

**Chapter 5:**  
**ACUTE TOXICITY**

**DEFINITIONS**

1. Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

**CLASSIFICATION CRITERIA FOR SUBSTANCES**

2. Chemicals can be allocated to one of five toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values are shown in the table below. Explanatory notes are shown in italics following the table.

**Table 1: Acute toxicity hazard categories and (approximate) LD50/LC50 values defining the respective categories.**

Exposure Route	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	5	50	300	2000	5000 See detailed criteria in note e
Dermal (mg/kg)	50	200	1000	2000	
Gases (ppm) see: Note a	100	500	2500	5000	
Vapours (mg/l) see: Note a Note b Note c	0.5	2.0	10	20	
Dusts and Mists (mg/l) see: Note a Note d	0.05	0.5	1.0	5	

Notes to Table 1:

- a: *Inhalation cut-off values in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which has been generated according to 1 hour exposures should be by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists.*
- b: *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. (e.g. UN Recommendations for the Transport of Dangerous Goods).*
- c: *For some chemicals the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other chemicals the test atmosphere may consist of a vapour which is near the gaseous phase. In these latter cases, classification should be based on ppm as follows: Category 1 (100 ppm), Category 2 (500 ppm), Category 3 (2500 ppm), Category 4 (5000 ppm). Work in the OECD Test Guidelines Programme should be undertaken to better define the terms "dusts", "mists" and "vapours" in relation to inhalation toxicity testing.*
- d: *The values for dusts and mists should be reviewed to adapt to any future changes to OECD Test Guidelines with respect to technical limitation in generating, maintaining and measuring dust and mist concentrations in respirable form.*
- e: *Criteria for Category 5 are intended to enable the identification of substances which are of relatively low acute toxicity hazard but which, under certain circumstances may present a danger to vulnerable populations. These substances are anticipated to have an oral or dermal LD50 in the range of 2000-5000 mg/kg or equivalent doses for other routes. The specific criteria for Category 5 are:*
- 1) *The substance is classified in this Category if reliable evidence is already available that indicates the LD50 or (LC50) to be in the range of Category 5 values or other animal studies or toxic effects in humans indicate a concern for human health or an acute nature.*
  - 2) *The substance is classified in this Category, through extrapolation, estimation or measurement of data, if assignment to a more hazardous category is not warranted, and :*
    - reliable information is available indicating significant toxic effects in humans; or*
    - any mortality is observed when tested up to Category 4 values by the oral, inhalation, or dermal routes; or*
    - where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance, or*
    - where expert judgement confirms reliable information indicating the potential for significant acute effects from other animal studies.*

*Recognising the need to protect animal welfare, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such a test would have a direct relevance for protecting human health.*

### **Considerations**

3. The harmonised classification system for acute toxicity has been developed in such a way as to accommodate the needs of existing systems. A basic principle set by the IOMC CG/HCCS is that "harmonisation means establishing a common and coherent basis for chemical hazard classification and communication from which the appropriate elements relevant to means of transport, consumer, worker and environment protection can be selected." To that end, five categories have been included in the acute toxicity scheme.

4. The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. As noted by the

CG/HCCS, "Test data already generated for the classification of chemicals under existing systems should be accepted when reclassifying these chemicals under the harmonised system." When experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD50 value from among valid, well-performed tests.

5. Category 1, the highest toxicity category, has cut off values of 5 mg/kg by the oral route, 50 mg/kg by the dermal route, 100 ppm for gases or gaseous vapours, 0.5 mg/l for vapours, and 0.05 mg/l for dusts and mists. These toxicity values are currently used primarily by the transport sector for classification for packing groups.

6. Category 5 is for chemicals which are of relatively low acute toxicity but which, under certain circumstances, may pose a hazard to especially vulnerable populations. Criteria for identifying substances in Category 5 are provided in addition to the table. These substances are anticipated to have an oral or dermal LD50 value in the range 2000 - 5000 mg/kg or equivalent doses for other routes of exposure. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance for protecting human health.

