

氫氧化四甲基銨(TMAH)中毒

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摘要

氫氧化四甲基銨 (Tetramethylammonium hydroxide, TMAH) 被廣泛運用在半導體及光電產業，但對人體的健康影響資料有限，近來台灣已有三例因皮膚暴露TMAH的致死案例。本文整理TMAH的解離產物TMA經口與皮膚暴露之臨床表現、致病機轉與急救措施進行文獻整理與討論。

過去文獻中的TMA中毒個案報告屈指可數，且多因誤食含有四甲基銨離子 (tetramethylammonium ions, TMA) 的腹足綱貝類造成。TMA在腸道可快速吸收，並主要經由腎臟排泄；過去則缺乏經皮吸收的資料。TMA被認為是擬膽鹼性作用劑 (cholinergic agonist)，可引起神經細胞去極化阻斷 (depolarization blockade)、骨骼肌鬆弛型麻痺 (flaccid paralysis) 與腺體分泌。食物中毒的臨床表現主要包括視覺障礙、肌肉無力及頭痛頭暈等症狀，常在誤食後數小時內發作，皮膚暴露個案則在一小時內死亡；臨床表現可由周邊菸鹼性及毒蕈鹼性作用解釋，是否影響中樞神經系統則尚未有定論。呼吸抑制被認為是TMA中毒的主要致死原因，但心臟功能的影響可能也會惡化呼吸衰竭。及早除污是現場急救第一要務，治療中毒病患時需密切觀察並維持呼吸與心臟功能。目前缺乏解毒劑的使用資料。

皮膚暴露TMAH足以致命，但目前仍缺乏相關毒理研究。建議相關職場工安衛生人員及急救醫師應注意高科技產業中可能的TMAH暴露。

關鍵字：氫氧化四甲基銨、皮膚暴露、四甲基銨離子、擬膽鹼性作用劑、呼吸抑制

前言

半導體及液晶螢幕(LCD, liquid crystal display)製造等光電產業涉及較先進的研發與技術，也具備較嚴格的工作區潔淨度，而常被認為是乾淨且安全的產業。但因為製程中所使用的化學物質複雜且具相

當毒性，如：砷、氫氟酸、2-甲氧乙基乙酯及酸鹼溶液等，及需要較極端的製程環境，如：無塵室、黃光區及長時間輪班作業等^[1-4]，實際上半導體產業相關的職業傷病並不如一般人想像中的少^[5]。近年來液晶螢幕製造產業中常以

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民國95年12月29日受理；民國96年02月08日受理刊登



2.38% 氫氧化四甲基銨(TMAH, tetramethylammonium hydroxide)水溶液作為顯影劑(developer)之用^[6-8]，使用在液晶螢幕前段製作玻璃基板時的光顯影(photolithography)製程，利用鹼性的顯影液與經曝光之光阻層部份進行酸鹼中和反應，使其與未經光阻層結構部份形成對比而達到顯像效果。另外，半導體及光電產業也大量使用TMAH取代氫氧化鈉等強鹼溶液作為清潔晶圓之溶劑使用^[9-11]。熱分析實驗(thermochemolysis)或聚合酵素鏈鎖反應(polymerase chain reaction)時也常使用TMAH溶液^[12-15]；25%TMAH為PH值高達13以上之強鹼性溶劑，網路上取得的相關物質安全資料表(MSDS)多著墨在強鹼的腐蝕性，相關毒理資料則記載不明。

2003年12月南部地區某公司於設備維修時因TMAH外洩噴濺而造成一致死案例^[16]，而2007年2月於高雄地區又造成二名技術人員因噴濺暴露而致死案例^[17]。鑒於此一化合物之劇毒表現與各界對其瞭解尚少，本文收集TMAH的解離產物，四甲基銨離子(TMA, tetramethylammonium ions)過去的中毒報告及毒理研究，針對臨床表現、致病機轉、暴露途徑與急救措施進行探討整理，冀能對產業界安全衛生工作人員及急救醫護人員提供些許處理建議。

