TRIMETHYLAMINE

Document History
Published: 1980
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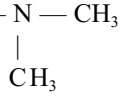
I. IDENTIFICATION

Chemical Name: Trimethylamine
Synonyms: N-Trimethylamine, N,N-Dimethylmethanamine, TMA
CAS Number: 75–50–3
DOT Number: UN 1083 Anhydrous
UN 1297 Aqueous Solution
Molecular Formula: C_3H_9N
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1-7]

Physical State and Appearance: Colorless gas at room temperature, anhydrous liquefied gas 99% under pressure
Odor Description: pungent, disagreeable, fishy
Odor Threshold: 0.21–0.8 ppb
Molecular Weight: 59.13 g/mole
Conversion Factors: 1 ppm = 2.4 mg/m^3
1 mg/m^3 = 0.42 ppm
Freezing Point: -117.3°C (-243°F)
Boiling Point: 2.9°C (37°F) at 760 mmHg;
Vapor Pressure: 1650 mmHg at 25°C (77°F)
Vapor Density: 2 (air =1)
Saturated Vapor Concentration: No data.
Flammability Limits: LEL: 2% ; UEL: 11.6%
Flash Point: -6°C (20°F)
Autoignition Temperature: 190°C (374°F)
Specific Gravity: 0.63 gm/mL at 25°C (77°F)
Water solubility: 0.86 × 10^6 mg/L
Reactivity and Incompatibilities: No data.
pH: forms alkaline solutions in water

III. USES AND VOLUME

Trimethylamine is used in the manufacture of quaternary ammonium compounds and as an insect attractant.

IV. TOXICOLOGY DATA

A. Acute Toxicity (1 to 5 day studies)

1. Oral

Rats: LD_{50} 500 mg/kg[8]
LD_{50} 460 mg/kg[9]
LD_{50} 766 mg/kg[10]

Dogs: Administration of 1000 mg/kg TMA resulted in vomiting 10 minutes after administration and eventual diarrhea.[11]

2. Eye Irritation

In a Draize eye irritation test, a 45% solution of TMA was irritating to rabbit eyes.[10]

Tests of single drops of aqueous solution of TMA have shown that a 1% solution of TMA causes severe irritation, a 5% solution causes edema, and a 16.5% solution causes hemorrhages in the conjunctiva, corneal opacities, and edema in rabbits.[12]

Vapors of volatile ethyl and methylamines have been reported to cause eye irritation with lacrimation, conjunctivitis, and corneal edema at concentrations greater than 50 ppm in rabbits.[13]

3. Skin

a. Skin Irritation

In a Draize dermal irritation test, a 45% solution of TMA applied to rabbit skin resulted in necrosis.[10]

b. Skin Absorption

The dermal LD_{50} of a 45% solution of TMA was found to be > 5000 mg/kg in rats.[10]

c. Skin Sensitization

No Information Found

4. Inhalation

Rat: 1-hour LC_{50} >2000 ppm [8]
4-hour LC_{50} >2478 ppm [10]
4-hour approximate-lethal-concentration (ALC) 3500 ppm [14]

Mouse: 2-hour LC_{50} 7866 ppm[15]
4-hour LC_{50} 4326 ppm[16]

Lethality-concentration data from a more recent inhalation study in rats is given in Table 1. Concentrations reported were based on continuous measurement with gas-phase infrared spectrophotometry using a Foxboro Miran® Model 1A.

Table 1. Rat Lethality Data for Acute Inhalation Exposures[17]

Exposure Duration	LC_{01} ppm	LC_{10} ppm	LC_{50} ppm	95% Confidence Intervals (LC_{50})
6 Minutes	N/A	N/A	>18,600	N/A
20 minutes	5900	8066	12,000	10,700–13,200
60 minutes	4227	6270	7910	7300–8580

a. Sensory Irritation:

61 ppm 15-min RD_{50} in OF-1 Mice[18]

B. Subacute Toxicity (6 to 14-day studies)

Groups of 10 rats were exposed nose-only for 6 hours/day, 5 days/week, for 2 weeks to 0, 74, 240, or 760 ppm TMA in air. Groups of 5 rats from each exposure group were subjected to histopathological examination as well as urinalysis and clinical chemical examinations after the tenth exposure, and after a 2-week recovery. After 10 exposures, all exposed rats showed a dose-dependent irritation of the nasal turbinates and mucosa that ranged subjectively from mild to severe. The rats in the 240 and 760 ppm exposure groups exhibited a slight increase in red cell mass, and decreased kidney weights. The 760 ppm rats showed dehydration, mild emphysematous alveoli, increased lung and heart weights, and decreased spleen and thymus weights. Following the recovery period, nasal irritation persisted in all levels, with improvement. All other effects observed were reversible. The only effect in the 74 ppm exposed group was mild nasal irritation that persisted throughout the recovery period.[14,19]

