UNITED NATIONS

ST

Secretariat

Distr.
GENERAL

ST/SG/AC.10/C.4/2001/23
26 October 2001

ENGLISH ONLY

COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS
Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals
(Second session, 12 -14 December 2001, agenda item 3)

GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Chapters 3.5-3.10

Transmitted by the Inter-Organization Programme for the Sound Management of Chemicals (IOMC)

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Chapter 3.5

Germ cell Mutagenicity

DEFINITIONS AND GENERAL CONSIDERATIONS

1. 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.

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

3. 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.

4. 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.

CLASSIFICATION CRITERIA FOR SUBSTANCES

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

CATEGORY 1:

CHEMICALS KNOWN TO INDUCE HERITABLE MUTATIONS OR TO BE REGARDED AS IF THEY INDUCE HERITABLE MUTATIONS IN THE GERM CELLS OF HUMANS

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

Criterion: Positive evidence from human epidemiological studies**.**

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

Criteria:

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

CATEGORY 2:

CHEMICALS 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:

- Somatic cell mutagenicity tests *in vivo*, in mammals; or
- Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

NOTE:

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

Specific Considerations

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

7. 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.

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

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

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

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

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

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

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

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

12. Examples of genotoxicity tests in somatic cells are:

Liver Unscheduled DNA Synthesis (UDS) *in vivo* (OECD 486)
Mammalian bone marrow sister chromatid exchanges (SCE)

13. Examples of *in vitro* mutagenicity tests are:

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

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

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of mixtures when data are available for the complete mixture

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

Classification of mixtures when data are not available for the complete mixture

Bridging principles

16. Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

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

Batching

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

Substantially similar mixtures

19. Given the following:

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

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

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

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

Table 1: Cut-off values/concentration limits of ingredients of a mixture classified as germ cell mutagens that would trigger classification of the mixture.

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

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

HAZARD COMMUNICATION

Allocation of label elements

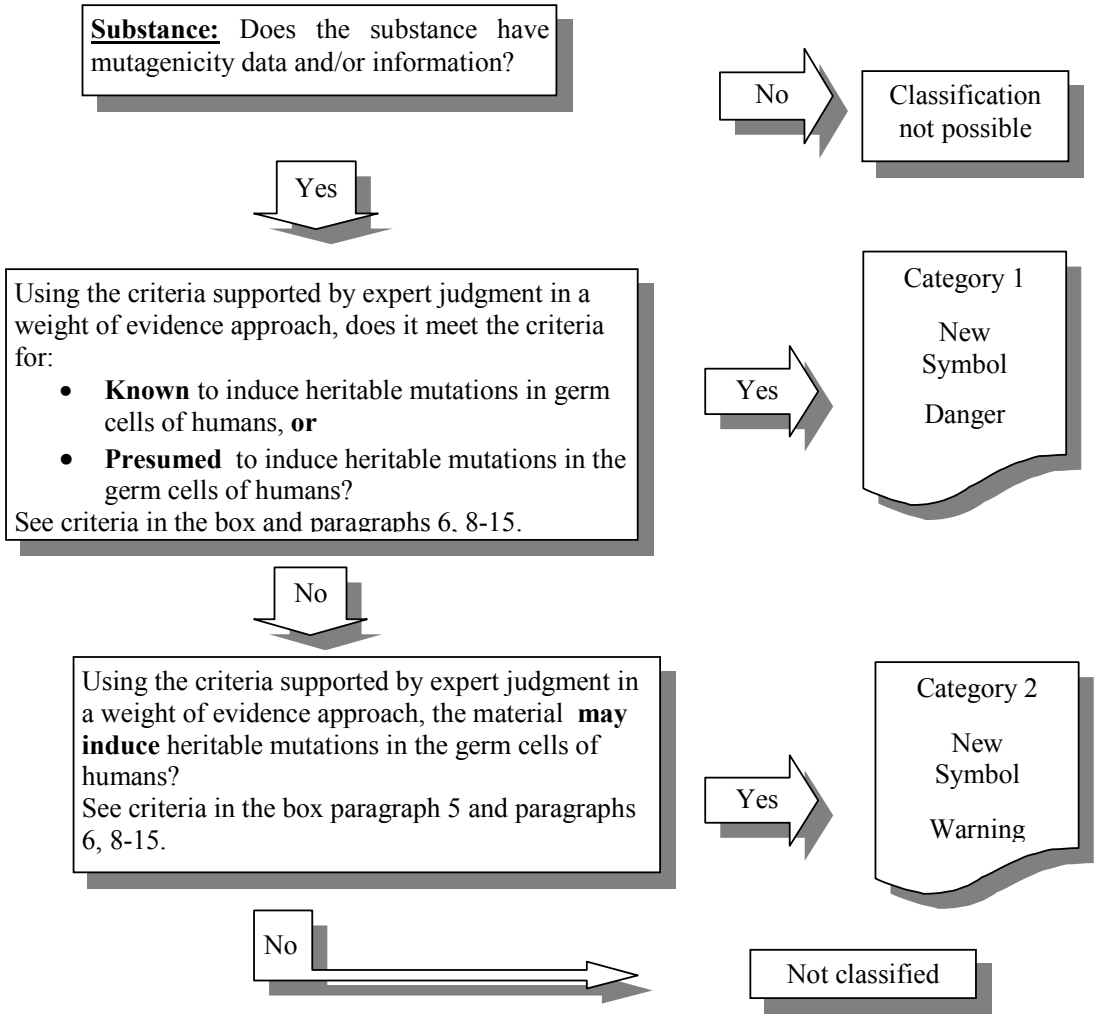
21. General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures classified as germ cell mutagens based on the criteria in this chapter.

Table 2: Label elements of germ cell mutagenicity

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

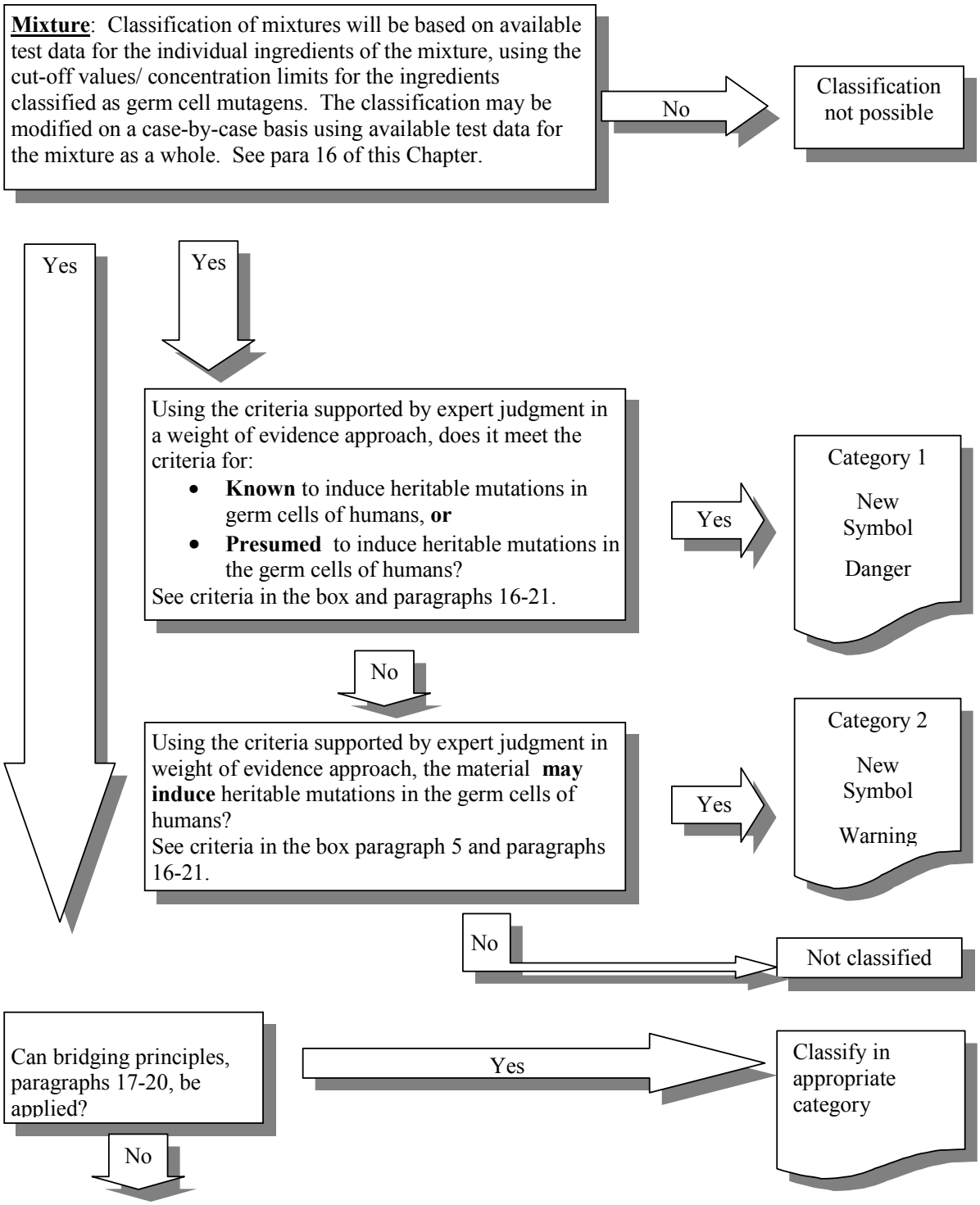
22. DECISION LOGIC AND GUIDANCE [1]

Substances



[1] *The decision logic and guidance which follows is not part of the agreed text on the harmonised classification system developed by the OECD Task Force-HCL, but has been provided here as additional guidance on classification of substances and mixtures for germ call mutagenicity.*

Mixtures



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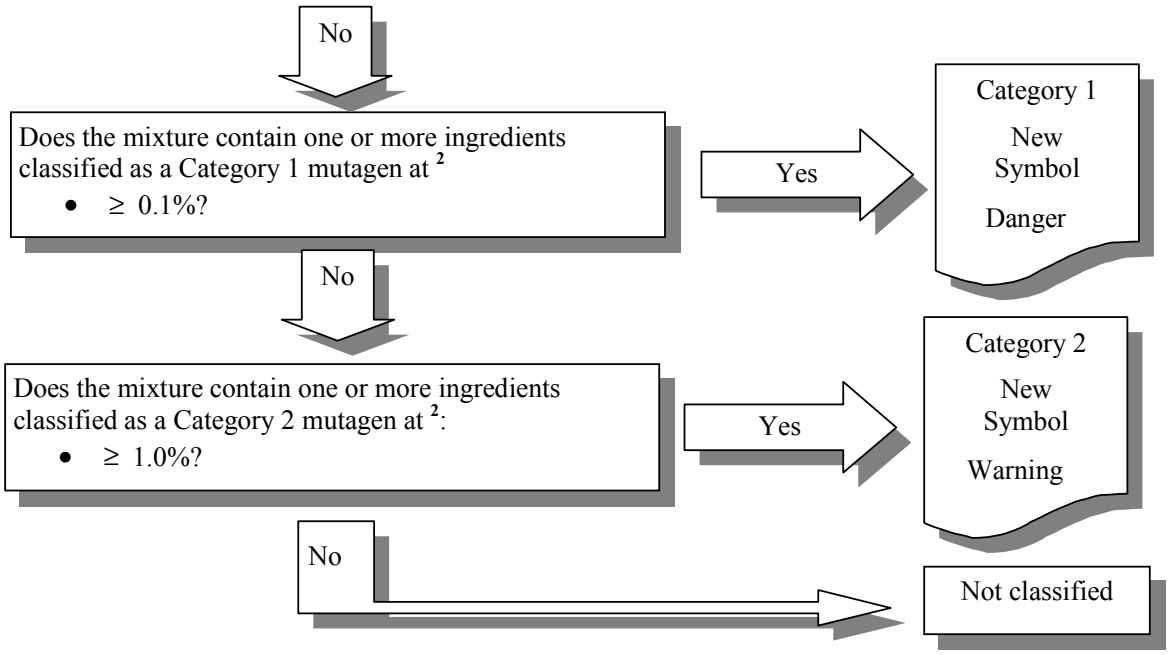

Note on the implications of the mutagenic properties of a chemical for its potential classification as a carcinogen [3]

23. It is increasingly accepted that the process of chemical-induced tumorigenesis in man and animals involves genetic changes in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of chemicals in somatic and/or germ cells of mammals *in vivo* may have implications for the potential classification of these chemicals as carcinogens (See also Carcinogenicity, Chapter 3.6, paragraph 10).