TMAH之歷史

TMAH為TMA加上一個氫氧基，溶於水中解離度大呈強鹼性。工業用25%原液酸鹼值高於13，因為氫氧基在接觸人體後容易受到中和產生水分子，推測TMAH毒性應主要來自TMA。TMA為四級銨化合物(quaternary ammonium)，早在1875年，Weith即利用甲醇及氯化銨合成出氯化四甲基銨^[18]。半世紀後Ackermann等人首次報告可於自然界海葵(sea anemone)中分離出TMA^[19]，後來陸續從刺絲胞動物門

(Cnidaria)，腔腸動物門的珊瑚蟲、水螅、水母^[19, 20]，軟體動物門(Mollusca)中腹足綱的峨螺、法螺及頭足綱的美洲大赤魷^[21-30]，苔蘚動物門(Bryozoa)^[31]及陸生植物白花菜科(Capparidaceae)^[32]等動植物體內皆可發現TMA的存在。峨螺體內TMA以唾腺濃度最高，約在12 mg/g至數個mg/g之間，估算全身總含量多不超過數個毫克。

TMA中毒之臨床表現

過去零星的個案報告指出，誤食含TMA的有毒螺類會造成包括複視、畏光、弱視、暫時性失明、肌肉抽搐(muscle twist)、步伐蹣跚、虛弱無力、噁心、嘔吐、腹痛、頭痛、頭暈目眩、及蕁麻疹等臨床症狀^[23, 28-30, 33, 34]。這些症狀多半在三十分鐘至一個小時內出現，並於一天內完全恢復。症狀的表現常以視覺障礙開始，接著是肌肉無力，最後才是噁心、嘔吐及腹痛等腸胃道症狀。在實驗動物身上注射螺類萃取物時，則發現主要作用於骨骼肌，可造成肌肉震顫(fasciculation)、痙攣(convulsion)、平衡感喪失(loss of balance)、運動麻痺，甚至呼吸停止；其他作用則包括造成大量眼淚及唾液分泌^[29, 30, 33, 34]。過去唯一的一例致死的報告乃因誤食白花菜科植物根部造成的中毒案例^[32]。

TMA脂溶性差且帶有正電荷，被認為不利通過細胞膜，應主要分布在細胞外(extracellular)^[35, 36]。但動物實驗以低濃度TMA灌食大鼠(rat)腸道時，發現TMA幾乎可完全吸收，且TMA的吸收現象與膽鹼(choline)等含氮三甲基化合物(N-trimethyl group)的存在呈現競爭性抑制反應^[37]。注射TMA於小鼠腹腔內後，在血漿中之半衰期極短，十分鐘後有45%分布於腎臟；其他分佈臟器包括肝臟、膀胱、唾腺、腸黏膜、棕脂肪、胸腺、腎上

腺皮質、脾臟、胰臟，甚至心肌及骨骼肌等部位^[38]。這些證據顯示TMA可快速通過腸道黏膜及腎絲球，單純以擴散作用(diffusion)及血管分布密度難以解釋TMA在體內的分布，推測可能由特殊載體，如膽鹼載體，負責運輸通過腸黏膜或腎臟血管等細胞膜^[35, 37-40]。過去文獻並未發現TMA經皮吸收的臨床個案報告及藥物動力學研究，無法推估人體皮膚暴露時可能吸收速率及比例。最近皮膚組織中的纖維母細胞(fibroblasts)^[41, 42]及角質細胞(keratinocytes)^[43, 44]陸續被發現具有膽鹼載體，但目前並不清楚是否影響皮膚暴露TMA的吸收效果。另一方面，雖然低脂溶性與帶電荷不利TMA經皮膚吸收，當暴露在TMAH溶液的強鹼環境之中，氫氧基會造成深入皮膚的腐蝕，破壞皮膚表面角質層等防護，推測可能因而加速TMA的吸收^[45, 46]。TMA在腎臟的排泄被認為透過腎絲球濾過作用及特殊載體的分泌^[47, 48]，高達96%經由腎臟從尿液中排出，透過肝臟膽汁的分泌只佔一小部分；而TMA在血漿及尿液中皆沒有發現化學結構上的變化^[37]。

