ANNEX I
Classification and labelling requirements for hazardous substances and mixtures

This Annex establishes the criteria for the classification of substances and mixtures as hazardous and it specifies labelling elements for each hazard class or category.

The Annex consists of 6 parts.

Part 1 is an introduction to the Annex and specifies in more detail the rules set out in Titles I to III on the general principles for classification and labelling.

Parts 2, 3 and 4 of this Annex implement the criteria for classification that have been established in the Globally Harmonised System of Classification and Labelling of Chemicals[1] (GHS) at the UN level.

Part 2 deals with physical hazards, Part 3 with health hazards and Part 4 with environmental hazards.

Part 5 of this Annex deals with the hazard class "hazardous for the ozone layer" and is part of the current EU system for classification of hazardous substances and mixtures but which has not yet been included in the Globally Harmonised System.

Part 6 contains rules for the application of precautionary statements.

Any reference in this Annex to a "Part", "chapter" "section" or "paragraph" is a reference to the rules of this Annex, unless stated otherwise.

Note that Annex II contains further criteria for the labelling and packaging of classified substances and mixtures.

1. PART 1: INTRODUCTION GENERAL PRINCIPLES FOR CLASSIFICATION AND LABELLING

1.1. CLASSIFICATION OF SUBSTANCES AND MIXTURES

1.1.1. Purpose and general obligations

The purpose of the classification and labelling procedure is to identify and communicate whether a substance or mixture has an intrinsic capacity or property to cause an effect which is considered to be hazardous. Criteria for identifying such hazardous substances and mixtures are described in this Annex.

Substances and mixtures shall be classified as hazardous when the hazard information fulfils any of the criteria set out in Parts 2 to 5 of this Annex.

[1] Globally Harmonized System of Classification and Labelling of Chemicals (GHS), first revised edition, United Nations, New York and Geneva, 2005 (ST/SG/AC.10/30/Rev.1)

To this end, in accordance with Articles 1 to 10, any supplier of a substance or mixture shall normally perform the following three steps when classifying a substance or mixture:

– Identify relevant information regarding the hazards of a substance or mixture;

– Evaluate this information to ascertain the hazards associated with the substance or mixture; and

– Take a decision on whether the hazard information on the substance or mixture meets the criteria for classification as hazardous. The hazard category(ies), if defined, shall be specified for each hazard class for which the criteria are fulfilled. If the criteria are not fulfilled for any hazard class, the reasons shall be provided (i.e. if data are lacking, inconclusive, or conclusive but not sufficient for classification).

The identification and evaluation of the information shall be based on the actual substance or mixture involved, i.e. on the substance or mixture, in the form and/or physical state as placed on the market.

The supplier of a substance or mixture shall consider all hazard classes, as the objective is to identify all the hazardous physical, toxicological and ecotoxicological properties of the substance or mixture, and if within a hazard class whose criteria are fulfilled, hazard categories are defined, the supplier needs to decide to which of these hazard categories the substance or mixture shall be ascribed.

1.1.2. Hazard Identification

1.1.2.1. There is no requirement to generate new test data for the purpose of hazard identification and classification of any substance or mixture under this Regulation, as set out in Article 5 (2)[2]. However, information required for classification may be obtained from a number of different sources, for example:

– the results of existing test data;

– for substances subject to registration according to the REACH-Regulation, information generated according to the provisions of that Regulation;

– information required by international rules on the transport of dangerous goods;

– information required by other legislation concerning e.g. biocides within the scope of Directive 98/8/EC or plant protection products within the scope of Directive 91/414/EEC;

– information taken from reference works and other literature;

– information derived from practical experience; or

[2] GHS §1.3.2.4.1 (in part)

– for mixtures, by application of the methods referred to in Section 1.1.5;

– where appropriate, the results of the use of valid structure-activity relationship models and expert judgement.; or

– grouping of substances and use of read-across.

1.1.2.2. For health, environmental and some physical hazards, the criteria are test method neutral, in the sense that they allow different approaches to be used for purposes of hazard determination as long as the tests[3]:

– are scientifically sound and conducted and validated according to internationally recognised scientific principles and procedures for the hazard of concern and produce mutually acceptable data, e.g. OECD Test Guidelines;

– according to Article 7.2, for other test methods, the available data shall be evaluated by comparing the test methods employed with those indicated in Article 5(4).

For substances or mixtures covered by Directives 91/414/EEC and 98/8/EEC, data for classification are also acceptable from other internationally recognised methods in accordance with the provisions of those Directives.

1.1.3. Hazard evaluation and classification

The identified relevant information shall be evaluated as set out in Article 7.

[3] GHS § 1.3.2.4.3, modified

1.1.3.1. In addition to Article 7 the following rules for the hazard evaluation and classification of a substance or mixture in accordance with Article 7 (1) shall apply:

1.1.3.1.1 Where it can be demonstrated by epidemiological studies, by scientifically valid case studies as specified in this Annex or by statistically-backed experience such as the assessment of data from poison information units or concerning occupational diseases that toxicological effects on humans differ from those suggested by the application of the methods outlined in this Annex, then the substance or mixture shall be classified according to its effects on humans. Testing on humans for the purpose of this Regulation shall not be carried out[4].

1.1.3.1.2 Positive effects which are consistent with the criteria for classification, whether seen in humans or animals, shall normally justify classification[5].

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

1.1.3.2.1 As set out in Article 7 (3), where a classification cannot be directly made on the basis of available identified information, a weight of evidence determination using expert judgment shall be applied[6].

Examples for cases in which expert judgment particularly shall be applied are the following:

– when there are difficulties in determining the quality of data, especially when derived from older studies;

– when available information is not sufficient to decide whether the criteria are fulfilled; applying expert judgment ensures that existing information can be used for as many substances or mixtures as possible to provide protection for human health and the environment;

– the criteria are semi-quantitative or qualitative and therefore expert judgement is required to interpret the available information[7];

– to interpret information for hazard classification of mixtures;

– when considered appropriate to apply the results of the use of valid structure-activity relationship models provided that the conditions in Annex XI 1.3 of the REACH Regulation are met.

– Substances whose physical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances provided that the conditions in Annex XI 1.5 of the REACH regulation are met. Application of the group concept requires that physical properties, human health effects and environmental effects or environmental fate may be predicted from data for a

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4 Annex VI §3.1.1, para 2.and GHS § 1.3.2.4.7 modified

5 GHS § 1.3.2.4.9.3

6 GHS § 1.3.2.4.8, in part with modifications

7 GHS § 1.3.2.1.2 in part §1.3.2.4.8, in part

reference substance within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.

The similarities may be based on[8]:

(1) a common functional group;

(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar substances; or

(3) a constant pattern in the changing of the potency of the properties across the category.

If the group concept is applied, substances shall be classified and labelled on this basis.

[8] REACH Annex XI, 1.5

1.1.3.2.2 A weight of evidence determination means that all available information bearing on the determination of toxicity is considered together, like for example the results of suitable in vitro tests, relevant animal data, information from the application of the category approach and human experience such as epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data are important. Evaluation of substances or mixtures related to the substance or mixture being classified shall generally be included, 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[9].

1.1.3.2.3 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 shall have precedence over other data. However, well designed and conducted epidemiological studies may lack sufficient number of subject to detect relatively rare but still significant effect, to assess potentially confounding factors. 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 and quality of both the human and animal data[10].

1.1.3.2.4 Route of exposure, mechanistic information and metabolism studies are pertinent to determining the relevance of an effect in humans. When such information 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 shall not be classified[11].

1.1.3.2.5 Both positive and negative results are assembled together in the weight of evidence determination. However, a single positive study performed according to good scientific principles and with statistically and biologically significant positive results may justify classification[12].

1.1.3.3. Consideration of additional information according to Article 7 (5)

1.1.3.3.1 In accordance with Article 7 (5), if adequate information is available to demonstrate in practice that the physical properties of substances and mixtures, apart from organic peroxides, are different from those revealed by the test methods, then such substances and mixtures shall be classified according to the hazard they present to those handling the substances and mixtures or to other persons. The classification derived from the direct application of the criteria may be refined accordingly[13].

1.1.3.3.2 The effect of a substance or mixture on biological and environmental systems is influenced, among other factors, by the physical properties of the substance or mixture and/or ingredient substances in the mixture and the way in which ingredient

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9 GHS § 1.3.2.4.9.1 and 1.3.2.4.9.2

10 GHS § 1.3.2.4.9.3

11 GHS § 1.3.2.4.9.4

12 GHS § 1.3.2.4.9.5

13 New text based on notes in the physical hazards section of the GHS and the draft of Note T to be included in the 30th ATP.

substances are biologically available. Some groups of substances may present special problems in this respect, for example, some polymers and metals. The supplier needs not to classify a substance or mixture when it can be shown by conclusive experimental data from internationally acceptable test methods that the substance or mixture is not biologically available[14]. For the classification of a mixture bioavailability data on ingredient substances of this mixture shall be taken into account and the classification may need to be refined accordingly[15]. However the information on the hazards of the substance in other forms shall be communicated in the Safety Data Sheet or shall be provided in accordance with Article 32 of the REACH Regulation.

1.1.4. Concentration limits

1.1.4.1. Concentration limits for the Classification of Substances containing Impurities, Additives or Individual constituents

The concentration limits for impurities, additives or individual constituents of substances that meet the criteria for classification themselves that a supplier needs to take into account for the classification of a substance referred to in Article 10 (1), shall be as defined below in Table 1.1, unless there is evidence that such an impurity, additive or individual constituent is still relevant for the classification of the substance below these concentration limits or where lower values have been specified in Annex VI or set out in each Part of Annex I[16].

Table 1.1

Hazard class	**Concentration limits/ cut off values to be taken into account**
Acute Toxicity	≥ 1,0%
Skin Corrosion/Irritation	≥ 1,0%
Serious damage to eyes/eye irritation	≥ 1,0%
Respiratory/Skin Sensitization	≥ 1,0%
Mutagenicity: Categories 1A, 1B	≥ 0,1%
Mutagenicity: Category 2	≥ 1,0%
Carcinogenicity: Categories 1A, 1B, 2	≥ 0,1%
Reproductive Toxicity: Categories 1A, 1B, 2	≥ 0,1%

14 Specific guidance will be provided by the agency on what would be regarded as acceptable evidence of non-bioavailability.

15 GHS 1.3.2.4.5

16 Annex VI §1.7.2 in part

Additional category for effects on and via lactation	≥ 0,3%
Specific Target Organ Systemic Toxicity (Single Exposure)	≥ 1,0%
Specific Target Organ Systemic Toxicity (Repeat Exposure)	≥ 1,0%
Hazardous to the Aquatic Environment	≥ 1,0%
Ozone depletion	≥ 0,1%

Note
The concentration limit/cut-off value does not necessarily trigger classification. Equally for some categories the concentration limits/cut-off values to be taken into account may be lower than the generic presented in the table, see limits in each Part of Annex I.

1.1.4.2. Concentration limits for the classification of mixtures

1.1.4.2.1 According to Article 10 (2) the supplier of a mixture shall take into account for the classification of untested mixture, substances classified as hazardous on the basis of their health and/or environmental effects, also if they are only present as impurities or additives, when their concentrations are equal to, or greater than

(a) specific concentration limits that have been set in Annex VI; or

(b) if no specific concentration limits have been set in Annex VI, generic concentration limits/cut-off values defined in Table 1.1 above in 1.1.4.1 of this Annex, unless the generic cut-off values or other concentration limits for the classified substances in the mixture have been set for specific hazard classes in the Parts 3, 4 or 5 of this Annex. Applying the methods referred to in Article 6 (b) (ii), for example for the additivity formula for acute toxicity, these are the values to be used for the evaluation of untested mixtures[17].

1.1.4.2.2 In derogation from the above, instead of the limits specified a supplier of a substance may set a specific concentration limit that he has derived in accordance with the following rules:

– The supplier shall set those specific concentration limits in accordance with the criteria set out in the chapters of this Annex and in the guidance made available by the Agency, and he shall include the justification for it either in his notification according to the classification and labelling inventory or in his registration according to the REACH Regulation. The supplier shall consider any

[17] Annex VI §1.7.3, 2nd para., amended

specific concentration limits included in the classification and labelling inventory.

– Where the supplier has information that the hazard of a substance in a mixture will be evident below the generic cut-off/concentration limits set in the provisions for any hazard class in Parts 3, 4 or 5, the mixture containing that ingredient shall be classified accordingly[18] and inline with the guidance made available by the Agency.

– On occasion, conclusive data may show that the hazard of a substance in a mixture will not be evident when present at a level above the generic concentration limit(s)/cut-off vale(s) set in the provisions for that hazard class. In these cases the mixture may be classified according to those data and inline with the guidance made available by the Agency, provided the data exclude the possibility that the ingredient would behave in the mixture in a manner that would increase the hazard over that of the pure substance and the mixture does not contain ingredients that would affect that determination[19].

1.1.5. Further rules for the identification and evaluation of hazard information for mixtures

Mixtures shall be classified on the basis of the information and methods outlined in Article 6. In accordance with Article 6 (b) and 1.1.7, the classification of an untested mixture shall be based on bridging principles as described under each chapter in this Annex. If available data do not allow application of bridging principles, the methods outlined in each chapter in this Annex considering the application of cut off limits and for some hazards, additivity formula, shall be applied[20]. In addition to Article 6, the following shall apply for the hazard identification of mixtures:

(a) Without prejudice to the requirements of Directive 91/414/EEC and 98/8/EC, only where it can be scientifically demonstrated by the supplier of the mixture that the toxicological properties of the mixture cannot correctly be determined by the methods outlined in Article 6 (b), or on the basis of existing test results, the methods outlined in Article 5 (4) may be used[21], e.g. to provide evidence about possible occurrence of synergistic or antagonistic effects which cannot otherwise be predicted.

(b) In the case of mixtures containing at least one substance classified as hazardous for carcinogenicity, mutagenicity or reproductive toxicity in accordance with Chapters 3.5, 3.6 and/or .3.7, the supplier shall apply the concentration limit/cut-off method referred to in Part 3, paragraphs 3.5.3.3.1, 3.6.3.3.1 or 3.7.3.3.1 for the classification of the mixture[22].

(c) The classification may be modified on a case-by-case basis for mixtures where test data are available for these hazards, In such cases, the test results for the

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18 GHS § 1.3.3.2.2, modified

19 GHS § 1.3.3.2.3

20 67/548/EEC Annex VI Section 3 Intro. §3.1.3 and GHS Section 1.3.2.3, in part

21 1999/45/EC, Article 6.2, slightly amended

22 to capture the principle of "with the exception of the criteria of Chapter 4 for which only the conventional method is applicable" in Annex VI Gen. Intro. §1.7.3.

mixture as a whole must be shown to be conclusive, taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of germ cell mutagenicity/ carcinogenicity/reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request in accordance with Article 32.

1.1.6. Specific rules for the classification of mixtures

1.1.6.1. Article 9 (1) sets out that the classification of a mixture shall take into account all available information about the potential occurrence of synergistic effects between the substances contained in the mixture. The classification may only be lowered to a less hazardous category on the basis of antagonistic effects, provided the supplier has sufficient adequate and reliable data.

1.1.6.2 *In addition, the following shall apply in accordance with Article 9 (2):*

1.1.6.2.1 A mixture need not be classified for "explosive", "oxidising", or "flammable" properties provided that[23]:

- none of the constituents possesses such properties and that, on the basis of the information available to the supplier, the mixture is unlikely to present hazards of this kind,
- in the event of a change in the composition of a mixture of known composition, scientific evidence indicates that a reassessment of the hazards will not lead to a change in classification,
- a mixture placed on the market in the form of an aerosol satisfies the provisions of Article 9a of Directive 75/324/EEC.

1.1.6.2.2 The supplier need not consider any of the following cases for the classification of a mixture as the concentrations of the different substances produced by such reactions are typically considered to be sufficiently low that they do not affect the classification of the mixture, unless there is information that indicates the contrary:

- substances that react slowly with atmospheric gases, e.g. oxygen, carbon dioxide, water vapour, to form different substances;
- substances that react very slowly with other ingredient substances of a mixture to form different substances;
- substances that may self-polymerise to form oligomers or polymers[24].

23 1999/45/EC §5.2
24 GHS 1.3.3.1.4

1.1.7. Bridging Principles for the Classification of Mixtures where Test Data are not available for the complete mixture

To ensure that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals, the following shall apply:

Where the mixture itself has not been tested to determine its hazardous properties, but there are sufficient data on the individual hazardous ingredient substances and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the following bridging rules referred to in Article 6 for each individual hazard class in Part 3 and Part 4. This shall be subject to any specific provisions for mixtures in each hazard class.

1.1.7.1. Dilution

If a 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 the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in each Chapter 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 may be applied, or, in the case of acute toxicity, the method for classification of mixtures based on ingredients of the mixture (additivity formula).

1.1.7.2. Batching

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

1.1.7.3. Concentration of highly hazardous mixtures

In the case of the classification of mixtures covered by Chapters 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 ingredients of the mixture that are in that category or sub-category is increased, the new mixture shall be classified in that category or sub-category without additional testing.

1.1.7.4. Interpolation within one toxicity category

In the case of the classification of mixtures covered by Chapters 3.1, 3.2, 3.3, 3.8, 3.9, 3.10 and 4.1, for three mixtures with identical hazardous ingredient substances, where A and B are in the same hazard category and mixture C has the same active hazardous ingredient substances with concentrations intermediate to the concentrations of those hazardous ingredient substances in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B.

1.1.7.5. Substantially similar mixtures

Given the following:

(a) Two mixtures:

(i) A + B

(ii) C + B;

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

(c) The concentration of ingredient substance A in mixture (i) equals that of ingredient substance 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) is already classified in a particular hazard class based on test data, mixture (ii) may be assigned the same hazard category.

1.1.7.6. Aerosols

In the case of the classification of mixtures covered by Chapters 3.1, 3.2, 3.3, 3.4, 3.8 and 3.9, an aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of the mixture, provided that the added propellant does not affect the hazardous properties of the mixture upon spraying.

1.1.7.7. Review of classification in case of change of composition of a mixture[25].

For the review of classifications of mixtures in case of change of composition of the mixtures, the following concentration limits are defined for the application of Article 11(2), first indent:

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
$\leq 2.5\%$	± 30%
$2.5 < C \leq 10\%$	± 20%
$10 < C \leq 25\%$	± 10%

[25] 1999/45/EC, Articles 6 and 7.

