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TOXICITY SUMMARY

TRIMETHYLAMINE

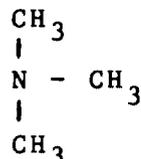
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This review reflects the available toxicity literature, both published and unpublished. Studies have not been evaluated for scientific merit.

Common Name: Trimethylamine
Chemical Name: Methanamine, N,N-dimethyl-
Synonyms: TMA
CAS Registry No.: 75-50-3
Chemical Structure:



Physical Properties: (17)

	<u>GAS</u>	<u>25% SOLUTION</u>
Description:	Colorless gas, fishy odor, threshold 0.2-0.44 ppb (8,28)*	Water white to pale-straw liquid
Molecular Weight:	59.13	59.13
Boiling Point:	2.9°C @ 760 mm Hg	43°C @ 760 mm Hg
Freezing Point:	-117.3°C	6°C
Density/Specific Gravity:	0.6270 g/mL @ 25°C (liquid)	0.930 g/mL @ 25°C
Vapor Pressure:	-----	340 mmHg @ 25°C
Flash Point/Flammability:	-----	42°F (closed cup)
Explosive Limits:	2.0 - 11.6 %	-----
Solubility:	Soluble in water	-----
Conversion Factors:	1 mg/L = 414 ppm ₃ 1 ppm = 2.4 mg/m ³	-----

This literature search contains 10 pages of text and 85 references.

This search was prepared by R. C. Graham. See the last page of this document for its updating history.

*See Related References 56-61 for additional information

Exposure Standards:

DuPont AEL = 5 ppm (8- and 12-hour TWA) (16)

TLV® = 10 ppm; STEL = 15 ppm (4)

DOT Classification:

Flammable gas and liquid (11c)

EPA RCRA Status:

Hazardous substance under Federal Water Pollution Control Act (11b)

FDA Status:

TMA is cleared for the following food-related use:

Cleared under §173.20 (ion-exchange membranes) in production of membranes used in the processing of grapefruit juice (11a).

TSCA Inventory:

Yes

TOXICITY

Summary:

Trimethylamine (TMA) is moderately toxic by the acute oral route with an LD50 in rats of 500 mg/kg. A concentrated aqueous solution of TMA applied to intact human skin caused severe burning and hyperemia. A 1% aqueous solution produced severe irritation in the eyes of laboratory animals. By the acute inhalation route of exposure, TMA is slightly toxic with a four-hour ALC in the rat of 3500 ppm. In a two-week subchronic inhalation study, rats were exposed six hours a day to 74, 240 or 760 ppm of TMA. Dose-dependent nasal irritation was seen in all groups and it persisted through the two-week recovery period. No information is available on the carcinogenic potential of TMA but several studies have shown it capable of producing nitrosamines under suitable conditions. In the Ames test, TMA was not mutagenic. In aquatic organisms, TMA produces toxic effects by increasing the pH of the water.

- In accidental exposure to the vapor of trimethylamine, there were no mechanical injuries, but it was observed that the epithelium had been lost from the cornea. The epithelium healed promptly. There was no edema of the corneal stroma and the eye was entirely normal within four or five days (20).

4. Inhalation

- Four-hour ALC (rat) = 3500 ppm (16, 23)
- One-hour LC50 (rats) = 2000 ppm (5)
- Two-hour LC16 (mice) = 5920 ppm (35)
- Two-hour LC50 (mice) = 7866 ppm (35)
- Two-hour LC84 (mice) = 10,267 ppm (35)
- Excitation with gradual transition into depression was the primary element of the clinical picture of acute poisoning in mice. Motor dyscoordination and attacks of clonic spasms lasting two-three minutes were observed at the beginning of the second hour of exposure. The animals flocked together and did not respond to extraneous stimuli (35).
- See Related References 56-61 for additional information.

5. Injection Studies *

a) Subcutaneous

- ALD (rabbit) = 800 mg/kg (15)
- ALD (mouse) = 1000 mg/kg (9)
- In dogs, injection of 700 mg/kg caused vomiting, diarrhea and suppuration at the site of injection. If the nausea was prevented by previous administration of 20 mg of morphine, the subcutaneous injection of 1000 mg/kg led to lip smacking and strong salivation, timidity, occasionally a stiff, clumsy gait and extension spasms. Two hours after administration the

* See Related References 62-64 for additional information.

temperature fell to 35.8°C and then gradually rose to 37.4°C. On the following day the dogs were again normal (24).

