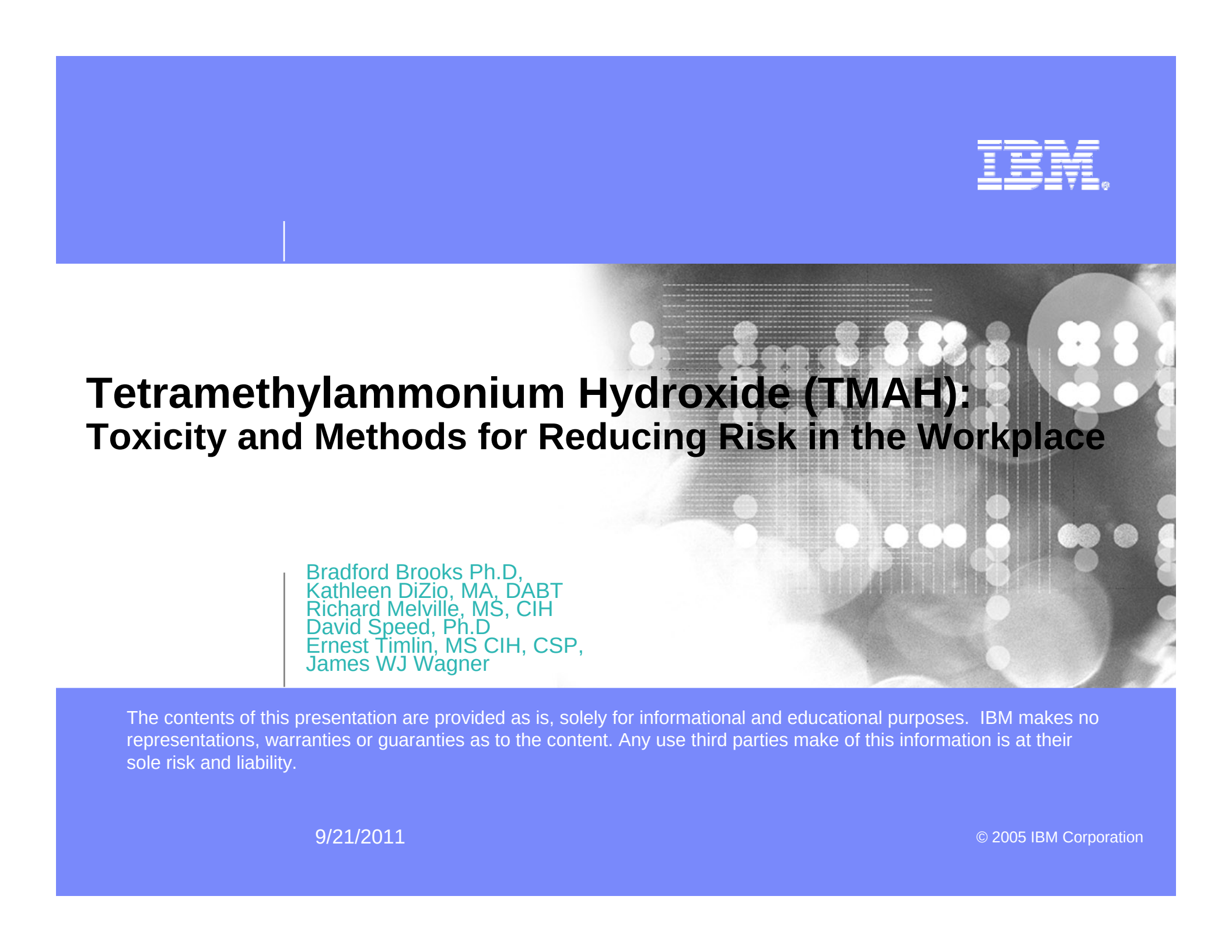

Tetramethylammonium Hydroxide (TMAH):
Toxicity and Methods for Reducing Risk in the Workplace