TMA中毒之病理生理學機轉

TMA的生理機轉主要為擬膽鹼性作用(acetylcholine agonist)，可直接作用於菸鹼性(nicotinic)及毒蕈鹼性(muscarinic)受體。在自主神經系統中，TMA結合在菸鹼性受體或毒蕈鹼性受體上，造成交感與副交感系統節後神經元(post-synaptic neurons)傳導性增加(conductance increase)，但因無法被及時移除而形成去極化阻斷(depolarization block)，伴隨後續可能發生細胞膜離子幫浦的過度極化(hyperpolarization)作用，而降低神經元的興奮能力^[49-53]。除了作用在神經節，TMA也可以直接作用在自主神經系統的末端部位，包括：平滑肌、心肌、汗腺、

腎上腺及胃黏膜等^[54, 59]；合併來自上游自主神經節的作用，而影響到這些器官的收縮或分泌的能力。對骨骼肌而言，TMA作用在肌肉神經交接處(neuromuscular junction)的菸鹼性受體^[60, 62]，在造成肌肉短暫興奮後，緊接著阻斷傳導。臨床上可依序觀察到短暫肌肉震顫、運動無力(motor weakness)及鬆弛麻痺(flaccid paralysis)的表現。參考其他類似藥物的表現，推測TMA首先影響小型快速運動的肌肉群，如眼球及手指的肌肉，接著是四肢、頸部及軀幹的肌肉，最後才波及肋間肌與橫膈肌^[61, 63]。TMA雖然可間接透過乙醯膽鹼酯酶(acetylcholinesterase)拮抗作用造成擬膽鹼性作用，但與直接作用的強度相較之下顯得微不足道^[64]。

比照過去食物中毒的臨床表現，TMA的中毒機轉類似於菸鹼中毒^[65]。TMA在上頸及睫狀神經節(superior cervical and ciliary ganglia)合併末端神經肌肉交接處的作用會造成眼外肌肉群無法控制，產生複視、畏光等異常視覺症狀。副交感神經節與膽鹼性神經末梢興奮後會導致腸胃道快速蠕動與張力增加，再加上迷走神經興奮後的作用，產生噁心、嘔吐及垂涎等腸胃道症狀。頭痛、頭暈、虛弱、步態不穩或痙攣等症狀可能來自於TMA對中樞神經系統的作用，但也可能是週邊系統不適的併發症狀。TMA可能經由膽鹼載體的運輸而通過血腦障壁(blood brain barrier)^[66]，然而，相較於其他部位，動物實驗中並沒有在中樞神經系統觀察到明顯的分布^[38]；是否可經由中樞神經的直接作用而影響其他如呼吸或循環系統的功能，目前並沒有足夠的證據加以推論。

TMA中毒致死之可能原因與急救方法

至於TMA致死的作用機轉，目前認為主要來自呼吸肌肉群的抑制^[23, 32, 65]；呼吸困難可能還會受到呼吸道中平滑肌收

縮及腺體分泌的惡化。此外，心肌的收縮力及節律性、心跳節律的自主神經作用、動脈小體及頸動脈體(aortic and carotid bodies)的化學受器調控或腎上腺素的分泌等也會受到TMA作用而影響心臟循環功能，是否因此而更進一步惡化呼吸衰竭的威脅，則需要更多研究來加以證實。過去文獻指出，TMA的成年男子口服致死劑量(lethal dose)推估約為3~4 mg/kg或250~1000mg^[32, 65]；皮下注射TMA在兔子、小鼠及天竺鼠的致死劑量分別為5、13.5及13.5 mg/kg。

