



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

Sixtieth session

Geneva, 27 June-6 July 2022

Item 3 of the provisional agenda

Listing, classification and packing

Revision of classification of tetramethylammonium hydroxide

Transmitted by the expert from the Netherlands*

Introduction

1. At the fifty-ninth session of the Sub-Committee a document was presented (informal document INF.12 (59th session) to discuss a revision of the classification of tetramethylammonium hydroxide (TMAH). Many delegates who provided comments during that session or through written correspondence supported the additional assignment of Division 6.1 to TMAH. The Netherlands is very grateful for the valuable comments that have been received.

2. TMAH is a quaternary ammonium compound used in the chemical industry in its solid form and as a solution. The solid form is assigned to UN 3423 TETRAMETHYLAMMONIUM HYDROXIDE, SOLID, Class 8, PG II, whereas TMAH solutions are assigned to UN 1835 TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION Class 8, PG II or III. TMAH solutions are commonly transported at concentrations of 2.38 %, 20 %, and 25 %.

3. According to literature, TMAH has alkaline corrosive properties that can cause chemical skin burns, as well as systemic neurotoxic (cholinergic agonistic) effects that can lead to respiratory failure and cardiac arrest. The corrosivity of TMAH solutions damages the skin allowing for increased dermal uptake of TMAH. Solid TMAH is hygroscopic and will take up water or dissolve into the surface moisture of the skin¹. The current classification of TMAH in the Dangerous Goods List does not reflect the acute toxic properties of the substance. The current TMAH data sheets are shown in Annexes III (solid) and IV (solution) for informational purposes.

4. The Model Regulations state in several places that assignment of packing groups shall take human experience into account: in 2.6.2.2.2 for toxic substances and for corrosive substances in 2.8.3.1 and 2.8.3.2. However, quantitative criteria for classification using evidence from human experience are not given.

5. Updating the classification of TMAH based on the most recent insights is necessary to ensure the safety of people, property and the environment. By doing so the Sub-Committee

* A/75/6 (Sect.20), para. 20.51

¹ <https://pubchem.ncbi.nlm.nih.gov/compound/Tetramethylammonium-hydroxide>

aligns itself with the Sustainable Development Goal number 3: ensure healthy lives and promote well-being for all at all ages.

6. This working document starts first with an overview of the available data on human incidents followed by an analysis of those incidents and a proposed assignment of packing groups for both the toxic and corrosive effects. Second, the outcome of the animal test data is summarized accompanied with a classification based on these data (the data itself is presented in Annexes I and II). In a third step the proposed classification outcomes of the human incidents and animal test data are summarized in one overview and a new classification for TMAH with prioritizing the human data is proposed. Finally, the transport conditions are updated to match with the new proposed classification, as shown in paragraph 21 of this document.

Human data

7. Three literature studies^{1,2,3} report in total 37 incidents involving accidental human exposure, four of which have resulted in death (see Table 1). The accidents occurred with various TMAH concentrations ranging from 0.5 % to 25 %. Cases in which the concentration of TMAH was unknown have been removed from the table since these cannot be used for classification purposes. In some cases, the victims were treated with Diphoterine solution which is a decontamination substance which resulted in less severe health effects. The cases are listed per incident by the concentration of the solution that got spilled, the percentage of exposed body surface area, the time that elapsed from the spill and until the decontamination of the exposed person, the clinical and laboratory abnormalities, and the treatment/outcome. The original publications list additional information on details of some of the cases and the clinical signs that were noted.

Table 1: Incidents involving accidental human exposure to TMAH, dermal exposure

<i>TMAH solution</i>	<i>Exposed body surface area</i>	<i>Elapsed time to decontamination</i>	<i>Clinical abnormalities and laboratory abnormalities</i>	<i>Treatment/outcome</i>	<i>Reference</i>
0.50 %	Nearly entire body	30 min	None	Supportive/ survived	Huang et al.
0.50 %	Nearly entire body	30 min	None	Supportive/ survived	Huang et al.
1–3 %	< 1 %	None	First-degree chemical burn	Supportive/ survived	Huang et al.
2.36 %	< 2 %	N/A	None	Supportive/ survived	Huang et al.
2.38 %	28 %	10 min	Second to third degree chemical burn, dyspnea, salivation, respiratory failure, weakness, hyperglycemia, leukocytosis	Intensive care/survived	Lin et al.
2.38 %	5 %	< 10 min	First to third degree chemical burn, dermal pain, skin rashes	Supportive/survived	Lin et al.
2.38 %	< 1 %	< 10 min	None	Supportive/survived	Lin et al.
2.38 %	< 1 %	< 10 min	None	Supportive/survived	Lin et al.
2.38 %	18 %	Unknown	First to second degree chemical burn	Supportive/survived	Lin et al.
2.38 %	5 % (face)	< 1 min	Limb weakness, skin rashes	Supportive/survived	Lin et al.
2.38 %	1 % (finger)	2 h	Dermal pain and swelling, skin rashes	Supportive/survived	Lin et al.
2.38 %	Eye	< 1 min	Conjunctivitis	Supportive/survived	Lin et al.
2.38 %	2 %	< 1 min	First to second degree chemical burn, dermal pain, skin rashes	Supportive/survived	Lin et al.

¹ Chun-Chi Lin, Chen-Chang Yang, Jiin Ger, Jou-Fang Deng & Dong-Zong Hung (2010) Tetramethylammonium hydroxide poisoning, *Clinical Toxicology*, 48:3, 213-217, DOI: 10.3109/15563651003627777.

² Park SH, Park J, You KH, Shin HC, Kim HO. Tetramethylammonium hydroxide poisoning during a pallet cleaning demonstration. *J Occup Health*. 2013;55(2):120-4. doi: 10.1539/joh.12-0143-cs. Epub 2013 Jan 18. PMID: 23327884.

