limits to be used to determine if the mixture shall be classified as irritant or as seriously damaging to the eye.

3.3.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances 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 %.

3.3.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as classification criteria (see paragraph 3.3.2.3) since pH will be a better indicator of serious eye damage than the generic concentration limits of Table 3.3.3.

3.3.3.3.4.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach (Table 3.3.3), due to chemical characteristics that make this approach unworkable, shall be classified as Category 1 for effects on the eye if it contains ≥ 1 % of a corrosive ingredient and as 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 concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture shall be classified according to those data. On other occasions, when it is expected that the skin corrosion/irritation hazards or the reversible/irreversible eye effects of an

ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture shall be considered. In those cases, the tiered weight of evidence strategy shall be applied.

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 shall be classified accordingly.

Table 3.3.3
Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 x Eye Effects Category 1) + Eye effects Category 2		≥ 10 %
Skin Corrosive Category 1A, 1B, 1C + Eye effects Category 1	≥ 3 %	≥ 1 % but < 3 %
10 x (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

Table 3.3.4
Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that 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

3.3.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.3.5.

Table 3.3.5

Label elements for serious eye damage/eye irritation

Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H318: Causes serious eye damage	H319: Causes serious eye irritation
Precautionary Statement Prevention	P280	P264 P280
Precautionary Statement Response	P305 + P351 + P338 P310	P305 + P351 + P338 P337 + P313
Precautionary Statement Storage		
Precautionary Statement Disposal		

3.4. RESPIRATORY OR SKIN SENSITISATION

3.4.1. Definitions and general considerations

3.4.1.1. Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance.

3.4.1.2. Skin sensitiser means a substance that will lead to an allergic response following skin contact.

3.4.1.3. For the purpose of section 3.4, sensitisation includes two phases: the first phase is induction of specialised immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen.

3.4.1.4. For respiratory sensitisation, the pattern of induction followed by elicitation phases is shared in common with skin sensitisation. For skin sensitisation, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise

when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardised elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitisation in humans normally is assessed by a diagnostic patch test.

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

3.4.1.6. The hazard class Respiratory and Skin Sensitisation is differentiated into:

– Respiratory Sensitisation;

– Skin Sensitisation.

3.4.2. Classification criteria for substances

3.4.2.1. Respiratory sensitisers

3.4.2.1.1. Hazard categories

3.4.2.1.1.1. Respiratory sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation.

3.4.2.1.1.2. Where data are sufficient a refined evaluation according to 3.4.2.1.1.3 shall allow the allocation of respiratory sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other respiratory sensitisers.

3.4.2.1.1.3. Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitisers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

3.4.2.1.1.4. Substances shall be classified as respiratory sensitisers in accordance with the criteria in Table 3.4.1:

Table 3.4.1

Hazard category and sub-categories for respiratory sensitisers

Category	Criteria

Category	Criteria
Category 1	Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests*. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests*. Severity of reaction may also be considered.

(*) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

3.4.2.1.2. Human evidence

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

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

(a) the size of the population exposed;

(b) the extent of exposure.

The use of human data is discussed in sections 1.1.1.3, 1.1.1.4 and 1.1.1.5.

3.4.2.1.2.3. The evidence referred to above could be

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) in vivo immunological test (e.g. skin prick test);

(ii) in vitro immunological test (e.g. serological analysis);

(iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from one or more 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 shall 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 shall 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

3.4.2.1.3.1. Data from appropriate animal studies* which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans** may include:

(a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters in mice;

(b) specific pulmonary responses in guinea pigs.

3.4.2.2. Skin sensitisers

3.4.2.2.1. Hazard categories

3.4.2.2.1.1 Skin sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation.

3.4.2.2.1.2 Where data are sufficient a refined evaluation according to section 3.4.2.2.1.3 allows the allocation of skin sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other skin sensitisers.

3.4.2.2.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitisers as described in section 3.4.2.2.2. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in sections 3.4.2.2.2.1 and 3.4.2.2.3.2 for sub-category 1A and in sections 3.4.2.2.2.2 and 3.4.2.2.3.3 for sub-category 1B.

3.4.2.2.1.4 Substances shall be classified as skin sensitisers in accordance with the criteria in Table 3.4.2:

Table 3.4.2

Hazard category and sub-categories for skin sensitisers

Category	Criteria
Category 1	Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test (see specific criteria in section 3.4.2.2.4.1).
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.

Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.

3.4.2.2.2. Human evidence

3.4.2.2.2.1 Human evidence for sub-category 1A can include:

(a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

3.4.2.2.2.2 Human evidence for sub-category 1B can include:

(a) positive responses at > 500 µg/cm2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;

(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

The use of human data is discussed in sections 1.1.1.3, 1.1.1.4 and 1.1.1.5.

3.4.2.2..3. Animal studies

3.4.2.2.3.1 For Category 1, when an adjuvant type test method for skin sensitisation is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of three or more is considered a positive response in the local lymph node assay. Test methods for skin sensitisation 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. For example, the mouse ear swelling test (MEST) could be a reliable screening test to detect moderate to strong sensitisers, and could be used as a first stage in the assessment of skin sensitisation potential.

3.4.2.2.3.2 Animal test results for sub-category 1A can include data with values indicated in Table 3.4.3

Table 3.4.3

Animal test results for sub-category 1A

Assay	**Criteria**
Local lymph node assay	EC3 value ≤ 2%
Guinea pig maximisation test	≥ 30% responding at ≤ 0,1% intradermal induction dose or ≥ 60% responding at > 0,1% to ≤ 1% intradermal induction dose
Buehler assay	≥15% responding at ≤ 0,2% topical induction dose or ≥ 60% responding at > 0,2% to ≤ 20% topical induction dose

3.4.2.2.3.3 Animal test results for sub-category 1B can include data with values indicated in Table 3.4.4 below:

Table 3.4.4

Animal test results for sub-category 1B

Assay	**Criteria**
Local lymph node assay	EC3 value > 2%
Guinea pig maximisation test	≥ 30% to < 60% responding at > 0,1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose
Buehler assay	≥ 15% to < 60% responding at > 0,2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose

3.4.2.2.4 Specific considerations

3.4.2.2.4.1 For classification of a substance, evidence should include any or all of the following using a weight of evidence approach:

(a) positive data from patch testing, normally obtained in more than one dermatology clinic;

(b) epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;

(c) positive data from appropriate animal studies;

(d) positive data from experimental studies in man (see section 1.3.2.4.7);

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

(f) severity of reaction may also be considered.

3.4.2.2.4.2 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 skin sensitisation 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. For both animal and human data, consideration should be given to the impact of vehicle.

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

(a) Isolated episodes of allergic contact dermatitis;

(b) epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;

(c) data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in section 3.4.2.2.3, but which are sufficiently close to the limit to be considered significant;

(ç) positive data from non-standard methods;

(d) positive results from close structural analogues.

3.4.2.2.4.4 Immunological contact urticaria

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

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 sensitisation.

_____

(*) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

(**) The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitisers. 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 hyper reactivity, they should not be considered as respiratory sensitisers.";

3.4.3. Classification criteria for mixtures

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

3.4.3.1.1. 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 shall be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive.

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 sensitising properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

3.4.3.3. Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.4.3.3.1. The mixture shall be classified as a respiratory or skin sensitiser when at least one ingredient has been classified as a respiratory or skin sensitiser and is present at or above the appropriate generic concentration limit as shown in Table 3.4.5 for solid/liquid and gas respectively.

3.4.3.3.2. Some substances that are classified as sensitisers may elicit a response, when present in a mixture in quantities below the concentrations established in Table 3.4.5, in individuals who are already sensitised to the substance or mixture (see Note 1 to Table 3.4.6).

Table 3.4.5

Generic concentration limits of components of a mixture classified as either respiratory sensitisers or skin sensitisers that trigger classification of the mixture

Component classified as:	**Generic concentration limits triggering classification of a mixture as:**		
	Respiratory sensitiser Category 1		**Skin sensitiser Category 1**
	Solid/Liquid	**Gas**	**All physical states**
Respiratory sensitiser Category 1	≥ 1,0%	≥ 0,2%	
Respiratory sensitiser Sub-category 1A	≥ 0,1%	≥ 0,1%	
Respiratory sensitiser Sub-category 1B	≥ 1,0%	≥ 0,2%	
Skin sensitiser Category 1			≥ 1,0%
Skin sensitiser Sub-category 1A			≥ 0,1%
Skin sensitiser Sub-category 1B			≥ 1,0%

Table 3.4.6

Concentration limits for elicitation of components of a mixture

Component classified as:	Respiratory sensitiser Category 1		Skin sensitiser Category 1
	Solid/Liquid	Gas	All physical states
Respiratory sensitiser Category 1	≥ 0,1% (Note 1)	≥ 0,1% (Note 1)	
Respiratory sensitiser Sub-category 1A	≥ 0,01% (Note 1)	≥ 0,01% (Note 1)	
Respiratory sensitiser Sub-category 1B	≥ 0,1% (Note 1)	≥ 0,1% (Note 1)	
Skin sensitiser Category 1			≥ 0,1% (Note 1)
Skin sensitiser Sub-category 1A			≥ 0,01% (Note 1)
Skin sensitiser Sub-category 1B			≥ 0,1% (Note 1)

Note 1:

This concentration limit for elicitation is used for the application of the special labelling requirements of Annex 2 section 2.8 to protect already sensitised individuals. A SDS is required for the mixture containing a component above this concentration. For sensitising substances with specific concentration limit lower than 0,1%, the concentration limit for elicitation should be set at one tenth of the specific concentration limit.