25 < C ≤ 100%	± 5%

The supplier shall carry out a new evaluation of a human health or environmental hazard for a mixture of known composition, if he introduces changes of the composition of the initial concentration of one or more of the hazardous constituents in concentrations outside the limits in Table 1.2 above.

Note that:

– according to Article 11 (2) second indent, the supplier shall do the same, if he introduces changes of composition involving the substitution or addition of one or more constituents, in concentrations above the limits referred to in Table 1.1 of this Annex; and

– according to Article 11 (2), a new evaluation need not be performed if there is valid scientific justification for considering that a re-evaluation of the hazard will not result in a change of classification.

1.2. ALLOCATION OF HAZARD STATEMENTS

The hazard statements assigned to each hazard category within each hazard class in accordance with Article 12.1 (c) before the application of the precedence rules as set out in Article 15 shall be specified in the Safety Data Sheet and in the classification and labelling inventory.

1.3. LABELLING

1.3.1. Purpose and general obligations

1.3.1.1. The labelling requirements of the Regulation aim at providing a primary means by which the general public and persons at work are given essential information about the hazards of substances and mixtures[26].

Labelling forms one part of hazard communication, whose other part is the supply of safety data sheets that provides even more information to professional users of substances and mixtures[27].

The label draws the attention of persons using substances and mixtures to their intrinsic hazards, and may also serve to draw attention the safety data sheet[28].

The supplier of a substance or mixture that has been classified for any physical, health and environmental hazards in accordance with the criteria of this Annex, shall then label that substance or mixture to indicate the hazard(s).

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26 67/548/EEC Annex VI §1.5 in part

27 GHS Chapter 1.1 §1.1.2.5 (i) and parameter 1, modified

28 67/548/EEC Annex VI §1.3, 2nd & 3rd sentences

The labelling requirements take account of all potential hazards which are likely to be faced in the use of hazardous substances and mixtures in the form in which they are placed on the market[29].

Hazards are highlighted generally by pictograms and the hazards are specified in standard hazard statements and signal words. Precautionary statements give advice on recommended measures to minimise or prevent adverse effects.

1.3.1.2. Content of the label

The content of the label is set out in Title III. Details for the different label elements for each of the hazard categories for each hazard class are set out in the individual tables in Parts 2, 3, 4 and 5 of this Annex and in Annex II.

The hazard pictograms including symbols are also shown in Annex V, hazard statements in Annex III and precautionary statements in Annex IV.

1.3.1.3. The label shall include all label elements that have been assigned in each of the hazard categories for each hazard class in the individual tables in Parts 2, 3, 4 and 5 of this Annex or as a result of the application of Annex II, subject to Article 15 and Chapter 1.3.3 except where exceptions are given in this Annex or in the Annex II. Precautionary statements shall be chosen in accordance with Part 6[30].

1.3.2. Precedence rules for label elements

1.3.2.1. In the case where there is only a single package the label elements following from the application of both transport regulations and of this Regulation, the transport label elements have precedence for the same hazard and need not be repeated on the same package[31].

The pictograms from the UN RTDG Model regulations shall use a background and symbol colour as specified by those regulations.

Pictograms not included in the UN RTDG model regulations shall have a black symbol on a white background with a red frame sufficiently wide to be clearly visible.

1.3.2.2. For substances and mixtures covered by the UN Recommendations on the Transport of Dangerous Goods, Model Regulations[32], the precedence of the symbols for physical hazards shall follow the rules of the UN Model Regulations[33].

1.3.2.3. In accordance with Article 15 (1), if a substances or mixture is classified according to more than one health hazard class, the following shall apply:

(a) If the skull and cross bones applies, the exclamation mark shall not appear[34];

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29 67/548/EEC Annex VI §1.4, slightly amended

30 *New text*

31 New text

32 GHS § 1.4.10.5.3,1.

33 67/458/EEC Annex VI 7.3.2 includes a precedence rule for physical hazards "the obligation to indicate 'E' makes the symbol 'F+', 'F' and 'O' optional.

(b) If the corrosive symbol applies, the exclamation mark shall not appear on the label for skin or eye irritation[35];

(c) If the hazard symbol for respiratory sensitisation applies, the exclamation mark to be applied for skin sensitisation or for skin and eye irritation shall not appear on the label[36].

1.3.2.4. If the signal word "danger" applies, the word "warning" shall not appear on the label[37].

1.3.2.5. Note that there are specific derogations from labelling in Section 1.4 (Special Labelling Arrangements) for certain cases, where some substances or mixtures, although classified, 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.

1.3.2.6. Precedence for allocation of Hazard Statements

Unless there is evident duplication or redundancy all hazard statements resulting from the classification shall appear on the label[38].

1.3.2.7. Precedence for allocation of Precautionary Statements

The final choice of precautionary statements from the list in Annex IV in accordance with Part 6 must have regard to the hazard statements indicated on the label and to the intended/identified use(s) of the substance or mixture[39].

As a general rule, to formulate the most appropriate safety advice generally not more than six precautionary statements shall be chosen.

When choosing precautionary statements, particular attention must be given to the foreseen conditions of use of certain substances and mixtures, e.g. spraying or other aerosol effects.

Where the precautionary statements selected according to the criteria in Part 6 of this Annex result in redundancy or ambiguity or are clearly unnecessary given the specific product/package, then some statements may be omitted.

For substances and mixtures sold to the general public, one precautionary statement shall address disposal. For other substances and mixtures, a precautionary statement addressing disposal may be omitted, if it is clear that disposal of the material and its container does not present a hazard for human health or the environment.

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34 GHS 1.4.10.5.3.1 (a)
35 GHS 1.4.10.5.3.1 (b)
36 GHS 1.4.10.5.3.1 (c)
37 GHS 1.4.10.5.3.2
38 GHS § 1.4.10.5.3.3.
39 67/548/EEC Annex VI section 7.5.2, modified

1.3.3. Dimensions of the label elements

1.3.3.1. All hazard pictograms on a label shall be in the shape of a square set at a point[40]. Each pictogram shall cover at least one-twenties of the surface area of the harmonised label but shall not be less than 1 cm^2 [41].

1.3.3.2. The dimensions of the label for the application of Article 17 (5) shall be as follows[42]:

Table 1.3

Capacity of the package	**Dimensions (in millimetres)**
Not exceeding 3 litres:	If possible, at least 52 x 74
Greater than 3 litres but, not exceeding 50 litres:	At least 74 x 105
Greater than 50 litres but not exceeding 500 litres:	At least 105 x 148
Greater than 500 litres:	At least 148 x 210

1.4. Derogations from labelling requirements for special cases

In Accordance with Article 13 (2) the following derogations shall apply:

1.4.1. Mobile gas cylinders[43]

For mobile gas cylinders, in derogation from Article 17 (1) and (5) to (7) one of the following alternatives may be used for gas cylinders with a water capacity of less than or equal to 150 litres:

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

(b) the information specified in Article 12 may be provided on a durable information disc or label held captive on the cylinder.

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40 GHS § 1.4.10.4.2.1
41 67/548/EEC Annex VI §7.7
42 1999 /45/EC Art. 11.2 and 67/548/EEC Annex VI §7.7
43 67/548/EEC Annex VI §8.1 and §9.1.2

1.4.2. Gas containers intended for propane, butane or liquefied petroleum gas (LPG)[44].

1.4.2.1. 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.

1.4.2.2. No information concerning the effects on human health and the environment is required on the label. The supplier shall provide the information concerning effects on human health and the environment which shall have appeared on the label without the derogation in 1.4.2.1 to downstream users or distributors in the safety data sheet.

1.4.2.3. For the consumer, sufficient information shall be transmitted to enable them to take all necessary measures for health and safety as shown in Annex II Part 5 below.

1.4.3. Metals in massive form, alloys, mixtures containing polymers, mixtures containing elastomers[45]

1.4.3.1. Metals in massive form, alloys, mixtures containing polymers, and mixtures containing elastomers, do not require a label according to the provisions of 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 in accordance with the criteria of this Annex.

1.4.3.2. The supplier shall provide the information which shall have appeared on the label without the derogation in 1.4.3.1 to downstream users or distributors in the safety data sheet.

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

With regard to the application of Paragraph 3.10.4 of Part 3, substances or mixtures classified in accordance with the criteria of Sections 3.10.2 and 3.10.3 of that Part need not be labelled for this hazard when placed on the market in aerosol containers or in containers fitted with a sealed spray attachment[46].

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

The packaging and labelling provisions of this Annex shall not apply to explosives placed on the market with a view to obtaining an explosive or pyrotechnic effect[47].

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44 67/548/EEC Annex VI §8.2 & §9.2

45 67/548/EEC Annex VI §8.3 & 9.3 & GHS § 1.4.10.5.5

46 67/548/EEC Annex VI §8.4 & §9.4

47 1999/45/EC Art. 12.1

1.4.6. Small Quantity Exemptions[48]

If the contents of the package for substances or mixtures do not exceed 125 ml, the following shall apply[49]:

(a) Hazard and precautionary statements need not be indicated on the package, if the substance or mixture is classified in accordance with the criteria of this Annex as:

(i) Flammable Aerosol of Category 2

(ii) Oxidising Gas of Category 2

(iii) Flammable Liquid of Category 2 or 3

(iv) Flammable Solid of Category 1 or 2

(v) Substances which in contact with water emit Flammable Gases of categories 2 or 3

(vi) Oxidising Liquid of Category 2 or 3

(vii) Oxidising Solid of Category 2 or 3

(viii) Skin Irritant of Category 2

(ix) Eye Irritant of Category 2

(x) Acutely Aquatic Hazardous of Category 1

(xi) Chronically Aquatic Hazardous of Category 1 or 2

(xii) Acutely Toxic of Category 4, if the substances or mixtures are not supplied to the general public[50].

(xiii) Chronically Aquatic Hazardous of Category 3 or 4.

1.4.6.1. The Agency may also prepare draft adaptations to technical progress to this Annex to be sent to the Commission for the purpose of Article 35 specifying[51]:

(a) conditions for packages of substances or mixtures which are either too small or otherwise unsuitable for labelling in accordance with the provisions of this Annex and any appropriate exemptions from the labelling provisions set out above in this Annex ;

(b) other quantities for which there is no reason to fear any risk to workers or human health or the environment and any appropriate exemptions from the

48 1999/45/EC Art. 1.6
49 1999/45/EC Art. 10.4
50 67/548/EEC Art. 23.3
51 1999/45/EC Art. 12.3

labelling provisions set out above in this Annex for substances and mixtures which are classified as one or more of the following;

(i) Flammable Gases

(ii) Flammable Aerosols

(iii) Oxidising Gases

(iv) Flammable Liquids

(v) Flammable Solids

(vi) Substances which in contact with water emit Flammable Gases

(vii) Oxidising Liquids

(viii) Oxidising Solids

(ix) Acutely Toxic of Category 4

(x) Skin Irritant of Category 2

(xi) Eye Irritant of Category 2

(xii) Hazardous to the Environment

(c) conditions for packages of substances or mixtures which are either too small for the labelling provided for in this Annex and for which there is no reason to fear any risk to persons handling such mixtures or to other persons or the environment and any appropriate exemptions from the labelling provisions set out above in this Annex.

2. 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) Substance, mixtures and articles not mentioned under (a) and (b) which are manufactured with the view to producing a practical, explosive or pyrotechnic effect.

2.1.1.2. For the purposes of this Regulation 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 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.

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 results of the test in Part I of the Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods[52].

Special precautions are necessary for substances, mixtures and articles of this class.

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[53]:

(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;

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[52] Text based on Table 2.1.1 and footnote added to GHS criteria to specifically include unstable explosives in this class.

[53] Text from 2.1.2.1 of GHS

(d) 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;

(e) 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;

(f) 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 above based on Test Series 2 to 8 in Part I of the UN Recommendations on the Transport of Dangerous Goods, 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

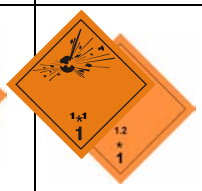
Category	Criteria
Unstable explosives or explosives of Division **1.1 to 1.6**	For explosives of Divisions 1.1 to 1.6, the following are the core set of tests that need to be performed: According to UN Test Series 2 (Section 12 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). Intentional explosives[54] shall not be subject to UN Test Series 2. According to UN Test Series 3 (Section 13 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). According to UN Test 3(c) (Sub-section 13.6.1 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). Further tests are necessary to allocate the correct Division.

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

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.

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**
Pictogram						
Signal word	Danger	Danger	Danger	Danger	Warning	Danger
Hazard statement	Unstable Explosive	Explosive; mass explosion hazard	Explosive; severe projection hazard	Explosive; fire, blast or projection hazard	Fire or projection hazard	May mass explode in fire
Precautionary Statement	TBA	TBA	TBA	TBA	TBA	TBA

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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, is necessary.

For advice on the framework of classification, see the UN GHS Criteria, paragraph 2.1.4 and Figures 2.1.1 to 2.1.4[55].

Step 1 is to ascertain whether the substance or mixture has explosive effects (Test Series 1).

Step 2 is the acceptance procedure (Test Series 2 to 4).

Step 3 is the assignment to a hazard division (Test Series 5 to 7).

The Test Series 8 tests assess whether a candidate for “ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE)” is insensitive

[55] Note: testing strategy introduced instead of referring to the GHS book.

enough for inclusion as an oxidising liquid (Chapter 2.13) or an oxidising solid (Chapter 2.14).

The classification procedure is according to the decision logic in 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)

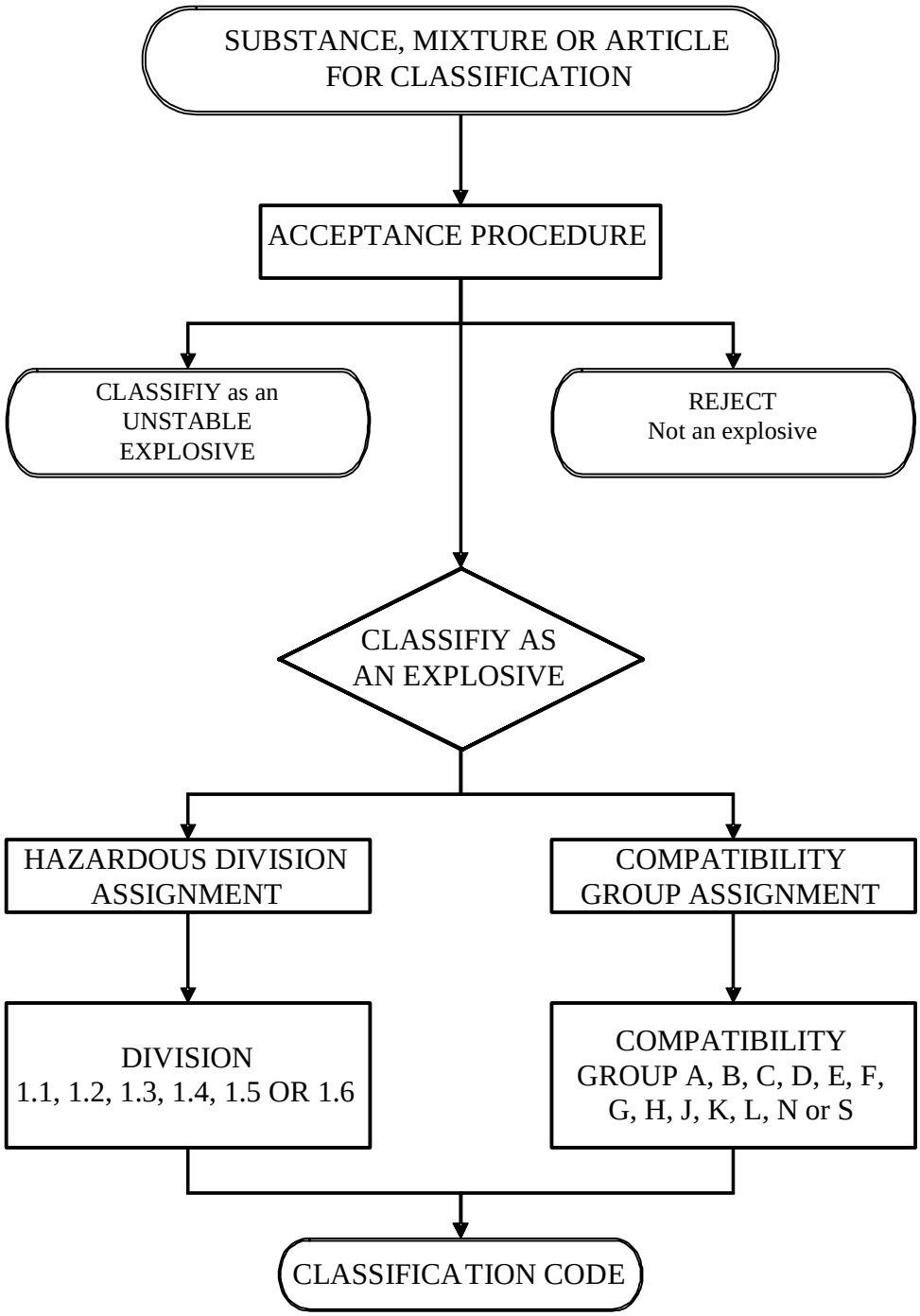
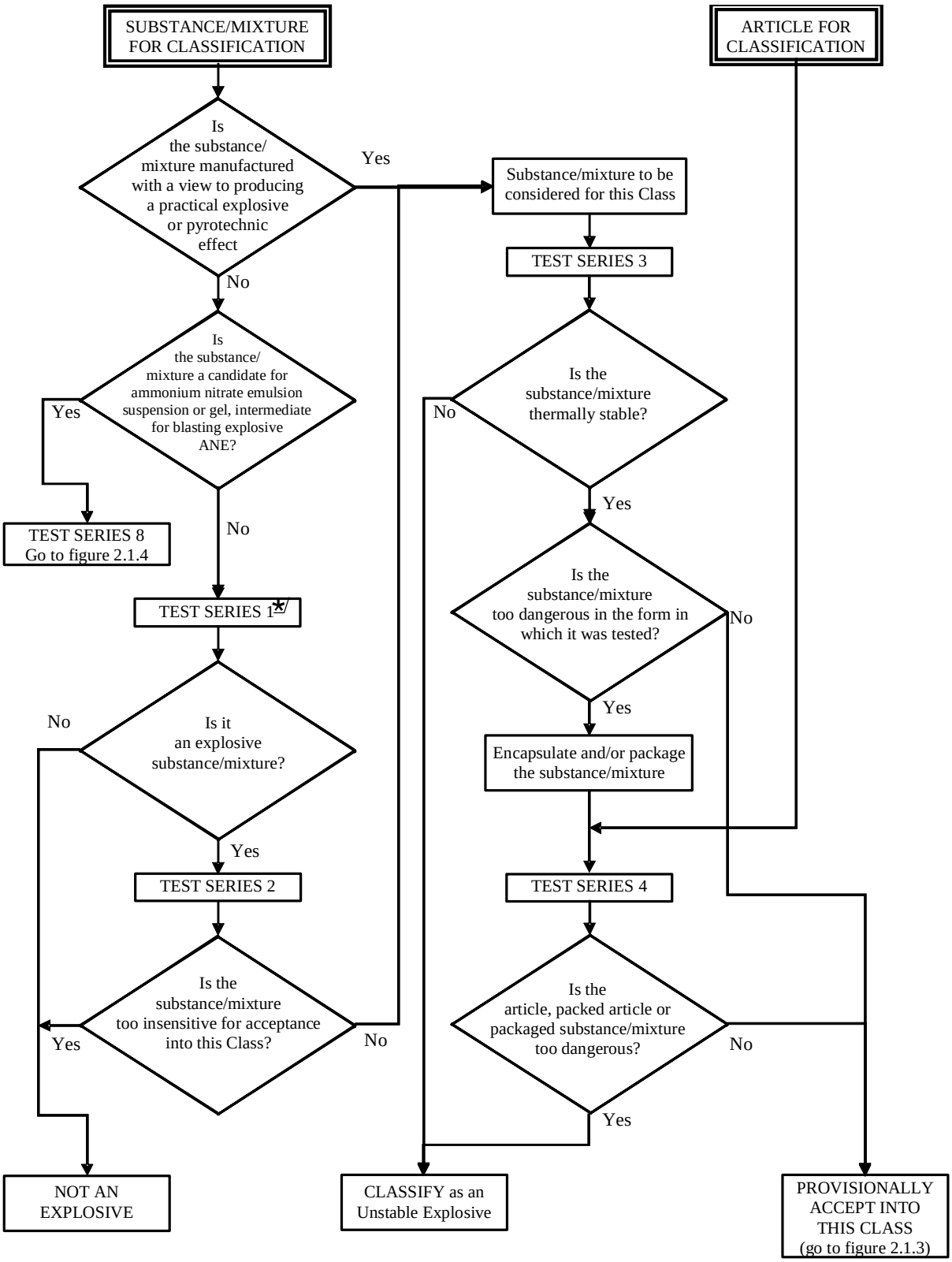