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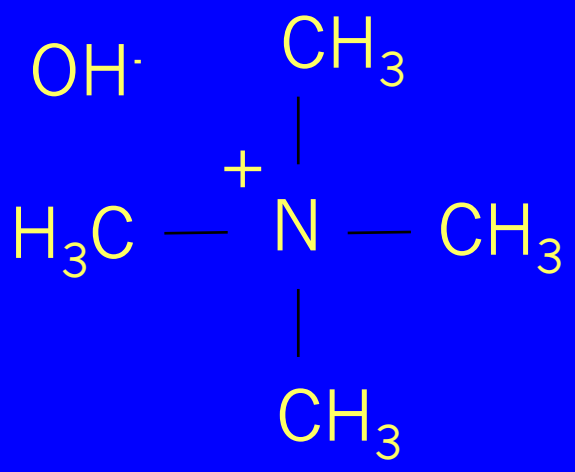
Purpose

- **There are a growing number of semiconductor processing applications which propose to use TMAH at high concentrations and sometimes at elevated temperatures.**
- **Tool vendors, chemical formulators, and other semiconductor companies may not be aware of TMAH's high acute systemic toxicity.**
- **This presentation describes:**
  - Current information on the acute systemic toxicity in humans and supporting data in animals.
  - Results of toxicity testing in animals, sponsored by IBM, on the effects of repetitive dermal contact and the potential underlying mechanisms of toxicity.
  - Evaluation and safety precautions implemented by IBM to minimize the potential risk

Tetramethylammonium hydroxide



- **Quaternary ammonium compound (cation)**
- **Strong base with similar strength to NaOH**
- **Methyl groups provide organic character**
- **Highly water soluble, density of 1.0**
- **Essentially non-volatile**
  - Boils to solid state
  - Generation of trimethylamine (strong odorant)
  - Inhalation may occur with exposure to aerosol or mist
- **High acute systemic toxicity based on oral and dermal LD50s in animals**
- **Corrosive to skin, eyes and respiratory tract. pH of 25% soln > 13**
- **Toxic to *Ceriodaphnia dubia* at sub ppm levels**

Recent case reports of TMAH poisoning/intoxication

- **Publications**

  1. Wu, Su, Chen, Lin, and Guo,
     J Occup Health, vol 50, p99-102, 2008
  2. Lin, Yang, Ger, and Deng
     Clin Toxicol, vol 46(7), p595, 2008 (abstract only)
  3. Lin, Yang, Ger, Deng, and Hung
     Clin Toxicol, vol 48, p213-217, 2010

- **Reports analyzed for**
  - Threshold concentration associated with serious intoxication
  - % body surface area affected
  - Period before decontamination
  - Possibility of concurrent inhalation and dermal exposure
  - Pattern of symptoms that may indicate mechanism of systemic toxicity.

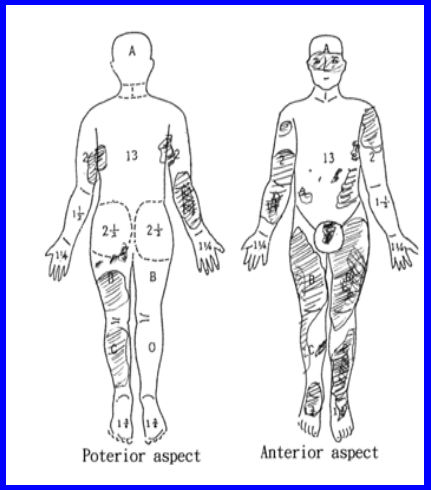
Human case reports

- **Male, 22 yrs old, sprayed from overhead by 25% TMAH**

  (Wu et. al., J. Occup. Health, Vol. 50, 2008)

  - 29% body surface area affected
  - Subject was wearing cleanroom suit, plastic goggles, no mask
  - Immediately closed valve and showered
  - Second and third degree burns on skin

    but no corrosive injury in the mouth or nose
  - Symptoms
    - 15 min - general weakness and salivation
    - 30 min – loss of consciousness, weak pulse, pinpoint pupils
    - Resuscitated in hospital but never regained consciousness
    - Died 8 days later