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[2] *See "The Use of Cut-off Values/Concentration Limits" in Chapter 1.2 and Table 1 of this Chapter.*

[3] *The text which follows is not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL, but has been provided here as additional guidance.*

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Chapter 3.6

Carcinogenicity

DEFINITIONS AND GENERAL CONSIDERATIONS

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

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

CLASSIFICATION CRITERIA FOR SUBSTANCES

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

CATEGORY 1: KNOWN OR PRESUMED HUMAN CARCINOGENS

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

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

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

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

Classification: Category 1 (A and B) Carcinogen

CATEGORY 2: **SUSPECTED HUMAN CARCINOGENS**

The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1.

Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Classification: Category 2 Carcinogen

Specific considerations

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

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

6. **Strength of evidence** involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms "sufficient" and "limited" are used here as they have been defined by the International Agency for Research on Cancer (IARC) and are outlined in the section *Background Guidance*: paragraphs 23 – 26 of this chapter.

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

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

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

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

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

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

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

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

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

13. 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.

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

15. The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation Carcinogenic potency as used here does not preclude risk assessment. (See Annex 12: *Areas to be Considered for Future Work*). The proceedings of a WHO/IPCS working group to harmonised risk assessment for carcinogenicity points to a number of scientific questions arising for classification of chemicals e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens.

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of mixtures when data are available for the complete mixture

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

Classification of mixtures when data are not available for the complete mixture

Bridging Principles

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

the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

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

Batching

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

Substantially similar mixtures

20. Given the following:

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

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

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

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

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

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

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

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

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

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

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

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

HAZARD COMMUNICATION ELEMENTS

Allocation of label elements

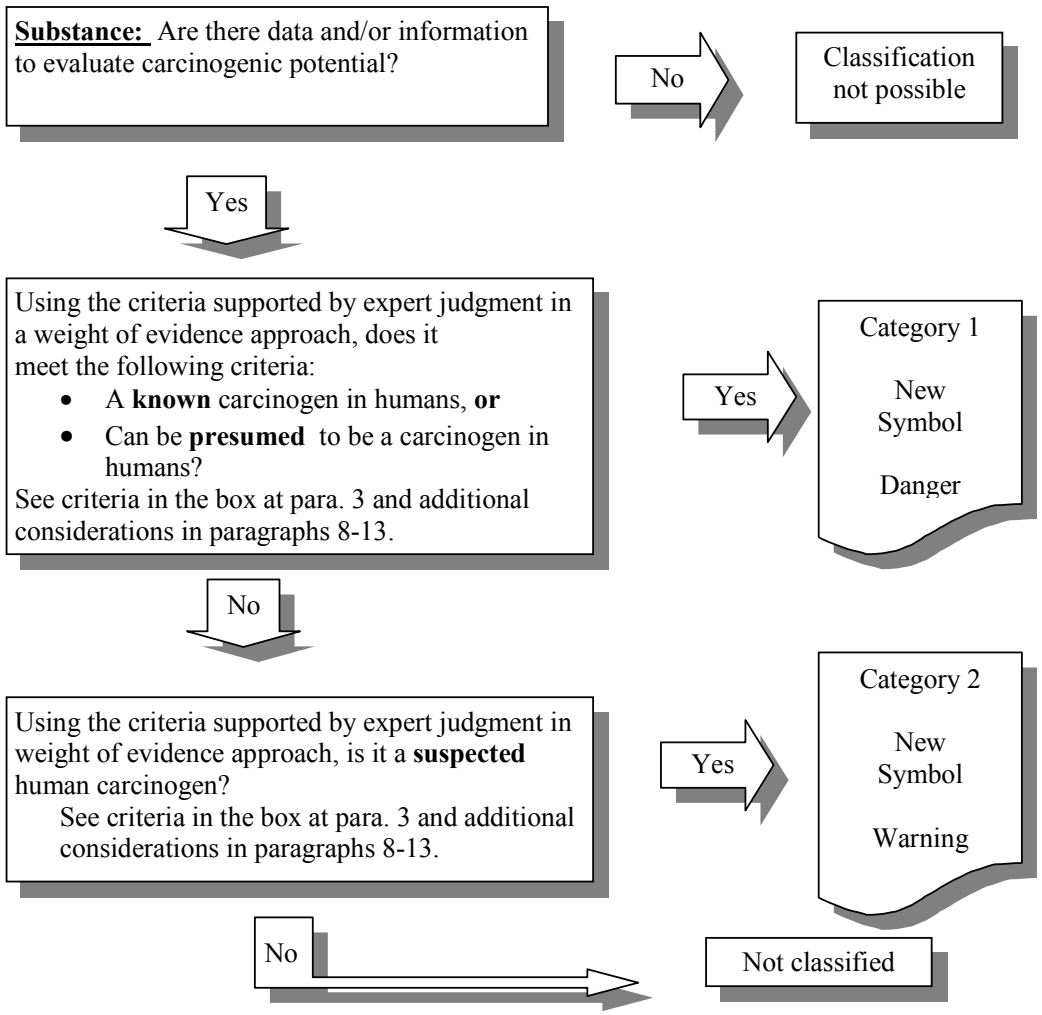
22. General and specific considerations concerning labelling requirements are provided in *Hazard Communication:* Labelling (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 2 below presents specific label elements for substances and mixtures that are classified as carcinogenic based on the criteria set forth in this chapter.

Table 2: Label elements for carcinogenicity

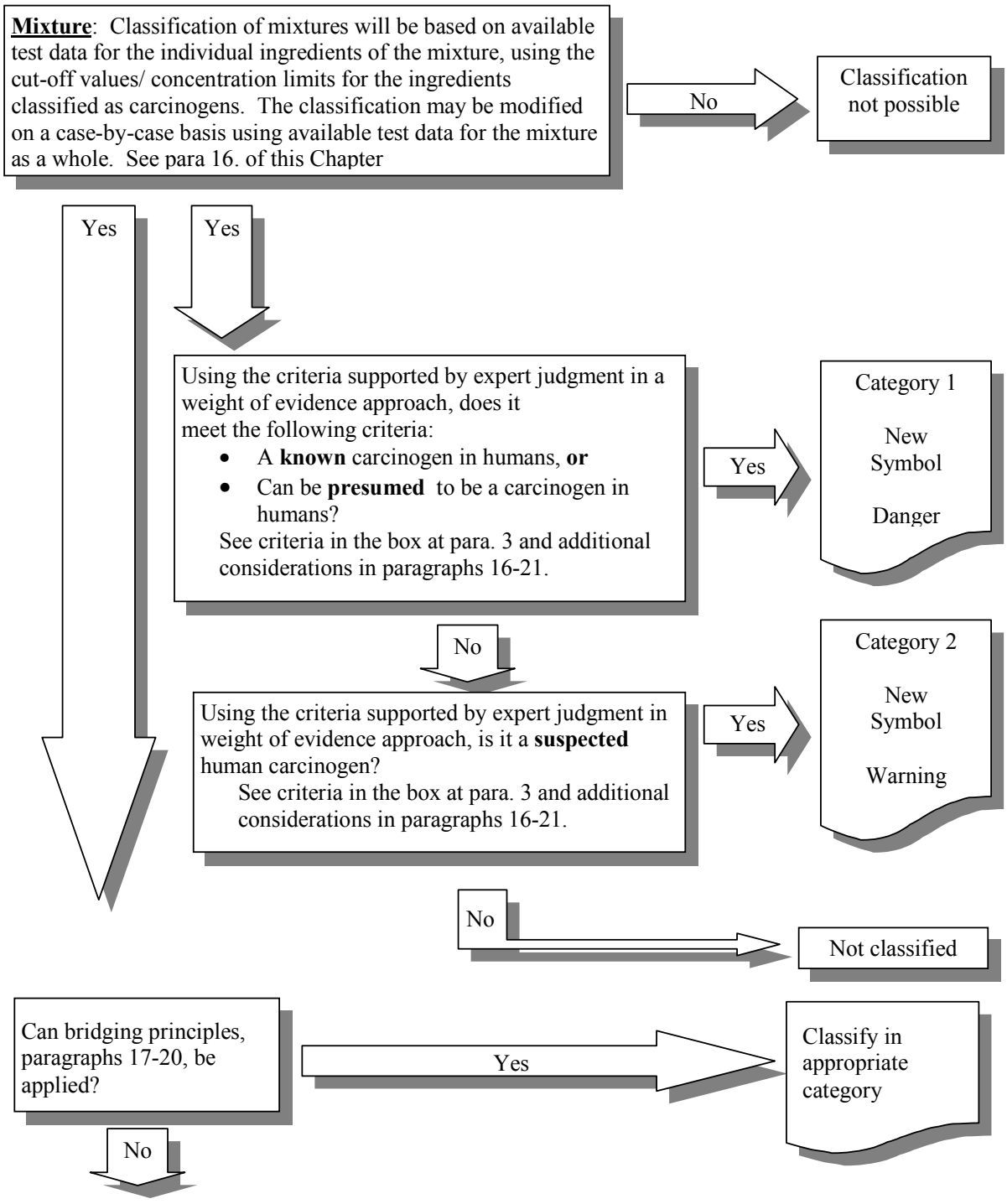
	Category 1A	**Category 1B**	**Category 2**
Symbol	New health hazard symbol	New health hazard symbol	New health hazard symbol
Signal Word	Danger	Danger	Warning
Hazard Statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May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

23. **Decision Logic for Carcinogenicity**[2]

Substances



[2] *The decision logic and guidance which follows is not part of the agreed text on the harmonised classification system developed by the OECD Task Force-HCL, but has been provided here as additional guidance on classification of substances and mixtures for carcinogenicity.*



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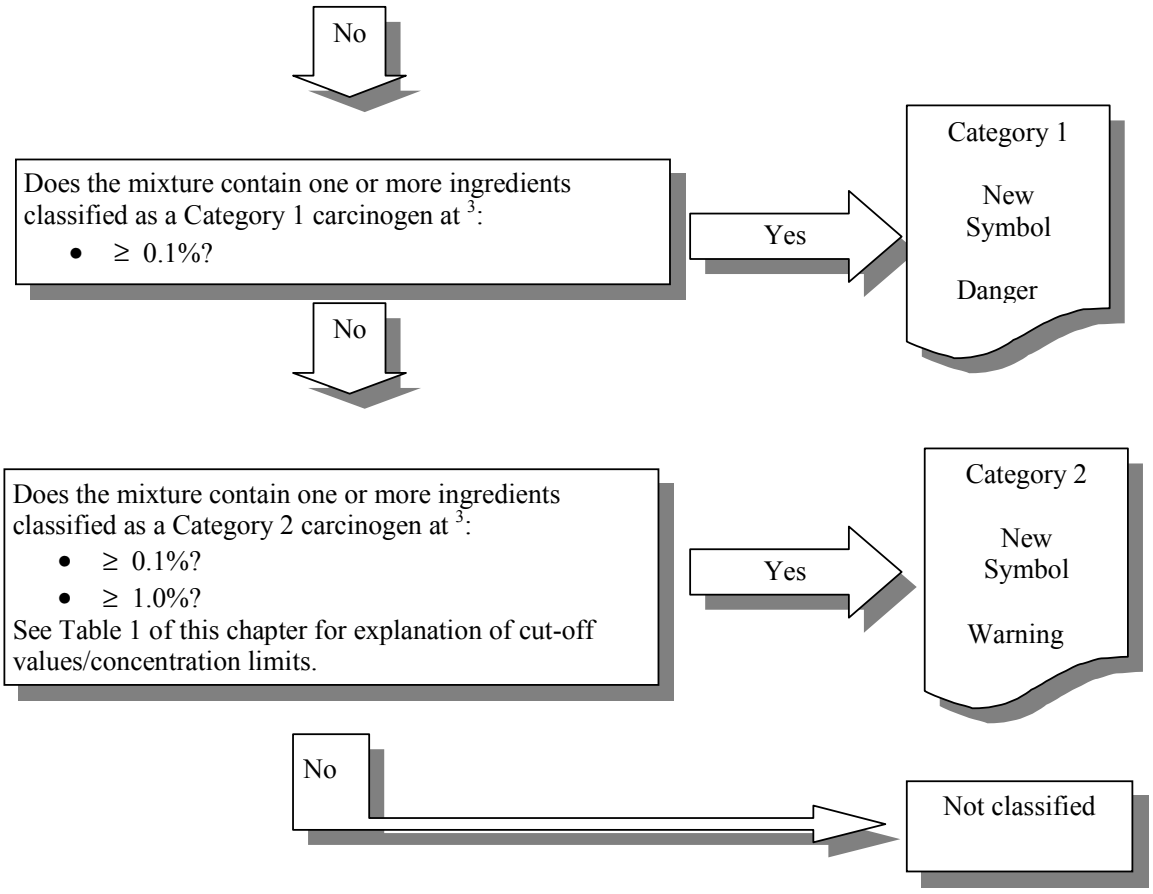

[3] *See "The use of Cut-off Values/Concentration Limits" in Chapter 1.2.*

Background Guidance [4]

24. Excerpts from the International Agency for Research on Cancer (IARC) Evaluation of the Strength of Evidence for Carcinogenicity Arising from Human and Experimental Data Adopted by follow as paragraphs 24 – 26. 5

Carcinogenicity in humans

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

- Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;
- Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

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

Carcinogenicity in experimental animals

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

- Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols;
- Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset;
- Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

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

[5] *See para 6 of this Chapter.*

EXAMPLES

Under Review

Chapter 3.7

Reproductive Toxicity

DEFINITIONS AND GENERAL CONSIDERATIONS

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

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

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

Adverse effects on reproductive ability or capacity

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

Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately. (See paragraph 9 of this Chapter) This is because it is desirable to be able to classify chemicals specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

Adverse effects on development of the offspring

4. Taken in its widest sense, developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women and men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

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

CLASSIFICATION CRITERIA FOR SUBSTANCES

Hazard categories

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

CATEGORY 1: KNOWN OR PRESUMED HUMAN REPRODUCTIVE OR DEVELOPMENTAL TOXICANT

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

CATEGORY 1A: KNOWN to have produced an adverse effect on reproductive ability or capacity or on development in humans. The placing of the substance in this category is largely based on evidence from humans.