³ Huang, CK., Hall, A.H., Wu, ML. *et al.* Presentations of tetramethylammonium hydroxide dermal exposure and the valuable potential of diphoterine solution in decontamination: a retrospective observational study. *BMC Pharmacol Toxicol* **21**, 83 (2020). <https://doi.org/10.1186/s40360-020-00465-8>.

2.38 %	< 1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	< 1 %	N/A	First-degree chemical burn. Diphoterine used	Supportive/ survived	Huang et al.
2.38 %	< 1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	< 1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	< 1 %	N/A	None	Supportive/ survived	Huang et al.
2.38 %	1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	< 1 %	< 5 min	None	Supportive/ survived	Huang et al.
2.38 %	< 1 %	< 5 min	None	Supportive/ survived	Huang et al.
2.38 %	< 1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	2 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
2.38 %	N/A (Right arm)	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
3%	N/A (Bil. forearm)	N/A	None	Supportive/ survived	Huang et al.
8.75 %	12 %	15 - 80 min*	Chemical burns	Died	Park et al.
20 % diluted	1 %	< 1 min	First-degree chemical burn	Supportive/ survived	Huang et al.
25 %	3 %	< 30 min	Second to third degree chemical burn, dermal pain, skin rashes	Supportive/survived	Lin et al.
25 %	7 %	< 1 min	Second to third degree chemical burn, coma, dyspnea, shock, ventricular tachycardia, hyperglycemia, leukocytosis, metabolic acidosis	Intensive care/died	Lin et al.
25 %	7 %	< 1 min	Second to third degree chemical burn, coma, dyspnea, shock, hyperglycemia, leukocytosis	Intensive care/died	Lin et al.
25 %	29 %	> 30 min	Bradycardia, second to third degree chemical burn, coma, miosis, shock, salivation, weakness, hyperglycemia, leukocytosis, metabolic acidosis	Intensive care/died	Lin et al.
25 %	5 %	5 min	First to second degree chemical burn, dyspnea, drowsiness, bradycardia. Diphoterine used	Supportive, intensive care/survived	Huang et al.
25 %	2 %	N/A	Second-degree chemical burn	Supportive, intensive care/survived	Huang et al.
25 %	1 %	< 1 min	First-degree chemical burn. Diphoterine used	Supportive/ survived	Huang et al.
25 %	< 1 %	< 1 min	First-degree chemical burn. Diphoterine used	Supportive/ survived	Huang et al.
25 %	< 1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.
25 %	1 %	N/A	First-degree chemical burn	Supportive/ survived	Huang et al.

* Exposure time has not been recorded but based on the case presentation in Park et al. it is assumed the exposure time was between 15 and 80 minutes.

8. Corrosivity – the incidents led to various corrosive effects on the victims ranging from no effect to third degree chemical burns. In the low concentration incidents (up to 3 % TMAH), most of the 25 incidents had minor (skin rashes, swelling, first degree burns) or no health effects. Two of those 25 incidents led to second or third degree chemical burns. The exposure time, if documented, ranged from less than a minute up to 2 hours. In the majority of the cases the exposure time was less than one hour and the exposed body surface area was small. The incidents with a large exposed body surface area led to more severe effects such as second degree burns.

9. The incidents with a higher TMAH concentration (≥ 8.75 %) led to more severe effects with a minimum of first degree burns. In six incidents out of 12, effects were at least second degree burns with sometimes skin peeling even with relatively low exposed body surface area (e.g. 7 %). The remaining six incidents led to first degree burns although some victims were treated with Diphoterine which reduced the health effects. In three incidents the documented exposure time was below one minute and at most other incidents it was under one hour.

10. The corrosivity criteria in the Model Regulations focus on the exposure time, observation period and effect (paragraph 2.8.3.3). However, these criteria were developed for animal models and not for human incidents and therefore the criteria cannot directly be used for classification purposes, but they do provide supportive evidence of the corrosive effects. Nevertheless, based on the parameters of 2.8.3.3 this would suggest that TMAH solutions with a concentration of 25 % to be assigned packing group I due to the short exposure time (< 3 minutes) and the severe health effects such as third degree chemical burns. TMAH solutions with a concentration of 8.75 % would correspond to at least a packing group III hazard due to the longer exposure time of more than 3 minutes at which severe effects were noted. Although the exact exposure time in this incident is unknown, the victim was found 80 minutes after exposure and before decontamination. This would correspond to a packing group III hazard (exposure time > 1 h ≤ 4 h). The exposure time of the incidents with lower TMAH concentrations was predominantly less than one hour and most of the incidents led to relatively small health effects (maximum first degree chemical burns).

11. Toxicity - three fatalities were exposed to 25 % TMAH solution and one fatality to 8.75 % TMAH solution. According to the autopsy report of the latter incident, it was determined that the cause of death was TMAH poisoning. TMAH can cause systemic neurotoxic (cholinergic agonistic) effects that can lead to respiratory failure and cardiac arrest. Generally, corrosive effects of an exposed body surface area of 12 % without any complications do not lead to death (Park et al. 2013). Although the exact elapsed time to decontamination is unknown, from the documentation it is clear that the victim died within 1.5 hours after exposure, with unsuccessful decontamination. From these fatal incidents it is clear that TMAH presents a very severe toxicity hazard. Based on the human incidents, this corresponds to packing group I for ≥ 8.75 % TMAH solution.

