



**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****Sixty-first session**

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Item 3 of the provisional agenda

Listing, classification and packing**Revision of classification of tetramethylammonium hydroxide****Submitted by the European Chemical Industry Council (Cefic) and
Dangerous Goods Advisory Council (DGAC)¹****I. Introduction**

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 % 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.

¹ A/75/6 (Sect.20), para. 20.51

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 % 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 % 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.

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

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>)

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”², 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.

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

² 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>)

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

26. 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

27. 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, Toxic liquid, corrosive, inorganic, n.o.s., etc.)”

28. 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	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 LP01		T7	TP2
3423	TETRAMETHYLAMMONIUM HYDROXIDE, SOLID	6.1 8	8	II	279	4 kg 0	E2 E5	P002 IBC 08 IBC 99	B2, B4	T3 T6	TP33

Option 2

29. 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, Toxic liquid, corrosive, inorganic, n.o.s., etc).”

30. 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.”

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

32. 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)	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	<u>279</u> <u>XXX</u>	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	<u>279</u> <u>XXX</u>	1 L	E2	P00 1 IBC 02		T7	TP2
1835	TETRAMETHYLAMMONIUM HYDROXIDE AQUEOUS SOLUTION with less than 2.5 % tetramethylammonium hydroxide	8		III	<u>279</u> <u>223</u> <u>XXX</u>	5 L	E1	P00 1 IBC 03 LP0 1		T7	TP2

Annex I

[English only]

**REPORT ON PACKING GROUP ASSIGNMENT
UNDER UN TDG FOR TETRAMETHYLAMMONIUM HYDROXIDE**

Prepared by:
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Milford, CT
August 21, 2022

As requested, I have reviewed the available toxicity data for tetramethylammonium hydroxide (TMAH) (CAS 75-59-2) to determine the appropriate transport packing groups for the substance and mixtures (aqueous solutions) based on dermal toxicity under the UN Model Regulations on the Transport of Dangerous Goods.

Division 6.1 covers toxic substances. Substances of Division 6.1 are assigned to three packing groups based on their degree of hazard. The UN Model regulations tell us that we need to take human experience into account but that in the absence of human experience, the assignment is based on animal data. The criteria for Class 6.1 dermal toxicity packing group assignment based on animal test data is shown below.

Packing Group	Dermal toxicity LD50 (mg/kg)
I	<=50
II	>50 and <=200
III	>200 and <=1000

This packing group assignment corresponds with the GHS dermal toxicities of categories 1, 2 and 3.

GHS Category	Dermal toxicity LD50 (mg/kg)
1	<=50
2	>50 and <=200
3	>200 and <=1000

The main source of data on the acute dermal toxicity of TMAH is the EU REACH Registration for the substance. These data are summarized below.

The National Library of Medicine's Hazardous Substance Data Bank (HSDB) reports 2 values from a 2011 article in Toxicology and Industrial Health. The article describes a dermal rat study but there is no reference to a standardized study methodology. The doses applied to the rats were not provided. The OECD method specifies that the chemical be applied to the dorsal/flank area of the rat after the fur is closely clipped the day prior to the test. The method states that care must be taken to avoid abrading the skin to avoid affecting the permeability of the skin. In the article it was stated that the hair was shaved with an electric razor, which could abrade the skin. In the OECD method, the test chemical is applied as uniformly as possible to the prepared area covering at least 10% of the total body surface (estimated to be approximately 25 cm²). In the article it is stated that glass rings with an internal diameter of 3.1 cm, 3.5 cm external diameter and 2.5 cm height were glued to the back of the rat. The test solutions were then applied to this small area (9.7 cm²). The exposure time was 4 hours while the OECD method requires 24 hours, and the area is covered so the animal cannot ingest the chemical. In the article some of the rats were dosed with atropine after 5 minutes. It is not clear whether this was a separate test or part of the protocol. It is unknown what effect this might have had on the results. Given these uncertainties, I have not used these results in my evaluation as they cannot be considered reliable and are not comparable to the standard study results.

All reported dermal studies were conducted in rats as specified by OECD Guideline 405 (Acute Dermal Toxicity) following Good Laboratory Practice (GLP). The duration of exposure for each was 24 hours. Each of the dermal studies reported in the REACH Registration were given a reliability rating of 1 (reliable without restriction). There were no dermal studies with pure TMAH. All 4 studies used aqueous solutions of TMAH, either 2.5% or 25%. From these results, the authors of 3 studies determined an equivalent LD50 for the pure substance (100% TMAH). The registrants concluded that the dermal toxicity classification for the substance TMAH is Category 1.