Human case reports *(continued)*

- **13 cases reported to Taiwan Poison Control Center between Jan 1986 and Aug 2009**
  Lin, Yang, Ger & Deng, Clin Toxicol, vol 46(7), p595, 2008
  Lin, Yang, Ger, Deng, & Hung, Clinical Toxicology, vol 48, p213-217, 2010
  - Three of four victims sprayed with 25% TMAH died
    - Key differentiator in survival was % body surface affected
      - Fatalities at ≥ 7% body surface area
      - Survival at < 3% body surface area
  - Wide variability in time to decontamination
    - < 1 minute to < 30 minutes
  - Signs and symptoms
    - 2nd to 3rd degree burns of skin
    - Irregular breathing and heart beat
    - Progressing to coma, shock and, in most cases, death
      - All deaths occurred before victims were hospitalized

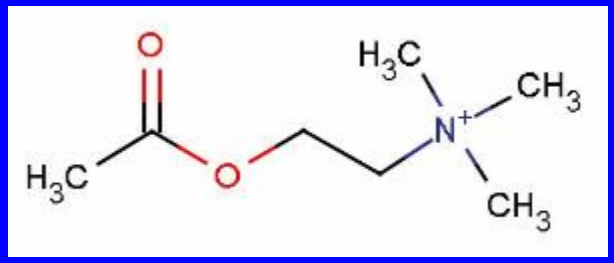
Human case reports *(continued)*

- **13 cases reported to Taiwan Poison Control Center between Jan 1986 and Aug 2009 *(continued)***
  - Nine victims were exposed to 2.38% TMAH
    - only one was a serious poisoning/intoxication
  - Again, key differentiator was % body surface
    - One worker with 28% of body surface contaminated developed muscle weakness, salivation, dyspnea, hyperglycemia, and 1st and 2nd degree burns
    - Victim required medical intervention with endotracheal intubation and intensive care.
  - Other individuals, with 1% to 18% of body surface affected, displayed 1st or 2nd degree burns and required only mild supportive care.
    - One individual, 5% BSA exposed, experienced muscle weakness

Conclusions from human case reports

- **TMAH concentration is the most important factor associated with serious poisoning/intoxication**
- **% body surface area also appears important**
  - Differences in contact with skin and the effectiveness of personal protective equipment make a direct comparison difficult
- **Time to decontamination does not appear as important**
  - Absorption thru the skin may be very rapid
- **Lack of 2nd and 3rd degree burns in the mouth and nasal passages indicates lesser exposure via inhalation**

Possible underlying mechanism based on symptoms in humans and animals

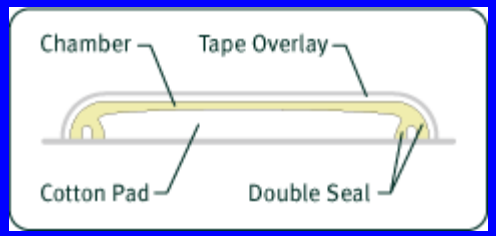


- **TMAH may mimic the effect of acetylcholine on the muscarinic receptors of the parasympathetic nervous system.**
- **Symptoms of muscarinic stimulation**
  - Constricted pupils
  - Salivation and sweating
  - Slowed heart rate
  - Constricted bronchi
- **TMAH binds to muscarinic receptors in biochemical studies on receptor structure and function**
  - In vitro studies, 5 to 50 mM concentrations in culture
    - *Am J Physiology*, 1995, 268 (6 Pt 1); p1414-1417

TMAH acute toxicity in animals

- **Oral LD_{50} in rats between 34 and 50 mg/kg**
  (Ministry of Health, Labour & Welfare, Japan 2001)
  - Symptoms of acute toxicity include decreased activity, hypothermia, ataxia, convulsions, salivation, and slowed breathing.
- **Dermal LD_{50} in guinea pigs 25 to 50 mg/kg**
  (NTIS/OTS0570994)
  - Rats exposed to 12% and 25% TMAH in the initial phase of the repetitive dosing study died within 3 hours.