12. In two of the lethal incidents, the persons were exposed to 25 % TMAH solution for less than one minute with a total exposure surface of 7 %. It is possible to provide an indication of human toxicity based on this information. It is assumed that the body surface⁵ of an average person is 17,000 cm². The exposed surface would then be 7 % x 17,000 cm² = 1,190 cm². Due to the short exposure time and the low viscosity of water, most of the water will run down the skin. Assuming that the thickness of the layer that contributes to the dermal toxicity is 0.01 cm, the exposure is then 1,190 cm² x 0.01 cm = 11.9 cm³ of a 25 % (0.25 g/mL) solution. The total exposure to TMAH is 11.9 cm³ x 0.25 g/mL = 2.975 grams. If this is converted to kilograms bodyweight (average of 70 kg) this amounts to 2975 mg / 70 kg = 43 mg/kg bodyweight. If the same calculation is applied to the incident with 8.75 % TMAH solution the lethal dose of this incident would correspond to 25.5 mg/kg bodyweight. However, these calculated lethal doses are not LD50 values. If they would have been LD50 values, they would correspond with classification criteria for PG I as stated in 2.6.2.2.4.1 of the Model Regulations. Although these criteria have been developed for animal models and not for humans, it does provide supportive evidence for the severe toxic properties of TMAH.

Animal data

13. There is animal test data available on the hazardous properties of TMAH. However, not all of the studies meet the guidelines as set out in the Model Regulations. This is especially the case for the acute dermal toxicity studies and the corrosivity results for solid TMAH. Despite the drawbacks, all data do underline the toxic and corrosive properties of TMAH. An overview of the acute toxic and corrosive properties of TMAH, based on *in vivo* and *in vitro* studies, is shown in Annexes I and II.

14. A summary of the results is shown in the table below. There is no information available for inhalation toxicity. The results of the oral and dermal toxicity are extrapolated to pure TMAH by using the formula in 2.6.2.3.2. The dermal toxicity studies have been performed on rats and not on rabbits as specified in 2.6.2.1.2 of the Model Regulations. Nevertheless, the results clearly indicate a toxic effect. The corrosivity study on solid TMAH

⁵ HEEG OPINION Biocidal products: model for dipping of hands/forearms in a diluted solution (https://echa.europa.eu/documents/10162/19680902/heeg_opinion_16_dipping_of_hands_forearms_en.pdf/471333fe-84d3-4601-b7cf-89881c5a2cff)

is less suitable for classification purposes. The results do indicate dermal effects ranging from no effect to severe corrosive effects.

Table 2. Summary of acute toxicity and corrosivity studies of TMAH

Hazard	TMAH solution	Class/Division	Packing Group	Comment
Oral toxicity	25 %	6.1	III	None
Oral toxicity	Solid	6.1	II	Extrapolation according to 2.6.2.3.2
Dermal toxicity	2.38 %	6.1	II	None
Dermal toxicity	25 %	6.1	I	Rat instead of rabbit
Dermal toxicity	Solid	6.1	I	Rat instead of rabbit and extrapolation according to 2.6.2.3.2
Corrosivity	2.38 %	8	III	None
Corrosivity	Solid	8	II	Less reliable results

Discussion

15. The available human and animal data indicate a corrosive and toxic hazard of TMAH. The data also shows that a distinction in packing groups is necessary, due to the various outcomes of the incidents and test results. According to the Model Regulations, the human data takes precedence over the animal data. Additionally for this specific substance, based on the literature the victims of the fatal incidents have died due to TMAH poisoning and not due to the corrosive effects of TMAH. It is known that TMAH can cause systematic neurotoxic (cholinergic agonistic) effects leading to respiratory failure and cardiac arrest. In three of the deadly incidents listed in table 1, the corrosive effects are probably not the primary cause of death due to the small exposed body surface area (7 – 12 %). It is therefore proposed that while prioritizing the human data, the toxic effects should also prevail the corrosive effects even when the precedence of hazards table indicates otherwise.

16. For some concentrations, the incidents and data provide a clear assignment of packing groups. Although the use of concentration limits in the description of the proper shipping name will provide clarity on the proper classification, the concentration limits themselves are based on known incidents and data, not on research. This makes the assignment of concentration limits pragmatic and the expert from the Netherlands invites the Sub-Committee to share their views on the assignment of the concentration limits.

17. Furthermore, the type of hazards differs per concentration limit. Based on the incidents, 8.75 % TMAH solutions can have lethal toxic effects which results in a packing group I classification. Below this concentration of TMAH solution it is unclear how to distinguish between toxic effects. For the corrosive hazard, 25 % TMAH solution effects correspond to packing group I, while 8.75 % corresponds best to packing group III due to the longer exposure time. The proposed concentration limit that distinguishes between packing group I and II is based on the toxic hazard. Based on the human incidents, there is no further distinction possible for the lower concentrations of TMAH solutions. The proposed concentration limit between packing groups II and III is therefore based on animal test data.

18. For solid TMAH it is proposed to classify based on the extrapolated human data. These data are in line with the animal test data for the solid TMAH dermal toxicity. Both the extrapolated human data and animal test data indicate a Division 6.1 PG I hazard.

19. All data are summarized in the table below. The less reliable animal test data on the corrosivity are not taken into account. The table shows an overview of the proposed classification based on the human data and on animal test data. The first column shows the concentration of the TMAH solution and the second and third column the class or division

and packing group, respectively. In the final column the origin of the data (human or animal) and any other comments are provided.

Table 3: overview of the proposed classification for TMAH based on human incidents and animal test data

TMAH concentration	Class/ Division	Packing group	Comment
8.75 %	8	III	Human data, dermal route, Exposure time estimated
8.75 %	6.1	I	Human data, dermal route
25 %	6.1	I	Human data, dermal route
25 %	8	I	Human data, dermal route
Solid	6.1	I	Human data, dermal route, extrapolation
2.38 %	6.1	II	Animal data, dermal route
2.38 %	8	III	Animal data, dermal route
25 %	6.1	III	Animal data, oral route
25 %	6.1	I	Animal data, dermal route, rat instead of rabbit
Solid	6.1	II	Animal data, oral route, extrapolation according to 2.6.2.3.2
Solid	6.1	I	Animal data, dermal route, rat instead of rabbit and extrapolation according to 2.6.2.3.2

20. The above data leads to a new classification for TMAH. Furthermore, as pointed out by one delegation at the 59th session, special provision 279 can be assigned to substances of which the classification is based on human experience. It is therefore proposed to add special provision 279 to the revised TMAH entries that have been classified based on human experience. In this case, this applies to all packing group I entries.

