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

Sub-Committee of Experts on the Globally
Harmonized System of Classification
and Labelling of Chemicals

Eleventh session, 12 (p.m) - 14 July 2006
Item 2(b) of the provisional agenda

**UPDATING OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION
AND LABELLING OF CHEMICALS (GHS)**

Health hazards

Toxic gas mixtures

Transmitted by the Organization for Economic Co-operation and Development (OECD)

In July 2004, the UN Sub-Committee of Experts on the GHS agreed on a mandate* for the OECD work on toxic gas mixtures. The summary report of the expert group meeting on toxic gas mixtures, which met in Paris on 17 February 2005, is added as an appendix to this document; it includes the expert group responses to the six questions asked by the UN SCEGHS.

* *Work requested by the UN SCEGHS*

According to the mandate given by the UN Sub-Committee of Experts on the GHS, experts from both TDG and GHS Sub-Committees as well as industry experts should be invited to participate in the work. The OECD Expert Group should initiate the work by reviewing the step 1 documents on acute toxicity and mixtures. If additional information is needed to consider the issues, this should be developed by the group. The charge is to review the criteria as follows:

- (1) *Investigate the applicability of the additivity formula and identify any problems that arise with regard to gases, considering inter-alia the release of gases into enclosed spaces;*
- (2) *Examine the effect of the physical state of the gas on the potential for adverse health effects (e.g. types of containment, compression);*
- (3) *Examine the use of LC50 data for classification cut-offs, and appropriate cut-off levels;*
- (4) *Consider whether the problems raised can be addressed by label guidance rather than a change in classification;*
- (5) *Determine whether the problems raised involve intrinsic properties (hazard) or potential for exposure (risk) and how this relates to possible solutions; and*
- (6) *Examine whether existing analytical test methods must be adapted based on any changes recommended for the criteria.*

The work will not address the relationship of the classification criteria to occupational exposure limits, or the conversion factor for one-hour versus four-hour test data.

Executive summary

1. When mixtures of gases that contain hazardous gases are classified and labelled according to GHS criteria, certain gaseous mixtures would not be classified or labelled as posing an acute inhalation toxic hazard even though such mixtures are currently classified or labelled in North America and Europe or have caused intoxication, including deaths, in humans. The GHS cut off values are too low to provide adequate protection in these cases and human fatal intoxication could be possible because labelling would not be adequate.
2. Application of the GHS in its present form would mean that hazardous gases in mixtures would not be classified (Category 5 or Category 4) unless they are more than 80- or 200- fold concentrated compared to the rat 4 h LC₅₀.
3. Gas mixtures containing hazardous gases may be appropriately classified [under GHS] when the rat LC₅₀ is more than one order of magnitude lower than the human intoxication concentration (see PH₃) which is only exceptionally the case.
4. The problem can be solved and protection improved by using higher cut off values for category 4/5 for classification of gases under the GHS. The OECD will continue to develop approaches to extend coverage of the GHS for inhalation of toxic gas mixtures.

The problem

5. Acute intoxication may be the consequence of inhalation of a hazardous gas either for only a few moments or after hours of exposure. The latter case may be true when a hazardous gas does not smell, is not pungent or is not an irritant, as these effects may provide warning to avoid exposure and hence intoxication. In addition, after repeated exposure, workers may become more tolerant to smell, pungency, or irritancy of a hazardous gas and may not be adequately warned to avoid exposure to a gas in toxic concentrations. Thus, in enclosed spaces there may be a risk of human acute intoxication in cases of elevated exposure to humans. For the oral and the dermal route, no such problem exists.
6. In the GHS, the acute toxicity of mixtures for oral, dermal or inhalation toxicity (Acute Toxicity Estimate, ATE) is determined by calculation using the following formula:

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i} \quad (\text{GHS 3.1.3.6.1})$$

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.