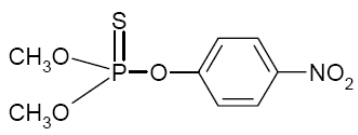
與常見引起擬膽鹼性作用的有機磷農藥如甲基巴拉松比較(表一)，可以發現雖然兩者的臨床表現相似，主要包括膽鹼性及菸鹼性作用；但兩者致病機轉不同，有機磷農藥的作用為抑制乙醯膽鹼脂酶而間接提高神經傳訊物質濃度，而TMA則直接作用在受器。過去誤食含TMA食物中毒的發作時間常在數小時內，雖然工業上最可能的經皮暴露吸收應較腸道吸收效率低，但數起案例的死亡時間皆在半小時至一小時內^[16, 17]，顯示目前高濃度TMAH經皮暴露吸收仍可在短時間內達到致死劑量；甲基巴拉松暴露也多在數小時內出現中毒症狀。有機磷中毒除了急性期症狀之外，還會引起肌肉病變、中間期症候群、延遲性周邊多發神經病變及行為異常等後續變化；TMA則沒有相關慢毒性報告。兩者致死主因皆為呼吸衰竭；有機磷農藥的急性中毒目前已知可使用Atropine及Pralidoxime作為解毒劑，而TMA中毒則

缺乏解毒劑的相關資料。從致病機轉上推測，使用Atropine應可減輕其毒蕈鹼受體的作用，但使用時機與劑量不明；Pralidoxime的作用在結合有機磷並恢復膽鹼脂酶活性，與TMA的毒理機轉不同，並不建議在臨床使用。現場處理時建議應首重除污，以大量清水沖洗患處，減少強鹼灼傷及TMA的吸收；送醫過程中應隨時注意呼吸、心跳及血壓的變化；因為TMA的體內半衰期短，未經代謝即快速經腎臟排泄，臨床醫師急救時除了呼吸與心臟循環的監控與維持外，建議可進行大量的等張溶液灌注以加速TMA的排泄。

結論

高科技光電及半導體產業的盛行雖然為人們帶來便利舒適的生活，其繁複的製程與原料藥劑卻也為從事的勞工及環境帶來不可忽視的影響，工業上使用的TMAH為帶有劇毒的強鹼性水溶液，主要意外暴露途徑為經皮吸收，可能的暴露劑量遠遠超出過去零星食物中毒個案，而經強鹼腐蝕後的皮膚也會增加TMA的吸收。目前認為TMAH的毒性主要來自TMA，是一種擬膽鹼性作用劑，致死原因推測為呼吸衰竭，因缺乏解毒劑的資料，急救時建議著重現場除污、儘速送醫、維持呼吸及心臟循環功能等。台灣已有數例因皮膚暴露25% TMAH而急性中毒死亡的案例，相關職場工安衛生人員及急救醫師應注意相關產業中可能的TMAH暴露。