Figure 2.1.2
Procedure for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1 for transport)



* 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)

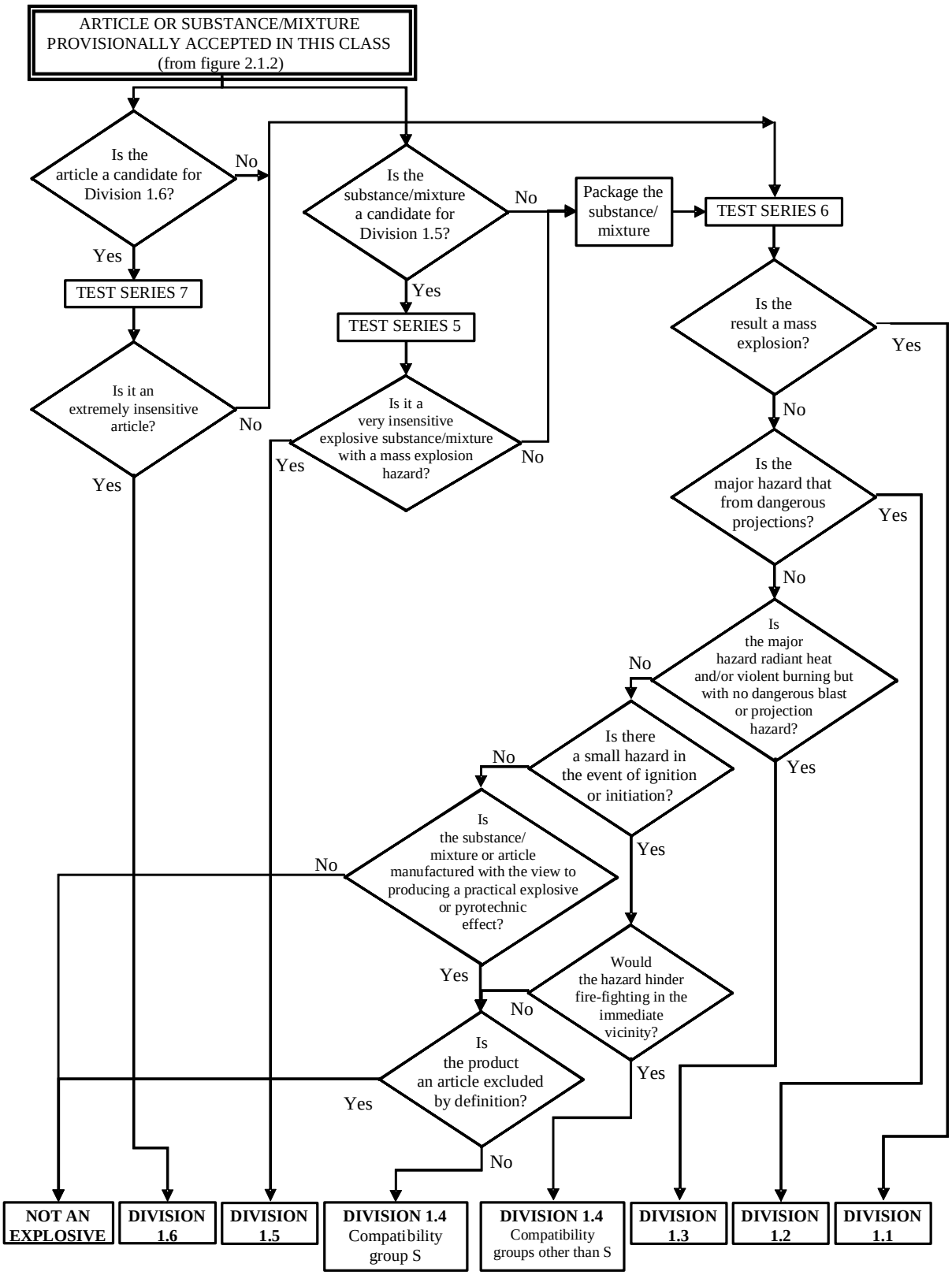
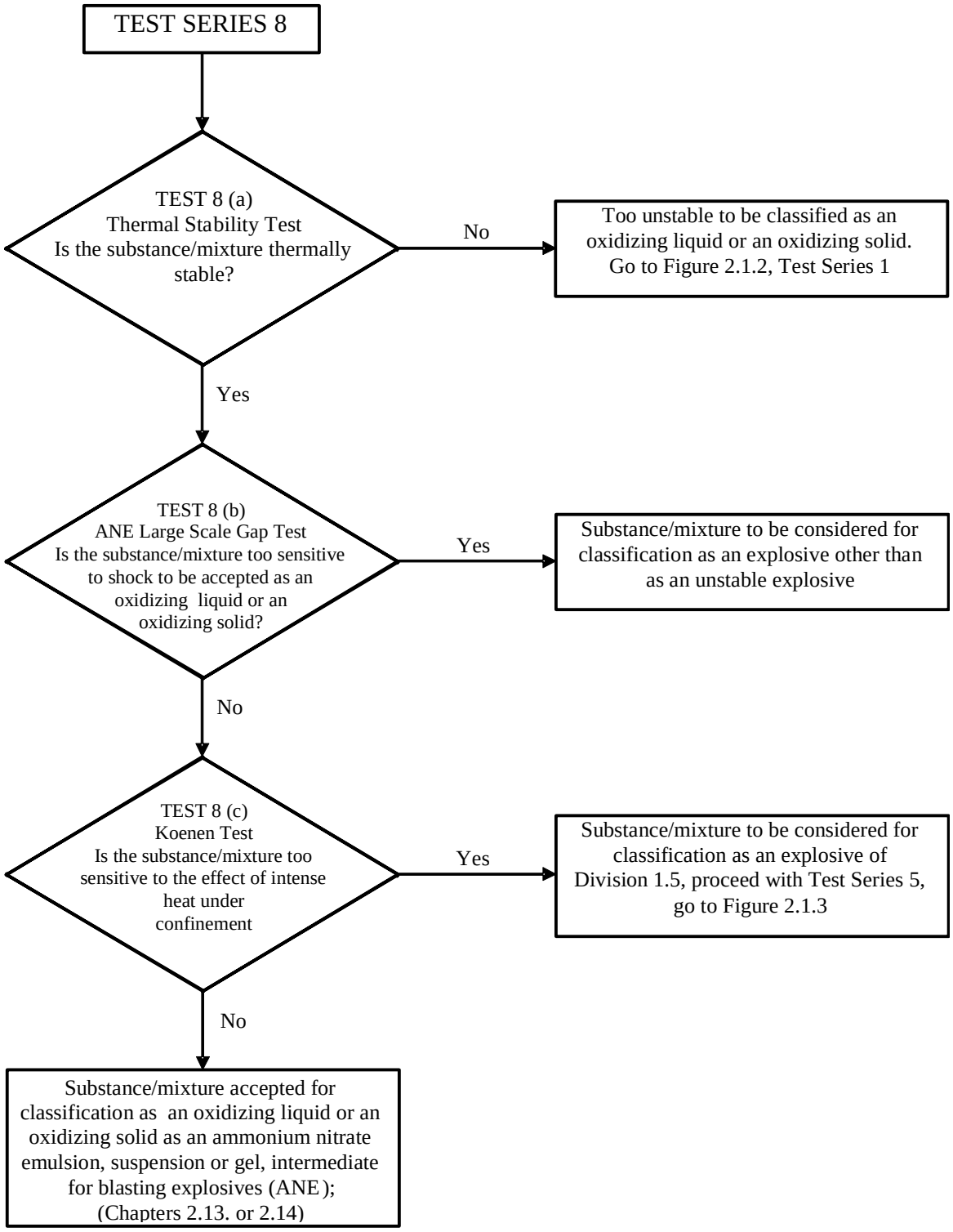


Figure 2.1.4
Procedure for classification of ammonium nitrate emulsions, suspensions or gels



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 Recommendations on the Transport of Dangerous Goods, 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.

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 Recommendations on the Transport of Dangerous Goods, Manual or 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:

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

(c) When the organic substance or a homogenous mixture of organic substances contain 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 may be determined using a suitable calorimetric technique; or

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

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

– less than 30% by mass, if the oxidizing 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.

2.1.4.5. Some explosive substances and mixtures are wetted with water or alcohols or diluted with other substances to suppress their explosive properties. They are treated differently from explosive substances and mixtures (as desensitised explosives)[56].

[56] Note (modified) transferred from GHS Classification Table.

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.

[Note 1:
Ammonia and methyl bromide are regarded as special cases[57].]

Note:
For the classification of aerosols, see 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.

[57] An appropriate place for this information is in Annex VI.

Table 2.2.2
Label elements for flammable gases

Classification	**Category 1**
Pictograms	
Signal word	Danger
Hazard statement	Extremely flammable gas
Precautionary Statements	TBA

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 may be used.

2.3. FLAMMABLE AEROSOLS

2.3.1. Definitions

Aerosol (aerosol dispensers) means 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.:

– Flammable liquids (see 2.6);

– Flammable gases (see 2.2);

– Flammable solids (see 2.7).

Note:
Flammable components do not cover pyrophoric, self-heating or water-reactive

substances and mixtures because such components are never used as aerosol contents.

2.3.2.2. A flammable aerosol shall be is 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 Table 2.3.1:

Table 2.3.1
Criteria for flammable aerosols[58]

Category	Criteria
1	Contains ≥ 85% of Flammable Components; and the chemical heat of combustion is ≥ 30 kJ/g; or a) for spray aerosols, in the ignition distance test, ignition occurs at a distance ≥ 75 cm, or b) for foam aerosols, in the foam test (i) the flame height is ≥ 20 cm and the flame duration ≥ 2 s; or (ii) the flame height is ≥ 4 cm and the flame duration ≥ 7 s
2	Contains > 1% flammable components, or the heat of combustion is ≥ 20 kJ/g; and a) for spray aerosols, in the ignition distance test, ignition occurs at a distance ≥ 15 cm, or in the enclosed space ignition test, the (i) time equivalent is ≤ 300 s/m^3; or (ii) deflagration density is ≤ 300 g/m^3 b) for foam aerosols, in the foam test, the flame height is ≥ 4 cm and the flame duration is ≥ 2 s and it does not meet the criteria for Category 1

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.

[58] Note: This table is not in the GHS text, it has been developed by Alan K Brown, UK HSL and WG Machin.

Table 2.3.2
Label elements for flammable aerosols

Classification	**Category 1**	**Category 2**
Pictograms		
Signal word	Danger	Warning
Hazard statement	Extremely flammable aerosol	Flammable aerosol
Precautionary Statements	TBA	TBA

2.3.4. Additional Classification Considerations

2.3.4.1. To classify a flammable aerosol, data on its flammable components, on its chemical heat of combustion and, if applicable, the results of the foam test (for foam aerosols), and the results of the ignition distance test and enclosed space test (for spray aerosols) are required[59].

Guidance on the classification based on this information is shown in Decision Logics shown in 2.3.4.1 of the GHS. The decision logic and guidance are not part of the harmonised classification system.

2.3.4.2. 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:

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

where:

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

[59] GHS 2.3.4

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, ISO/FDIS 13943 (E/F), as amended, 86.l to 86.3 and NFPA 30B as amended).

2.3.4.3. See sub-sections 31.4, 31.5, and 31.6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, for ignition distance test, enclosed space ignition test and aerosol foam flammability test.

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:
Mixtures containing up to 23,5% vol% oxygen may be regarded as not oxidizing when no other oxidising gases are present.

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**
Pictograms	
Signal word	Danger
Hazard statement	May cause or intensify fire; oxidizer
Precautionary Statements	TBA

2.4.4. Additional Classification Considerations

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

2.5. GASES UNDER PRESSURE[60]

2.5.1. Definition

2.5.1.1. Gases under pressure are gases or gas mixtures which are contained in a receptacle at a pressure not less than 280 kPa at 20°C or as a refrigerated liquid.

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:

[60] Note: “with exemption for REACH”

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
Pictograms				
Signal word	Warning	Warning	Warning	Warning
Hazard statement	Contains gas under pressure; may explode if heated	Contains gas under pressure; may explode if heated	Contains refrigerated gas; may cause cryogenic burns or injury	Contains gas under pressure; may explode if heated

Precautionary Statements	TBA	TBA	TBA	TBA

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.

In order to classify a gas, the above data are needed. Data can be found in literature, calculated or determined by testing. Most pure gases are already classified in the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.* Most one off mixtures require additional calculations.

2.6. FLAMMABLE LIQUIDS[61]

2.6.1. Definition

Flammable liquid means a liquid having a flash point of not more than 93°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[62]

[61] Note: Cat 4 will not included as transport will not include this category.

[62] Gas oils, diesel and light heating oils in the flash point range of 55°C to 75°C may be regarded as Category 3 for transport.

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**
Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	Extremely flammable liquid and vapour	Highly flammable liquid and vapour	Flammable liquid and vapour
Precautionary Statements	TBA	TBA	TBA

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 by a closed-cup test method. Open-cup tests are acceptable only in special cases.

2.6.4.2. In the case of mixtures[63] 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 below, is at least 5°C 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 flash point (closed-cup as given in 2.6.4.4 below) of each component is known (an appropriate correlation has to be applied when these data are extrapolated to other temperatures than test conditions);

[63] Screening procedures are well established for ideal mixtures of solvents, i.e. mainly hydrocarbons

(c) The activity coefficient is known for each component as present in the mixture including the temperature dependence;

(d) The liquid phase is homogeneous.

2.6.4.3. One suitable method is described in Gmehling and Rasmussen (Ind. Eng. Chem. Fundament, 21, 186, (1982)). For a mixture containing non-volatile components, e.g. polymers or additives, 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. Table 2.6.3 is a non-inclusive list of documents describing possible methods for determining the flash point of flammable liquids:

Table 2.6.3
Methods for determining the flash point of flammable liquids:

International standards:	ISO 1516 as amended
	ISO 1523 as amended
	ISO 3679 as amended
	ISO 3680 as amended
National standards:	
Association française de normalisation, AFNOR:	NF M 07 – 019 as amended
	NF M 07 - 011 / NF T 30 - 050 / NF T 66 – 009 as amended
	NF M 07 – 036 as amended
British Standards Institute,	BS EN 22719 as amended
	BS 2000 Part 170 as amended
Deutsches Institut für Normung	DIN 51755 (flash points below 65 °C) as amended
	DIN 51758 (flash points 65 °C to 165 °C) as amended
	DIN 53213 (for varnishes, lacquers and similar viscous liquids with flash points below 65 °C) as amended
State Committee of the Council of Ministers for Standardization, Russia	GOST 12.1.044 as amended
Industry standards:	
American Society for Testing Materials International	ASTM D 3828 as amended, Standard test methods for flash point by small scale closed tester
	ASTM D 56 as amended, Standard test method for flash point by tag closed tester
	ASTM D 3278 as amended, Standard test methods for flash point of liquids by setaflash closed-cup apparatus

	ASTM D 0093 as amended, Standard test methods for flash point by Pensky-Martens closed cup tester

2.6.4.5. Liquids with a flash point of more than 35°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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*[64].

2.6.4.6. Certain viscous flammable liquids such as paints, enamels, lacquers, varnishes, adhesives and polishes may be regarded as a special group for transport[65].

2.7. FLAMMABLE SOLIDS

2.7.1. Definition

2.7.1.1. Flammable solid means a solid substance or mixture which is readily combustible, or may cause or contribute to fire as a result of 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 regarded 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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*[66], 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.

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64 Note: transferred from GHS Classification Table.

