COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the
Transport of Dangerous Goods

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ISSUES RELATING TO THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Implementation of acute toxicity criteria of the GHS
into Division 6.1 of the UN Recommendations on the Transport of Dangerous Goods

Transmitted by the expert from Germany

1. Taking into account resolution 2003/64 of 25 July 2003 of the United Nations Economic and Social Council, inviting governments and organisations to implement the GHS criteria, the Sub-Committee of Experts on the Transport of Dangerous Goods is committed to implement the GHS criteria into the UN Model Regulations.

2. On the occasion of documents submitted by the expert from the Netherlands in 2008 on the implementation of corrosivity criteria (ST/SG/AC.10/C.3/2008/48, ST/SG/AC.10/C.3/2008/83, UN/SCETDG/33/INF.17 and UN/SCETDG/34/INF.19) the Sub-Committee supported unanimously the need for harmonization with the GHS (refer to ST/SG/AC.10/C.3/68, para. 108) and deferred further consideration of the text proposal by the Netherlands to the current biennium.

3. At the July 2009 session, the Sub-Committee continued its discussion on the basis of ST/SG/AC.10/C.3/2009/15 (Netherlands) and informal documents 3, 12,15, 21 and 25. There was no consensus within the Sub-Committee as to the approach to be followed as regards the corrosivity criteria to be used in the transport sector. It was finally agreed that document ST/SG/AC.10/C.3/2009/15 should be carried forward to the next session, for consideration by a working group.

4. In order to further promote harmonization of health-related classification, the expert from Germany supports the extension of the approach of the Netherlands to the criteria and procedures for the classification of acute toxicity. This is based on the results of an analysis of present differences between the UN Recommendations and the GHS with regard to acute toxicity classification as well as a proposal for the amendment of Chapter 2.6 of the UN Model Regulations.

5. While classification cut-off values for acute toxicity by the oral and dermal routes as well as by inhalation of dusts and mists are already harmonized between TDG Division 6.1, packing groups I-III, and GHS Acute Toxicity categories 1-3, respectively, significant differences remain regarding the data used for classification, the criteria for acute toxicity by inhalation of vapours, and the methods for determining the toxicity of mixtures.

6. Experimental animal data used for the assignment of packing groups in TDG Division 6.1 are expressed in terms of LD_{50} and LC_{50} values, respectively. The GHS criteria, on the other hand, are based on the acute toxicity estimate (ATE), which can be identical with an available LD_{50} or LC_{50}, but can also be derived by conversion from results of range tests or from existing classifications. Application of the ATE takes account of regulatory changes in some regions, which for the sake of animal welfare have abolished the determination of LD_{50} or LC_{50} values in favour of the performance of limit or range tests for acute toxicity. The use of results from limit or range tests for the calculation of the toxicity of mixtures is facilitated by the ATE concept. The presented proposal for an amendment of TDG Chapter 2.6 therefore includes the adoption of the ATE concept into the transport regulations.

7. TDG Division 6.1 includes provisions for the classification of liquids having toxic vapours, which take into account both the toxicity of the vapour (LC_{50}) and the volatility of the substance (saturated vapour concentration). The GHS includes only rules for the classification of the vapour, based on its toxicity, without further considerations, but notes that the saturated vapour concentration is used as an additional element in some regulatory systems, including the UN TDG Recommendations. Thus, the differences between the two systems in this point are not a violation against the principle of harmonisation. The presented proposal for an amendment of TDG Chapter 2.6 therefore in principle retains the current TDG concept for the classification of liquids having toxic vapours with two modifications: The use of LC_{50} values is substituted by the ATE as explained above, and the description of threshold toxicity tests (paragraph 2.6.2.2.4.8) is deleted as it may conflict with national or regional legislation regarding test methods approved for regulatory purposes.

8. Compared to the current provisions in TDG Chapter 2.6 for the determination of the toxicity of mixtures, the GHS contains several additional approaches in order to make the most efficient use of available data and to facilitate the classification of mixtures. The presented proposal for an amendment of TDG Chapter 2.6 therefore includes the adoption of additional GHS concepts for the classification of mixtures based on available data.

9. A proposal for amendment of TDG Chapter 2.6 is presented in Annex 1 (‘track changes’ version) and in Annex 2 (‘clean’ version), respectively. The proposal is deemed to serve as a starting point for further discussions, also depending on the outcome of the working group on the harmonization of corrosivity criteria.

Annex 1

Text proposal "track changes" version

"CHAPTER 2.6

CLASS 6 - TOXIC AND INFECTIOUS SUBSTANCES

Introductory notes

NOTE 1: *Genetically modified microorganisms and organisms which do not meet the definition of an infectious substance shall be considered for classification in Class 9 and assignment to UN 3245.*

NOTE 2: *Toxins from plant, animal or bacterial sources which do not contain any infectious substances, or toxins that are contained in substances which are not infectious substances, shall be considered for classification in Division 6.1 and assignment to UN 3172.*

2.6.1 Definitions

Class 6 is divided into two divisions as follows:

(a) Division 6.1 *Toxic substances*

These are substances liable either to cause death or serious injury or to harm human health swallowed or inhaled or by skin contact;

(b) Division 6.2 *Infectious substances*

These are substances known or reasonably expected to contain pathogens. Pathogens are defined as microorganisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals.