CATEGORY 1B: PRESUMED to produce an adverse effect on reproductive ability or capacity or on development in humans. The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of specific reproductive toxicity in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

CATEGORY 2: SUSPECTED HUMAN REPRODUCTIVE OR DEVELOPMENTAL TOXICANT

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

EFFECTS ON OR VIA LACTATION

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

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

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

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

Specific Considerations

(A) Basis of classification

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

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

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

(B) Weight of evidence

9. Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scarce.

The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also paragraph 8).

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

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

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

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

(C) Maternal toxicity

14. Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. So, in the interpretation of the developmental outcome to decide classification for developmental

effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, should be used to determine the degree of influence that should be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus should be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

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

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

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

Maternal Mortality: An increased incidence of mortality among the treated dams over the controls should be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10% is considered excessive and the data for that dose level should not normally be considered for further evaluation.

Mating Index (no. animals with seminal plugs or sperm/no. mated x 100)[2]

Fertility Index (no. animals with implants/no. of matings x 100) [2]

Gestation Length (if allowed to deliver)

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

Body Weight and Body Weight Change: Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight should be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

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

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

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

(D) Animal and experimental data

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

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

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

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

22. 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.

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

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

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

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

27. Further discussions are needed on the inclusion within the criteria of a specified dose as a limit dose. (See Annex 12: Possible Areas for Future Work).

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of mixtures when data are available for the complete mixture

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

Classification of mixtures when data are not available for the complete mixture

Bridging Principles

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

Dilution

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

Batching

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

Substantially similar mixtures

32. Given the following:

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

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

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

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

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

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

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

Table 1 : Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants that would trigger classification of the mixture.[3]

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

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

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

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

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

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

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

34. Harmonised criteria for the classification of mixtures containing substances which have effects on lactation have to date not been developed. The data base for this hazard category is extremely limited, and experience will have to be gained in using the category in the harmonised system before the issue of classification of mixtures containing components which can contaminate breast milk can be addressed. This issue should be considered in the future (see Annex 12: Possible Areas of Future Work).

HAZARD COMMUNICATION ELEMENTS

35. General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

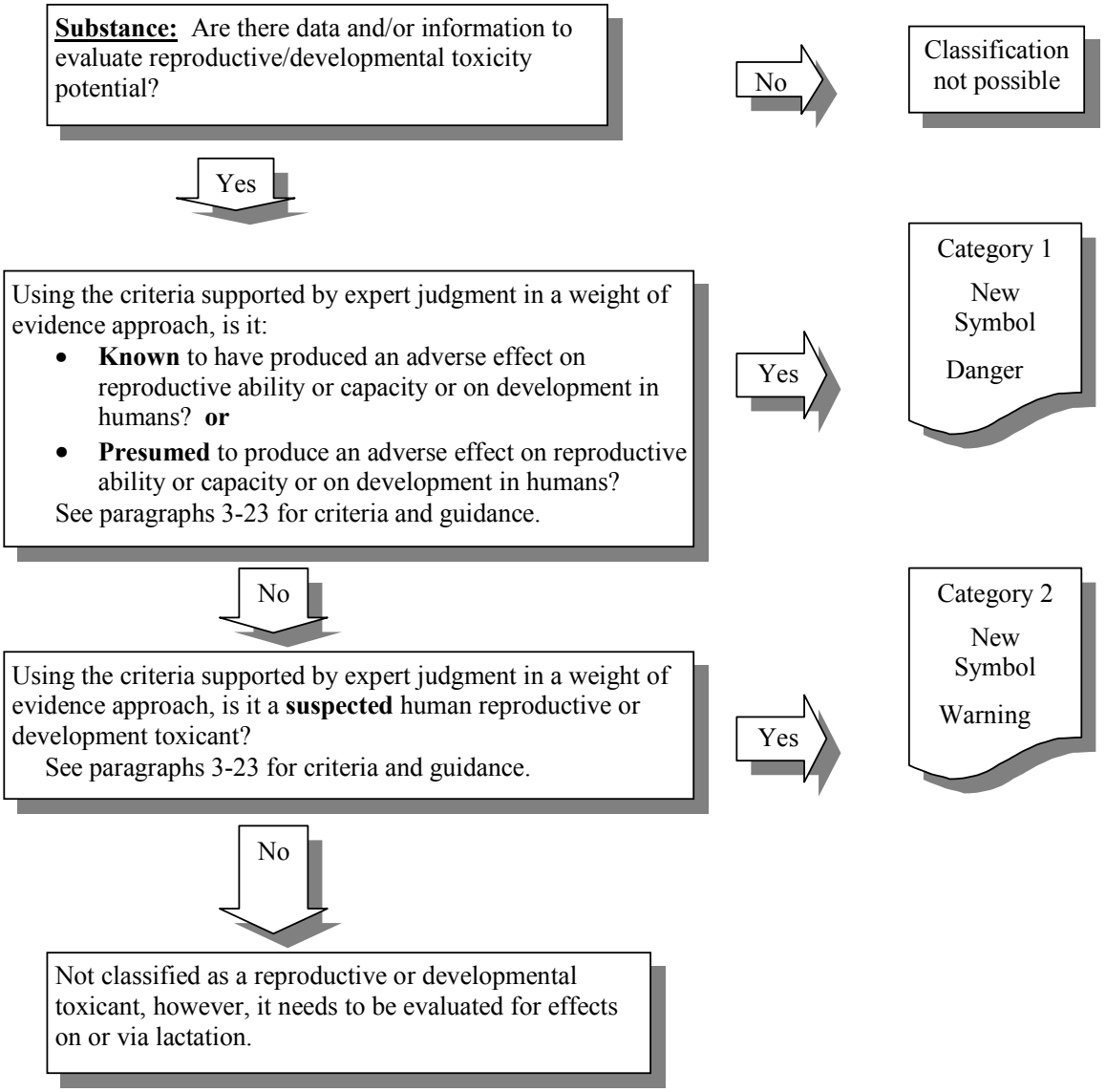
Table 2: Label elements for reproductive toxicity

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

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

36. **DECISION LOGIC FOR CLASSIFICATION OF REPRODUCTIVE TOXICITY**[5]

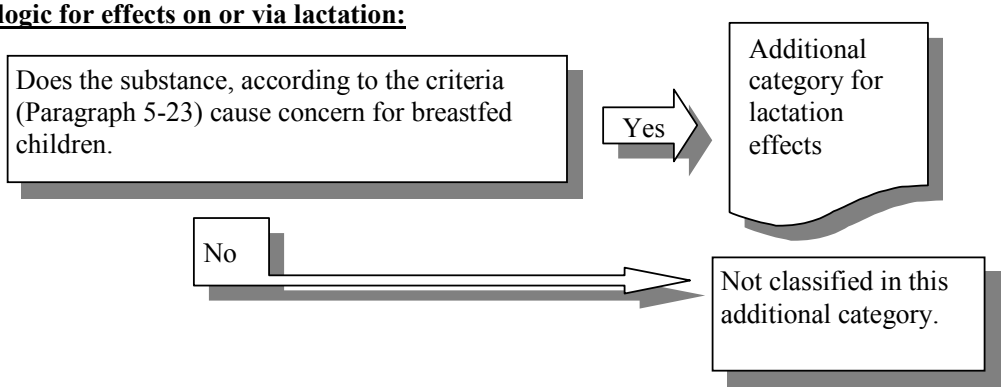
Substance (See also decision logic for effects on or via lactation)



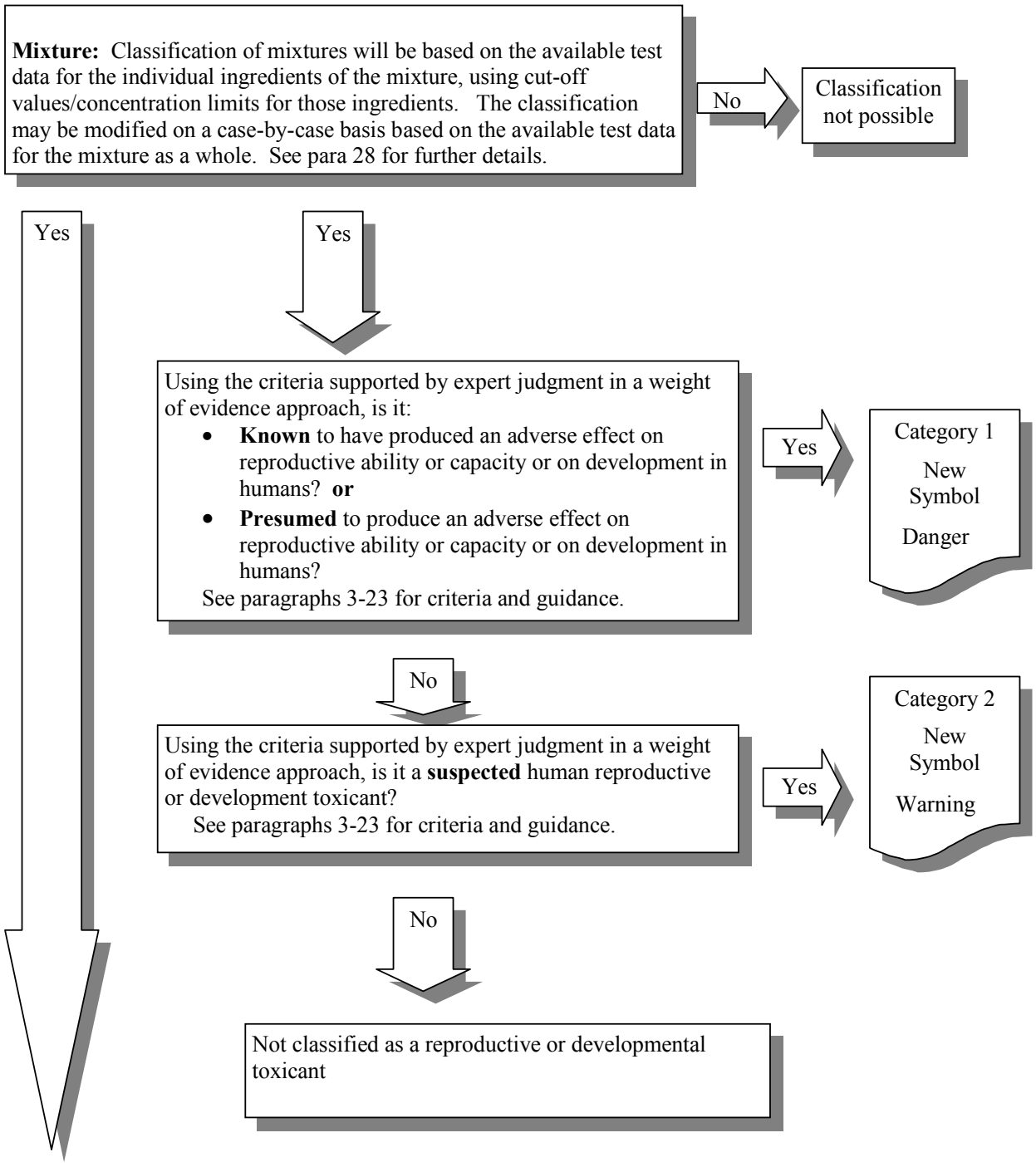
Continued on next page

[5] *The decision logics which follow are not part of the agreed text on the harmonised classification system developed by the OECD Task Force-HCL, but has been provided here as additional guidance on classification of substances and mixtures for reproductive toxicity.*

