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MECLAS Tool for Complex Materials from the Metals Sector

Submitted by: Australia

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MECLAS (METALS CLASSIFICATION) Tool for Complex Materials from the Metals Sector

Problem Statement: The hazard identification and classification of complex inorganic materials present a huge challenge to industry and regulatory authorities alike. In addition to including metal compounds with different toxicity profiles, the content and composition of these materials is often variable and the choice of a clear representative substance is often not obvious. In addition information pertaining to more than one classification framework (e.g., CLP, GHS) may be needed. This can lead to inconsistent and variable classifications assigned to similar materials.

Scientific Issues: The toxicity of complex substances and mixtures is an issue of great interest at the moment. Toxicity data is usually gathered for pure individual substances.

Current risk assessment: The lack of a centralized database on hazard classification information further hinders the possibility of adopting consistent and robust classification for complex inorganic materials worldwide.

Discussion questions:

1. *Were you aware of MECLAS before this workshop?*
2. *If not, what other databases/tools are available to you for the classification of complex metal mixtures? Do they have the same functionality as MECLAS?*
3. *Knowing about MECLAS capabilities would you be likely to use it in any of your ongoing activities? If no, could you please explain what the main hurdles would be?*
4. *Would you be interested in additional features/modules currently not present in MeClas?*

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Summary:

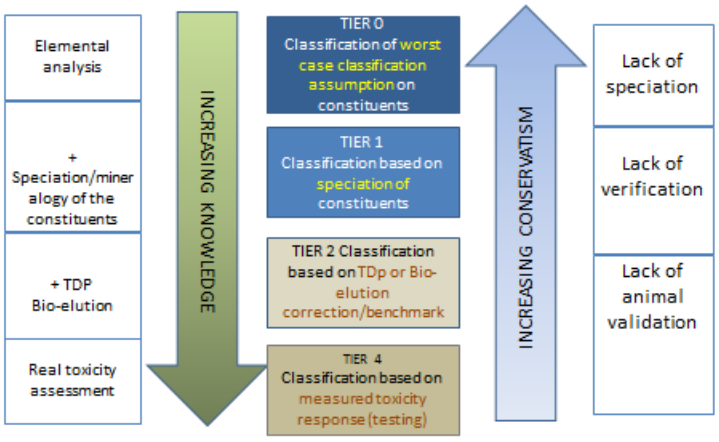
ARCHE-consulting and Eurometaux have designed and developed an automated expert system for the **hazard identification** and **classification/labelling** of complex inorganic materials like **ores and concentrates, complex UVCB intermediates, slags and alloys** under the Global Harmonised System (GHS).

The MECLAS tool has been designed as a **web-based**, **flexible** and **user-friendly** hazard identification tool. It recognises the specific properties and assessment techniques for inorganics and uses the most updated information on (eco)toxicity references and self-classifications available. Physico-chemical data/classification rules are however not covered.

It is built on a limited number of simple and basic principles:

- A tiered and inorganic-specific approach, allowing refinement in accordance with following key aspects like e.g. speciation, mineralogy, bioavailability; depending on the available data

SCHEMATIC OVERVIEW of the TIERED CLASSIFICATION APPROACH FOR COMPLEX MATERIALS



Tier 0: when only elemental concentrations are known

⇨ Assessment based on a worst-case speciation and default hazard assumption (100% solubility)

Tier 1: when chemical speciation data and/or mineralogical evidence are available

⇨ Assessment making use of speciation knowledge

Tier 2: when relevant release/solubility data available on the complex material (transformation dissolution protocol data and/or bioelution data)

⇨ Assessment of Tier 1 corrected for reduced/enhanced release rate

Tier 3: relevant direct ecotoxicity evidence available for the (complex) inorganic material recognizing its physical form

⇨ Direct toxicity evidence overrules calculated hazard classification (for environment)

The tiers are not necessarily sequential and a Tier 2 assessment makes the hazard classification usually relevant to the specific properties of metals and metal mixtures like alloys

- An **up-to-date database** including the official EU harmonised classifications, the self-classifications under GHS, the US classifications; but

also the specific concentration limits, M-factors, (eco)toxicity reference values (ERVs) values,...