2.6.2 Division 6.1 - Toxic substances

2.6.2.1 ***Definitions***

For the purposes of these Regulations:

2.6.2.1.1 The acute toxicity estimate (ATE) for the classification of a substance is derived using the LD_{50}/LC_{50} where available.

2.6.2.1.2 The acute toxicity estimate (ATE) for a substance in a mixture is derived using:

(i) the LD_{50}/LC_{50} where available; otherwise,

(ii) the appropriate conversion value from Table 2.6.2 that relates to the results of a range test; or

(iii) the appropriate conversion value from Table 2.6.2 that relates to a packing group.

[Text copied from GHS Table 3.1.1, Notes (a) and (b)]

2.6.2.1.~~1~~3 *LD_{50} (median lethal dose) for acute oral toxicity* is the statistically derived single dose of a substance that can be expected to cause death within 14 days in 50 per cent of ~~young adult albino rats~~ test animals when administered by the oral route. The LD_{50} value is expressed in terms of mass of test substance per mass of test animal (mg/kg).

2.6.2.1.~~2~~4 *LD_{50} for acute dermal toxicity* is that dose of the substance which, administered by continuous contact for 24 hours with the bare skin of ~~albino rabbits~~ test animals, is most likely to cause death within 14 days in one half of the animals tested. ~~The number of animals tested shall be sufficient to give a statistically significant result and be in conformity with good pharmacological practice.~~ The result is expressed in milligrams per kg body mass.

2.6.2.1.~~3~~5 *LC_{50} for acute toxicity on inhalation* is that concentration of vapour, mist or dust which, administered by continuous inhalation to both male and female ~~young adult albino rats~~ test animals for one to four hours, is most likely to cause death within 14 days in one half of the animals tested. A solid substance shall be tested if at least 10% (by mass) of its total mass is likely to be dust in a respirable range, e.g. the aerodynamic diameter of that particle fraction is 10 microns or less. A liquid substance shall be tested if a mist is likely to be generated in a leakage of the transport containment. Both for solid and liquid substances more than 90% (by mass) of a specimen prepared for inhalation toxicity shall be in the respirable range as defined above. The result is expressed in milligrams per litre of air for dusts and mists or in millilitres per cubic metre of air (parts per million) for vapours.

2.6.2.1.6 The terms “dust”, “mist” and “vapour” are defined as follows:

(i) Dust: solid particles of a substance or mixture suspended in a gas (usually air);

(ii) Mist: liquid droplets of a substance or mixture suspended in a gas (usually air);

(iii) Vapour: the gaseous form of a substance or mixture released from its liquid or solid state.

Dust is generally formed by mechanical processes. Mist is generally formed by condensation of supersaturated vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from less than 1 to about 100 µm.

[Text copied from GHS Table 3.1.1, Note (e)]

2.6.2.2 *Assignment of packing groups*

2.6.2.2.1 Substances of Division 6.1, including pesticides, are allocated among the three packing groups according to their degree of toxic hazard in transport as follows:

(a) *Packing group I*: Substances and preparations presenting a very severe toxicity risk;

(b) *Packing group II*: Substances and preparations presenting a serious toxicity risk;

(c) *Packing group III*: Substances and preparations presenting a relatively low toxicity risk.

2.6.2.2.2 In making this grouping, account shall be taken of human experience in instances of accidental poisoning and of special properties possessed by any individual substance, such as liquid state, high volatility, any special likelihood of penetration, and special biological effects.

2.6.2.2.3 In the absence of human experience the grouping shall be based on data obtained from animal experiments. Three possible routes of administration shall be examined. These routes are exposure through:

(a) Oral ingestion;

(b) Dermal contact; and

(c) Inhalation of dusts, mists or vapours.

When a substance exhibits a different order of toxicity by two or more of these routes of administration, the highest degree of danger indicated by the tests shall be assigned. [Text moved here from 2.6.2.2.3.1]

2.6.2.2.3.1 ~~Appropriate animal tests for the various routes of exposure are described in 2.6.2.1.~~ 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. Test data already generated should be accepted. When experimental data for acute toxicity are available in several animal species, scientific judgment should be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests. [Text copied from GHS 3.1.2.3] ~~When a substance exhibits a different order of toxicity by two or more of these routes of administration, the highest degree of danger indicated by the tests shall be assigned.~~

2.6.2.2.4 The criteria to be applied for grouping a substance according to the toxicity it exhibits by all three routes of administration are presented in the following paragraphs.

2.6.2.2.4.1 The grouping criteria for the oral and dermal routes as well as for inhalation of dusts and mists are as shown in the following table.

Table 2.6.1 GROUPING CRITERIA FOR ADMINISTRATION THROUGH ORAL INGESTION, DERMAL CONTACT AND INHALATION OF DUSTS AND MISTS

Packing group	Oral toxicity ~~LD_{50}~~ ATE (mg/kg)	Dermal toxicity ~~LD_{50}~~ ATE (mg/kg)	Inhalation toxicity by dusts and mists ~~LC_{50}~~ ATE (mg/l)
I	≤ 5.0	≤ 50	≤ ~~0.2~~ 0.05
II	> 5.0 and ≤ 50	> 50 and ≤ 200	> ~~0.2~~ 0.05 and ≤ ~~2.0~~ 0.5
III[a]	> 50 and ≤ 300	> 200 and ≤ 1 000	> ~~2.0~~ 0.5 and ≤ ~~4~~ 1.0
			[previous TDG criteria replaced by GHS criteria due to considerations in para 2.6.2.2.4.3]

[a] *Tear gas substances shall be included in packing group II even if their toxicity data correspond to packing group III values.*

NOTE: *Substances meeting the criteria of Class 8 and with an inhalation toxicity of dusts and mists (~~LC_{50}~~ ATE) leading to packing group I are only accepted for an allocation to Division 6.1 if the*

toxicity through oral ingestion or dermal contact is at least in the range of packing group I or II. Otherwise an allocation to Class 8 is made when appropriate (see 2.8.2.3).