REACH Registration Reported Dermal Toxicity Data Summary

Study Number	Species	Test Material	Dermal LD50 mg/kg	Discussion
1	Rat	2.5% Aqueous Solution Equivalent 100%	>1000- <2000 >25- <50	Doses-200, 1000 and 2000 mg/kg 3 rats at 200 and 2000 mg/kg; 10 rats at 1000 mg/kg; all animals died at 2000 mg/kg; no mortality at 200 and 1000 mg/kg
2	Rat	25% Aqueous Solution Equivalent 100%	>50-200 >12.5 - <50	Doses – 50, 200, 1000 and 2000 mg/kg 10 rats at 50 and 200 mg/kg; 3 rats at 1000 and 2000 mg/kg

				All animals died at 1000 and 2000 mg/kg; at 200 mg/kg 8 of 10 animals died; no mortality at 50 mg/kg
3	Rat	25% Aqueous Solution Equivalent 100%	449.1 112	Doses – 200, 400 and 500 mg/kg 5 rats at 200 and 500 mg/kg and 10 rats at 400 mg/kg 3 of 5 animals died at 500 mg/kg; 2 of 10 animals dies at 400 mg/kg; no mortality at 200 mg/kg
4	Rat	25% Aqueous Solution Equivalent 100%	>200-<1000 >50 - <250	Doses – 200, 1000 and 2000 mg/kg 10 rats at 200 mg/kg, 3 rats at 1000 and 2000 mg/kg All animals died at 1000 and 2000 mg/kg; no mortality at 200 mg/kg

It is recognized that the transport regulations specify dermal toxicity testing in rabbits rather than rats. However, many experts have concluded that the dermal toxicity values for these two species are comparable and since 2017 OECD 402 has specified that the adult rats are the preferred species to be used for dermal toxicity testing. Prior to 2017, rats, rabbits and guinea pigs were listed as options.

The GHS specifies both rats and rabbits as the preferred species for dermal toxicity testing with no adjustment of the criteria. In the case where both rat and rabbit data are available and the data disagrees the GHS advises; “When experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD50 value from among valid, well-performed tests.” This recognizes that all useful animal data should be used for classification, assigning both the hazard class and category (equivalent to the packing group).

In a 2004 article by C. Auletta titled “Current in vivo Assays for Cutaneous Toxicity: Local and Systemic Toxicity Testing” published in the journal *Basic & Clinical Pharmacology & Toxicology* the author states:

“The albino rabbit has historically been the model of choice for local toxicity (irritation) and for acute and subchronic systemic toxicity evaluations. The choice of this model was based on factors such as size and ease of handling and the high permeability of its skin. However, because of the rabbit’s enhanced sensitivity to dermal insult, it is generally considered to be over-predictive and the relevance to humans of irritation seen in rabbits has been questioned (National Academy of Sciences 1977). Many current regulations specify the albino rat as preferable to the rabbit, although the rabbit is still the standard for local toxicity (irritation) evaluations. The guinea pig is generally listed in testing guidelines as an acceptable species, but it is rarely used in toxicity evaluations.”

In the OECD Guidance Notes on Dermal Absorption (Draft Second Edition) from October 2019, it is stated “However, the rat is the preferred species for in vivo studies because of consistency and the fact that more extensive and complete data can be collected in this species (e.g. excreta and carcass).” It further states “As rat (or rabbit) skin is more permeable than human skin, an appropriately conducted in vitro or in vivo study is unlikely to underestimate dermal absorption in humans.”

Based on the fact that the current OECD method for dermal toxicity specifies the rat as the preferred species and many other regulatory systems require these tests for registration and other regulatory purposes, almost all new testing is being conducted with rats. Both GHS and transport classifications are being based on these data. To conduct an additional test in rabbits solely for transport classification would result in unnecessary animal testing. In this case, as we have no valid rabbit test data, it is appropriate to use the rat data that was generated using accepted international standards and good laboratory practice to assign transport packing groups.

Under the GHS, some countries have reviewed TMAH and have assigned hazard classifications for TMAH as a substance. In some cases these classifications are mandatory and in others advisory. The following are Competent Authority Assigned Dermal Toxicity Classifications for TMAH.

- Japan – Category 2 (recommended)
- Australia – Category 3 (recommended)
- New Zealand – No dermal classification
- Korea – Category 1 (mandatory)

Australia has developed a Human Health Tier II assessment for TMAH and its pentahydrate. This was published June 28, 2019, and is available [here](#). The data reported are the same as cited above from the REACH Registration. This assessment concluded a GHS classification of Acute Toxicity Oral and Dermal Category 3, relying on the 112 mg/kg data point.