- An **open building block structure**, enabling the inclusion of specific side modules if relevant (for ores and concentrates, for Transport Classification, additional reference lists (e.g. Japan), alloys, etc.). The core engine contains the UN-GHS, CLP hazard identification rulings, which form the base of the MeClas tool.
- **Confidentiality assurance for proprietary information**: Confidentiality of proprietary data is assured by having the ERVs for such substances hidden from normal users of the tool in a dedicated layer of MeClas.
- **Output:** For every endpoint, the classification is given for EU CLP and GHS. The major driver for this classification is also mentioned. In addition, the pictograms for labelling are given for the different classified endpoints. A summary report with the assumptions and the classification result can be downloaded in PDF or Excel.

MECLAS has been available since 15 August 2010; interested parties may request information via the special web-address: info@meclas.eu or directly via the website: www.meclas.eu

MECLAS is freely available for non-commercial uses and regularly updated.

More information on both the principles and the formats can be found on www.meclas.eu

CHAPTER 3.9

SPECIFIC TARGET ORGAN TOXICITY REPEATED EXPOSURE

3.9.1 Definitions and general considerations

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

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

3.9.1.3 Classification depends upon the availability of reliable evidence that a repeated exposure to the substance or mixture 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 recognized that human data will be the primary source of evidence for this hazard class.

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

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

3.9.1.6 Non-lethal toxic effects observed after a single-event exposure are classified in the GHS as described in *Specific target organ toxicity – Single exposure* (Chapter 3.8) and are therefore excluded from the present chapter. Other specific toxic effects, such as acute toxicity, serious eye damage/eye irritation, skin corrosion/irritation, respiratory or skin sensitization, carcinogenicity, germ cell mutagenicity, reproductive toxicity and aspiration toxicity are assessed separately in the GHS and consequently are not included here.

3.9.2 Classification criteria for substances

3.9.2.1 Substances are classified as specific target organ 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 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

Figure 3.9.1: Hazard categories for specific target organ toxicity following repeated exposure

CATEGORY 1: **Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure**

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

(a) reliable and good quality evidence from human cases or epidemiological studies; or,

(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated 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 3.9.2.9) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

NOTE: *For 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 toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, 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.*

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

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

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

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

3.9.2.6 In exceptional cases, based on expert judgement, it may be appropriate to place certain substances with human evidence of specific target organ 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 substance that warrant Category 1 classification, the substance should be classified as Category 1.

3.9.2.7 ***Effects considered to support classification***

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

3.9.2.7.2 It is recognized 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.

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

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

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

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

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

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

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

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

3.9.2.8 ***Effects considered not to support classification***

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

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

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

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

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

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

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

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

3.9.2.9.2 In order to help reach a decision about whether a substance should be classified or not, and to what degree it would be classified (Category 1 vs. Category 2), dose/concentration "guidance values" are provided in Table 3.9.1 for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimize the test objective and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

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

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

3.9.2.9.5 The guidance values proposed refer 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.

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

Table 3.9.1: Guidance values to assist in Category 1 classification

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

***Note**: "bw" is for "body weight", "h" for" hour" and "d" for "day".*

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

Table 3.9.2: Guidance values to assist in Category 2 classification

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

***Note**: "bw" is for body weight,"h" for" hour" and "d" for "day".*

3.9.2.9.8 The guidance values and ranges mentioned in 3.9.2.9.6 and 3.9.2.9.7 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

3.9.2.9.9 Thus it is feasible that a specific profile of toxicity is seen to occur in repeat-dose animal studies at a dose/concentration below the guidance value, 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.

3.9.2.10 *Other considerations*

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

3.9.2.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ 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 toxic effect, the substance should be classified.

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

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

3.9.3 Classification criteria for mixtures

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

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

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

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

3.9.3.3.1 Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize 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 characterizing the hazards of the mixture without the necessity of additional testing in animals.

3.9.3.3.2 *Dilution*

If a tested 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 diluted mixture may be classified as equivalent to the original tested mixture.

3.9.3.3.3 *Batching*

The toxicity of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when 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 untested batch has changed. If the latter occurs, a new classification is necessary.

3.9.3.3.4 *Concentration of highly toxic mixtures*

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

3.9.3.3.5 *Interpolation within one hazard category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same hazard category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B.

3.9.3.3.6 *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) or (ii) is already classified by testing, then the other mixture can be assigned the same hazard category.

3.9.3.3.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolized 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 aerosolized mixtures for inhalation toxicity should be considered separately.