2.6.2.2.4.2 The criteria for inhalation toxicity of dusts and mists in 2.6.2.2.4.1 are based on ~~LC_{50}~~ quantitative experimental data relating to ~~1~~ 4 hours exposures and where such information is available it shall be used. However, where only ~~LC_{50}~~ data relating to ~~4~~ 1 hour~~s~~ exposures to dusts and mists are available, such figures can be ~~multiplied~~ divided by four and the product substituted in the above criteria, i.e. ~~LC_{50}~~ATE (~~4~~1 hour~~s~~) ~~÷~~ × 4 is considered the equivalent of ~~LC_{50}~~ ATE (~~4~~1 hours).

[previous TDG criteria replaced by GHS criteria due to considerations in para 2.6.2.2.4.3]

2.6.2.2.4.3 Of particular importance is the use of well articulated values in the high toxicity packing groups 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 table 2.6.1 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.

[Text copied from GHS 3.1.2.6.4]

2.6.2.2.4.~~3~~4 Liquids having toxic vapours shall be assigned to the following packing groups, where "V" is the saturated vapour concentration in millilitres per cubic metre of air (volatility) at 20 °C and standard atmospheric pressure:

(a) Packing group I: If $V \geq 10$ ~~LC_{50}~~ ATE and ~~LC_{50}~~ ATE $\leq$ 1 000 ml/m^3;

(b) Packing group II: If $V \geq$ ~~LC_{50}~~ ATE and ~~LC_{50}~~ ATE $\leq$ 3 000 ml/m^3, and not meeting the criteria for packing group I;

(c) Packing group III[1]: If $V \geq 1/5$ ~~LC_{50}~~ ATE and ~~LC_{50}~~ ATE $\leq$ 5 000 ml/m^3, and not meeting the criteria for packing groups I or II.

2.6.2.2.4.~~4~~5 In Figure 2.6.1, the criteria according to 2.6.2.2.4.~~3~~4 are expressed in graphical form, as an aid to easy classification. However, because of approximations inherent in the use of graphs, substances on or near packing group borderlines shall be checked using numerical criteria.

Figure 2.6.1: Inhalation toxicity: packing group borderlines

2.6.2.2.4.~~5~~6 The criteria for inhalation toxicity of vapours in 2.6.2.2.4.~~3~~4 are based on ~~LC_{50}~~ data relating to 1 hour exposure, and where such information is available it shall be used. However, where only ~~LC_{50}~~ data relating to 4 hours exposures to the vapours are available, such figures can be multiplied by two and the product substituted in the above criteria, i.e. ~~LC_{50}~~ ATE (4 hours) × 2 is considered to be the equivalent of ~~LC_{50}~~ ATE (1 hour).

[1] *Tear gas substances are included in Packing group II even if their toxicity data correspond to packing group III values*.

~~2.6.2.2.4.6 Mixtures of liquids that are toxic by inhalation shall be assigned to packing groups according to 2.6.2.2.4.7 or 2.6.2.2.4.8.~~

~~2.6.2.2.4.7 If LC_{50} data are available for each of the toxic substances comprising a mixture, the packing group may be determined as follows:~~

~~(a) Estimate the LC_{50} of the mixture using the formula:~~

~~where: f_i = mole fraction of the i^{th} component substance of the mixture;~~

~~LC_{50i} = mean lethal concentration of the i^{th} component substance in ml/m^3;~~

~~(b) Estimate the volatility of each component substance comprising the mixture using the formula:~~

~~where: P_i = partial pressure of the i^{th} component substance in kPa at 20 °C and one atmosphere pressure;~~

~~(c) Calculate the ratio of the volatility to the LC_{50} using the formula:~~

~~(d) Using the calculated values LC_{50}(mixture) and R, the packing group for the mixture is determined:~~

~~(i) *Packing group I*: R ≥ 10 and LC_{50}(mixture) ≤ 1 000 ml/m^3;~~

~~(ii) *Packing group II* : R ≥ 1 and LC_{50}(mixture) ≤ 3 000 ml/m^3 and not meeting criteria for packing group I;~~

~~(iii) *Packing group III*: R ≥ 1/5 and LC_{50}(mixture) ≤ 5 000 ml/m^3 and not meeting criteria for packing groups I or II.~~

[Text moved to end of section 2.6.2.3]

~~2.6.2.2.4.8 In the absence of LC_{50} data on the toxic constituent substances, the mixture may be assigned a packing group based on the following simplified threshold toxicity tests. When these threshold tests are used, the most restrictive packing group determined is used for transporting the mixture.~~

~~(a) A mixture is assigned to packing group I only if it meets both of the following criteria:~~

~~(i) A sample of the liquid mixture is vaporized and diluted with air to create a test atmosphere of 1 000 ml/m^3 vaporized mixture in air. Ten albino rats (five male and five female) are exposed to the test atmosphere for one hour and observed for fourteen days. If five or more of the animals die within the fourteen day observation period, the mixture is presumed to have an LC_{50} equal to or less than 1 000 ml/m^3;~~