The findings in laboratory animals are consistent with the human experience with TMAH and the toxic effects are similar. In these dermal studies TMAH was absorbed through the skin to cause acutely lethal effects when the doses were high enough. These studies were all conducted following internationally accepted standardized methods using good laboratory practice. Based on both human experience and the animal data presented above, it is appropriate to conclude that TMAH should be assigned during transport to Division 6.1 (in addition to any other hazards). Since 2 of the 4 studies indicate a dermal toxicity of <50 mg/kg, it would seem appropriate to assign 100% TMAH to packing group I based on dermal toxicity.

Human Experience

There have been a number of reported cases of worker exposure to TMAH where toxic effects were observed. These reports support the conclusion that TMAH should be classified for acute toxicity in addition to corrosivity for transport. These cases were summarized in the report by Charles River Laboratories titled: “Expert Statement on the co-exposure of TMAH and Ethoxylated Alcohols and its toxicological relevance” In the summary, it is observed that there has been only one case of death resulting where the exposures were to concentrations below 25%. In that case, the individual was exposed to a mixture containing several additional chemicals including 5% monoethanolamine and 10% ethoxylated alcohol (a non-ionic surfactant). The concentration of TMAH in the mixture was 8.75%. This exposure was not to a simple aqueous solution of TMAH.

This exposure was not a transportation accident. The exposure occurred when an employee was conducting a demonstration of a pellet cleaning formulation. The worker had created a temporary enclosure for the cleaning solution by placing pallets to form a well in the center for the cleaning bath. While standing in the well, he opened the bung of the drum. The liquid quickly poured out wetting his Skin and work clothing on his legs, hands and arms. He was not wearing any impervious protective clothing – only safety shoes, cotton gloves and normal work clothing. He continued to fill the bath with the cleaner and water for about 10 minutes while wearing the wet clothing. He went to a washroom to rinse his clothes after approximately 18 minutes but returned 2-3 minutes later stating that he could not rinse his clothing there. He was directed to a shower room a few minutes later. The worker was found unconscious in front of the shower room door an hour later. He was undressed but was not wet so had apparently not actually showered. The authors of the article on this accident did not discuss the label or SDS for this cleaner but since the product contained 8.75% TMAH, it should have been classified minimally as corrosive and appropriate protective clothing and equipment including impervious gloves, clothing, boots and eye/face protection should have been used. A safety shower and eye wash should have been in the immediate area where corrosive chemicals are handled. This was a tragic industrial accident resulting from extremely poor work practices that could easily have been prevented.

It is well known that surfactants enhance skin absorption of chemicals. Surfactants are currently used as penetration enhancers in dermal drug delivery systems. In the articles “Role of Surfactants as Penetration Enhancer in Transdermal Drug Delivery Systems” by A. Pandey et al. published in the Journal of Molecular Pharmaceutics & Organic Processes” in 2014 and “Status of surfactants as penetration enhancers in transdermal drug delivery” by I. Som et al. published in the Journal of Pharmacy and Bioallied Sciences in 2012, the authors observe that surfactants are used to increase the transfer of drugs through the skin. Both articles discuss the use of nonionic surfactants such as ethoxylated alcohols in these applications. The presence of this surfactant in this mixture could have acted to enhance the absorption of TMAH resulting in a more serious poisoning than would have occurred with a simple aqueous solution.

This case supports the conclusion that TMAH presents a dermal toxicity hazard but should not be used to assign a degree of hazard to aqueous TMAH solutions because of the confounding factors.

Mixture Classification

While incidental human exposure can certainly provide valuable information regarding potential hazards of chemicals, these unfortunate incidents cannot accurately inform us on assignment of packing groups. The information from these incidents is not detailed or well reported enough to provide the dose data needed to assign packing groups under the agreed criteria. While we cannot ignore human experience, where good quality animal test data are available, we should rely on those data for assignment of the appropriate packing group.

Under the UN TDG Regulations, the toxicity of mixtures is determined following the procedures at 2.6.2.3 to classify and assign the packing group.

2.6.2.3 Methods for determining oral and dermal toxicity of mixtures

2.6.2.3.1 When classifying and assigning the appropriate packing group to mixtures in Division 6.1, in accordance with the oral and dermal toxicity criteria in 2.6.2.2, it is necessary to determine the acute LD₅₀ of the mixture.