Proposal

21. The above classification results are merged into a revised classification for TMAH. Below are two options to handle the revised classification for TMAH. Option 1 is with concentration limits in the description and option 2 is without concentration limits. The updated transport conditions are based on the rationale of the Model Regulations and Guiding Principles. Proposed changes to the Dangerous Goods List in Chapter 3.2 are underlined and in ~~strikethrough~~.

Option 1

UN No.	Name and description	Class or division	Subsidiary hazard	UN packing group	Special provisions	Limited & excepted quantities		4		Portable tanks and bulk containers	
								Packing instruction	Special packing provisions	Instructions	Special provisions
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with more than 8.75 % tetramethylammonium hydroxide	<u>6.1</u>	<u>8</u>	<u>I</u>	<u>279</u>	<u>0</u>	<u>E5</u>	P001		<u>T14</u>	<u>TP2</u>
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with not less than 2.38 % but not more than 8.75 % tetramethylammonium hydroxide	<u>6.1</u> 8	<u>8</u>	<u>II</u>		1 L 100 ml	E2 <u>E4</u>	P001 IBC02		T7	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION with less than 2.38 % tetramethylammonium hydroxide	8		<u>III</u>	223	5 L	E1	P001 IBC03 LP01		T7	TP2
3423	TETRAMETHYLAMMONIUM HYDROXIDE, SOLID	<u>6.1</u> 8	<u>8</u>	<u>II</u>	<u>279</u>	1 kg 0	E2 <u>E5</u>	P002 IBC08 IBC99	B2, B4	T3 <u>T6</u>	TP33

Option 2

UN No.	Name and description	Class or division	Subsidiary hazard	UN packing group	Special provisions	Limited & excepted quantities		4		Portable tanks and bulk containers	
								Packing instruction	Special packing provisions	Instructions	Special provisions
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION	<u>6.1</u>	<u>8</u>	<u>I</u>	<u>279</u>	<u>0</u>	<u>E5</u>	P001		<u>T14</u>	<u>TP2</u>
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION	<u>6.1</u> 8	<u>8</u>	<u>II</u>		1 L 100 ml	E2 <u>E4</u>	P001 IBC02		T7	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE SOLUTION	8		<u>III</u>	223	5 L	E1	P001 IBC03 LP01		T7	TP2
3423	TETRAMETHYLAMMONIUM HYDROXIDE, SOLID	<u>6.1</u> 8	<u>8</u>	<u>II</u>	<u>279</u>	1 kg 0	E2 <u>E5</u>	P002 IBC08 IBC99	B2, B4	T3 <u>T6</u>	TP33

Annex I

Experimental acute toxicity studies in animals

1.1 Oral route

Acute toxicity studies via the oral route are available for 2.5 % and 25 % concentrations of TMAH. All studies were performed in rats in accordance with Organisation for Economic Co-operation and Development (OECD) guidelines and Good Laboratory Practice (GLP) principles. The results are shown in table 1 below. Column 2 shows the LD50 value obtained with the test material with the corresponding packing group shown in parenthesis. Column 3 shows the LD50 values extrapolated to the pure form using the formula in 2.6.2.3.2 of the Model Regulations, with the corresponding packing group shown in parenthesis.

Table 1: Acute toxicity in rats, oral route

<i>TMAH solution tested (%)</i>	<i>LD50 in mg/kg using the test solution (PG)</i>	<i>LD50 in mg/kg if extrapolated pure TMAH (PG)</i>	<i>Reference</i>
2.5 %	300-2000 mg/kg bw (NDG*)	7.5-50 mg/kg bw (PG II)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/2
25 %	50-500 mg/kg bw (PG III/NDG)	>12.5- <125 mg/kg bw (PG II/III)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/2/?documentUUID=5567b827-5f89-4158-bb92-05dcb8fec961
25 %	174 mg/kg bw (PG III)	43.5 mg/kg bw (PG II)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/2/?documentUUID=e864d832-06d8-46e8-8a4f-fac7a93605e3
25 %	50-300 mg/kg bw (PG III)	12.5-75 mg/kg bw (PG II)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/2/?documentUUID=8cf1b039-7bcb-4209-9260-45cf6592c0e4

*NDG = not dangerous goods

bw = body weight

The above data on oral toxicity would lead to the classification of TMAH 25 % solution as Division 6.1 PG III and solid TMAH as Division 6.1 PG II.

1.2 Dermal route

Acute toxicity studies via the dermal route are available for 2.38 %, 2.5 % and 25 % concentrations of TMAH. All studies were performed in rats in accordance with OECD guidelines and GLP principles. The results are shown in table 2. Column 2 shows the LD50 value obtained with the test material with the corresponding packing group shown in parenthesis. Column 3 shows the LD50 values extrapolated to the pure form using the formula in 2.6.2.3.2 of the Model Regulations, with the corresponding packing group shown in parenthesis.