65 Modified note 3 transferred from GHS Classification Table.

66 There is no reference in this text to the test methods currently described in Annex V to Directive 67/548/EEC.

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 Recommendations on the Transport of Dangerous Goods, 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 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 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

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**
Pictograms		
Signal word	Danger	Warning
Hazard statement	Flammable Solid	Flammable Solid
Precautionary Statements	TBA	TBA

2.8. SELF-REACTIVE SUBSTANCES AND MIXTURES[67]

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 or mixtures classified according to this Part as explosives, organic peroxides or as oxidising.

2.8.1.2. A self-reacting 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

[67] Note: This class should be included, however Type C to G "with exemption for REACH"

more of combustible organic substances shall be classified as self-reactive substances according to the procedure defined in the 2.8.2.2 below;

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

(d) Their heat of decomposition is less than 300 J/g; or

(e) Their self-accelerating decomposition temperature (SADT) is greater than 75°C for a 50 kg package[68].

2.8.2.2. Mixtures of oxidizing substances, meeting the criteria for classification as oxidizing substances, which contain 5% or more of combustible organic substances and which do not meet the criteria mentioned in (a), (c), (d) or (e) above, 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.

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**;

(d) 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**;

[68] See United Nations Manual of Tests and Criteria, chapter 28.1, 28.2, 28.3 and Table 28.3.

(e) 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**;

(f) 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**;

(g) 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 (self-accelerating decomposition temperature 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**.

2.8.2.4. Criteria for temperature control

Self-reactive substances need to be subjected to temperature control if their self-accelerating decomposition temperature (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 Recommendations on the Transport of Dangerous Goods, 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
Pictograms					There are no label elements allocated to this hazard category
Signal word	Danger	Danger	Warning	Warning	
Hazard statement	Heating may cause an explosion	Heating may cause a fire or explosion	Heating may cause a fire	Heating may cause a fire	
Precautionary Statements	TBA	TBA	TBA	TBA	

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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*. The procedure for classification is described in Figure 2.8.1.

For detailed schemes for the decision logic for classification and the tests to be carried for ascertaining the different categories, see the UN GHS Criteria Decision Logic 2.8.

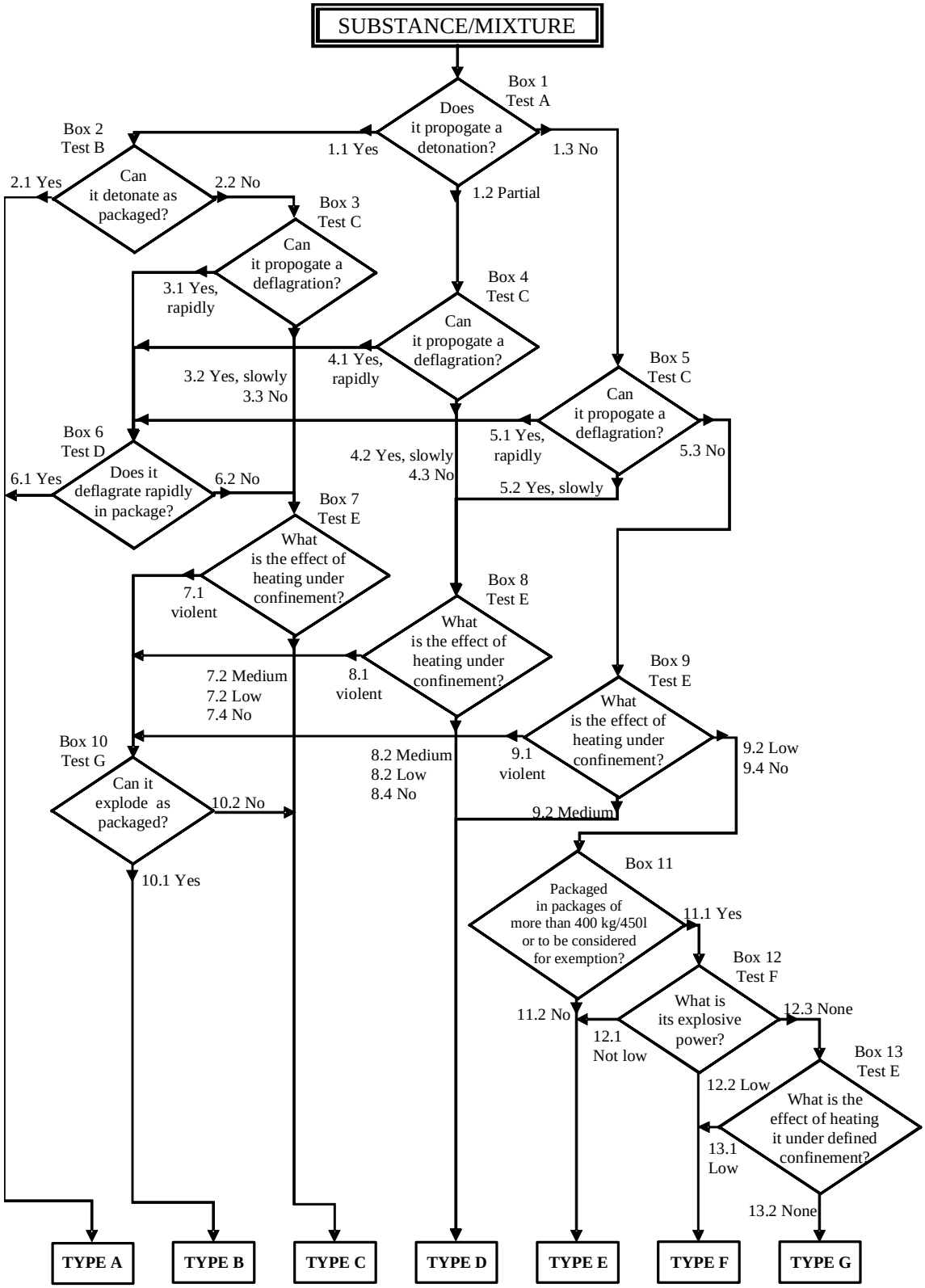
2.8.4.2. The classification procedures for self-reactive substances and mixtures need not be applied if:

(a) There are no chemical groups present in the molecule associated with explosives or self reactive properties; examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* or

(b) For a single organic substance or a homogeneous mixture or organic substances, the estimated SADT is greater than 75°C or the exothermic

decomposition energy is less than 300J/g. The onset temperature and decomposition energy may be estimated using a suitable calorimetric technique (see Part II, sub-section 20.3.3.3 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*).

Figure 2.8.1
Self –reactive substances and mixtures[69]



69 Note: Should be included, testing strategy.

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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* according to the following table:

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**
Pictograms	
Signal word	Danger
Hazard statement	Catches fire spontaneously if exposed to air
Precautionary Statements	TBA

2.9.4. Additional Classification Considerations

2.9.4.1. The classification procedure for pyrophoric liquids need not be applied when experience in production manufacture or handling shows that the substance 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 Recommendations on the Transport of Dangerous Goods, 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.

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**
Pictograms	
Signal word	Danger
Hazard statement	Catches fire spontaneously if exposed to air
Precautionary Statements	TBA

2.10.4. Additional Classification Considerations

2.10.4.1. The classification procedure for pyrophoric solids need not be applied when experience in production manufacture or handling shows that the substance 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[70]

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 substances or mixtures, leading to spontaneous combustion, is caused by reaction of the substance or mixture with oxygen (in the air) and the heat developed not being conducted away rapidly enough to the surroundings. Spontaneous combustion occurs when the rate of heat production exceeds the rate of heat loss and the auto-ignition temperature is reached.

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 N.4 in Part III, sub-section 33.3.1.6 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria:

(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 positive result is obtained using a 100 mm cube sample at 100°C.

(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 unit volume of the substance is more than 450 litres;

(d) 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

[70] Note: included in Annex I, but "with exemption for REACH"

the unit volume of the substance is more than 3 m^3;

2.11.2.2. A self-heating substance or mixture shall be classified in one of the two categories for this class if, in test performed in accordance with test method N.4 in Part III, sub-section 33.3.1.6 of the UN Recommendations on the Transport of Dangerous Goods, 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) It does not meet the criteria for Category 1; and a positive result is obtained in a test using a 100 mm sample cube at 140°C; Exemptions from (a) for classification in Category 2 (i) a negative result is obtained in a test using a 100 mm cube sample at 100°C and the unit volume of the substance is 450 litres or less; (ii) a negative result is obtained in a test using a 100 mm cube sample at 120°C and the unit volume of the substance is 3 m^3 or less; (b) It does not meet the criteria for Category 1; and a positive result is obtained in a test using a 100 mm sample cube at 140°C; and it is not a substances exempted under (a), that gives a positive result in a test using a 100 mm cube sample at 100°C;

2.11.2.3. Substances and mixtures with a temperature of spontaneous combustion higher than 50°C for a volume of 27 m^3 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
Pictograms		
Signal word	Danger	Warning
Hazard statement	Self-heating; may catch fire	Self-heating in large quantities; may catch fire
Precautionary Statements	TBA	TBA

2.11.4. Additional Classification Considerations

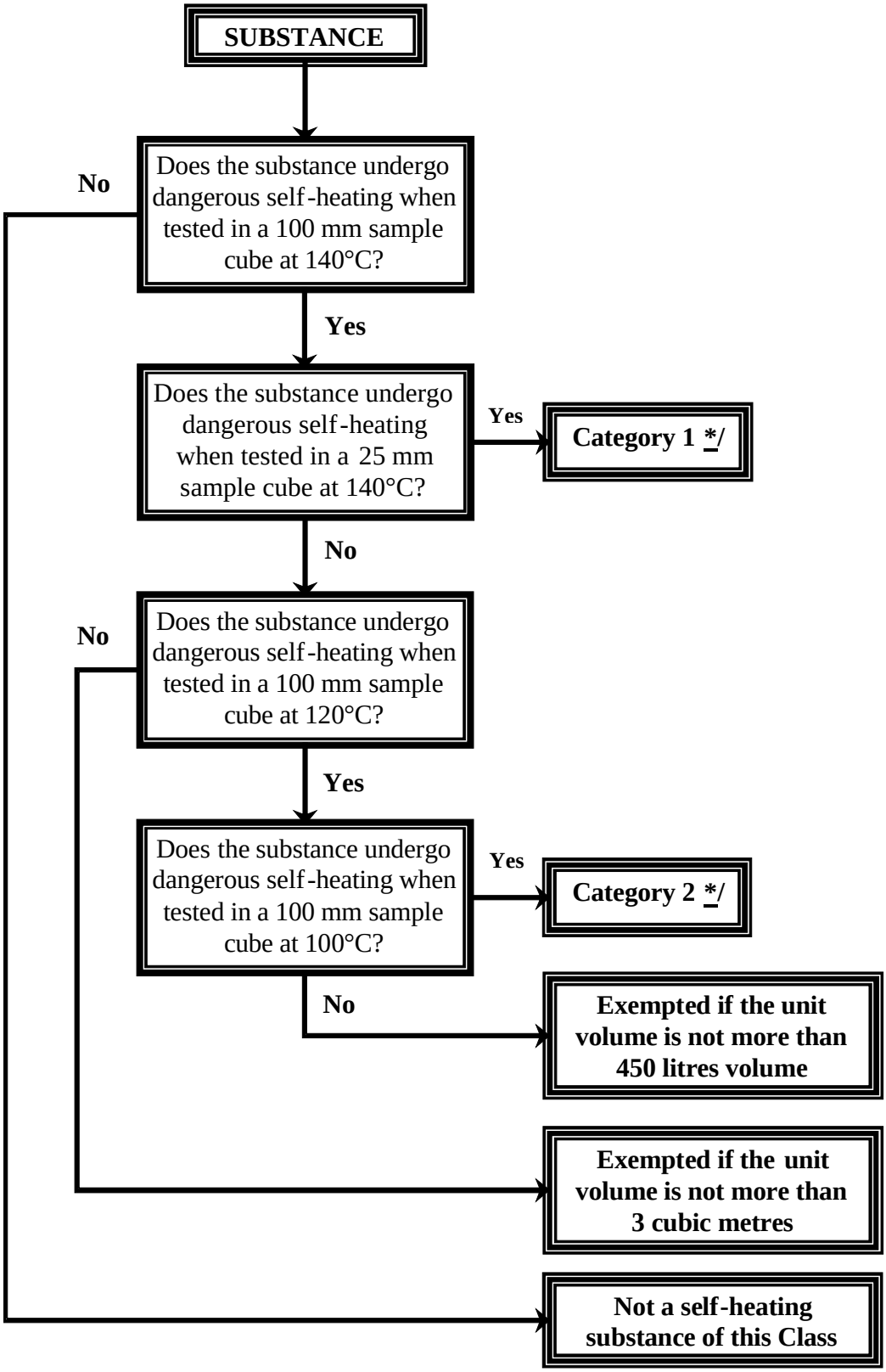
2.11.4.1. For detailed schemes for the decision logic for classification and the tests to be carried out for ascertaining the different categories, see Figure 2.11.1 below.

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
CLASSIFICATION OF SELF-HEATING SUBSTANCES[71]



[71] Note: This table is not yet in the GHS. The table was worked out by Alan K Brown and WG Machin

* Substances with a temperature for spontaneous combustion higher than 50°C for 27 m^3 shall not be classified.

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, emit 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 Recommendations on the Transport of Dangerous Goods, 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.

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**
Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	In contact with water releases flammable gases which may ignite spontaneously	In contact with water releases flammable gases	In contact with water releases flammable gases
Precautionary Statements	TBA	TBA	TBA

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 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 Recommendations on the Transport of Dangerous Goods, 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 and cellulose tested, spontaneously ignites; or the mean pressure rise time of a 1:1 mixture, by mass, of substance 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 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[72]	Any substance or mixture which, in the 1:1 mixture, by mass, of substance 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.

[72] Note: the category included in Annex I, but "with exemption for Reach".

Table 2.13.2
Label elements for oxidising liquids

Classification	Category 1	Category 2	Category 3
Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	May cause fire or explosion; strong oxidizer	May intensify fire; oxidizer	May intensify fire; oxidizer
Precautionary Statements	TBA	TBA	TBA

2.13.4. Additional Classification Considerations

2.13.4.1. For organic substances or mixtures the classification procedure for this class does 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 does 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, 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, it shall be necessary to repeat the test described in Part III, sub-section 34.4.2 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* with an inert substance, e.g. diatomite (kieselguhr), in place of the cellulose in order to clarify the nature of the reaction.

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 Recommendations on the Transport of Dangerous Goods, 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[73]	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.

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.

[73] Note: the category included in Annex I, but "with exemption for Reach"

Table 2.14.2
Label elements for oxidising solids

	Category 1	Category 2	Category 3
Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	May cause fire or explosion; strong oxidiser	May intensify fire; oxidiser	May intensify fire; oxidiser
Precautionary Statements	TBA	TBA	TBA

2.14.4. Additional Classification Considerations

2.14.4.1. For organic substances or mixtures the classification procedure for this class does 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 does 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, judgments based on known experience shall take precedence over test results.

2.15. ORGANIC PEROXIDES

2.15.1. Definition

2.15.1.1. Organic peroxide means a liquid or solid organic substance 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 may undergo exothermic self-accelerating decomposition. In addition, they may 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 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**;

(d) 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**;

(e) 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**;

(f) 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**;

(g) 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 self-accelerating decomposition temperature is 60°C or higher for a 50 kg package[74], 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**[75].

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**.

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[76] with an SADT • 50° C or showing a low or no effect when heated under confinement with an SADT • 45° C; and

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74 See United Nations Manual of Tests and Criteria, chapter 28.1, 28.2, 28.3 and Table 28.3.

75 Note: the Type G included in Annex I, but "with exemption for Reach"

76 As determined by test series E as prescribed in the Manual of Tests and Criteria, Part II.

(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 Recommendations on the Transport of Dangerous Goods, 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.

Table 2.15.1
Label elements for organic peroxides

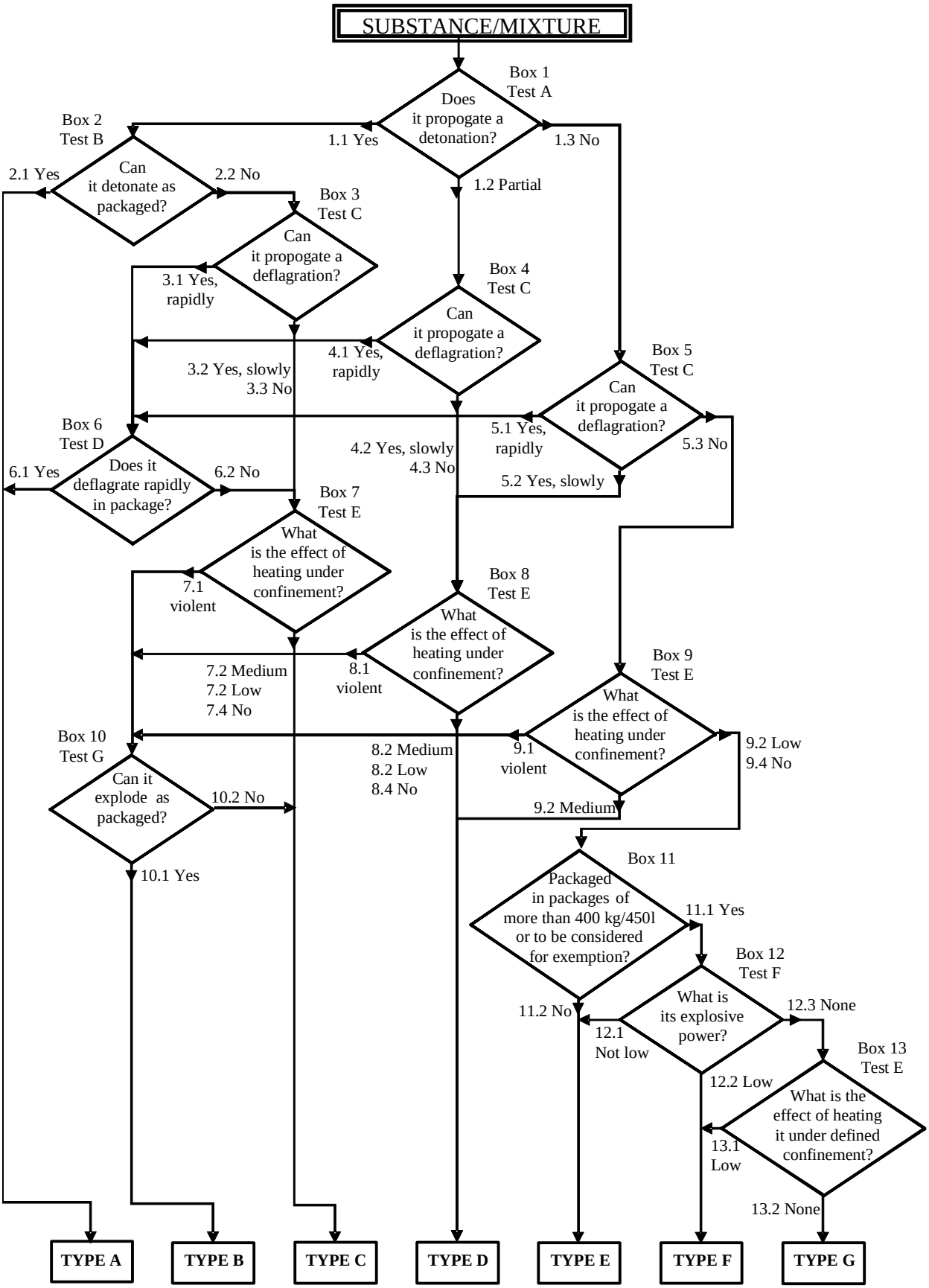
Classification	**Type A**	**Type B**	**Type C & D**	**Type E & F**	**Type G**
Pictograms					There are no label elements allocated to this hazard category
Signal word	Danger	Danger	Warning	Warning	
Hazard statement	Extremely flammable liquid and vapour	Highly flammable liquid and vapour	Flammable liquid and vapour	Combustible liquid	
Precautionary Statements	TBA	TBA	TBA	TBA	

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 Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*. The procedure for classification is described in Figure 2.8.1.