Repetitive dosing studies in rats sponsored by IBM (*conducted by IITRI Lab, Chicago*)



Hilltop chamber

- **Design of initial study**
  - Rats were dermally exposed to TMAH concentrations of
    - 0% (control), 0.25%, 0.55%, 1.0%, 5%, 12% and 25%
    - 6 hours/day, 5 days/week, 4 weeks
    - 10 males and 10 females in each dose group
    - Constant dosing volume of 1 ml/kg equated to systemic doses of: 5.5 mg/kg @ 0.55%, 50 mg/kg @ 5%, 120 mg/kg @ 12% and 250 mg/kg @ 25%
- **Results**
  - All rats treated with 1 ml/kg 12% and 25% TMAH died within 3 hours
    - Signs of toxicity included lethargy, convulsions, tremor and death
  - One rat in 5% group died after first exposure. Others died within 2 weeks.
  - No rats in lower dose groups died
  - Severe erythema and edema, and necrosis at application site in higher dose groups.

IBM Studies: Repetitive dosing at lower doses

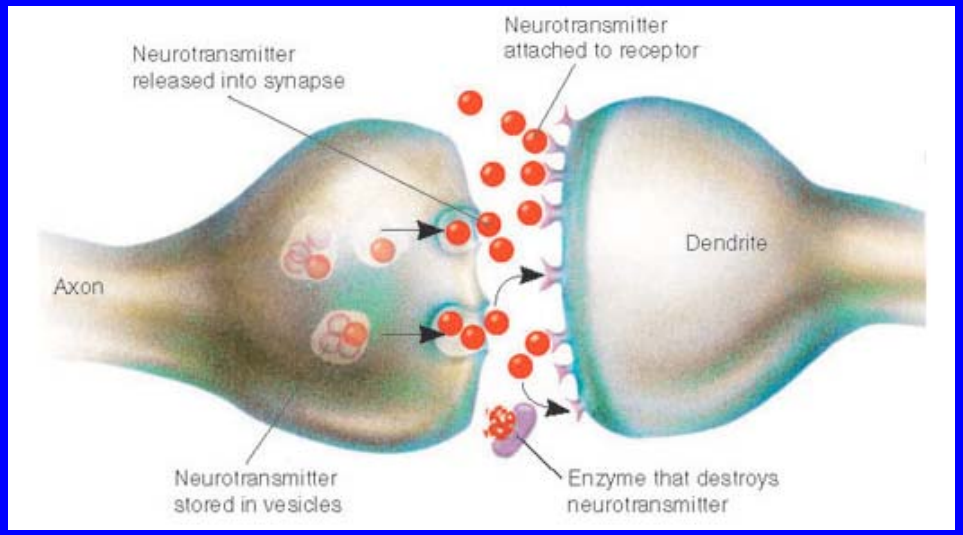
- **Study design**
  - 10 male and 10 female rats exposed to 0%, 0.25%, 0.55%, 1.0%, 3% and 5% TMAH
  - 6 hours/day, 5 days/week/ 4 weeks
  - 5% NaOH positive control
    - terminated by day 3 because of skin corrosion
- **Results**
  - 9/10 male and female rats in 5% group died within 3 days
  - 8/10 male and female rats exposed to 3% TMAH died by day 14.
  - No deaths in $\leq$ 1% TMAH groups
  - Threshold for irritation with repetitive exposure = 0.55%

IBM Studies: Duration of exposure associated with lethality

- **Duration of exposure associated with lethality**
  - 5 groups of 3 male and 3 female rats
  - Exposed to 25% TMAH for 15 min, 30 min, 45 min, 1 hour or 2 hours
- **Results**
  - Clinical signs prior to death included tremors, ptosis, hypoactivity, ataxia, coma, dyspnea and convulsion
  - No deaths with 15 min exposure; some deaths at 30 min
  - All male rats in 1 hour and 2 hour groups died.
  - Severe irritation present at application site

IBM Studies: Effects on nerve transmission in rats

- **Study design: 9 male and 9 female rats exposed to 25% TMAH for 3 hours --- divided into 3 sub-groups**
  - First group exposed and not washed
  - Second group exposed and acetylcholinesterase (AChE) levels in red blood cells and plasma measured
  - Third group administered atropine, an agent that blocks ACh receptor 30 minutes prior to TMAH