Table 2: Acute toxicity in rats, dermal route

<i>TMAH solution tested (%)</i>	<i>LD50 in mg/kg using the test solution (PG)</i>	<i>LD50 in mg/kg if extrapolated to pure TMAH (PG)</i>	<i>Reference</i>
2.38 %	85.9 mg/kg (PG II)	2.0 mg/kg (PG I)	https://pubmed.ncbi.nlm.nih.gov/21310775/
2.5 %	1000-2000 mg/kg bw (NDG)	25-50 mg/kg bw (PG I)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=51d64548-5ca0-41d2-8c10-e89bbaa9f54a
25 %	>50-<200 mg/kg bw (PG II)	>12.5-<50 mg/kg bw (PG I)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=bb4ce5a-d439-4078-9287-49656ba91ab6
25 %	499 mg/kg bw (PG III)	112 mg/kg bw (PG II)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=644286ad-1b78-4a56-b774-66f48d0adb96
25 %	200-1000 mg/kg bw (PG III)	50-250 mg/kg bw (PG II)	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=02eaa4c8-2487-4c07-b2a6-dea7706fb090
25 %	28.7 mg/kg bw (PG I)	7.2 mg/kg bw (PG I)	https://pubmed.ncbi.nlm.nih.gov/21310775/

The data presented above shows different results for the same or comparable concentrations. It indicates a dermal toxicity classification of TMAH 2.38 % solution as Division 6.1 PG II, TMAH 25 % solution as Division 6.1 PG I and solid TMAH as Division 6.1 PG I. However, the studies have been performed on rats instead of on rabbits as specified in 2.6.2.1.2 of the Model Regulations.

1.3 Acute toxicity via the inhalation route

No acute toxicity studies via the inhalation route have been identified for TMAH.

Annex II

Experimental corrosivity studies in animals and in vitro

Experimental studies on the corrosive properties are available for 2.38 % solution (in vivo) and solid TMAH (in vitro). The animal study has been performed in rabbits in accordance with OECD and GLP guidelines. The in vitro study results are from Corrositex tests which have a reliability score of 2 (reliable with restrictions) according to the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation. The results are shown in table 3. Column 2 shows the results of the study with the corresponding packing group in parenthesis.

Table 3: Experimental corrosivity studies in animals

<i>TMAH solution tested (%)</i>	<i>Test results (PG)</i>	<i>Reference</i>
2.38 %	No dermal irritation was observed following application for 3 minutes. Application for one hour elicited well-defined dermal irritation. Application for 4 hours resulted in well-defined to severe dermal irritation in all animals, with necrosis in one animal (III). Erythema score 2.43, edema score 1.33.	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/4/2/?documentUID=803ad984-f2c4-4804-b90e-4a4534a8806c
Solid	According to the Corrositex database, TMAOH pentahydrate should be classified as packing group II for transport (ADR/DOT) based on experimental results from Corrositex testing (II).	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/4/2/?documentUID=60d2e288-0a41-4843-861e-8d72b1575014

The above data on corrosivity would lead to the classification of TMAH 2.38 % solution as Class 8 PG III and solid TMAH as Class 8 PG II, although the latter results are less reliable.

Supporting but incomplete information on the corrosive effects of TMAH is available in the study summaries of the acute dermal toxicity tests in rats. The corrosive effects are shown in the table below. Also included is a secondary reference on a guinea pig corrosivity study that was included in the OECD High Production Volume Chemical review on TMAH.

Table 3: Corrosive effects of TMAH in dermal acute toxicity studies in rats (solution) and guinea pigs (solid)

<i>TMAH test material</i>	<i>Effects described in the study summary</i>	<i>Reference</i>
2.5 % solution	Scales, scabs and/or erythema maculate were noted in the treated skin area of several animals between days 3 and 10.	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=51d64548-5ca0-41d2-8c10-e89bbaa9f54a
25 % solution	Necropsy of the animals that died revealed abnormalities of the treated skin. At all dosages, dermal effects were seen ranging from well-defined to severe on day 1 and absent to severe on days 7 and 14. Surviving animals showed slight oedema and eschar formation.	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=bbb4ce5a-d439-4078-9287-49656ba91ab6
25 % solution	The skin of one animal found dead (from the group dosed with 500 mg/kg bw) showed well-defined erythema. The skin of the other animals showed no signs of irritation.	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=644286ad-1b78-4a56-b774-66f48d0adb96
25 % solution	At treated skin site: erythema, scales and scabs during the study period.	https://echa.europa.eu/registration-dossier/-/registered-dossier/14295/7/3/4/?documentUUID=02eaa4c8-2487-4c07-b2a6-dea7706fb090
Solid	Solid tetramethylammonium hydroxide pentahydrate moistened with water was applied to the skin of guinea pigs by occlusive covering at doses of 25 to 1000 mg/kg bw. 24 hours: Slight edema. All of patch area was necrotic with band either severe erythema or hemorrhagic at periphery. 1 week: Depressed heavy eschar breaking away at edges. Some raw areas and secondary eschar forming. 2 weeks: Depressed eschars with raised edges. Scarring at periphery. Five animals died within 24 hours after application. Based on these observations, it was concluded that tetramethylammonium hydroxide pentahydrate is extremely severe corrosive irritant to skin.	https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?key=05f8249f-1562-4e9f-950c-2ac1b42e7b20&idx=0 (zipfile)

The results in the table are not sufficient to be used for classification purposes. Nevertheless, the results do indicate dermal effects ranging from no effect to severe corrosive effects.

Annex III

DATA SHEET TO BE SUBMITTED TO THE UNITED NATIONS FOR NEW OR AMENDED CLASSIFICATION OF SUBSTANCES

Submitted by SACHEM

Date: 2 November 2021

Supply all relevant information including sources of basic classification data. Data should relate to the product in the form to be transported. State test methods. Answer all questions - if necessary state "not known" or "not applicable" - If data is not available in the form requested, provide what is available with details. Delete inappropriate words.

