Figure A.3.1 Tiered Evaluation for serious eye damage and eye irritation (See also Figure A.2.1)

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal serious eye damage/eye irritation data [a] →	Serious eye damage →	**Category 1**
	↘	Eye irritant →	**Category 2**[b]
	↓ Negative data/Insufficient data/No data ↓		
1b:	Existing human or animal data, skin corrosion →	Skin corrosion →	**Category 1**
	↓ Negative data/Insufficient data/No data ↓		
1c:	Existing human or animal serious eye damage/eye irritation data [a] →	Existing data showing that substance does not cause serious eye damage or eye irritation →	**Not classified**
	↓ No/Insufficient data ↓		
2:	Other, existing skin/eye data in animals [c] →	Yes, other existing data showing that substance may cause serious eye damage →	**Category 1**[b]
	↘	Yes, other existing data showing that substance may cause eye irritation →	**Category 2**[b]
	↓ No/Insufficient data ↓		
3:	Existing *ex vivo/in vitro eye* data[d] →	Positive: serious eye damage →	**Category 1**

Step	Parameter	Finding	Conclusion
	↓ ↘ No/Insufficient data/Negative response ↓	Positive: eye irritant →	**Category 2**[b]
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) [a] → ↓ Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve ↓	pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve →	**Category 1**
5:	↗ Validated Structure Activity Relationship (SAR) methods → ↓ ↘ No/Insufficient data ↓	Severe damage to eyes →	**Category 1**
		Eye irritant →	**Category 2**[b]
		Skin corrosive →	**Category 1**
6:	Consideration of the total weight of evidence [f] → ↓ ↘	Serious eye damage →	**Category 1**
		Eye irritant →	**Category 2**[b]
	No concern based on consideration of the sum of available data ↓		
7:	**Not classified**		

[a] *Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data from accident or poison center databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain;*

[b] *Classify in the appropriate category as applicable;*

[f] *Existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information. It is recognized that not all skin irritants are eye irritants. Expert judgment should be exercised prior to making such a determination;*

[d] *Evidence from studies using validated protocols with isolated human/animal tissues or other non-tissue-based, validated protocols should be assessed. Examples of internationally accepted, validated test methods for identifying eye corrosives and severe irritants (*i.e.*, Serious Eye Damage) include OECD Test Guidelines 437 (Bovine Corneal Opacity and Permeability (BCOP)), 438 (Isolated Chicken Eye (ICE) and 460 (Fluorescein leakage (FL)). Presently there are no validated and internationally accepted in vitro test methods for identifying eye irritation. A positive test result from a validated in vitro test on skin corrosion would lead to the conclusion to classify as causing serious eye damage;*

[e] *Measurement of pH alone may be adequate, but assessment of acid/alkaline reserve (buffering capacity) would be preferable. Presently, there is no validated and internationally accepted method for assessing this parameter;*

[f] *All information that is available on a substance must be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. The weight of evidence including information on skin irritation may lead to classification for eye irritation. Negative results from applicable validated in vitro tests are considered in the total weight of evidence evaluation.*

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A.3.4 Classification Criteria for Mixtures

A.3.4.1 Classification of Mixtures When Data Are Available for the Complete Mixture

A.3.4.1.1 The mixture will be classified using the criteria for substances, and taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure A.3.1).

A.3.4.1.2 When considering testing of the mixture, chemical manufacturers shall use a tiered approach 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 to avoid unnecessary animal testing. In the absence of any other information, a mixture is considered to cause serious eye damage (Category 1) if it has a pH ≤2 or ≥11.5. However, if consideration of acid/alkaline reserve suggests the mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further evaluation may be necessary.

A.3.4.2 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.3.4.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or eye irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles, as found in paragraph A.0.5 of this appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one hazard category, Substantially similar mixtures, and Aerosols.

A.3.4.3 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.3.4.3.1 For purposes of classifying the serious eye damage/eye irritation hazards of mixtures in the tiered approach:

The ''relevant ingredients'' of a mixture are those which are present in concentrations ≥1% (weight/weight for solids, liquids, dusts, mists and vapors and volume/volume for gases). If the classifier has reason to suspect that an ingredient present at a concentration <1% will affect classification of the mixture for serious eye damage/eye irritation, that ingredient shall also be considered relevant.

A.3.4.3.2 In general, the approach to classification of mixtures as seriously damaging to the eye or eye irritant when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each skin corrosive or serious eye damage/eye irritant ingredient contributes to the overall serious eye damage/eye irritation properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for skin corrosive and serious eye damaging ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as serious eye damaging/eye irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

A.3.4.3.3 Table A.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture must be classified as seriously damaging to the eye or an eye irritant.

A.3.4.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in A.3.4.3.1 and A.3.4.3.2 might not work given that many of such substances are seriously damaging to the eye/eye irritating at concentrations <1%. For mixtures containing strong acids or bases, the pH should be used as classification criteria (See A.3.4.1) since pH will be a better indicator of serious eye damage (subject to consideration of acid/alkali reserve) than the concentration limits of Table A.3.3. A mixture containing skin corrosive or serious eye damaging/eye irritating ingredients that cannot be classified based on the additivity approach applied in Table A.3.3 due to chemical characteristics that make this approach unworkable, should be classified as serious eye damage (Category 1) if it contains ≥1% of a skin corrosive or serious eye damaging ingredient and as Eye Irritation (Category 2) when it contains ≥3% of an eye irritant ingredient. Classification of mixtures with ingredients for which the approach in Table A.3.3 does not apply is summarized in Table A.3.4.

A.3.4.3.5 On occasion, reliable data may show that the irreversible/reversible 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 A.3.3 and A.3.4. In these cases the mixture could be classified according to those data (See also A.0.4.3 Use of cut-off values/concentration limits''). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables A.3.3 and A.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence approach should be applied as referred to in section A.3.3, Figure A.3.1 and explained in detail in this chapter.

A.3.4.3.6 If there are data showing that (an) ingredient(s) may be corrosive to the skin or seriously damaging to the eye/eye irritating at a concentration of <1% (corrosive to the skin or seriously damaging to the eye) or <3% (eye irritant), the mixture shall be classified accordingly (See also paragraph A.0.4.3, Use of cut-off values/concentration limits).

TABLE A.3.3—CONCENTRATION OF INGREDIENTS OF A MIXTURE CLASSIFIED AS SKIN CATEGORY 1 AND/OR EYE CATEGORY 1 OR 2 THAT WOULD TRIGGER CLASSIFICATION OF THE MIXTURES AS HAZARDOUS TO THE EYE

Sum of ingredients classified as	Concentration triggering classification of a mixture as	
	Serious eye damage	Eye irritation
	Category 1	Category 2/2A
Skin corrosion (Category 1) + Serious eye damage (Category 1) [a]	≥3%	≥1% but <3%.
Eye irritation (Category 2)		[b] ≥10%.
10 × (Skin corrosion (Category 1) + Serious eye damage (Category 1)) [a] + Eye irritation (Category 2)		≥10%.

Notes:
[a] If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation.
[b] A mixture may be classified as Eye Irritation Category 2B in cases when all relevant ingredients are classified as Eye Irritation Category 2B.

TABLE A.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:
Acid with pH ≤2	≥1	Serious eye damage (Category 1).
Base with pH ≥11.5	≥1	Serious eye damage (Category 1).
Other skin corrosive or serious eye damage (Category 1) ingredients.	≥1	Serious eye damage (Category 1).
Other eye irritant (Category 2) ingredients	≥3	Eye irritation (Category 2).

A.4 Respiratory or Skin Sensitization

A.4.1 Definitions and General Considerations

A.4.1.1 Respiratory sensitization refers to hypersensitivity of the airways occurring after inhalation of a substance or mixture.

Skin sensitization refers to an allergic response occurring after skin contact with a substance or mixture.

A.4.1.2 For the purpose of this chapter, sensitization includes two phases: The first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, *i.e.,* production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen.

A.4.1.3 For respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization. For skin sensitization, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

A.4.1.4 Usually, for both skin and respiratory sensitization, lower levels are necessary for elicitation than are required for induction.

A.4.1.5 The hazard class ''respiratory or skin sensitization'' is differentiated into:

(a) Respiratory sensitization; and
(b) Skin sensitization.

A.4.2 Classification Criteria for Substances

A.4.2.1 Respiratory Sensitizers

A.4.2.1.1 Hazard categories

A.4.2.1.1.1 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table A.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

A.4.2.1.1.2 Where data are not sufficient for sub-categorization, respiratory sensitizers shall be classified in Category 1.

TABLE A.4.1—HAZARD CATEGORY AND SUB-CATEGORIES FOR RESPIRATORY SENSITIZERS

Category 1:	Respiratory sensitizer
	A substance is classified as a respiratory sensitizer: (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.[1]
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests.1 Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests.[1] Severity of reaction may also be considered.

A.4.2.1.2 Human evidence

A.4.2.1.2.1 Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

[1] *At this writing, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.*

A.4.2.1.2.2 When considering the human evidence, it is necessary that in addition to the evidence from the cases, the following be taken into account:

(a) The size of the population exposed;

(b) The extent of exposure.

A.4.2.1.2.3 The evidence referred to above could be:

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

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

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

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

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

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

A.4.2.1.2.4 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood and smoking history.

A.4.2.1.2.5 The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is, however, recognized that in practice many of the examinations listed above will already have been carried out.

A.4.2.1.3 Animal studies

A.4.2.1.3.1 Data from appropriate animal studies [2] which may be indicative of the potential of a substance to cause sensitization by inhalation in humans [3] may include:

(a) Measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice.

(b) Specific pulmonary responses in guinea pigs.

A.4.2.2 Skin Sensitizers

A.4.2.2.1 Hazard categories

A.4.2.2.1.1 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitizers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table A.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in A.4.2.2.2.1 and A.4.2.2.3.2 for sub-category 1A and in A.4.2.2.2.2 and A.4.2.2.3.3 for sub-category 1B.

A.4.2.2.1.2 Where data are not sufficient for sub-categorization, skin sensitizers shall be classified in Category 1.

TABLE A.4.2—HAZARD CATEGORY AND SUB-CATEGORIES FOR SKIN SENSITIZERS

Category 1:	Skin sensitizer
	A substance is classified as a skin sensitizer: (a) If there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

A.4.2.2.2 Human evidence

A.4.2.2.2.1 Human evidence for sub-category 1A may include:

(a) Positive responses at ≤500 μg/cm2 (Human Repeat Insult Patch Test (HRIPT), Human Maximization Test (HMT)—induction threshold);

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

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

A.4.2.2.2.2 Human evidence for sub-category 1B may include:

(a) Positive responses at >500 μg/cm^2 (HRIPT, HMT—induction threshold);

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

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

A.4.2.2.3 Animal studies

A.4.2.2.3.1 For Category 1, when an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of three or more is considered a positive response in the local lymph node assay.[4]

A.4.2.2.3.2 Animal test results for sub-category 1A can include data with values indicated in Table A.4.3 below:

TABLE A.4.3—ANIMAL TEST RESULTS FOR SUB-CATEGORY 1A

Assay	Criteria
Local lymph node assay	EC3 value ≤2%.
Guinea pig maximization test.	≥30% responding at ≤0.1% intradermal induction dose *or* ≥60% responding at >0.1% to ≤1% intradermal induction dose.

[2] *At this writing, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.*

[3] *The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventive measures, these substances are considered respiratory sensitizers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperactivity, they should not be considered as respiratory sensitizers.*

[4] *Test methods for skin sensitization are described in OECD Guideline 406 (the Guinea Pig Maximization test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are scientifically validated. The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used, in accordance with professional judgment, as a first stage in the assessment of skin sensitization potential.*

TABLE A.4.3—ANIMAL TEST RESULTS FOR SUB-CATEGORY 1A—Continued

Assay	Criteria
Buehler assay	≥15% responding at ≤0.2% topical induction dose *or* ≥60% responding at >0.2% to ≤20% topical induction dose.

Note: EC3 refers to the estimated concentration of test chemical required to induce a stimulation index of 3 in the local lymph node assay.

A.4.2.2.3.3 Animal test results for sub-category 1B can include data with values indicated in the following Table A.4.4:

TABLE A.4.4—ANIMAL TEST RESULTS FOR SUB-CATEGORY 1B

Assay	Criteria
Local lymph node assay	EC3 value >2%.
Guinea pig maximization test.	≥30% to <60% responding at >0.1% to ≤1% intradermal induction dose *or* ≥30% responding at >1% intradermal induction dose.
Buehler assay	≥15% to <60% responding at >0.2% to ≤20% topical induction dose *or* ≥15% responding at >20% topical induction dose.

Note: EC3 refers to the estimated concentration of test chemical required to induce a stimulation index of 3 in the local lymph node assay.

A.4.2.2.4 Specific considerations

A.4.2.2.4.1 For classification of a substance, evidence shall include one or more of the following using a weight of evidence approach:

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

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

(c) Positive data from appropriate animal studies;

(d) Positive data from experimental studies in humans (See paragraph A.0.2.6 of this appendix);

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

(f) Severity of reaction.