7. The same formula (GHS 3.1.3.6.1) can be used to determine the concentration at which a mixture containing hazardous gas(s) would be classified in a GHS category. When this formula is applied to toxic gas mixtures, the acute inhalation cut points are such that certain mixtures would be classified only when toxic components are present at concentrations which are higher

than those currently classified in Europe or North America. This is exemplified with hydrogen sulfide: Applying the formula in GHS 3.1.3.6.1, a gaseous mixture containing only hydrogen sulfide ($LC_{50} = 356$ ppm) is classified under the GHS in concentrations above 2.84% (v/v) ($100\%/12500\text{ppm} = Ci/356$ ppm) with Category 5 for acute inhalation toxicity. Category 5 carries no symbol. In concentrations above 7.12% (v/v) ($100\%/5000\text{ppm} = Ci/356$ ppm), this gaseous mixture is classified with Category 4 for acute inhalation toxicity and has to be labelled with the exclamation mark symbol. In Europe, hydrogen sulfide in mixtures has to be classified in concentrations above 0.02% (v/v) and has to be labelled with St. Andrew's Cross.

8. Table 1 cites literature reports of concentrations of 12 hazardous gases which have caused human acute fatal intoxication. (Data bases searched were RTECS, HSDB, ATSDR.) Toxic concentrations were compared to cut points of the GHS gas mixtures classification. For each gas, Table 1 displays concentration ratios between concentrations reported to be fatal to humans and concentrations above which the GHS calls for classification. For example, a gas mixture containing sulfur dioxide would be classified in Category 4¹ in the GHS when sulfur dioxide is contained in the gas mixture in a concentration 250-fold above the concentration reported to lead to fatal human intoxication or 100-fold above the fatal concentration for classification in Category 5. This means that sulfur dioxide is only classified in a gas mixture at a concentration which is 2-3 orders of magnitude above the concentration causing fatal human intoxication. The situation is similar for all gases in Table 1 except PH_3 . Thus, the current cut off values in the GHS do not provide adequate protection.

9. An approach to overcome this problem is as follows: hazardous gases may cause fatal intoxication after only a few breaths. In contrast to exposures via the oral or the dermal route, a high uptake of a hazardous gas by breathing may be unavoidable. In the standard case of exposure to a gas mixture containing one or more hazardous gases in the workplace, the gas mixture may be leaking from a container and be diluted with workplace air. Thus, it is expected that workers are exposed to a diluted (i.e., less toxic) gas mixture.

10. To handle this dilution effect, it is recommended that a hazardous gas should be classified in a mixture when concentrated tenfold or higher than the air equilibrium concentration causing fatal intoxication in humans. This would mean that a gas classified according to GHS as an acute inhalation toxicant Category 1 to Category 4 should be classified in a mixture in a concentration which is one order of magnitude higher than the (equilibrium) concentration in air which caused fatal intoxication.

11. 11 of the 12 gases in Table 1 are not adequately classified in mixtures, because the respective concentration ratios (columns 6 and 7 in Table 1) are mostly higher than the proposed factor of 10 when applying the existing GHS. For 5 gases (CO , Cl_2 , Br_2 , H_2S , SO_2), the reported data in Table 1 lead to a broader range of concentration ratios. The reason is that several data with different exposure durations are available. The data show that the longer the exposure duration, the lower the human fatal concentrations are, which is plausible. Thus, higher concentration ratios are the outcome for longer exposures. Moreover, it can be seen from the table that the problem exists for all gases independent of their toxic potency, as this table of

¹ *Acute toxicity Category 4 and not Category 5 is referred to because hazard communication is communicated with the exclamation mark symbol, which is considered adequate for a hazardous gas mixture. Category 5 does not have a symbol. Moreover, Category 5 is related to vulnerable populations.*

human incident reports contains gases classified for acute inhalation toxicity in GHS ranging from Category 1 (e.g., NO₂) to Category 4 (e.g., CH₃Cl).

12. The classification of gases in the GHS should be consistent for both gas substances and mixtures, which is taken into account by the proposed solution. The problem could be resolved by elevating the upper concentrations for acute inhalation toxicity classification of gases in GHS for example to a maximum of 40,000 ppm.