3.4.4. Hazard communication

3.4.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.4.7.

Table 3.4.7

Respiratory or skin sensitisation label elements.

Classification	Respiratory sensitisation	Skin sensitisation
	Category 1 and sub-categories 1A and 1B	Category 1 and sub-categories 1A and 1B
GHS pictograms		
Signal word	Danger	Warning
Hazard statement	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled	H317: May cause an allergic skin reaction
Precautionary statement prevention	P261 P285	P261 P272 P280
Precautionary statement response	P304 + P341 P342+ P311	P302 + P352 P333 + P313 P321 P363
Precautionary statement storage		
Precautionary statement disposal	P501	P501

3.5. GERM CELL MUTAGENICITY

3.5.1. Definitions and general considerations

3.5.1.1. A mutation means 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 specific base pair changes and chromosomal translocations). The term "mutagenic" and "mutagen" will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

3.5.1.2. The more general terms "genotoxic" and "genotoxicity" apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a

non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

3.5.2. Classification criteria for substances

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

3.5.2.2. For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

Table 3.5.1

Hazard categories for germ cell mutagens

Categories	Criteria
CATEGORY 1:	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
Category 1A:	The classification in Category 1A is based on positive evidence from human epidemiological studies.
Category 1B:	Substances to be regarded as if they induce heritable mutations in the germ cells of humans. The classification in Category 1B is based on: – 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. It is possible to derive this supporting evidence from mutagenicity/genotoxicity 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.

CATEGORY 2:	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans The classification in Category 2 is based on: – 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: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

3.5.2.3. Specific considerations for classification of substances as germ cell mutagens

3.5.2.3.1. 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 shall also be considered.

3.5.2.3.2. The system is hazard based, classifying substances 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 substances.

3.5.2.3.3. Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in By Law on Test Methods such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.4. In vivo heritable germ cell mutagenicity tests, such as:

– rodent dominant lethal mutation test;

– mouse heritable translocation assay.

3.5.2.3.5. In vivo somatic cell mutagenicicty tests, such as:

– mammalian bone marrow chromosome aberration test;

– mouse spot test;

– mammalian erythrocyte micronucleus test.

3.5.2.3.6. Mutagenicity/genotoxicity tests in germ cells, such as:

(a) mutagenicity tests:

– mammalian spermatogonial chromosome aberration test;

– spermatid micronucleus assay;

(b) Genotoxicity tests:

– sister chromatid exchange analysis in spermatogonia;

– unscheduled DNA synthesis test (UDS) in testicular cells.

3.5.2.3.7. Genotoxicity tests in somatic cells such as:

– liver Unscheduled synthesis test (UDS) in vivo;

– mammalian bone marrow Sister Chromatid Exchanges (SCE);

3.5.2.3.8. In vitro mutagenicity tests such as:

– in vitro mammalian chromosome aberration test;

– in vitro mammalian cell gene mutation test;

– bacterial reverse mutation tests.

3.5.2.3.9. The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall 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 substance compared to the route of human exposure shall also be taken into account.

3.5.3. Classification criteria for mixtures

3.5.3.1. Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.5.3.1.1. The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2

Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.

Ingredient classified as:	**Concentration limits triggering classification of a mixture as:**		
	Category 1A mutagen	Category 1B mutagen	Category 2 mutagen
Category 1A mutagen	≥ 0,1 %	–	–
Category 1B mutagen	–	≥ 0,1 %	–
Category 2 mutagen	–	–	≥ 1,0 %

Note:

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.3.2. Classification of mixtures when data are available for the complete mixture

3.5.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. 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, sensitivity and statistical analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.5.3.3. Classification of mixtures when data are not available for the complete mixture: bridging principles

3.5.3.3.1. 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 (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.4. Hazard communication

3.5.4.1. Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.3

Label elements of germ cell mutagenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

3.5.5. Additional classification considerations

It is increasingly accepted that the process of chemical-induced tumorigenesis in humans and animals involves genetic changes for example in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of substances in somatic and/or germ cells of mammals in vivo may have implications for the potential classification of these substances as carcinogens (see also Carcinogenicity, section 3.6, paragraph 3.6.2.2.6).

3.6. CARCINOGENICITY

3.6.1. Definition

3.6.1.1. Carcinogen means a substance or a mixture of 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.

3.6.2. Classification criteria for substances

3.6.2.1. For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

Table 3.6.1

Hazard categories for carcinogens

Categories	Criteria
CATEGORY 1:	Known or presumed human carcinogens A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A:	Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B:	Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.
	The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or – animal experiments for which there is sufficient[1] evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

[1] Note: See 3.6.2.2.4.

	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.
CATEGORY 2:	Suspected human carcinogens The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited[1] evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

3.6.2.2. Specific considerations for classification of substances as carcinogens

3.6.2.2.1. Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

3.6.2.2.2. Classification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

3.6.2.2.3. 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 substance 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

[1] Note: See 3.6.2.2.4.

"limited" have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:

(a) Carcinogenicity in humans

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

– sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;

– limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

– sufficient evidence of carcinogenicity: 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 (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide

sufficient evidence. A single study in one species and sex 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, or when there are strong findings of tumours at multiple sites;

– limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

3.6.2.2.4. Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

3.6.2.2.5. 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.

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

(a) tumour type and background incidence;

(b) multi-site responses;

(c) progression of lesions to malignancy;

(ç) reduced tumour latency;

(d) whether responses are in single or both sexes;

(e) whether responses are in a single species or several species;

(f) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;

(g) routes of exposure;

(ğ) comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(h) the possibility of a confounding effect of excessive toxicity at test doses;

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

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 substance has a potential for carcinogenic effects.

3.6.2.2.7. A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B 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.

3.6.2.2.8. The classification shall take into consideration whether or not the substance 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.

3.6.2.2.9. 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.

3.6.3. Classification criteria for mixtures

3.6.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture.

3.6.3.1.1. The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 carcinogen and is present at or above the appropriate generic concentration limit as shown in Table 3.6.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.6.2

Generic concentration limits of ingredients of a mixture classified as carcinogen that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:		
	Category 1A carcinogen	Category 1B carcinogen	Category 2 carcinogen
Category 1A carcinogen	≥ 0,1 %	-	-
Category 1B carcinogen	-	≥ 0,1 %	-
Category 2 carcinogen	-	-	≥ 1,0 % [Note 1]

Note: :

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1:

If a Category 2 carcinogen is present in the mixture as an ingredient at a concentration ≥ 0,1 % a SDS shall be available for the mixture upon request.

3.6.3.2. Classification of mixtures when data are available for the complete mixture

3.6.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as carcinogens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. 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, sensitivity and statistical analysis of carcinogenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.6.3.3. Classification of mixtures when data are not available for the complete mixture: bridging principles

3.6.3.3.1. 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 (subject to paragraph 3.6.3.2.1) to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.6.4. Hazard Communication

3.6.4.1. Label elements shall be used in accordance with Table 3.6.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.6.3

Label elements for carcinogenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal Word	Danger	Warning

Hazard Statement	H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H351: Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

3.7. REPRODUCTIVE TOXICITY

3.7.1. Definitions and general considerations

3.7.1.1. Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document N°225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

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

(a) adverse effects on sexual function and fertility;

(b) adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.

3.7.1.2. For the purpose of classification the hazard class Reproductive Toxicity is differentiated into:

adverse effects

- on sexual function and fertility, or
- on development;
- effects on or via lactation.

3.7.1.3. Adverse effects on sexual function and fertility

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

3.7.1.4. Adverse effects on development of the offspring

Developmental toxicity includes, in its widest sense, 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 for 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 (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

3.7.1.5. Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (see Table 3.7.1 (b)). This is because it is desirable to be able to classify substances specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

3.7.2. Classification criteria for substances

3.7.2.1. Hazard categories

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

Table 3.7.1(a)

Hazard categories for reproductive toxicants

Categories	Criteria
CATEGORY 1	Known or presumed human reproductive toxicant Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when 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. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
Category 1A	Known human reproductive toxicant The classification of a substance in Category 1A is largely based on evidence from humans.
Category 1B	Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

CATEGORY 2	Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed 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.