~~(ii) A sample of the vapour in equilibrium with the liquid mixture at 20 °C is diluted with 9 equal volumes of air to form a test atmosphere. Ten albino rats (five male and five female) are exposed to the test atmosphere for one hour and observed for fourteen days. If five or more of the animals die within the fourteen day observation period, the mixture is presumed to have a volatility equal to or greater than 10 times the mixture LC_{50};~~

~~(b) A mixture is assigned to packing group II only if it meets both of the following criteria, and the mixture does not meet the criteria for packing group I:~~

~~(i) A sample of the liquid mixture is vaporized and diluted with air to create a test atmosphere of 3 000 ml/m^3 vaporized mixture in air. Ten albino rats (five male and five female) are exposed to the test~~

~~atmosphere for one hour and observed for fourteen days. If five or more of the animals die within the fourteen day observation period, the mixture is presumed to have an LC_{50} equal to or less than 3 000 ml/m³;~~

~~(ii) A sample of the vapour in equilibrium with the liquid mixture at 20 °C is used to form a test atmosphere. Ten albino rats (five male and five female) are exposed to the test atmosphere for one hour and observed for fourteen days. If five or more of the animals die within the fourteen day observation period, the mixture is presumed to have a volatility equal to or greater than the mixture LC_{50};~~

~~(c) A mixture is assigned to packing group III only if it meets both of the following criteria, and the mixture does not meet the criteria for packing groups I or II:~~

~~(i) A sample of the liquid mixture is vaporized and diluted with air to create a test atmosphere of 5 000 ml/m³ vaporized mixture in air. Ten albino rats (five male and five female) are exposed to the test atmosphere for one hour and observed for fourteen days. If five or more of the animals die within the fourteen day observation period, the mixture is presumed to have an LC_{50} equal to or less than 5 000 ml/m³;~~

~~(ii) The vapour pressure of the liquid mixture is measured and if the vapour concentration is equal to or greater than 1 000 ml/m³, the mixture is presumed to have a volatility equal to or greater than 1/5 the mixture LC_{50}.~~

[Text deleted as the described methods may be conflict with endorsed test methods by regional legislation]

2.6.2.3 Methods for determining ~~oral and dermal~~ the toxicity of mixtures

2.6.2.3.1 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 and there is no relevant evidence to suggest acute toxicity by multiple routes When there is relevant evidence of toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. [Text copied from GHS 3.1.3.2] If the acute toxicity is determined for more than one route of exposure, the packing group shall be assigned according to the highest degree of danger indicated. Mixtures shall be classified and assigned to packing groups for the oral and dermal routes as well as for inhalation of dusts and mists according to 2.6.2.3.2 - 2.6.2.3.10.

2.6.2.3.~~1~~2 When classifying and assigning the appropriate packing group to mixtures in Division 6.1, in accordance with the ~~oral and dermal~~ toxicity criteria in 2.6.2.2, it is necessary to determine the acute ~~LD_{50}~~ toxicity estimate of the mixture. In order to make use of all available data for purposes of classifying the hazards of mixtures, certain assumptions have been made:

(a) The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w) , unless there is a reason to suspect that an ingredient present at a concentration <1% is still relevant for classifying the mixture for acute toxicity. This point is particularly relevant when classifying untested mixtures which contain ingredients to which packing group I or II is assigned.

(b) 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 formula in 2.6.2.3.10.

(c) If the converted acute toxicity point estimates for all ingredients of a mixture are within the same packing group, then the mixture should be assigned to that packing group;

(d) When only range data (or information about Division 6.1 packing groups) are available for ingredients in a mixture, they may be converted to point estimates in accordance with Table 2.6.2 when calculating the classification of the new mixture using the formula in 2.6.2.3.10.

[Text copied from GHS 3.1.3.3]

Table 2.6.2: Conversion from experimentally obtained acute toxicity range values or Division 6.1 packing groups to acute toxicity point estimates for use in the formulas for the classification of mixtures with regard to oral ingestion, dermal contact and inhalation of dusts and mists

Exposure routes	**Packing group or experimentally obtained acute toxicity range estimate**	**Converted Acute Toxicity point estimate** (see Note)
Oral (mg/kg)	0 < PG I ≤ 5	0.5
	5 < PG II ≤ 50	5
	50 < PG III ≤ 300	100
Dermal (mg/kg)	0 < PG I ≤ 50	5
	50 < PG II ≤ 200	50
	200 < PG III ≤ 1000	300
Vapours (ml/m^3)	0 < PG I ≤ 1000	100
	1000 < PG II ≤ 3000	1000
	3000 < PG III ≤ 5000	3200
Dust/mist (mg/l)	0 < PG I ≤ 0.05	0.005
	0.05 < PG II ≤ 0.5	0.05
	0.5 < PG III ≤ 1.0	0.5

NOTE: *These values are designed to be used in the calculation of the ATE for classification of a mixture based on its ingredients and do not represent test results. The values are conservatively set at the lower end of the range of packing groups I and II, and at a point approximately 1/10th from the lower end of the range for packing group III.*

[Table and Note copied from GHS (Table 3.1.2, Note 2) and modified]