13. For most hazardous gases, valid human exposure data on fatal intoxication are not available. Therefore, animal LC₅₀ can be used as standardized surrogate parameter for the classification of hazardous gases in mixtures. Using 40,000 ppm as a maximum cut off value for GHS classification, it can be seen that for none of the 12 gases in Table 1, the proposed concentration ratio (low classification threshold of concentration fatal to human) of 10 would be exceeded when relating to the concentration causing human intoxication after short exposure duration (except hydrogen sulfide where the ratio is only slightly exceeded with 13). For 5 of the 12 evaluated gases, namely CO, Cl₂, Br₂, H₂S, and SO₂, the data on longer exposure durations still would lead to concentration ratios of greater than 10. However, as a longer duration of strongly elevated exposure to a hazardous gas is likely to be rare and would normally not go undiscovered, it appears that use of 40,000 ppm, as the highest value for hazard classification of acutely toxic gases in GHS, would be adequate.

14. In the existing systems for workplace in the USA and Canada, hazard communication is triggered when gas mixtures contain toxic gases at concentrations above 1%. In the EU, hazardous gases have to be classified for acute inhalation toxicity in mixtures in concentrations above 0.02%; 0.5%; or 5% depending on the classification of the gas as very toxic, toxic or harmful, respectively (or unless a specific limit has been established).

Table 1: Survey on gases. Rat LC₅₀s, human fatal concentrations, and lower GHS gas mixture classification thresholds for Category 4 and 5 acute inhalation toxicity

gas	rat 4 h LC ₅₀ [ppm] ²	acutely life-threatening/lethal to humans after inhalation [%]	low classification threshold, GHS gas mixture [%]			conc. ratio (low classification threshold cf. conc. fatal to human)		
			Cat. 4	Cat. 5	proposal 40,000 ppm	Cat. 4	Cat. 5	proposal 40,000 ppm
PH ₃	10	lethal 0.04-0.06/30 min-1 h[HSDB] lethal 0.1/ few breaths[HSDB]	0.2	0.08	0.025	<4	<1.6	<0.5
COCl ₂	2.5	lethal 0.0025/30 min (1968) [RTECS] lethal 0.0088/30 min (1982) [RTECS]	0.05	0.02	0.006	5-20	2-8	≤1
AsH ₃	10	0.0025-0.005/30 min[HSDB] 0.025 instantly[HSDB]	0.2	0.08	0.025	8-40	3-16	1-5
CH ₃ Cl	4,150	lethal human 2/2h (1969) [RTECS]	83	33	10.3	40	16	5
CO	1,880	0.075/4h (1988)[RTECS] 0.15; 0.2; 0.26/1h; 0.29/20 min; 0.43/7 min; 0.49/2min; 1.21/1min (1988)[RTECS]	37.6	15.0	4.7	30-270	12-108	4-34
Cl ₂	147	0.05/5min (1933) [RTECS] 0.1/5min (1989) [RTECS] 0.0030/30min (1989) [RTECS]	3.0	1.2	0.375	30-1,000	12-400	4-125
NH ₃	2,000	0.5-1 rapidly fatal, short exposure [HSDB] lethal human 1/3 hr[HSDB]	40	16	0.5	40	16	5
CH ₃ Br	425	acute fatal intoxication: 0.03-0.04[HSDB] IDLH 0.2	8.5	3.4	1.0	40	16	5
NO ₂	57.5	lethal human 0.02/1 min (1974)[RTECS]	1.15	0.46	0.14	60	24	7.5
Br ₂	407 (1976, 1989) [RTECS]	lethal human 0.1, etng ³ (1969) [RTECS] lethal human 0.0033, etng (1989) [RTECS]	8.0	3.2	1.0	80-2,400	32-960	10-300
H ₂ S	356	0.015-0.02/4 h; 0.04-0.07/15 min-30 min [Maskell 1984] 0.08/5 min (1933); 0.06/30 min (1968) [RTECS]	7.1	2.8	0.89	100-355	142	13-44
SO ₂	1260	0.1/10 min (1972) [RTECS] 0.3/5 min (1933)[RTECS]	25	10	3.1	250-1000	100-400	10-31

² If not specifically cited, the LC₅₀ value has been taken from from ST/SG/AC.10/C.4/2004/7.

³ etng, exposure time not given.