A.4.2.2.4.2 Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on skin sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must, therefore, be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should be given to the impact of vehicle.

A.4.2.2.4.3 If none of the above-mentioned conditions are met, the substance need not be classified as a skin sensitizer. However, a combination of two or more indicators of skin sensitization, as listed below, may alter the decision. This shall be considered on a case-by-case basis.

(a) Isolated episodes of allergic contact dermatitis;

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

(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in A.4.2.2.3, 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.

A.4.2.2.4.4 Immunological contact urticaria

A.4.2.2.4.4.1 Substances meeting the criteria for classification as respiratory sensitizers may, in addition, cause immunological contact urticaria. Consideration shall be given to classifying these substances as skin sensitizers.

A.4.2.2.4.4.2 Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers shall be considered for classification as skin sensitizers.

A.4.2.2.4.4.3 There is no recognized animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence, similar to that for skin sensitization.

A.4.3 Classification Criteria for Mixtures

A.4.3.1 Classification of Mixtures When Data Are Available for the Complete Mixture

When reliable and good quality evidence, as described in the criteria for substances, from human experience or appropriate studies in experimental animals, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of these data. Care must be exercised in evaluating data on mixtures that the dose used does not render the results inconclusive.

A.4.3.2 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.4.3.2.1 Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles as found in paragraph A.0.5 of this appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one hazard category/subcategory, Substantially similar mixtures, and Aerosols.

A.4.3.3 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

The mixture shall be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value/concentration limit for the specific endpoint as shown in Table A.4.5.

TABLE A.4.5—CUT-OFF VALUES/CONCENTRATION LIMITS OF INGREDIENTS OF A MIXTURE CLASSIFIED AS EITHER RESPIRATORY SENSITIZERS OR SKIN SENSITIZERS THAT WOULD TRIGGER CLASSIFICATION OF THE MIXTURE

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Respiratory sensitizer Category 1		Skin sensitizer Category 1
	Solid/Liquid (%)	Gas	All physical states (%)
Respiratory Sensitizer: Category 1	≥0.1	≥0.1	.....
Respiratory Sensitizer: Sub-category 1A	≥0.1	≥0.1	.....
Respiratory Sensitizer: Sub-category 1B	≥1.0	≥0.2	.....
Skin Sensitizer: Category 1	.....	.....	≥0.1
Skin Sensitizer: Sub-category 1A	.....	.....	≥0.1
Skin Sensitizer: Sub-category 1B	.....	.....	≥1.0

A.5 Germ Cell Mutagenicity

A.5.1 Definitions and General Considerations

A.5.1.1 Germ cell mutagenicity refers to heritable gene mutations, including heritable structural and numerical chromosome aberrations in germ cells occurring after exposure to a substance or mixture.

A.5.1.2 A mutation is defined as a permanent change in the amount or structure of the genetic material in a cell. The term mutation applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including, for example, specific base pair changes and chromosomal translocations). The term mutagenic and mutagen will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

A.5.1.3 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.

A.5.1.4 This hazard class is primarily concerned with chemicals that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, mutagenicity/genotoxicity tests in vitro and in mammalian somatic cells in vivo are also considered in classifying substances and mixtures within this hazard class.

A.5.2 Classification Criteria for Substances

A.5.2.1 The classification system provides for two different categories of germ cell mutagens to accommodate the weight of evidence available. The two-category system is described in the Figure A.5.1.

FIGURE A.5.1—HAZARD CATEGORIES FOR GERM CELL MUTAGENS

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 germ cells of humans. Positive evidence from human epidemiological studies.

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

(a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or

(b) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or

(c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

CATEGORY 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.

Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:

(a) Somatic cell mutagenicity tests *in vivo*, in mammals; or

(b) Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

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

A.5.2.2 Specific considerations for classification of substances as germ cell mutagens:

A.5.2.2.1 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in in vitro tests shall also be considered.

A.5.2.2.2 The system is hazard based, classifying chemicals on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of chemical substances.

A.5.2.2.3 Classification for heritable effects in human germ cells is made on the basis of scientifically validated tests. Evaluation of the test results shall be done using expert judgment and all the available evidence shall be weighed for classification.

A.5.2.2.4 The classification of substances shall be based on the total weight of evidence available, using expert judgment. In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. The relevance of the route of exposure used in the study of the substance compared to the route of human exposure should also be taken into account.

A.5.3 Classification Criteria for Mixtures[5]

A.5.3.1 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.5.3.1.1 Classification of mixtures shall be based on the available test data for the

[5] *It should be noted that the classification criteria for health hazards usually include a tiered scheme in which test data available on the complete mixture are considered as the first tier in the*

individual ingredients of the mixture using cut-off values/concentration limits for the ingredients classified as germ cell mutagens.

A.5.3.1.2 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 above the appropriate cut-off value/concentration limit as shown in Table A.5.1 below for Category 1 and 2 respectively.

TABLE A.5.1—CUT-OFF VALUES/CONCENTRATION LIMITS OF INGREDIENTS OF A MIXTURE CLASSIFIED AS GERM CELL MUTAGENS THAT WOULD TRIGGER CLASSIFICATION OF THE MIXTURE

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 mutagen	Category 2 mutagen
Category 1A/B 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).*

A.5.3.2 Classification of Mixtures When Data Are Available for the Mixture Itself

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.

A.5.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.5.3.3.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution, Batching, and Substantially similar mixtures.

A.5.4 Examples of Scientifically Validated Test Methods

A.5.4.1 Examples of *in vivo* heritable germ cell mutagenicity tests are:

(a) Rodent dominant lethal mutation test (OECD 478)

(b) Mouse heritable translocation assay (OECD 485)

(c) Mouse specific locus test

A.5.4.2 Examples of *in vivo* somatic cell mutagenicity tests are:

(a) Mammalian bone marrow chromosome aberration test (OECD 475)

(b) Mammalian erythrocyte micronucleus test (OECD 474)

A.5.4.3 Examples of mutagenicity/genotoxicity tests in germ cells are:

(a) Mutagenicity tests:

(i) Mammalian spermatogonial chromosome aberration test (OECD 483)

(ii) Spermatid micronucleus assay

(b) Genotoxicity tests:

(i) Sister chromatid exchange analysis in spermatogonia

(ii) Unscheduled DNA synthesis test (UDS) in testicular cells

A.5.4.4 Examples of genotoxicity tests in somatic cells are:

(a) Liver Unscheduled DNA Synthesis (UDS) *in vivo* (OECD 486)

(b) Mammalian bone marrow Sister Chromatid Exchanges (SCE)

A.5.4.5 Examples of *in vitro* mutagenicity tests are:

(a) *In vitro* mammalian chromosome aberration test (OECD 473)

(b) *In vitro* mammalian cell gene mutation test (OECD 476)

(c) Bacterial reverse mutation tests (OECD 471)

A.5.4.6 As new, scientifically validated tests arise, these may also be used in the total weight of evidence to be considered.

A.6 Carcinogenicity

A.6.1 Definitions

Carcinogenicity refers to the induction of cancer or an increase in the incidence of cancer occurring after exposure to a substance or mixture. Substances and mixtures which have induced benign and malignant tumors 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 tumor formation is not relevant for humans.

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

A.6.2 Classification Criteria for Substances[6]

A.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 weight of evidence considerations. In certain instances, route-specific classification may be warranted.

FIGURE A.6.1—HAZARD CATEGORIES FOR CARCINOGENS

CATEGORY 1: Known or presumed human carcinogens. The classification of a substance as a Category 1 carcinogen is done on the basis of epidemiological and/or animal data. This classification is further distinguished on the basis of whether the evidence for classification is largely from human data (Category 1A) or from animal data (Category 1B):

Category 1A: Known to have carcinogenic potential for humans. Classification in this category is largely based on human evidence.

Category 1B: Presumed to have carcinogenic potential for humans. Classification in this category is largely based on animal evidence. The classification of a substance in Category 1A and 1B is based on strength of evidence together with weight of evidence considerations (See paragraph A.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); or

—animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

In addition, on a case by case basis, scientific judgment 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.

evaluation, followed by the applicable bridging principles, and lastly, cut-off values/concentration limits or additivity. However, this approach is not used for Germ Cell Mutagenicity. These criteria for Germ Cell Mutagenicity consider the cut-off values/concentration limits as the primary tier and allow the classification to be modified only on a case-by-case evaluation based on available test data for the mixture as a whole.

[6] See *Non-mandatory appendix F of this section, part A for further guidance regarding hazard classification for carcinogenicity. This appendix is consistent with the GHS and is provided as guidance excerpted from the International Agency for Research on Cancer (IARC) ''Monographs on the Evaluation of Carcinogenic Risks to Humans'' (2006).*

FIGURE A.6.1—HAZARD CATEGORIES FOR CARCINOGENS—Continued

CATEGORY 2: Suspected human carcinogens. The classification 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 B. This classification is based on strength of evidence together with weight of evidence considerations (See paragraph A.6.2.5). Such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Other considerations: Where the weight of evidence for the carcinogenicity of a substance does not meet the above criteria, any positive study conducted in accordance with established scientific principles, and which reports statistically significant findings regarding the carcinogenic potential of the substance, must be noted on the safety data sheet.

A.6.2.2 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for substances which have an intrinsic property to produce such toxic effects. The evaluations are to be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

A.6.2.3 *Carcinogen classification* is a one-step, criterion-based process that involves two interrelated determinations: Evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

A.6.2.4 *Strength of evidence* involves the enumeration of tumors in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumors. 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. (Guidance on consideration of important factors in the classification of carcinogenicity and a more detailed description of the terms ''limited'' and ''sufficient'' have been developed by the International Agency for Research on Cancer (IARC) and are provided in non-mandatory appendix F of this section.)

A.6.2.5 *Weight of evidence:* Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

A.6.2.5.1 These factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally, there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumor findings and the other factors in a case-by-case manner.

A.6.2.5.2 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) Tumor type and background incidence;

(b) Multisite responses;

(c) Progression of lesions to malignancy;

(d) Reduced tumor latency;

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

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

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

(g) Structural similarity or not to a 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; and,

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

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

A.6.2.5.3 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 tumor 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.

A.6.2.5.4 The classification should also take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumors at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

A.6.2.5.5 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.

A.6.3 Classification Criteria for Mixtures[7]

A.6.3.1 The mixture shall be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as shown in Table A.6.1.

TABLE A.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 1 carcinogen	Category 2 carcinogen
Category 1 carcinogen	≥0.1%	
Category 2 carcinogen		≥0.1% (note 1)

Note: *If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, information is required on the SDS for a product. However, a label warning is optional. If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥1%, both an SDS and a label is required and the information must be included on each.*

[7] *It should be noted that the classification criteria for health hazards usually include a tiered scheme in which test data available on the complete mixture are considered as the first tier in the evaluation, followed by the applicable bridging principles, and lastly, cut-off values/concentration limit or additivity. However, this approach is not used for Carcinogenicity. These criteria for Carcinogenicity consider the cut-off values/concentration limits as the primary tier and allow the classification to be modified only on a case-by-case evaluation based on available test data for the mixture as a whole.*

A.6.3.2 Classification of Mixtures When Data Are Available for the Complete Mixture

A mixture may be classified 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.

A.6.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution; Batching; and Substantially similar mixtures.

A.6.4 Classification of Carcinogenicity[8]

A.6.4.1 Chemical manufacturers, importers and employers evaluating chemicals may treat the following sources as establishing that a substance is a carcinogen or potential carcinogen for hazard communication purposes in lieu of applying the criteria described herein:

A.6.4.1.1 National Toxicology Program (NTP), ''Report on Carcinogens'' (latest edition);

A.6.4.1.2 International Agency for Research on Cancer (IARC) ''Monographs on the Evaluation of Carcinogenic Risks to Humans'' (latest editions)

A.6.4.2 Where OSHA has included cancer as a health hazard to be considered by classifiers for a chemical covered by this section subpart, chemical manufacturers, importers, and employers shall classify the chemical as a carcinogen.

A.7 Reproductive Toxicity

A.7.1 Definitions and General Considerations

A.7.1.1 *Reproductive toxicity* refers to *adverse effects on sexual function and fertility* in adult males and females, as well as developmental toxicity in the offspring, occurring after exposure to a substance or mixture. Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances and mixtures with these effects shall be classified as reproductive toxicants.

For classification purposes, the known induction of genetically based inheritable effects in the offspring is addressed in *Germ cell mutagenicity* (See A.5).

A.7.1.2 *Adverse effects on sexual function and fertility* means any effect of chemicals that interferes with reproductive ability or sexual capacity. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

A.7.1.3 *Adverse effects on development of the offspring* means any effect of chemicals which interferes with normal development of the conceptus either before or after birth, which is induced during pregnancy or results from parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth and functional deficiency.

