Chapter 13:

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY (TOST) FOLLOWING REPEATED EXPOSURE

DEFINITIONS

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

2.   Classification depends upon the availability of reliable evidence that 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.

3.   Assessment of specific target organ/systemic toxicity 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.

CONSIDERATIONS

4.   The purpose of this document is to provide a means of classifying substances that produce specific target organ/systemic toxicity arising from repeated exposure that is not specifically addressed elsewhere in the harmonised classification system (GHS). All significant health effects that can impair function, both reversible and irreversible, following repeated or long-term exposure, are included. Other specific toxic effects, such as acute lethality/toxicity, eye and skin corrosivity/irritation, skin and respiratory sensitisation, carcinogenicity, mutagenicity and reproductive toxicity are assessed separately in the GHS and consequently are not included in the present proposal.

5.   Non-lethal toxic effects observed after a single-event exposure are classified elsewhere in the GHS as a separate chapter and, therefore, are excluded from the present chapter.

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

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 classes, 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).

The classified substance may be named for the specific target organ/system that has been primarily affected, or generally as a general systemic toxicant. Attempts should be made to determine the primary target organ 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. hepatotoxin can secondarily produce effects of the nervous or gastro-intestinal systems.

8.   The classified substance should be named for the relevant route of exposure.

Criteria

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/incident is usually restricted to 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 or 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.

Rationale

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, this 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 Class

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

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 (TOST) Target Organ Systemic Toxicant	$\geq 1.0\%$ (note 1)	$1.0 \leq$ ingredient $< 10\%$ (note 3)
	$\geq 10\%$ (note 2)	$1.0 \leq$ ingredient $< 10\%$ (note 3)
Category 2 (TOST) Target Organ Systemic Toxicant		$\geq 1.0\%$ (note 4)
		$\geq 10\%$ (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 authorities would require information on the MSDS 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 $\geq 10\%$, both an MSDS 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 MSDS 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.

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[1] This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. Although it is recognised that this may result in a lack of harmonisation for some mixtures, the OECD Expert Group is recommending to the ILO Hazard Communication Work Group that this compromise be accepted as a way to move the process forward. 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. All of these hazard communication recommendations are subject to review by the ILO Work Group, and may be affected by that group's determinations regarding the possibility of using risk considerations in labelling in the consumer sector.

Note 5: If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of $\geq 10\%$, both an MSDS 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.

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.
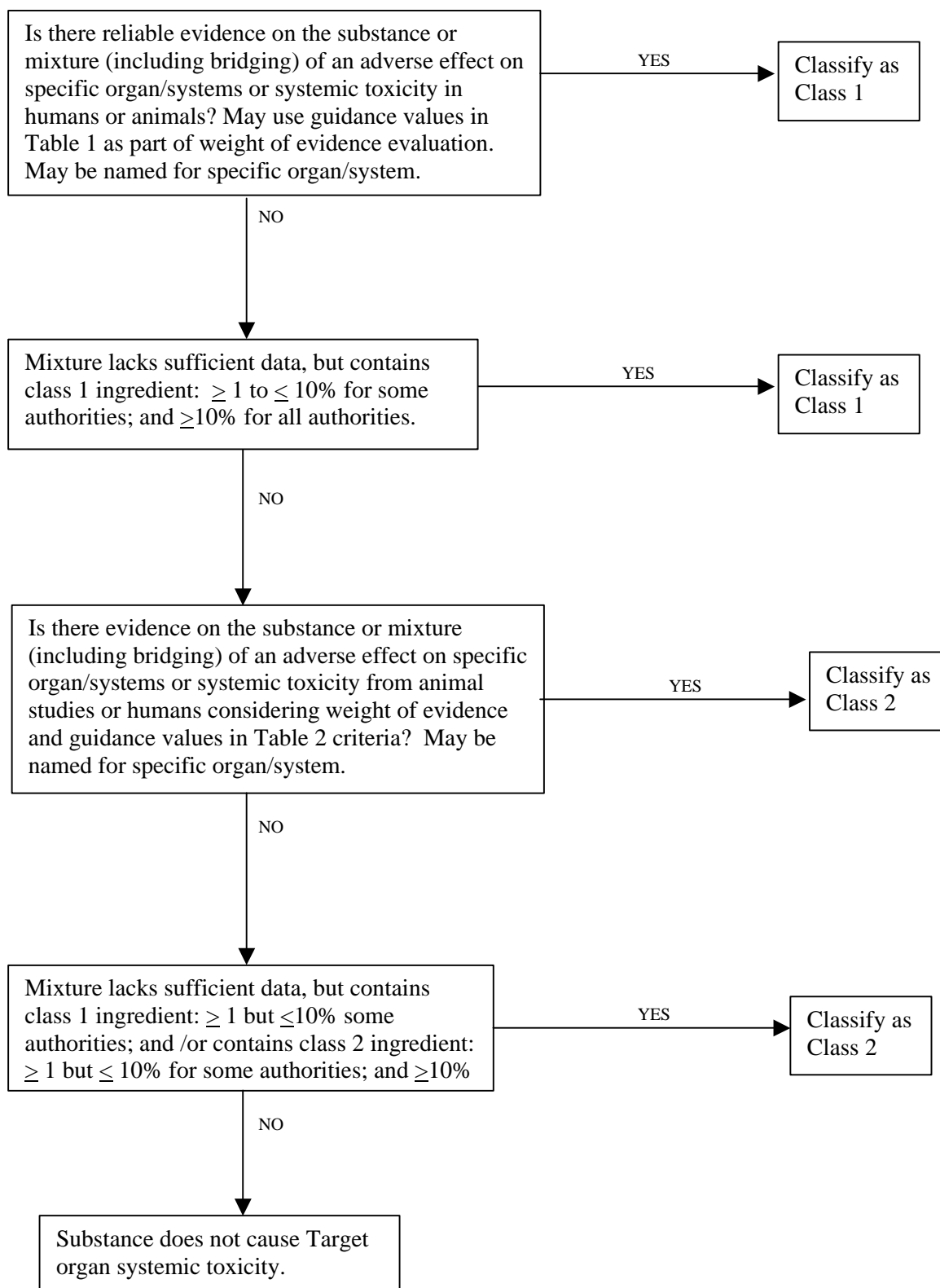