Section 1. SUBSTANCE IDENTITY

- 1.1 Chemical name
Tetramethylammonium hydroxide (pentahydrate)
- 1.2 Chemical formula
C4H12N.5H2O.HO
- 1.3 Other names/synonyms
Methanaminium, N,N,N,N-tetramethyl-, hydroxide, hydrate (1:1:5)
Tetramethylammonium hydroxide pentahydrate
Tetramethylazanium hydroxide pentahydrate
- 1.4.1 UN number
UN 3423
- 1.4.2 CAS number
10424-65-4
- 1.5 Proposed classification for the Recommendations
- 1.5.1 Proper shipping name (3.1.2)
Tetramethylammonium hydroxide, solid
- 1.5.2 Class/division with subsidiary hazard(s) **8 packing group II**
- 1.5.3 Proposed special provisions, if any
- 1.5.4 Proposed packing instruction(s)

Section 2. PHYSICAL PROPERTIES

- 2.1 Melting point or range**63-70 °C (solid)**
- 2.2 Boiling point or range**Not available.**
- 2.3 Relative density at:
- 2.3.1.....**1.13 (20 °C)**
- 2.4 Vapour pressure at:
- 2.4.1.....**0.154 mPa @ 25 °C**
- 2.5 Viscosity at 20 °C**No data available**
- 2.6 Solubility in water at 20 °C **100 g/100 ml**
- 2.7 Physical state at 20°C (2.2.1.1) **solid crystalline**
- 2.8 Appearance at normal transport temperatures, including colour and odour
Solid crystalline, white, light yellow. Slight amine odour.

2.9 Other relevant physical properties **in water: pH > 13**

Section 3. FLAMMABILITY – the product is not flammable

3.1 Flammable vapour

3.1.1 Flash point (2.3.3) **No data available**

3.1.2 Is combustion sustained? (2.3.1.3)

3.2 Autoignition temperature **No data available**

3.3 Flammability range (LEL/UEL) **Not applicable**

3.4 Is the substance a flammable solid? (2.4.2¹) **No**

3.4.1 If yes, give details

Section 4. CHEMICAL PROPERTIES

4.1 Does the substance require inhibition/stabilization or other treatment such as nitrogen blanket to prevent hazardous reactivity? **No**

If yes, state:

4.1.1 Inhibitor/stabilizer used

4.1.2 Alternative method

4.1.3 Time effective at 55 °C

4.1.4 Conditions rendering it ineffective.....

4.2 Is the substance an explosive according to paragraph 2.1.1.1? (2.1¹) **No**

4.2.1 If yes, give details

4.3 Is the substance a desensitized explosive? (2.4.2.4¹) **No**

4.3.1 If yes, give details

4.4 Is the substance a self-reactive substance? (2.4.1¹) **No**

If yes, state:

4.4.1 Exit box of flow chart.....

What is the self-accelerating decomposition temperature (SADT) for a 50 kg package? °C

Is the temperature control required? (2.4.2.3.4¹) yes/no

4.4.2 Proposed control temperature for a 50 kg package..... °C

4.4.3 Proposed emergency temperature for a 50 kg package °C

4.5 Is the substance pyrophoric? (2.4.3¹) **No**

4.5.1 If yes, give details

4.6 Is the substance liable to self-heating? (2.4.3¹) **No**

4.6.1 If yes, give details

4.7 Is the substance an organic peroxide (2.5.1) **No**

If yes state:

¹ This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.

² See definition of "liquid" in 1.2.1 of the Model Regulations on the Transport of Dangerous Goods.

- 4.7.1 Exit box of flow chart
 What is the self-accelerating decomposition temperature (SADT) for a 50 kg package? °C
 Is temperature control required? (2.5.3.4.1¹) yes/no
- 4.7.2 Proposed control temperature for a 50 kg package °C
- 4.7.3 Proposed emergency temperature for a 50 kg package °C
- 4.8 Does the substance in contact with water emit flammable gases? (2.4.4¹) **No**
- 4.8.1 If yes, give details
- 4.9 Does the substance have oxidizing properties (2.5.1¹) **No**
- 4.9.1 If yes, give details
- 4.10 Corrosivity (2.8¹) to: **No information available**
- 4.10.1mild steel yes
- 4.10.2aluminium yes mm/year at..... °C
- 4.10.3other packaging materials (specify)
- 4.11 Other relevant chemical properties

Section 5. HARMFUL BIOLOGICAL EFFECTS

- 5.1 LD₅₀, oral (2.6.2.1.1¹) **oral LD50 of 7.5-50 mg/kg bw in rat**
- 5.2 LD₅₀, dermal (2.6.2.1.2¹) **dermal LD50 of 2.0 mg/kg bw in rat**
- 5.3 LC₅₀, inhalation (2.6.2.1.3¹)...mg/l.....Exposure time hours **No information available**
 or..... ml/m³...Animal species
- 5.4 Saturated vapour concentration at 20 °C (2.6.2.2.4.3¹) **No information available**
- 5.5 Skin exposure (2.8¹) results

Skin irritation/corrosion:

An acute dermal irritation /corrosion test according to OECD 404 with 2.38% TMAH was performed under GLP circumstances. No dermal irritation was observed following application for 3 minutes. Application for one hour elicited well-defined dermal irritation. Application for 4 hours resulted in well-defined to severe dermal irritation in all animals, with necrosis in one animal. Due to the severity in this animal and the irreversibility of the effect, the 2.38% TMAH-solution was shown to be corrosive to the skin, category 1C (according to EC regulation No 1272/2008).

The pH of a 10% TMAH solution in water is 13.6.

According to the Corrositex database, TMAOH pentahydrate should be classified as packing group II for transport (ADR/DOT) based on experimental results from Corrositex testing. (Based on the fact that the criteria for packing group II are identical to the criteria for the classification as skin corrosive 1B from OECD guideline 435, TMAOH pentahydrate is classified as skin corrosive 1B.)

- 5.6 Other data.
- 5.7 Human experience

Several fatal incidents have occurred with TMAOH.