A.7.1.4 Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (See A.7.2.1).

A.7.2 Classification Criteria for Substances

A.7.2.1 For the purpose of classification for reproductive toxicity, substances shall be classified in one of two categories in accordance with Figure A.7.1(a). Effects on sexual function and fertility, and on development, shall be considered. In addition, effects on or via lactation shall be classified in a separate hazard category in accordance with Figure A.7.1(b).

FIGURE A.7.1(a)—HAZARD CATEGORIES FOR REPRODUCTIVE TOXICANTS

CATEGORY 1: Known or presumed human reproductive toxicant. Substance shall be classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Category 1A: Known human reproductive toxicant. The classification of a substance in this category is largely based on evidence from humans.

Category 1B: Presumed human reproductive toxicant. The classification of a substance in this category is largely based on evidence from experimental animals. Data from animal studies shall provide sufficient 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 shall be 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, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this, Category 2 would be the more appropriate classification.

FIGURE A.7.1(b)—HAZARD CATEGORY FOR EFFECTS ON OR VIA LACTATION

Effects on or Via Lactation

Effects on or via lactation shall be classified in a separate single category. Chemicals that are absorbed by women and have been shown to interfere with lactation or that may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified to indicate this property. Classification for effects via lactation shall be assigned on the basis of:

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

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

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

[8] See *Non-mandatory appendix F of this section for further guidance regarding hazard classification for carcinogenicity and how to relate carcinogenicity classification information from IARC and NTP to GHS.*

A.7.2.2 Basis of Classification

A.7.2.2.1 Classification is made on the basis of the criteria, outlined above, an assessment of the total weight of evidence, and the use of expert judgment. 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 should not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

A.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.

A.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 be from well conducted epidemiological studies, if available, which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans may be sufficient for a Category 1A classification if supplemented with adequate data from studies in experimental animals, but classification in Category 1B may also be considered.

A.7.2.3 Weight of Evidence

A.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence using expert judgment. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are considered together in 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 A.7.2.2.3).

A.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 is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a chemical which produces an adverse effect on reproduction in experimental animals should not be classified.

A.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 effects include, for example, small changes in semen parameters or in the incidence of spontaneous defects in the fetus, small changes in the proportions of common fetal variants such as are observed in skeletal examinations, or in fetal weights, or small differences in postnatal developmental assessments.

A.7.2.3.4 Data from animal studies shall provide sufficient 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 (mother), the potential influence of the generalized adverse effects should be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/fetus first, and then evaluate maternal toxicity, along with any other factors which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses should not be automatically discounted. Discounting developmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

A.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity should not be used to negate findings of embryo/fetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, *e.g.,* irreversible effects such as structural malformations. In some situations it is reasonable to assume that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, for example if the chemical is so toxic that dams fail to thrive and there is severe inanition; they are incapable of nursing pups; or they are prostrate or dying.

A.7.2.4 Maternal Toxicity

A.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 judgment and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence to be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/fetus 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.

A.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 fetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited numbers of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, *e.g.,* irreversible effects such as structural malformations, embryo/fetal lethality, or significant post-natal functional deficiencies.

A.7.2.4.3 Classification shall not automatically be discounted for chemicals that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a chemical is so toxic that maternal death or severe inanition results, or the dams (mothers) are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, *e.g.,* a small reduction in fetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

A.7.2.4.4 Some of the endpoints used to assess maternal toxicity are provided below. Data on these endpoints, if available, shall be evaluated in light of their statistical or biological significance and dose-response relationship.

(a) Maternal mortality: An increased incidence of mortality among the treated dams over the controls 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 to need further evaluation.

(b) Mating index (Number of animals with seminal plugs or sperm/Number of mated × 100).

(c) Fertility index (Number of animals with implants/Number of matings × 100).

(d) Gestation length (If allowed to deliver).

(e) Body weight and body weight change: Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight 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 fetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be a useful indicator of maternal toxicity because of normal fluctuations in body weight during pregnancy.

(f) Food and water consumption (if relevant): The observation of a significant decrease in the average food or water consumption in treated dams (mothers) 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 must be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

(g) Clinical evaluations (including clinical signs, markers, and hematology and clinical chemistry studies): The observation of increased incidence of significant clinical signs of toxicity in treated dams (mothers) relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication include, but are not limited to: Coma, prostration, hyperactivity, loss of righting reflex, ataxia, or labored breathing.

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

A.7.2.5 Animal and Experimental Data

A.7.2.5.1 A number of scientifically validated test methods are available, including 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, 443).

A.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 the quality of this evidence is less reliable than that obtained through full studies.

A.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive function and which occur in the absence of significant generalized toxicity, may be used as a basis for classification, *e.g.,* histopathological changes in the gonads.

A.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 judgment must be used to assess the adequacy of the data. Inadequate data shall not be used as a primary support for classification.

A.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

A.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 are not normally the basis for classification.

A.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. Some test guidelines specify a limit dose, other test guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

A.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) do not normally lead to classification, unless other information is available, for example, toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate.

A.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.

A.7.3 Classification Criteria for Mixtures[9]

A.7.3.1 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.7.3.1.1 The mixture shall 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 specified in Table A.7.1 for Category 1 and 2, respectively.

A.7.3.1.2 The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate cut-off value/concentration limit specified in Table A.7.1 for the additional category for effects on or via lactation.

[9] *It should be noted that the classification criteria for health hazards usually include a tiered scheme in which test data available on the complete mixture are considered as the first tier in the evaluation, followed by the applicable bridging principles, and lastly, cut-off values/concentration limits or additivity. However, this approach is not used for Reproductive Toxicity. These criteria for Reproductive Toxicity consider the cut-off values/concentration limits as the primary tier and allow the classification to be modified only on a case-by-case evaluation based on available test data for the mixture as a whole.*

TABLE A.7.1—CUT-OFF VALUES/CONCENTRATION LIMITS OF INGREDIENTS OF A MIXTURE CLASSIFIED AS REPRODUCTIVE TOXICANTS OR FOR EFFECTS ON OR VIA LACTATION THAT TRIGGER CLASSIFICATION OF THE MIXTURE

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Category 1 reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1 reproductive toxicant	≥0.1%		
Category 2 reproductive toxicant	.....	≥0.1%	
Additional category for effects on or via lactation	.....	.....	≥0.1%

A.7.3.2 Classification of Mixtures When Data Are Available for the Complete Mixture

Available test data for the mixture as a whole may be used for classification on a case-by-case basis. 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.

A.7.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.7.3.3.1 Where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution, Batching, and Substantially similar mixtures.

A.8 Specific Target Organ Toxicity Single Exposure

A.8.1 Definitions and General Considerations

A.8.1.1 *Specific target organ toxicity—single exposure, (STOT–SE)* refers to specific, non-lethal toxic effects on target organs occurring after 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 A.1 to A.7 and A.10 of this appendix are included. Specific target organ toxicity following repeated exposure is classified in accordance with *SPECIFIC TARGET ORGAN TOXICITY—REPEATED EXPOSURE* (A.9 of this appendix) and is therefore not included here.

A.8.1.2 Classification identifies the chemical as being a specific target organ toxicant and, as such, it presents a potential for adverse health effects in people who are exposed to it.

A.8.1.3 The 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 hematology of the organism, and these changes are relevant for human health. Human data is the primary source of evidence for this hazard class.

A.8.1.4 Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

A.8.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, *i.e.,* principally oral, dermal or inhalation.

A.8.1.6 The classification criteria for specific target organ toxicity—single exposure are organized as criteria for substances Categories 1 and 2 (See A.8.2.1), criteria for substances Category 3 (See A.8.2.2) and criteria for mixtures (See A.8.3). See also Figure A.8.1.

A.8.2 Classification Criteria for Substances

A.8.2.1 Substances of Category 1 and Category 2

A.8.2.1.1 Substances shall be classified for immediate or delayed effects separately, by the use of expert judgment on the basis of the weight of all evidence available, including the use of recommended guidance values (See A.8.2.1.9). Substances shall then be classified in Category 1 or 2, depending upon the nature and severity of the effect(s) observed, in accordance with Figure A.8.1.

FIGURE A.8.1—HAZARD CATEGORIES FOR SPECIFIC TARGET ORGAN TOXICITY FOLLOWING SINGLE EXPOSURE

CATEGORY 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure: Substances are classified in Category 1 for STOT–SE 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 A.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 STOT–SE 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 A.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 A.8.2.1.6).

CATEGORY 3: Transient target organ effects: There are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances are classified specifically for these effects as discussed in A.8.2.2.

Note: *The primary target organ/system shall be identified where possible, and where this is not possible, the substance shall be identified as a general toxicant. The data shall be evaluated and, where possible, shall not include secondary effects (e.g., a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).*

A.8.2.1.2 The relevant route(s) of exposure by which the classified substance produces damage shall be identified.

A.8.2.1.3 Classification is determined by expert judgment, on the basis of the weight of all evidence available including the guidance presented below.

A.8.2.1.4 Weight of evidence of all available data, including human incidents, epidemiology, and studies conducted in experimental animals is used to substantiate specific target organ toxic effects that merit classification.

A.8.2.1.5 The information required to evaluate specific target organ toxicity comes either from single exposure in humans (*e.g.,* exposure at home, in the workplace or environmentally), or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

A.8.2.1.6 In exceptional cases, based on expert judgment, it may be appropriate to place certain substances with human evidence of target organ toxicity in Category 2: (a) When the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the chemical shall be classified as Category 1.

A.8.2.1.7 Effects considered to support classification for Category 1 and 2.

A.8.2.1.7.1 Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

A.8.2.1.7.2 Evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

A.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. Relevant toxic effects in humans and/or animals include, but are not limited to:

(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, hematology, 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; and,

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

A.8.2.1.8 Effects considered not to support classification for Category 1 and 2.

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

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

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

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

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

(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.

A.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.

A.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 vs. Category 2), dose/concentration ''guidance values'' are provided for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged.

A.8.2.1.9.2 Thus, in animal studies, when significant toxic effects are observed that indicate classification, consideration of the dose/concentration at which these effects were seen, in relation to the suggested guidance values, provides useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the dose/concentration).

A.8.2.1.9.3 The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table A.8.1.

TABLE A.8.1—GUIDANCE VALUE RANGES FOR SINGLE-DOSE EXPOSURES

		Guidance value ranges for:		
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	$C \leq 300$	$2{,}000 \geq C > 300$	Guidance values do not apply.
Dermal (rat or rabbit)	mg/kg body weight	$C \leq 1{,}000$	$2{,}000 \geq C > 1{,}000$.	
Inhalation (rat) gas	ppmV/4h	$C \leq 2{,}500$	$20{,}000 \geq C > 2{,}500$.	
Inhalation (rat) vapor	mg/1/4h	$C \leq 10$	$20 \geq C > 10$.	
Inhalation (rat) dust/mist/fume.	mg/l/4h	$C \leq 1.0$	$5.0 \geq C > 1.0$.	

A.8.2.1.9.4 The guidance values and ranges mentioned in Table A.8.1 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. Guidance values are not provided for Category 3 since this classification is primarily based on human data; animal data may be included in the weight of evidence evaluation.

A.8.2.1.9.5 Thus, it is feasible that a specific profile of toxicity occurs at a dose/concentration below the guidance value, *e.g.,* <2,000 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.,* ≥2,000 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 is the prudent action to take.

A.8.2.1.10 Other considerations.

A.8.2.1.10.1 When a substance is characterized only by use of animal data the classification process includes reference to dose/concentration guidance values as one of

the elements that contribute to the weight of evidence approach.

A.8.2.1.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to single exposure to a substance, the substance shall be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because specific target organ toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

A.8.2.1.10.3 A substance that has not been tested for specific target organ toxicity shall, where appropriate, be classified on the basis of data from a scientifically validated structure activity relationship and expert judgment-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.

A.8.2.2 Substances of Category 3

A.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 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'' should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory tract irritation;

(d) There are currently no scientifically 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; and,

(e) This special classification will occur only when more severe organ effects including the respiratory system are not observed as those effects would require a higher classification.

A.8.2.2.2 Criteria for narcotic effects.

The criteria for classifying substances in 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; and,

(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 be considered for classification as Category 1 or 2.

A.8.3 Classification Criteria for Mixtures

A.8.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

A.8.3.2 Classification of Mixtures When Data Are Available for the Complete Mixture

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture shall 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.

A.8.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.8.3.3.1 Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one hazard category, Substantially similar mixtures, or Aerosols.

A.8.3.4 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.8.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit specified in Table A.8.2 for Categories 1 and 2, respectively.

TABLE A.8.2—CUT-OFF VALUES/CONCENTRATION LIMITS OF INGREDIENTS OF A MIXTURE CLASSIFIED AS A SPECIFIC TARGET ORGAN TOXICANT THAT WOULD TRIGGER CLASSIFICATION OF THE MIXTURE AS CATEGORY 1 OR 2

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1: Target organ toxicant	≥1.0%	.....
Category 2: Target organ toxicant	.....	≥1.0%

A.8.3.4.2 These cut-off values and consequent classifications shall be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

A.8.3.4.3 Mixtures shall be classified for either or both single and repeated dose toxicity independently.