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 self-accelerating decomposition temperature (SADT) of the mixture shall be determined.

Figure 2.15.1
Organic Peroxides



2.16. CORROSIVE TO METALS[77]

2.16.1. Definition

A substance or a mixture that is corrosive to metal 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 metal is classified in a single category for this class, using the test in part III, section 37, paragraph 37.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, according to the following table:

Table 2.16.1
Criteria for substances corrosive to metals

Category	Criteria
1	Corrosion rate on steel or aluminium surfaces exceeding 6.25 mm per year at a test temperature of 55°C.

2.16.3. Hazard Communication

Label elements shall be used for substances, 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 corrosive to metals

Classification	**Category 1**
Pictograms	
Signal word	Warning
Hazard statement	May be corrosive to metals
Precautionary Statements	TBA

[77] Note: this class included in Annex I, but "with exemption for Reach"

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 Recommendations on the Transport of Dangerous Goods, 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.

3. 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.

3.1.2. 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 cut-off criteria shown in table 3.1.1 below. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (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)	$LD_{50} \leq 5$	$5 < LD_{50} \leq 50$	$50 < LD_{50} \leq 300$	$300 < LD_{50} \leq 2000$
Dermal (mg/kg bodyweight) See Note (a)	$LD_{50} \bullet 50$	$50 < LD_{50} \leq 200$	$200 < LD_{50} \leq 1000$	$1000 < LD_{50} \leq 2000$
Gases (ppmV[78]) see: Note (a) Note (b)	$LC_{50} \leq 100$	$100 < LC_{50} \leq 500$	$500 < LC_{50} \leq 2500$	$2500 < LC_{50} \leq 5000$
Vapours (mg/l) see: Note (a) Note (b) Note (c) Note (d)	$LC_{50} \leq 0.5$	$0.5 < LC_{50} \leq 2.0$	$2.0 < LC_{50} \leq 10.0$	$10.0 < LC_{50} \leq 20.0$
Dusts and Mists (mg/l) see: Note (a) Note (b)	$LC_{50} \leq 0.05$	$0.05 < LC_{50} \leq 0.5$	$0.5 < LC_{50} \leq 1.0$	$1.0 < LC_{50} \leq 5.0$

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 LD50/LC50 where available,

78 Gases concentration are expressed in parts per million per volume (ppmV)

– 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."

(b) Inhalation cut-off values 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.

(c) (c) 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 or mixtures 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 (5000 ppmV)[79].

(d) For specific cut-off values for certain gases see Annex VI

The terms "dust", "mist" and "vapour" are defined as follows[80]:

– 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 supersatured 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 LD50 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.

79 GHS note (c) has been deleted as being primarily relevant to classification for transport, GHS note (d) has been renumbered as (c).

80 Revised definitions for dust, mist and vapours are currently under discussion.

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. The cut-off values in the table for dusts and mists allow clear distinctions to be made for materials with a wide range of toxicities measured under varying test conditions.

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. 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 below outlines the process to be followed.

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

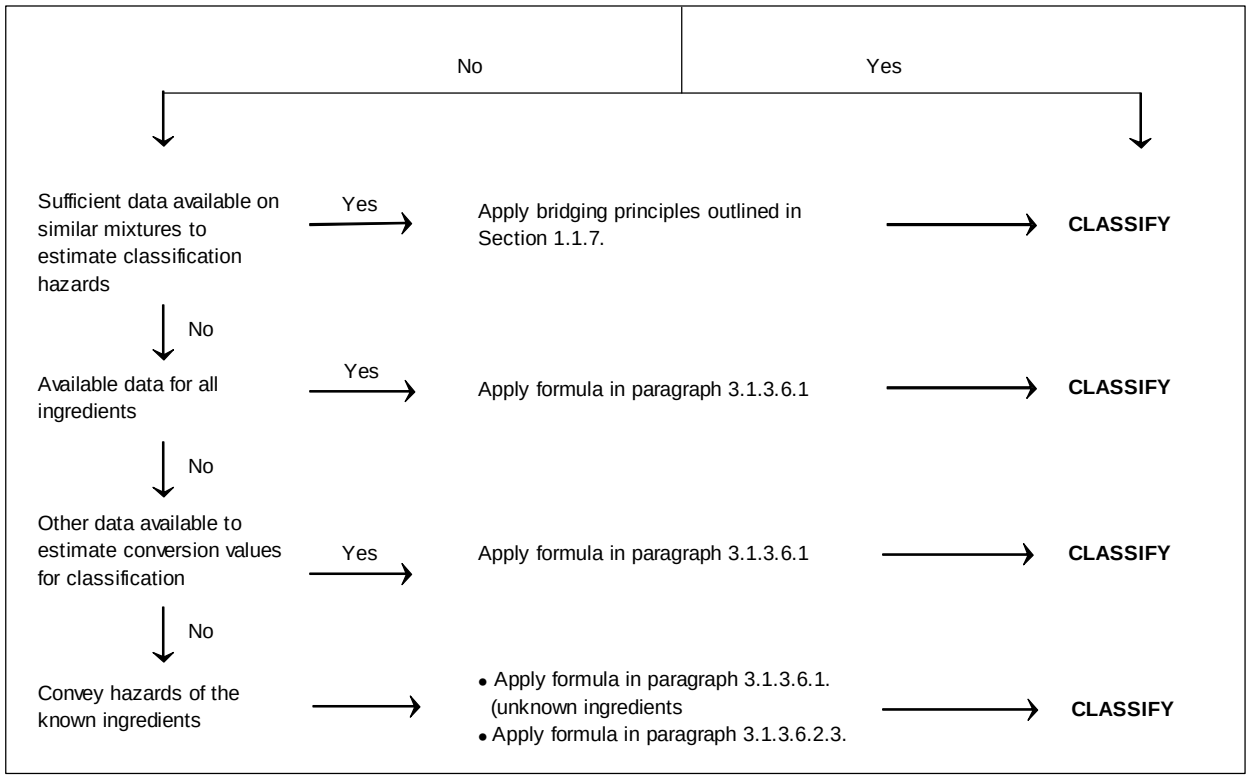
3.1.3.3. In order to make use of all available data for purposes of classifying the hazards of the mixtures, certain assumptions have been made and are applied where appropriate in the tiered approach:

(a) The “relevant ingredients” of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1% is still relevant for classifying the mixture for acute toxicity. This point is particularly relevant when classifying untested mixtures which contain ingredients that are classified in Category 1/2;

(b) Where a classified mixture is used as an ingredient of another mixture, the

actual or derived acute toxicity estimate (ATE) for that mixture may be used, , when calculating the classification of the new mixture using the formulas in paragraphs 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:
Test Data on the mixture as a whole



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 will be classified according to the same criteria as those used for substances, presented in Table 3.1.1. If test data for the mixture are not available, the procedures presented below shall be followed.

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

3.1.3.5.1 Where the mixture itself has not been tested to determine its acute toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the bridging rules set out in Section 1.1.7

3.1.3.5.2 If a mixture is diluted with water or other totally non-toxic material, the toxicity of the mixture can be calculated from test data on the undiluted mixture. For example, if a mixture with an LD50 of 1000 mg/kg bodyweight were diluted with an equal volume of water, the LD50 of the diluted mixture would be 2000 mg/kg bodyweight.

3.1.3.6. 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 ingredients if the oral limit test does not show acute toxicity at 2000 mg/kg bodyweight.

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

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

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

where:

C_i = concentration of ingredient i

i = the individual ingredient from 1 to n

n = the number of ingredients

ATE_i = 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 as laid out in Table 3.1.2, the formula in paragraph 3.1.3.6.1 may be applied.

This may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates[81]. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;

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

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

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

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

This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert (expert judgement, see Section 1.3.7.1), to reliably estimate acute toxicity. If such information is not available, proceed to the provisions of paragraph 3.1.3.6.2.3.

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

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

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

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

Exposure routes	**Classification category or experimentally obtained acute toxicity range estimate**		**Converted Acute Toxicity point estimate** (*see Note 1*)
Oral (mg/kg bodyweight)	Category 1	$LD_{50} \leq 5$	0.5
	Category 2	$5 < LD_{50} \leq 50$	5
	Category 3	$50 < LD_{50} \leq 300$	100
	Category 4	$300 < LD_{50} \leq 2000$	500

Dermal (mg/kg bodyweight)	Category 1	$LD_{50} \leq 50$	5
	Category 2	$50 < LD_{50} \leq 200$	50
	Category 3	$200 < LD_{50} \leq 1000$	300
	Category 4	$1000 < LD_{50} \leq 200$	1100
Gases (ppmV)	Category 1	$LC50 \leq 100$	10
	Category 2	$100 < LC_{50} \leq 500$	100
	Category 3	$500 < LC_{50} \leq 2500$	700
	Category 4	$2500 < LC_{50} \leq 5000$	3000
Vapours (mg/l)	Category 1	$LC50 \leq 0.5$	0.05
	Category 2	$0.5 < LC_{50} \leq 2.0$	0.5
	Category 3	$2.0 < LC_{50} \leq 10.0$	3
	Category 4	$10.0 < LC_{50} \leq 20.0$	11
Dust/mist (mg/l)	Category 1	$LC_{50} \leq 0.05$	0.005
	Category 2	$0.05 < LC_{50} \leq 0.5$	0.05
	Category 3	$0.5 < LC_{50} \leq 1.0$	0.5
	Category 4	$1.0 < LC_{50} \leq 5.0$	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

Table 3.1.3
Acute toxicity label elements

Classification	Category 1	Category 2	Category 3	Category 4
Pictograms				
Signal word	Danger	Danger	Danger	Warning
Hazard statement: **- Oral**	Fatal if swallowed	Fatal if swallowed	Toxic if swallowed	Harmful if swallowed
- Dermal	Fatal in contact with skin	Fatal in contact with skin	Toxic in contact with skin	Harmful in contact with skin
- Inhalation (see Note 1)	Fatal if inhaled	Fatal if inhaled	Toxic if inhaled	Harmful if inhaled
Precautionary statements (oral, dermal, inhalation)	TBA	TBA	TBA	TBA

Note 1
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 advice at 3.1.2.3.3. That is, in addition to an appropriate acute toxicity pictogram, a corrosivity pictogram (used for skin and eye corrosivity) may be added along with a corrosivity hazard statement such as "corrosive" or "corrosive to the respiratory tract".

Note 2
In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1% or greater, the mixture shall be labelled with the additional statement that "*x percent of the mixture consists of ingredient(s) of unknown toxicity*" – see detailed advice at 3.1.3.6.2.2

3.2. SKIN CORROSION/IRRITATION[82]

3.2.1. Definitions and General Considerations

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 and mixtures before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. Existing human experience and data including from single or repeated exposure and animal observations and data shall be the first line of analysis, as they give information directly relevant to effects on the skin. In some cases enough information may be available from structurally related compounds to make classification decisions.

3.2.2.2. Likewise, pH extremes like • 2 and • 11.5 may indicate skin effects, especially when associated with significant buffering capacity, although the correlation is not perfect. Generally, such substances are expected to produce significant effects on the skin and shall be considered as corrosive, also when the buffering capacity is unknown. The acid/alkali reserve may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

3.2.2.3. It also stands to reason that if a substance or a mixture is highly toxic by the dermal route, a skin irritation/corrosion study may not be practicable since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations are made of skin irritation/corrosion in acute toxicity studies and are observed up through the limit dose, additional testing would not be needed, provided that the dilutions used and species tested are equivalent. In vitro alternatives that have been validated and accepted may also be used to help make classification decisions (see article 5).

3.2.2.4. All the above information that is available on a substance or a mixture shall be used in determining the need for in vivo skin irritation testing.

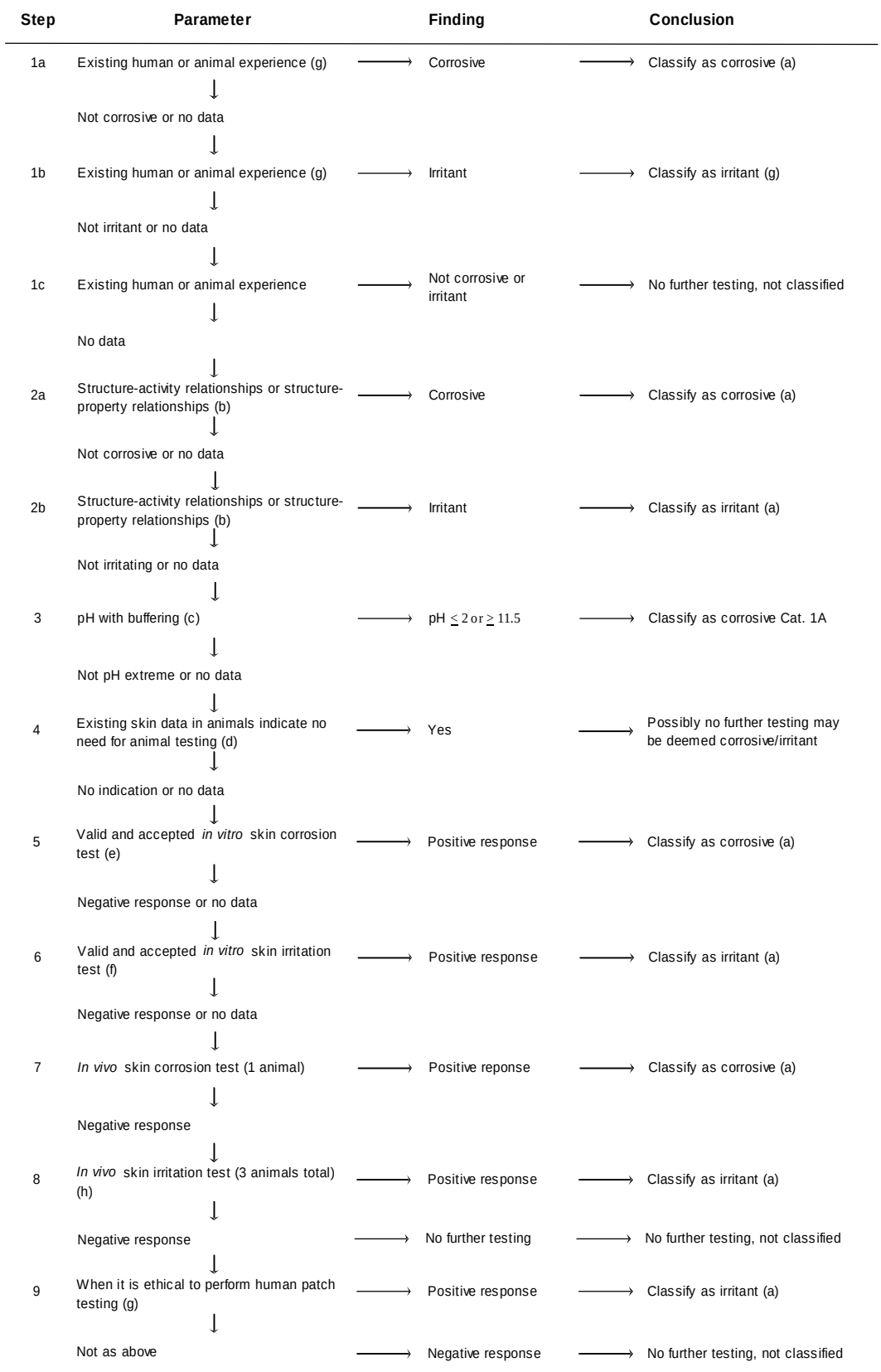
The provisions of paragraph 1.1.5. (a) regarding testing of mixtures shall also be noted.

82 The text follows that of GHS document Chapter 3.2, with editorial amendments.

Although information might be gained from the evaluation of single parameters within a tier (see paragraph 3.2.1.6), 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 (Figure 3.2.1), recognising that all elements may not be relevant in certain cases.

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



Notes to Figure 3.2.1:

(a) Classify in the appropriate category, as shown in Table 3.2.1 or 3.2.2 as appropriate

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

(c) Measurement of pH alone may be adequate, with pH extremes of • 2.0 and • 11.5 indicative of a potential for corrosivity. Such physical properties shall be considered as leading to classification for corrosivity. The acid/alkali reserve may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance may not have the potential to corrosivity 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. Methods are needed to assess buffering capacity

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

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

(f) Presently there are no validated and internationally accepted in vitro test methods for skin irritation (see article 5);

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

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

3.2.2.6. Corrosion

3.2.2.6.1 A substance is classified as corrosive on the basis of the results of animal testing, as shown in Table 3.2.1. A corrosive is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 of 3 tested animals after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology 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 Sections 3.2.2.1 and 3.2.2.4 and also in Part 1, paragraphs 1.1.3.1.1 and.1.1.3.2.3

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 A single irritant category (Category 2) is presented in the table using the results of animal testing. The use of human data is discussed in Sections 3.2.2.1 and 3.2.2.4 and also in Part 1, paragraph 1.1.3.1.1. and 1.1.3.2.3. The major criterion for the irritant category is that at least 2 tested animals have a mean score of • 2.3 - • 4.0.