Table 3.7.1(b)

Hazard category for lactation effects

EFFECTS ON OR VIA LACTATION

Effects on or via lactation are allocated to a separate single category. It is recognised 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, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; 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) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

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 (see 1.1.1). Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

The classification of a substance is derived from the hazard categories in the following order of precedence: Category 1A, Category 1B, Category 2 and the additional Category for effects on or via lactation. If a substance meets the criteria for classification into both of the main categories (for example Category 1B for effects on sexual function and fertility and also Category 2 for development) then both hazard differentiations shall be communicated by the respective hazard statements. Classification in the additional category for effects on or via lactation will be considered irrespective of a classification into Category 1A, Category 1B or Category 2.

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 (see section 3.7.2.4).

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 shall 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 shall be supplemented with adequate data from studies in experimental animals and classification in Category 1B shall 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, see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together, 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 substance under study may also be included, particularly when information on the substance 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, the presence of maternal toxicity in experimental animal studies, level of statistical significance for inter-group 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. A single, positive study performed according to good scientific principles and with statistically

or biologically significant positive results may justify classification (see also 3.7.2.2.3).

3.7.2.3.2. Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information which reduces or increases concerns about the hazard to human health. If it is 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. If, in some reproductive toxicity studies in experimental animals the only effects recorded are considered to be of low or minimal toxicological significance, classification may not necessarily be the outcome. These effects include 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 shall 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 shall 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 shall 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 shall 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 can be assumed that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, if the substance 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. 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, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall 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, 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 number 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 shall be considered where there is a 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 shall not automatically be discounted for substances 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 substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

3.7.2.4.4. Some of the end points used to assess maternal effects 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 shall 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 shall not normally be considered for further evaluation.

Mating index (no. animals with seminal plugs or sperm/no. mated x 100)[1]

Fertility index (no. animals with implants/no. of matings x 100)

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 shall 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

[1] It is recognised that the Mating index and the Fertility index can also be affected by the male.

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.

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 is useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption need to 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 is 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 shall be reported in the study. 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, including 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), 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 function 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 shall 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 shall not be classified.

3.7.2.5.6. Studies involving routes of administration such as intravenous or intraperitoneal injection, which result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs,

including irritation, must be interpreted with extreme caution and on their own are not normally 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 is considered to be outside the criteria which lead to classification, but not regarding the inclusion within the criteria of a specific dose as a limit dose. However, some guidelines for test methods, specify a limit dose, others 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 is not 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 (3.7.2.4) 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 has been recommended as a limit dose, unless expected human response indicates the need for a higher dose level.

3.7.3. Classification criteria for mixtures

3.7.3.1. Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.7.3.1.1. The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 reproductive toxicant and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for Category 1A, Category 1B and Category 2 respectively.

3.7.3.1.2. The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above

the appropriate generic concentration limit as shown in Table 3.7.2 for the additional category for effects on or via lactation.

Table 3.7.2

Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]

Note

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1

If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0,1 %, a SDS shall be available for the mixture upon request.

3.7.3.2. Classification of mixtures when data are available for the complete mixture

3.7.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. 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, sensitivity and statistical analysis of reproduction test

systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.7.3.3. Classification of mixtures when data are not available for the complete mixture: bridging principles

3.7.3.3.1. Subject to paragraph 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 shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.7.4. Hazard Communication

3.7.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3

Table 3.7.3

Label elements for reproductive toxicity

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.

Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281	P201 P260 P263 P264 P270
Precautionary Statement Response	P308 + P313	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405	
Precautionary Statement Disposal	P501	P501	

3.8. SPECIFIC TARGET ORGAN TOXICITY - SINGLE EXPOSURE

3.8.1. Definitions and general considerations

3.8.1.1. Specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in sections 3.1 to 3.7 and 3.10 are included (see also 3.8.1.6).

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

3.8.1.3. These adverse health effects produced by a single exposure include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism, and these changes are relevant for human health.

3.8.1.4. Assessment shall 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 toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.8.1.6. Specific target organ toxicity following a repeated exposure is classified as described in Specific target organ toxicity – Repeated exposure (section 3.9) and is therefore excluded

from section 3.8. Other specific toxic effects, listed below, are assessed separately and consequently are not included here:

(a) Acute toxicity (section 3.1);
(b) Skin corrosion/irritation (section 3.2);
(c) Serious eye damage/eye irritation (section 3.3);
(ç) Respiratory or skin sensitisation (section 3.4);
(d) Germ cell mutagenicity (section 3.5);
(e) Carcinogenicity (section 3.6);
(f) Reproductive toxicity (section 3.7); and
(g) Aspiration toxicity (section 3.10).

3.8.1.7. The hazard class Specific Target Organ Toxicity – Single Exposure is differentiated into:

– Specific target organ toxicity – single exposure, Category 1 and 2;
– Specific target organ toxicity – single exposure, Category 3.

See Table 3.8.1.

Table 3.8.1

Categories for specific target organ toxicity-single exposure

Categories	Criteria
Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.

Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure Substances are classified in Category 2 for specific target organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.6).
Category 3	Transient target organ effects This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. Substances are classified specifically for these effects as laid down in 3.8.2.2.
Note: Attempts shall be made to determine the primary target organ of toxicity and to classify for that purpose, such as hepatotoxicants, neurotoxicants. The data shall be carefully evaluated and, where possible, secondary effects should not be included (e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).	

3.8.2. Classification criteria for substances

3.8.2.1. Substances of Category 1 and Category 2

3.8.2.1.1. Substances are classified for immediate or delayed effects separately, by the use of expert judgement (see 1.1.1) on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1.9). Substances are then placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Table 3.8.1).

3.8.2.1.2. The relevant route or routes of exposure by which the classified substance produces damage shall be identified (see 3.8.1.5).

3.8.2.1.3. Classification is determined by expert judgement (see section 1.1.1), on the basis of the weight of all evidence available including the guidance presented below.

3.8.2.1.4. Weight of evidence of all data (see section 1.1.1), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification.

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

3.8.2.1.6. In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of target organ toxicity in Category 2:

(a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or

(b) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

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

3.8.2.1.7.1. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

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

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

(a) morbidity resulting from single exposure;

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

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

(ç) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(d) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

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

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

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

It is recognised that effects may be seen which do not justify classification. Such effects in humans and/or animals include, but are not limited to:

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

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

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

(ç) adaptive responses that are not considered toxicologically relevant;

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

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

3.8.2.1.9.1. In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 or 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 substances are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged.

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

3.8.2.1.9.3. The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.2.

Table 3.8.2

Guidance value ranges for single-dose exposures[a]

			Guidance value ranges for:	
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	C ≤ 300	2000 ≥ C > 300	Guidance values do not apply[b]
Dermal (rat or rabbit)	mg/kg body weight	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	ppmV/4h	C ≤ 2500	20000 ≥ C > 2500	
Inhalation (rat) vapour	mg/l/4h	C ≤ 10	20 ≥ C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1,0	5,0 ≥ C > 1,0	

Note:

(a) The guidance values and ranges mentioned in Table 3.8.2 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.

(b) Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data, if available, shall be included in the weight of evidence evaluation.

3.8.2.1.10. Other considerations

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

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

3.8.2.1.10.3. A substance that has not been tested for specific target organ toxicity may, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue

that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

3.8.2.1.10.4. Saturated vapour concentration shall be considered, where appropriate, as an additional element to provide for specific health and safety protection

3.8.2.2. Substances of Category 3: Transient target organ effects

3.8.2.2.1. Criteria for respiratory tract irritation

The criteria for classifying substances as Category 3 for respiratory tract irritation are:

(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data;

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

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

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

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

3.8.2.2.2 Criteria for narcotic effects

The criteria for classifying substances as Category 3 for narcotic effects are:

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

(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure.

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 shall be classified for specific target organ toxicity following single exposure.

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

3.8.3.2.1. 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 shall be classified by weight of evidence evaluation of these data (see 1.1.1.4). Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

3.8.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

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 shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as mentioned in Table 3.8.3 for Category 1 and 2 respectively.

3.8.3.4.2. These generic concentration limits and consequent classifications shall be applied appropriately to single-dose specific target organ toxicants.

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

Table 3.8.3

Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture as Category 1 or 2

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as:	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10 %	1,0 % ≤ concentration < 10 %
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10 % [(Note 1)]

Note 1:

If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1,0 % a SDS shall be available for the mixture upon request.