### **Special Considerations for Inhalation Toxicity**

7. Values for inhalation toxicity are based on 4 hour tests in laboratory animals. When experimental values are taken from tests using a 1 hour exposure, they can be converted to a 4 hour equivalent by dividing the 1 hour value by a factor of 2 for gases and vapours and 4 for dusts and mists.

8. Units for inhalation toxicity are a function of the form of the inhaled material. Values for dusts and mists are expressed in mg/l. Values for gases are expressed in ppm. Acknowledging the difficulties in testing vapours, some of which consist of mixtures of liquid and vapours phases, the table provides values in units of mg/l. However, for those vapours which are near the gaseous phase, classification should be based on ppm. As inhalation test methods are updated, the OECD and other test guideline programs will need to define vapours in relation to mists for greater clarity.

9. Vapour inhalation values are intended for use in classification of acute hazard for all sectors. It is also recognised that the saturated vapour concentration of a chemical is used by the transport sector as an additional element in classifying chemicals for packing groups.

10. Of particular importance is the use of well articulated values in the high toxicity categories for dusts and mists. Inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/l. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats. The cut off values in the table for dusts and mists allow clear distinctions to be made for materials with a wide range of toxicities measured under varying test conditions. The values for dusts and mists should be reviewed in the future to adapt to any future changes in OECD or other test guidelines with respect to technical limitations in generating, maintaining, and measuring dust and mist concentrations in respirable form.