Table 3.2.2
Skin irritation categories

Categories	**Criteria**
Irritant (Category 2)	(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 main 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 over all the animals tested. A separate irritant

criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test.

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 a limited degree of alopecia, 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 Category 1A) 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 needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

3.2.3.2. Classification of mixtures when data are not available for the complete mixture: Bridging principles.

3.2.3.2.1 Where the mixture itself has not been tested to determine its skin irritation/corrosion hazards, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the bridging rules set out in Section 1.1.7.

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 concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such components exceeds a threshold cut-off value/concentration limit.

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

3.2.3.3.4 Particular care must be taken when classifying certain types of 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%. 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 will be a better indicator of corrosion than the concentration limits of Table 3.2.3. 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 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 below.

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 cut-off levels mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture may be classified according to that data (see also Section 1.3.5, the Use and Setting of Cut-Off Values/Concentration Limits, paragraphs 1.3.5.5 and 1.3.5.6). On other occasions, when it is expected that the skin corrosion/irritation hazard of an ingredient will not be evident when present at a level above the generic concentration cut-off levels mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy shall be applied, as described in paragraph 3.2.2.5 and illustrated in Figure 3.2.1.

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

Table 3.2.3
Concentration of ingredients classified for skin corrosive/irritant hazard (Category 1 or 2) that would trigger classification of the mixture

Sum of ingredients classified as:	**Concentration triggering classification of a mixture as:**	
	Skin Corrosive	**Skin Irritant**
	Category 1	**Category 2**

	(see note below)	
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 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
Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as corrosive/irritant to skin

Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH £ 2	≥ 1%	Category 1 A
Base with pH ³ 11.5	≥ 1%	Category 1 A
Other corrosive (Categories 1A, 1B, 1C) ingredients for which additivity does not apply	≥ 1%	Category 1 A
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
Pictograms		
Signal word	Danger	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes skin irritation
Precautionary statements	TBA	TBA

3.3. SERIOUS EYE DAMAGE /EYE IRRITATION[83]

[83] The text follows that of GHS document Chapter 3.3, with editorial amendments.

3.3.1. Definitions and General Considerations

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 structure-activity relationships (SAR) or structure-property relationships (SPR) and the output of validated in vitro tests in order to avoid unnecessary animal testing.

3.3.2.2. 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 an agent causes serious (i.e. irreversible) damage to the eyes. If a substance or mixture 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 ≥ 11.5 may produce serious eye damage, especially when associated with significant buffering capacity. Such agents are expected to produce significant effects on the eyes, also when the buffering capacity is unknown. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. In vitro alternatives that have been validated and accepted may be used to make classification decisions (see Article 5).

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.

The provisions of Paragraph 1.1.5. (a) regarding testing of mixtures shall also be noted.

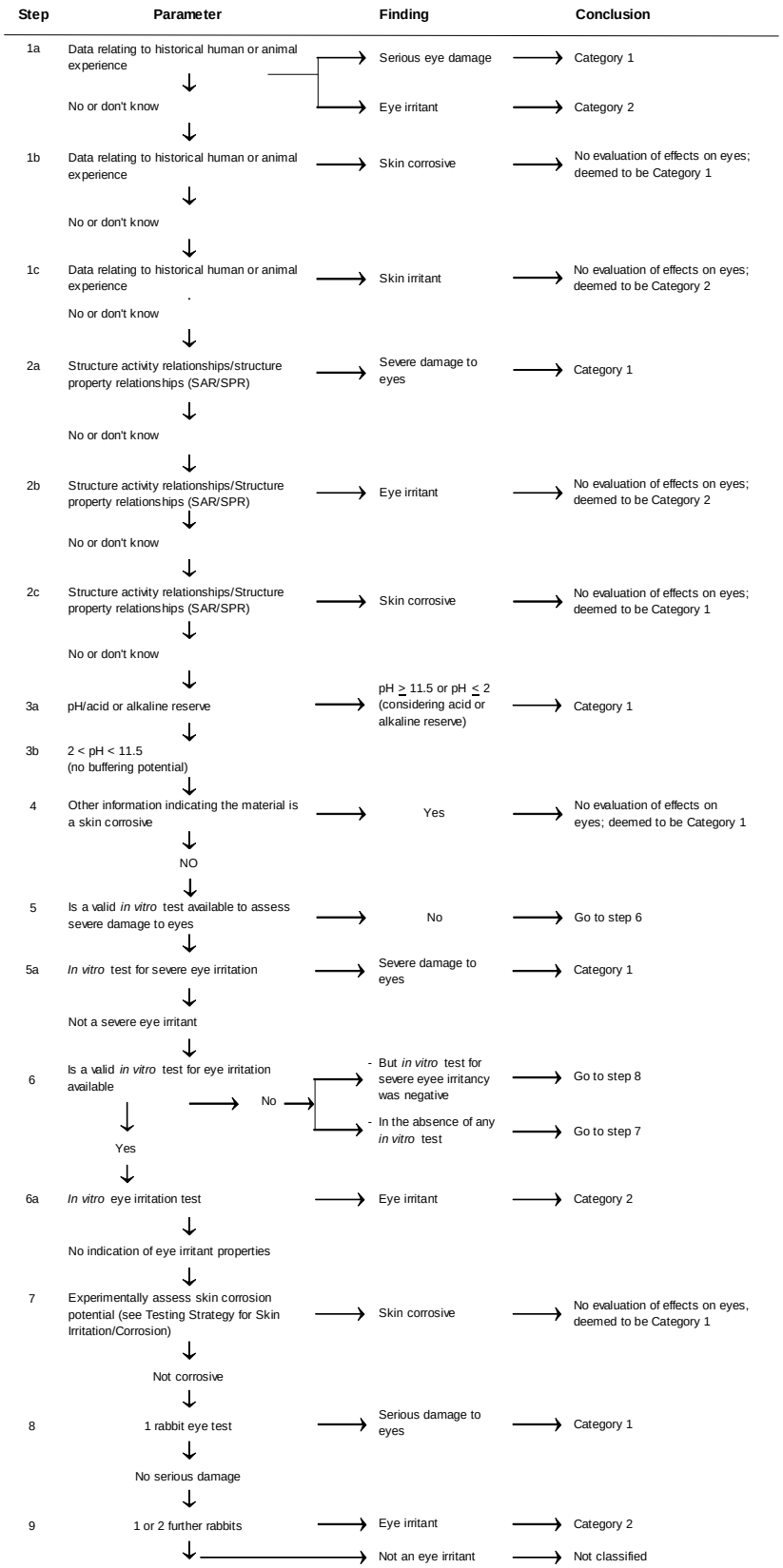
Although information may be gained from the evaluation of single parameters within a tier (e.g., caustic alkalis with extreme pH shall be considered as local corrosives), the totality of existing information shall be considered in making an overall weight of evidence determination, particularly when 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 as outlined in Figure 3.3.1 shall be considered where applicable, while recognising that all elements may not be relevant in certain cases.

3.3.2.6. The proposed tiered testing approach provides good guidance on how to organize existing information on a substance or mixture and to make a weight-of-evidence decision about hazard assessment and hazard classification – ideally without conducting new animal tests.

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



Notes to Figure 3.3.1:

Step 1a/b

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

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

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

Step 2 a/b/c

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

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

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

Step 3

pH extremes of • 2.0 and • 11.5 are indicative of a potential for severe local effects and substances exhibiting such physical properties shall be considered as leading to serious damage to eyes (Category 1). The acid/alkali reserve may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance 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 validate in vitro test.

Step 4

All attainable information shall be used, including human experience. But this information shall be restricted to that which pre-exists (e.g. the results of a dermal LD50 test or historical information on skin corrosion).

Step 5

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

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

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

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

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

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

3.3.2.7.1 Substances that have the potential to seriously damage the eyes are classified in Category 1[84] (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 days observation period.

Table 3.3.1
Categories for irreversible eye effects

Categories	**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

84 Wording slightly modified from GHS 3.3.2.8.

	- 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.

3.3.2.7.2 The use of human data is discussed in Sections 3.3.2.1, 3.3.2.4,and also in Part I Paragraphs 1.1.3.1.1 and.1.1.3.2.3

3.3.2.8. Reversible effects on the eye (Category 2)

3.3.2.8.1 A single category is adopted for substances that have the potential to induce reversible eye irritation. Substances are classified in this hazard category on the basis of the results of animal testing, in accordance with the criteria listed in Table 3.3.2.

Table 3.3.2
Categories for reversible eye effects

Categories	**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 ≥ 2.0 - conjunctival oedema (chemosis) ≥ 2.0 - 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

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

3.3.3. Classification criteria for Mixtures

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

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 classes.

3.3.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of substances or 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 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 of 2 or less or 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

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

3.3.3.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the bridging rules set out in Section 1.1.7.

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% can still be relevant for classifying the mixture for eye irritation/serious eye damage.

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

3.3.3.3.3 Table 3.3.3 below provides the cut-off value/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 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 %. 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 concentration limits of Table 3.3.3. 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 skin corrosive ingredient and as Category 2 when it contains ≥ 3% of an skin 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 below.

3.3.3.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture may 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/ cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy shall be applied as referred to in paragraph 3.3.2.6 and in Figure 3.3.1.

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
Concentration of ingredients of a mixture classified as Skin corrosive Category 1 and/or eye Category 1 or 2 for effects on the eye that would 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 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
Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye.

Ingredient	**Concentration**	**Mixture classified as: Eye**
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other Skin corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other Skin 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**
Pictograms		
Signal word	Danger	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation
Precautionary statements	TBA	TBA

3.4. RESPIRATORY OR SKIN SENSITISATION[85]

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.

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

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 standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

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

3.4.2. Classification criteria for substances

3.4.2.1. Respiratory sensitisers

Substances shall be classified as respiratory sensitisers (Category 1) 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.

3.4.2.1.1 Human evidence

3.4.2.1.1.1 Evidence that a substance can induce specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an

85 The text that follows is that of GHS document Chapter 3.4, with editorial amendments.

allergic reaction. However, immunological mechanisms do not have to be demonstrated.

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

(a) the size of the population exposed;

(b) the extent of exposure.

3.4.2.1.1.3 The evidence referred to above could be

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

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

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

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

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

(b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

3.4.2.1.1.4 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.

3.4.2.1.1.5 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.

3.4.2.1.2 Animal studies

3.4.2.1.2.1 Data from appropriate animal studies[86] which may be indicative of the

86 At present recognised animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, animal testing may be used, e.g. a modification of the guinea pig maximisation test for determination of relative allergenicity of proteins. However, these tests still need further validation.

potential of a substance to cause sensitisation by inhalation in humans[87] may include:

(i) measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;

(ii) specific pulmonary responses in guinea pigs.

3.4.2.2. Skin sensitisers

3.4.2.2.1 Substances shall be classified as contact sensitisers (Category 1) in accordance with the following criteria:

(i) If there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or

(ii) If there are positive results from an appropriate animal test (see specific criteria in paragraph 3.4.2.2.4.1).

3.4.2.2.2 Specific consideration

3.4.2.2.2.1 For classification of a substance as a skin sensitiser, evidence shall include any or all of the following:

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

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

(c) Positive data from appropriate animal studies;

(d) Positive data from experimental studies in man (see Article 5 (2);

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

3.4.2.2.2.2 Positive effects seen in either humans or animals will normally justify classification. Evidence from animal studies (see Section 3.4.2.2.4) is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on contact sensitisation are usually derived from case-control or other, less defined studies. Evaluation of human data

87 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.

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 can not normally be used to negate positive results from animal studies.

3.4.2.2.2.3 If none of the above mentioned conditions are met the substance need not be classified as a contact sensitiser. However, a combination of two or more indicators of contact 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 paragraph 3.4.2.2.4.1, but which are sufficiently close to the limit to be considered significant;

(d) Positive data from non-standard methods;

(e) Positive results from close structural analogues.

3.4.2.2.3Immunological contact urticaria

3.4.2.2.3.1 Substances or mixtures meeting the criteria for classification as respiratory sensitisers may in addition cause immunological contact urticaria. Consideration shall be given to classifying these substances also as contact sensitisers. Information concerning contact urticaria shall be included by the use of appropriate precautionary information on the label or in the Safety Data Sheet.

3.4.2.2.3.2 For substances or mixtures which produce signs of immunological contact urticaria but which do not fulfil the criteria as a respiratory sensitiser, consideration shall be given to classification as a skin sensitiser. 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.

3.4.2.2.4Animal studies

3.4.2.2.4.1 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. Test methods for skin sensitisation are described in Test Method Regulation [ ]. Other methods may be used provided that they are well-validated and scientific justification is given.

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 will be used in accordance with the bridging rules set out in Section 1.1.7.

3.4.3.3. Classification of mixtures when data are available for all components or only for some components 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 cut-off value/concentration limit for the specific endpoint as shown in Table 3.4.1 below for solid/liquid and gas respectively.

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

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

Note 1[88]:
This cut-off value/concentration limit is generally used for the application of the special labelling requirements of Annex II 2.10 to protect already sensitised individuals. A SDS would be required for the mixture containing an ingredient above this cut off limit.

88 Notes modified from notes to Table 3.4.1 in part 3 of GHS.

Note 2:
This cut-off value/concentration limit is used to trigger classification of a mixture as a skin sensitiser.

Note 3:
This cut-off value/concentration limit is used to trigger classification of a mixture as a respiratory sensitiser.

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 3.4.2

Table 3.4.2
Respiratory or skin sensitisation label elements.

Classification	**Respiratory sensitisation** **Category 1**	**Skin sensitisation** **Category 1**
Pictograms		
Signal Word	Danger	Warning
Hazard Statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction
Precautionary statement	TBA	TBA

3.5. GERM CELL MUTAGENICITY[89]

3.5.1. Definitions and General Considerations

89 The text that follows is that of GHS document Chapter 3.5, with editorial amendments.

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

3.5.1.2. 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, mutagenicity or genotoxicity tests in vitro and in mammalian somatic cells in vivo are also considered in classifying substances and mixtures within this hazard class.

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

Figure 3.5.1
Hazard categories for 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**
Category 1A	**Substances known to induce heritable mutations in the germ cells of humans** 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. This supporting evidence may, for example, be derived from

	mutagenicity/genotoxic tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or – Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
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 may also be considered[90].

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

90 GHS para 3.5.2.2.

(quantitative) risk assessment of substances[91].

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 the Test Method Regulation [ ]. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification[92].

3.5.2.3.4 The classification of individual substances shall be based on the total weight of evidence available, using expert judgement. In those instances where a single well-conducted test is used for classification, it 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[93].

3.5.3. Classification criteria for Mixtures

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

3.5.3.1.1 Classification of mixtures for germ cell mutagenicity will be based on the available test data on germ cell mutagenicity for the individual ingredients of the mixture using cut-off values/concentration limits as laid down in paragraph 3.5.3.3.1 for those ingredients classified as germ cell mutagens.

3.5.3.1.2 In the case of mixtures that have been manufactured and tested for germ cell mutagenicity outside the Community, the classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

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

3.5.3.2.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to the provisions of paragraph 3.5.3.1.2), to adequately characterise the hazards of the mixture, these data will be used in accordance with the applicable bridging rules set out in Section 1.1.7

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

3.5.3.3.1 The mixture will 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

91 GHS para 3.5.2.3.

92 GHS para 3.5.2.4.

93 GHS para 3.5.2.10

above the appropriate cut-off value/concentration limit as shown in Table 3.5.1 for Category 1A, Category 1B and 2 respectively.

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

Ingredient classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**		
	Category 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 cut-off values/concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.4. Hazard Communication

3.5.4.1. Label elements shall be used in accordance with Table 3.5.2, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.2
Label elements of germ cell mutagenicity

Classification	**Category 1A/1B**	**Category 2**
Pictograms		
Signal Word	Danger	Warning
Hazard Statement	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	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	TBA	TBA

3.6. CARCINOGENICITY[94]

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 carcinogenic 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.

Figure 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. The classification of a substance can be further distinguished:
Category 1A	**Known to have carcinogenic potential for humans; largely based on human evidence**
Category 1B	**Presumed to have carcinogenic potential for humans; largely based on animal evidence** The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see Section 3.6.2.5). Such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human

94 The text that follows is that of GHS document Chapter 3.6, with editorial amendments.

	carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
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 from either limited 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[95]

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

3.6.2.2.2 Classification of a substance as a carcinogen is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place 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[96] human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient.

3.6.2.2.4 Additional considerations (weight of evidence). 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 an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

3.6.2.2.5 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 are needed 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;

(d) Reduced tumour latency.

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

95 Sections that follow are GHS Paragraphs 3.6.2.2 onwards.

96 The terms "sufficient" and "limited" are used here as they have been defined by the International Agency for Research on Cancer (IARC).

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

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

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

(h) Routes of exposure;

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

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

(k) Mode of action and its relevance for humans, such as 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 The following additional consideration applies to classification of substances into either Category 1A, Category 1B or Category 2. 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 the complete mixture

3.6.3.1.1 Classification of mixtures will be based on the available test data of the individual ingredients of the mixture using cut-off values/concentration limits for those ingredients as laid down in paragraph 3.6.3.3.1.

3.6.3.1.2 In the case of mixtures that have been manufactured and tested for carcinogenic hazard outside the Community, the classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g.: statistical analysis, test sensitivity) of carcinogenicity test systems. Adequate

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

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

3.6.3.2.1 Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to the provisions of paragraph 3.6.3.1.2) to adequately characterise the hazards of the mixture, these data may be used in accordance with the applicable bridging rules set out in Section 1.1.7.

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

3.6.3.3.1 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 cut-off value/concentration limit as shown in Table 3.6.1 below for Category 1 and 2 respectively.

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

Ingredient classified 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 cut-off values/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 would be required for the mixture.

3.6.4. Hazard Communication

3.6.4.1. Label elements shall be used in accordance with Table 3.6.2, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.6.2
Label elements for carcinogenicity

Classification	Category 1A/1B	Category 2

Pictograms		
Signal Word	Danger	Warning
Hazard Statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement	TBA	TBA

3.7. REPRODUCTIVE TOXICITY[97]

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* (Chapter 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

For classification purposes, therefore, 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, would be classified as reproductive toxicants with a general hazard statement.