15. Table 2 shows the concentrations above which the gases referred to in this document would be classified in Category 5 in the current and proposed – amended GHS (according to the formula in 3.1.3.6.1) and in the existing systems in USA/Canada, and Europe.

Table 2: Classification of a hazardous gas in a mixture for acute inhalation toxicity above concentration [%]

Gas	Classification above %			
	Current GHS Cat. 5 (12500 ppm)	Amended GHS Cat. 5 (40000 ppm)	USA/Canada	EU
COCl ₂	0.02	0.006	1	0.02
PH ₃	0.08	0.025	1	0.02
AsH ₃	0.08	0.025	1	0.02
NO ₂	0.46	0.14	1	0.1
Cl ₂	1.2	0.375	1	0.5
H ₂ S	2.85	0.89	1	0.02
Br ₂	3.2	1.0	1	0.02
CH ₃ Br	3.4	1.0	1	0.5
SO ₂	10	3.1	1	0.5
CO	15.04	4.7	1	0.5
NH ₃	16	5	1	0.5
CH ₃ Cl	33.2	10.3	1	5

16. In contrast to existing workplace regulations in the US and Canada, 4 out of 12 gases (COCl₂, PH₃, AsH₃, and NO₂) would be classified in the current GHS for acute inhalation toxicity as Category 5 in mixtures at concentrations below 1%. For these 4 gases, the level of protection in GHS would be increased. Eight of 12 gases in the table (Cl₂, H₂S, Br₂, CH₃Br, SO₂, CO, NH₃, and CH₃Cl) are classified in mixtures according to the current GHS only at concentrations above 1%. For instance, CH₃Cl would have to be classified in GHS above 33.2%. The level of protection for these 8 gases would decrease with the current GHS. With the proposed cut point of 40,000 ppm for Category 5, protection of 8 gases currently in place in Canada and US would be maintained, with the protection lowered for only 4 gases.

17. According to the existing system in the EU, all gases would be classified in mixtures in concentrations which are lower than in current GHS. The level of protection for all the tabled gases would generally be lowered by the GHS. The amended proposal would maintain protection for 4 of the 12 gases (as a previous evaluation for 54 gases by EIGA has shown [UN document ST/SG/AC.10/C.4/2004/7]). In this paper, it was shown that 94% (51/54) of the evaluated hazardous gases are classified in GHS mixtures in higher concentrations than in the existing EU system. 67% (36/54) of these gases are not classified in mixtures at a concentration of 1%, which is the case in the existing regulation in USA/Canada.

18. Implementing a change to a level of 40,000 ppm for gas classification in Category 5 would mean that the GHS would come closer to the existing systems of USA/Canada and EU for the gases in mixtures for which the level of protection would be decreased by the current GHS. The OECD is considering various approaches to implement solutions to the problem.

19. The OECD will develop approaches to extend coverage of the GHS for inhalation of toxic gas mixtures. Recommendations will be provided to the UN Subcommittee at a future date.

20. The OECD observes that the criteria for inhalation of toxic gas substances may also require attention.

Annex 1

Overview of existing data

A database search was performed to collect air concentration data of gases for which fatal human intoxication was reported. All gases for which data on human acute fatal intoxication could be found were included in the evaluation at Table 1. These data are compared to the current GHS classification cut-offs (for the lowest gas concentration in the mixture leading to GHS classification in a specific category).

For H₂S, a gas mixture below 71,200 ppm (7.12% v/v) H₂S would not have to be classified according to the existing GHS. In case of inhalation exposure to such mixture, a 200-fold dilution (i.e. 356 ppm) still would be an equilibrium air concentration causing intoxication in humans. In case of H₂S, as exemplified above, a concentration factor of 10 (i.e., gaseous mixture was concentrated tenfold compared to the lower threshold concentration of acute intoxication) may lead to fainting.

For most gases in Table 1, the lower GHS classification for threshold gas mixtures is more than an order of magnitude higher than the concentration leading to severe or fatal human intoxication. These values are not considered safe. This shows that for most of the gases listed, acute, serious, or even fatal intoxications in the workplace are possible, because many hazardous gas mixtures would not be classified using the existing GHS.

