
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

11 November 2022

Sixty-first session

Geneva, 28 November-6 December 2022

Item 3 of the provisional agenda

Listing, classification and packing

Revised version of document ST/SG/AC.10/C.3/2022/72

Revision of classification of tetramethylammonium hydroxide

Submitted by the European Chemical Industry Council (Cefic) and
Dangerous Goods Advisory Council (DGAC)

Note

Following the submission of document ST/SG/AC.10/C.3/2022/72, Cefic and DGAC noticed that part of Option 2 of the proposal was inadvertently omitted in the official posted version. The missing portion is essential for our proposal to make sense and be viable. Some further corrections to errors were also included in this informal document. The revised version below reflects all the changes in “Track Changes” mode.

I. Introduction

In addition, we noted that we had made some errors in our submitted version, and these also need to be corrected.

1. At the sixtieth session of the Sub-Committee, document ST/SG/AC.10/C.3/2022/24 was submitted by the expert from the Netherlands proposing to reclassify tetramethylammonium hydroxide (TMAH) and its solutions based on human experience. That formal document was a follow-up to informal document INF.12 presented at the fifty-ninth session.

2. TMAH is mainly used in the semiconductor and display manufacturing industry. It is used as a main substance in developers for photolithography and is one of the most critical substances in the microchip manufacturing process. As such, every chip and Liquid Crystal Display (LCD) or Organic Light Emitting Diode (OLED) display is manufactured using TMAH. In these applications, TMAH is most commonly shipped as a simple aqueous solution containing only water and tetramethylammonium hydroxide in varying concentrations generally ranging from ~~2.5 %~~ ~~2.0%~~ to 25 %, although the lower concentrations may contain additional constituents comprising less than 1 % of the total formulation. These aqueous solutions are packaged in a variety of packaging types, including IBCs, drums, boxes, jerricans, etc. The 25 % aqueous solutions are most commonly packaged in intermediate bulk containers (IBCs) and the authors believe about 0.5 million IBCs of 25 % aqueous solutions are shipped worldwide on a yearly basis. The shipped volume of the lower concentrations is almost certainly substantially higher.

3. Updating the classification of TMAH will help to ensure the safety of people, property and the environment. By doing so the Sub-Committee aligns itself with the Sustainable Development Goal 3: ensure healthy lives and promote well-being for all at all ages.

II. Overview and discussion

4. TMAH is currently listed in the Model Regulations as UN 3423, Class 8, Packing Group (PG) II. TMAH solutions are listed as UN 1835, Class 8, PG II/III (without concentration limits). Both the informal document presented at the fifty-ninth session and the official document presented at the sixtieth session reported on several workplace incidents where workers were exposed to solutions of TMAH in various formulations. Most of these exposures were to simple aqueous solutions, similar to those discussed in paragraph 2 above, but others were more complex formulations and one of the more complex formulations contained significant concentrations of constituents other than TMAH and water to the extent that it raises the question whether it should even be characterized as a “TMAH solution” or would more properly be characterized as an ethoxylated alcohol solution.

5. Based on these incidents, document ST/SG/AC.10/C.3/2022/24 proposed a revision of the classification of both the substance (UN 3423, TMAH solid) and UN 1835 (TMAH solutions). Two options were presented:

Option 1 proposed:

- to reclassify solid TMAH (UN 3423) as Class 6.1 (8), PG I, from Class 8, PG II, and to add special provision 279 to Column 6,
- to add a new PG I entry for TMAH solutions (UN 1835) whereby concentrations with more than 8.75 % would be reclassified as 6.1 (8), PG I, and to add special provision 279 (matching the entry for the pure substance),
- to revise the PG II entry for TMAH solutions (UN 1835) so that it applies to solutions with not less than 2.38% but not more than 8.75%, and reclassify them to 6.1 (8), II from 8, II, and
- to revise the entry for PG III solutions so that it applies to solutions with less than 2.38 %, but with no proposed change to the existing classification so that these would remain classified as currently listed, i.e., 8, III.
- Special provision 223 would be assigned only to the PG III entry, as it is currently.

Option 2 would not show concentration limits but would otherwise be identical to Option 1.