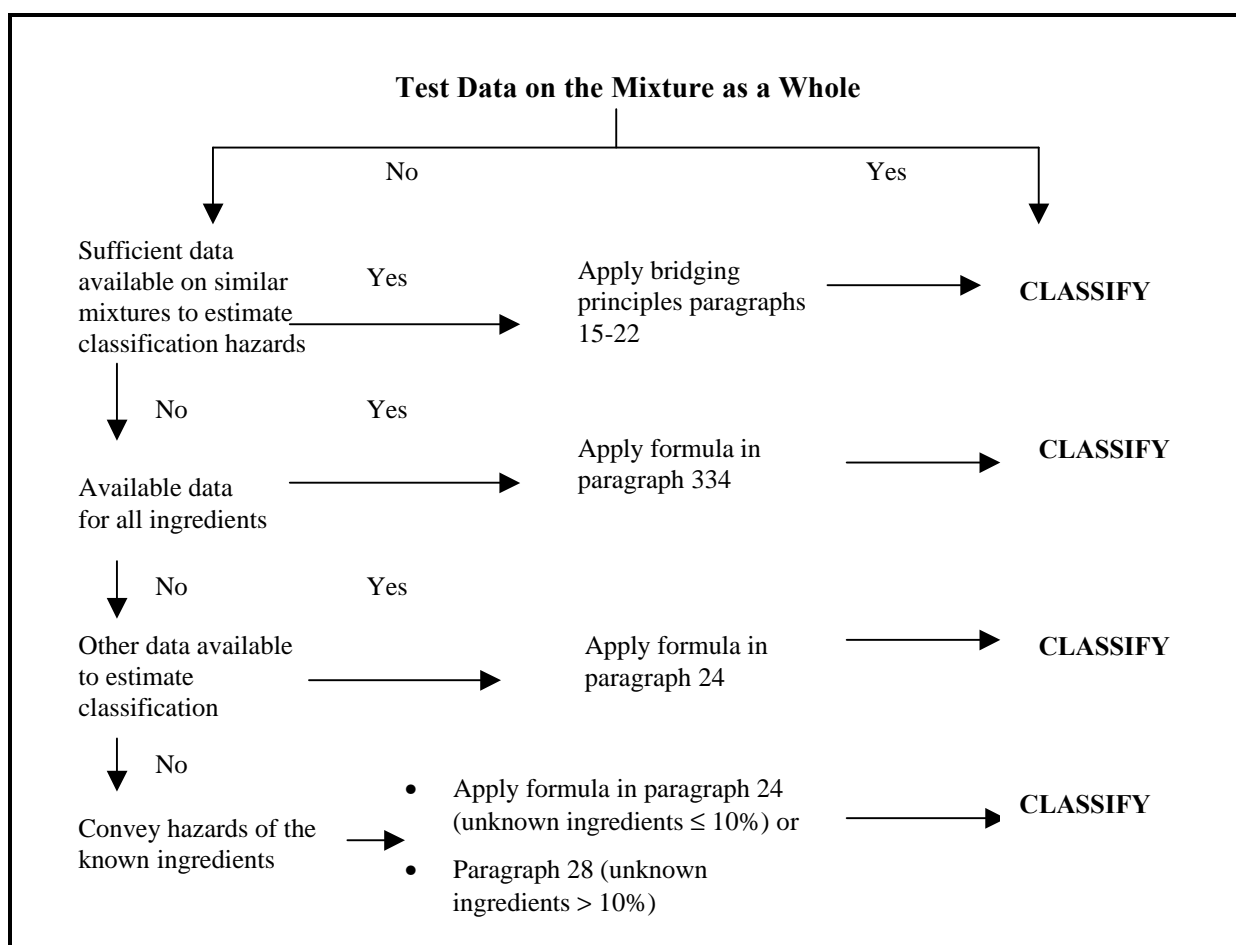
## **CLASSIFICATION CRITERIA FOR MIXTURES**

### **Considerations**

11. The criteria for substances classify acute toxicity by use of lethal dose data (tested or derived). For mixtures, it is necessary to obtain or derive information that allows the criteria to be applied to the mixture for the purpose of classification. The approach to classification for acute

toxicity is tiered, and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure 1 below outlines the process to be followed:

**Figure 1: Tiered approach to classification of mixtures for acute toxicity**



12. Classification of mixtures for acute toxicity can be carried out for each route of exposure, but is only needed for one route of exposure as long as this route is followed (estimated or tested) for all ingredients. If the acute toxicity is determined for more than one route of exposure, the more severe hazard category will be used for classification. All available information should be considered and all relevant routes of exposure should be identified for hazard communication.

13. In order to make use of all available data for purposes of classifying the hazards of the mixtures, certain assumptions have been made and are applied where appropriate in the tiered approach:

- a) The “relevant ingredients” of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for acute toxicity.<sup>1</sup>
- b) The acute toxicity estimate (ATE) for an ingredient in a mixture is derived using:
  - The LD<sub>50</sub>/LC<sub>50</sub> where available,

<sup>1</sup> this is particularly relevant in the case of ingredients classified in Category 1 and Category 2.

- The appropriate conversion value from Table 2 that relates to the results of a range test for an ingredient, or
  - The appropriate conversion value from Table 2 that relates to a classification for the ingredient
- c) Where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used when calculating the classification of the new mixture using the formulas in paragraph 24 - 28.

### **Classification of Mixtures Where Acute Toxicity Test Data are Available for the Complete Mixture.**

14. Where the mixture itself has been tested to determine its acute toxicity, it will be classified according to the criteria that have been agreed for substances. In situations where such test data for the mixture are not available, the procedures presented below should be followed.

### **Classification of Mixtures Where Acute Toxicity Test Data are not Available for the Complete Mixture.**

#### **Bridging Principles**

15. Where the mixture itself has not been tested to determine its acute 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

16. If a mixture is diluted with a substance that has an equivalent or lower toxicity classification than 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. Alternatively, the formula explained in paragraph 24 could be applied.

17. If a mixture is diluted with water or other totally non-toxic material, the toxicity of the mixture can be calculated from test data on the undiluted mixture. For example, if a mixture with an LD50 of 1000 mg/kg were diluted with an equal volume of water, the LD50 of the diluted mixture would be 2000 mg/kg.

#### Batching

18. The toxicity of one production batch of a concentration 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

19. If a mixture is classified in Category 1, and the concentration of the ingredients of the mixture that are in Category 1 is increased, the new mixture should be classified in Category 1 without additional testing.

### Interpolation Within One Toxicity Category

20. For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has toxicologically active ingredients with 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.