Section 6. SUPPLEMENTARY INFORMATION

- 6.1 Recommended emergency action
- 6.1.1 Fire (include suitable and unsuitable extinguishing agents)

¹ This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.

Suitable Extinguishing Media

Use. Water spray. Carbon dioxide (CO₂). Foam. Dry chemical.

Specific hazards arising from the chemical

Causes severe burns. Hazardous combustion products. Carbon monoxide. May burn violently. Decomposition may be self-accelerating and produce large amounts of gases. May be fatal if inhaled, absorbed through skin, or swallowed.

Protective equipment and precautions for firefighters

In the event of fire and/or explosion do not breathe fumes. In case of fire: Wear self-contained breathing apparatus. Wear personal protective clothing. Avoid contact with eyes, skin and clothing.

6.1.2 Spillage

Personal precautions, protective equipment and emergency procedures

Avoid dust formation. Do not breathe dust/fume/gas/mist/vapours/spray. Do not ingest. Do not get in eyes, on skin, or on clothing. Wear personal protective clothing.

Environmental precautions

Prevent further leakage or spillage if safe to do so. Prevent product from entering drains. Local authorities should be advised if significant spillages cannot be contained. Do not flush into surface water or sanitary sewer system.

Methods and materials for containment and cleaning up

Contain and collect spillage with non-combustible absorbent material, (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local / national regulations (see section 13)

Methods for cleaning up

Pick up and transfer to properly labelled containers. Soak up with inert absorbent material. Clean contaminated surface thoroughly. Retain washings as contaminated waste.

6.2 Is it proposed to transport the substance in:

6.2.1 Bulk Containers (6.8¹)?

6.2.2 Intermediate Bulk Containers (6.5¹)?

6.2.3 Portable tanks (6.7¹)?

If yes, give details in Sections 7, 8 and/or 9.

Section 7. BULK CONTAINERS (only complete if yes in 6.2.1)

7.1 Proposed type(s)

Section 8. INTERMEDIATE BULK CONTAINERS (IBCs) (only complete if yes in 6.2.2)

8.1 Proposed type(s)

Section 9. MULTIMODAL TANK TRANSPORT (only complete if yes in 6.2.3)

9.1 Description of proposed tank (including IMO tank type if known)

9.2 Minimum test pressure

9.3 Minimum shell thickness

9.4 Details of bottom openings, if any

9.5 Pressure relief arrangements

9.6 Degree of filling

9.7 Unsuitable construction materials

Annex IV**DATA SHEET TO BE SUBMITTED TO THE UNITED NATIONS
FOR NEW OR AMENDED CLASSIFICATION OF SUBSTANCES**

Submitted by SACHEM

Date: 2 November 2021

Supply all relevant information including sources of basic classification data. Data should relate to the product in the form to be transported. State test methods. Answer all questions - if necessary state "not known" or "not applicable" - If data is not available in the form requested, provide what is available with details. Delete inappropriate words.

Section 1. SUBSTANCE IDENTITY

- 1.4 Chemical name
Tetramethylammonium hydroxide solution
- 1.5 Chemical formula
C4H12N.HO
- 1.6 Other names/synonyms
Tetramethylazanium hydroxide solution
- 1.4.1 UN number
UN 1835
- 1.4.2 CAS number
75-59-2
- 1.5 Proposed classification for the Recommendations
- 1.5.1 Proper shipping name (3.1.2)
Tetramethylammonium hydroxide solution
- 1.5.2 Class/division with subsidiary hazard(s)
8 packing group II and III
- 1.5.3 Proposed special provisions, if any
- 1.5.4 Proposed packing instruction(s)

Section 2. PHYSICAL PROPERTIES

- 2.1 Melting point or range **63-70 °C (solid)**
- 2.2 Boiling point or range**ca. 102 °C**
- 2.3 Relative density at: **No information available**
- 2.4 Vapour pressure at:
- 2.4.1.....**16.0 mm Hg @ 25 °C**
- 2.5 Viscosity at 20 °C**3.13 centipoise @ 19 °C**
- 2.6 Solubility in water at 20 °C (**solid: 100 g/100ml**)
- 2.7 Physical state at 20°C (2.2.1.1) **liquid**
- 2.8 Appearance at normal transport temperatures, including colour and odour
Liquid, colourless, light yellow. Slight amine odour.
- 2.9 Other relevant physical properties **pH > 13**

Section 3. FLAMMABILITY – not flammable

- 3.1 Flammable vapour
- 3.1.1 Flash point (2.3.3) > **95 °C**
- 3.1.2 Is combustion sustained? (2.3.1.3) **No information available**
- 3.2 Autoignition temperature **No information available**
- 3.3 Flammability range (LEL/UEL) **No information available**
- 3.4 Is the substance a flammable solid? (2.4.2¹)
- 3.4.1 If yes, give details

Section 4. CHEMICAL PROPERTIES

- 4.1 Does the substance require inhibition/stabilization or other treatment such as nitrogen blanket to prevent hazardous reactivity? **No**
- If yes, state:
- 4.1.1 Inhibitor/stabilizer used
- 4.1.2 Alternative method
- 4.1.3 Time effective at 55 °C
- 4.1.4 Conditions rendering it ineffective.....
- 4.2 Is the substance an explosive according to paragraph 2.1.1.1? (2.1¹) **No**
- 4.2.1 If yes, give details
- 4.3 Is the substance a desensitized explosive? (2.4.2.4¹) **No**
- 4.3.1 If yes, give details
- 4.4 Is the substance a self-reactive substance? (2.4.1¹) **No**
- If yes, state:
- 4.4.1 Exit box of flow chart.....
- What is the self-accelerating decomposition temperature (SADT) for a 50 kg package?°C
- Is the temperature control required? (2.4.2.3.4¹) yes/no
- 4.4.2 Proposed control temperature for a 50 kg package..... °C
- 4.4.3 Proposed emergency temperature for a 50 kg package °C
- 4.5 Is the substance pyrophoric? (2.4.3¹) **No**
- 4.5.1 If yes, give details
- 4.6 Is the substance liable to self-heating? (2.4.3¹) **No**
- 4.6.1 If yes, give details
- 4.7 Is the substance an organic peroxide (2.5.1) **No**
- If yes state:
- 4.7.1 Exit box of flow chart
- What is the self-accelerating decomposition temperature (SADT) for a 50 kg package?°C

¹ This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.