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

3.8.3.4.5. Care shall be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A generic concentration limit of 20 % is appropriate; however, it shall be recognised that this concentration limit may be higher or lower depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20 % value. Expert judgement shall be exercised. Respiratory tract irritation and narcotic effects are to be evaluated separately in accordance with the criteria given in section 3.8.2.2. When conducting classification for these hazards, the contribution of each component should be considered additive, unless there is evidence that the effects are not additive.

3.8.4. Hazard Communication

3.8.4.1 Label elements shall be used in accordance with Table 3.8.4., for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.8.4

Label elements for specific target organ toxicity after single exposure

Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal Word	Danger	Warning	Warning
Hazard Statement	H370: Causes damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H371: May cause damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H335: May cause respiratory irritation; or H336: May cause drowsiness or dizziness
Precautionary Statement Prevention	P260 P264 P270	P260 P264 P270	P261 P271
Precautionary Statement Response	P307 + P311 P321	P309 + P311	P304 + P340 P312
Precautionary Statement Storage	P405	P405	P403 + P233 P405
Precautionary Statement Disposal	P501	P501	P501

3.9. SPECIFIC TARGET ORGAN TOXICITY –REPEATED EXPOSURE

3.9.1. Definitions and general considerations

3.9.1.1. Target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. However, other specific toxic effects that are specifically addressed in sections 3.1 to 3.8 and 3.10 are not included here.

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

3.9.1.3. These adverse health effects include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health.

3.9.1.4. Assessment shall 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 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 as described in Specific target organ toxicity – Single exposure (section 3.8) and are therefore excluded from section 3.9.

3.9.2. Classification criteria for substances

3.9.2.1. Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), 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 (Table 3.9.1).

Table 3.9.1

Categories for specific target organ toxicity-repeated exposure

Categories	Criteria
Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) 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 3.9.2.9), to be used as part of a weight-of- evidence evaluation.
Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

Note:

Attempts shall be made to determine the primary target organ of toxicity and classify for that purpose, such as hepatotoxicants, neurotoxicants. One shall carefully evaluate the data and, where possible, not include secondary effects (a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).

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

3.9.2.3. Classification is determined by expert judgement (see section 1.1.1), 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 (see section 1.1.1), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification. This taps the considerable body

of industrial toxicology data collected over the years. Evaluation shall be based on all existing data, including peer-reviewed published studies and additional acceptable data.

3.9.2.5. The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, such as 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 shall also be used, if available. Other long-term exposure studies, such as on carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

3.9.2.6. In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of specific target organ toxicity in Category 2:

(a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification; and/or

(b) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

3.9.2.7. Effects considered to support classification for specific target organ toxicity following repeated exposure

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

3.9.2.7.2. Evidence from human experience/incidents is usually restricted to reports of adverse health consequence, 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, 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, shall be taken into consideration in the classification process, including but not limited to the following toxic effects in humans and/or animals:

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

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

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

(ç) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(d) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

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

(f) 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 for specific target organ toxicity following repeated exposure

3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals which do not justify classification. Such effects include, but are not limited to:

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

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

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

(ç) adaptive responses that are not considered toxicologically relevant;

d) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health.

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 shall be classified or not, and to what degree it shall be classified (Category 1 or 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 substances 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 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 refer 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 shall be done on a case-by-case basis; for a 28-day study the guidance values below is increased by a factor of three.

3.9.2.9.6. Thus classification in Category 1 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur at or below the guidance values (C) as indicated in Table 3.9.2:

Table 3.9.2

Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg body weight/day	C ≤ 10
Dermal(rat or rabbit)	mg/kg body weight/day	C ≤ 20
Inhalation (rat)gas	ppmV/6h/day	C ≤ 50
Inhalation (rat)vapour	mg/litre/6h/day	C ≤ 0,2
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	C ≤ 0,02

3.9.2.9.7. Classification in Category 2 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges as indicated in Table 3.9.3:

Table 3.9.3

Guidance values to assist in Category 2 classification

Route of Exposure	Units	Guidance Value Ranges: (dose/concentration)
Oral (rat)	mg/kg body weight/day	$10 < C \leq 100$
Dermal (rat or rabbit)	mg/kg body weight/day	$20 < C \leq 200$
Inhalation (rat) gas	ppmV/6h/day	$50 < C \leq 250$
Inhalation (rat)vapour	mg/litre/6h/day	$0,2 < C \leq 1,0$
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	$0,02 < C \leq 0,2$

3.9.2.9.8. The guidance values and ranges mentioned in paragraphs 3.9.2.9.6 and 3.9.2.9.7 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 occurs in repeat-dose animal studies at a dose/concentration below the guidance value, such as < 100 mg/kg bw/day by the oral route, however the nature of the effect, such as 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, such as ≥ 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, such as other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification is the prudent action to take.

3.9.2.10. Other considerations

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

3.9.2.10.2. When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a

substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

3.9.2.10.3. A substance that has not been tested for specific target organ toxicity may, 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. Saturated vapour concentration shall be considered, where appropriate, as an additional element 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 shall be classified for specific target organ toxicity following repeated exposure.

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

3.9.3.2.1. 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 (see 1.1.1.4), then the mixture shall be classified by weight of evidence evaluation of these data. Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

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

3.9.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

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 shall be classified as a specific target organ 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 specific target organ toxicant and is present at or above the appropriate generic concentration limit as laid out in Table 3.9.4 for Category 1 and 2 respectively.

Table 3.9.4

Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as:	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10 %	1,0 % ≤ concentration < 10 %
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10 % [(Note 1)]

Note1

If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1,0 % a SDS shall be available for the mixture upon request.

3.9.3.4.2. These generic concentration limits and consequent classifications apply to repeated-dose target organ toxicants.

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

3.9.3.4.4. Care shall 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

3.9.4.1. Label elements shall be used in accordance with Table 3.9.5 for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.9.5

Label elements for specific target organ toxicity after repeated exposure

Classification	Category 1	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard Statement	H372: 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)	H373: 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)
Precautionary Statement Prevention	P260 P264 P270	P260
Precautionary Statement Response	P314	P314
Precautionary Statement Storage		
Precautionary Statement Disposal	P501	P501

3.10. ASPIRATION HAZARD

3.10.1. Definitions and general considerations

3.10.1.1. These criteria provide a means of classifying substances or mixtures that may pose an aspiration toxicity hazard to humans.

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

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

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

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

3.10.1.6. Specific considerations

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

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

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

3.10.1.6.2a Although the definition of aspiration in section 3.10.1.2 includes the entry of solids into the respiratory system, classification according to point (b) in Table 3.10.1 for Category 1 is intended to apply to liquid substances and mixtures only.

3.10.1.6.3. Classification of aerosol/mist products

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

3.10.2. Classification criteria for substances

Table 3.10.1

Hazard category for aspiration toxicity

Category	Criteria
Category 1	Substances known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard A substance is classified in Category 1: (a) based on reliable and good quality human evidence or (b) if it is a hydrocarbon and has a kinematic viscosity of 20,5 mm^2/s or less, measured at 40°C.

Note:

Substances in Category 1 include but are not limited to certain hydrocarbons, turpentine and pine oil.

3.10.3. Classification criteria for mixtures

3.10.3.1. Classification when data are available for the complete mixture

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

3.10.3.2. Classification when data are not available for the complete mixture: bridging principles

3.10.3.2.1. Where the mixture itself has not been tested to determine its aspiration toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazard of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3. However, in the case of application of the dilution bridging principle, the concentration of aspiration toxicant(s) shall be 10 % or more.

3.10.3.3. Classification when data are available for all components or only some components of the mixture

3.10.3.3.1. Category 1

3.10.3.3.1.1. A mixture which contains a total of 10 % or more of a substance or substances classified in Category 1, and has a kinematic viscosity of 20,5 mm^2/s or less, measured at 40°C, shall be classified in Category 1.

3.10.3.3.1.2. In the case of a mixture which separates into two or more distinct layers, one of which contains 10 % or more of a substance or substances classified in Category 1 and has a kinematic viscosity of 20,5 mm^2/s or less, measured at 40°C, then the entire mixture is classified in Category 1.

3.10.4. Hazard Communication

3.10.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.10.2.

Table 3.10.2

Aspiration toxicity label elements

Classification	Category 1
GHS Pictogram	
Signal Word	Danger
Hazard Statement	H304: May be fatal if swallowed and enters airways
Precautionary Statement Prevention	
Precautionary Statement Response	P301 + P310 P331
Precautionary Statement Storage	P405
Precautionary Statement Disposal	P501

PART 4

ENVIRONMENTAL HAZARDS

4.1. HAZARDOUS TO THE AQUATIC ENVIRONMENT

4.1.1. Definitions and General Considerations

4.1.1.1. Definitions

(a) “acute aquatic toxicity” means the intrinsic property of a substance to be injurious to an aquatic organism in a short-term exposure to that substance.