C. Subchronic Toxicity (15-day to 6-month studies)

No information located

D. Chronic Toxicity (6-months to lifetime studies)

Groups of 12 rats were exposed to 0, 10, or 31 ppm TMA, 5 hours/day, 5 days/week, for 7 months. The rats in all treatment groups exhibited irritation and aggressive behavior during the first 3 to 4 weeks of the study. Statistically significant reduction in leukocyte count accompanied by a relative neutrophilia was noted in the 31 ppm treatment group, starting at the fourth month of exposure. The authors reported that pathological examinations revealed bronchopneumonia and hemorrhage in lung tissues with destruction of interalveolar septa. Pathological examination also revealed passive hyperemia and isolated hemorrhaging in the liver, kidneys, and spleen; and increased weight of the adrenal glands in the 31 ppm group. Similar but less severe pathological findings were reported in the 10 ppm exposure group. This was considered to be a minimal effect level (NOAEL) by the authors.[15]

E. Reproductive/Developmental Toxicity

Doses of 1 to 7.5 mM/kg/day (59–443 mg/kg/day) of TMA delivered by intraperitoneal injection on days 6 to day 15 of gestation caused a dose-dependent decrease in fetal weights and postnatal growth in mice.[20] The NOAEL was 59 mg/kg/day for this study.

Daily intraperitoneal injection of 0, 2.5, or 5 mM/kg/day (0, 148, or 296 mg/kg/day) of TMA in pregnant mice from days 1–17 of gestation produced decreased fetal body weight but had no effect on placental weight or maternal body weight gain.[21] The NOAEL was 148 mg/kg/day for this study.

F. Genotoxicity/Mutagenicity

TMA was not mutagenic in the Ames *Salmonella typhimurium* test in strains TA1535, TA1537, TA97, TA98, and TA100 with and without metabolic activation.[22]

TMA was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, with and without metabolic activation.[23]

G. Metabolism/Pharmacokinetics

In 7 strains of rats, oral administration of radiolabeled TMA resulted in urinary excretion of more than 75% of the radiolabel within the first day. 9% was eliminated via feces.[24]

V. HUMAN USE AND EXPERIENCE

A. Odor Data

The odor threshold for TMA has been reported to be 0.21–0.8 ppb.[7,25-27]

B. Toxicity Data

Two volunteers were exposed to various airborne concentrations of triethylamine. Subjective visual disturbances described as "haze" and "halos" were reported, and were supported by observation of corneal edema in the volunteers, following an 8-hour exposure to an analytically determined exposure level of 9.7 ppm (18 mg/m^3). These visual disturbances were reported to be transient and resolved following cessation of exposure.[28]

C. Workplace Experience

Moderate irritation of the upper respiratory system occurred in humans exposed to 20 ppm or more of TMA. The NOAEL was reported to be 8 ppm.[29]

In an accidental exposure to TMA vapors, there were no corrosive injuries, but it was observed that the corneal epithelium had been lost. There was no edema of the corneal stroma, and the eye was entirely normal within 5 days.[30]

Employee exposures to concentrations of TMA have been documented ranging from 0.1–8 ppm in the plants of a producer and a formulator. Most of the workplace exposures are less than 5 ppm as an 8-hour TWA. Routine medical surveillance by the producer and the formulator have not identified any adverse effects in employees at these levels.[13]

Vision was reported to become misty, and halos appeared in the visual field several hours after workers had been exposed to the vapors of amines, including TMA at concentrations which were too low to cause discomfort or disability during several hours of exposure.[31] "Halovision," "blue haze," and "blue-grey vision" have also been used to describe this effect.[7,31-33]

D. Epidemiology

No information located.

VI. RATIONALE

The acute inhalation toxicity of trimethylamine is moderate. The 1-hour LC_{50} for rats is 7900 ppm. It is severely irritating to the eyes and skin. The NOAEL for developmental toxicity in mice for TMA ranged between 59 and 148 mg/kg/day. It is not genotoxic and is rapidly excreted in the urine. In subacute exposures, TMA affected the nasal epithelium, formed elements of the blood, kidneys, and other organ weights, and alveoli of rats exposed to 760 ppm. All effects were reversible within 2 weeks except the nasal epithelium irritation, which had improved, but was not resolved. In chronic exposure of rats to 31 ppm, neutrophilia, bronchopneumonia, destruction of interalveolar septa, and hemorrhaging of the lungs, liver, kidneys, and spleen were noted. Only minimal changes in the olfactory epithelium were noted at 10 ppm. No evidence of carcinogenicity was noted. In volunteers, respiratory irritation was noted at concentrations of 20 ppm, and workers reported transient halovision following prolonged exposure to approximately 10 ppm. At TMA concentrations of 8 ppm or lower, no adverse effects have been reported in workers.

Based on these results, an OEL of 1 ppm is recommended. This level should protect against "halovision," olfactory epithelial damage, and fetotoxicity. A level of 1 ppm will not protect against odor.

VII. RECOMMENDED OEL GUIDE

1 ppm as the 8-hour TWA

VIII. REFERENCES

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