2.6.2.3.~~2~~3 If a mixture contains only one toxicologically active substance, and the ~~LD_{50}-~~ATE of that constituent is known, in the absence of reliable acute ~~oral and dermal~~ toxicity data on the actual mixture to be transported, the ~~oral or dermal LD_{50}~~ATE may be obtained by the following method:

$$\text{ATE mixture} = \frac{\text{ATE of active substance} \times 100}{\text{percentage of active substance by mass}}$$

2.6.2.3.~~3~~4 If a mixture contains more than one active constituent, ~~there are three possible~~ the approaches according to 2.6.2.3.5 – 2.6.2.3.11~~that~~ may be used to determine the ~~oral or dermal LD_{50}~~ATE of the mixture. ~~The preferred method is to obtain reliable acute oral and dermal toxicity data on the actual~~

~~mixture to be transported. If reliable, accurate data are not available, then either of the following methods may be performed:~~

~~(a) Classify the formulation according to the most hazardous constituent of the mixture as if that constituent were present in the same concentration as the total concentration of all active constituents; or~~2.6.2.3.5 Where the mixture itself has been tested to determine its acute toxicity, it will be classified according to the same criteria as those used for substances, presented in Table 2.6.1. [Text copied from GHS 3.1.3.4]

2.6.2.3.6 *Dilution:* If a tested mixture is diluted with a diluent 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 diluted mixture may be classified as equivalent to the original tested mixture. [Text copied from GHS 3.1.3.5.2]

2.6.2.3.7 *Concentration of highly toxic mixtures:* If a tested mixture is classified in Division 6.1 and assigned to packing group I, and the concentration of the ingredients of the tested mixture that are in packing group I is increased, the resulting untested mixture should be assigned to packing group I without additional testing. [Text copied from GHS 3.1.3.5.4]

2.6.2.3.8 *Interpolation within one packing group:* For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and in the same packing group, 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 packing group as A and B. [Text copied from GHS 3.1.3.5.5]

2.6.2.3.9 *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 Division 6.1 packing group and are not expected to affect the toxicity of B

If mixture (i) or (ii) is already classified in Division 6.1 and assigned to a packing group based on test data, then the other mixture can be assigned to the same packing group. [Text copied from GHS 3.1.3.5.6]

~~(b)~~2.6.2.3.10 Based on available data for all ingredients of a mixture, the ATE of the mixture is determined according to the following formula ~~Apply the formula~~:

$$\frac{100}{T_M} = \sum \frac{C_i}{T_i}$$

where: C_i = the % concentration of constituent ~~A, B ... Z~~ i in the mixture;

T_i = the ~~oral LD_{50} values~~ ATE of constituent ~~A, B ... Z~~ i;

T_M = the ~~oral LD_{50} value~~ ATE of the mixture.

~~***NOTE:*** *This formula can also be used for dermal toxicities provided that this information is available on the same species for all constituents. The use of this formula does not take into account any potentiation or protective phenomena.*~~

2.6.2.3.11 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 2.6.2.3.10 may be applied. This may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates[2]. Such an evaluation could require appropriate toxicodynamic and toxicokinetic 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.

This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity. [Text copied from GHS 3.1.3.6.2.1]

2.6.2.3.12 Mixtures of liquids that are toxic by inhalation shall be assigned to packing groups according to 2.6.2.3.13 [Text moved here from 2.6.2.2.4.6].

2.6.2.3.13 If quantitative experimental data are available for each of the toxic substances comprising a mixture, the packing group may be determined as follows:

(a) Estimate the ATE of the mixture using the formula:

$$\text{ATE (mixture)} = \frac{1}{\sum \frac{f_i}{ATE_i}}$$

where: f_i = mole fraction of the i^{th} component substance of the mixture;

ATE_i = acute toxicity estimate of the i^{th} component substance in ml/m^3;

(b) Estimate the volatility of each component substance comprising the mixture using the formula:

[2] *When mixtures contain ingredients that do not have acute toxicity data for each route of exposure, acute toxicity estimates may be extrapolated from the available data and applied to the appropriate routes.*

$$V_i = \frac{P_i \times 10^6}{101.3} ml/m^3$$

where: P_i = partial pressure of the i^{th} component substance in kPa at 20 °C and one atmosphere pressure;

(c) Calculate the ratio of the volatility to the ATE using the formula:

$$R = \sum \frac{V_i}{ATE_i}$$

(d) Using the calculated values ATE(mixture) and R, the packing group for the mixture is determined:

(i) *Packing group I*: R ≥ 10 and ATE (mixture) ≤ 1 000 ml/m^3;

(ii) *Packing group II* : R ≥ 1 and ATE (mixture) ≤ 3 000 ml/m^3 and not meeting criteria for packing group I;

(iii) *Packing group III*: R ≥ 1/5 and ATE (mixture) ≤ 5 000 ml/m^3 and not meeting criteria for packing groups I or II.

[Text moved here from 2.6.2.2.4.7]

2.6.2.4 Classification of pesticides

2.6.2.4.1 All active pesticide substances and their preparations for which the ~~LC_{50} and/or LD_{50}~~ ATE values are known and which are classified in Division 6.1 shall be classified under appropriate packing groups in accordance with the criteria given in 2.6.2.2. Substances and preparations which are characterized by subsidiary risks shall be classified according to the precedence of hazard table in Chapter 2.0 with the assignment of appropriate packing groups.