Decision logic for effects on or via lactation:



Mixtures



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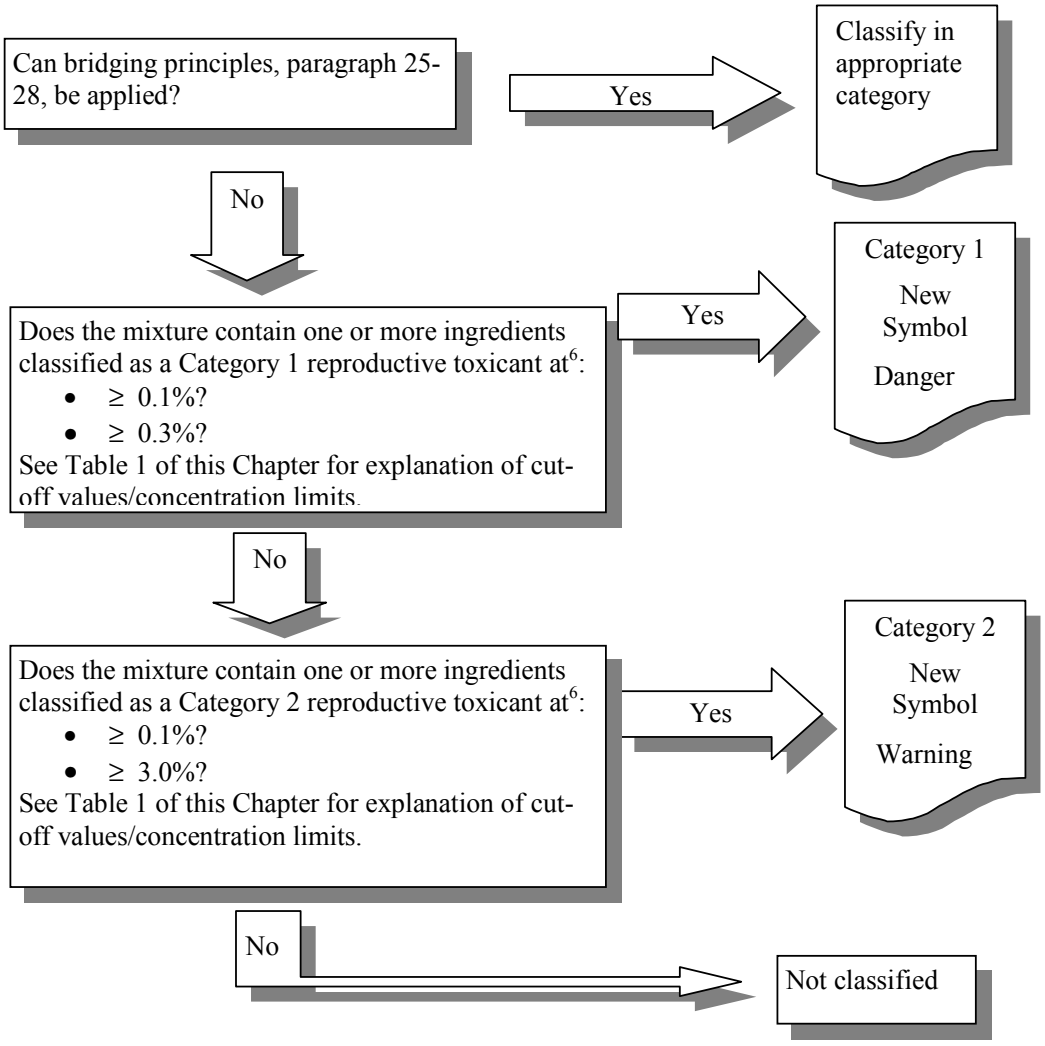


[6] *See "The use of Cut-off Values/Concentration Limits" in Chapter 1.2.*

Chapter 3.8

Specific target organ systemic toxicity - Single exposure

DEFINITIONS AND GENERAL CONSIDERATIONS

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

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

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

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

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

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

CLASSIFICATION CRITERIA FOR SUBSTANCES

7. Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see paragraphs 17-21). Then substances are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

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

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

- reliable and good quality evidence from human cases or epidemiological studies; or,
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see paragraphs 17-21) 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

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see paragraphs 17-21) in order to help in classification.
In exceptional cases, human evidence can also be used to place a substance in Category 2 (see paragraph 12).

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

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

Specific Considerations

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

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

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

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

Effects considered to support classification

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

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

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

- Morbidity resulting from single exposure;
- Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell);
- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;
- Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;
- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;
- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;

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

Effects considered not to support classification

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

- Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;
- Small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;
- Changes in organ weights with no evidence of organ dysfunction;
- Adaptive responses that are not considered toxicologically relevant;
- Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification;
- Where there are only local effects, at the site of administration for the routes tested, and especially when adequate testing by other principal routes show lack of specific target organ/systemic toxicity.

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

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

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

19. The guidance value ranges proposed for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 1 below:

Table 1: Guidance value ranges for single-dose exposures

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

20. It is important to recognise that the guidance values and ranges mentioned in paragraph 19 above are intended only for guidance purposes, i.e., to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.

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

Other considerations

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

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

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

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

CLASSIFICATION CRITERIA FOR MIXTURES

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

Classification of mixtures when data are available for the complete mixture

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

Classification of mixtures when data are not available for the complete mixture

Bridging principles

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

Dilution

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

Batching

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

Concentration of highly toxic mixtures

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

Interpolation within one toxicity category

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

Substantially similar mixtures

33. Given the following:

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

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

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

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

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

Aerosols

34. An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolised form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolised mixtures for inhalation toxicity should be considered separately.

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

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

Table 2: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture[1]

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

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

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

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

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

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

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

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

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

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

HAZARD COMMUNICATION

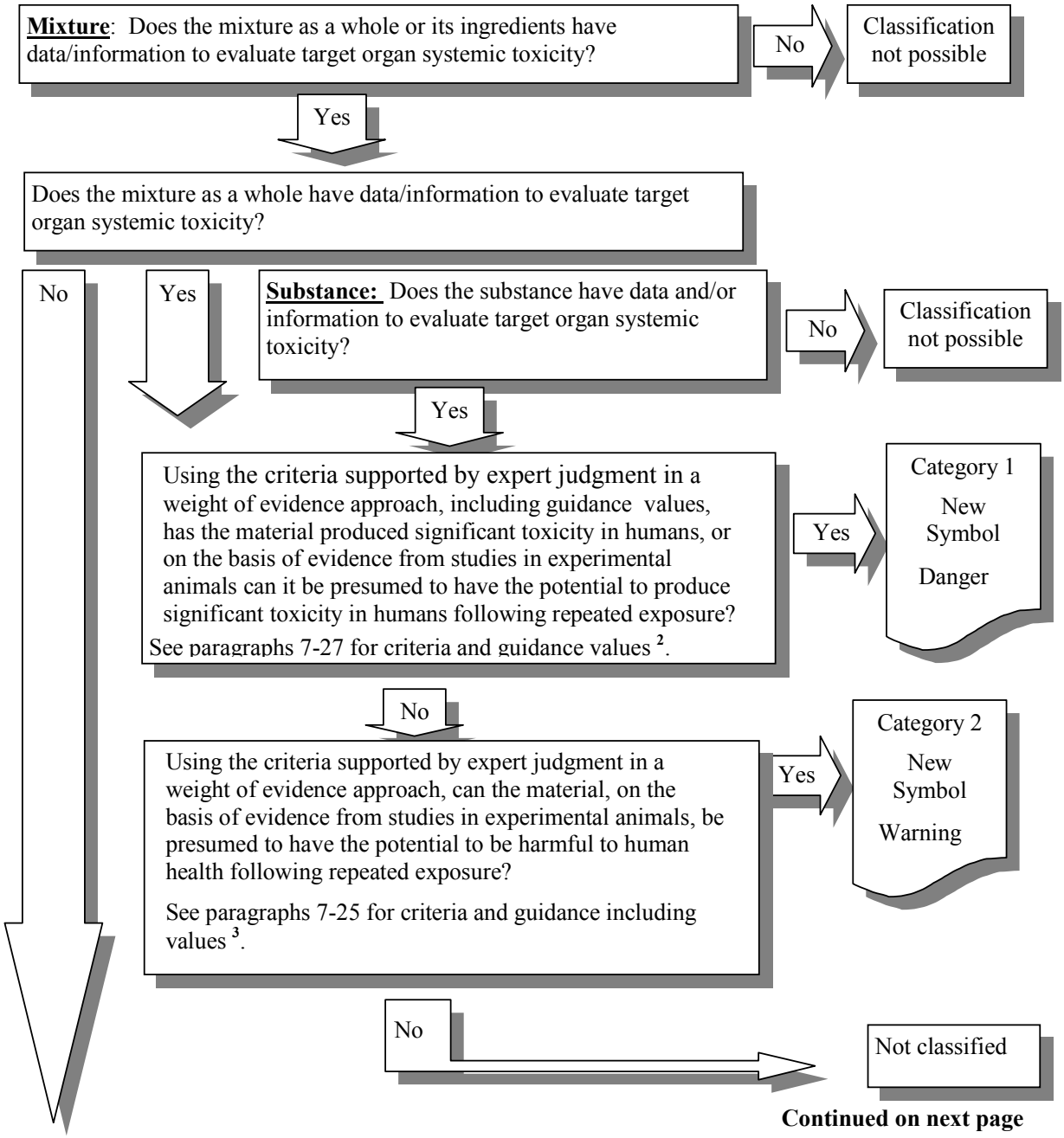
Allocation of label elements

39. General and specific considerations concerning labelling requirements are provided in *Hazard* Communication*: Labelling* (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3: Label elements for target organ systemic toxicity after single exposure

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

40. **DECISION LOGIC FOR TARGET ORGAN SYSTEMIC TOXICITY FROM SINGLE EXPOSURE[2]**



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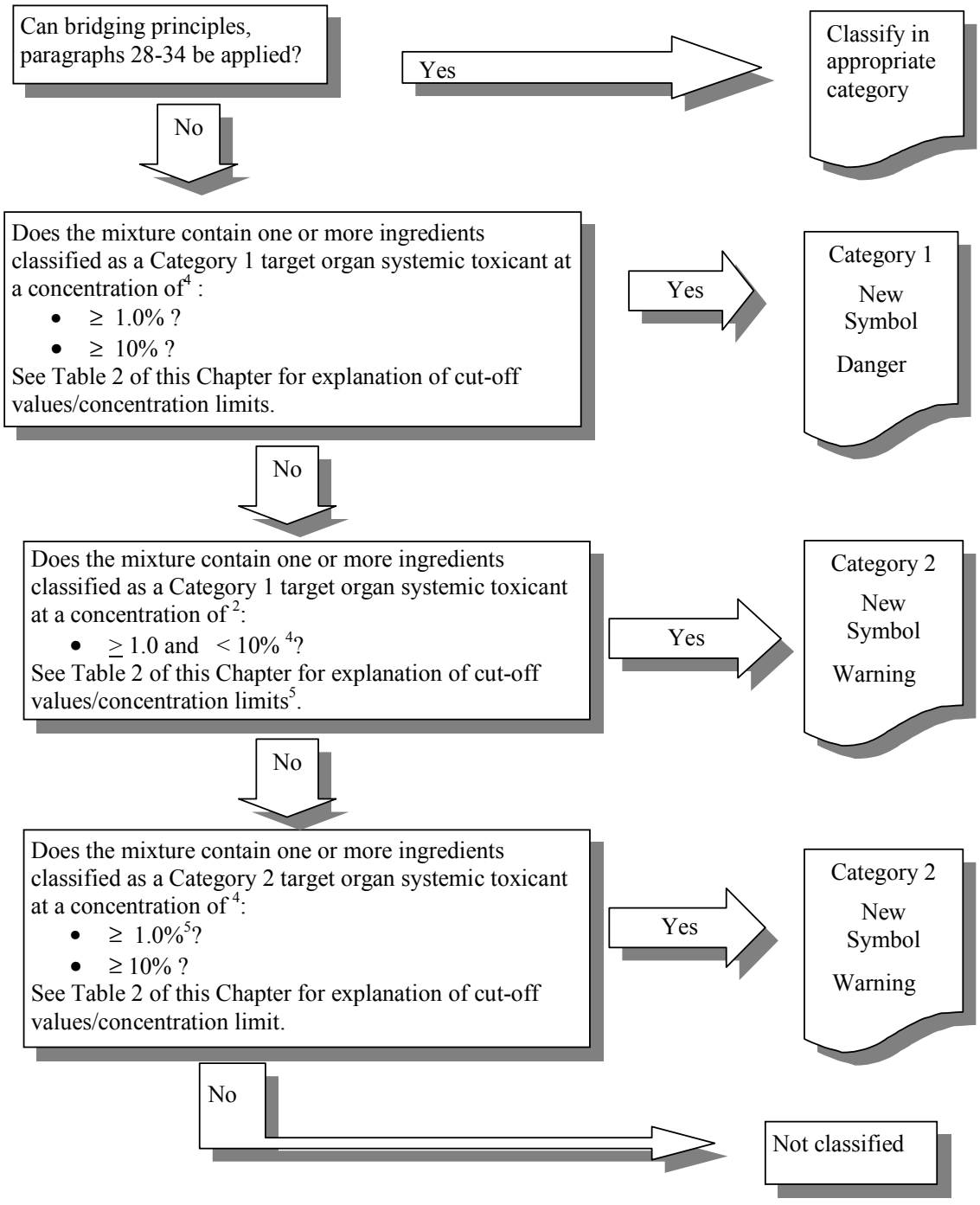
[2] *The decision logic in paragraph 40 is not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL but has been provided here as additional guidance.*