2.6.2.3.2 If a mixture contains only one active substance, and the LD₅₀ of that constituent is known, in the absence of reliable acute oral and dermal toxicity data on the actual mixture to be transported, the oral or dermal LD₅₀ may be obtained by the following method:

$$\text{LD}_{50} \text{ value of preparation} = \frac{\text{LD}_{50} \text{ value of active substance} \times 100}{\text{percentage of active substance by mass}}$$

Aqueous solutions of TMAH contain only one active substance but 2.6.2.3.2 states that the dermal toxicity of the mixture is determined using the formula in the absence of reliable data on the actual mixture to be transported. We have three reliable animal studies of 25% aqueous solutions of TMAH. The lowest reported LD₅₀ from these studies is >50 – 200 mg/kg. That would result in this mixture being assigned to packing group II. We also have one reliable study with a 2.5% aqueous solution that would result in that mixture not being classified as 6.1 for transport.

If the mixture contains only one active substance, and the LD₅₀ of that constituent is known, in the absence of reliable data on the actual mixture, the dermal LD₅₀ may be obtained by calculation using the formula above. This approach can also be used to determine the concentration of the active substance in a mixture at which a packing group assignment would be applied.

We know that the 2 lowest substance dermal LD₅₀ based on reliable animal studies are >12.5 - <50 mg/kg and >25 - <50 mg/kg. Based on these data, we can conclude that the LD₅₀ of the substance is between 25 and 50 mg/kg. If we use the active substance LD₅₀ value of 25 mg/kg we can calculate that concentration which would be assigned to PG II using the formula.

$$51 \text{ mg/kg} = \frac{25 \times 100}{X} \quad x = 49\%$$

If we use the lowest value that can fall within the range of >12.5 - <50 mg/kg, the calculated LD 50 that would result in a PG II assignment would be 24.7%.

$$51 \text{ mg/kg} = \frac{12.6 \times 100}{X} \quad x = 24.7\%$$

Using 12.6 mg/kg, we can calculate very conservatively that the PG II concentration would be at least 24.7%. However, we have 3 reliable dermal rat studies with 25% aqueous solutions of TMAH with the reported dermal LD₅₀s above 50 mg/kg (>50 – 200 mg/kg, 449.1 mg/kg and >200 – 1000 mg/kg).

Therefore, based on the both the calculation method in the TDG and reliable animal test data, we can conclude that an aqueous solution of TMAH with a concentration of 25% and lower would be assigned to packing group II. The actual concentration limit for PG I should fall somewhere between >25-49%.

Based on this analysis using the reliable animal data, the calculation would suggest that aqueous solutions of TMAH should be classified as follows:

>25% PG I, 6.25 - 25% PG II and >2.5 - <6.25% PG III.

However, since we have reliable LD₅₀ data on a 2.5% aqueous TMAH solution of 1000-2000 mg/kg, which would not result in classification as 6.1, a higher concentration limit for packing group 3 may be more appropriate.

Respectfully Submitted;



Denese A. Deeds, CIH, FAIHA, SDSRP
Senior Consultant

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FINAL STATEMENT

**Expert Statement on the co-exposure of TMAH and Ethoxylated Alcohols
and its toxicological relevance**

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5301 KP ZALTBOMMEL
The Netherlands

TEST FACILITY:
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AUTHENTICATION STATEMENT

We confirm that the information used in this statement is in accordance with the information provided by the sponsor. This information represents the current understanding and knowledge of the products. If more (detailed) information becomes available or if updated guidance becomes available, the statement might be subject to review.



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1. RESPONSIBLE PERSONNEL**1.1. Test Facility**

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1.2. Sponsor

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Sponsor Study Monitor/Representative

Mr. M. van der Werf

2. SUMMARY

The objective of this study was to determine the relevance of an accident with 8.75% TMAH for classification as described in Park, et al. (2013).

TMAH is known for its corrosive properties and for its effect on the central nervous system as a cholinergic agonist. In several case studies, accidents with TMAH were described (Huang, et al., 2020; Lin, et al., 2010). Deadly cases only occurred with 25% TMAH at a dose of ≥ 42.5 mg/kg bw. In all other cases, victims exposed to $< 25\%$ TMAH survived the accident, except for the case exposed to 8.75% TMAH. In this case the accidental dose TMAH was 25.5 mg/kg bw (Park, et al., 2013). However, it should be noted that there was an incident with 25% TMAH where the potential exposure was 30.36 mg/kg bw and the victim survived. It is therefore possible that the deadly outcome with 8.75% TMAH is an exception which can be explained by circumstances and possible co-exposure.