6. Cefic and DGAC, along with most members of the Sub-Committee, agreed that these incidents of human experience warranted the addition of division 6.1 as an additional classification for the substance and for its solutions in higher concentration. However,

- noting the difficulties with assigning a packing group based solely on human experience,
- noting that available animal data indicates that aqueous solutions with ~~less than~~ 25 % or less TMAH should be assigned to PG II, not PG I,
- noting that the proposal aimed to reclassify all solutions containing TMAH based solely on the concentration of TMAH without regard to the complexity of the formulation (i.e., without regard to the presence or absence of other constituents),
- noting that the proposal to classify all TMAH solutions with concentrations above 8.75% was based on one single incident where there was a tragic outcome to an

exposure to a complex formulation containing multiple chemicals including a surfactant (the specific incident contained a type of surfactant known to also be used to enhance the efficacy of dermal medications) in an even greater concentration than the TMAH, and

- noting the significant implications for the carriage of aqueous solutions of TMAH if reclassified from PG II to PG I, including disallowing the use of IBCs, currently the most commonly used type of packaging,

Cefic and DGAC submitted informal document INF.22 (sixtieth session) suggesting that a careful review of the available data is necessary before a final decision on packing group assignments is made and offering to undertake such a review. The Sub-Committee welcomed this suggested review of data, and the expert from the Netherlands volunteered to submit a revised proposal to the next session taking into account the comments received.

7. Industry has undertaken that review of data as promised. Various studies and sources of information were evaluated. An overarching report was prepared by the Industrial Health and Safety Consultants (IHSC, LLC) and a comprehensive study of the 8.75 % incident was undertaken by Charles River. Those two reports are presented as Annex 1 and Annex 2 respectively. In short, Cefic and DGAC find that the available data do support the addition of division 6.1 in the classification for the substance and many of its solutions, but also that the data show it is not feasible to develop a single set of cut-off values to determine the packing group of every formulation that happens to contain TMAH. These findings are consistent with the general approach to classification presented in the Model Regulations that assigns a classification for a mixture on the basis of the characteristics of the mixture, not primarily on the characteristics of the constituents in the mixture. Specifically, Cefic and DGAC find that aqueous solutions can be reliably classified based on the concentration of TMAH in water, but that more complex formulations containing TMAH and other constituents are not susceptible to such an approach. In short, the available data do support the addition of division 6.1 in the classification for the substance and most of its solutions, but do not support the assignment of PG I to aqueous solutions containing ~~less than~~ 25 % or less TMAH (see Annex 1).

III. Classification by human experience should be refined by animal data

8. There have been a number of reported cases of worker exposure to TMAH where toxic effects were observed (see Table 1 of document ST/SG/AC.10/C.3/2022/24). These reports support the conclusion that TMAH should be classified for acute toxicity in addition to corrosivity for transport.

9. While incidental human exposure can certainly provide valuable information regarding potential hazards of chemicals, there are limitations inherent to retrospective observational studies of incidents that occurred in uncontrolled conditions. As discussed by Huang et al.¹, a small number of included cases in retrospective studies does not allow an accurate assessment of the severity of TMAH poisoning. For example, data collection is often based on telephone consultations which, they indicate, likely introduces additional variation among cases.

¹ Huang, CK; Hall, A. H.; Wu, ML; Yang, CC; Hung, DZ; Mao, YC; Deng, JF (2020) Presentations of tetramethylammonium hydroxide dermal exposure and the valuable potential of diphoterine solution in decontamination: a retrospective observational study. *BMC Pharmacology and Toxicology*. 21:83. (<https://doi.org/10.1186/s40360-020-00465-8>)

10. As stated in the Model Regulations, whenever human experience indicates a characteristic of corrosivity and/or toxicity, the relevant hazard class should be assigned accordingly. It is far more complicated to assign a packing group on this basis. Due to the absence of defining criteria for classification by human experience, due to the variability in the exposure times and in the reporting of such incidents, and due to the variability of circumstances, lack of reproducibility, and lack of controls of incidents of human exposure, it is difficult to make a complete classification solely on the basis of human experience. Consistent, reliable, applicable, experimentally derived animal data should be used to refine, but not override, data from human experience when available.

11. A considerable amount of such experimentally derived animal data is available for use in refining the classification of TMAH solutions and was included in the review by industry. It is important to note that although these data were generated by tests conducted on rats, rather than rabbits as indicated in the Model Regulations, the IHSC report goes into detail as to why these results are now the preferred data in other regulatory applications, and why they are useful, valid, and can be substituted for rabbit data, even for transport classifications, and are “unlikely to underestimate dermal absorption in humans” (see Annex 1). The Model Regulations even seems to anticipate this problem, and allow for it, based on the Note to 2.6.2.3.3, wherein the discussion of methods for determining the classification of a toxic mixture for which data on the mixture are not available allows for a classification based on a knowledge of the constituents “provided this information is available on the same species for all constituents” (emphasis added).