2.6.2.4.2 If the ~~oral or dermal LD_{50} value~~ ATE for a pesticide preparation is not known, but the ~~LD_{50} value~~ ATE of its active substance(s) is known, the ~~LD_{50} value~~ ATE for the preparation may be obtained by applying the procedures in 2.6.2.3.

NOTE: *LD_{50} toxicity data for a number of common pesticides may be obtained from the most current edition of the document "The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification" available from the International Programme on Chemical Safety, World Health Organisation (WHO), 1211 Geneva 27, Switzerland. While that document may be used as a source of LD_{50} data for pesticides, its classification system shall not be used for purposes of transport classification of, or assignment of packing groups to, pesticides, which shall be in accordance with these regulations.*

2.6.2.4.3 The proper shipping name used in the transport of the pesticide shall be selected on the basis of the active ingredient, of the physical state of the pesticide and any subsidiary risks it may exhibit."

Annex 2

Text proposal "clean" version

"CHAPTER 2.6

CLASS 6 - TOXIC AND INFECTIOUS SUBSTANCES

Introductory notes

NOTE 1: *Genetically modified microorganisms and organisms which do not meet the definition of an infectious substance shall be considered for classification in Class 9 and assignment to UN 3245.*

NOTE 2: *Toxins from plant, animal or bacterial sources which do not contain any infectious substances, or toxins that are contained in substances which are not infectious substances, shall be considered for classification in Division 6.1 and assignment to UN 3172.*

2.6.1 Definitions

Class 6 is divided into two divisions as follows:

(a) Division 6.1 *Toxic substances*

These are substances liable either to cause death or serious injury or to harm human health swallowed or inhaled or by skin contact;

(b) Division 6.2 *Infectious substances*

These are substances known or reasonably expected to contain pathogens. Pathogens are defined as microorganisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals.

2.6.2 Division 6.1 - Toxic substances

2.6.2.1 *Definitions*

For the purposes of these Regulations:

2.6.2.1.1 The acute toxicity estimate (ATE) for the classification of a substance is derived using the LD_{50}/LC_{50} where available.

2.6.2.1.2 The acute toxicity estimate (ATE) for a substance in a mixture is derived using:

(i) the LD_{50}/LC_{50} where available; otherwise,

(ii) the appropriate conversion value from Table 2.6.2 that relates to the results of a range test; or

(iii) the appropriate conversion value from Table 2.6.2 that relates to a packing group.

2.6.2.1.3 *LD_{50} (median lethal dose) for acute oral toxicity* is the statistically derived single dose of a substance that can be expected to cause death within 14 days in 50 per cent of test animals when administered by the oral route. The LD_{50} value is expressed in terms of mass of test substance per mass of test animal (mg/kg).

2.6.2.1.4 *LD_{50} for acute dermal toxicity* is that dose of the substance which, administered by continuous contact for 24 hours with the bare skin of test animals, is most likely to cause death within 14 days in one half of the animals tested. The result is expressed in milligrams per kg body mass.

2.6.2.1.5 *LC_{50} for acute toxicity on inhalation* is that concentration of vapour, mist or dust which, administered by continuous inhalation to both male and female test animals for one to four hours, is most likely to cause death within 14 days in one half of the animals tested. A solid substance shall be tested if at least 10% (by mass) of its total mass is likely to be dust in a respirable range, e.g. the aerodynamic diameter of that particle fraction is 10 microns or less. A liquid substance shall be tested if a mist is likely to be generated in a leakage of the transport containment. Both for solid and liquid substances more than 90% (by mass) of a specimen prepared for inhalation toxicity shall be in the respirable range as defined above. The result is expressed in milligrams per litre of air for dusts and mists or in millilitres per cubic metre of air (parts per million) for vapours.

2.6.2.1.6 The terms “dust”, “mist” and “vapour” are defined as follows:

(i) Dust: solid particles of a substance or mixture suspended in a gas (usually air);

(ii) Mist: liquid droplets of a substance or mixture suspended in a gas (usually air);

(iii) Vapour: the gaseous form of a substance or mixture released from its liquid or solid state.

Dust is generally formed by mechanical processes. Mist is generally formed by condensation of supersaturated vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from less than to about 100 μm.

2.6.2.2 *Assignment of packing groups*

2.6.2.2.1 Substances of Division 6.1, including pesticides, are allocated among the three packing groups according to their degree of toxic hazard in transport as follows:

(a) *Packing group I*: Substances and preparations presenting a very severe toxicity risk;

(b) *Packing group II*: Substances and preparations presenting a serious toxicity risk;

(c) *Packing group III*: Substances and preparations presenting a relatively low toxicity risk.

2.6.2.2.2 In making this grouping, account shall be taken of human experience in instances of accidental poisoning and of special properties possessed by any individual substance, such as liquid state, high volatility, any special likelihood of penetration, and special biological effects.

2.6.2.2.3 In the absence of human experience the grouping shall be based on data obtained from animal experiments. Three possible routes of administration shall be examined. These routes are exposure through:

(a) Oral ingestion;

(b) Dermal contact; and

(c) Inhalation of dusts, mists, or vapours.

When a substance exhibits a different order of toxicity by two or more of these routes of administration, the highest degree of danger indicated by the tests shall be assigned.

2.6.2.2.3.1 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. Test data already generated should be accepted. When experimental data for acute toxicity are available in several animal species, scientific judgment should be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.

2.6.2.2.4 The criteria to be applied for grouping a substance according to the toxicity it exhibits by all three routes of administration are presented in the following paragraphs.

