Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

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Item 3 of the provisional agenda
Listing, classification and packing

Additional data on proposal ST/SG/AC.10/C.3/2022/24 - Revision of classification of tetramethylammonium hydroxide

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

Results of corrosivity and toxicity testing

1. This informal document is a reaction to official document ST/SG/AC.10/C.3/2022/24 proposing to revise the classification of tetramethylammonium hydroxide (TMAH).

2. The specific substance (TMAH) is mainly used in the semiconductor and display manufacturing industry. TMAH is used as a main substance in developers for photolithography, a reoccurring process and is one of the most critical substances in the microchip manufacturing process. As such, every chip and LCD/OLED display is manufactured using TMAH. In this industry, TMAH is most commonly supplied in intermediate bulk containers (IBCs) containing 25% concentration, which is further diluted by formulators and end users. For the production of TMAH based developer, about 0.5 million IBCs of TMAH 25% are shipped worldwide on a yearly basis. Since the typical concentration in the electronic industry is about 2-3%, the shipped volumes of these TMAH based formulations is substantially higher.

3. Presently, TMAH solutions (UN 1835) are classified as Class 8, Packaging Group II or III depending on concentration. The transport classification for TMAH solid (UN 3423) is Class 8, PG II.

4. The paper presented by the Dutch Authorities introduces the Toxic classification combined with PG I and PG II classification for TMAH solutions. PG III remains linked to the Class 8 classification (for lower concentrations)

The Dutch authorities propose 2 options for this implementation

- Option 1 makes use of specific concentration limits, where concentration of > 8.75% are considered as a PG I:
    - TMAH solutions > 8.75% would be classified as Class 6.1 (8), PG I
    - TMAH solutions ≥ 2.38% and ≤ 8.75% would be classified as Class 6.1 (8), PG II
    - TMAH solutions < 2.38% would remain Class 8, PG III
- Option 2 does not specify the concentrations linked to the different packaging groups.

  Additionally, the proposal would revise the classification of TMAH solid (UN3423) to Class 6.1 (8), PG I

  Main implications for TMAH concentrations classified under PG I:

- Transport by IBC no longer allowed; drums could be an alternative. This would result in
    - 5x increase in number of packages required.
    - More chemical exposure to both end user workers and transport workers.
    - More surface area to clean means more waste disposal.
    - More packaging waste disposal.
- Other implications
    - Toxic substances of PG I are considered as High Consequence Dangerous Goods as per 1.10 of ADR.
    - Segregation of TMAH products in storage
    - Other storage limitations per local ordinance

5. We understand the basis of 6.1 (toxic) transport classification and support this revision. In accordance with GHS the product is already classified as toxic and the corresponding marking and labelling requirements for product safety are commonly applied by the industry.

However, Cefic does not believe Packing Group I for concentrations between 8.75% and 25% is justified, based on existing data and analysis.

The 25% TMAH solution is currently GHS classified as dermal toxicity category 2 based on its LD50 value as published in the REACH documentation (as listed in table 2 of Annex I of the proposal). Based on the Model Regulations (paragraph 2.6.2.2.4.1.) the classification for such solution with this LD50 value should be toxic packing group II. Based on test data (LD50 dermal) and calculation rules, PG I is justified for concentrations >25% TMAH.

We believe a more thorough review of TMAH incidents as well as all available toxicity test data is indicated before making a final decision.

6. The decision to move from 25% threshold to 8.75% is based on a single incident unrelated to the transport of TMAH. In addition, the 8.75% TMAH incident involved a blended product also containing an alcohol ethoxylate known to have a CNS (Central Nervous System) health impact (see annex 1)[1]. The toxicological properties of a substance should not be concluded based on data from a mixture.

Proposed action plan forward:

(a) Additional review of all existing data.

- Human health-related incidents.
- Animal studies (determination of oral, dermal LD50).

(b) Evaluate full scope of unintended outcomes associated with the proposed changes, specifically change from PG II to PG I.

Conclusion

Cefic supports the classification of TMAH as 6.1 (toxic) and the principle to foresee 3 packing groups. Cefic questions based on available data the classification of TMAH concentrations < 25% under packing group I.

Cefic requests to put final decision on TMAH classification on hold to review all data and to make further recommendations in collaboration with interested delegations.

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[1] The annex to this document shown on the following pages reproduces the:
Expert statement on the co-exposure of TMAH and Ethoxylated Alcohols and its toxicological relevance", Charles River Laboratories Den Bosch BV, 24 May 2022.

charles river

FINAL STATEMENT

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

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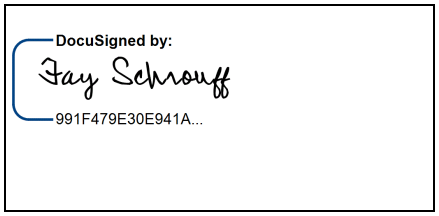
AUTHENTICATION STATEMENT

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

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2. SUMMARY

The objective of this study was to determine 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 an 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 ≤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.

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. Diphoterine 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 ≤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 vlues

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) is it 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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