A.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.

A.8.3.4.5 Care shall be exercised when extrapolating the toxicity of a mixture that contains Category 3 ingredient(s). A cut-off value/concentration limit of 20%, considered as an additive of all Category 3 ingredients for each hazard endpoint, is appropriate; however, this cut-off value/concentration limit may be higher or lower depending on the Category 3 ingredient(s) involved and the fact 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. Respiratory tract irritation and narcotic

effects are to be evaluated separately in accordance with the criteria given in A.8.2.2. When conducting classifications for these hazards, the contribution of each ingredient should be considered additive, unless there is evidence that the effects are not additive.

A.8.3.4.6 In cases where the additivity approach is used for Category 3 ingredients, the ''relevant ingredients'' of a mixture are those which are present in concentrations ≥1% (w/w for solids, liquids, dusts, mists, and vapours and v/v for gases), unless there is a reason to suspect that an ingredient present at a concentration <1% is still relevant when classifying the mixture for respiratory tract irritation or narcotic effects.

A.9 Specific Target Organ Toxicity Repeated or Prolonged Exposure

A.9.1 Definitions and General Considerations

A.9.1.1 *Specific target organ toxicity—repeated exposure (STOT–RE)* refers to specific toxic effects on target organs occurring after repeated 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 A.1 to A.7 and A.10 of this appendix are included. Specific target organ toxicity following a single-event exposure is classified in accordance with *SPECIFIC TARGET ORGAN TOXICITY–SINGLE EXPOSURE* (A.8 of this appendix) and is therefore not included here.

A.9.1.2 Classification identifies the substance or mixture as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

A.9.1.3 These adverse health effects produced by repeated 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 hematology of the organism and these changes are relevant for human health. Human data will be the primary source of evidence for this hazard class.

A.9.1.4 Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

A.9.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, *e.g.,* principally oral, dermal or inhalation.

A.9.2 Classification Criteria for Substances

A.9.2.1 Substances shall be classified as STOT–RE by expert judgment 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 A.9.2.9). Substances shall be placed in one of two categories, depending upon the nature and severity of the effect(s) observed, in accordance with Figure A.9.1.

FIGURE A.9.1—HAZARD CATEGORIES FOR SPECIFIC TARGET ORGAN TOXICITY FOLLOWING REPEATED EXPOSURE

CATEGORY 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated or prolonged exposure. Substances are classified in Category 1 for specific target organ toxicity (repeated 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 A.9.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated or prolonged exposure. Substances are classified in Category 2 for specific target organ toxicity (repeated 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 A.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 A.9.2.6).

Note: *The primary target organ/system shall be identified where possible, or the substance shall be identified as a general toxicant. The data shall be carefully evaluated and, where possible, shall not include secondary effects (e.g., a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).*

A.9.2.2 The relevant route of exposure by which the classified substance produces damage shall be identified.

A.9.2.3 Classification is determined by expert judgment, on the basis of the weight of all evidence available including the guidance presented below.

A.9.2.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification.

A.9.2.5 The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, *e.g.,* exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include hematological, clinico-chemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species may also be used. Other long-term exposure studies, *e.g.,* for carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

A.9.2.6 In exceptional cases, based on expert judgment, it may be appropriate to place certain substances with human evidence of specific target organ toxicity in Category 2: (a) When the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

A.9.2.7 Effects Considered To Support Classification

A.9.2.7.1 Classification is supported by reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect.

A.9.2.7.2 Evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

A.9.2.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, hematology, clinical chemistry, macroscopic and microscopic pathological examination and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently, all available evidence, and relevance to human health, must be taken into consideration in the classification process. Relevant toxic effects in humans and/or animals include, but are not limited to:

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

(b) Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of

central nervous system depression and effects on special senses (*e.g.,* sight, hearing and sense of smell);

(c) Any consistent and significant adverse change in clinical biochemistry, hematology, 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 (*e.g.,* severe fatty change in the liver); and,

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

A.9.2.8 Effects Considered Not To Support Classification

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

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

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

A.9.2.9 Guidance Values To Assist With Classification Based on the Results Obtained From Studies Conducted in Experimental Animals

A.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.

A.9.2.9.2 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 vs. Category 2), dose/concentration ''guidance values'' are provided in Table A.9.1 for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimize the test objective and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

A.9.2.9.3 Thus, in animal studies, when significant toxic effects are observed that indicate classification, consideration of the duration of experimental exposure and the dose/concentration at which these effects were seen, in relation to the suggested guidance values, provides useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the duration of exposure and the dose/concentration).

A.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.

A.9.2.9.5 The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment should be done on a case-by-case basis; for example, for a 28-day study the guidance values below would be increased by a factor of three.

A.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 (C) as indicated in Table A.9.1 would justify classification:

TABLE A.9.1—GUIDANCE VALUES TO ASSIST IN CATEGORY 1 CLASSIFICATION

[Applicable to a 90-day study]

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

A.9.2.9.7 For Category 2 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur within the (suggested) guidance value ranges as indicated in Table A.9.2 would justify classification:

TABLE A.9.2—GUIDANCE VALUES TO ASSIST IN CATEGORY 2 CLASSIFICATION

[Applicable to a 90-day study]

Route of exposure	Units	Guidance value range (dose/concentration)
Oral (rat)	mg/kg body weight/day	10 <C ≤100
Dermal (rat or rabbit)	mg/kg body weight/day	20 <C ≤200
Inhalation (rat) gas	ppmV/6h/day	50 <C ≤250
Inhalation (rat) vapor	mg/liter/6h/day	0.2 <C ≤1.0
Inhalation (rat) dust/mist/fume	mg/liter/6h/day	0.02 <C ≤0.2

A.9.2.9.8 The guidance values and ranges mentioned in A.2.9.9.6 and A.2.9.9.7 are intended only for guidance purposes, *i.e.,* to be used as part of the weight of evidence approach, and to assist with decisions about

classification. They are not intended as strict demarcation values.

A.9.2.9.9 Thus, it is possible that a specific profile of toxicity occurs in repeat-dose animal studies at a dose/concentration below the guidance value, *e.g.,* <100 mg/kg body weight/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 body weight/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 is prudent.

A.9.2.10 Other Considerations

A.9.2.10.1 When a substance is characterized only by use of animal data the classification process includes reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

A.9.2.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance shall be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

A.9.2.10.3 A substance that has not been tested for specific target organ toxicity may in certain instances, where appropriate, be classified on the basis of data from a scientifically validated structure activity relationship and expert judgment-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.

A.9.3 Classification Criteria for Mixtures

A.9.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

A.9.3.2 Classification of Mixtures When Data Are Available for the Complete Mixture

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

A.9.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.9.3.3.1 Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution; Batching; Concentration of mixtures; Interpolation within one hazard category; Substantially similar mixtures; and Aerosols.

A.9.3.4 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.9.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit specified in Table A.9.3 for Category 1 and 2 respectively.

TABLE A.9.3—CUT-OFF VALUE/CONCENTRATION LIMITS OF INGREDIENTS OF A MIXTURE CLASSIFIED AS A SPECIFIC TARGET ORGAN TOXICANT THAT WOULD TRIGGER CLASSIFICATION OF THE MIXTURE AS CATEGORY 1 OR 2

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1: Target organ toxicant	≥1.0%	
Category 2: Target organ toxicant		≥1.0%

A.9.3.4.2 These cut-off values and consequent classifications shall be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

A.9.3.4.3 Mixtures shall be classified for either or both single- and repeated-dose toxicity independently.

A.9.3.4.4 Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause specific target organ toxicity at <1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

A.10 Aspiration Hazard

A.10.1 Definitions and General Considerations

A.10.1.1 Aspiration hazard refers to severe acute effects such as chemical pneumonia, pulmonary injury or death occurring after aspiration of a substance or mixture.

A.10.1.2 Aspiration means the entry of a liquid or solid chemical directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system.

A.10.1.3 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.

A.10.1.4 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.

A.10.1.5 Specific Considerations

A.10.1.5.1 The classification criteria refer to kinematic viscosity. The following provides the conversion between dynamic and kinematic viscosity:

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

A.10.1.5.2 Although the definition of aspiration in A.10.1.1 includes the entry of solids into the respiratory system, classification according to (b) in table A.10.1 for Category 1 is intended to apply to liquid substances and mixtures only.

A.10.1.5.3 Classification of aerosol/mist products

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

A.10.2 Classification Criteria for Substances

TABLE A.10.1—CRITERIA FOR ASPIRATION TOXICITY

Category	Criteria
Category 1: Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard.	A substance shall be classified in Category 1: (a) If reliable and good quality human evidence indicates that it causes aspiration toxicity (See note); or (b) If it is a hydrocarbon and has a kinematic viscosity ≤20.5 mm2/s, measured at 40 °C.

Note: *Examples of substances included in Category 1 are certain hydrocarbons, turpentine and pine oil.*

A.10.3 Classification Criteria for Mixtures

A.10.3.1 Classification When Data Are Available for the Complete Mixture

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

A.10.3.2 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles

A.10.3.2.1 Where the mixture itself has not been tested to determine its aspiration toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazard of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this appendix: Dilution; Batching; Concentration of mixtures; Interpolation within one hazard category; and Substantially similar mixtures. For application of the dilution bridging principle, the concentration of aspiration toxicants shall not be less than 10%.

A.10.3.3 Classification of Mixtures When Data Are Available for All Ingredients or Only for Some Ingredients of the Mixture

A.10.3.3.1 The ''relevant ingredients'' of a mixture are those which are present in concentrations ≥1%.

A.10.3.3.2 *Category 1*

A.10.3.3.2.1 A mixture is classified as Category 1 when the sum of the concentrations of Category 1 ingredients is ≥10%, and the mixture has a kinematic viscosity of ≤20.5 mm2/s, measured at 40 °C.

A.10.3.3.2.2 In the case of a mixture which separates into two or more distinct layers, the entire mixture is classified as Category 1 if in any distinct layer the sum of the concentrations of Category 1 ingredients is ≥10%, and it has a kinematic viscosity of ≤20.5 mm2/s, measured at 40 °C.

Appendix B to § 1910.1200—Physical Hazard Criteria (Mandatory)

B.1 Explosives

B.1.1 Definitions and General Considerations

B.1.1.1 An *explosive chemical* is a solid or liquid chemical 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 chemicals are included even when they do not evolve gases.

A *pyrotechnic chemical* is a chemical 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 *explosive item* is an item containing one or more explosive chemicals.

A *pyrotechnic item* is an item containing one or more pyrotechnic chemicals.

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

An *intentional explosive* is a chemical or item which is manufactured with a view to produce a practical explosive or pyrotechnic effect.

B.1.1.2 The class of explosives comprises:

(a) Explosive chemicals;

(b) Explosive items, except devices containing explosive chemicals 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) Chemicals and items not included under (a) and (b) of this section which are manufactured with the view to producing a practical explosive or pyrotechnic effect.

B.1.2 Classification Criteria

Chemicals and items of this class shall be classified as unstable explosives or shall be assigned to one of the following six divisions depending on the type of hazard they present:

(a) Division 1.1—Chemicals and items which have a mass explosion hazard (a mass explosion is one which affects almost the entire quantity present virtually instantaneously);

(b) Division 1.2—Chemicals and items which have a projection hazard but not a mass explosion hazard;

(c) Division 1.3—Chemicals and items 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;

(d) Division 1.4—Chemicals and items which present no significant hazard: Chemicals and items 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 chemicals which have a mass explosion hazard: Chemicals 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 items which do not have a mass explosion hazard: Items which predominantly contain extremely insensitive detonating chemicals and which demonstrate a negligible probability of accidental initiation or propagation.

B.1.3 Additional Classification Considerations

B.1.3.1 Explosives shall be classified as unstable explosives or shall be assigned to one of the six divisions identified in B.1.2 in accordance with the three-step procedure in Part I of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6). The first step is to ascertain whether the substance or mixture has explosive effects (Test Series 1). The second step is the acceptance procedure (Test Series 2 to 4) and the third step is the assignment to a hazard division (Test Series

5 to 7). The assessment whether a candidate for ''ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE)'' is insensitive enough for inclusion as an oxidizing liquid (See B.13) or an oxidizing solid (See B.14) is determined by Test Series 8 tests.

Note 1: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

Note 2: Some explosive chemicals are wetted with water or alcohols, diluted with other substances or dissolved or suspended in water or other liquid substances to suppress or reduce their explosive properties. These chemicals shall be classified as desensitized explosives (see Chapter B.17).

Note 3: Chemicals with a positive result in Test Series 2 in Part I, Section 12, of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6) UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6)), still have explosive properties. The explosive properties of the chemical shall be communicated in Section 2 (Hazard identification) and Section 9 (Physical and chemical properties) of the Safety Data Sheet, as appropriate.