- In piglets, administration of 350 mg/kg of the hydrochloride salt in 10 mL of water produced lip smacking, salivation and repeated vomiting after about 15 minutes. 700 mg/kg produced in addition to similar symptoms, muscular tremors, rigid gait and paralysis-like weakness. Rapidly increasing paralysis led to death six hours after administration. Aside from gelatinous infiltration at the site of injection, there were no organic changes (24).

b) Intravenous

- LD50 (mice) = 90 mg/kg (14)
- ALD (rabbit) = 400-500 mg/kg (9)
- In dogs, TMA raises blood pressure somewhat, but excites respiration violently (1,2).
- In dogs, TMA hydrochloride is quite poisonous and very small doses dilate the bronchioles and at the same time produce a marked rise in the blood pressure (21).
- TMA did not produce its usual stimulating effect on respiration in dogs after removal of their carotid sinus (31).
- TMA causes hypoglycemia in rabbits (36).
- Injection into dogs of TMA hydrochloride in doses above 25 mg/kg, accelerated the flow of thoracic lymph and increased the arterial blood pressure after a transient fall (42).
- Trimethylamine-HCl was administered to rabbits and dogs by intravenous injection. It had a positive inotropic effect that may lead to systolic rigidity. Small intracisternal injections cause a slight increase in arterial pressure and mild hyperventilation (46).
- Rats, given 10 ug of TMA into the brain (via intraventricular catheter), showed significantly abnormal conditioned avoidance responses (39).

c) Intrarectal

- ALD (rabbit) = 800 mg/kg (15)

B. Extended Studies

1. Oral

- TMA hydrochloride in doses up to 100 mg per day had no effect on the liver fat of animals with fatty livers (30).
- Rats were administered a diet containing 0.16% trimethylamine for 90 days. There were no significant differences in urinalysis, hematology, plasma constituents, body or organ weights, or in histological appearance between the experimental and control rats. At 0.62% in the diet, trimethylamine produced significant alterations in the seminal vesicles and prostate (7).

2. Inhalation

- Groups of ten rats were exposed six hours a day, five days a week, for two weeks to 74, 240 or 760 ppm of trimethylamine. Rats were given pathological urinalysis and clinical chemical examinations after the tenth exposure and after two weeks recovery. After ten exposures, all exposed rats showed dose-dependent nasal cavity and turbinate irritation ranging from very mild to severe. The 240 and 760 ppm rats exhibited a slight increase in red cell mass and decreased kidney weights. The 760 ppm rats alone showed dehydration, depressed growth, mild emphysematous alveoli, increased lung and heart weights, and decreased spleen and thymus weights. After two weeks of recovery, the slight nasal irritation at the lower levels persisted but was less severe in the 760 ppm rats. All other effects were reversible. The only effect in the 74 ppm group was very mild nasal irritation which persisted for two weeks. Exposure to higher concentrations produced reversible lung damage and systemic effects (16,23).
- Groups of 12 rats were exposed to 10 or 31 ppm, five hours per day for seven months. The experimental animals were irritated and aggressive during the first three-four weeks of poisoning. Diarrhea was observed 20-30 minutes after the start of exposure.

The diarrhea ceased after two-three hours. Beginning from the second month of poisoning, the feces of the animals normalized and their behavior did not differ from that of the controls. The investigation of the leukocyte formula demonstrated a reduction of the lymphocyte count, accompanied by a relative neutrophilia in the 31 ppm group from the fourth month of poisoning. These changes were statistically significant. The dynamic study of the body weight, protein spectrum of the blood and detoxifying function of liver failed to demonstrate any substantial differences between the experimental animals and the control. Pathological examination, performed at the end of the experiment, demonstrated bronchopneumonia and hemorrhage into the lung tissues with destruction of the interalveolar septa, signs of passive hyperemia and isolated hemorrhages in the liver, kidneys, and spleen in the animals of the 31 ppm group. Analogous though less marked changes were also observed in the animals of the 10 ppm group. The measurement of the weight ratios of the internal organs of the animals demonstrated an increased weight of the adrenals (25,35).