During the incident with TMAH (8.75%) with deadly outcome the victim was exposed to a mixture containing, besides TMAH (8.75%), also ethoxylated alcohol (10%) (Park, et al. 2013). Ethoxylated alcohols are widely used, for instance in laundry and cleaning detergents. In cases of unintended exposure clinical effects have been reported, such as coma, seizure, pulmonary edema, and respiratory arrest. In animal studies, ethoxylated alcohols have been reported to produce neuropharmacological and local anesthetic effects. Therefore, it is possible that the pain caused by the corrosive properties of TMAH was masked due to the anesthetic properties of ethoxylated alcohols. As a consequence, an inadequate response, due to a delayed pain stimulus, resulting in a longer exposure time and potentially more severe effects may have occurred.

In conclusion, ethoxylated alcohol and TMAH both affect the central nervous system. The effects observed in the accidental human exposure to a pallet cleaner described in Park, et al. (2013) were reported to be the result of TMAH poisoning. Based on the available data the neuropharmacological effects and/or local anesthetic effects of ethoxylated alcohol have potentially contributed to the deadly outcome by hampering an adequate response to the TMAH exposure. Based on the circumstances, extremely long exposure duration for the 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.

3. BACKGROUND/SCOPE

The transport classification of the substance tetramethylammonium hydroxide (TMAH; CAS No.: 75-59-2) is being revised. Available data (human and animal data) is being evaluated by the authorities to determine the appropriate classification. Among the data is a paper describing an incident involving human exposure to a mixture containing 8.75% TMAH (Park, et al., 2013).

The incident was described as following:

The victim was a 39-year-old male researcher with 7 years of work experience employed by a surfactant production company. The accident occurred when he was conducting a field test of a newly developed pallet cleaner. The researcher spilled the cleaner on his work clothes in the area of both the hands/arms and legs. He was unconscious when discovered. An autopsy found no damage or injury that could have resulted in death other than burns to 12% of his body, and the cause of death was found to be acute poisoning by TMAH.

The following components were part of the pallet cleaner:

Components	CAS No.	Contents (%)
Water	7732-18-5	49.5 (75.75)
Tetramethylammonium hydroxide (TMAH, 25% solution)	75-59-2	35 (8.75)
Monoethanolamine	141-43-5	5
Sodium nitrilotriacetate	18662-53-8	0.5
Ethoxylated alcohol	8413-50-6	10

The actual contents of water and TMAH in the mixture are indicated in parentheses.

In the evaluation of data, the observed effects in this incident are concluded to be the results of TMAH poisoning and it is considered that 8.75 % TMAH solutions can have lethal toxic effects which results in a packing group I classification.

However, during the incident the victim was exposed to a mixture containing, besides TMAH (8.75%), also ethoxylated alcohol (10%). Available literature indicates that ethoxylated alcohols show relevant toxicological effects.

In this expert statement information from literature on ethoxylated alcohol and TMAH has been evaluated to determine whether the effects described in Park, et al. can be attributed to TMAH poisoning or whether a combined effect of TMAH and ethoxylated alcohol is more likely.

4. MATERIALS AND METHODS

4.1. Relevant substances

Identification	TMAH
CAS number	75-59-2
Chemical name	Tetramethylammonium hydroxide
Identification	Ethoxylated alcohol
CAS number	84133-50-6
Chemical name	Alcohols, C12-14-secondary, ethoxylated

5. RESULTS

5.1. TMAH

TMAH is known for its corrosive effects, as was observed in both human and animal data (Lin et al., 2010; Huang et al., 2020; Huntingdon Life Sciences Ltd., 2001). However, in an acute oral toxicity study in rats with 25% TMAH performed according to OECD 423 and in accordance with GLP principles clinical effects were observed associated with disturbance of the central nervous system, such as tremors, uncoordinated movements, and ptosis (NOTOX B.V., 2004). In another acute oral toxicity study in rats with 25% TMAH performed according to OECD 425 and in accordance with GLP principles deaths were preceded by clinical signs, e.g. lethargy, sagging eyelids, coma and ataxia (MB research Laboratories, 2005). Furthermore, in an acute dermal toxicity study in rats performed with 25% TMAH according to OECD 402 and in accordance with GLP principles clinical effects were observed, such as tremors, quick breathing and shallow respiration (NOTOX B.V., 2004). These data indicate the effects of TMAH on the central nervous system for which TMAH is classified (STOT SE 1) under the Classification and Labelling regulation (Regulation No 1272/2008).