Annex 2

Calculations

Calculation of the lower threshold of GHS classification in the gas mixture was done as follows (exemplified for hydrogen sulfide):

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:

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$$

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 .

Applied to the lower GHS threshold of Category 4 classification, this would mean to insert 5000 ppm as highest LC_{50} concentration warranting classification of a gas and 356 ppm as LC_{50} for H_2S :

$$100/5000 = C_i/356 \text{ ppm} \Rightarrow C_i = 71,200 \text{ ppm (i.e. 7.12\%)}$$

Alternatively, it was considered which lower GHS classification thresholds would result if acute toxicity Category 5 classification of the gases would be applied. It should be remarked that GHS Category 5 applies to vulnerable populations and the hazard communication (no symbol) may not provide adequate warning for certain toxic gas mixtures. For this purpose, 12,500 ppm was inserted in the above formula instead of 5000 ppm. With respect to the proposal made, 40,000 ppm was also used.

These values are inserted in the fourth to the sixth column of the table, respectively. Columns 7-9 contain the dilution factor (range) by which a gas mixture classified in GHS can be diluted, and still result in an equilibrium concentration leading to severe human intoxication. It should be noted that a dilution factor of 10 still allows for the 2 acute intoxication (fainting) cases for H_2S .

The problem can be solved by using higher concentrations for gas substances classification under GHS.

REFERENCES

Maskell, D. (1984), Hydrogen sulfide safety systems for oil and gas exploration, Fire International 90, 8, 23 - 25

HSDB Hazardous Substances Data Bank, <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>

RTECS, www.cdc.gov/niosh/rtecs.html

ATSDR, <http://www.atsdr.cdc.gov/toxpro2.htm>

Annex 3**Common denomination of the gases mentioned in the document**

COCL ₂	Phosgene
PH ₃	Phosphine
AsH ₃	Arsine
NO ₂	Nitric oxide
Cl ₂	Chlorine
H ₂ S	Hydrogen sulphide
Br ₂	Bromine
CH ₃ Br	Methyl Bromide
SO ₂	Sulphur dioxide
CO	Carbon monoxide
NH ₃	Ammonia
CH ₃ Cl	Methyl Chloride

Appendix

Summary Record of the Expert Group Meeting on Toxic Gas Mixtures

Paris, 17 February 2005

1. The Expert Group for toxic gas mixtures met at OECD in Paris on February 17, 2005. The meeting was chaired by Amy Rispin (US). EIGA, CGA, and government representatives from Europe, North America and Japan opened the meeting by describing regulatory programs currently in place for toxic gas mixtures. The Expert Group was mandated to consider the impact on workers of the GHS criteria for acute inhalation. To do so, they addressed the six questions provided below. In addition, Germany and EIGA will examine the adequacy of categories 4 and 5 for protection, taking into account the toxicity of gases and gas mixtures. In addition, they will evaluate the adequacy of the GHS HAZCOM provisions for category 5.

1. **Investigate the applicability of the additivity formula and identify any problems that arise with regard to gases, considering inter-alia the release of gases into enclosed spaces**

2. A leak of any sort can lead to problems in certain situations. The problem is more severe for compressed gases or for tanks with large tonnage (See #5). It was observed that use of GHS provisions for inhalation toxicity will decrease protection in the EU (which cuts off classification for the work place at 2500 ppm). Germany cited work place situations in which leaking H₂S gas caused workers to faint. In these cases, toxicity was anticipated to be greater than 2500 ppm based on the ATE and would not be classified under the GHS in Europe.

- (a) Participants acknowledged that the additivity formula gives the correct LC50 or ATE equivalent. There was a discussion of the point about experimental verification of the additivity formula;
- (b) Because the additivity formula is correct, it allows acute lethality of toxic gas mixtures to be ranked to compare severity of hazard;
- (c) Although the additivity formula has served transport well for release of gases into open spaces, the problem arises for accidental release of gases into more or less enclosed work spaces (i.e. specifically work places);
- (d) The problem may arise from anticipated implementation of acute inhalation levels 1, 2, and 3 for work place rather than from application of the additivity formula.