IBM Studies: Results of investigation on nerve transmission

- **Clinical signs of toxicity**
  - Tremor, drooping eyelids(ptosis), hypoactivity, ataxia, coma, irregular breathing, convulsions
- **All rats died within 2 hours**
- **No indication of change in AChE activity**
- **Atropine injection did not effect symptomology or survival.**

IBM Studies: Effect on blood gases

- **Study design**
  - 6 male / 6 female rats exposed to 0% or 5% TMAH, 1 to 4 hours
  - 8 male / 8 female rats exposed to 25% TMAH, 1 to 4 hours
- **Results**
  - A significant decrease in blood pH and increase in pCO_2 in males and females exposed to 25% TMAH
  - Decreased HCO_3 in males treated with 25%
  - Decrease in pO_2 only in males and females treated with 5% TMAH
  - Changes indicative of a disturbance in acid-base balance.

Safety and health actions

- **Updated MSDSs for IBM formulations containing TMAH**
- **Notification to US EPA under TSCA 8e**
  - NTIS/OTS0559697, NTIS/OTS 0559697-2
- **Permeation testing of gloves and coveralls**
- **Notification of employees, contractors, joint development partners**
  - Reinforcement of existing and enhanced work practices and controls
  - New education module created after reports of human fatalities
- **Shared a summary of the IBM-sponsored TMAH study results with ACC and SIA**
  - Cooperative effort with suppliers to identify technically-feasible alternatives

Safety and health actions *(Continued)*

- **Executive sponsored evaluations to determine:**
  - Whether a more benign chemical can be substituted for TMAH
  - Whether the TMAH concentration, pressure, and temperature can be minimized
- **Tool and recipe specific process hazard review (PHR) to identify and minimize the risks in using TMAH**
- **Enhanced controls to minimize exposure**

Examples of IBM exposure controls

- **Minimize manual handling of TMAH**
  - Bulk, double-contained, distribution systems where feasible
- **Engineering controls on chemical delivery, process equipment and waste treatment systems**
  - Process enclosures
  - Splash guards
  - Interlocks that terminate chemical delivery upon system breach
  - Double containment with liquid leak detection
  - Remotely activated equipment compartment cleanup showers, conductivity confirmation
  - Local exhaust ventilation
  - TMAH specific environmental controls

Examples of IBM exposure controls *(Continued)*

Double walled gasketed interlocked process enclosures

Remotely activated equipment compartment cleanup showers with conductivity confirmation

TMAH using process equipment

Examples of IBM exposure controls *(Continued)*

Conductivity measurement connectors

Shower actuation switches

Remotely activated equipment compartment cleanup showers with conductivity confirmation

Area of detail

Examples of IBM exposure controls *(Continued)*

TMAH bulk distribution system. Require use of PPE that covers the head, neck, shoulders and back (e.g., disposable coveralls) when the potential for overhead drenching or spraying exists.

Examples of IBM exposure controls *(Continued)*

Double walled chemical delivery lines

Local exhaust ventilation

Built in double glove access port

Interlocked enclosure for 330 gallon TMAH tote

Liquid containment trough with leak detection

Chemical supply cabinet for 25% TMAH

Examples of IBM exposure controls *(Continued)*

Exhausted drum covers equipped with chemical resistant gloves. **Note:** Use of chemical resistant gloves compatible with TMAH under drum cover drums is strongly recommended.

Examples of IBM exposure controls *(Continued)*

- **Administrative controls**
  - Training (e.g., chemical safety, HAZCOM, TMAH safety)
  - Safe work practices outlined in department safety procedures, manufacturing process specifications and maintenance procedures
  - Process hazard reviews
  - Do not walk into spills
  - Chemical labels (containers, chemical distribution and process equipment)
  - MSDSs
  - Store TMAH totes and drums at floor level, and do not remove pallet covers
- **Personal protective equipment**
  - Required PPE must be specified in a written PPE hazard assessment