B.1.3.2 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 in B.1.3.1 is aimed at identifying the presence of such reactive groups and the potential for rapid energy release. If the screening procedure identifies the chemical as a potential explosive, the acceptance procedure (See section 10.3 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6)) is necessary for classification.

Note: Neither a Series 1 type (a) propagation of detonation test nor a Series 2 type (a) test of sensitivity to detonative shock is necessary if the exothermic decomposition energy of organic materials is less than 800 J/g.

B.1.3.3 If a mixture contains any known explosives, the acceptance procedure is necessary for classification.

B.1.3.4 A chemical is not 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 ST/SG/AC.10 (incorporated by reference; See § 1910.6); 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:

$$C_xH_yO_z + [x + (y/4) - (z/2)]\ O2 \rightarrow x.\ CO_2 + (y/2)\ H_2O$$

using the formula:

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

; or

(c) The organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500 °C (932 °F). 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:

(i) Less than 15%, by mass, if the oxidizing substance is assigned to Category 1 or 2;

(ii) less than 30%, by mass, if the oxidizing substance is assigned to Category 3.

B.2 Flammable Gases

B.2.1 Definition

Flammable gas means a gas having a flammable range with air at 20 °C (68 °F) and a standard pressure of 101.3 kPa (14.7 psi).

A *pyrophoric gas* means a flammable gas that is liable to ignite spontaneously in air at a temperature of 54 °C (130 °F) or below.

A *chemically unstable gas* means a flammable gas that is able to react explosively even in the absence of air or oxygen.

B.2.2 Classification Criteria

B.2.2.1 A flammable gas shall be classified in Category 1A, 1B, or 2 in accordance with Table B.2.1:

Table B.2.1: Criteria for flammable gases

Category			Criteria
1A	Flammable gas		Gases, which at 20 °C (68 °F) and a standard pressure of 101.3 kPa (14.7 psi): (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 flammability limit, unless data show they meet the criteria for Category 1B.
	Pyrophoric gas		Flammable gases that ignite spontaneously in air at a temperature of 54 °C (130 °F) or below.
	Chemically unstable gas	A	Flammable gases which are chemically unstable at 20 °C (68 °F) and a standard pressure of 101.3 kPa (14.7 psi).
		B	Flammable gases which are chemically unstable at a temperature greater than 20 °C (68 °F) and/or a pressure greater than 101.3 kPa (14.7 psi).
1B	Flammable gas		Gases which meet the flammability criteria for Category 1A, but which are not pyrophoric, nor chemically unstable, and which have at least either: (a) a lower flammability limit of more than 6% by volume in air; or (b) a fundamental burning velocity of less than 10 cm/s.
2	Flammable gas		Gases, other than those of Category 1A or 1B, which, at 20 °C (68 °F) and a standard pressure of 101.3 kPa (14.7 psi), have a flammable range while mixed in air.

NOTE 1: Aerosols should not be classified as flammable gases. *See* B.3.

NOTE 2: In the absence of data allowing classification into Category 1B, a flammable gas that meets the criteria for Category 1A shall be classified by default in Category 1A.

NOTE 3: Spontaneous ignition for pyrophoric gases is not always immediate, and there may be a delay.

NOTE 4: In the absence of data on its pyrophoricity, a flammable gas mixture should be classified as a pyrophoric gas if it contains more than 1% (by volume) of pyrophoric component(s).

B.2.3 Additional Classification Considerations

B.2.3.1 Flammability shall be determined by tests or by calculation in accordance with ISO 10156 (Gases and Gas Mixtures—Determination of Fire Potential and Oxidizing Ability for the Selection of Cylinder Valve Outlets; 1996, first edition or 2010, third edition) (incorporated by reference; see § 1910.6) and, if using fundamental burning velocity for Category 1B, use ISO 817:2014 (third edition) (Refrigerants—Designation and safety classification, Annex C: Method of test for burning velocity measurement of flammable gases) (incorporated by reference; see § 1910.6). Where insufficient data are available to use this method, equivalent validated methods may be used.

B.2.3.2 Pyrophoricity shall be determined at 130 °F (54 °C) in accordance with either IEC 60079–20–1, edition 1.0 (2010–01) (Explosive atmospheres—Part 20–1: Material characteristics for gas and vapor classification—Test methods and data) (incorporated by reference; see § 1910.6) or DIN 51794 (2003) (Determining the ignition temperature of petroleum products) (incorporated by reference; see § 1910.6).

B.2.3.3 The classification procedure for pyrophoric gases need not be applied when experience in production or handling shows that the substance does not ignite spontaneously on coming into contact with air at a temperature of 130 °F (54 °C) or below. Flammable gas mixtures which have not been tested for pyrophoricity and which contain more than one percent pyrophoric components shall be classified as a pyrophoric gas. Expert judgement on the properties and physical hazards of pyrophoric gases and their mixtures should be used in assessing the need for classification of flammable gas mixtures containing one percent or less pyrophoric components. In this case, testing need only be considered if expert judgement indicates a need for additional data to support the classification process.

B.2.3.4 Chemical instability shall be determined in accordance with the method described in Part III of the UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6)]. If the calculations performed in accordance with ISO 10156 (Gases and Gas Mixtures—Determination of Fire Potential and Oxidizing Ability for the Selection of Cylinder Valve Outlets; 1996, first edition or 2010, third edition) (incorporated by reference; see § 1910.6) show that a gas mixture is not flammable, no additional testing is required for determining chemical instability for classification purposes.

B.3 Aerosols

B.3.1 Definition

Aerosol means any non-refillable receptacle containing a gas compressed, liquefied or dissolved under pressure, and fitted with a release device allowing the contents to be ejected as particles in suspension in a gas, or as a foam, paste, powder, liquid or gas.

B.3.2 Classification Criteria

B.3.2.1 Aerosols are classified in one of three categories, depending on their flammable properties and their heat of combustion. Aerosols shall be considered for classification in Categories 1 or 2 if they contain more than 1% components (by mass) which are classified as flammable in accordance with this appendix, *i.e.*:

Flammable gases (See B.2);

Flammable liquids (See B.6);

Flammable solids (See B.7);

or if their heat of combustion is at least 20 kJ/g.

Note 1: Flammable components do not include pyrophoric, self-heating or water-reactive chemicals.

Note 2: Aerosols do not fall additionally within the scope of flammable gases, gases under pressure, flammable liquids, or flammable solids. However, depending on their contents, aerosols may fall within the scope of other hazard classes.

B.3.2.2 An aerosol shall be classified in one of the three categories for this class in accordance with Table B.3.1.

TABLE B.3.1—CRITERIA FOR AEROSOLS

Category	Criteria
1	Contains ≥85% 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 (29.5 in), or (b) For foam aerosols, in the aerosol foam flammability test (i) The flame height is ≥20 cm (7.87 in) and the flame duration ≥2 s; or (ii) The flame height is ≥4 cm (1.57 in) 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 (5.9 in), or in the enclosed space ignition test, the (i) Time equivalent is ≤300 s/m3; or (ii) Deflagration density is ≤300 g/m3 (b) For foam aerosols, in the aerosol foam flammability test, the flame height is ≥4 cm and the flame duration is ≥2 s and it does not meet the criteria for Category 1.
3	The chemical does not meet the criteria for Categories 1 and 2. The chemical contains ≤1% flammable components (by mass) *and* has a heat of combustion <20 kJ/g.

Note: Aerosols containing more than 1% flammable components or with a heat of combustion of at least 20 kJ/g, which are not submitted to the flammability classification procedures in this appendix shall be classified as Category 1.

B.3.3 Additional Classification Considerations

B.3.3.1 To classify an aerosol, data on its flammable components, on its chemical heat of combustion and, if applicable, the results of the aerosol foam flammability test (for foam aerosols) and of the ignition distance test and enclosed space test (for spray aerosols) are necessary.

B.3.3.2 The chemical heat of combustion (ΔHc), in kilojoules per gram (kJ/g), is the product of the theoretical heat of combustion (ΔHcomb), 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:

$$\Delta Hc\ (product) = \sum_{i}^{n} [\ wi\% \times \Delta Hc(i)]$$

where:

ΔHc = chemical heat of combustion (kJ/g);
wi% = mass fraction of component i in the product;
ΔHc(i) = specific heat of combustion (kJ/g) of component i in the product;

The chemical heats of combustion shall be found in literature, calculated or determined by tests (See ASTM D240–02; ISO 13943, Sections 86.1 to 86.3; and NFPA 30B (incorporated by reference; See § 1910.6)).

B.3.3.3 The Ignition Distance Test, Enclosed Space Ignition Test and Aerosol Foam Flammability Test shall be performed in accordance with sub-sections 31.4, 31.5 and 31.6 of the of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6).

B.4 Oxidizing Gases

B.4.1 Definition

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

Note: ''Gases which cause or contribute to the combustion of other material more than air does'' means pure gases or gas mixtures with an oxidizing power greater than 23.5% (as determined by a method specified in ISO 10156 (Gases and Gas Mixtures—Determination of Fire Potential and Oxidizing Ability for the Selection of Cylinder Valve Outlets; 1996, first edition or 2010, third edition) (incorporated by reference; see § 1910.6) or 10156–2:2005 (E) (Gas cylinders—Gases and Gas Mixtures—Part 2: Determination of Oxidizing Ability of Toxic and Corrosive Gases and Gas Mixtures, First Edition) (incorporated by reference; see § 1910.6) or an equivalent testing method).

B.4.2 Classification Criteria

An oxidizing gas shall be classified in a single category for this class in accordance with Table B.4.1:

TABLE B.4.1—CRITERIA FOR OXIDIZING 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.

B.4.3 Additional Classification Considerations

Classification shall be in accordance with tests or calculation methods as described in ISO 10156 (Gases and Gas Mixtures—Determination of Fire Potential and Oxidizing Ability for the Selection of Cylinder Valve Outlets; 1996, first edition or 2010, third edition) (incorporated by reference; see § 1910.6) and ISO 10156–2:2005 (E) (Gas cylinders—Gases and Gas Mixtures—Part 2: Determination of Oxidizing Ability of Toxic and Corrosive Gases and Gas Mixtures, First Edition) (incorporated by reference; see § 1910.6).

B.5 Gases Under Pressure

B.5.1 Definition

Gases under pressure are gases which are contained in a receptacle at a pressure of 200 kPa (29 psi) (gauge) or more at 20 °C (68 °F), or which are liquefied or liquefied and refrigerated.

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

B.5.2 Classification Criteria

Gases under pressure shall be classified in one of four groups in accordance with Table B.5.1:

TABLE B.5.1—CRITERIA FOR GASES UNDER PRESSURE

Group	Criteria
Compressed gas	A gas which when under pressure is entirely gaseous at −50 °C (−58 °F), including all gases with a critical temperature [1] ≤ −50 °C (−58 °F).
Liquefied gas	A gas which when under pressure, is partially liquid at temperatures above −50 °C (−58 °F). A distinction is made between: (a) High pressure liquefied gas: A gas with a critical temperature1 between −50 °C (−58 °F) and +65 °C (149 °F); and (b) Low pressure liquefied gas: A gas with a critical temperature [1] above +65 °C (149 °F).
Refrigerated liquefied gas	A gas which is made partially liquid because of its low temperature.
Dissolved gas	A gas which when under pressure is dissolved in a liquid phase solvent.

[1] *The critical temperature is the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression.*
Note: *Aerosols should not be classified as gases under pressure. See appendix B.3 of this section.*

B.6 Flammable Liquids

B.6.1 Definition

Flammable liquid means a liquid having a flash point of not more than 93 °C (199.4 °F).

Flash point means the minimum temperature at which a liquid gives off vapor in sufficient concentration to form an ignitable mixture with air near the surface of the liquid, as determined by a method identified in Section B.6.3.

B.6.2 Classification Criteria

A flammable liquid shall be classified in one of four categories in accordance with Table B.6.1:

TABLE B.6.1—CRITERIA FOR FLAMMABLE LIQUIDS

Category	Criteria
1	Flash point <23 °C (73.4 °F) and initial boiling point ≤35 °C (95 °F).
2	Flash point <23 °C (73.4 °F) and initial boiling point >35 °C (95 °F).
3	Flash point ≥23 °C (73.4 °F) and ≤60 °C (140 °F).
4	Flash point >60 °C (140 °F) and ≤93 °C (199.4 °F).

Note: Aerosols should not be classified as flammable liquids. See appendix B.3 of this section.

B.6.3 Additional Classification Considerations

The flash point shall be determined in accordance with ASTM D56–05, ASTM D3278, ASTM D3828, ASTM D93–08 (incorporated by reference; See § 1910.6), any method specified in 29 CFR 1910.106(a)(14), or any other method specified in GHS Revision 7, Chapter 2.6.