### Substantially Similar Mixtures

21. 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 hazard category.

### Aerosols

22. 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 Based on Ingredients of the Mixture (Additivity Formula).**

### **Data Available For All Ingredients**

23. In order to ensure that classification of the mixture is accurate, and that the calculation need only be performed once for all systems, sectors, and categories, the acute toxicity estimate (ATE) of ingredients should be considered as follows:

- Include ingredients with a known acute toxicity, which fall into any of the GHS acute toxicity categories.
- Ignore ingredients that are presumed not acutely toxic (e.g., water, sugar).
- Ignore ingredients if the oral limit test does not show acute toxicity at 2,000 mg/kg/body weight.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE).

24. The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for Oral, Dermal or Inhalation Toxicity:

$$\frac{100}{ATE_{\text{mix}}} = \sum_{\eta} \frac{C_i}{ATE_i}$$

where:

$C_i$  = concentration of ingredient i

n ingredients and i is running from 1 to n

$ATE_i$  = Acute Toxicity Estimate of ingredient i

### **Data Are Not Available For One Or More Ingredients Of The Mixture.**

25. Where an ATE is not available for an individual ingredient of the mixture, but available information such as listed below can provide a derived conversion value, the formula in paragraph 24 may be applied.

This may include evaluation of:

- (a) Extrapolation between oral, dermal and inhalation acute toxicity estimates<sup>1</sup>. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;
- (b) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;
- (c) Evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or
- (d) Data from closely analogous substances using structure/activity relationships.

26. This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity. If such information is not available, proceed to the provisions of paragraph 27.

27. In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1% or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture should be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredient(s) of unknown toxicity.

28. If the total concentration of the ingredient(s) with unknown acute toxicity is ≤ 10% then the formula presented in paragraph 24 should be used. If the total concentration of the ingredient(s) with unknown toxicity is >10%, the formula presented in paragraph 24 should be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

$$\frac{100 - (\sum C_{\text{unknown if } > 10\%})}{ATE_{\text{mix}}} = \sum_{\eta} \frac{C_i}{ATE_i}$$

**Table 2: Conversion from the experimentally obtained acute toxicity range estimates or a classification to point estimates for the respective routes of exposure.**

	<b>Classification or experimentally obtained acute toxicity range estimate (see note 1)</b>	<b>Conversion value (note 2)</b>
<b>Oral</b> (mg/kg)	0 < Category 1 ≤ 5	0.5
	5 < Category 2 ≤ 50	5
	50 < Category 3 ≤ 300	100
	300 < Category 4 ≤ 2000	500
	2000 < Category 5 ≤ 5000	2500

<sup>1</sup>. For ingredients with acute toxicity estimates available for other than the most appropriate exposure route, values may be extrapolated from the available exposure route to the most relevant route. Dermal and inhalatory route data are not always required for ingredients. However, in case data requirements for specific ingredients include acute toxicity estimates for the dermal and inhalatory route, the values to be used in the formula need to be from the required exposure route.

<b><u>Dermal</u></b> (mg/kg)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1000 1000 < Category 4 ≤ 2000 2000 < Category 5 ≤ 5000	5 50 300 1100 2500
<b><u>Gases</u></b> (ppm)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2500 2500 < Category 4 ≤ 5000 Category 5	10 100 700 3000
<b><u>Vapours</u></b> (mg/l)	0 < Category 1 ≤ 0.5 0.5 < Category 2 ≤ 2.0 2.0 < Category 3 ≤ 10.0 10.0 < Category 4 ≤ 20.0 Category 5	0.05 0.5 3 11
<b><u>Dust/mist</u></b> (mg/l)	0 < Category 1 ≤ 0.05 0.05 < Category 2 ≤ 0.5 0.5 < Category 3 ≤ 1.0 1.0 < Category 4 ≤ 5.0 Category 5	0.005 0.05 0.5 1.5

Note1: Category 5 is for mixtures which are of relatively low acute toxicity but which under certain circumstances may pose a hazard to vulnerable populations. These mixtures are anticipated to have an oral or dermal LD<sub>50</sub> value in the range of 2000-5000mg/kg or equivalent dose for other routes of exposure. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance for protecting human health.