[3] *See also paragraph 7 in this Chapter and "The Use of Cut-off Values/Concentration Limits" in Chapter 1.2*



[4] *See paragraphs 7-25 of this Chapter and "The Use of Cut-off Values/Concentration Limits" in Chapter 1.2.*

[5] *See paragraphs 35-38 and Table 2 for explanation and guidance.*

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Chapter 3.9

Specific target organ systemic toxicity - Repeated exposure

DEFINITIONS AND GENERAL CONSIDERATIONS

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

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

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

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

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

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

CLASSIFICATION CRITERIA FOR SUBSTANCES

7. Substances are classified as specific target organ/systemic toxicant by expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see paragraphs 17-25), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

CATEGORY 1: SUBSTANCES THAT HAVE PRODUCED SIGNIFICANT TOXICITY IN HUMANS, OR THAT, ON THE BASIS OF EVIDENCE FROM STUDIES IN EXPERIMENTAL ANIMALS CAN BE PRESUMED TO HAVE THE POTENTIAL TO PRODUCE SIGNIFICANT TOXICITY IN HUMANS FOLLOWING REPEATED EXPOSURE.

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

- reliable and good quality evidence from human cases or epidemiological studies; or,
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see paragraphs 17-25) 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 EXPOSURE.

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see paragraphs 17-25) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see paragraph 12).

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

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

Specific considerations

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

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

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

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

Effects considered to support classification

13. Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect.

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

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

- 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 accumulation of effect owing to the ability of the de-toxification process becoming overwhelmed by repeated exposure to the substance or its metabolites.

- Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell).
- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters.
- Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination.
- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity.
- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver).
- Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

Effects considered not to support classification

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

- Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate “significant" toxicity.
- Small changes in clinical biochemistry, haematology or urinalysis parameters and /or transient effects, when such changes or effects are of doubtful or minimal toxicological importance.
- Changes in organ weights with no evidence of organ dysfunction.
- Adaptive responses that are not considered toxicologically relevant.
- Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification.

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

17. 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.

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

effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimise the test objective - and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

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

20. 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.

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

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

Table 1: Guidance values to assist in Category 1 classification

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

23. 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 2 below would justify classification:

Table 2: Guidance values to assist in Category 2 classification

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

24. It is important to recognise that the guidance values and ranges mentioned in paragraphs 22 and 23 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.

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

Other considerations

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

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

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

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

CLASSIFICATION CRITERIA FOR MIXTURES

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

Classification of mixtures when data are available for the complete mixture

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

Classification of mixtures when data are not available for the complete mixture

Bridging principles

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

Dilution

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

Batching

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

Concentration of highly toxic mixtures

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

Interpolation within one toxicity category

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

Substantially similar mixtures

37. Given the following:

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

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

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

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

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

Aerosols

38. An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolised form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolised mixtures for inhalation toxicity should be considered separately.

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

39. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a target organ/systemic toxicant (specific organ specified), following single exposure, repeat exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 target organ/systemic toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3 below for Category 1 and 2 respectively.

Table 3: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture.[1]

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

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

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

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

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

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

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

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

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

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

HAZARD COMMUNICATION

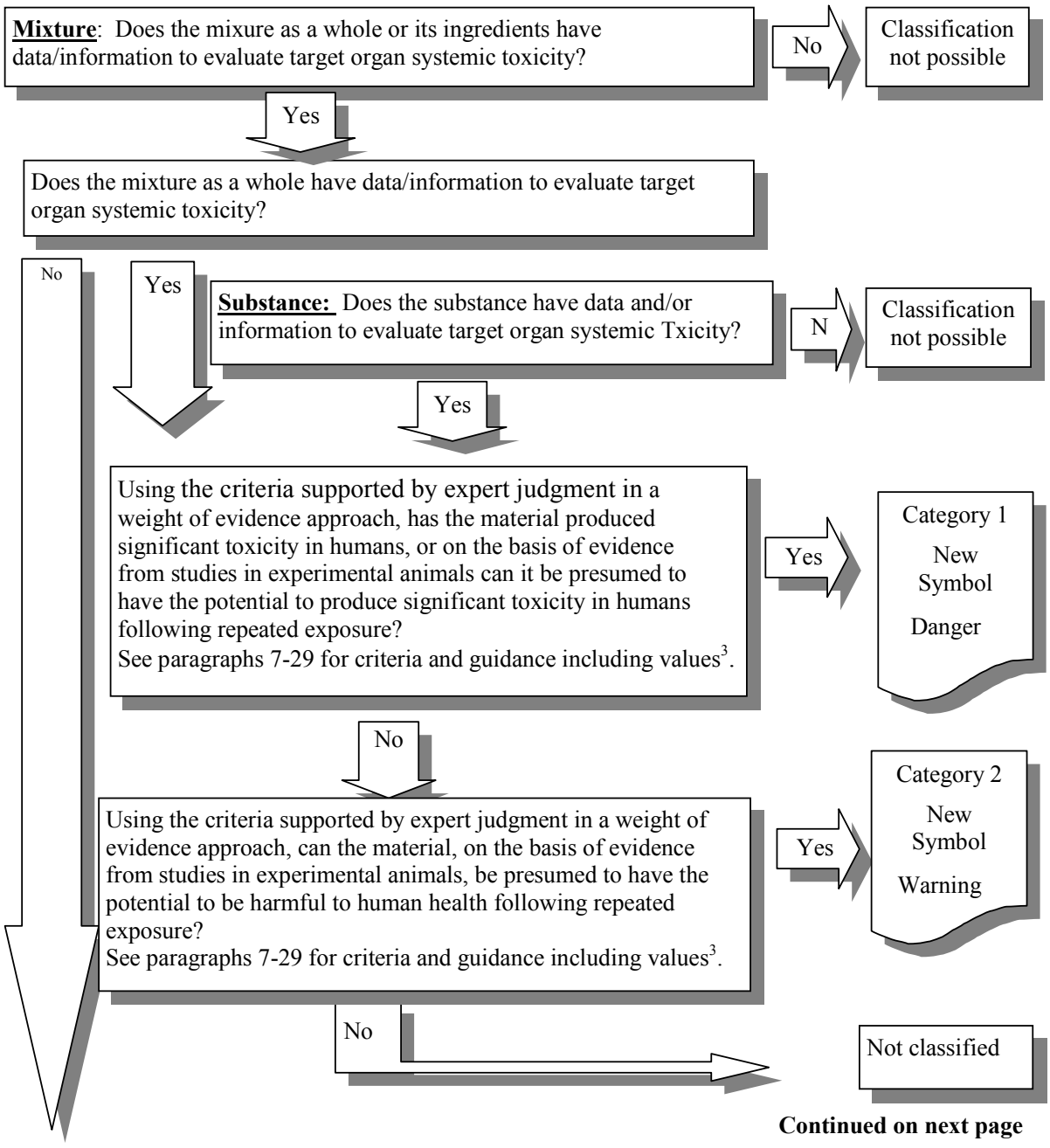
Allocation of label elements

43. General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 4: Label elements for target organ systemic toxicity after repeated exposure

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

44. **DECISION LOGIC FOR CLASSIFICATION OF TARGET ORGAN SYSTEMIC TOXICITY FOLLOWING REPEATED EXPOSURE[2]**



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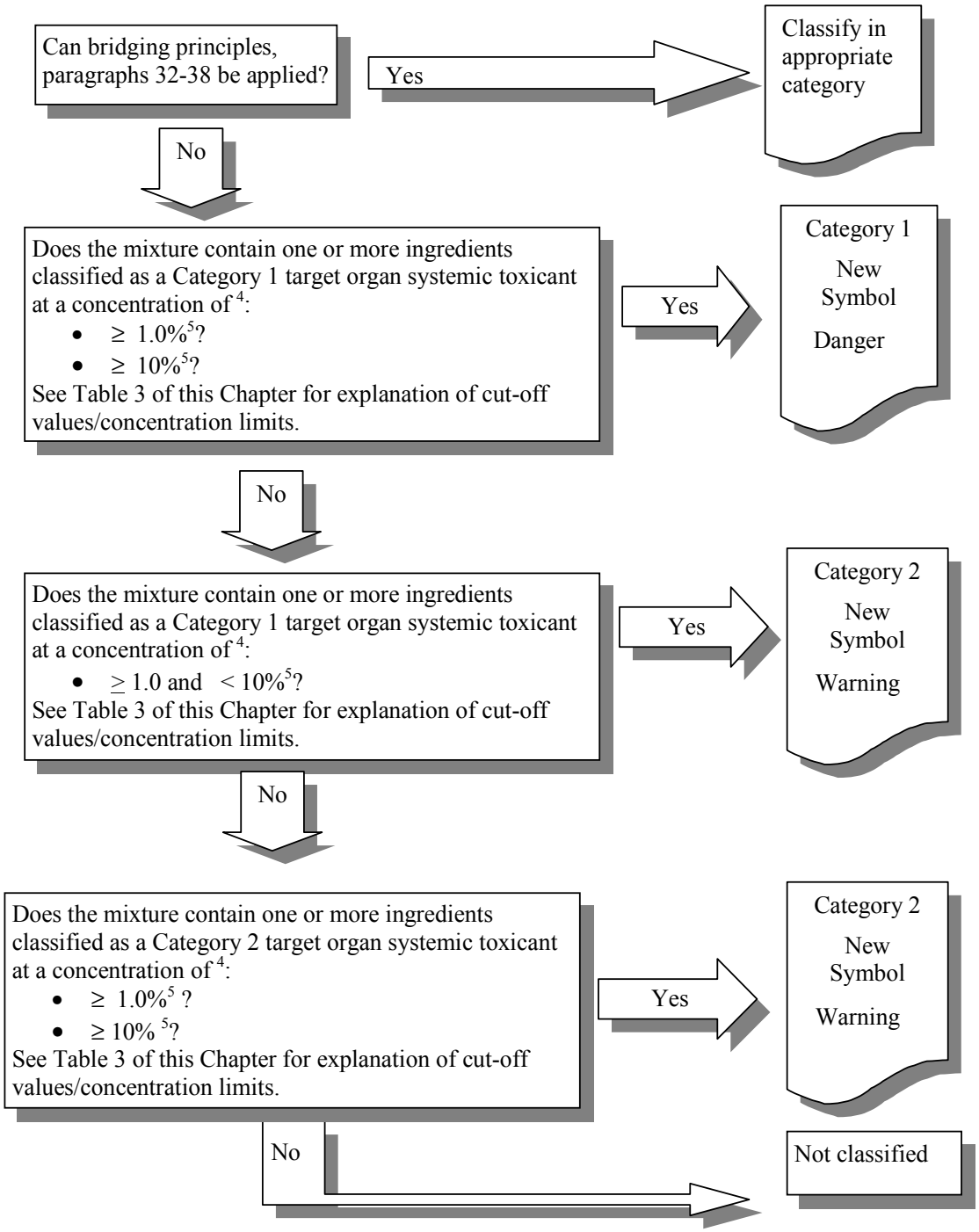
[2] *The decision logic which follows is not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL but has been provided here as additional guidance.*

[3] *In this chapter, see paragraphs 7-29, Tables 1 and 2, and in Chapter 1.2, see "The Use of Cut-off Values/Concentration Limits".*



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[4] *In this chapter, see paragraphs 7-29, Tables 1 and 2, and in Chapter 1.2, see "The Use of Cut-off Values/Concentration Limits".*

[5] *See paragraphs 39-43 and Table 3 for explanation and guidance.*

Chapter 3.10

Hazardous to the aquatic environment

DEFINITIONS AND GENERAL CONSIDERATIONS

1. The basic elements for use within the harmonised system are:

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

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

Acute toxicity

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

Bioaccumulation potential

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

Rapid degradability

5. Environmental degradation may be biotic or abiotic (e.g. hydrolysis) and the criteria used reflect this fact (See paragraph 24). Ready biodegradation can most easily be defined using the OECD biodegradability tests OECD Test Guideline 301 (A - F). A pass level in these tests can be considered as indicative of rapid degradation in most environments. These are freshwater tests and thus the use of the results from OECD Test Guideline 306 which is more suitable for marine environments has also been included. Where such data are not available, a BOD(5 days)/COD ratio > 0.5 is considered as indicative of rapid degradation.