(b) “acute (short-term) hazard” means for classification purposes the hazard of a substance or mixture caused by its acute toxicity to an organism during short-term aquatic exposure to that substance or mixture.

(c) “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).

(ç) “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 bioavailability.

(d) “bioaccumulation” means the 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).

(e) “bioconcentration” means the net result of uptake, transformation and elimination of a substance in an organism due to waterborne exposure.

(f) “chronic aquatic toxicity” means the intrinsic property of a substance to cause adverse effects to aquatic organisms during aquatic exposures which are determined in relation to the life-cycle of the organism.

(g) “degradation” means the decomposition of organic molecules to smaller molecules and eventually to carbon dioxide, water and salts.

(ğ) “EC_x” means the effect concentration associated with x% response.

(h) “long-term hazard” means for classification purposes the hazard of a substance or mixture caused by its chronic toxicity following long-term exposure in the aquatic environment.

(ı) “no observed effect concentration (NOEC)” means the test concentration immediately below the lowest tested concentration with statistically significant adverse effect. The NOEC has no statistically significant adverse effect compared to the control.

4.1.1.2. Basic elements

4.1.1.2.0. Hazardous to the Aquatic Environment is differentiated into:

– acute aquatic hazard,

– long-term aquatic hazard.

4.1.1.2.1. The basic elements used for classification for aquatic environmental hazards are:

– acute aquatic toxicity,

– chronic aquatic toxicity,

– potential for or actual bioaccumulation, and

– degradation (biotic or abiotic) for organic chemicals.

4.1.1.2.2. Preferably data shall be derived using the standardised test methods referred to in Article 10 (3). In practice data from other standardised test methods such as national methods shall also be used where they are considered as equivalent. Where valid data are available from non-standard testing and from non-testing methods, these shall be considered in classification provided they fulfil the requirements specified in section 1 of Annex 9 . In general, both freshwater and marine species toxicity data are considered suitable for use in classification provided the test methods used are equivalent. Where such data are not available classification shall be based on the best available data. See also Part 1 of this Annex.

4.1.1.3. Other considerations

4.1.1.3.1. Classification of substances and mixtures for environmental hazards requires the identification of the hazards they present to the aquatic environment. The aquatic environment is considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. The basis, therefore, of the identification of acute (short-term) and long-term hazards is the aquatic toxicity of

the substance or mixture, although this shall be modified by taking account of further information on the degradation and bioaccumulation behaviour, if appropriate.

4.1.1.3.2. While the classification system applies to all substances and mixtures, it is recognised that for special cases (e.g. metals) the Agency has issued guidance.

4.1.2. Classification criteria for substances

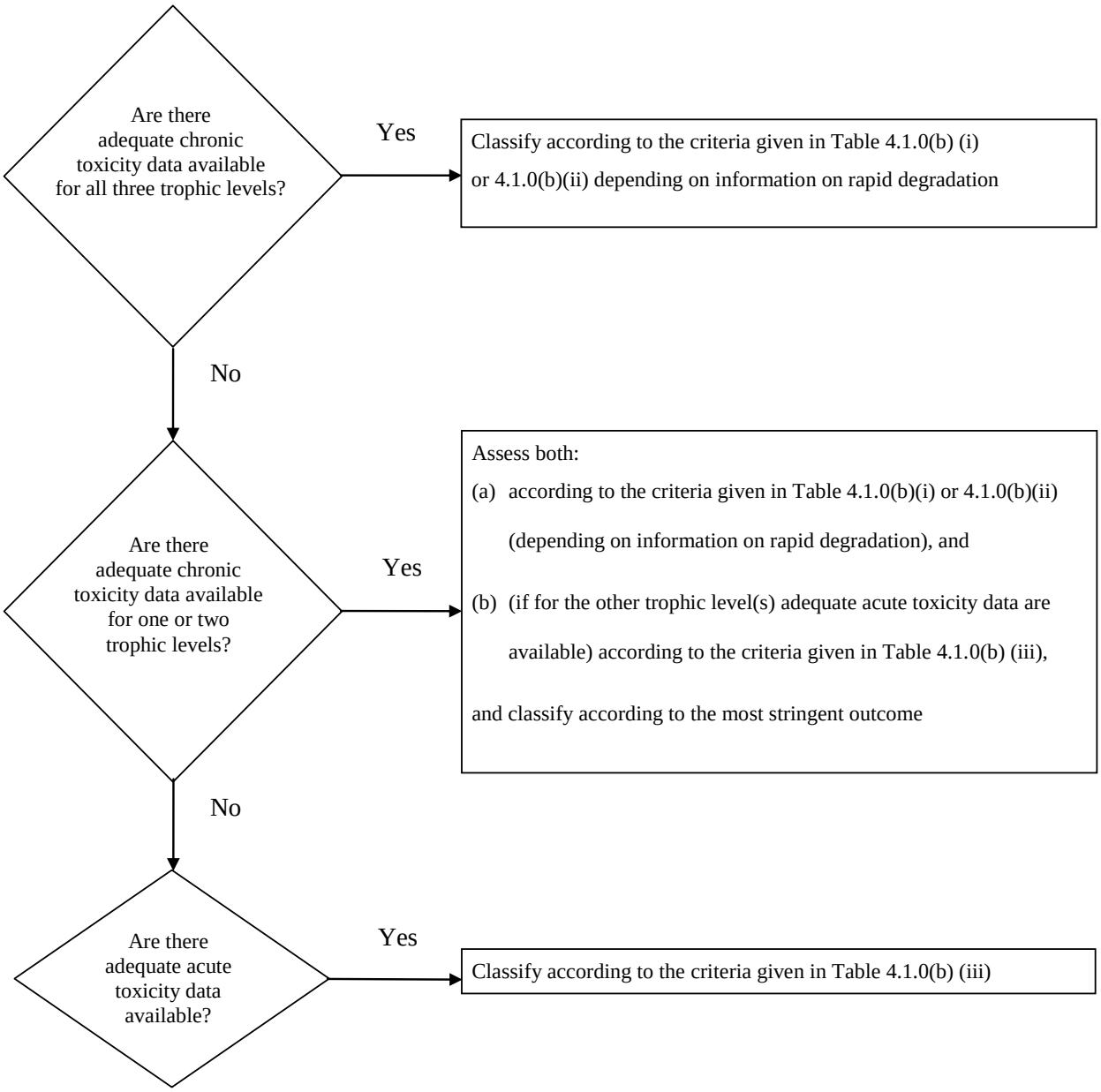
4.1.2.1. The system for classification recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and long-term hazard of a substance. For the long-term hazard, separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algea/aquatic plants) shall normally be used to define the appropriate hazard category(ies). There are circumstances, however, when a weight of evidence approach is appropriate.

4.1.2.2. The core classification system for substances consists of one acute classification category and three chronic classification categories. The acute and the chronic classification categories are applied independently.

4.1.2.3. The criteria for classification of a substance in category Acute 1 are defined on the basis of acute aquatic toxicity data only (EC_{50} or LC_{50}). The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tired approach where the first step is to see if available information on chronic toxicity merits long-term hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data 8degradability and bioaccumulation data) (see figure 4.1.1).

Figure 4.1.1

Categories for substances long-term hazardous to the aquatic environment



4.1.2.4. The system also introduces a "safety net" classification (referred to as category Chronic 4) for use when the data available do not allow classification under the formal criteria for acute 1 or chronic 1 to 3 but there are nevertheless some grounds for concern (see example in Table 4.1.0).

4.1.2.5 Substances with acute toxicity below 1mg/l or chronic toxicities below 0,1mg/l (if non-rapidly degradable) or 0,01mg/l (if rapidly degradable) contribute as components of a mixture to the toxicity of the mixture even at a low concentration and shall normally be given increased weight in applying the summation of classification approach (see note 1 of Table 4.1.0 and section 4.1.3.5.5).

4.1.2.6 The criteria for classifying and categorising substances as "hazardous to the aquatic environment" are summarised in Table 4.1.0

Table 4.1.0

Classification categories for hazardous to the aquatic environment

(a) Acute (short-term) aquatic hazard	
Category Acute 1: (Note 1)	
96 hr LC_{50} (for fish)	≤1 mg/l and/or
48 hr EC_{50} (for crustacea)	≤1 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/l. (Note 2)
(b) Long-term aquatic hazard	
(i) Non-rapidly degradable substances (Note 3) for which there are adequate chronic toxicity data available	
Category Chronic 1: (Note 1)	
Chronic NOEC or EC_x (for fish)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤0,1 mg/l.
Category Chronic 2:	
Chronic NOEC or EC_x (for fish)	>0,1 to ≤1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	>0,1 to ≤1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	>0,1 to ≤1 mg/l.
(ii) Rapidly degradable substances (Note 3) for which there are adequate chronic toxicity data available	
Category Chronic 1:(Note 1)	
Chronic NOEC or EC_x (for fish)	≤0,01 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤0,01 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤0,01 mg/l.
Category Chronic 2:	
Chronic NOEC or EC_x (for fish)	>0,01 to ≤0,1 mg/l and/or

Chronic NOEC or EC_x (for crustacea)	>0,01 to ≤0,1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	>0,01 to ≤0,1 mg/l.
Category Chronic 3:	
Chronic NOEC or EC_x (for fish)	>0,1 to ≤1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	>0,1 to ≤1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	>0,1 to ≤1 mg/l.

