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

Seventh session, 14-16 July 2004
Item 2 (b) (iv) of the provisional agenda

REVISED CHAPTER 3.8/PROPOSAL

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY - SINGLE EXPOSURE

This document, submitted by the OECD, contains the revised version of Chapter 3.8 with the proposed modifications of ST/SG/AC.10/C.4/2004/9 included in visible mode.

3.8.1 Definitions and general considerations

3.8.1.1 The purpose of this chapter is to provide a means of classifying substances that produce specific, non lethal target organ/systemic toxicity arising from a single exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in chapters 3.1 to 3.7 are included. See also Paragraph 3.8.1.6.

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

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

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

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

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

- acute lethality/toxicity (Chapter 3.1),

- skin corrosivity/irritation (Chapter 3.2),
- serious damage to eyes/irritation (Chapter 3.3),
- skin and respiratory sensitization (Chapter 3.4),
- mutagenicity (Chapter 3.5),
- carcinogenicity (Chapter 3.6), and
- reproductive toxicity (Chapter 3.7).

3.8.1.7 The classification criteria in this chapter are organized as criteria for substances Categories 1 and 2 (3.8.2), criteria for substances Category 3 (3.8.3) and criteria for mixtures (3.8.4). See Figure 3.8.1

3.8.2 Classification criteria for substances – Category 1 and 2

3.8.2.1 Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.9). Then substances are placed in ~~one of two categories~~ Category 1 or Category 2, depending upon the nature and severity of the effect(s) observed (Figure 3.8.1).

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

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 3.8.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following 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 3.8.2.9) in order to help in classification.
In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.9).

CATEGORY 3: Transient Target Organ effects

There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances/mixture may be classified specifically for these effects as discussed in 3.8.3.

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

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

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

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

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

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

3.8.2.7 ***Effects considered to support classification for Category 1 and 2***

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

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

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

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

- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;
- Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

3.8.2.8 ***Effects considered not to support classification for Category 1 and 2***

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

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

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

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

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

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

Table 3.8.1: Guidance value ranges for single-dose exposures[1]

		Guidance value ranges for :		
Route of exposure	**Units**	**Category 1**	**Category 2**	**Category 3**
Oral (rat)	mg/kg body weight	C ≤ 300	2000 ≥ C > 300	Guidance values do not apply [2]
Dermal (rat or rabbit)	mg/kg body weight	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	Ppm	C ≤ 2500	5000 ≥ C > 2500	
Inhalation (rat) vapour	mg/1	C ≤ 10	20 > C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1.0	5.0 > C > 1.0	

Note 1: The guidance values and ranges mentioned in Table 3.8.1 above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are *not intended as strict demarcation values*.
Note 2: Guidance values are not provided since this classification is primarily based on human data. Animal data may be included in the weight of evidence evaluation.

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

3.8.2.10 *Other considerations*

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

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

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

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

3.8.3 *Classification criteria for substances -- Category 3*

3.8.3.1 *Criteria for Respiratory Tract Irritation*

The criteria for respiratory tract irritation as category 3 are:

- Respiratory irritant effects (characterized by localised redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data.

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

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

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

- This special classification would occur only when more severe organ/systemic effects including in the respiratory system are not observed.

3.8.3.2 *Criteria for narcotic effect*

The criteria for narcotic effects as category 3 are:

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

- Narcotic effects observed in animal studies may include lethargy, lack of coordination righting reflex, narcosis, and ataxia. If these effects are not transient in nature than they should be considered for classification as category 1 or 2.

3.8.4~~3.8.3~~ Classification criteria for mixtures

3.8.~~3~~4.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for target organ/systemic toxicity following single exposure, repeated exposure, or both.

3.8.~~3~~4.2 *Classification of mixtures when data are available for the complete mixture*

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

3.8.~~3~~.4.3 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.8.~~3~~.4.3.1 Where the mixture itself has not been tested to determine its target organ/systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the following bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity of additional testing in animals.

3.8.~~3~~4.3.2 *Dilution*

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

3.8.~~3~~.4.3.3 *Batching*

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

3.8.~~3~~4.3.4 *Concentration of highly toxic mixtures*

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

3.8.~~3~~4.~~-~~3.5 *Interpolation within one toxicity category*

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

3.8.~~3~~4.3.6 *Substantially similar mixtures*

Given the following:

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

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

3.8.~~3~~4.3.7 *Aerosols*

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

3.8.~~3~~4.4 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.8.~~3~~4.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a target organ/systemic toxicant (specific organ specified), following single exposure, repeat exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 target organ/systemic toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.8.2 below for Category 1 and 2 respectively.

Table 3.8.2: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture as category 1 or 2[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.*

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

3.8.~~3~~4.4.3 Mixtures should be classified for either or both single- and repeated-dose toxicity independently.