The initial boiling point shall be determined in accordance with ASTM D86–07a or ASTM D1078 (incorporated by reference; see § 1910.6).[9]

B.7 Flammable Solids

B.7.1 Definitions

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

Readily combustible solids are powdered, granular, or pasty chemicals 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.

B.7.2 Classification Criteria

B.7.2.1 Powdered, granular or pasty chemicals shall be classified as flammable solids when the time of burning of one or more of the test runs, performed in accordance with the test method described in the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), Part III, sub-section 33.2.1, is less than 45 s or the rate of burning is more than 2.2 mm/s (0.0866 in/s).

B.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 min or less.

B.7.2.3 Solids which may cause fire through friction shall be classified in this class by analogy with existing entries (*e.g.,* matches) until definitive criteria are established.

B.7.2.4 A flammable solid shall be classified in one of the two categories for this class using Method N.1 as described in Part III, sub-section 33.2.1 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.7.1:

TABLE B.7.1—CRITERIA FOR FLAMMABLE SOLIDS

Category	Criteria
1	Burning rate test: Chemicals other than metal powders: (a) Wetted zone does not stop fire; and (b) Burning time <45 s or burning rate >2.2 mm/s. Metal powders: Burning time ≤5 min.
2	Burning rate test:

[9] To determine the appropriate flammable liquid storage container size and type, the boiling point shall be determined by methods specified under § 1910.106(a)(5) and then listed on the SDS. In addition, the manufacturer, importer, and distributor shall clearly note in sections 7 and 9 of the SDS if an alternate calculation was used for storage purposes.

TABLE B.7.1—CRITERIA FOR FLAMMABLE SOLIDS—Continued

Category	Criteria
	Chemicals other than metal powders: (a) Wetted zone stops the fire for at least 4 min; and (b) Burning time <45 s or burning rate >2.2 mm/s. Metal powders: Burning time >5 min and ≤10 min.

Note 1: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

Note 2: Aerosols should not be classified as flammable solids. See appendix B.3 of this section.

B.8 Self-Reactive Chemicals

B.8.1 Definitions

Self-reactive chemicals are thermally unstable liquid or solid chemicals liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). This definition excludes chemicals classified under this section as explosives, organic peroxides, oxidizing liquids or oxidizing solids.

A self-reactive chemical 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.

B.8.2 Classification Criteria

B.8.2.1 A self-reactive chemical shall be considered for classification in this class unless:

(a) It is classified as an explosive according to B.1 of this appendix;

(b) It is classified as an oxidizing liquid or an oxidizing solid according to B.13 or B.14 of this appendix, except that a mixture of oxidizing substances which contains 5% or more of combustible organic substances shall be classified as a self-reactive chemical according to the procedure defined in B.8.2.2;

(c) It is classified as an organic peroxide according to B.15 of this appendix;

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

(e) Its self-accelerating decomposition temperature (SADT) is greater than 75 °C (167 °F) for a 50 kg (110 lb) package.

B.8.2.2 Mixtures of oxidizing substances, meeting the criteria for classification as oxidizing liquids or oxidizing solids, which contain 5% or more of combustible organic substances and which do not meet the criteria mentioned in B.8.2.1(a), (c), (d) or (e), shall be subjected to the self-reactive chemicals classification procedure in B.8.2.3. Such a mixture showing the properties of a self-reactive chemical type B to F shall be classified as a self-reactive chemical.

B.8.2.3 Self-reactive chemicals 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 chemical which can detonate or deflagrate rapidly, as packaged, will be defined as self-reactive chemical TYPE A;

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

(c) Any self-reactive chemical possessing explosive properties when the chemical as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion will be defined as self-reactive chemical TYPE C;

(d) Any self-reactive chemical which in laboratory testing meets the criteria in (d)(i), (ii), or (iii) will be defined as self-reactive chemical TYPE D:

(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;

(e) Any self-reactive chemical which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement will be defined as self-reactive chemical TYPE E;

(f) Any self-reactive chemical 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 will be defined as self-reactive chemical TYPE F;

(g) Any self-reactive chemical 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 (140 °F) to 75 °C (167 °F) for a 50 kg (110 lb) package), and, for liquid mixtures, a diluent having a boiling point greater than or equal to 150 °C (302 °F) is used for desensitization will be defined as self-reactive chemical TYPE G. If the mixture is not thermally stable or a diluent having a boiling point less than 150 °C (302 °F) is used for desensitization, the mixture shall be defined as self-reactive chemical TYPE F.

B.8.3 Additional Classification Considerations

B.8.3.1 For purposes of classification, the properties of self-reactive chemicals shall be determined in accordance with test series A to H as described in Part II of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6).

B.8.3.2 Self-accelerating decomposition temperature (SADT) shall be determined in accordance with the UN ST/SG/AC.10, Part II, section 28 (incorporated by reference; See § 1910.6).

B.8.3.3 The classification procedures for self-reactive substances and mixtures need not be applied if:

(a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties; examples of such groups are given in Tables A6.1 and A6.2 in the Appendix 6 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6); or

(b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT is greater than 75 °C (167 °F) or the exothermic decomposition energy is less than 300 J/g. The onset temperature and decomposition energy may be estimated using a suitable calorimetric technique (See 20.3.3.3 in Part II of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6)).

B.9 Pyrophoric Liquids

B.9.1 Definition

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

B.9.2 Classification Criteria

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 ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.9.1:

TABLE B.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.

B.9.3 Additional Classification Considerations

The classification procedure for pyrophoric liquids need not be applied when experience in production or handling shows that the chemical 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)).

B.10 Pyrophoric Solids

B.10.1 Definition

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

B.10.2 Classification Criteria

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 ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.10.1:

TABLE B.10.1—CRITERIA FOR PYROPHORIC SOLIDS

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

Note: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

B.10.3 Additional Classification Considerations

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

B.11 SELF–Heating Chemicals

B.11.1 Definition

A self-heating chemical is a solid or liquid chemical, other than a pyrophoric liquid or solid, which, by reaction with air and without energy supply, is liable to self-heat; this chemical 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).

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

B.11.2 Classification Criteria

B.11.2.1 A self-heating chemical shall be classified in one of the two categories for this class if, in tests performed in accordance with test method N.4 in Part III, sub-section 33.3.1.6 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), the result meets the criteria shown in Table B.11.1.

TABLE B.11.1—CRITERIA FOR SELF-HEATING CHEMICALS

Category	Criteria
1	A positive result is obtained in a test using a 25 mm sample cube at 140 °C (284 °F).
2	A negative result is obtained in a test using a 25 mm cube sample at 140 °C (284 °F), a positive result is obtained in a test using a 100 mm sample cube at 140 °C (284 °F), and: (a) The unit volume of the chemical is more than 3 m^3; or (b) A positive result is obtained in a test using a 100 mm cube sample at 120 °C (248 °F) and the unit volume of the chemical is more than 450 liters; or (c) A positive result is obtained in a test using a 100 mm cube sample at 100 °C (212 °F).

Note: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

B.11.2.2 Chemicals with a temperature of spontaneous combustion higher than 50°C (122 °F) for a volume of 27 m3 shall not be classified as self-heating chemicals.

B.11.2.3 Chemicals with a spontaneous ignition temperature higher than 50 °C (122 °F) for a volume of 450 liters shall not be classified in Category 1 of this class.

B.11.3 Additional Classification Considerations

B.11.3.1 The classification procedure for self-heating chemicals 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.

B.11.3.2 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*.

B.12 Chemicals Which, in Contact With Water, Emit Flammable Gases

B.12.1 Definition

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

B.12.2 Classification Criteria

B.12.2.1 A chemical which, in contact with water, emits flammable gases shall be classified in one of the three categories for this class, using test N.5 in Part III, sub-section 33.4.1.4 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.12.1:

TABLE B.12.1—CRITERIA FOR CHEMICALS WHICH, IN CONTACT WITH WATER, EMIT FLAMMABLE GASES

Category	Criteria
1	Any chemical 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 liters per kilogram of chemical over any one minute.
2	Any chemical 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 liters per kilogram of chemical per hour, and which does not meet the criteria for Category 1.
3	Any chemical which reacts slowly with water at ambient temperatures such that the maximum rate of evolution of flammable gas is greater than 1 liter per kilogram of chemical per hour, and which does not meet the criteria for Categories 1 and 2.

Note: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

B.12.2.2 A chemical is classified as a chemical which, in contact with water, emits flammable gases if spontaneous ignition takes place in any step of the test procedure.

B.12.3 Additional Classification Considerations

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

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

(b) Experience in production or handling shows that the chemical does not react with water, (*e.g.,* the chemical is manufactured with water or washed with water); or

(c) The chemical is known to be soluble in water to form a stable mixture.

B.13 Oxidizing Liquids

B.13.1 Definition

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

B.13.2 Classification Criteria

An oxidizing 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 ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.13.1:

TABLE B.13.1—CRITERIA FOR OXIDIZING LIQUIDS

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

B.13.3 Additional Classification Considerations

B.13.3.1 For organic chemicals, the classification procedure for this class shall not be applied if:

(a) The chemical does not contain oxygen, fluorine or chlorine; or

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

B.13.3.2 For inorganic chemicals, the classification procedure for this class shall not be applied if the chemical does not contain oxygen or halogen atoms.

B.13.3.3 In the event of divergence between test results and known experience in the handling and use of chemicals which shows them to be oxidizing, judgments based on known experience shall take precedence over test results.

B.13.3.4 In cases where chemicals generate a pressure rise (too high or too low), caused by chemical reactions not characterizing the oxidizing properties of the chemical, the test described in Part III, sub-section 34.4.2 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6) shall be repeated with an inert substance (*e.g.,* diatomite (kieselguhr)) in place of the cellulose in order to clarify the nature of the reaction.

B.14 Oxidizing Solids

B.14.1 Definition

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

B.14.2 Classification Criteria

An oxidizing 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 or test O.3 in Part III, sub-section 34.4.3, of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.14.1:

TABLE B.14.1—CRITERIA FOR OXIDIZING SOLIDS

Category	Criteria using test O.1	Criteria using test O.3
1	Any chemical 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.	Any chemical which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate greater than the mean burning rate of a 3:1 mixture (by mass) of calcium peroxide and cellulose.

TABLE B.14.1—CRITERIA FOR OXIDIZING SOLIDS—Continued

Category	Criteria using test O.1	Criteria using test O.3
2	Any chemical 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.	Any chemical which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate equal to or greater than the mean burning rate of a 1:1 mixture (by mass) of calcium peroxide and cellulose and the criteria for Category 1 are not met.
3	Any chemical 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.	Any chemical which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate equal to or greater than the mean burning rate of a 1:2 mixture (by mass) of calcium peroxide and cellulose and the criteria for Categories 1 and 2 are not met.

Note 1: Some oxidizing solids may present explosion hazards under certain conditions (*e.g.,* when stored in large quantities). For example, some types of ammonium nitrate may give rise to an explosion hazard under extreme conditions and the ''Resistance to detonation test'' (International Maritime Solid Bulk Cargoes Code, IMO (IMSBC), Appendix 2, Section 5) may be used to assess this hazard. When information indicates that an oxidizing solid may present an explosion hazard, it shall be indicated on the Safety Data Sheet.

Note 2: Classification of solid chemicals shall be based on tests performed on the chemical as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, classification must be based on testing of the chemical in the new form.

B.14.3 Additional Classification Considerations

B.14.3.1 For organic chemicals, the classification procedure for this class shall not be applied if:

(a) The chemical does not contain oxygen, fluorine or chlorine; or

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

B.14.3.2 For inorganic chemicals, the classification procedure for this class shall not be applied if the chemical does not contain oxygen or halogen atoms.

B.14.3.3 In the event of divergence between test results and known experience in the handling and use of chemicals which shows them to be oxidizing, judgements based on known experience shall take precedence over test results.

B.15 Organic Peroxides

B.15.1 Definition

B.15.1.1 Organic peroxide means a liquid or solid organic chemical which contains the bivalent -0–0- structure and as such is considered a derivative 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 containing at least one organic peroxide. Organic peroxides are thermally unstable chemicals, which may undergo exothermic self-accelerating decomposition. In addition, they may have one or more of the following properties:

(a) Be liable to explosive decomposition;

(b) Burn rapidly;

(c) Be sensitive to impact or friction;

(d) React dangerously with other substances.

B.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.

B.15.2 Classification Criteria

B.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.

B.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 chemical 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 meets the criteria in (d)(i), (ii), or (iii) shall be defined as organic peroxide TYPE D:

(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;

(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 (self-accelerating decomposition temperature is 60 °C (140 °F) or higher for a 50 kg (110 lb) package), and, for liquid mixtures, a diluent having a boiling point of not less than 150 °C (302 °F) is used for desensitization, shall be defined as organic peroxide TYPE G. If the organic peroxide is not thermally stable or a diluent having a boiling point less than 150 °C (302 °F) is used for desensitization, it shall be defined as organic peroxide TYPE F.

B.15.3 Additional Classification Considerations

B.15.3.1 For purposes of classification, the properties of organic peroxides shall be determined in accordance with test series A to H as described in Part II of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6).