Note2: These values are designed to be used in the calculation of the ATE for a mixture based on its components and do not represent test results. The values are conservatively set at the lower end of the range of Categories 1 and 2, and at a point approximately 1/10<sup>th</sup> from the lower end of the range for Categories 3 – 5.

## HAZARD COMMUNICATION

### Allocation of Label Elements

29. General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 3 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 3: Acute Toxicity Label Elements**

	Category 1	Category 2	Category 3	Category 4	Category 5
Symbol	Skull and Crossbones	Skull and Crossbones	Skull and Crossbones	Exclamation Mark	No symbol is used
Signal Word	Danger	Danger	Danger	Warning	Warning
<u>Hazard Statement:</u> --Oral	Fatal if swallowed	Fatal if swallowed	Toxic if swallowed	Harmful if swallowed	May be harmful if swallowed
--Dermal	Fatal in contact with skin	Fatal in contact with skin	Toxic in contact with skin	Harmful in contact with skin	May be harmful in contact with skin
--Inhalation	Fatal if inhaled	Fatal if inhaled	Toxic if inhaled	Harmful if inhaled	May be harmful if inhaled

**Additional Information for Category 5 Classification**

30. As provided in Note e to Table 1, classification into Category 5 involves consideration of additional criteria, beyond the values contained in the classification table. When considering these criteria, the following guidance should be kept in mind.

31. “Reliable information” is considered to be information from tests that are conducted according to internationally recognised scientific principles.

Effects Considered to Support Classification

31. “Significant signs of toxicity” include:

- 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

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

### 33. Decision Tree for Classification of Acute Toxicity

Classify in Category 5 if assignment to a more hazardous class is not warranted

Does the substance/mixture have an:  
 LD<sub>50</sub> # 5 mg/kg (oral)  
 LD<sub>50</sub> # 50 mg/kg (dermal)  
 LC<sub>50</sub> # 100 ppm (gas)  
 LC<sub>50</sub> # 0.5 (mg/l) (vapour)  
 LC<sub>50</sub> # 0.05 (mg/l) (dust,mist)

Y Yes Y

Category 1

No

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Does the substance/mixture have an:  
 LD<sub>50</sub> between 5 and less than 50 mg/kg (oral)  
 LD<sub>50</sub> between 50 and less than 200 50 mg/kg (dermal)  
 LC<sub>50</sub> between 100 and less than 500 ppm (gas)  
 LC<sub>50</sub> between 0.5 and less than 2.0 (mg/l) (vapour)  
 LC<sub>50</sub> between 0.05 and less than 0.5 (mg/l) (dust,mist)

Y Yes Y

Category 2

No

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Does the substance/mixture have an  
 LD<sub>50</sub> between 50 and less than 300 mg/kg (oral)  
 LD<sub>50</sub> between 200 and less than 1000 mg/kg (dermal)  
 LC<sub>50</sub> between 500 and less than 2500 ppm (gas)  
 LC<sub>50</sub> between 2.0 and less than 10.0 (mg/l) (vapour)  
 LC<sub>50</sub> between 0.5 and less than 1.0 (mg/l) (dust,mist)

Y Yes Y

Category 3

No

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Does the substance/mixture have an  
 LD<sub>50</sub> between 300 and less than 2000 mg/kg (oral)  
 LD<sub>50</sub> between 1000 and less than 2000 mg/kg (dermal)  
 LC<sub>50</sub> between 2500 and less than 5000 ppm (gas)  
 LC<sub>50</sub> between 10.0 and less than 20.0 (mg/l) (vapour)  
 LC<sub>50</sub> between 1.0 and less than 5.0 (mg/l) (dust,mist)

Y Yes Y

Category 4

No

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Does the substance/mixture have an  
 LD<sub>50</sub> between 2000 and 5000 (oral)

Y Yes Y

Category 5

Is there reliable information is available indicating significant toxicity effects in humans?