3.8.~~3~~4.4.4 Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at <1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

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

3.8.4.4.5 Care should be exercised when extrapolating toxicity of a mixture that contains category 3 ingredient(s). A cut off value of 20% has been suggested, however, it should be recognised that this cut-off value may be higher or less depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgment should be exercised

3.8.4.5 Hazard communication

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

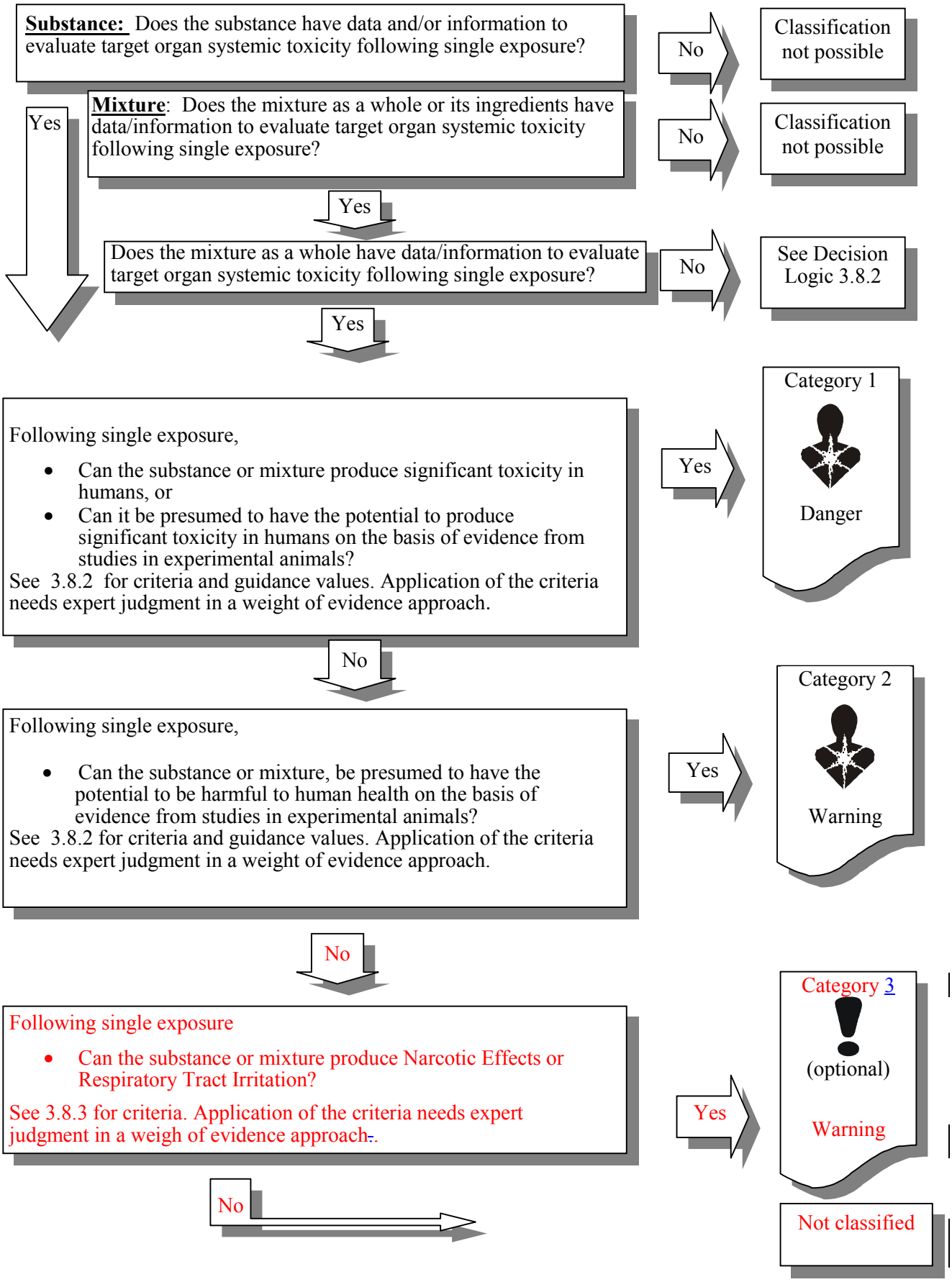
Table 3.8.3: Label elements for target organ systemic toxicity after single exposure

	Category 1	**Category 2**	**Category 3**
Symbol	Health Hazard	Health Hazard	Exclamation mark (Optional)
Signal word	Danger	Warning	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)	May cause respiratory irritation or May cause drowsiness and dizziness

3.8.5.6 Decision logic for Target Organ Systemic Toxicity from single exposure

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

Decision logic 3.8.1



Decision logic 3.8.2

Can bridging principles, as in 3.8.3.3, be applied?

Yes → Classify in appropriate category

No

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of [2] :

- ≥ 1.0% ?
- ≥ 10% ?

See Table 3.8.2 for explanation of cut-off values/concentration limits [3].

Yes → Category 1

Danger

No

Does the mixture contain one or more ingredients classified as a Category 1 target organ systemic toxicant at a concentration of [2]:

- ≥ 1.0 and < 10%?

See Table 3.8.2 for explanation of cut-off values/concentration limits [3].

Yes → Category 2

Warning

No

Does the mixture contain one or more ingredients classified as a Category 2 target organ systemic toxicant at a concentration of [2]:

- ≥ 1.0%?
- ≥ 10%?

See Table 3.8.2 for explanation of cut-off values/concentration limits [3].

Yes → Category 2

Warning

No

Does the mixture contain one or more ingredients classified as Category 3 target organ systemic toxicant at a concentration > 20%?
See 3.8.4.4.5 Care should be exercised when classifying such mixtures.

Yes → Category 3

(optional)

Warning"

No → Not classified

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

[3] *See 3.8.~~3~~4.4 and Table 3.8.2 for explanation and guidance.*