HAZARD COMMUNICATION

Allocation of Label Elements

43.   General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 5 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

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)

Decision Logic for Classification of Target Organ Systemic toxicity following Repeated Exposure

Is there reliable evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity in humans or animals? May use guidance values in Table 1 as part of weight of evidence evaluation. May be named for specific organ/system.	YES →	Classify as Class 1

NO ↓

Mixture lacks sufficient data, but contains class 1 ingredient: ≥ 1 to $\leq 10\%$ for some authorities; and $\geq 10\%$ for all authorities.	YES →	Classify as Class 1

NO ↓

Is there evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity from animal studies or humans considering weight of evidence and guidance values in Table 2 criteria? May be named for specific organ/system.	YES →	Classify as Class 2

NO ↓

Mixture lacks sufficient data, but contains class 1 ingredient: ≥ 1 but $\leq 10\%$ some authorities; and /or contains class 2 ingredient: ≥ 1 but $\leq 10\%$ for some authorities; and $\geq 10\%$	YES →	Classify as Class 2

NO ↓

Substance does not cause Target organ systemic toxicity.

Classification and Labelling Summary For Target Organ Systemic Toxicity Following Repeat Exposure:

If the substance or mixture meets one of the following criteria, classify and use corresponding communication elements. Some systems may use exposure and risk estimation to decide if the substance/mixture poses a substantial injury or illness thus necessitating hazard communication. If the criteria are not met then the substance or mixture need not be classified.

Class	Criteria	Hazard Communication Elements	
Class 1	Reliable evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity in humans or animals. May use guidance values in Table 1 as part of weight of evidence evaluation. May be named for specific organ/system Mixture that lacks sufficient data, but contains class 1 ingredient: ≥ 1 to $\leq 10\%$ for some authorities; and $\geq 10\%$ for all authorities.	*Signal Word*	New heath hazard symbol
		Symbol	Danger
		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)
	Mixture that lacks sufficient data, but contains class 1 ingredient at a concentration of $\geq 1\%$	MSDS	Hazard Statement as above
Class 2	Evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity from animal studies or humans considering weight of evidence and guidance values in Table 2 criteria. May be named for specific organ/system. Mixture that lacks sufficient data, but contains class 1 ingredient: ≥ 1 but $\leq 10\%$ for some authorities; and /or contains class 2 ingredient: ≥ 1 to $\leq 10\%$ for some authorities; and $\geq 10\%$ for all authorities	*Signal Word*	New heath hazard symbol
		Symbol	Warning
		Hazard Statement	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)
	Mixture that lacks sufficient data, but contains class 2 ingredient: $\geq 1\%$ concentration	MSDS	Hazard Statement as above

EXAMPLES

To be provided later this week