6. Abiotic degradation such as hydrolysis, primary degradation, both abiotic and biotic, degradation in non-aquatic media and proven rapid degradation in the environment may all be considered in

defining rapid degradability. Special guidance on data interpretation is provided in the Guidance Document (Annex 9).

Chronic toxicity

7. Chronic toxicity data are less available than acute data and the range of testing procedures less standardised. Data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), or 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) can be accepted (See also Chapter 3.3.2 of Annex 9). Other validated and internationally accepted tests could also be used. The NOECs or other equivalent L(E)Cx should be used.

Other considerations

8. The harmonised system for classifying chemical substances for the hazards they present to the aquatic environment is based on a consideration of systems existing listed in paragraph 11. The aquatic environment may be considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. To that extent, the proposal does not address aquatic pollutants for which there may be a need to consider effects beyond the aquatic environment such as the impacts on human health etc. The basis, therefore, of the identification of hazard is the aquatic toxicity of the substance, although this may be modified by further information on the degradation and bioaccumulation behaviour.

9. While the scheme is intended to apply to all substances and mixtures, it is recognised that for some substances, e.g. metals, poorly soluble substances etc., special guidance will be necessary.

10. Two Guidance Documents have been prepared to cover issues such as data interpretation and the application of the criteria defined below to such groups of substances. Considering the complexity of this endpoint and the breadth of the application of the system, the Guidance Documents are considered an important element in the operation of the harmonised scheme (see Annexes 9 and 10).

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

CLASSIFICATION CRITERIA FOR SUBSTANCES

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

13. Substances classified under the following criteria will be categorised as 'hazardous to the aquatic environment'. These criteria describe in detail the classification categories. They are diagrammatically summarised in Table 1.

Category: Acute I	**Acute toxicity**	
	96 hr LC50 (for fish)	≤1 mg/L and/or
	48 hr EC50 (for crustacea)	≤1 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/L.
Category: Acute I may be subdivided for some regulatory systems to include a lower band at $L(E)C_{50}$ ≤0 1 mg/L.		
Category: Acute II		
	96 hr LC_{50} (for fish)	>1 - ≤10 mg/L and/or
	48 hr EC_{50} (for crustacea)	>1 - ≤10 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 - ≤10 mg/L.
Category: Acute III		
	96 hr LC_{50} (for fish)	>10 - ≤100 mg/L and/or
	48 hr EC_{50} (for crustacea)	>10 - ≤100 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 - ≤100 mg/L.
Some regulatory systems may extend this range beyond an $L(E)C_{50}$ of 100 mg/L through the introduction of another category.		
Category: Chronic I		
	96 hr LC_{50} (for fish)	≤1 mg/L and/or
	48 hr EC50 (for crustacea)	≤1 mg/L and/or
	72 or 96hr ErC50 (for algae or other aquatic plants)	≤1 mg/L
and the substance is not rapidly degradable and/or the log Kow ≥ 4 (unless the experimentally determined BCF <500).		
Category: Chronic II		
	96 hr LC_{50} (for fish)	>1 to ≤10 mg/L and/or
	48 hr EC_{50} (for crustacea)	>1 to ≤10 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 to ≤10 mg/L
and the substance is not rapidly degradable and/or the log Kow ≥4 (unless the experimentally determined BCF <500), unless the chronic toxicity NOECs are > 1 mg/L.		
Category: Chronic III		
	96 hr LC_{50} (for fish)	>10 to ≤100 mg/L and/or
	48 hr EC_{50} (for crustacea)	>10 to ≤100 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 to ≤100 mg/L
and the substance is not rapidly degradable and/or the log Kow ≥4 (unless the experimentally determined BCF <500) unless the chronic toxicity NOECs are >1 mg/L.		
Category: Chronic IV		
Poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have a log Kow ≥ 4, indicating a potential to bioaccumulate, will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence would include an experimentally determined BCF <500, or a chronic toxicity NOECs > 1 mg/L, or evidence of rapid degradation in the environment.		

Table 1: Classification scheme for substances hazardous to the aquatic environment

Toxicity		**Degradability (note 3)**	**Bioaccumulation (note 4)**	**Classification categories**	
Acute (note 1)	**Chronic (note 2)**			**Acute**	**Chronic**
Box 1 value ≤ 1.00		**Box 5**	**Box 6**	**Category:** **Acute I** **Box 1**	**Category:** **Chronic I** **Boxes 1+5+6** **Boxes 1+5** **Boxes 1+6**
Box 2 1.00 < value ≤ 10.0		lack of rapid degradability	BCF ≥ 500 or, if absent log Kow ≥ 4	**Category:** **Acute II** **Box 2**	**Category:** **Chronic II** **Boxes 2+5+6** **Boxes 2+5** **Boxes 2+6** **Unless Box 7**
Box 3 10.0 < value ≤ 100				**Category:** **Acute III** **Box 3**	**Category:** **Chronic III** **Boxes 3+5+6** **Boxes 3+5** **Boxes 3+6** **Unless Box 7**
Box 4 No acute toxicity **(note 5)**	**Box 7** value > 1.00				**Category:** **Chronic IV** **Boxes 4+5+6** **Unless Box 7**

Notes to Table 1:

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

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

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

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

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

Note 4: *Potential to bioaccumulate, based on an experimentally derived BCF ≥ 500 or, if absent, a log Kow ≥ 4 provided log Kow is an appropriate descriptor for the bioaccumulation potential of the substance. Measured log Kow values take precedence over estimated values and measured BCF values take precedence over log Kow values.*

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

Specific considerations

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

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

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

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

18. Recognition is given to the classification goals of MARPOL 73/78 Annex II which covers the transport of bulk quantities in ships tanks, which are aimed at regulating operational discharges from ships and assigning of suitable ship types. They go beyond that of protecting aquatic ecosystems, although that clearly is included. Additional hazard categories may thus be used which take account of factors such as physico-chemical properties and mammalian toxicity.

Acute toxicity

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

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

Bioaccumulation

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

Rapid degradability

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

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

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

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

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

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

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

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

Inorganic compounds and metals

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

26. Poorly soluble inorganic compounds and metals may be acutely or chronically toxic in the aquatic environment depending on the intrinsic toxicity of the bioavailable inorganic species and the rate and amount of this species which may enter solution. A protocol for testing these poorly soluble materials is being developed and will be covered further in the special guidance.

Category Chronic IV

27. The system also introduces as 'safety net' classification (Category: Chronic IV) for use when the data available does not allow classification under the formal criteria but there are nevertheless some grounds for concern. The precise criteria are not defined with one exception. For poorly water

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

Use of QSARs

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

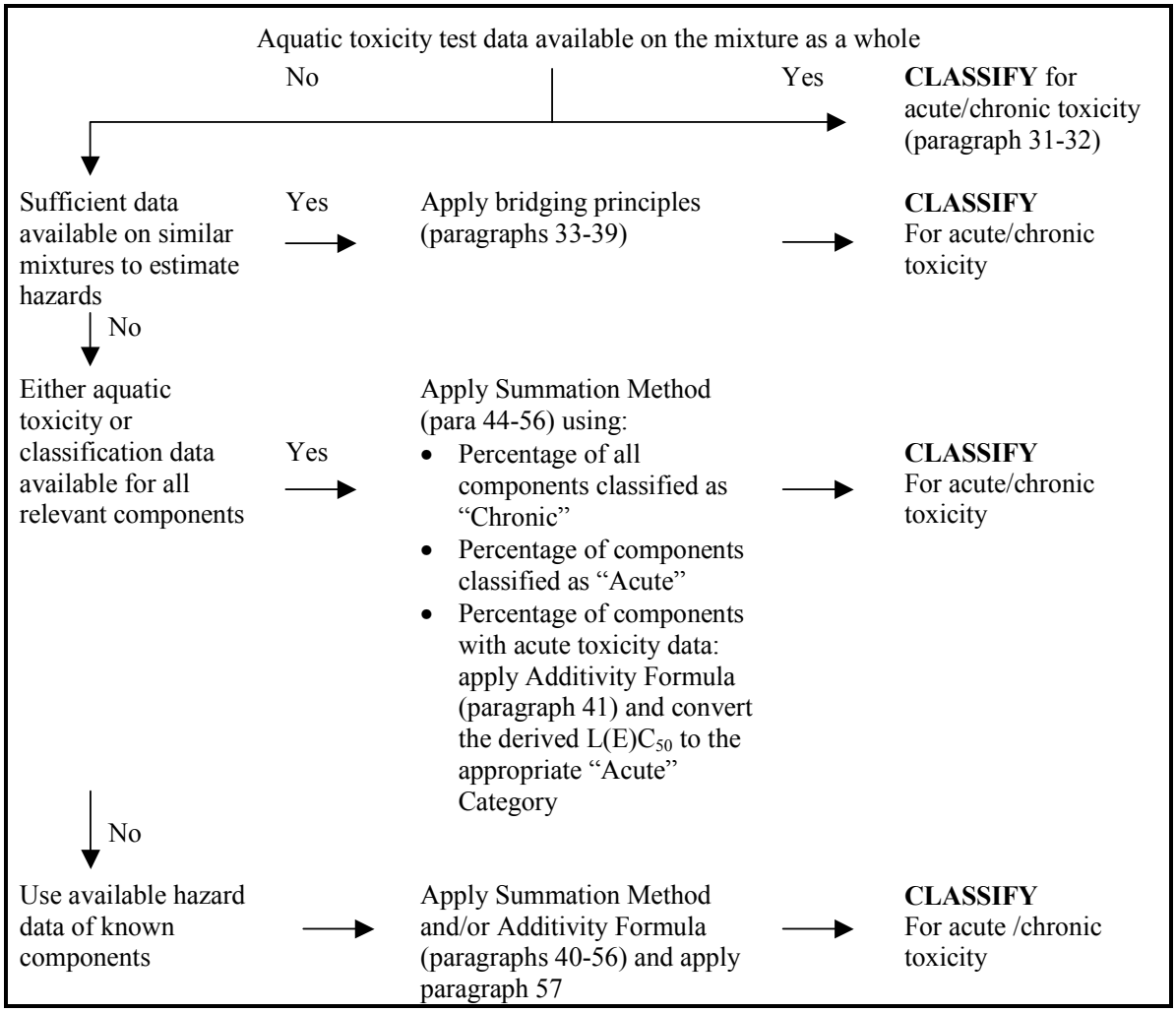
CLASSIFICATION CRITERIA FOR MIXTURES

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

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

30. The approach for classification of aquatic environmental hazards is tiered, and is dependent upon the type of information available for the mixture itself and for its components. Elements of the tiered approach include: i) classification based on tested mixtures; ii) classification based on bridging principles, iii) the use of "summation of classified components" and /or an "additivity formula". Figure 1 outlines the process to be followed.

Figure 1: Tiered approach to classification of mixtures for acute and chronic aquatic environmental hazards



Classification of mixtures when data are available for the complete mixture

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

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

- $L(E)C_{50}$ (LC_{50} or EC_{50}) of the tested mixture ≤ 100mg/L and NOEC of the tested mixture ≤ 1.0 mg/L or unknown:
  → Classify mixture as Category Acute I, II or III
  → Apply Summation of Classified Components approach (see paragraphs 51-56) for chronic classification (Chronic I, II, III, IV or no need of chronic classification).

- $L(E)C_{50}$ of the tested mixture ≤ 100mg/L and NOEC of the tested mixture > 1.0 mg/L:
  → Classify mixture as Category Acute I, II or III
  → Apply Summation of Classified Components approach (see paragraphs 51-56) for classification as Category Chronic I. If the mixture is not classified as Category Chronic I, then there is no need for chronic classification.

- $L(E)C_{50}$ of the tested mixture >100mg/L, or above the water solubility, and NOEC of the tested mixture ≤ 1.0mg/L or unknown:
  → No need to classify for acute toxicity
  → Apply Summation of Classified Components approach (see paragraphs 51-56) for Chronic classification (Category Chronic IV or no need for chronic classification).