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

Category Chronic 1:(Note 1)

96 hr LC_{50} (for fish)	≤1 mg/l and/or
48 hr EC_{50} (for crustacea)	≤1 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 2:

96 hr LC_{50} (for fish)	>1 to ≤10 mg/l and/or
48 hr EC_{50} (for crustacea)	>1 to ≤10 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	>1 to ≤10 mg/l (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 3:

96 hr LC_{50} (for fish)	> 10 to ≤ 100 mg/l and/or
48 hr EC_{50} (for crustacea)	> 10 to ≤ 100 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	> 10 to ≤ 100 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

"Safety net" classification

Category Chronic 4

Cases when data do not allow classification under the above criteria but there are nevertheless some grounds for concern. This includes, for example, poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility (note 4), and which are not rapidly degradable in accordance with section 4.1.2.9.5 and have an experimentally determined BCF ≥ 500 (or, if absent, a log K_{ow} ≥ 4), indicating a potential to bioaccumulate, which will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence includes chronic toxicity NOECs > water solubility or > 1 mg/l, or other evidence of rapid degradation in the environment than the ones provided by any of the methods listed in section 4.1.2.9.5.

Note 1

When classifying substances as Acute Category 1 and/or Chronic Category 1 it is necessary at the same time to indicate an appropriate M-factor (see table 4.1.3).

Note 2

Classification shall be based on the ErC_{50} [= EC_{50} (growth rate)]. In circumstances where the basis of the EC_{50} is not specified or no ErC_{50} is recorded, classification shall be based on the lowest EC_{50} available.

Note 3

When no useful data on degradability are available, either experimentally determined or estimated data, the substance should be regarded as not rapidly degradable.

Note 4

"No acute toxicity" is taken to mean that the L(E)C_{50}(s) is/are above the water solubility. Also for poorly soluble substances, (water solubility < 1 mg/l), where there is evidence that the acute test does not provide a true measure of the intrinsic toxicity.

4.1.2.7. Aquatic toxicity

4.1.2.7.1. Acute aquatic toxicity is normally determined using a fish 96 hour LC_{50}, a crustacea species 48 hour EC_{50} and/or an algal species 72 or 96 hour EC_{50}. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable. The aquatic plant growth inhibition tests are normally considered as chronic tests but the EC_{50}s are treated as acute values for classification purposes (see note 2).

4.1.2.7.2. For determining chronic aquatic toxicity for classification purposes data generated according to the standardised test methods referred to in Article 10(3) shall be accepted, as well as results obtained from other validated and internationally accepted test methods. The NOECs or other equivalent $L(E)C_x$ (e.g. EC_{10}) shall be used.

4.1.2.8. Bioaccumulation

4.1.2.8.1. Bioaccumulation of substances within aquatic organisms can give rise to toxic effects over longer time scales even when actual water concentrations are low. For organic substances the potential for bioaccumulation shall normally be determined by using the octanol/water partition coefficient, usually reported as a log K_{ow}. The relationship between the log K_{ow} of an organic substance and its bioconcentration as measured by the bioconcentration factor (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. While this represents a potential to bioaccumulate, an experimentally determined BCF provides a better measure and shall be used in preference if available. A BCF in fish of ≥ 500 is indicative of the potential to bioconcentrate for classification purposes. Some relationships can be observed between chronic toxicity and bioaccumulation potential, as toxicity is related to the body burden.

4.1.2.9. Rapid degradability of organic substances

4.1.2.9.1. Substances that rapidly degrade can be quickly removed from the environment. While effects of such substances can occur, particularly in the event of a spillage or accident, they are localised and of short duration. In the absence of rapid degradation in the environment a substance in the water has the potential to exert toxicity over a wide temporal and spatial scale.

4.1.2.9.2. One way of demonstrating rapid degradation utilises the biodegradation screening tests designed to determine whether an organic substance is "readily biodegradable". Where such data are not available, a BOD(5 days)/COD ratio ≥ 0,5 is considered as indicative of rapid degradation. Thus, a substance which passes this screening test is considered 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. Other evidence of rapid degradation in the environment may therefore also be considered and are of particular importance where the substances are inhibitory to microbial activity at the concentration levels used in standard testing. Thus, a further classification criterion is included which allows 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 is demonstrated under environmentally realistic conditions, then the criterion of "rapid degradability" is met.

4.1.2.9.3. Many degradation data are available in the form of degradation half-lives and these can be used in defining rapid degradation provided that ultimate biodegradation of the substance, i.e. full mineralisation, is achieved. Primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

4.1.2.9.4. The criteria used reflect the fact that environmental degradation may be biotic or abiotic. Hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment.

4.1.2.9.5. Substances are considered rapidly degradable in the environment if one of the following criteria holds true:

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

(i) tests based on dissolved organic carbon: 70 %

(ii) tests based on oxygen depletion or carbon dioxide generation: 60 % of theoretical maximum.

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, unless the substance is identified as an UVCB or as a complex,

multi-constituent substance with structurally similar constituents. In this case, and where there is sufficient justification, the 10-day window condition may be waived and the pass level applied at 28 days; 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.

4.1.2.10. Inorganic compounds and metals

4.1.2.10.1. For inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather, such substances may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally the use of bioaccumulation data shall be treated with care[1].

4.1.2.10.2. 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 enter solution. All evidence must be weighted in a classification decision. This would be especially true for metals showing borderline results in the Transformation/Dissolution Protocol.

4.1.3. Classification criteria for mixtures

4.1.3.1. The classification system for mixtures covers all classification categories which are used for substances, i.e. Acute Category 1 and Chronic Categories 1 to 4. In order to make use of all available data for purposes of classifying the aquatic environmental hazards of the mixture, the following is applied where appropriate:

The "relevant components" of a mixture are those which are classified "Acute 1"or "Chronic 1" and present in a concentration of 0,1 % (w/w) or greater, and those which are classified "Chronic 2", "Chronic 3" or "Chronic 4" and present in a concentration of 1 % (w/w) or greater, unless there is a presumption (such as in the case of highly toxic components (see 4.1.3.5.5.5)) that a component present in a

[1] Specific guidance has been issued by the European Chemicals Agency on how these data for such substances may be used in meeting the requirements of the classification criteria.

lower concentration can still be relevant for classifying the mixture for aquatic environmental hazards. Generally, for substances classified as "Acute 1" or "Chronic 1" the concentration to be taken into account is (0,1/M) %. (For explanation M-factor see 4.1.3.5.5.5).

4.1.3.2. 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. Figure 4.1.2 outlines the process to be followed.

Elements of the tiered approach include:

– classification based on tested mixtures;