3.7.1.2. *Adverse effects on sexual function and fertility* include any effect of substances that would interfere with reproductive ability or capacity. This may include, but not be limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive

97 The text follows that of GHS document Chapter 3.7, with editorial amendments.

senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (see Figure 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.

3.7.1.3. *Adverse effects on development of the offspring* or developmental toxicity include, 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 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.

3.7.2. 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 as separate issues. In addition, effects on lactation are allocated to a separate hazard category.

Figure 3.7.1 (a)
Hazard categories for reproductive toxicants

Category	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. For regulatory purposes, a substance can be further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Category 1A **Category 1B**	**Known human reproductive toxicant** The classification of a substance in this Category 1A is largely based on evidence from humans. **Presumed human reproductive toxicant** The classification of a substance in this 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. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 could be the more appropriate classification. 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 be considered not to be a secondary non-specific consequence of the other toxic effects.

Figure 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 labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

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

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

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

3.7.2.2. Basis of classification

3.7.2.2.1 Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence. Classification as a reproductive toxicant is intended to be used for 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.

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 also Section 1.3.7.5, 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 material under study may also be included, particularly when information on the material is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for 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. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also 3.7.2.2.3).

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

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

3.7.2.3.4 Data from animal studies ideally 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 may 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 is reasonable to assume that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, for example 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. So, in the interpretation of the

developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, 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, it is believed that maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited 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 may be reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification may not necessarily be the outcome in the case of minor developmental changes e.g. small reduction in foetal/pup body weight, retardation of ossification when seen in association with maternal toxicity.

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

Maternal mortality: an increased incidence of mortality among the treated dams over the controls 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)[98]

98 It is recognised that the Mating index and the Fertility Index can also be affected by the male.

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 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 may be useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption 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 may be useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Examples of frank clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

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

3.7.2.5. Animal and experimental data

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

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

evidence is less reliable than that obtained through full studies.

3.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive 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 may result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, e.g. by irritation, must be interpreted with extreme caution and on their own would not normally be the basis for classification.

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification, 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 would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

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

3.7.2.5.9 However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg 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 the complete mixture

3.7.3.1.1 Classification of mixtures for reproductive toxicity will be based on the available test data on reproductive toxicity for the individual ingredients of the mixture and using cut-off values/concentration limits as laid down in paragraph 3.7.3.3.1 for those ingredients classified as reproductive toxicants.

3.7.3.1.2 In the case of mixtures that have been manufactured and tested for reproductive toxicity outside the Community, the classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g.: statistical analysis, test sensitivity) of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

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

3.7.3.2.1 Subject to the provisions of paragraph 3.7.3.1.2, where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the applicable bridging rules set out in Section 1.1.7.

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

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

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

Table 3.7.1

Cut-off values/concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that would trigger classification of the mixture

	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 cut-off values/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 reproductive toxicant is present in the mixture as an ingredient at a concentration above 0.1%, a SDS would be required for the mixture. If a Category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration above 1.0% a SDS would be required for the mixture.

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 3.7.2

Table 3.7.2
Label elements for reproductive toxicity

Classification	**Category 1A/1B**	**Category 2**	**Additional labelling for effects on or via lactation**
Pictograms			No pictogram
Signal word	Danger	Warning	No signal word

Hazard statement	May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause harm to breast-fed children.
Precautionary Statement	TBA	TBA	TBA

3.8. SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY - SINGLE EXPOSURE[99]

3.8.1. Definitions and General Considerations

3.8.1.1. *Specific target organ systemic toxicity (single exposure)* is defined as specific, non lethal target organ/systemic 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 Chapters 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/systemic toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

3.8.1.3. 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. It is recognised that human data will be the primary source of evidence for this hazard class.

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

3.8.1.6. Specific target organ/systemic toxicity following a repeated exposure is classified as described in Specific target organ systemic toxicity – Repeated exposure

99 The text follows that of GHS document Chapter 3.8, with editorial amendments.

(Chapter 3.9) and is therefore excluded from the present chapter. Other specific toxic effects, listed below are assessed separately and consequently are not included here:

(a) Acute toxicity (Chapter 3.1),

(b) Skin corrosion/irritation (Chapter 3.2),

(c) Serious eye damage/eye irritation (Chapter 3.3),

(d) Respiratory or skin sensitisation (Chapter 3.4),

(e) Germ cell mutagenicity (Chapter 3.5),

(f) Carcinogenicity (Chapter 3.6),

(g) Reproductive toxicity (Chapter 3.7); and

(h) Aspiration toxicity (Chapter 3.10).

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

3.8.2. Classification criteria for substances

3.8.2.1. Substances of Category 1 and Category 2

3.8.2.1.1 Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1). Substances are then placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Figure 3.8.1).

Figure 3.8.1
Categories for specific target organ systemic 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 systemic 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 systemic 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 3.8.2.1.9).
Category 3	**Transient target organ effects** There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances or mixtures are classified specifically for these effects as laid in 3.8.2.2.

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

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

3.8.2.1.3 Classification is determined by expert judgement (see Section 1.1.3.2), 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 1.1.3.2), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ/systemic toxic effects that merit classification.

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

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

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

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

Dose/concentration levels in humans shall normally 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. Examples of relevant toxic effects in humans and/or animals are provided below:

(a) Morbidity resulting from single exposure;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it would 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 would indicate classification, consideration of the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the dose/concentration).

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

Table 3.8.1
Guidance value ranges for Category 1 and 2 after single-dose exposures

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

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

Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data may be included in the weight of evidence evaluation.

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

3.8.2.1.10 Other considerations

3.8.2.1.10.1 When a substance is characterised only by use of animal data (typical of new substances, but also true for many existing substances), the classification process

would include reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

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

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

3.8.2.1.10.4 Saturated vapour concentration may be used 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 (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data.

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

(c) The symptoms observed in humans 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 this classification endpoint.

(d) There are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened

mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation.

(e) This special classification would occur only when more severe organ/systemic 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 righting reflex, narcosis, and ataxia. If these effects are not transient in nature, then they shall normally be considered for classification as Category 1 or 2.

3.8.3. Classification criteria for Mixtures

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

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 can be classified by weight of evidence evaluation of this data. 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/systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the bridging principles set out in Section 1.1.7

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

3.8.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a specific target organ/systemic toxicant (specific organ

specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ/systemic toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.8.2 below for Category 1 and 2 respectively.

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

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

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

	Category 1	**Category 2**
Category 1 **Specific Target Organ Systemic Toxicant**	Concentration ≥ 10% [(Note 1)]	1.0% ≤ concentration < 10%
Category 2 **Specific Target Organ Systemic Toxicant**		Concentration ≥ 10% [(Note 1)]

Note 1
If a Category 1 or 2 specific target organ/systemic toxicant is present in the mixture as an ingredient at a concentration above 1.0% a SDS would be required for the mixture.

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 cut-off value/concentration limit of 20% may be appropriate; however, it shall be recognised that this cut-off value/concentration limit may be higher or less depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgment-shall be exercised.

3.8.4. Hazard Communication

3.8.4.1. Label elements shall be used in accordance with Table 3.8.3., for substances or mixtures meeting the criteria for classification in this hazard class.

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

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

3.9. SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY - REPEATED EXPOSURE[100]

100 The text follows that of GHS document Chapter 3.9, with editorial amendments.

3.9.1. Definition and General Considerations

3.9.1.1. *Target organ systemic toxicity (repeated exposure)* means specific, target organ/systemic 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 chapters 3.1 to 3.8 and chapter 3.10 are not included here.

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

3.9.1.3. 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. It is recognised that human data will be the primary source of evidence for this hazard class.

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

3.9.1.6. Non-lethal toxic effects observed after a single-event exposure are classified as described in Specific target organ systemic toxicity – Single exposure (Chapter 3.8) and are therefore excluded from the present chapter.

3.9.2. Classification criteria for substances

3.9.2.1. Substances are classified as specific target organ/systemic toxicants following repeated exposure by the use of expert judgement, on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed (Figure 3.9.1).

Figure 3.9.1
Categories for specific target organ systemic toxicity-repeated exposure

Categories	
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 systemic

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

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

3.9.2.3. Classification is determined by expert judgement (see Section 1.1.3.2), on the basis of the weight of all evidence available including the guidance in 3.9.2.4.

3.9.2.4. Weight of evidence of all data (see Section 1.1.3.2), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ/systemic toxic effects that merit classification. This taps the considerable body of industrial toxicology data collected over the years. Evaluation 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/systemic toxicity comes either from repeated exposure in humans, e.g., exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include haematological, clinicochemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species may also be used. Other long-term exposure studies, e.g. for carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ/systemic toxicity that could be used in the assessment of classification.

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

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

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

Dose/concentration levels in humans shall normally 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/systemic 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, must be taken into consideration in the classification process. Examples of relevant toxic effects in humans and/or animals are provided below:

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

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

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

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

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

3.9.2.8. Effects considered not to support classification for specific target organ/systemic toxicity following repeated exposure

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

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

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

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

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

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

classification.

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

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

3.9.2.9.2 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it would 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 would indicate classification, consideration of the duration of experimental exposure and the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the duration of exposure and the dose/concentration).

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

3.9.2.9.5 The guidance values proposed refer 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; e.g.: for a 28-day study the guidance values below would be increased by a factor of three.

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

Table 3.9.1
Guidance values to assist in Category 1 classification

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

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

Table 3.9.2
Guidance values to assist in Category 2 classification

Route of Exposure	Units	Guidance Value Ranges: (dose/concentration)
Oral (rat)	mg/kg body weight/day	10 - 100
Dermal (rat or rabbit)	mg/kg body weight/day	20 - 200
Inhalation (rat) gas	ppmV/6h/day	50 - 250
Inhalation (rat)vapour	mg/litre/6h/day	0.2 - 1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	0.02 - 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 is seen to occur in repeat-dose animal studies at a dose/concentration below the guidance value, e.g. < 100 mg/kg bw/day by the oral route, however the nature of the effect, e.g. nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, e.g. • 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, e.g., other long-term administration studies, or human case experience,

which supports a conclusion that, in view of the weight of evidence, classification would be the prudent action to take.

3.9.2.10. Other considerations

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

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

3.9.2.10.3 A substance that has not been tested for specific target organ/systemic toxicity may in certain instances and, 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 may be used 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 may be classified for specific target organ/systemic toxicity following single exposure, repeated exposure, or both.

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

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, then the mixture can be classified by weight of evidence evaluation of this 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/systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the bridging principles set out in Section 1.1.7.

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

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

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

	Category 1	**Category 2**
Category 1 **Specific Target Organ Systemic Toxicant**	Concentration ≥ 10% [(Note 1)]	1.0% ≤ concentration < 10%
Category 2 **Specific Target Organ Systemic Toxicant**		Concentration ≥ 10% [(Note 1)]

Note 1
If a Category 1 or 2 specific target organ/systemic toxicant is present in the mixture as an ingredient at a concentration above 1.0% a SDS would be required for the mixture.

3.9.3.4.2 These cut-off values and consequent classifications apply to both single- and repeated-dose target organ toxicants. Mixtures shall be classified for either or both single- and repeated-dose toxicity independently.

3.9.3.4.3 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 3.9.4 for substances or mixtures meeting the criteria for classification in this hazard class.

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

Classification	**Category 1**	**Category 2**

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

3.10. ASPIRATION HAZARD [101]

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 may have consequences for labelling, particularly where, due to acute toxicity, a recommendation may be considered to induce vomiting after ingestion. However, if the substance/mixture also presents an aspiration toxicity hazard, the recommendation to induce vomiting may need to be modified.

3.10.1.6. Specific considerations

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

101 The text follows that of GHS document Chapter 3.10, with editorial amendments.

been shown to pose an aspiration hazard only in animal studies.

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

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

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

3.10.1.6.4 Classification of aerosol/mist products

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

3.10.2. Classification criteria for substances

Table 3.10.1
Hazard categories for aspiration toxicity

Categories	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:
Examples of substances included in Category 1 are 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 characterize the hazard of the mixture, these data will be used in accordance with the bridging principles set out in Section 1.1.7. However, in the case of application of the dilution bridging principle, the concentration of aspiration toxicant(s) shall not drop below 10%.

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, will be classified in Category 1.

3.10.3.3.1.2 In the case of a mixture which separates into two or more distinct layers, one of which contains 10 % 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**
Pictogram	
Signal word	Danger
Hazard statement	May be fatal if swallowed and enters airways

Precautionary Statement	TBA

4. PART 4: ENVIRONMENTAL HAZARDS

4.1. HAZARDOUS TO THE AQUATIC ENVIRONMENT102

4.1.1. Definitions and General Considerations

4.1.1.1. Definitions

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

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

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

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).

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

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

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

4.1.1.2. Basic elements

4.1.1.2.1 The basic elements used for classification on the basis of aquatic environmental effects are:

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102 The guidance made available by the Agency will refer to the guidance documents Annex9 and Annex 10 of the GHS (ST/SE/AC.10/30 as amended). Considering the complexity of this hazard class and the breadth of the application of the system, the Guidance Documents are considered an important element in the operation of the classification system.

(a) Acute aquatic toxicity;

(b) Potential for or actual bioaccumulation;

(c) Degradation (biotic or abiotic) for organic chemicals; and

(d) Chronic aquatic toxicity.

4.1.1.2.2 Data are preferably to be derived using EU test methods, OECD Test Guidelines or equivalent according to the principles of GLP. While data from internationally harmonised test methods are preferred, in practice data from other test methods such as national methods may also be used where they are considered as equivalent. Where valid data are available from non-standard testing, these may be considered in classification if they are considered to represent an equivalent endpoint to the standard data. In general, it has been agreed that freshwater and marine species toxicity data can be considered as equivalent data. Where such data are not available classification shall be based on the best available data. See also Part 1.

4.1.1.3. Other considerations

4.1.1.3.1 Classification of substances and mixtures on the basis of environmental effects requires the identification of the hazards they present to the aquatic environment. The aquatic environment may be considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. To that extent, the classification scheme does not address aquatic pollutants for which there may be a need to consider effects beyond the aquatic environment such as[103] effects on other ecosystems, whose constituents may range from soil microflora and microfauna to primates, the impacts on human health etc. The basis, therefore, of the identification of hazard is the aquatic toxicity of the substance or mixture, although this may be modified by taking account of further information on the degradation and bioaccumulation behaviour.

4.1.1.3.2 While the classification system applies to all substances and mixtures, it is recognised that in some cases, e.g. metals or poorly soluble inorganic compounds, special guidance is necessary.

4.1.2. Classification criteria for substances

4.1.2.1. The core classification system for substances consists of one acute classification category and three chronic classification categories. The criteria for classification of a substance in acute Category I is defined on the basis of acute aquatic toxicity data only (EC_{50} or LC_{50}). The criteria for classification of a substance into the chronic categories combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data).

4.1.2.2. The system also introduces as “safety net” classification (referred to as Category: Chronic 4) for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern.

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[103] Extract from 1[sr] para of Section 5.1 of Annex VI of Directive 67/548/EEC

4.1.2.3. The system for classification recognises that the core intrinsic hazard to aquatic organisms is represented by both the acute and chronic toxicity of a substance. Separate hazard categories are defined for both properties representing a gradation in the level of hazard identified. The lowest of the available toxicity values shall normally be used to define the appropriate hazard category(ies). There may be circumstances, however, when a weight of evidence approach may be used.

4.1.2.4. The principal hazard of a 'hazardous to the aquatic environment' substance is defined by chronic toxicity, although acute toxicity at L(E)C50 levels ≤1 mg/L are also considered hazardous. The intrinsic properties of a lack of rapid degradability and/or a potential to bioconcentrate in combination with acute toxicity is used to assign a substance to a chronic hazard category.

4.1.2.5. Substances with acute toxicities well below 1 mg/l 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 4.1.1 and 4.1.3.5.5).

4.1.2.6. The criteria for classifying and categorised substances as 'hazardous to the aquatic environment' are summarised in Table 4.1.1.

Figure 4.1.1
Classification categories for hazardous to the aquatic environment

Acute (short-term) aquatic hazard	
Category: Acute Category 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)
Chronic (long-term) aquatic hazard	
Category: Chronic Category 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 $K_{ow} \geq 4$).	
Category: Chronic Category 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 $K_{ow} \geq 4$).	

Category: Chronic Category 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 $K_{ow} \geq 4$).	
"Safety net" classification	
Category: Chronic Category 4	
Cases when data do not allow classification under the formal criteria (Tables 4.1.1, and 4.1.2), 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 3), and which are not rapidly degradable and have an experimentally determined BCF • 500 (or, if absent, a log $K_{ow} \geq 4$), indicating a potential to bioaccumulate, will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence would include chronic toxicity NOECs > water solubility or > 1 mg/L, or evidence of rapid degradation in the environment.	

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.

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 and no ErC_{50} is recorded, classification shall be based on the lowest EC_{50} available.

Note 3 "No acute toxicity" is taken to mean that the $L(E)C_{50}$s is above the water solubility. Also for poorly soluble substances, (water solubility < 1.00 mg/l), where there is evidence that the acute test would not have provided a true measure of the intrinsic toxicity.

4.1.2.7. Aquatic toxicity

4.1.2.7.1 The organisms fish, crustacea and algae are tested as surrogate species covering a range of trophic levels and taxa, and the test methods are highly standardised. Data on other organisms may also be considered, however, provided they represent equivalent species and test endpoints. The algal growth inhibition test is a chronic test but the EC50 is treated as an acute value for classification purposes. (Above in nota 2)

4.1.2.7.2 Aquatic toxicity testing, by its nature, involves the dissolution of the substance under test in the water media used and the maintenance of a stable bioavailable exposure concentration over the course of the test.

4.1.2.7.3 Acute aquatic toxicity is normally determined using a fish 96 hour LC50 (OECD Test Guideline 203 or equivalent), a crustacea species 48 hour EC50 (OECD Test Guideline 202 or equivalent) and/or an algal species 72 or 96 hour EC50 (OECD Test Guideline 201 or equivalent). These species are considered as surrogate for all aquatic organisms and data on other species (e.g. *Lemna spp.*) may also be

considered if the test methodology is suitable.