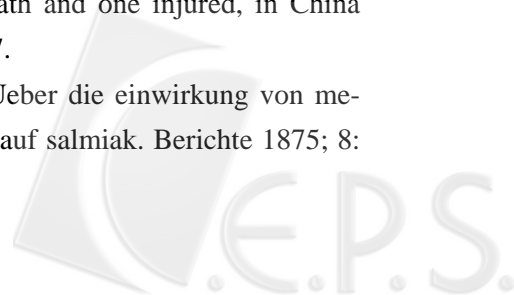
表一、TMAH與甲基巴拉松（有機磷農藥）的毒性作用比較

	TMAH	甲基巴拉松 (Methyl parathion)
工業用途	晶圓、液晶螢幕等蝕刻製程；熱化學分析及PCR等實驗室技術。	農藥。
結構	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{N}^+-\text{CH}_3 \\ \\ \text{CH}_3 \end{array} \text{OH}^-$	
主要作用機制	擬膽鹼性作用劑。	乙醯膽鹼脂酶抑制劑。
暴露途徑		
口服吸收	可。	可。
經皮吸收	無資料。	可。
呼吸吸收	無資料。	可。
中毒發作時間	誤食含TMA食物後數小時，不超過一天；皮膚暴露25% TMAH則在半小時內。	常於5至30分鐘內出現，偶爾可延長至數小時後，極罕於24小時後出現。
急性中毒表現		
毒蕈鹼性作用	眼淚及唾液分泌；噁心、嘔吐、腹痛。	分泌物增加、瞳孔縮小、腹瀉、大小便失禁、腹痛、心跳減緩等。
菸鹼性作用	複視、畏光、弱視、暫時性失明、肌肉震顫、肌肉抽搐、痙攣、運動麻痺，呼吸停止。	血壓增高、心跳增快、四肢無力、肌肉抽搐、高血糖、流汗增加。
中樞神經系統	可能有。	焦慮、頭痛、眩暈、步態不穩、混亂、抽搐、低血壓、呼吸抑制。
其他慢毒性	無資料。	肌肉病變、中間期症候群、延遲性周邊多發神經病變及行為異常等。
致死原因	主要是呼吸衰竭。	呼吸衰竭，可來自呼吸中樞抑制、呼吸肌肉群麻痺與氣管痙攣及分泌物過多等共同作用。
致死劑量	大鼠口服LD ₅₀ : 45~50 mg/kg	大鼠口服LD ₅₀ : 12~24.5 mg/kg 大鼠經皮LD ₅₀ : 67 mg/kg
解毒劑	無資料。	Atropine及Pralidoxime。
文獻	[23-25, 29, 32, 65]	[67, 68]

註：TMAH為強鹼性水溶液，具有強腐蝕性，但表中討論主要針對TMA的毒性。

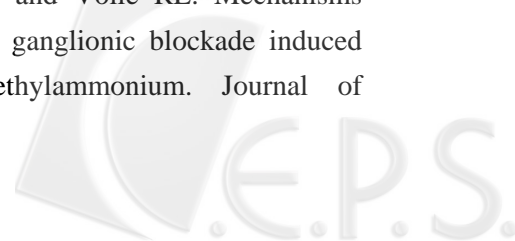
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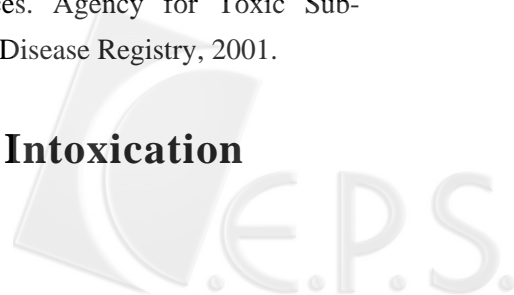
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Tetramethylammonium Hydroxide Intoxication



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Abstract

Tetramethylammonium hydroxide (TMAH) is widely used in the semiconductor and liquid crystal display (LCD) industries nowadays, but information regarding its effects on human health is limited. There were three mortalities of dermal exposure to TMAH at work in Taiwan in recent years. This review collected and discussed the references of TMA intoxication focused on the clinical presentations, mechanisms, and emergency managements especially for dermal exposure and ingestion.

Only a few reports of intoxication are available, and they are on cases from eating food, mostly gastropods, containing tetramethylammonium ions (TMA). TMA was absorbed near completely in the gastrointestinal tract, and mainly excreted by kidney. There was no available data for the dermal absorption of TMA. As a cholinergic agonist agent, TMA can induce depolarization blockade in the nervous system, lead to flaccid paralysis of skeletal muscles, and stimulate secretion of glands. For food intoxication, the most clinical presentations included vision deteriorations, muscle weakness, headache and dizziness. They usually initiated in several hours after oral intake. The three dermal exposed cases were all dead in one hour. They were related to nicotinic and muscarinic effects, but the CNS effects could not be ruled out. The inhibition of respiratory may cause mortality in exposed workers and alternation of cardiac function would facilitate the mortality. Early decontamination is the most important first aid procedure; respiratory and cardiac functions should be closely monitored and maintained in treating the exposed patients. Specific antidote need further research and develop.

Whereas few toxicological data were found in the literature, dermal exposure to TMAH can be fatal. Industrial hygienists and physicians should be aware of the potential occupational and environmental exposures.

Key words: Tetramethylammonium hydroxide, dermal exposure, Tetramethylammonium ions, cholinergic agonist, inhibition of respiratory

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