2.6.2.2.4.1 The grouping criteria for the oral and dermal routes as well as for inhalation of dusts and mists are as shown in the following table.

Table 2.6.1: Grouping criteria for administration through oral ingestion, dermal contact and inhalation of dusts and mists

Packing group	Oral toxicity ATE (mg/kg)	Dermal toxicity ATE (mg/kg)	Inhalation toxicity by dusts and mists ATE (mg/l)
I	≤ 5.0	≤ 50	≤ 0.05
II	> 5.0 and ≤ 50	> 50 and ≤ 200	> 0.05 and ≤ 0.5
III[a]	> 50 and ≤ 300	> 200 and ≤ 1 000	> 0.5 and ≤ 1.0

[a] *Tear gas substances shall be included in packing group II even if their toxicity data correspond to packing group III values.*

NOTE: *Substances meeting the criteria of Class 8 and with an inhalation toxicity of dusts and mists (ATE) leading to packing group I are only accepted for an allocation to Division 6.1 if the toxicity through oral ingestion or dermal contact is at least in the range of packing group I or II. Otherwise an allocation to Class 8 is made when appropriate (see 2.8.2.3).*

2.6.2.2.4.2 The criteria for inhalation toxicity of dusts and mists in 2.6.2.2.4.1 are based on data relating to 4 hours exposures and where such information is available it shall be used. However, where only data relating to 1 hour exposures to dusts and mists are available, such figures can be divided by four and the product substituted in the above criteria, i.e. ATE (1 hour) ÷ 4 is considered the equivalent of ATE (4 hours).

2.6.2.2.4.3 Of particular importance is the use of well articulated values in the high toxicity packing groups 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 table 2.6.1 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.

2.6.2.2.4.4 Liquids having toxic vapours shall be assigned to the following packing groups, where "V" is the saturated vapour concentration in millilitres per cubic metre of air (volatility) at 20 °C and standard atmospheric pressure:

(a) Packing group I: If $V \geq 10$ ATE and ATE $\leq 1\,000$ ml/m^3;

(b) Packing group II: If $V \geq$ ATE and ATE $\leq 3\,000$ ml/m^3, and not meeting the criteria for packing group I;

(c) Packing group III[1]: If $V \geq 1/5$ ATE and ATE $\leq 5\,000$ ml/m^3, and not meeting the criteria for packing groups I or II.

2.6.2.2.4.5 In Figure 2.6.1, the criteria according to 2.6.2.2.4.4 are expressed in graphical form, as an aid to easy classification. However, because of approximations inherent in the use of graphs, substances on or near packing group borderlines shall be checked using numerical criteria.

Figure 2.6.1: Inhalation toxicity: packing group borderlines

2.6.2.2.4.6 The criteria for inhalation toxicity of vapours in 2.6.2.2.4.4 are based on data relating to 1 hour exposure, and where such information is available it shall be used. However, where only data relating to 4 hours exposures to the vapours are available, such figures can be multiplied by two and the product substituted in the above criteria, i.e. ATE (4 hours) × 2 is considered to be the equivalent of ATE (1 hour).

2.6.2.3 Methods for determining the toxicity of mixtures

2.6.2.3.1 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 and there is no relevant evidence to suggest acute toxicity by multiple routes When there is relevant evidence of toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. If the acute toxicity is determined for more than one route of exposure, the packing group shall be assigned according to the highest degree of danger indicated. Mixtures shall be classified and assigned to packing groups for the oral and dermal routes as well as for inhalation of dusts and mists according to 2.6.2.3.2 - 2.6.2.3.10.

2.6.2.3.2 When classifying and assigning the appropriate packing group to mixtures in Division 6.1, in accordance with the toxicity criteria in 2.6.2.2, it is necessary to determine the acute toxicity estimate of the mixture. In order to make use of all available data for purposes of classifying the hazards of mixtures, certain assumptions have been made:

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[1] *Tear gas substances are included in Packing group II even if their toxicity data correspond to packing group III values.*

(a) The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w) , unless there is a reason to suspect that an ingredient present at a concentration <1% is still relevant for classifying the mixture for acute toxicity. This point is particularly relevant when classifying untested mixtures which contain ingredients to which packing group I or II is assigned.

(b) 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 formula in 2.6.2.3.10.

(c) If the converted acute toxicity point estimates for all ingredients of a mixture are within the same packing group, then the mixture should be assigned to that packing group;

(d) When only range data (or information about Division 6.1 packing groups) are available for ingredients in a mixture, they may be converted to point estimates in accordance with Table 2.6.2 when calculating the classification of the new mixture using the formula in 2.6.2.3.10.