IV. The 8.75 % solution is not representative of aqueous solutions

12. Cefic and DGAC are aware of only one reported fatality resulting from an exposure to a TMAH concentration below 25 %. In this case, the individual was not exposed to a simple aqueous solution of TMAH, but to a mixture containing 8.75 % TMAH in addition to several additional chemicals, including 5 % monoethanolamine and 10 % ethoxylated alcohol (a non-ionic surfactant). This complex formulation was created to be used as a pallet cleaning solution and is not representative of the simple aqueous solutions transported in the electronics industry. This tragic industrial accident resulted from poor work practices and should have been prevented, but it should not be used as a basis for assignment of packing groups to aqueous solutions in transport due to the presence of both an anesthetic agent and a substantial amount of surfactant in the mixture. With respect to this incident, Charles River concluded:

“Based on the circumstances, extremely long exposure duration for surface percentage exposed and given that a higher incidental exposure was reported where the victim survived, the case with 8.75 % TMAH described in Park, et al. (2013) can be considered an exceptional case and therefore its relevance for determining the percentage warranting UN packaging group I is questionable. (see Annex 2)”

13. In “Guidance on dermal absorption”¹, a guidance on critical aspects related to the setting of dermal absorption values to be used in risk assessments of active substances in Plant Protection Products, the European Food Safety Authority lists surfactants as “other factors affecting absorption”. In fact, when extrapolating dermal absorption data on an active substance to a formulated product, the procedure states that data or justifications need to be generated in case the formulation under consideration is water based with surfactants.

¹ Buist, H.; Craig, P.; Dewhurst, I.; Hougaard Bennekou, S.; Kneuer, C.; Machera, K.; Pieper, C.; Court Marques, D.; Guillot, G.; Ruffo, F.; Chiusolo, A (2017) Guidance on dermal absorption. *EFSA Journal*; 15(6):4873. (<https://doi.org/10.2903/j.efsa.2017.4873>)

14. Although the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) takes a slightly different tack, under the Model Regulations, intrinsic properties are not the sole, or even primary, basis for classification, the effect of an exposure to the material (without regard to whether it is a substance or a mixture) due to an unplanned, uncontrolled release during transport is the basis for classification. (There are many examples of this in Part 2, e.g., the classification of class 1 explosives is based on a combination of the characteristics of the explosive and the characteristics of the package itself; the classification of division 2.2 materials is often based solely on the pressure exerted in the packaging, i.e., the characteristic(s) of the gas itself are not always taken into consideration for purposes of classification; the classification of division 4.1 desensitized explosives is based on the fact that a sufficient quantity of water, alcohol, or plasticizer is present to suppress the explosive properties; the classification in division 6.1 based on acute toxicity on inhalation of dusts is disregarded in cases where the solid is comprised of a sufficient percentage of dust particles with a size greater than ten microns.)

15. The IHSC report in Annex 1 refers to several articles that describe how nonionic surfactants, such as the 10 % ethoxylated alcohol (an incredibly high concentration of surfactant present in the 8.75 % incident), can be used to increase the transfer of drugs through the skin. Moreover, the employee did not react immediately upon spilling the solution on his clothing, hands, arms, and legs. A constituent of the 8.75 % solution almost certainly resulted in an anesthetic effect, contributing to the delay in the employee seeking to counter the effects of the exposure. The conclusion can be made that these phenomena exacerbated the impact of the 8.75 % TMAH incident and that this 8.75 % datapoint should not be used to determine the PG I concentration limit for every solution containing TMAH without regard to the other constituents in the formulation.

V. Cut-off values for aqueous solutions of TMAH

16. Toxicity data from reliable animal tests is available for aqueous solutions of TMAH and has been reviewed by experts in toxicology who find it is consistent with the human experience data for division 6.1 packing groups.

17. For simple aqueous solutions, the data show the lower concentration limit for PG I is greater than 25 %. This is based on most conservative animal LD₅₀ values. Human experience (see Table 1 of ST/SG/AC.10/C.3/2022/24) supports this approach (see also Annex 1). The lower concentration limit for PG II for dermal toxicity (6.1) is calculated as 6.25 %. However, since this concentration still falls under a PG II classification for corrosivity (8), the 6.25 % is not relevant in the determination of the transport classification and is not taken over in the proposal below. The concentration range for PG III dermal toxicity is greater than 2.5 % but less than 6.25 %. In summary, the data show the following concentration ranges:

> 25 % PG I
6.25 to 25 % PG II
> 2.5 to < 6.25 % PG III.

