

CHRONIC TOXICITY SUMMARY

TRIETHYLAMINE*(diethylaminoethane; ethanamine; N,N-diethylethanamine)***CAS Registry Number: 121-44-8****I. Chronic Toxicity Summary**

<i>Inhalation reference exposure level</i>	200 $\mu\text{g}/\text{m}^3$ (40 ppb)
<i>Critical effect(s)</i>	Eye effects in rats and humans
<i>Hazard index target(s)</i>	Eyes

II. Physical and Chemical Properties (Nelson and Bull, 1990, except as noted)

<i>Description</i>	Colorless, volatile liquid
<i>Molecular formula</i>	$\text{C}_6\text{H}_{15}\text{N}$
<i>Molecular weight</i>	101.9 g/mol
<i>Density</i>	0.726 g/cm ³ @ 25°C
<i>Boiling point</i>	89.3°C
<i>Melting point</i>	-114.7°C (CRC, 1994)
<i>Vapor pressure</i>	400 torr @ 31.5°C
<i>Odor threshold</i>	480 ppb (Amoore and Hautala, 1983)
<i>Solubility</i>	soluble in acetone, benzene and chloroform
<i>Conversion factor</i>	1 ppm = 4.14 mg/m ³ 25°C

III. Major Uses or Sources

Triethylamine (TEA) is primarily used as a cross-linking catalyst in the production of polyurethane foam used in the manufacture of cores for metal castings (Albrecht and Stephenson, 1988). Triethylamine is also used as a catalyst for epoxy resins, and as a corrosion inhibitor for polymers (Nelson and Bull, 1990). TEA is one of the amines emitted from cattle feedlots (Mosier *et al.*, 1973). In the gas phase TEA can react with nitric acid to form amine nitrates that become part of atmospheric particulates. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 4152 pounds of triethylamine (CARB, 2000).

IV. Effects of Human Exposures

Acute, high level triethylamine exposures (20 mg/m³ (4.8 ppm) for 8 hours) resulted in reversible ocular effects that included corneal swelling and halo vision in 4 out of 5 volunteer subjects (Akersson *et al.*, 1988). Jarvinen *et al.* (1999) reported exposure chamber studies of ocular

responses to TEA in volunteer subjects, who were industrial workers exposed to TEA during the course of their normal jobs (but had good general and ocular health). Four people were exposed for 4 hours to 3.0, 6.5, or 40.6 mg/m³ triethylamine. Corneal thickness was measured by ultrasonography, clinical observations were recorded using ocular microscopy, and statistical analysis of the size, density and distribution of corneal endothelial cells was performed by automated analysis of photographs. Visual acuity and contrast sensitivity were evaluated using test charts. After exposure to 40.6 mg/m³ there was a marked edema in the corneal epithelium, and subepithelial microcysts. However, corneal thickness increased only minimally. Vision was blurred in all subjects and visual acuity and contrast sensitivity decreased in three of the four. After exposure to 6.5 mg/m³ two subjects experienced symptoms (e.g., blurred vision), and contrast sensitivity decreased in three of the four. There were no symptoms or decreases in contrast sensitivity after exposure to 3.0 mg/m³ triethylamine for 4 hours.

A medical examination of 19 workers exposed at a polyurethane foam production plant to a time-weighted average concentration of 13 mg/m³ (3.1 ppm) TEA showed reversible corneal edema in 5 workers (Akesson *et al.*, 1986). Peak concentrations were up to twice the time-weighted average level. A questionnaire on self-reported symptoms of visual disturbances revealed repeated occurrences of temporary eye irritation and “foggy vision.” Small quantities of dimethylethanolamine, toluene diisocyanate, and methylene diphenyl isocyanate were also present in the workplace atmosphere.

Jarvinen and Hyvärinen (1997) reported loss of visual acuity and contrast sensitivity in 41 foundry workers (core makers) exposed to TEA. Concentrations of TEA were reported to have a mean of 46 mg/m³ and a maximum of 486 mg/m³, but were highly variable with numerous large excursions above a background of about 20 mg/m³ during a two-hour period of continuous monitoring. It is therefore difficult to determine an effect level for the observed symptoms. Jarvinen (1998) also reported that cold box core makers exposed to TEA had a somewhat increased incidence of mild headaches.