Table 2.6.2: Conversion from experimentally obtained acute toxicity range values or Division 6.1 packing groups to acute toxicity point estimates for use in the formulas for the classification of mixtures with regard to oral ingestion, dermal contact and inhalation of dusts and mists

Exposure routes	**Packing group or experimentally obtained acute toxicity range estimate**	**Converted Acute Toxicity point estimate** (see Note)
Oral (mg/kg)	0 < PG I ≤ 5	0.5
	5 < PG II ≤ 50	5
	50 < PG III ≤ 300	100
Dermal (mg/kg)	0 < PG I ≤ 50	5
	50 < PG II ≤ 200	50
	200 < PG III ≤ 1000	300
Vapours (ml/m^3)	0 < PG I ≤ 1000	100
	1000 < PG II ≤ 3000	1000
	3000 < PG III ≤ 5000	3200
Dust/mist (mg/l)	0 < PG I ≤ 0.05	0.005
	0.05 < PG II ≤ 0.5	0.05
	0.5 < PG III ≤ 1.0	0.5

NOTE: *These values are designed to be used in the calculation of the ATE for classification of a mixture based on its ingredients and do not represent test results. The values are conservatively set at the lower end of the range of packing groups I and II, and at a point approximately 1/10th from the lower end of the range for packing group III.*

2.6.2.3.3 If a mixture contains only one toxicologically active substance, and the ATE of that constituent is known, in the absence of reliable acute toxicity data on the actual mixture to be transported, the ATE may be obtained by the following method:

$$\text{ATE mixture} = \frac{\text{ATE of active substance} \times 100}{\text{percentage of active substance by mass}}$$

2.6.2.3.4 If a mixture contains more than one active constituent, the approaches according to 2.6.2.3.5 – 2.6.2.3.11 may be used to determine the ATE of the mixture.

2.6.2.3.5 Where the mixture itself has been tested to determine its acute toxicity, it will be classified according to the same criteria as those used for substances, presented in Table 2.6.1.

2.6.2.3.6 *Dilution:* If a tested mixture is diluted with a diluent 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 diluted mixture may be classified as equivalent to the original tested mixture.

2.6.2.3.7 *Concentration of highly toxic mixtures:* If a tested mixture is classified in Division 6.1 and assigned to packing group I, and the concentration of the ingredients of the tested mixture that are in packing group I is increased, the resulting untested mixture should be assigned to packing group I without additional testing.

2.6.2.3.8 *Interpolation within one packing group:* For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and in the same packing group, 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 packing group as A and B.

2.6.2.3.9 *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 Division 6.1 packing group and are not expected to affect the toxicity of B:

If mixture (i) or (ii) is already classified in Division 6.1 and assigned to a packing group based on test data, then the other mixture can be assigned to the same packing group.

2.6.2.3.10 Based on available data for all ingredients of a mixture, the ATE of the mixture is determined according to the following formula :

$$\frac{100}{T_M} = \sum \frac{C_i}{T_i}$$

where: C_i = the % concentration of constituent i in the mixture;

T_i = the ATE of constituent i;

T_M = the ATE of the mixture.

2.6.2.3.11 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 2.6.2.3.10 may be applied. This may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates[2]. Such an evaluation could require appropriate toxicodynamic and toxicokinetic 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.

This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity.

2.6.2.3.12 Mixtures of liquids that are toxic by inhalation shall be assigned to packing groups according to 2.6.2.3.13.

2.6.2.3.13 If quantitative experimental data are available for each of the toxic substances comprising a mixture, the packing group may be determined as follows:

(a) Estimate the ATE of the mixture using the formula:

$$\text{ATE (mixture)} = \frac{1}{\sum \frac{f_i}{ATE_i}}$$

where: f_i = mole fraction of the i^{th} component substance of the mixture;

ATE_i = acute toxicity estimate of the i^{th} component substance in ml/m^3;

(b) Estimate the volatility of each component substance comprising the mixture using the formula:

$$V_i = \frac{P_i \times 10^6}{101.3} ml/m^3$$

where: P_i = partial pressure of the i^{th} component substance in kPa at 20 °C and one atmosphere pressure;

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[2] *When mixtures contain ingredients that do not have acute toxicity data for each route of exposure, acute toxicity estimates may be extrapolated from the available data and applied to the appropriate routes.*

(c) Calculate the ratio of the volatility to the ATE using the formula:

$$R = \sum \frac{V_i}{ATE_i}$$

(d) Using the calculated values ATE(mixture) and R, the packing group for the mixture is determined:

(i) *Packing group I*: R ≥ 10 and ATE(mixture) ≤ 1 000 ml/m^3;

(ii) *Packing group II* : R ≥ 1 and ATE(mixture) ≤ 3 000 ml/m^3 and not meeting criteria for packing group I;

(iii) *Packing group III*: R ≥ 1/5 and ATE(mixture) ≤ 5 000 ml/m^3 and not meeting criteria for packing groups I or II.

2.6.2.4 Classification of pesticides

2.6.2.4.1 All active pesticide substances and their preparations for which the ATE values are known and which are classified in Division 6.1 shall be classified under appropriate packing groups in accordance with the criteria given in 2.6.2.2. Substances and preparations which are characterized by subsidiary risks shall be classified according to the precedence of hazard table in Chapter 2.0 with the assignment of appropriate packing groups.

2.6.2.4.2 If the ATE for a pesticide preparation is not known, but the ATE of its active substance(s) is known, the ATE for the preparation may be obtained by applying the procedures in 2.6.2.3.

NOTE: *LD_{50} toxicity data for a number of common pesticides may be obtained from the most current edition of the document "The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification" available from the International Programme on Chemical Safety, World Health Organisation (WHO), 1211 Geneva 27, Switzerland. While that document may be used as a source of LD_{50} data for pesticides, its classification system shall not be used for purposes of transport classification of, or assignment of packing groups to, pesticides, which shall be in accordance with these regulations.*

2.6.2.4.3 The proper shipping name used in the transport of the pesticide shall be selected on the basis of the active ingredient, of the physical state of the pesticide and any subsidiary risks it may exhibit.