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

Classification of mixtures when data are not available for the complete mixture

Bridging principles

33. Where the mixture itself has not been tested to determine its aquatic environmental hazard, but there are sufficient data on the individual components and similar tested mixtures to adequately characterise the hazards of the mixture, this data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

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

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

Batching

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

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

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

Interpolation within one toxicity category

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

Substantially similar mixtures

39. Given the following:

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

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

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

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

40. The classification of a mixture is based on summation of the classification of its components. The percentage of components classified as "Acute" or "Chronic" will feed straight in to the summation method. Details of the summation method are described in paragraphs 44-56.

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

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

where:

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

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

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

Summation method

Rationale

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

45. When a mixture contains components classified as Acute Category I, attention should be paid to the fact that such components, when their acute toxicity is well below 1 mg/L contribute to the toxicity of the mixture even at a low concentration. (See also *Classification of Hazardous Substances and Mixtures* (Chapter 1.3, paragraph 28)). Active ingredients in pesticides often

possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application of the normal cut-off values/concentration limits may lead to an "underclassification" of the mixture. Therefore, multiplying factors should be applied to account for highly toxic components, as described in paragraph 56.

Classification procedure

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

Classification for the Acute Categories I, II and III

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

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

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

50. The classification of mixtures for acute hazards based on this summation of classified components, is summarised in Table 2 below.

Table 2: Classification of a mixture for acute hazards, based on summation of classified components

Sum of components classified as:		Mixture is classified as:
Acute I x M[1]	>25%	Acute I
(M x 10 x Acute I) +Acute II	>25%	Acute II
(M x 100 x Acute I)+ (10 x Acute II) + Acute III	>25%	Acute III

[1] *For explanation of the M factor, see paragraph 56.*

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

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

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

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

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

55. The classification of mixtures for chronic hazards, based on this summation of classified components, is summarised in Table 3 below.

Table 3: Classification of a mixture for chronic hazards, based on summation of classified components

Sum of components classified as:		Mixture is classified as:
Chronic I x M[1]	>25%	Chronic I
(M x 10 x Chronic I)+Chronic II	>25%	Chronic II
(M x 100 x Chronic I)+(10x Chronic II)+Chronic III	>25%	Chronic III
Chronic I + Chronic II + Chronic III +Chronic IV	> 25%	Chronic IV

[1] *For explanation of the M factor, see paragraph 56.*

Mixtures with highly toxic components

56. Acute Category 1 components with toxicities well below 1 mg/L may influence the toxicity of the mixture and should be given increased weight in applying the summation of classification approach. When a mixture contains components classified as Acute or Chronic Category I, the tiered approach described in paragraphs 47-55 should be applied using a weighted sum by multiplying the concentrations of Acute Category I components by a factor, instead of merely adding up the percentages. This means that the concentration of "Acute I" in the left column of Table 2 and the concentration of "Chronic I" in the left column of Table 3 are multiplied by the appropriate multiplying factor. The multiplying factors to be applied to these components are

defined using the toxicity value, as summarised in Table 4 below. Therefore, in order to classify a mixture containing Acute/Chronic I components, the classifier needs to be informed of the value of the M factor in order to apply the summation method. Alternatively, the additivity formula (paragraph 41) may be used when toxicity data are available for all highly toxic components in the mixture and there is convincing evidence that all other components, including those for which specific acute toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture.

Table 4: Multiplying factors for highly toxic components of mixtures

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

Classification of mixtures with components without any useable information

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

HAZARD COMMUNICATION

Allocation of label elements

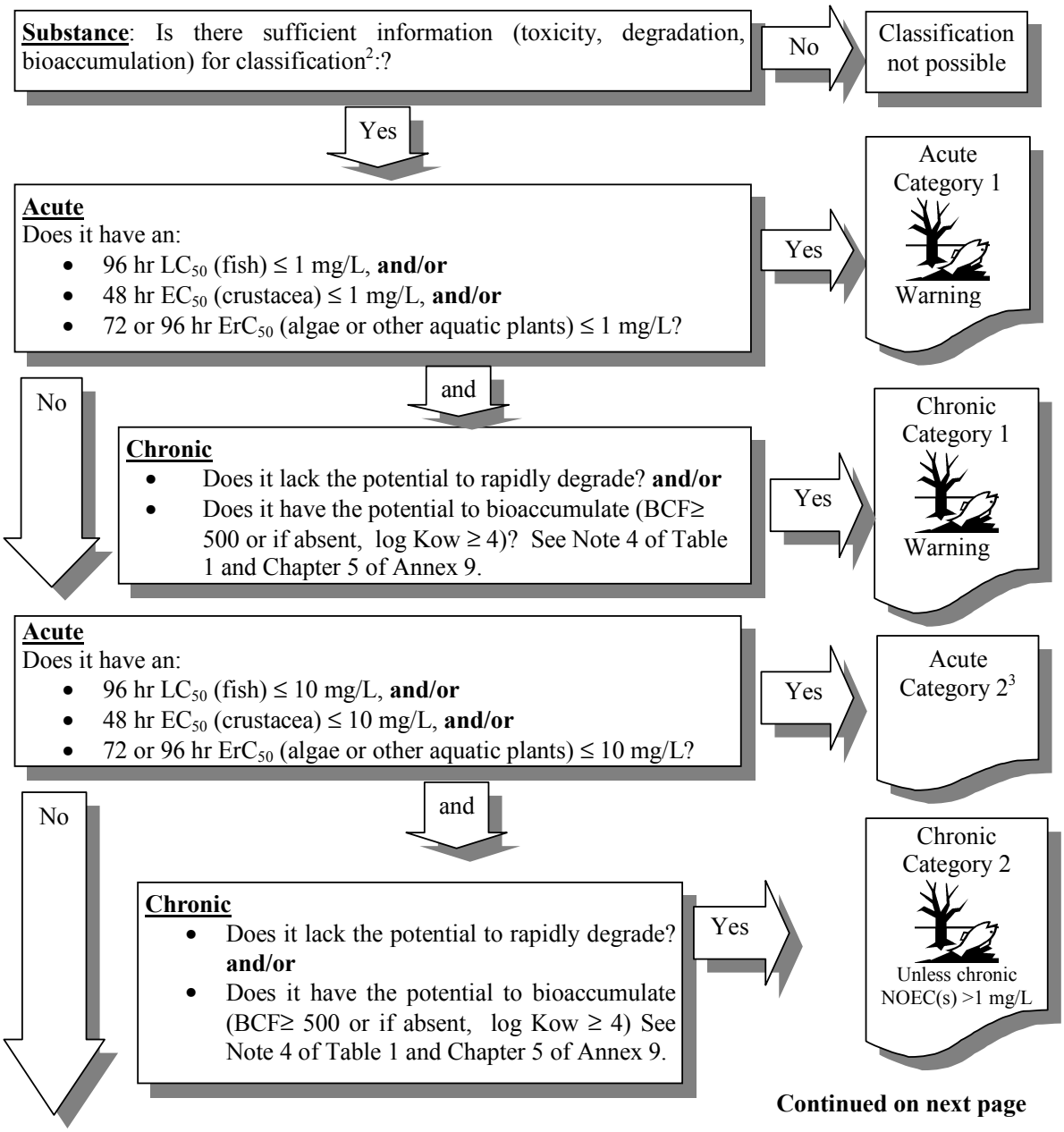
58. General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.3). Annex 4 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 5: Label elements for hazardous to the aquatic environment

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

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

59. **DECISION LOGIC AND GUIDANCE**[1]



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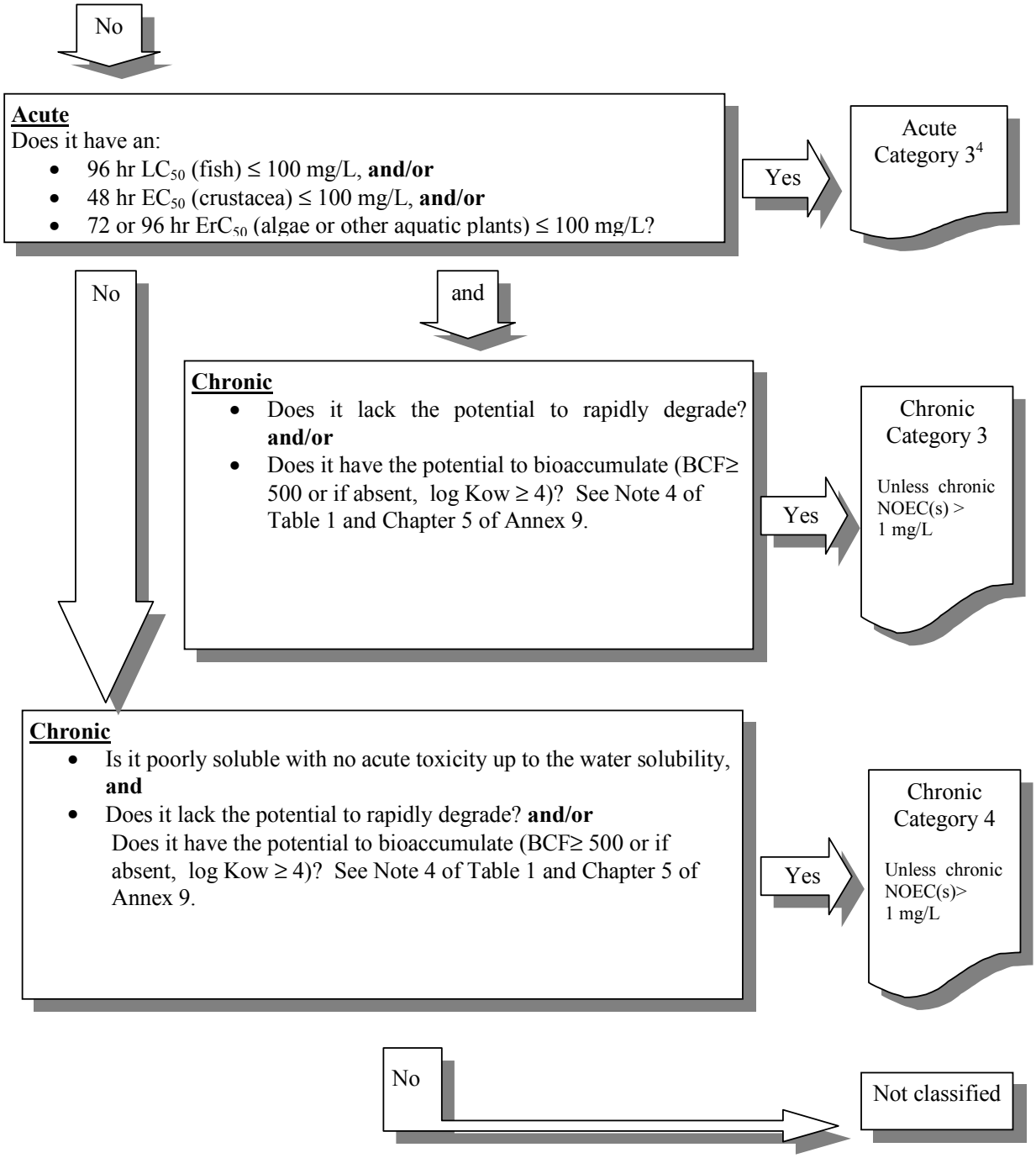
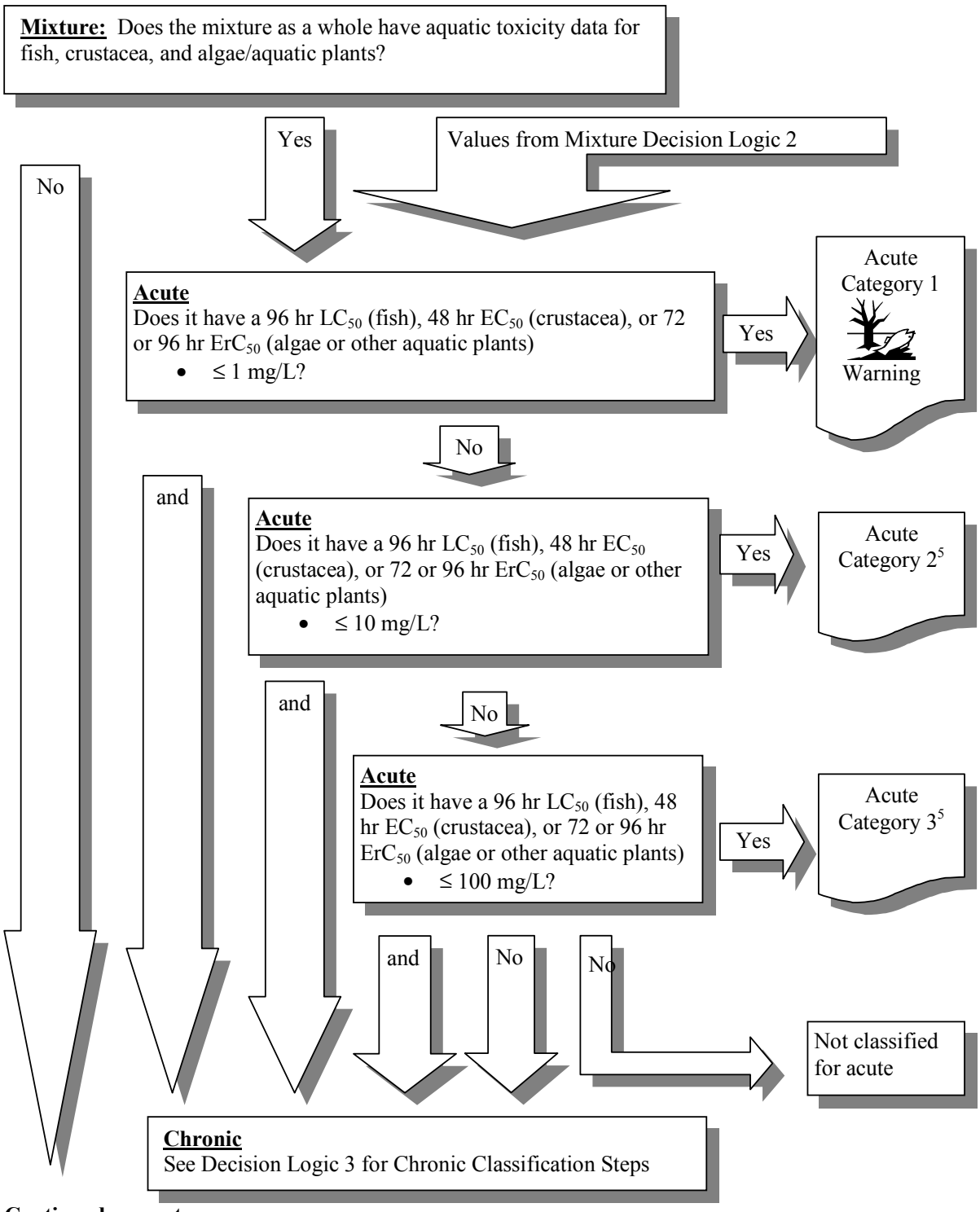
[1] *The decision logic which follows is not part of the agreed text on the harmonized classification system developed* by *the OECD Task Force – HCL, but has been provided here as additional guidance on classification of substances and mixtures for hazardous to the aquatic environment.*