B.15.3.2 Self-accelerating decomposition temperature (SADT) shall be determined in accordance with the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), Part II, section 28.

B.15.3.3 Mixtures of organic peroxides may be classified as the same type of organic peroxide as that of the most dangerous ingredient. However, as two stable ingredients can form a thermally less stable mixture, the SADT of the mixture shall be determined.

B.16 Corrosive to Metals

B.16.1 Definition

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

B.16.2 Classification criteria

A chemical which is corrosive to metals shall be classified in a single category for this class, using the test in Part III, sub-section 37.4 of the UN ST/SG/AC.10 (incorporated by reference; See § 1910.6), in accordance with Table B.16.1:

TABLE B.16.1—CRITERIA FOR CHEMICALS CORROSIVE TO METAL

Category	Criteria
1	Corrosion rate on either steel or aluminium surfaces exceeding 6.25 mm per year at a test temperature of 55 °C (131 °F) when tested on both materials.

Note: Where an initial test on either steel or aluminium indicates the chemical being tested is corrosive the follow-up test on the other metal is not necessary.

B.16.3 Additional Classification Considerations

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, Unified Numbering System (UNS) G 10200, or SAE 1020;

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

Chapter B.17

Desensitized Explosives

B.17.1 Definitions and General Considerations

Desensitized explosives are solid or liquid explosive chemicals which are phlegmatized [10] to suppress their explosive properties in such a manner that they do not mass explode and do not burn too rapidly and therefore may be exempted from the hazard class ''Explosives'' (Chapter B.1; see also Note 2 of paragraph B.1.3).[11]

B.17.1.2 The class of desensitized explosives comprises:

(a) *Solid desensitized explosives:* Explosive substances or mixtures which are wetted with water or alcohols or are diluted with other substances, to form a homogeneous solid mixture to suppress their explosive properties.

Note: This includes desensitization achieved by formation of hydrates of the substances.

(b) *Liquid desensitized explosives:* Explosive substances or mixtures which are dissolved or suspended in water or other liquid substances, to form a homogeneous liquid mixture to suppress their explosive properties.

B.17.2 Classification Criteria

B.2.17.2.1 Any explosive which is desensitized shall be considered in this class, unless:

(a) It is intended to produce a practical, explosive or pyrotechnic effect; or

(b) It has a mass explosion hazard according to test series 6(a) or 6(b) or its corrected burning rate according to the burning rate test described in part V, subsection 51.4 of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6) is greater than 1200 kg/min; or

(c) Its exothermic decomposition energy is less than 300 J/g.

Note 1: Substances or mixtures which meet the criterion (a) or (b) shall be classified as explosives (see Chapter B.1). Substances or mixtures which meet the criterion (c) may fall within the scope of other physical hazard classes.

Note 2: The exothermic decomposition energy may be estimated using a suitable calorimetric technique (see section 20, sub-section 20.3.3.3 in Part II of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6).

B.17.2.2 Desensitized explosives shall be classified in one of the four categories of this class depending on the corrected burning rate (Ac) using the test ''burning rate test (external fire)'' described in Part V, sub-section 51.4 of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations of the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6), according to Table B.17.1:

TABLE B.17.1 CRITERIA FOR DESENSITIZED EXPLOSIVES

Category	Criteria
1	Desensitized explosives with a corrected burning rate (A_C) equal to or greater than 300 kg/min but not more than 1200 kg/min.
2	Desensitized explosives with a corrected burning rate (A_C) equal to or greater than 140 kg/min but less than 300 kg/min.
3	Desensitized explosives with a corrected burning rate (A_C) equal to or greater than 60 kg/min but less than 140 kg/min.
4	Desensitized explosives with a corrected burning rate (A_C) less than 60 kg/min.

Note 1: Desensitized explosives shall be prepared so that they remain homogeneous and do not separate during normal storage and handling, particularly if desensitized by wetting. The manufacturer, importer, or distributor shall provide information in Section 10 of the safety data sheet about the shelf-life and instructions on verifying desensitization. Under certain conditions the content of desensitizing agent (*e.g.,* phlegmatizer, wetting agent or treatment) may decrease during supply and use, and thus, the hazard potential of the desensitized explosive may increase. In addition, Sections 5 and/or 8 of the safety data sheet shall include advice on avoiding increased fire, blast or protection hazards when the chemical is not sufficiently desensitized.

Note 2: Explosive properties of desensitized explosives shall be determined using data from Test Series 2 of UN ST/SG/

[10] *Phlegmatized* means that a substance (or ''phlegmatizer'') has been added to an explosive to enhance its safety in handling and transport. The phlegmatizer renders the explosive insensitive, or less sensitive, to the following actions: Heat, shock, impact, percussion or friction. Typical phlegmatizing agents include, but are not limited to: Wax, paper, water, polymers (such as chlorofluoropolymers), alcohol and oils (such as petroleum jelly and paraffin). (As defined in Chapter 2.1 of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Test Criteria) (incorporated by reference; see § 1910.6)).

[11] Unstable explosives as defined in Chapter B.1 can also be stabilized by desensitization and consequently may be re-classified as desensitized explosives, provided all criteria of Chapter B.17 are met. In this case, the desensitized explosive should be tested according to Test Series 3 (Part I of UN ST/SG/AC.10/30/Rev. 6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6)) because information about its sensitiveness to mechanical stimuli is likely to be important for determining conditions for safe handling and use. The results shall be communicated on the safety data sheet.

AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6) and shall be communicated in the safety data sheet. For testing of liquid desensitized explosives, refer to section 32, sub-section 32.3.2 of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6). Testing of solid desensitized explosives is addressed in section 33, sub-section 33.2.3 of UN ST/SG/AC.10/30/Rev.6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6).

Note 3: Desensitized explosives do not fall additionally within the scope of chapters B.1 (explosives), B.6 (flammable liquids) and B.7 (flammable solids).

B.17.3 Additional Classification Considerations

B.17.3.1 The classification procedure for desensitized explosives does not apply if:

(a) The substances or mixtures contain no explosives according to the criteria in Chapter B.1; or

(b) The exothermic decomposition energy is less than 300 J/g.

B.17.3.2 The exothermic decomposition energy shall be determined using the explosive already desensitized (*i.e.,* the homogenous solid or liquids mixture formed by the explosive and the substance(s) used to suppress its explosive properties). The exothermic decomposition energy may be estimated using a suitable calorimetric technique (see Section 20, sub-section 20.3.3.3 in Part II of UN ST/SG/AC.10/30/Rev. 6 (UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria) (incorporated by reference; see § 1910.6).

Appendix C to § 1910.1200—Allocation of Label Elements (Mandatory)

C.1 The label for each hazardous chemical shall include the product identifier used on the safety data sheet.

C.1.1 The labels on shipped containers shall also include the name, address, and telephone number of the chemical manufacturer, importer, or responsible party.

C.2 The label for each hazardous chemical that is classified shall include the signal word, hazard statement(s), pictogram(s), and precautionary statement(s) specified in C.4 for each hazard class and associated hazard category, except as provided for in C.2.1 through C.2.4.

C.2.1 Precedence of hazard information

C.2.1.1 If the signal word ''Danger'' is included, the signal word ''Warning'' shall not appear;

C.2.1.2 If the skull and crossbones pictogram is included, the exclamation mark pictogram shall not appear where it is used for acute toxicity;

C.2.1.3 If the corrosive pictogram is included, the exclamation mark pictogram shall not appear where it is used for skin or eye irritation;

C.2.1.4 If the health hazard pictogram is included for respiratory sensitization, the exclamation mark pictogram shall not appear where it is used for skin sensitization or for skin or eye irritation.

C.2.2 Hazard statement text

C.2.2.1 The text of all applicable hazard statements shall appear on the label, except as otherwise specified. The information in italics shall be included as part of the hazard statement as provided. For example: ''Causes damage to organs (state all organs affected) through prolonged or repeated exposure (state route of exposure if no other routes of exposure cause the hazard)''. Hazard statements may be combined where appropriate to reduce the information on the label and improve readability, as long as all of the hazards are conveyed as required.

C.2.2.2 If the chemical manufacturer, importer, or responsible party can demonstrate that all or part of the hazard statement is inappropriate to a specific substance or mixture, the corresponding statement may be omitted from the label.

C.2.3 Pictograms

C.2.3.1 Pictograms shall be in the shape of a square set at a point and shall include a black hazard symbol on a white background with a red frame sufficiently wide to be clearly visible. A square red frame set at a point without a hazard symbol is not a pictogram and is not permitted on the label.

C.2.3.2 One of eight standard hazard symbols shall be used in each pictogram. The eight hazard symbols are depicted in Figure C.1. A pictogram using the exclamation mark symbol is presented in Figure C.2, for the purpose of illustration.

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Figure C.1 – Hazard Symbols and Classes

Flame	Flame Over Circle	Exclamation Mark	Exploding Bomb
 Flammables Self Reactives Pyrophorics Self-heating Emits Flammable Gas Organic Peroxides Desensitized Explosives	 Oxidizers	 Irritant Dermal Sensitizer Acute Toxicity (harmful) Narcotic Effects Respiratory Tract Irritation HNOC (non-mandatory)	 Explosives Self Reactives Organic Peroxides
Corrosion	**Gas Cylinder**	**Health Hazard**	**Skull and Crossbones**
 Corrosives	 Gases Under Pressure	 Carcinogen Respiratory Sensitizer Reproductive Toxicity Target Organ Toxicity Mutagenicity Aspiration Toxicity	 Acute Toxicity (severe)

Figure C.2 – Exclamation Mark Pictogram

C.2.3.3 The exclamation mark pictogram is permitted (but not required) for HNOCs as long as the words ''Hazard Not Otherwise Classified'' or the letters ''HNOC'' appear below the pictogram.

C.2.3.4 Pictograms may only appear once on a label. If multiple hazards require the use of the same pictogram, it may not appear a second time on the label.

C.2.4 Precautionary statement text

C.2.4.1 There are four types of precautionary statements presented, ''prevention,'' ''response,'' ''storage,'' and ''disposal.'' The core part of the precautionary statement is presented in bold print. This is the text, except as otherwise specified, that shall appear on the label. Where additional information is required, it is indicated in plain text.

C.2.4.2 When a backslash or diagonal mark (/) appears in the precautionary

statement text, it indicates that a choice has to be made between the separated phrases. In such cases, the chemical manufacturer, importer, or responsible party can choose the most appropriate phrase(s). For example, ''Wear protective gloves/protective clothing/eye protection/face protection'' could read ''wear eye protection''.

C.2.4.3 When three full stops (. . .) appear in the precautionary statement text, they indicate that all applicable conditions are not listed. For example, in ''Use explosion-proof electrical/ventilating/lighting/. . ./equipment'', the use of ''. . .'' indicates that other equipment may need to be specified. In such cases, the chemical manufacturer, importer, or responsible party can choose the other conditions to be specified.

C.2.4.4 When text *in italics* is used in a precautionary statement, this indicates specific conditions applying to the use or allocation of the precautionary statement. For example, ''Use explosion-proof electrical/ventilating/lighting/. . ./equipment'' is only required for flammable solids ''*if dust clouds can occur*''. Text in italics is intended to be an explanatory, conditional note and is not intended to appear on the label.

C.2.4.5 Where square brackets ([ ]) appear around text in a precautionary statement, this indicates that the text in square brackets is not appropriate in every case and should be used only in certain circumstances. In these cases, conditions for use explaining when the text should be used are provided. For example, one precautionary statement states: ''[In case of inadequate ventilation] wear respiratory protection.'' This statement is given with the condition for use ''—text in square brackets may be used if additional information is provided with the chemical at the point of use that explains what type of ventilation would be adequate for safe use''. This means that, if additional information is provided with the chemical explaining what type of ventilation would be adequate for safe use, the text in square brackets should be used and the statement would read: ''In case of inadequate ventilation wear respiratory protection.'' However, if the chemical is supplied without such ventilation information, the text in square brackets should not be used, and the precautionary statement should read: ''Wear respiratory protection.''

C.2.4.6 Precautionary statements may be combined or consolidated to save label space and improve readability. For example, ''Keep away from heat, sparks and open flame,'' ''Store in a well-ventilated place'' and ''Keep cool'' can be combined to read ''Keep away from heat, sparks and open flame and store in a cool, well-ventilated place.''

C.2.4.7 Precautionary statements may incorporate minor textual variations from the text prescribed in this appendix if these variations assist in communicating safety information (*e.g.,* spelling variations, synonyms or other equivalent terms) and the safety advice is not diluted or compromised. Any variations must be used consistently on the label and the safety data sheet.

C.2.4.8 In most cases, the precautionary statements are independent (*e.g.,* the phrases for explosive hazards do not modify those related to certain health hazards, and products that are classified for both hazard classes shall bear appropriate precautionary statements for both). Where a chemical is classified for a number of hazards, and the precautionary statements are similar, the most stringent shall be included on the label (this will be applicable mainly to preventive measures).