Y Yes Y

No

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No

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Was any mortality is observed when tested up to Class 4 values by the oral, inhalation or dermal routes?

Y Yes Y

Classify in Category 5 if assignment to a more hazardous class is not warranted.

No  
\  
No

Is there expert judgement that confirms significant clinical signs of toxicity, when tested up to class 4 values, except for diarrhoea, piloerection or an ungroomed appearance?

Y Yes Y

No  
\  
No

Is there expert judgement that confirms reliable information indicating the potential for significant acute effects from other animals?

Y Yes Y

Classify in Category 5 if assignment to a more hazardous class is not warranted.

No  
\  
No

Classify in Category 5 if assignment to a more hazardous class is not warranted.

Substance is not acutely toxic

#### 40. Classification and Labelling Summary

Does the substance/mixture meet the criteria below?

No <sup>o</sup> The substance/mixture is not classified as a acutely toxic.

Yes <sup>o</sup> See the hazard communication elements appropriate to the criteria.

	Criteria	Hazard Communication Elements	
Category 1	LD <sub>50</sub> # 5 mg/kg (oral) LD <sub>50</sub> # 50 mg/kg (dermal) LC <sub>50</sub> # 100 ppm (gas) LC <sub>50</sub> # 0.5 (mg/l) (vapour) LC <sub>50</sub> # 0.05 (mg/l) (dust,mist)	<i>Signal Word</i>	Danger
		<i>Symbol</i>	Skull and Crossbones
		<i>Hazard Statement</i>	Fatal if swallowed. (oral) Fatal in contact with skin (dermal) Fatal if inhaled (gas, vapour, dust, mist)
Category 2	LD <sub>50</sub> between 5 and less than 50 mg/kg (oral) LD <sub>50</sub> between 50 and less than 200 50 mg/kg (dermal) LC <sub>50</sub> between 100 and less than 500 ppm (gas) LC <sub>50</sub> between 0.5 and less than 2.0 (mg/l) (vapour) LC <sub>50</sub> between 0.05 and less than 0.5 (mg/l) (dust,mist)	<i>Signal Word</i>	Danger
		<i>Symbol</i>	Skull and Crossbones
		<i>Hazard Statement</i>	Fatal if swallowed. (oral) Fatal in contact with skin (dermal) Fatal if inhaled (gas, vapour, dust, mist)
Category 3	LD <sub>50</sub> between 50 and less than 300 mg/kg (oral) LD <sub>50</sub> between 200 and less than 1000 mg/kg (dermal) LC <sub>50</sub> between 500 and less than 2500 ppm (gas) LC <sub>50</sub> between 2.0 and less than 10.0 (mg/l) (vapour) LC <sub>50</sub> between 0.5 and less than 1.0 (mg/l) (dust,mist)	<i>Signal Word</i>	Danger
		<i>Symbol</i>	Skull and Crossbones
		<i>Hazard Statement</i>	Toxic if swallowed. (oral) Toxic in contact with skin (dermal) Toxic if inhaled (gas, vapour, dust, mist)
Category 4	LD <sub>50</sub> between 300 and less than 2000 mg/kg (oral) LD <sub>50</sub> between 1000 and less than 2000 mg/kg (dermal) LC <sub>50</sub> between 2500 and less than 5000 ppm (gas) LC <sub>50</sub> between 10.0 and less than 20.0 (mg/l) (vapour) LC <sub>50</sub> between 1.0 and less than 5.0 (mg/l) (dust,mist)	<i>Signal Word</i>	Warning
		<i>Symbol</i>	Exclamation Mark
		<i>Hazard Statement</i>	Harmful if swallowed. (oral) Harmful in contact with skin (dermal) Harmful if inhaled (gas, vapour, dust, mist)

Category 5	LD <sub>50</sub> between 2000 and 5000 (oral)  See also the additional criteria (para xx)	<i>Signal Word</i>	Warning
		<i>Symbol</i>	No symbol
		<i>Hazard Statement</i>	May be harmful if swallowed (oral) May be harmful in contact with skin (dermal) May be harmful if inhaled (gas, vapour, dust, mist)

Additional Acute Toxicity Criteria:

41. A substance is classified in Category 5, if assignment to a more hazardous class is not warranted, through extrapolation, estimation or measurement of data if:

- reliable information is available indicating significant toxicity effects in humans
- any mortality is observed when tested up to Category 4 values by the oral, inhalation or dermal routes.
- where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance, or
- where expert judgement confirms reliable information indicating the potential for significant acute effects from other animals.