3.9.3.4 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

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

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

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

[a] *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 harmonized approach.*

NOTE 1: *If a Category 1 specific target organ 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 specific target organ 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 specific target organ 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 toxicant, whereas others would not.*

NOTE 4: *If a Category 2 specific target organ 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 specific target organ toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

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

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

3.9.3.4.4 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 specific target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

3.9.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 1 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.

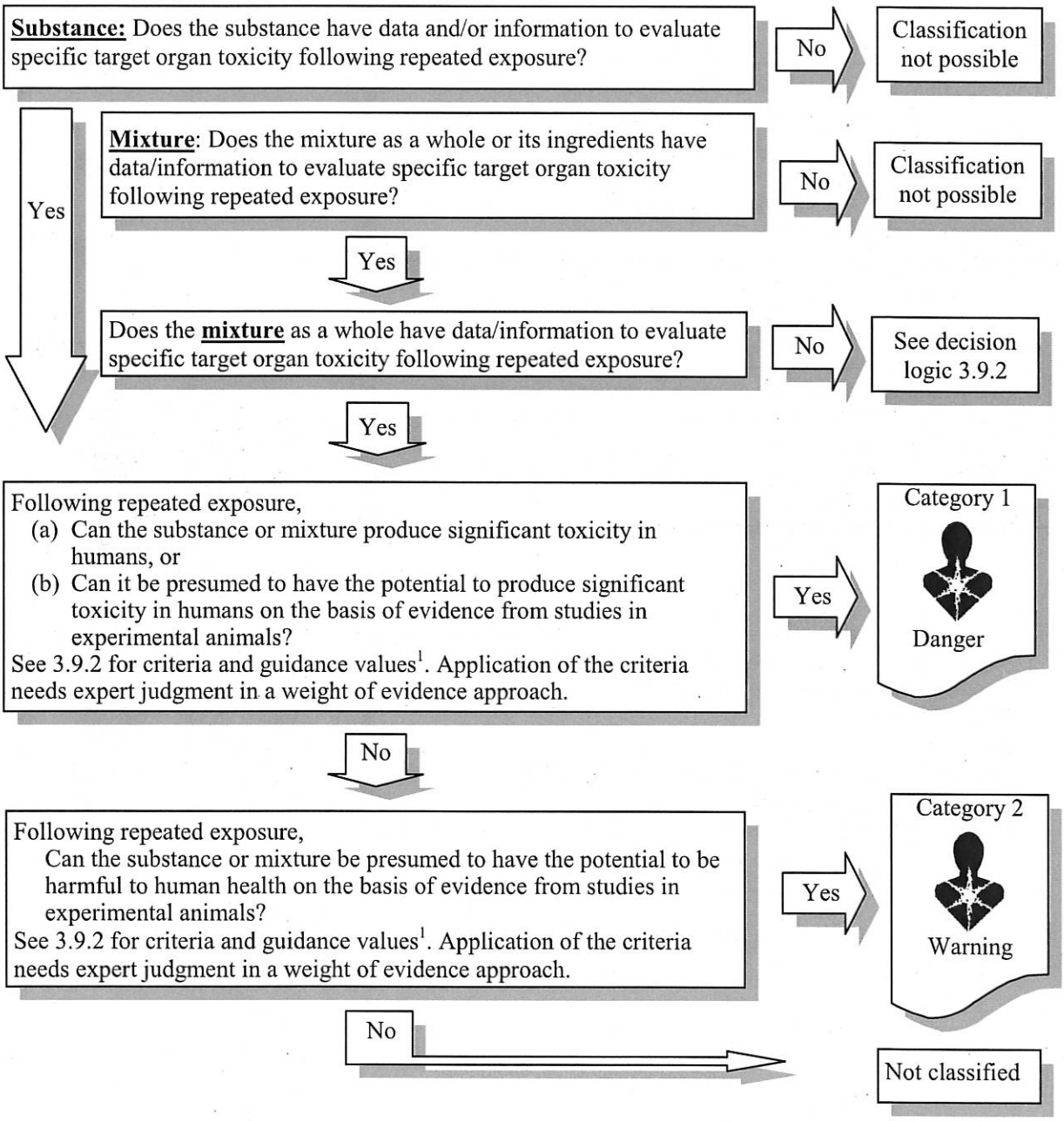
Table 3.9.4: Label elements for specific target organ toxicity following repeated exposure

	Category 1	Category 2
Symbol	Health hazard	Health hazard
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)

3.9.5 Decision logic for specific target organ toxicity following repeated 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 studies the criteria before and during use of the decision logic.