4.1.2.7.4 For determining chronic aquatic toxicity for classification purposes data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) can be accepted. Other validated and internationally accepted tests may also be used. The NOECS or other equivalent L(E)Cx (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. The potential for bioaccumulation shall normally be determined by using the octanol/water partition coefficient, usually reported as a log Kow determined by OECD Test Guideline 107 or 117 or equivalent. The relationship between the log Kow of an organic substance and its bioconcentration as measured by the BCF in fish has considerable scientific literature support. Using a cut-off value of log Kow ≥ 4 is intended to identify only those substances with a real potential to bioconcentrate. While this represents a potential to bioaccumulate, an experimentally determined bioconcentration Factor (BCF) provides a better measure and shall be used in preference when available. A BCF shall be determined according to OECD Test Guideline 305 or equivalent. A BCF in fish of < 500 is considered as indicative of a low level of bioconcentration.

4.1.2.9. Rapid degradability

4.1.2.9.1 Substances that rapidly degrade can be quickly removed from the environment. While effects can occur, particularly in the event of a spillage or accident, they will be localised and of short duration. The absence of rapid degradation in the environment can mean that a substance in the water has the potential to exert toxicity over a wide temporal and spatial scale.

4.1.2.9.2 One way of demonstrating rapid degradation utilises the biodegradation screening tests designed to determine whether a substance is 'readily biodegradable', i.e. OECD Test Guideline 301 (A - F) and OECD Test Guideline 306 or equivalent. 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 one that is likely to biodegrade 'rapidly' in the aquatic environment, and is thus unlikely to be persistent. However, a fail in the screening test does not necessarily mean that the substance will not degrade rapidly in the environment. Other evidence of rapid degradation in the environment may therefore also be considered and may be of particular importance where the substances are inhibitory to microbial activity at the concentration levels used in standard testing. 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 definition 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 would not

normally qualify 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 the following criteria hold true:

(a) if, in 28-day ready biodegradation studies, 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 maxima.

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

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

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

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, the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally the use of bioaccumulation data shall be treated with care[104].

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 may enter solution.

4.1.3. Classification for Mixtures

4.1.3.1. The classification system for mixtures covers all classification categories which are used for substances, meaning 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 assumption is made and is applied where appropriate.

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

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:

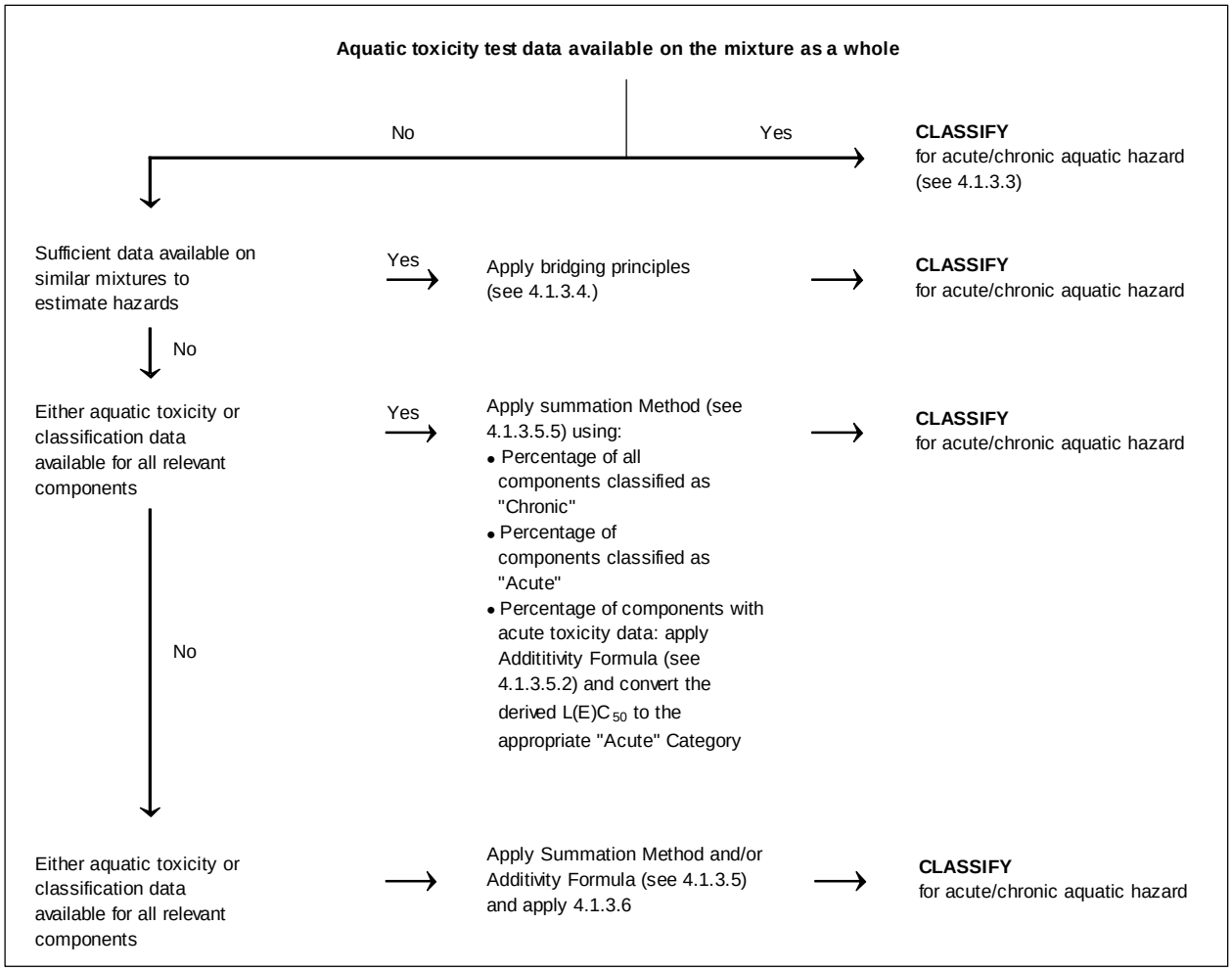
(a) classification based on tested mixtures;

(b) classification based on bridging principles,

(c) the use of "summation of classified components" and /or an "additivity formula".

[104] Specific guidance will be provided by the agency on how these data for such substances may be used in meeting the requirements of the classification criteria.

Figure 4. 1.2
Tiered approach to classification of mixtures for acute and chronic 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, it is classified according to the criteria that have been agreed for substances, but only for acute toxicity. The classification is normally based on the data for fish, crustacea and algae/plants. Classification of mixtures by using LC_{50} or EC_{50} data for the mixture as a whole is not possible for chronic categories since both toxicity data and environmental fate data are needed, and there are no degradability and bioaccumulation data for mixtures as a whole. It is not possible to apply the criteria for chronic classification because the data from degradability and bioaccumulation tests of mixtures cannot be interpreted; they are meaningful only for single substances.

4.1.3.3.2 When there is acute toxicity test data (LC50 or EC50) available for the mixture as a whole, this data as well as information with respect to the classification of components for chronic toxicity shall be used to complete the classification for tested mixtures as follows. When chronic (long-term) toxicity data (NOEC) is also available, this shall be used as well.

(a) $L(E)C_{50}$ (LC_{50} or EC_{50}) of the tested mixture ≤ 100 mg/L and NOEC of the tested mixture ≤ 1 mg/L or unknown:

– Classify mixture as Acute Category 1 (LC50 or EC50 of the tested mixture ≤ 1 mg/L)

– Apply Summation of Classified Components approach (see 4.1.3.5.5) for chronic classification (Chronic Category 1, 2, 3, 4 or no need for chronic classification).

(b) $L(E)C_{50}$ of the tested mixture ≤ 100 mg/L and NOEC(s) of the tested mixture > 1 mg/L:

– No need to classify for acute toxicity

– Apply Summation of Classified Components approach (see 4.1.3.5.5) for classification as Chronic Category 1. If the mixture is not classified as Chronic Category 1, then there is no need for chronic classification.

(c) $L(E)C_{50}$(s) of the tested mixture > 100 mg/L, or above the water solubility, and NOEC of the tested mixture ≤ 1 mg/L or unknown:

– No need to classify for acute toxicity

– Apply Summation of Classified Components approach (see 4.1.3.5.5) for Chronic classification (Chronic Category 4 or no need for chronic classification).

(d) $L(E)C_{50}$(s) of the tested mixture > 100 mg/L, or above the water solubility, and NOEC(s) of the tested mixture > 1 mg/L:

– - No need to classify for acute or chronic toxicity

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 1.1.7. However, in relation to application of the bridging rule for dilution, Paragraphs 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 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 mixture may be classified as equivalent to the original mixture or substance.

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

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 classification of its 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 Category 1 and/or Chronic Category 1, 2, 3 or 4) and those for which adequate test data is available. When adequate toxicity data is available for more than one component in the mixture, the combined toxicity of those components is calculated using the following additivity formula, and the calculated toxicity is used to assign that portion of the mixture an acute category which is then subsequently used in applying the summation method.

$$\frac{\sum Ci}{L(E)C_{50\,m}} = \sum_{\eta} \frac{Ci}{L(E)C_{50\,i}}$$

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

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 species (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 species). However, when toxicity data for each component are not available in the same species, 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 toxicity is then used to classify this part of the mixture as Acute Category 1 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 Acute Category 1 or Chronic Category 1 to Chronic Category 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 may therefore contribute to the classification of a mixture in a lower band. The calculation of these classification categories therefore needs to consider the contribution of all substances classified as Acute Category 1/Chronic Category 1, Chronic Category 2 and Chronic Category 3 together.

4.1.3.5.5.1.2 When a mixture contains components classified as Acute Category 1 or Chronic Category 1, attention must be paid to the fact that such components, when their acute toxicity is well below 1 mg/L contribute to the toxicity of the mixture even at a low concentration. Active ingredients in pesticides often possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application of the normal cut-off values/concentration limits may lead to an “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 for chronic toxicity with Chronic Category 1 overrides a classification with Chronic Category 2. As a consequence, in this example, the classification procedure is already completed if the result of the classification is Chronic Category 1. A more severe classification than Chronic Category 1 is not possible, therefore it is not necessary to undergo the further classification procedure.

4.1.3.5.5.3 Classification for Acute Category 1

4.1.3.5.5.3.1 First all components classified as Acute Category 1 are considered. If the sum of these components is greater than 25% the whole mixture is classified as Acute Category 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 below.

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 Category 1 x M[a] >25%	Acute Category 1

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

4.1.3.5.5.4 Classification for the Chronic Categories 1, 2, 3 and 4

4.1.3.5.5.4.1 First all components classified as Chronic Category 1 are considered. If the sum of these components is greater than 25% the mixture is classified as Chronic Category 1. If the result of the calculation is a classification of the mixture as Chronic Category 1 the classification procedure is completed.

4.1.3.5.5.4.2 In cases where the mixture is not classified as Chronic Category 1, classification of the mixture as Chronic Category 2 is considered. A mixture is classified as Chronic Category 2 if 10 times the sum of all components classified as Chronic Category 1 plus the sum of all components classified as Chronic Category 2 is greater than 25%. If the result of the calculation is classification of the mixture as Chronic Category 2, the classification process is completed.

4.1.3.5.5.4.3 In cases where the mixture is not classified either as Chronic Category 1 or Chronic Category 2, classification of the mixture as Chronic Category 3 is considered. A mixture is classified as Chronic Category 3 if 100 times the sum of all components classified as Chronic Category 1 plus 10 times the sum of all components classified with Chronic Category 2 plus the sum of all components classified as Chronic Category 3 is greater than 25%.

4.1.3.5.5.4.4 If the mixture is still not classified in Chronic Category 1, 2 or 3, classification of the mixture as Chronic Category 4 shall be considered. A mixture is classified as Chronic Category 4 if the sum of the percentages of components classified as Chronic Category 1, 2, 3 and 4 is greater than 25%.

4.1.3.5.5.4.5 The classification of mixtures for chronic hazards, based on this summation of classified components, is summarised in Table 4.1.2 below.

Table 4.1.2
Classification of a mixture for chronic hazards, based on summation of classified components

Sum of components classified as:	Mixture is classified as:
Chronic Category 1 x M[a] >25%	Chronic Category 1
(M x 10 x Chronic Category 1) + Chronic Category 2 >25%	Chronic Category 2
(M x 100 x Chronic Category 1) + (10 x Chronic Category 2) + Chronic Category 3 >25%	Chronic Category 3
Chronic Category 1 + Chronic Category 2 + Chronic Category 3 + Chronic Category 4 > 25%	Chronic Category 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 Category 1 and Chronic Category 1 components with toxicities well below 1 mg/L may influence the toxicity of the mixture and shall be given increased weight in applying the summation of classification approach. When a mixture contains components classified as Acute or Chronic Category 1, the tiered approach described in 4.1.3.5.5.3 and 4.1.3.5.5.4 shall be applied using a weighted sum by multiplying the concentrations of Acute Category 1 and Chronic Category 1 components by a factor, instead of merely adding up the percentages. This means that the concentration of "Acute Category 1" in the left column of Table 4.1.1 and the concentration of "Chronic Category 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 below. Therefore, in order to classify a mixture containing Acute/Chronic Category 1 components, the classifier needs to be informed of the value of the M factor in order to apply the summation method. Alternatively, the additivity formula (see 4.1.3.5.2) may be used when toxicity data are available for all highly toxic components in the mixture and there is convincing evidence that all other components, including those for which specific acute toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture..

Table 4.1.3
Multiplying factors for highly toxic components of mixtures

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

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 chronic aquatic hazard is available for one or more relevant components, it is concluded that the mixture cannot be attributed (a) definitive hazard category(ies). In this situation the mixture shall be classified based on the known components only, with the additional statement that: "x percent of the mixture consists of component of 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	
	Category 1
Pictogram	
Signal word	Warning
Hazard Statement	Very toxic to aquatic life
Precautionary	TBA

Statement	

CHRONIC				
	Category 1	**Category 2**	**Category 3**	**Category 4**
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	Very toxic to aquatic life with long lasting effects	Toxic to aquatic life with long lasting effects	Harmful to aquatic life with long lasting effects	May cause long lasting harmful effects to aquatic life
Precautionary Statement	TBA	TBA	TBA	TBA

Note 1: In the event that no useable information on acute and/or chronic aquatic hazard is available for one or more relevant components, the mixture shall be labelled with the additional statement that "*x percent of the mixture consists of components of unknown hazards to the aquatic environment*" – see detailed advice at 4.1.3.6.1

5. PART 5: ADDITIONAL EU HAZARD CLASS

5.1. Hazardous FOR THE OZONE LAYER[105]

5.1.1. Definitions and general considerations

5.1.1.1. *Substance Hazardous for 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 Annex I to Council Regulation (EC) No 2037/2000 on substances that deplete the ozone layer (OJ No L 244, 29.9.2000, p.1) and its subsequent amendments.

5.1.2. Classification criteria for substances

[105] 67/548/EEC Annex VI 5.2.2.2

5.1.2.1. A substance shall be classified as Hazardous for the Ozone Layer when 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 for the Ozone Layer on the basis of the individual concentration of the substance(s) contained therein that are also classified as Hazardous for the Ozone Layer, in accordance with Table 5.1.

Table 5.1
Cut-off values/concentration limits for substances (in a mixture), classified as Hazardous for the Ozone Layer, that would trigger classification of the mixture as Hazardous for the Ozone Layer

Classification of the substance	Classification of the mixture
Hazardous for the ozone layer	$C \geq 0.1\%$

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 for the Ozone Layer[106]

Symbol/pictogram	
Signal Word	Danger
Hazard Statement	Hazardous for the Ozone Layer
Precautionary statements	Pm

6. PART 6: APPLICATION OF PRECAUTIONARY STATEMENTS

6.1. Criteria for choice of precautionary statements

6.1.1. Introduction

6.1.1.1. Precautionary statements shall be assigned to hazardous substances and mixtures.

[106] The use of the GHS pictogram or the EU symbol is discussed in the project report.

6.1.1.2. This part provides the criteria on the use of the precautionary statements, including the selection of appropriate statements for each hazard class and category. The rules set out in Title IV and in Part 1 of this Annex shall apply.

6.1.1.3. Precautionary statements shall appear on a label along with the other label elements (pictograms, signal words and hazard statements).

[Placeholder: This part will contain criteria on the use of precautionary statements, these criteria can only be included at the stage when the ongoing work at the UN level has reached a stable stage, probably October 2006. However, an amendment might be needed to adapt to the final UN decision envisaged for December 2006. An example on how the criteria on the use of precautionary statements could be structured is provided below.

Table 6.1
Precautionary statements - General

1 Code	2 Precautionary Statements - General	3 Hazard Class / Hazard Categories	4 Conditions for use
[P101]	If medical advice is needed, have product container or label at hand.		Consumer Products
[xxx]	Keep out of reach of children.		Consumer Products
[xxx]	Read label before use.		Consumer Products

Table 6.2
Precautionary statements - Prevention

1 Code	2 Recommended Precautionary Statements - Prevention	3 Hazard Class / Hazard Categories	4 Conditions for use
[xxx]	Obtain special instructions before use.	Unstable explosives Germ Cell Mutagenicity, hazard categories 1A, 1B, 2 Carcinogenicity, hazard categories 1A, 1B, 2 Reproductive Toxicity Hazard categories 1A, 1B, 2 Additional category (effects on or via Lactation)	

[xxx]	Do not handle until all safety precautions have been read and understood.	Unstable Explosives Germ Cell Mutagenicity, hazard categories 1An 1B, 2 Carcinogenicity, hazard categories 1A, 1B, 2 Reproductive Toxicity, hazard categories 1A, 1B, 2	
[xxx]	Keep away from heat/sparks/open flame/hot surfaces. – No smoking.	Explosives, Divisions 1.1, 1.2, 1.3, 1.4, 1.5 Flammable Gases, hazard categories 1, 2 Flammable Aerosols, hazard categories 1, 2 Flammable Liquids, hazard categories 1, 2, 3 Flammable Solids, hazard categories 1, 2 Self-Reactive Substances and Mixtures, Types A, B, C, D, E, F Pyrophoric Liquids Pyrophoric Solids Organic Peroxide, Types A, B, C, D, E, F	Manufacturing/supplier or the competent au specify applicable ignition source(s).

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