² See definition of "liquid" in 1.2.1 of the Model Regulations on the Transport of Dangerous Goods.

- Is temperature control required? (2.5.3.4.1¹) yes/no
- 4.7.2 Proposed control temperature for a 50 kg package °C
- 4.7.3 Proposed emergency temperature for a 50 kg package °C
- 4.8 Does the substance in contact with water emit flammable gases? (2.4.4¹) **No**
- 4.8.1 If yes, give details
- 4.9 Does the substance have oxidizing properties (2.5.1¹) **No**
- 4.9.1 If yes, give details
- 4.10 Corrosivity (2.8¹) to:
- 4.10.1mild steel **yes**
- 4.10.2aluminium **yes** mm/year at..... °C
- 4.10.3other packaging materials (specify)
- 4.11 Other relevant chemical properties

Section 5. HARMFUL BIOLOGICAL EFFECTS

- 5.1 LD₅₀, oral (2.6.2.1.1¹) **oral LD50 of 50-300 mg/kg bw in rat**
- 5.2 LD₅₀, dermal (2.6.2.1.2¹) **dermal LD50 of 28.7 mg/kg bw in rat**
- 5.3 LC₅₀, inhalation (2.6.2.1.3¹)...mg/l.....Exposure time hours **No information available**
or..... ml/m³...Animal species
- 5.4 Saturated vapour concentration at 20 °C (2.6.2.2.4.3¹) **No information available**
- 5.5 Skin exposure (2.8¹) results

Skin irritation/corrosion:

An acute dermal irritation /corrosion test according to OECD 404 with 2.38% TMAH was performed under GLP circumstances. No dermal irritation was observed following application for 3 minutes. Application for one hour elicited well-defined dermal irritation. Application for 4 hours resulted in well-defined to severe dermal irritation in all animals, with necrosis in one animal. Due to the severity in this animal and the irreversibility of the effect, the 2.38% TMAH-solution was shown to be corrosive to the skin, category 1C (according to EC regulation No 1272/2008).

The pH of a 10% TMAH solution in water is 13.6.

According to the Corrositex database, TMAOH pentahydrate should be classified as packing group II for transport (ADR/DOT) based on experimental results from Corrositex testing. (Based on the fact that the criteria for packing group II are identical to the criteria for the classification as skin corrosive 1B from OECD guideline 435, TMAOH pentahydrate is classified as skin corrosive 1B.)

- 5.6 Other data.
- 5.7 Human experience

Several fatal incidents have occurred with TMAOH.

- 6.1 Recommended emergency action
- 6.1.1 Fire (include suitable and unsuitable extinguishing agents)

Suitable Extinguishing Media

Use. Water spray. Carbon dioxide (CO₂). Foam. Dry chemical.

¹This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.

Specific hazards arising from the chemical

Causes severe burns. Hazardous combustion products. Carbon monoxide. May burn violently. Decomposition may be self-accelerating and produce large amounts of gases. May be fatal if inhaled, absorbed through skin, or swallowed. Product may decompose into trimethylamine, which is a flammable gas and methanol, which can produce flammable vapours.

Protective equipment and precautions for firefighters

In the event of fire and/or explosion do not breathe fumes. In case of fire: Wear self-contained breathing apparatus. Wear personal protective clothing. Avoid contact with eyes, skin and clothing.

6.1.2 Spillage

Personal precautions, protective equipment and emergency procedures

Do not breathe vapor or mist. Do not ingest. Do not get in eyes, on skin, or on clothing. Wear personal protective clothing (see section 8).

Environmental precautions

Prevent further leakage or spillage if safe to do so. Prevent product from entering drains. Local authorities should be advised if significant spillages cannot be contained. Do not flush into surface water or sanitary sewer system. Do not release into waterways or aquatic systems.

Methods and materials for containment and cleaning up

Contain and collect spillage with non-combustible absorbent material, (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local / national regulations (see section 13)

Methods for cleaning up

Soak up with inert absorbent material. Clean contaminated surface thoroughly. Retain washings as contaminated waste. Product may decompose into trimethylamine, which is a flammable gas and methanol, which can produce flammable vapours. Empty containers may contain one or both flammable gases and should be handled appropriately. All equipment used in cleaning containers should be grounded and bonded, including the container, to prevent build-up and discharge of static electricity which may cause fire or explosion.

6.2 Is it proposed to transport the substance in:

6.2.1 Bulk Containers (6.8¹)?6.2.2 Intermediate Bulk Containers (6.5¹)?6.2.3 Portable tanks (6.7¹)?

If yes, give details in Sections 7, 8 and/or 9.

Section 7. BULK CONTAINERS (only complete if yes in 6.2.1)

7.1 Proposed type(s)

Section 8. INTERMEDIATE BULK CONTAINERS (IBCs) (only complete if yes in 6.2.2)

8.1 Proposed type(s)

Section 9. MULTIMODAL TANK TRANSPORT (only complete if yes in 6.2.3)

9.1 Description of proposed tank (including IMO tank type if known)

9.2 Minimum test pressure

9.3 Minimum shell thickness

9.4 Details of bottom openings, if any

9.5 Pressure relief arrangements

9.6 Degree of filling

9.8 Unsuitable construction materials