In a simplified table (Table 1) the incidental dose of cases described in Park, et al. (2013), Huang, et al. (2020) and Lin, et al. (2010) are described according to the calculation as reported by the UN (2022). This calculation takes both the concentration as well as the exposed surface area into account and assumes a body weight of 70 kg. In this table it can be observed that all victims exposed to $\leq 2.38\%$ TMAH survived the accident. The highest calculated incidental dose observed when exposed to 2.38% TMAH is 16.18 mg/kg bw. Victims exposed to 25% TMAH survived when the dose was ≤ 30.36 mg/kg bw and died at a dose ≥ 42.50 mg/kg bw. The person exposed to 30.36 mg/kg bw TMAH was treated with diphoterine, but still first degree burns were reported and therefore it can be assumed that TMAH was also available systemically.

Table 1 Accidental cases with TMAH and the incidental dose (mg/kg bw) per case

TMAH solution	Exposed body surface area	Elapsed time to decontamination	Incidental dose (mg/kg bw) ¹	Clinical abnormalities and laboratory abnormalities	Outcome	Reference
2.36 %	< 2 %	N/A	1.15	None	Supportive/survived	Huang et al.

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2.38 %	28%	10 min	16.18	Second to third degree chemical burn, dyspnea, salivation, respiratory failure, weakness, hyperglycemia, leukocytosis	Intensive care/survived	Lin et al.
2.38 %	5%	<10 min	2.89	First to third degree chemical burn, dermal pain, skin rashes	Supportive/survived	Lin et al.
2.38 %	<1 %	<10 min	0.58	None	Supportive/survived	Lin et al.
2.38 %	<1 %	<10 min	0.58	None	Supportive/survived	Lin et al.
2.38 %	18%	Unknown	10.40	First to second degree chemical burn	Supportive/survived	Lin et al.
2.38 %	5 % (face)	<1 min	2.89	Limb weakness, skin rashes	Supportive/survived	Lin et al.
2.38 %	1 % (finger)	2 h	0.58	Dermal pain and swelling, skin rashes	Supportive/survived	Lin et al.
2.38 %	2%	<1 min	1.16	First to second degree chemical burn, dermal pain, skin rashes	Supportive/survived	Lin et al.
2.38 %	< 1 %	N/A	0.58	First-degree chemical burn	Supportive/survived	Huang et al.
2.38 %	< 1 %	N/A	0.58	First-degree chemical burn. Diphtherine used	Supportive/survived	Huang et al.
2.38 %	< 1 %	N/A	0.58	First-degree chemical burn	Supportive/survived	Huang et al.
2.38 %	< 1 %	N/A	0.58	First-degree chemical burn	Supportive/survived	Huang et al.
2.38 %	< 1 %	N/A	0.58	None	Supportive/survived	Huang et al.
2.38 %	1%	N/A	0.58	First-degree chemical burn	Supportive/survived	Huang et al.
2.38 %	< 1 %	< 5 min	0.58	None	Supportive/survived	Huang et al.
2.38 %	< 1 %	< 5 min	0.58	None	Supportive/survived	Huang et al.
2.38 %	< 1 %	N/A	0.58	First-degree chemical burn	Supportive/survived	Huang et al.
2.38 %	2%	N/A	1.16	First-degree chemical burn	Supportive/survived	Huang et al.
8.75 %	12%	15 - 80 min	25.50	Chemical burns	Died	Park et al.
20 % diluted	1%	< 1 min	4.86	First-degree chemical burn	Supportive/survived	Huang et al.
25%	3%	<30 min	18.21	Second to third degree	Supportive/survived	Lin et al.

				chemical burn, dermal pain, skin rashes		
25%	7%	<1 min	42.50	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	42.50	Second to third degree chemical burn, coma, dyspnea, shock, hyperglycemia, leukocytosis	Intensive care/died	Lin et al.
25%	29%	>30 min	176.07	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	30.36	First to second degree chemical burn, dyspnea, drowsiness, bradycardia. Diphoterine used.	Supportive, intensive care/survived	Huang et al.
25%	2%	N/A	12.14	Second-degree chemical burn	Supportive, intensive care/survived	Huang et al.
25%	1%	< 1 min	6.07	First-degree chemical burn. Diphoterine used.	Supportive/ survived	Huang et al.
25%	< 1 %	< 1 min	6.07	First-degree chemical burn. Diphoterine used.	Supportive/ survived	Huang et al.
25%	< 1 %	N/A	6.07	First-degree chemical burn	Supportive/ survived	Huang et al.
25%	1%	N/A	6.07	First-degree chemical burn	Supportive/ survived	Huang et al.