## 42. EXAMPLES

### MIXTURE A CONTAINING HAZARDOUS SUBSTANCE Y

Substance Y is used as a carpet cleaner and supplied as mixture A that is an 18% solution of substance Y in water. How should mixture A be classified and labelled?

In order to reach a conclusion about the classification and labelling of mixture A, we must first define how its components are classified. As water is not classified as hazardous, it is the classification of substance Y that is of importance here.

#### *Classification and labelling of substance Y*

We have data available from published literature to indicate that substance Y is acutely toxic but is not hazardous to health in other ways.

The acute toxicity is summarised in the table below.

Type of study	Experimental results	GHS Category
Rat, single oral administration	ATE <sub>i</sub> = 200 mg/kg	Category 3
Rat, single 4-hour inhalation to the vapour	ATE <sub>i</sub> = 5 mg/l	Category 3
Dermal administration	No data	No classification

The ATE<sub>i</sub> (Acute Toxicity Estimate of the substance) is calculated from an acute toxicity, single exposure study and indicates the exposure level that is associated with severe signs of toxicity in the species studied.

See paragraph 2 for the acute toxicity classification criteria.

Therefore the classification of substance Y is as follows:

*Acute Toxicity Category 3 (by the oral and inhalation routes)*

Although not needed for the classification of Mixture A, the labelling of Substance Y can be determined at this point. Given that it is in Category 3 for acute toxicity, reference to Table 3, paragraph 29 shows that the following label information is appropriate:

Signal word  
Symbol  
Hazard statements

Danger  
Skull & crossbones  
Toxic if swallowed and if inhaled

### *Classification and labelling of mixture A*

There are no toxicological data available for mixture A and therefore according to the classification criteria (paragraph 23-24) its classification and labelling must be determined by a calculation method using a standard equation.

As indicated above, we need only consider the hazard of substance Y and the calculations that are required are shown below.

The classification criteria define the equation  $100/ATE_{mix} = ATE_i / \%$ ,  
where:  $ATE_i$  is the Acute Toxicity Estimate of substance A;  
 $ATE_{mix}$  is the Acute Toxicity Estimate of mixture Y; and  
% is the percentage value of substance A in mixture Y.

This standard equation can be expressed alternatively as  
 $ATE_{mix} = 100 \times ATE_i / \%$ .

As we know that mixture A contains 18% of substance Y, the value of the % term is 18. We can determine the classification of the mixture as follows:

Acute oral toxicity: $ATE_i = 200 \text{ mg/kg}$ $ATE_{mix} = 100 \times 200/18$ $ATE_{mix} = 1111 \text{ mg/kg}$
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The  $ATE_{mix}$  value of 1111 mg/kg indicates Class 4 is appropriate.

Acute inhalation: $ATE_i = 5 \text{ mg/l (vapour)}$ $ATE_{mix} = 100 \times 5/18$ $ATE_{mix} = 27.8 \text{ mg/l}$
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The  $ATE_{mix}$  value of 27.8 mg/l indicates Category 5 is appropriate.

Therefore the classification of mixture A is as follows:  
*Acute toxicity Class 4 (oral route) and Acute toxicity Category 5 (inhalation route)*

Having determined that mixture A should be classified in Category 4, we can determine from the labelling rules (see table 3, paragraph 29) that the following label information is appropriate:

Signal word	Warning
Symbol	Exclamation Mark
Hazard statements	Harmful if swallowed and may be harmful if inhaled