3. Injection Studies

- Groups of about 20 rats were subcutaneously administered 10, 20, 100 or 200 mg/kg of trimethylamine daily (every other day at the 200 mg/kg dose) for an average of 21 days. Apart from outright local ulcers, weaker solutions lead to subcutaneous edema which was later replaced by hardening of the skin. The hardening of the skin seriously interferes with further injections. A slight retardation of weight was noted. The growth retardation was more pronounced with higher dosages. No other signs of toxicity were seen and the experimental animals were as vigorous as the controls (47).
- Two groups of rats were given 50 or 100 mg/kg intraperitoneal injections either daily (50 mg/kg dose) or every other day (100 mg/kg dose) for 20 and 24 days, respectively. A growth retardation was seen in the males but not the females. No other signs of toxicity aside from the local irritant effect were seen (47).
- Continuous subcutaneous administration of TMA produces a blood picture, similar to pernicious anemia (27).

C. Carcinogenic Potential

- No specific information is available. Related References 65-74 contain information on the formation of nitrosamines from TMA and nitrite.

D. Mutagenic Potential

- Trimethylamine was found to be nonmutagenic in Salmonella typhimurium strains TA 1535, TA 1537, TA 98 and TA 100, with and without activation (16).
- Trimethylamine pyrolysates were mutagenic to Salmonella typhimurium strains TA 98 and TA 100, with and without S-9 mix (34).

E.-F Developmental and Reproductive Toxicity

- The effects of trimethylamine (dosages 10-200 mg/kg) on the onset of sexual maturity were studied in 25 litters of rats (254 animals). The trimethylamine-injected animals showed no significant difference from the controls in the onset of sexual maturity as indicated by testicular descent and vaginal opening (47)
- See Related References 75 and 76 for additional information.

G. Aquatic/Environmental Studies

- Rainbow trout were exposed to a trimethylamine concentration of 268 mg/L. The resulting pH was 9.62 and the temperature was 13-13.5°C. The fish responded instantly in an adverse fashion, turned over in about four minutes, and made their last motion in 11 to 14 minutes (12).
- 24-hour LC50 (killifish) = 1000 mg/L (44,45).
- TMA at 13.2 mg/kg of diet prolonged guppy survival times in seawater 50% (13).
- Feeding experiments with TMA hydrochloride showed that small amounts may be deposited in the muscles of goldfish (22).
- TMA was very difficult to decompose. BOD, COD and simultaneous decrease of total organic carbon was measured (33).

- See Related References 77-81 for additional information.

H. Clinical Reports of Human Exposure

- No information available.

I. Epidemiology

- No information available.

J. Metabolism

- TMA is not destroyed in dogs after oral administration. Trimethylamine oxide was recovered (19).
- Guinea pigs converted 41% of orally administered TMA and 32% of injected TMA to trimethylamine oxide. For rats the amounts were 19 and 11%, respectively. Some of the TMA was recovered unchanged. No urea was found (32).
- In rabbits administered up to 125 mg/kg of TMA in their diet, from 80 to 96% is metabolized and part, if not all, of the nitrogen seems to be excreted as urea. A small amount of dimethylamine is excreted but no methylamine (26).
- In chickens administered radiolabeled TMA intravenously, almost the entire dose was metabolized to TMA oxide and excreted in the urine (3).
- Radiolabeled TMA was injected intraperitoneally into cod. Trimethylamine oxide was produced by the oxidation of TMA (6).
- When trimethylamine hydrochloride is given orally to man, it appears in the urine as trimethylamine oxide (43).
- The basal urinary TMA/creatinine ratio was lower in normal subjects than in patients with liver disease (2.2 and 15.5, respectively). TMA metabolism is apparently disturbed in liver disease (79).

- TMA, generated in the small bowels in uremia, produces a serum TMA which may play an important role in the metabolic derangements that cause uremic symptomatology (10,37-40,41,48).
- See Related References 82-84 for additional information.

K. Biochemical Studies

- See Related Reference 85.

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