¹ Cases where the TMAH concentration or exposed surface area were not specified were not included in this table since no incidental dose could be determined.

Deadly cases only occurred with 25% TMAH at a dose of ≥ 42.5 mg/kg bw. In all other cases, victims exposed to $< 25\%$ TMAH survived the accident, except for the case 8.75% TMAH. In this case the calculated incidental dose TMAH was 25.5 mg/kg bw (Park, et al., 2013). This is lower than the calculated incidental dose for the incident with 25% TMAH where the potential exposure was 30.36 mg/kg bw and the victim survived. It is therefore possible that the deadly outcome with 8.75% TMAH is an exception which can be explained by circumstances and possible co-exposure.

5.2. Ethoxylated alcohols

During the incident with TMAH (8.75%) with deadly outcome the victim was exposed to a mixture containing, besides TMAH (8.75%), also ethoxylated alcohol (10%) (Park, et al. 2013).

Ethoxylated alcohols are a group of non-ionic surfactants characterized by a hydrophobic alkyl chain attached via an ether linkage to a hydrophilic ethylene oxide chain. Ethoxylated alcohols are widely used in, for example, household laundry and cleaning detergents. Children are sometimes unintendedly exposed to laundry detergent pods. In a study in the US, data was examined from children (younger than 6 years) exposed to detergent pods (Valdez, et al., 2014). Generally, clinical effects observed in children that ingested laundry detergent pods are less serious effects, such as vomiting or nausea. However, in some cases very serious effects were observed such as coma, seizure, pulmonary edema, and respiratory arrest (Valdez, et al., 2014). Furthermore, automatic dishwashing rinse aids typically contain concentrations of $\leq 30\%$ of ethoxylated alcohols. One of the observations reported after ingestion of these rinse aids is central nervous system depression (Day, et al., 2020). This effect could be explained by the presence of the ethoxylated alcohols (HERA, 2009). The acute oral toxicity of alcohol ethoxylates has been extensively evaluated in numerous studies with rats (HERA, 2009; Gingell and Lu, 1991). Effects reported in these studies are, among other things, decreased activity, ataxia, changes in breathing, lethargy, and tremors. Furthermore, in acute dermal toxicity studies with ethoxylated alcohols similar effects were reported (HERA, 2009). In a study by Zerkle, et al. (1987), rats were dosed intraperitoneally with ethoxylated alcohols and showed severe neuropharmacological effects, such as ataxia, loss of righting reflex, at the lowest dose tested (110 mg/kg bw) (Zerkle, et al., 1987). Apart from these neuropharmacological effects it has been reported that ethoxylated alcohols produce local anesthetic effects when injected subcutaneously to rats. It was described that ethoxylated alcohols delayed or prevented pain-induced responses (Talmage, 1994).

LD50 values for oral exposure in rats were reported to be between 0.6 and > 10 g/kg bw (HERA, 2009). For dermal exposure, the LD50 values in rats were reported to be between 0.7 - 5 g/kg bw and in rabbits 2-5.2 g/kg bw (HERA, 2009). In comparison, in one study where ethoxylated alcohols were administered intravenously to rats the LD50 was reported to be 41 mg/kg bw. In another study, using a similar protocol an LD50 of 164 mg/kg bw was calculated (Talmage, 1994). Furthermore, in two studies where ethoxylated alcohols were administered intraperitoneally to rats the LD50 values were calculated to be 190 mg/kg bw and 760 mg/kg bw (CIR, 1988). It was observed that ethoxylated alcohols are more toxic when administered intravenously/intraperitoneally compared to oral/dermal administration. The reason for these difference in LD50 for the different routes is not known. A potential explanation for the higher oral LD50 value could be the first pass effect, which reduces the concentration of ethoxylated alcohols greatly before becoming systemically available. Furthermore, the higher dermal LD50 value could be explained by the barrier function of the

skin, which results in a lower bioavailability of ethoxylated alcohols. See [Table 2](#) for an overview of the administration routes and reported LD50 values.