C.2.4.9 If the chemical manufacturer, importer, or responsible party can demonstrate that a precautionary statement is inappropriate to a specific substance or mixture, the precautionary statement may be omitted from the label.

C.2.4.10 Where a substance or mixture is classified for a number of health hazards, this may trigger multiple precautionary statements relating to medical response, *e.g.,* calling a poison center/doctor/. . . and getting medical advice/attention.

In general, the following principles should be applied:

(a) Where the classification of a substance or mixture triggers several different precautionary statements, a system of prioritization should be applied. Usually, the label need only include one precautionary statement reflecting the response at the highest level with the greatest urgency, which should always be combined with at least one route of exposure or symptom ''IF'' statement.

(b) Routes of exposure, including ''IF exposed or concerned,'' may be combined when triggered with a medical response statement. If the response statement is triggered with three or more routes of exposure, ''IF exposed or concerned'' may be used. However, relevant ''IF'' statements describing symptoms must be included in full. If a route of exposure is triggered multiple times, it need only be included once.

(c) This does not apply to ''Get medical advice/attention if you feel unwell'' or ''Get immediate medical advice/attention'' when they are combined with an ''If'' statement and should appear without prioritization.

C.3 Supplementary hazard information

C.3.1 To ensure that non-standardized information does not lead to unnecessarily wide variation or undermine the required information, supplementary information on the label is limited to when it provides further detail and does not contradict or cast doubt on the validity of the standardized hazard information.

C.3.2 Where the chemical manufacturer, importer, or distributor chooses to add supplementary information on the label, the placement of supplemental information shall not impede identification of information required by this section.

C.3.3 Where an ingredient with unknown acute toxicity is used in a mixture at a concentration ≥1%, and the mixture is not classified based on testing of the mixture as a whole, a statement that X% of the mixture consists of ingredient(s) of unknown acute toxicity (oral/dermal/inhalation) is required on the label and safety data sheet.

C.4 REQUIREMENTS FOR SIGNAL WORDS, HAZARD STATEMENTS, PICTOGRAMS, AND PRECAUTIONARY STATEMENTS

C.4.1 ACUTE TOXICITY – ORAL
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	Signal word	Hazard statement
1	Danger	Fatal if swallowed
2	Danger	Fatal if swallowed
3	Danger	Toxic if swallowed

Pictogram
Skull and crossbones

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wash …thoroughly after handling. … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Do not eat, drink or smoke when using this product.**	**If swallowed: Immediately call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see … on this label)** … Reference to supplemental first aid instruction. *- if immediate administration of antidote is required.* **Rinse mouth.**	**Store locked up.**	**Dispose of contents/container to…** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.1 ACUTE TOXICITY – ORAL (CONTINUED)
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	**Signal word**	**Hazard statement**
4	Warning	Harmful if swallowed

Pictogram
Exclamation mark

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wash … thoroughly after handling. … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Do not eat, drink or smoke when using this product.**	**If swallowed: Call a poison center/doctor/…/ if you feel unwell.** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Rinse mouth.**		**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.2 ACUTE TOXICITY - DERMAL
(Classified in Accordance with Appendix A.1 of this section)

Hazard category	Signal word	Hazard statement	Pictogram
1	Danger	Fatal in contact with skin	Skull and crossbones
2	Danger	Fatal in contact with skin	

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Do not get in eyes, on skin, or on clothing. **Wash … thoroughly after handling.** … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Do not eat, drink or smoke when using this product.** **Wear protective gloves/protective clothing.** Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If on skin: Wash with plenty of water/...** … Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate, or may recommend an alternative agent in exceptional cases if water is clearly inappropriate. **Immediately call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. *- if immediate measures such as specific cleansing agent is advised.* **Take off immediately all contaminated clothing and wash it before reuse.**	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/ international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.2 ACUTE TOXICITY - DERMAL (CONTINUED)
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	Signal word	Hazard statement	Pictogram
3	Danger	Toxic in contact with skin	Skull and crossbones

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wear protective gloves/protective clothing. Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If on skin: Wash with plenty of water/…** … Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate, or may recommend an alternative agent in exceptional cases if water is clearly inappropriate. **Call a poison center/doctor/…/if you feel unwell.** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. *- if immediate measures such as specific cleansing agent is advised.* **Take off immediately all contaminated clothing and wash it before reuse.**	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.2 ACUTE TOXICITY – DERMAL (CONTINUED)
(Classified in Accordance with Appendix A.1 of this Section)

Pictogram
Exclamation mark

Hazard category	Signal word	Hazard statement	
4	Warning	Harmful in contact with skin	

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wear protective gloves/protective clothing. Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If on skin: Wash with plenty of water/...** … Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate, or may recommend an alternative agent in exceptional cases if water is clearly inappropriate. **Call a poison center/doctor/…/if you feel unwell.** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. *- if measures such as specific cleansing agent is advised.* **Take off contaminated clothing and wash it before reuse.**		**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.3 ACUTE TOXICITY - INHALATION
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	Signal word	Hazard statement
1	Danger	Fatal if inhaled
2	Danger	Fatal if inhaled

Pictogram
Skull and crossbones

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Do not breathe dust/fume/gas/mist/ vapors/spray. Chemical manufacturer, importer, or distributor to specify applicable conditions. **Use only outdoors or in a well-ventilated area.** **[In case of inadequate ventilation] wear respiratory protection.** Chemical manufacturer, importer, or distributor to specify equipment. - *Text in square brackets may be used if additional information is provided with the chemical at the point of use that explains what type of ventilation would be adequate for safe use.*	**If inhaled: Remove person to fresh air and keep comfortable for breathing.** **Immediately call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment is urgent (see ... on this label)** ... Reference to supplemental first aid instruction. - *if immediate administration of antidote is required.*	**Store in a well-ventilated place. Keep container tightly closed.** - *if the chemical is volatile and may generate a hazardous atmosphere.* **Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.3 ACUTE TOXICITY – INHALATION (CONTINUED)
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	Signal word	Hazard statement	Pictogram
3	Danger	Toxic if inhaled	Skull and crossbones 

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Avoid breathing dust/fume/gas/mist/vapors/spray. Chemical manufacturer, importer, or distributor to specify applicable conditions. **Use only outdoors or in a well-ventilated area.**	**If inhaled: Remove person to fresh air and keep comfortable for breathing.** **Call a poison center/doctor/...** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. *- if immediate specific measures are required.*	**Store in a well-ventilated place. Keep container tightly closed.** *- if the chemical is volatile and may generate a hazardous atmosphere.* **Store locked up.**	**Dispose of content/container to…** … in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.3 ACUTE TOXICITY – INHALATION (CONTINUED)
(Classified in Accordance with Appendix A.1 of this Section)

Hazard category	**Signal word**	**Hazard statement**	**Pictogram**
4	Warning	Harmful if inhaled	Exclamation mark

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Avoid breathing dust/fume/gas/mist/vapors/spray. Chemical manufacturer, importer, or distributor to specify applicable conditions. **Use only outdoors or in a well-ventilated area.**	**If inhaled: Remove person to fresh air and keep comfortable for breathing.** **Call a poison center/doctor/.../if you feel unwell.** ... Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice.		

C.4.4 SKIN CORROSION/IRRITATION
(Classified in Accordance with Appendix A.2 of this Section)

Hazard category	Signal word	Hazard statement	Pictogram
1A to 1C	Danger	Causes severe skin burns and eye damage	Corrosion 

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Do not breathe dusts or mists. *- if inhalable particles of dusts or mists may occur during use.* **Wash …thoroughly after handling.** …Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Wear protective gloves/protective clothing/eye protection/face protection.** Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If swallowed: Rinse mouth. Do NOT induce vomiting.** **If on skin (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower].** *- text in square brackets to be included where the chemical manufacturer, importer or distributor considers it appropriate for the specific chemical.* **Wash contaminated clothing before reuse.** **If inhaled: Remove person to fresh air and keep comfortable for breathing.** **Immediately call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. - Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate. **If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.**	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/ international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.4 SKIN CORROSION/IRRITATION (CONTINUED)
(Classified in Accordance with Appendix A.2 of this Section)

Pictogram
Exclamation mark

Hazard category	Signal word	Hazard statement
2	Warning	Causes skin irritation

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wash … thoroughly after handling. … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Wear protective gloves.** Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If on skin: Wash with plenty of water/...** … Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate, or may recommend an alternative agent in exceptional cases if water is clearly inappropriate. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. - Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate. **If skin irritation occurs: Get medical advice/attention.** - Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate. **Take off contaminated clothing and wash it before reuse.**		

C.4.5 EYE DAMAGE/IRRITATION
(Classified in Accordance with Appendix A.3 of this Section)

Pictogram
Corrosion

Hazard category	Signal word	Hazard statement	
1	Danger	Causes serious eye damage	

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wear eye protection/face protection. Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.** **Immediately call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice.		

C.4.5 EYE DAMAGE/IRRITATION (CONTINUED)
(Classified in Accordance with Appendix A.3 of this Section)

Hazard category	Signal word	Hazard statement	Pictogram
2A	Warning	Causes serious eye irritation	Exclamation mark 

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wash … thoroughly after handling. … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Wear eye protection/face protection.** Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.** **If eye irritation persists: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.		

C.4.5 EYE DAMAGE/IRRITATION (CONTINUED)
(Classified in Accordance with Appendix A.3 of this Section)

Pictogram
No Pictogram

Hazard category	**Signal word**	**Hazard statement**
2B	Warning	Causes eye irritation

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Wash … thoroughly after handling. … Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling.	**If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.** **If eye irritation persists: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.		

C.4.6 SENSITIZATION - RESPIRATORY
(Classified in Accordance with Appendix A.4 of this Section)

Pictogram
Health hazard

Hazard category	Signal word	Hazard statement
1 (including both sub-categories 1A and 1B)	Danger	May cause allergy or asthma symptoms or breathing difficulties if inhaled

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Avoid breathing dust/fume/gas/mist/ vapors/spray. Chemical manufacturer, importer, or distributor to specify applicable conditions. **[In case of inadequate ventilation] wear respiratory protection.** Chemical manufacturer, importer, or distributor to specify equipment. *- text in square brackets may be used if additional information is provided with the chemical at the point of use that explains what type of ventilation would be adequate for safe use.*	**If inhaled: Remove person to fresh air and keep comfortable for breathing.** **If experiencing respiratory symptoms: Call a poison center/doctor/…** … Chemical manufacturer, importer, or distributor to specify the appropriate source of emergency medical advice.		**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.7 SENSITIZATION - SKIN
(Classified in Accordance with Appendix A.4 of this Section)

Pictogram
Exclamation mark

Hazard category	Signal word	Hazard statement
1 (including both sub-categories 1A and 1B)	Warning	May cause an allergic skin reaction

Precautionary statements

Prevention	Response	Storage	Disposal
Avoid breathing dust/fume/gas/mist/vapors/spray. Chemical manufacturer, importer, or distributor to specify applicable conditions. **Contaminated work clothing must not be allowed out of the workplace.** **Wear protective gloves.** Chemical manufacturer, importer, or distributor may further specify type of equipment where appropriate.	**If on skin: Wash with plenty of water/...** ... Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate, or may recommend an alternative agent in exceptional cases if water is clearly inappropriate. **If skin irritation or rash occurs: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate. **Specific treatment (see ... on this label)** ... Reference to supplemental first aid instruction. Chemical manufacturer, importer, or distributor may specify a cleansing agent if appropriate. **Take off contaminated clothing and wash it before reuse.**		**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.8 GERM CELL MUTAGENICITY
(Classified in Accordance with Appendix A.5 of this Section)

Pictogram
Health hazard

Hazard category	Signal word	Hazard statement
1A and 1B	Danger	May cause genetic defects <...>
2	Warning	Suspected of causing genetic defects <...>

< > *(state route of exposure if no other routes of exposure cause the hazard)*

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Obtain special instructions before use. **Do not handle until all safety precautions have been read and understood.** **Wear protective gloves/protective clothing/eye protection/face protection/hearing protection/...** Chemical manufacturer, importer, or distributor to specify the appropriate personal protective equipment.	**If exposed or concerned: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

C.4.9 CARCINOGENICITY
(Classified in Accordance with Appendix A.6 of this Section)

Pictogram
Health hazard

Hazard category	**Signal word**	**Hazard statement**
1A and 1B	Danger	May cause cancer <...>
2	Warning	Suspected of causing cancer <...>

< > *(state route of exposure if no other routes of exposure cause the hazard)*

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Obtain special instructions before use. **Do not handle until all safety precautions have been read and understood.** **Wear protective gloves/protective clothing/eye protection/face protection/hearing protection/...** Chemical manufacturer, importer, or distributor to specify the appropriate personal protective equipment.	**If exposed or concerned: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container or both.

Note: If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, information is required on the SDS for a product; however, a label warning is optional. If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an SDS and a label is required and the information must be included on each.