[2] *Classification can be based on either measured data and/or calculated data (see para 28 of this chapter and Annex 9) and/or analogy decisions (see para 277 of Annex 9).*

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



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



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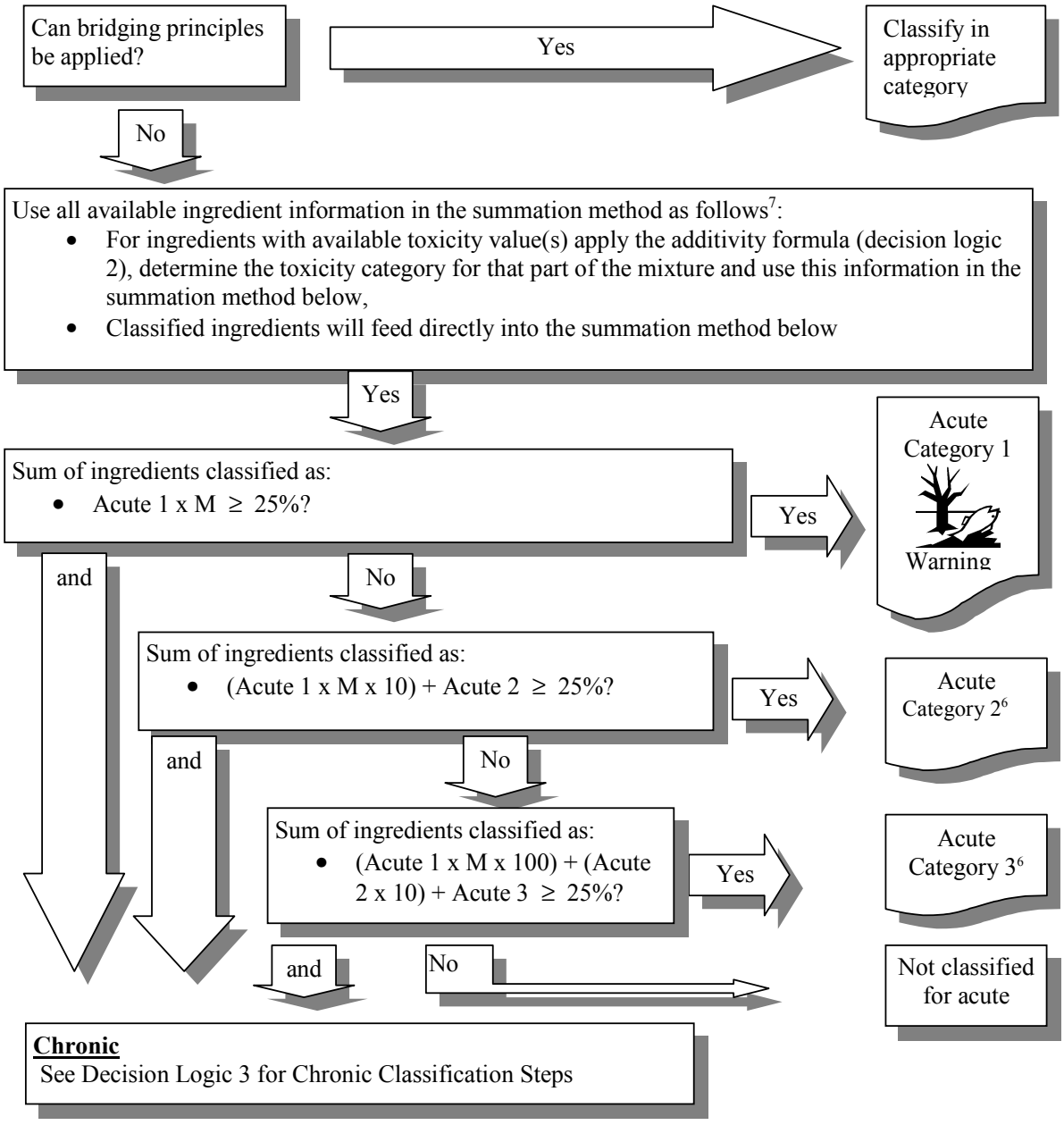
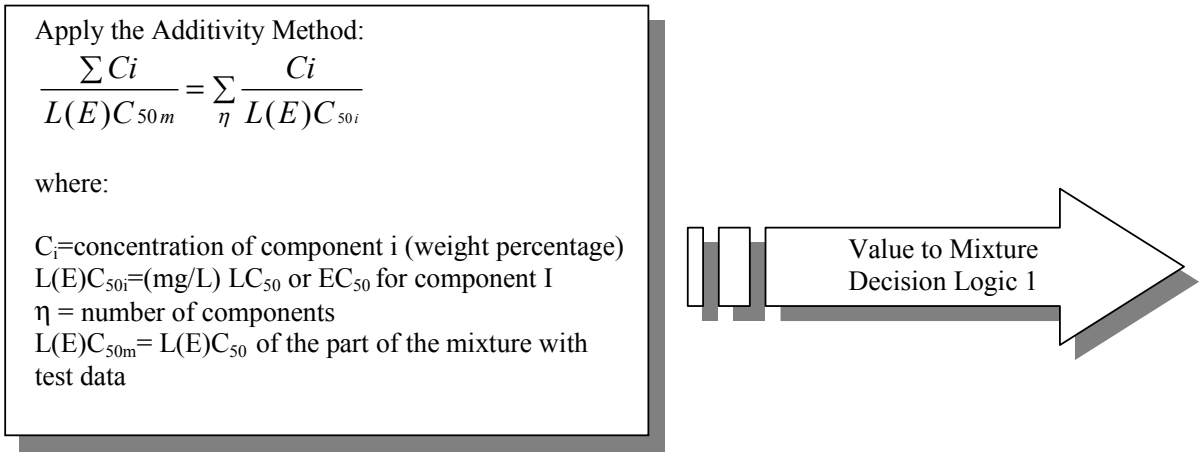
[5] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*



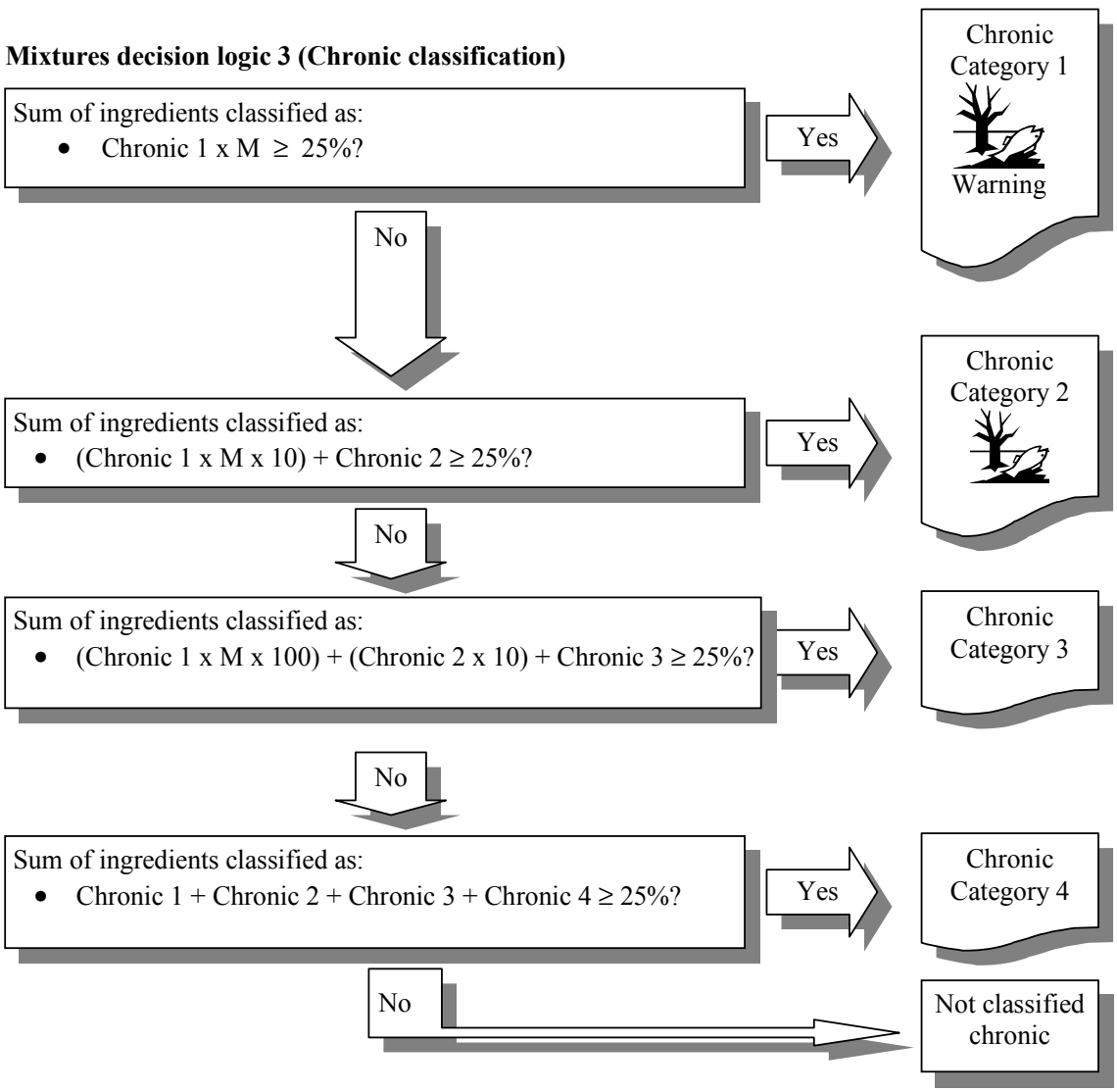
[6] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*

[7] *If not all components have information, include the statement "x percent of the mixture consists of ingredients(s) of unknown hazards to the aquatic environment" on the label. Alternatively, in the case of a mixture with highly toxic ingredients, if toxicity values are available for these highly toxic ingredients and all other ingredients do not significantly contribute to the hazard of the mixture, than the additivity formula may be applied. (See paragraph 56). In this case and other cases where toxicity values are available for all ingredients, the acute classification may be made solely on the basis of the additivity formula.*

Mixtures decision logic 2 (Additivity method)



Mixtures decision logic 3 (Chronic classification)



EXAMPLES

Under Review