18. In addition, based on the precedence of hazard guidelines, Cefic and DGAC believe that for PG II the primary hazard shall be class 8 with a subsidiary hazard of division 6.1.

VI. Conclusion

19. Our original approach dismissed the 8.75 % TMAH solution as irrelevant to the classification of existing TMAH aqueous solutions of differing concentrations which are currently shipped worldwide in vast quantities for use in manufacturing of electronics components. Cefic and DGAC focused on the fact that the 8.75 % solution contained a variety

of other chemicals, most notably, a surfactant (ethoxylated alcohol) at an even higher concentration than the TMAH, and this surfactant, along with the presence of other chemicals, unquestionably had an impact on the hazardous characteristics of the 8.75 % solution so that it is not comparable to an aqueous solution.

20. However, this 8.75 % solution was an actual formulation, apparently intended for eventual development as a commercial product, and presumably would subsequently be offered for transport. Accommodation needed to be made for its classification, yet it could not be classified based on the parameters of existing aqueous solutions, nor could it properly be used to reclassify aqueous solutions. It, and formulations like it, needs to be treated separately. Cefic and DGAC also had to acknowledge that accommodation must be made for the existing (even if relatively few) solutions containing a small concentration of TMAH mixed with an even smaller concentration (generally less than 1 %) of other chemicals, as well as for the classification of an unlimited number of potential other solutions, existing or future, comprised of unknowable formulations.

21. In short, Cefic and DGAC recognized that it is not possible to rely on a single UN number with different combinations of primary and subsidiary hazards and packing groups to be simultaneously applied across the board to both simple, dilute, aqueous solutions and at the same time reliably guide the classification of more complex formulations that happen to contain TMAH.

22. Therefore, Cefic and DGAC are proposing enhancements to the classification of both the substance tetramethylammonium hydroxide, and to its solutions. Our proposal recognizes the human experience data across the board, but takes into account the differences between simple aqueous solutions of tetramethylammonium hydroxide and more complex formulations. It applies a refinement derived from animal test data to the packing group cut off values for aqueous solutions but offers two options for the classification of the more complex formulations. Although Cefic and DGAC prefer Option 1, Option 2 essentially adopts the proposal from ST/SG/AC.10/C.3/2022/24 with respect to solutions that are not simple aqueous solutions.

23. Option 1 prescribes cut-off values for all three packing groups, to be applied exclusively to simple aqueous solutions. More complex formulations are to be classified according to the general principles of the Model Regulations, i.e., determine the classification on the basis of the characteristics of the mixture, followed by the assignment of an appropriate generic or n.o.s. proper shipping name/UN number. This option also, as was proposed by the Netherlands in ST/SG/AC.10/C.3/2022/24, revises the entry for the substance (UN 3423), to a primary hazard of 6.1, subsidiary hazard of 8, and a packing group I. It also, again, as proposed by the Netherlands, adds a PG I entry to UN 1835 and makes various revisions to the existing PG II and PG III entries for UN 1835, including the addition of a primary hazard of 6.1 to PG II. It adds text in column 2 limiting UN 1835 to aqueous solutions, and introduces a new special provision XXX to clarify the meaning of aqueous solutions.

24. Option 2 also distinguishes between aqueous solutions and other mixtures, treats aqueous solutions identically to Option 1, and also treats the substance (UN 3423) the same as in Option 1. However, for non-purely aqueous solutions/mixtures, it proposes a new UN number and assigns a classification, borrowing the cut-off values proposed by the Netherlands in ST/SG/AC.10/C.3/2022/24. It also introduces a new special provision, YYY, to clarify the difference between UN 1835 and UN XXXX.

~~25. — In both options, Cefic and DGAC believe special provision 279 is appropriate against all packing groups for all entries, and the Sub-Committee is invited to consider whether special provision 223 was appropriately applied.~~

VII. Proposals

~~2625~~. The Sub-Committee is invited to consider the overview provided above, the more detailed technical information presented in the annexes, and the following proposal.