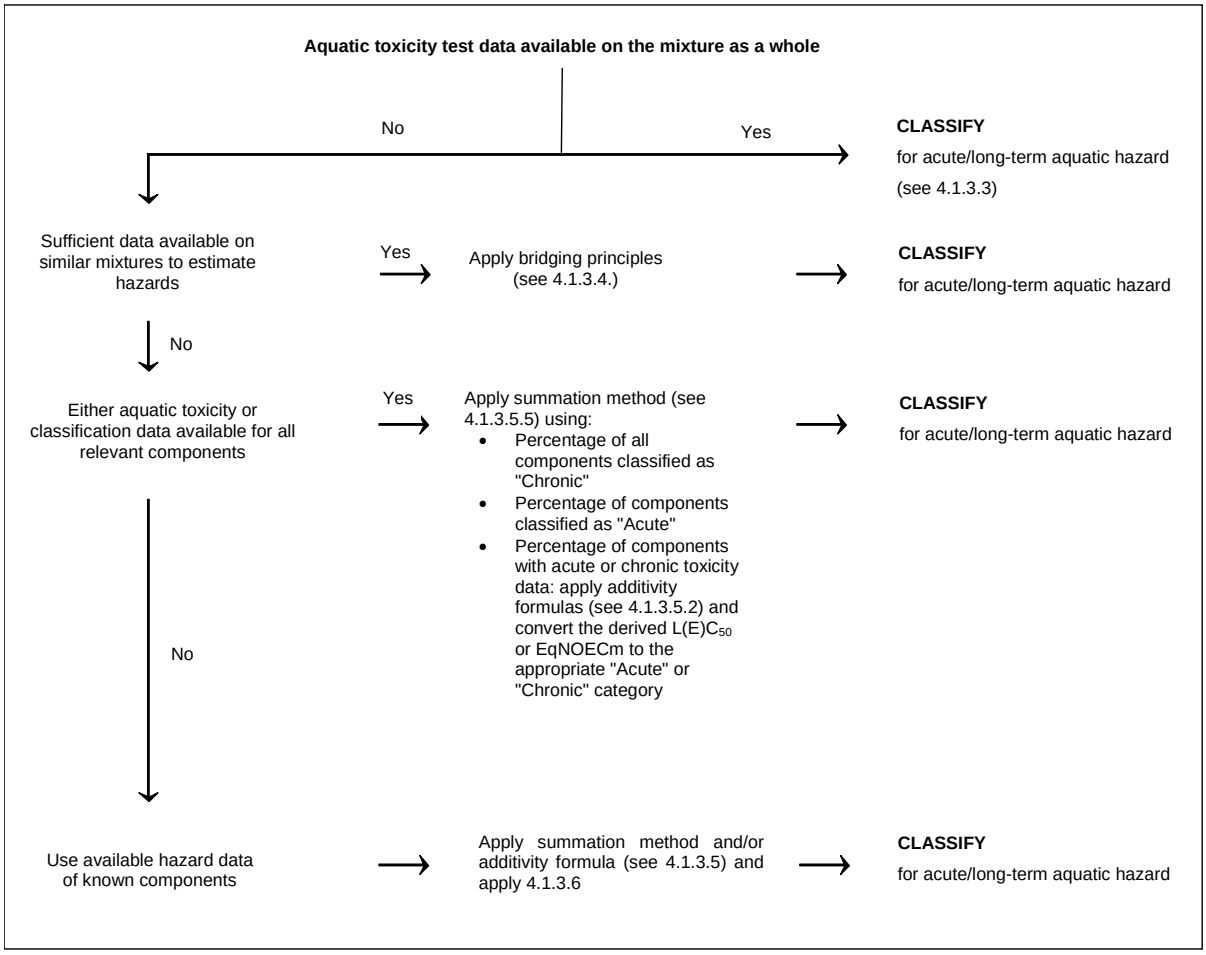
– classification based on bridging principles;

– the use of "summation of classified components" and/or an "additivity formula".

Figure 4.1.2

Tiered approach to classification of mixtures

for acute and long-term aquatic environmental hazards



4.1.3.3. Classification of mixtures when data are available for the complete mixture

4.1.3.3.1. When the mixture as a whole has been tested to determine its aquatic toxicity, this information can be used for classifying the mixture according to the criteria that have been agreed for substances. The classification is normally based on the data for fish, crustacea and algae/plants (see sections 4.1.2.7.1 and 4.1.2.7.2). When adequate acute or chronic toxicity data for the mixture as a whole are lacking, “bridging principles” or “summation method” should be applied (see sections 4.1.3.4 and 4.1.3.5).

4.1.3.3.2. The long-term hazard classification of mixtures requires additional information on degradability and in certain cases bioaccumulation. Degradability and bioaccumulation tests for mixtures are not used as they are usually difficult to interpret, and such tests may be meaningful only for single substances.

4.1.3.3.3 Classification for category Acute 1

(a) When there are adequate acute toxicity test data (LC_{50} or EC_{50}) available for the mixture as a whole showing $L(E)C_{50} \leq 1$ mg/l:

Classify mixture as Acute 1 in accordance with point (a) of Table 4.1.0.

(b) When there are acute toxicity test data ($LC_{50}(s)$ or $EC_{50}(s)$) available for the mixture as a whole showing $L(E)C_{50}(s) > 1$mg/l for normally all trophic levels:

No need to classify for acute hazard.

4.1.3.3.4 Classification for categories Chronic 1, 2 and 3

(a) When there are adequate chronic toxicity data (EC_x or NOEC) available for the mixture as a whole showing EC_x or NOEC of the tested mixture ≤ 1mg/l:

(i) Classify the mixture as Chronic 1, 2 or 3 in accordance with point (b) (ii) of Table 4.1.0 as rapidly degradable if the available information allows the conclusion that all relevant components of the mixture are rapidly degradable.

(ii) Classify the mixture as Chronic 1 or 2 in all other cases in accordance with point (b) (i) of Table 4.1.0 as non-rapidly degradable;

(b) When there are adequate chronic toxicity data (ECx or NOEC) available for the mixture as a whole showing ECx(s) or NOEC(s) of the tested mixture >1 mg/l for normally all trophic levels:

No need to classify for lon-term hazard in categories Chronic 1, 2 or 3.

4.1.3.3.5 Classification for category Chronic 4

If there are nevertheless reasons for concern:

Classify the mixture as Chronic 4 (safety net classification) in accordance with Table 4.1.0.

4.1.3.4. Classification of mixtures when data are not available for the complete mixture: bridging principles

4.1.3.4.1. 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 shall be used in accordance with the bridging rules set out in section 1.1.3. However, in relation to application of the bridging rule for dilution, sections 4.1.3.4.2 and 4.1.3.4.3 shall be used.

4.1.3.4.2. Dilution: if a mixture is formed by diluting another tested mixture or a substance classified for its aquatic environmental hazard 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 resulting mixture may be classified as equivalent to the original mixture or substance. Alternatively, the method explained in section 4.1.3.5 may be applied.

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

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

4.1.3.5.1. The classification of a mixture is based on summation of the concentration of its classified components. The percentage of components classified as "Acute" or "Chronic" is fed straight in to the summation method. Details of the summation method are described in 4.1.3.5.5.

4.1.3.5.2. Mixtures can be made of a combination of both components that are classified (as Acute 1 and/or Chronic 1, 2, 3, 4) and others for which adequate toxicity test data is available. When adequate toxicity data are available for more than one component in the mixture, the combined toxicity of those components is calculated using the following additivity formulas (a) or (b), depending on the nature of toxicity data.

(a) Based on acute aquatic toxicity:

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

where:

C_i = concentration of component i (weight percentage)

$L(E)C_{50\,i}$ = (mg/l) LC_{50} or EC_{50} for component i

η = number of components

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

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;

(b) Based on chronic aquatic toxicity:

$$\frac{\sum Ci + \sum Cj}{EqNOEC_m} = \sum_n \frac{Ci}{NOECi} + \sum_n \frac{Cj}{0{,}1 \times NOECj}$$

where:

C_i	=	concentration of component i (weight percentage) covering the rapidly degradable components;
Cj	=	concentration of component j (weight percentage) covering the non- rapidly degradable components;
NOECi	=	NOEC (or other recognised measures for chronic toxicity) for component i covering the rapidly degradable components, in mg/l;
NOECj	=	NOEC (or other recognised measures for chronic toxicity) for component j covering the non-rapidly degradable components, in mg/l;
n	=	number of components, and i and j are running from 1 to n;
EqNOECm	=	Equivalent NOEC of the part of the mixture with test data;

The equivalent toxicity thus reflects the fact that non-rapidly degrading substances are classified one hazard category level more “severe” than rapidly degrading substances.

The calculated equivalent toxicity may be used to assign that portion of the mixture a long-term hazard category, in accordance with the criteria for rapidly degradable substances (point (b)(ii) of Table 4.1.0.), which is then subsequently used in applying the summation method.

4.1.3.5.3. 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 taxonomic group (i.e. fish, daphnia, algae or equivalent) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three taxonomic groups). However, when toxicity data for each component are not available in the same taxonomic group, the toxicity value of each component is 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 and chronic toxicity is then used to assess whether this part of the mixture shall be classified as Acute 1 and/or Chronic 1, 2 or 3 using the same criteria described for substances.

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

4.1.3.5.5. Summation method

4.1.3.5.5.1. Rationale

4.1.3.5.5.1.1. In case of the substance classification categories Chronic 1 to Chronic 3, 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 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 as Chronic 1, 2 or 3.

4.1.3.5.5.1.2. When a mixture contains components classified as Acute 1 or Chronic 1, attention must be paid to the fact that such components, when their acute toxicity is below 1 mg/l and/or chronic toxicity is below 0,1 mg/l (if non rapidly degradable) and 0,01 mg/l (if rapidly degradable) contribute to the toxicity of the mixture even at a low concentration. 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 generic concentration limits leads to an "under-classification" of the mixture. Therefore, multiplying factors shall be applied to account for highly toxic components, as described in paragraph 4.1.3.5.5.5.

4.1.3.5.5.2. Classification procedure

4.1.3.5.5.2.1. In general a more severe classification for mixtures overrides a less severe classification, e.g. a classification with Chronic 1 overrides a classification with Chronic 2. As a consequence, in this example, the classification procedure is already completed if the result of the classification is Chronic 1. A more severe classification than Chronic 1 is not possible. Therefore it is not necessary to undergo the further classification procedure.