Table 2 Administration route and reported LD50 values

Administration route	Reported LD50 values
Oral	600 and > 10000 mg/kg bw (rats)
Dermal	700 - 5000 mg/kg bw (rats); 2000-5200 mg/kg bw (rabbits)
Intravenously	41 mg/kg bw (rats); 164 mg/kg bw (rats)
Intraperitoneally	190 mg/kg bw (rats); 760 mg/kg bw (rats)

6. DISCUSSION AND CONCLUSION

Park, et al. (2013) reported that exposure to a mixture, containing both TMAH and ethoxylated alcohol, blocked nerve conduction from the nerve cells and blocked depolarization, which can cause respiratory and cardiac arrest in a short period of time. Furthermore, the paper describes that TMAH can be the only ingredient of the cleaner to cause acute poisoning. However, the information presented above shows that ethoxylated alcohols can also affect the central nervous system and even cause very serious effects related to central nervous system depression such as coma, seizure and respiratory arrest. Similar effects were observed in animal studies (e.g. tremors, changes in breathing, and ataxia) when comparing the clinical effects of ethoxylated alcohols and TMAH. Animal studies thus show that both TMAH and ethoxylated alcohols can cause acute poisoning. Furthermore, the corrosive properties of TMAH resulted in burns on 12% of the skin of the victim, as described in Park, et al. (2013). Therefore, the corrosive properties of TMAH affected the barrier function of the skin, which could result in an easier uptake of the ethoxylated alcohol and a higher systemic bioavailability. This is why the LD50 data as described in acute dermal toxicity studies are not applicable in this case since these are performed on intact skin. Because of the affected barrier function, the LD50 values after intravenous/intraperitoneally administration are likely most comparable due to the high bioavailability. If it is assumed that, besides all of the TMAH, all ethoxylated alcohol that was in contact with the skin was absorbed in the case described in Park, et al. (2013), the incidental exposure of 29.1 mg/kg bw ethoxylated alcohol approximates the lowest intravenous LD50 value of 41 mg/kg bw reported and neuropharmacological effects could occur.

The exposure time in Park, et al. was quite long (15-80 minutes). As previously described in this statement, ethoxylated alcohols have been reported to produce local anesthetic effects. Therefore, it is possible that the pain caused by the corrosive properties of TMAH have been masked due to the anesthetic properties of ethoxylated alcohols. As a consequence, an inadequate response, due to a delayed/absent pain stimulus, could have resulted in a longer exposure time and potentially more severe effects.

Deadly cases only occurred with 25% TMAH at a dose of ≥ 42.5 mg/kg bw. In all other cases, victims exposed to <25% TMAH survived the accident. The incidental dose in Park, et al. (2013) was calculated to be approximately 25.5 mg/kg bw TMAH. This calculated exposure is lower than the calculated incidental dose of 30.36 mg/kg bw for the incident with 25% TMAH where the victim survived. Furthermore, it should be taken into account that the incidental dose of ethoxylated alcohol was calculated to be 29.1 mg/kg bw (calculated with the same calculation as for TMAH (UN, 2022)) which approximates dose levels where neuropharmacological effects and death have been describe in animal studies. For ethoxylated alcohols the working mechanism is not clear. Based on the animals studies ethoxylated alcohols affect the central nervous system. However, a similar mechanism as

TMAH (cholinergic agonist) is not likely. Still, simultaneous exposure to both substances could lead to a more severe outcome, as the neuropharmacological effects and local anesthetic effects of ethoxylated alcohol could hamper an adequate response to TMAH exposure. Apart from the toxicological effects observed in Park, et al. (2013) it is important to note that this case study only describes one single case, while the other case studies (Huang, et al., 2020; Lin, et al., 2010) report multiple cases in which TMAH is the only component. Moreover, the case described in Park, et al (2013) is very unique since ethoxylated alcohols and TMAH are rarely combined. Furthermore, the exposure duration was extremely long given the surface percentage that was exposed. This combination of circumstances has likely led to the deadly outcome. This is supported by the incident with 25% TMAH resulting in a higher incidental exposure of 30.36 mg/kg bw, compared to the 8.75% TMAH incident, where the victim survived.

Available animal data suggest very steep dose-response curve for TMAH related CNS effects. In human case studies, calculated incidental exposures up to 18.21 mg/kg bw were reported not needing intensive care. Calculated incidental exposures between 12.14 and 30.36 mg/kg bw were reported needing intensive care while calculated incidental exposures above 42.50 mg/kg bw led to death. These observations are in line with the steep dose-response observed in animal studies. Only limited human data is available between 2.38% and 25% TMAH. Therefore, a conclusion on what percentage TMAH (below 25%, but above 2.38%) warrants classification as UN packing group I cannot be drawn.

In conclusion, ethoxylated alcohol and TMAH both affect the central nervous system. The effects observed in the accidental human exposure to a pallet cleaner described in Park, et al. (2013) were reported to be the result of TMAH poisoning. Based on the available data, acute toxicity and neuropharmacological effects, ethoxylated alcohol, another component of the pallet cleaner, has potentially contributed to the deadly outcome by hampering an adequate response to the TMAH exposure. 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.

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