2. **Examine the effect of the physical state of the gas on the potential for adverse health effects (e.g., types of containment, compression)**

3. The exposure from gases is by inhalation, therefore involuntary, distinguishing them from solids or liquids. There was consensus that the physical state (including compression) does not matter; the worker exposed at his nose to a toxic chemical is exposed to the chemical no matter how it got there.

4. **Industry and regulatory organizations have set standards for high integrity containers for the containment of gases, i.e., types of cylinders, valves, etc., to help ensure safety**

5. Because most industrial gases/mixtures are compressed, leaks in enclosed spaces may rapidly lead to toxicity and/or lethality.

6. However, CGA noted that even if the toxic gas is diluted and the container is not labeled, but used under controlled conditions, TLVs must be met using risk-based considerations (See #5).

7. Germany and U.S. noted that compression does not matter - 5% of a toxic gas which is compressed is still available at a 5% level when it leaks.

8. Under typical transport conditions, there would be a problem only if the compressed gas container catastrophically compromised and the contents instantly fill the environment with a gas of known toxicity or whose toxicity is predicted by the additivity formula.

3. **Examine the use of LC50 data for classification cut-offs, and appropriate cut-off levels**

9. Germany, Belgium and EIGA noted that 2500 ppm is the cut off of GHS classification of gases as toxic. Under GHS, up to 5000 ppm a gas is considered harmful. Using these values in the additivity formula leads to insufficient hazard communication, because gas mixtures which are toxic would be considered to be harmful or not even classified at all. 5000 ppm is expected to be the largest LC50 value to be regulated in Europe for the work place (or consumers) inhalation lethality under the GHS. Participants from North America noted that:

Under the GHS, the ATE of a gas is only one of various considerations for classification for acute toxicity. Footnotes in the classification table can also be used. These allow classification based on human incident data.

The 12,500 ppm limit (category 5) may work well for consumer products.

Noting that the 1% mixtures rule for work place in the U.S. is similar to use of 12,500 ppm \approx 1.25%, where as, possible use of 2,500 ppm for work place classification as toxic may be insufficiently protective.

4. Consider whether the problems raised can be addressed by label guidance rather than a change in classification

10. The Expert Group agreed that classification, along with symbols and signal words is necessary for protection. To that end, the group considered use of paragraph 1.3.3.2 and/or supplementary labeling.

11. Germany noted several Category 5 chemicals would be expected to pose problems if Category 4 becomes the maximum level used for work place classification.

12. Although paragraph 1.3.3.2 is available for identifying exceptions to default mixtures levels for toxic gases which might pose problems, most industrially important toxic gases would be classified and labeled by exception. Therefore, there was no consensus in the Expert Group that it should be used to resolve the problems anticipated.

13. Some industry experts advocated use of supplementary labeling to advise about toxicity. Other industry experts were against use of supplementary labeling for certain toxic gas mixtures on the grounds that it would not ensure harmonization.

5. Determine whether the problems raised involve intrinsic properties (hazard) or potential for exposure (risk) and how this relates to possible solutions

14. It would appear that the problems cited in #1 and #2 are due to various elements of exposure - i.e., duration of any leak; compression of toxic gases, allowing them to rapidly fill enclosed work spaces at atmospheric pressure; or total quantity of toxic gas available in enclosed work spaces.

- In North America and Japan, a combination of hazard classification provisions, based on intrinsic properties of toxic gases or toxic gas mixtures, and risk based regulations which take potential for exposure into account (e.g., size of container, enclosed area), allows for management and mitigation of gases used in the work place in enclosed spaces;
- However, the EU system uses cut off values and risk phrases based on classification to trigger other downstream consequences. A European directive for occupational limits is triggered by the Dangerous Substances Directive. In Europe, 20mg/L for gases is currently the highest level for classification under the Dangerous Substance Directive. Toxic gases are regulated through fixed cut off limits to bring them to safe levels (as regulated by the EU Preparation Directive);
- Participants noted that a simple classification system is essential for worldwide use.

6. Examine whether existing analytical test methods must be adapted based on any changes recommended for the criteria

15. Analytical methods do not pose a problem.