Examples of IBM exposure controls *(Continued)*

Chemical name

IBM assigns health hazard rating of 4 for Mixtures containing >1% TMAH

Fatality warning statement for Mixtures containing >1% TMAH

Identification of TMAH in mixture

```
IBM,PROCESS CHEM,PHOSPHATE
BUFFER

HMIS Health Rating:          4
HMIS Flammability:           0
HMIS Physical Hazard:        1
Hazard Warning Statement:
DANGER! MAY BE FATAL IF
SWALLOWED, INHALED OR ABSORBED
THROUGH SKIN OR EYES.  MAY CAUSE
BURNS OR SEVERE IRRITATION UPON
CONTACT WITH SKIN, EYES OR
RESPIRATORY TRACT.  CONTAINS
TETRAMETHYLAMMONIUM HYDROXIDE
(TMAH)

Storage Type Statement:
CORROSIVE BASE (GRAY)
Date Updated: 04/14/2010
```

Warning label for TMAH-containing mixtures used for secondary chemical containers and workstations.

Examples of IBM exposure controls *(Continued)*

TMAH tote storage on floor level.

Examples of IBM exposure controls *(Continued)*

Representative TMAH Task	Minimum Required PPE			
	Eye and face	Hand	Body	Foot
Pouring	Goggles and Face shield (Face shield not required when working behind a hood sash)	Sol-Vex or Trionic gloves	Chemical resistant apron coat	N/A
Maintenance where accidental contact could occur	Goggles and face shield or full face respirator (if contact with mist could occur)	Sol-Vex or Trionic gloves	Chemical resistant apron coat	N/A
Maintenance after drain, flush and pH reduced to 6-9	Goggles	Sol-Vex or Trionic gloves	Optional	N/A
Installing and removing dip tubes in drums	Goggles and face shield	Sol-Vex or Trionic gloves	Chemical resistant apron coat	N/A
Operations with the potential for area flooding	Goggles and face shield	Sol-Vex or Trionic gloves	Chemical resistant apron coat	Chemical resistant boots
Operations with the potential for spraying: e.g. non-seamless containment, containment without a leak proof/ resistant secondary shield, or operations with potential for overhead drenching	Goggles and face shield or full face respirator (if contact with mist could occur)	Sol-Vex or Trionic gloves	Chemical hazmat body suit with head, neck and back coverage.	Chemical resistant boots

Note: Each operation requires a PPE hazard assessment to determine if a higher level of PPE is needed

Examples of IBM exposure controls *(Continued)*

Permeation Testing Data Against 25% TMAH[1]

Material	Breakthrough time (min)
Ansell Sol-Vex® 37-165 gloves (22 mil)	>480
MAPA® Professional E-194 TRIonic® gloves (20 mil)	>480
Tychem® SL coveralls	>480

1. Testing performed in accordance with ASTM F739.

Representative IBM emergency equipment and procedures

- **Emergency eyewash and showers installed near TMAH-using operations in accordance with ANSI Z358.1***
  - shall require no more than 10 seconds to reach
    - not be separated from the hazard by a wall or partition which would require passage through a door unless the hazard requires escape from the immediate area
    - the unit shall be located on the same level as the hazard
    - the area around the unit shall be well-lighted
    - emergency eyewash and shower equipment locations shall be identified with signs positioned so that they are visible within the area served by the unit
- **Emergency personnel shall be contacted immediately in the event of exposure to or a spill or leak of TMAH**
  - remove all clothing from the exposed individual and continue showering until the arrival of emergency personnel
  - respiratory support is a central element of emergency treatment

*American National Standard for Emergency Eyewash Equipment.

Summary and conclusions

- **TMAH is a hazardous chemical which can cause serious injury or death from skin contact with concentrations above 1% TMAH in water.**
- **The semiconductor industry uses concentrations from <1 % up to 25%**
- **TMAH is corrosive to the skin, eye, and upper respiratory tract**
  - contact with the concentrated liquid may permanently damage the skin and eye
  - inhalation exposure to the mist may cause inflammation and edema of the larynx and bronchi and pulmonary edema
- **Management engagement and employee training**
- **Engineering controls commensurate with the hazards posed by TMAH are essential to minimizing the potential for exposure**
- **Microorganisms used in conventional biological waste water treatment processes (activated sludge) have a limited ability to assimilate TMAH**
- **TMAH is toxic to the aquatic toxicity test organism, *Ceriodaphnia dubia* , at very low concentrations.**