Option 1

~~2726~~. In 3.3, add a new special provision XXX as follows:

“XXX This entry applies only to aqueous solutions comprised of water, tetramethylammonium hydroxide (TMAH), and no more than 1 % other constituents. Other formulations containing tetramethylammonium hydroxide must be assigned to an appropriate generic or n.o.s. entry (e.g., UN ~~2389~~2927, Toxic liquid, corrosive, ~~inorganic~~ organic, n.o.s., etc.)”

~~2827~~. Modify the entries for UN 1835 as follows (new text is underlined, deleted text strikethrough):

UN No.	Name and description	Class or division	Subsidiary hazard	UN packing group	Special provisions	Limited & excepted quantities		Packagings and IBCs		Portable tanks and bulk containers	
						(7a)	(7b)	Packing instruction	Special packing provisions	Instructions	Special provisions
(1)	(2)	(3)	(4)	(5)	(6)	(7a)	(7b)	(8)	(9)	(10)	(11)
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with more than 25% tetramethylammonium hydroxide	6.1	8	I	279 XXX	0	E5	P00 1		T14	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with not less than 2.5 % but not more than 25 % tetramethylammonium hydroxide	8	6.1	II	279 XXX	1 L	E2	P00 1 IBC 02		T7	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with less than 2.5 % tetramethylammonium hydroxide	8		III	279 223 XXX	5 L	E1	P00 1 IBC 03 LP0 1		T7	TP2
3423	TETRAMETHYLAMMONIUM HYDROXIDE, SOLID	6.1 8	8	II	279	4 kg 0	E2 E5	P00 2 IBC 08 IBC 99	B2, B4	T3 T6	TP33

Option 2

~~2928~~. In 3.3, add a new special provision XXX as follows:

“XXX This entry applies only to aqueous solutions comprised of water, tetramethylammonium hydroxide (TMAH), and no more than 1 % other constituents. Other formulations containing tetramethylammonium hydroxide must be assigned to ~~UN XXXX, an appropriate generic or n.o.s. entry (e.g., UN 2389, Toxic liquid, corrosive, inorganic, n.o.s., etc.).~~”

~~3029~~. In 3.3, add a new special provision YYY as follows:

“YYY This entry applies only to formulations, with or without water, containing tetramethylammonium hydroxide and more than 1% other constituents.”

~~3130~~. Insert a new UN number XXXX for formulations, with or without water, containing tetramethylammonium hydroxide and more than 1 % other constituents.

~~3231~~. Modify the entries for UN 1835 and UN 3423 and insert entries for UN XXXX as follows:

UN No.	Name and description	Class or division	Subsidiary hazard	UN packing group	Special provisions	Limited & excepted quantities		Packagings and IBCs		Portable tanks and bulk containers	
						(7a)	(7b)	Packaging instruction	Special packaging provisions	Instructions	Special provisions
(1)	(2)	(3)	(4)	(5)	(6)	(7a)	(7b)	(8)	(9)	(10)	(11)
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with more than 25% tetramethylammonium hydroxide	6.1	8	I	279 XXX	0	E5	P001		T14	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with not less than 2.5 % but not more than 25 % tetramethylammonium hydroxide	8	6.1	II	279 XXX	1 L	E2	P001 IBC 02		T7	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with less than 2.5 % tetramethylammonium hydroxide	8		III	279 223 XXX	5 L	E1	P001 IBC 03 LP0 1		T7	TP2
<p><u>Author's note: The following information was inadvertently omitted when the paper was reformatted for posting. Except for the UN number change from 1835 to XXXX, it is taken directly from the proposal in Option 1 of ST/SG/AC.10/C.3/2022/24 of the 60th session.</u></p>											
XXX X	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with more than 8.75 % tetramethylammonium hydroxide	6.1	8	I	279 YYY	0	E5	P001		T14	TP2
XXX X	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with not less than 2.38 % but not more than 8.75 % tetramethylammonium hydroxide	6.1	8	II	279 YYY	1 L 100 ml	E2 E4	P001 IBC 02		T7	TP2

XXX X	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with less than 2.38 % <u>tetramethylammonium hydroxide</u>	8		III	<u>279</u> 223 <u>YYY</u>	5 L	E1	P00 1 IBC 03 LP0 1		T7	TP2
3423	TETRAMETHYLAMMONIUM HYDROXIDE, SOLID	<u>6.1</u> 8	<u>8</u>	II	<u>279</u>	4 kg <u>0</u>	E2 <u>E5</u>	P00 2 IBC 08 <u>IBC</u> <u>99</u>	B2, B4	T3 <u>T6</u>	TP33