4.1.3.5.5.3. Classification for category Acute 1

4.1.3.5.5.3.1. First all components classified as Acute 1 are considered. If the sum of the concentrations (on %) of these components multiplied by their corresponding M-factors is greater than 25 % the whole mixture is classified as Acute 1.

4.1.3.5.5.3.2. The classification of mixtures for acute hazards based on this summation of classified components is summarised in Table 4.1.1.

Table 4.1.1

Classification of a mixture for acute hazards,

based on summation of classified components

Sum of components classified as:	Mixture is classified as:
Acute 1 x M([a]) ≥ 25 %	Acute 1

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

4.1.3.5.5.4. Classification for the categories Chronic 1, 2, 3 and 4

4.1.3.5.5.4.1. First all components classified as Chronic 1 are considered. If the sum of these components multiplied by their corresponding M-factors is equal to or greater than 25 %, the mixture is classified as Chronic 1. If the result of the calculation is a classification of the mixture as Chronic 1 the classification procedure is completed.

4.1.3.5.5.4.2. In cases where the mixture is not classified as Chronic 1, classification of the mixture as Chronic 2 is considered. A mixture is classified as Chronic 2 if 10 times the sum of the concentrations (in %) of all components classified as Chronic 1 multiplied by their corresponding M-factors plus the sum of the concentrations (in %) of all components classified as Chronic 2 is equal to or greater than 25 %. If the result of the calculation is classification of the mixture as Chronic 2, the classification process is completed.

4.1.3.5.5.4.3. In cases where the mixture is not classified either as Chronic 1 or Chronic 2, classification of the mixture as Chronic 3 is considered. A mixture is classified as

Chronic 3 if 100 times the sum of the concentrations (in %) of all components classified as Chronic 1 multiplied by their corresponding M-factors plus 10 times the sum of the concentrations (in %) of all components classified with Chronic 2 plus the sum of the concentrations (in %) of all components classified as Chronic 3 is ≥ 25 %.

4.1.3.5.5.4.4. If the mixture is still not classified in Chronic 1, 2 or 3, classification of the mixture as Chronic 4 shall be considered. A mixture is classified as Chronic 4 if the sum of the concentrations (in %) of all components classified as Chronic 1, 2, 3 and 4 is equal to or greater than 25 %.

4.1.3.5.5.4.5. The classification of mixtures for long-term hazards, based on this summation of the concentration of classified components, is summarised in Table 4.1.2.

Table 4.1.2

Classification of a mixture for long-term hazards,

based on summation of the concentrations of classified components

Sum of components classified as:	Mixture is classified as:
Chronic 1 x M (ª) ≥ 25 %	Chronic 1
(M x 10 x Chronic 1) + Chronic 2 ≥ 25 %	Chronic 2
(M x 100 x Chronic 1) + (10 x Chronic 2) + Chronic 3 ≥ 25 %	Chronic 3
Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25 %	Chronic 4

(ª) For explanation of the M-factor, see 4.1.3.5.5.5

4.1.3.5.5.5. Mixtures with highly toxic components

4.1.3.5.5.5.1. Acute 1 and Chronic 1 components with toxicities below 1 mg/l and/or chronic toxicities below 0,1 mg/l (if non-rapidly degradable) and 0,01 mg/l (if rapidly degradable) contribute to the toxicity of the mixture even at a low concentration and shall normally be given increased weight in applying the summation of classification approach. When a mixture contains components classified as Acute or Chronic 1, one of the following shall be applied:

– the tiered approach described in 4.1.3.5.5.3 and 4.1.3.5.5.4 using a weighted sum by multiplying the concentrations of Acute 1 and Chronic 1 components by a factor, instead of merely adding up the percentages. This means that the concentration of "Acute 1" in the left column of Table 4.1.1 and the concentration of "Chronic 1" in the left column of Table 4.1.2 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 4.1.3. Therefore, in order to classify a mixture containing Acute/Chronic 1 components, the classifier needs to be informed of the value of the M-factor in order to apply the summation method,

– the additivity formula (see 4.1.3.5.2) provided that 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 and/or chronic toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture.

Table 4.1.3

Multiplying factors for highly toxic components of mixtures

Acute toxicity	**M factor**	**Chronic toxicity**	**M factor**	
L(E)C_{50} value mg/l		**NOEC value mg/l**	**NRD ([a]) components**	**RD([b]) components**
0,1 < L(E)C_{50} ≤ 1	1	0,01 < NOEC ≤ 0,1	1	-
0,01 < L(E)C_{50} ≤ 0,1	10	0,001 < NOEC ≤ 0,01	10	1
0,001 < L(E)C_{50} ≤ 0,01	100	0,0001 < NOEC ≤ 0,001	100	10
0,0001 < L(E)C_{50} ≤ 0,001	1 000	0,00001 < NOEC ≤ 0,0001	1 000	100
0,00001 < L(E)C_{50} ≤ 0,0001	10 000	0,000001 < NOEC ≤ 0,00001	10 000	1 000
(continue in factor 10 intervals)		(continue in factor 10 intervals)		

([a]) Non-rapidly degradable

([b]) Rapidly degradable

4.1.3.6. Classification of mixtures with components without any useable information

4.1.3.6.1. In the event that no useable information on acute and/or long-term aquatic hazard is available for one or more relevant components, it is concluded that the mixture cannot be attributed to one or more definitive hazard category(ies). In this situation the mixture shall be classified based on the known components only, with the additional statement on the label and in the SDS that: "Contains x % of components with unknown hazards to the aquatic environment".

4.1.4. Hazard Communication

4.1.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 4.1.4.

Table 4.1.4

Label elements for hazardous to the aquatic environment

	ACUTE AQUATIC HAZARD
	Acute 1
GHS Pictogram	
Signal word	Warning
Hazard statement	H400: Very toxic to aquatic life
Precautionary statement prevention	P273
Precautionary statement response	P391
Precautionary statement storage	
Precautionary statement disposal	P501

LONG-TERM AQUATIC HAZARD				
	Chronic 1	Chronic 2	Chronic 3	Chronic 4
GHS pictograms			No pictogram is used	No pictogram is used
Signal word	Warning	No signal word is used	No signal word is used	No signal word is used
Hazard statement	H410: Very toxic to aquatic life with long lasting effects	H411: Toxic to aquatic life with long lasting effects	H412: Harmful to aquatic life with long lasting effects	H413: May cause long lasting harmful effects to aquatic life
Precautionary statement prevention	P273	P273	P273	P273
Precautionary statement response	P391	P391		
Precautionary statement storage				
Precautionary statement disposal	P501	P501	P501	P501

PART 5

ADDITIONAL EU HAZARD CLASS

5.1. HAZARDOUS TO THE OZONE LAYER

5.1.1. Definitions and general considerations

5.1.1.1. Ozone depleting potential (ODP) is an integrative quantity, distinct for each halocarbon source species, that represents the extent of ozone depletion in the stratosphere expected from the halocarbon an a mass-for-mass basis relative to CFC-11. The formal definition of ODP is the ratio of integrated perturbations to total ozone, for a differential mass emission of a particular compound relative to an equal emission of CFC-11.

Substance hazardous to the ozone layer means a substance which, on the basis of the available evidence concerning its properties and its predicted or observed environmental fate and behaviour may present a danger to the structure and/or the functioning of the stratospheric ozone layer. This includes substances which are listed in By-Law on Decreasing the substances that deplete the ozone layer published in the Official Gazzette dated 12/11/2008 and numbered 27052.

5.1.2. Classification criteria for substances

5.1.2.1. A substance shall be classified as hazardous to the ozone layer (Category 1) if the available evidence concerning its properties and its predicted or observed environmental fate and behaviour indicate that it may present a danger to the structure and/or the functioning of the stratospheric ozone layer.

5.1.3. Classification criteria for mixtures

5.1.3.1. Mixtures shall be classified as hazardous to the ozone layer (Category 1) on the basis of the individual concentration of the substance(s) contained therein that are also classified as hazardous to the ozone layer (Category 1), in accordance with Table 5.1.

Table 5.1

Generic concentration limits for substances (in a mixture), classified as hazardous to the ozone layer (Category 1), that trigger classification of the mixture as hazardous to the ozone layer (Category 1)

Classification of the substance	Classification of the mixture
Hazardous to the ozone layer	C > 0,1 %

5.1.4. Hazard communication

5.1.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 5.2

Table 5.2

Label elements for Hazardous to the Ozone Layer

Symbol/pictogram	
Signal word	Warning
Hazard statement	H420: Harms public health and the environment by destroying ozone in the upper atmorsphere
Precautionary statements	P273 P501