3.9.5.1 *Decision logic 3.9.1*



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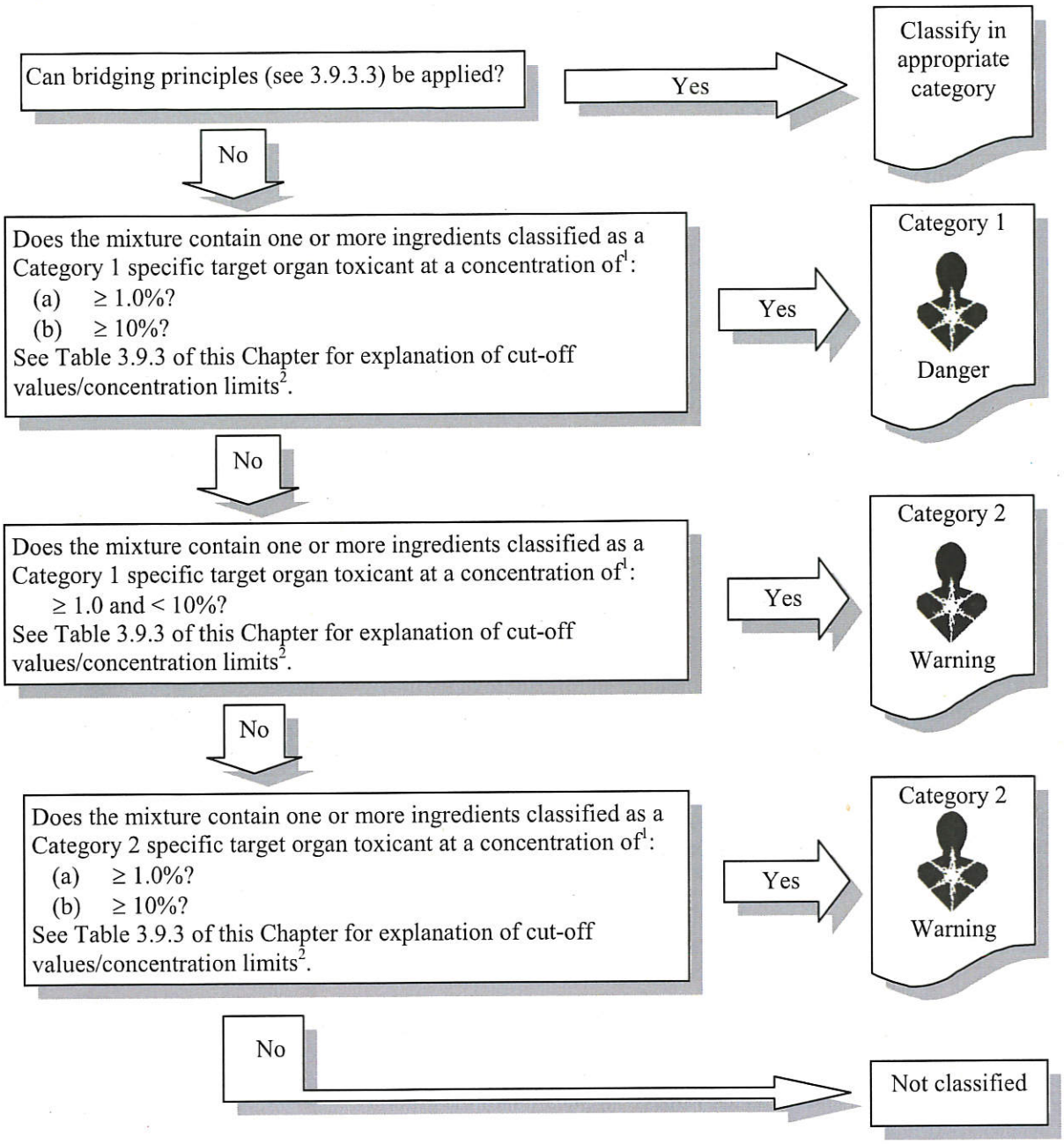
[1] *See 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2 "The use of cut-off values/concentration limits".*

3.9.5.2 *Decision logic 3.9.2*



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1 *See 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2 "The use of cut-off values/concentration limits".*

2 *See 3.9.3.4 and 3.9.4 and Table 3.9.3 for explanation and guidance.*