V. Effects of Animal Exposures

Lynch *et al.* (1990) exposed male and female Fischer 344 rats to triethylamine at concentrations of 0, 25, or 247 ppm (0, 103.4, or 1022.2 mg/m³) for 6 hours/day, 5 days/week. Groups of rats were necropsied at approximately 30, 60, and 120 days of exposure. The last corresponds to an elapsed time of 28 weeks. Endpoints examined included gross and histopathological examination of all major organs, including the lungs, nasal passages, and eyes. Clinical enzyme and nitrogen levels (BUN, ALT, AST, CPK, and creatinine), and hematological values (hemoglobin, RBC count) were also measured. No gross or histological effects in any organ were observed in any group. Clinical and hematological parameters were unchanged with exposure. However, all rats exposed to 247 ppm TEA manifested irritation. “At 247 ppm TEA the rats kept their eyes closed and noses buried in their fur during the entire exposure period.” Thus 247 ppm is a LOAEL and 25 ppm is a NOAEL for eye and nose irritation in the rat.

In a short-term study by the same authors for Virginia Chemicals (1987), necrotizing inflammation of the nasal cavity, metaplasia of the trachea, and thymic atrophy were observed

after exposure to 1000 ppm (4140 mg/m³) triethylamine 6 hours per day for 10 days. Two of five males and one of five females died from pulmonary edema after the seventh day. Thymic atrophy was noted in 7 out of 10 animals, and all animals exhibited necrotizing inflammation in the nasal epithelium.

Rabbits (6-12 per group), exposed to 48 or 100 ppm (199 or 414 mg/m³) triethylamine for 7 hours/day, 5 days/week, for 6 weeks, showed concentration-dependent pathology in the eyes, lungs, liver, kidney, and heart (Brieger and Hodes, 1951). The eyes showed multiple punctate erosions of the corneal epithelium, and corneal edema at 48 ppm. Lung lesions included thickening of vascular walls; liver lesions included parenchymal degeneration. Overall the lesions in the 48 ppm group were less severe than those seen in the 100 ppm group. No control animals were included in this study, nor were the incidences of histologic effects among the exposed animals reported. All animals did survive the exposures. The lesser effects at 48 ppm in the rabbit (compared to those at 100 ppm) are consistent with the findings of Lynch *et al.* (1990) where 25 ppm was a NOAEL in the rat for eye and nose irritation.

A chronic 3-generation reproductive study in rats (10/sex/group) was inconclusive due to excessive mortality in controls (Davison *et al.*, 1965). In this study, rats were exposed to 0, 2, or 200 ppm triethylamine. The third generation of the 200 ppm group was changed to 500 ppm since no effects were noted in the 200 ppm group. Exposure of this group to 500 ppm resulted in decreased body weight and decreased water consumption.

VI. Derivation of Reference Exposure Level

<i>Study</i>	Lynch <i>et al.</i> , 1990; Brieger and Hodes, 1951
<i>Study population</i>	Rats; rabbits
<i>Exposure method</i>	Discontinuous whole-body inhalation
<i>Critical effects</i>	Eye irritation; lung and liver toxicity
<i>LOAEL</i>	48 ppm (Brieger and Hodes, 1951)
<i>NOAEL</i>	25 ppm (Lynch <i>et al.</i> , 1990)
<i>Exposure continuity</i>	6 or 7 hours/day, 5 days/week
<i>Exposure duration</i>	28 weeks; 6 weeks
<i>Average experimental exposure</i>	4.46 ppm for NOAEL group (25 x 6/24 x 5/7)
<i>Human equivalent concentration</i>	4.46 ppm (18.5 mg/m ³) for NOAEL group
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	1 (NOAEL is based on a 28 wk study in rats)
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference exposure level</i>	0.04 ppm (40 ppb; 200 µg/m ³)

The U.S. EPA (1995) based its Reference Concentration (RfC) of 7 µg/m³ (2 ppb) for triethylamine on Lynch *et al.* (1990) but included a Modifying Factor (MF) of 10 for “database deficiencies” - “lack of developmental and reproductive effects, and of appropriate data in a second species.” The criteria for use of modifying factors are not well specified by U.S. EPA.

Such modifying factors were not used by OEHHA. In addition OEHHA applied a subchronic UF of 1 since 24 male and 24 female rats in the NOAEL group were exposed to 25 ppm TEA for 28 weeks, while USEPA used a subchronic UF of 10. U.S. EPA considered 247 ppm to be a NOAEL. However, the Lynch *et al.* (1990) study indicates that the animals closed their eyes and buried their noses in their fur, likely to prevent the irritant effects of TEA on their eyes and respiratory tract. Thus adverse effects occurred at 247 ppm, although they could be considered repeated acute effects. Brieger and Hodes (1951) observed adverse effects in the eyes, lungs, and livers of rabbits after six weeks of discontinuous exposure to TEA. Thus 48 ppm is a LOAEL in this study.

For comparison, the five affected workers studied by Akesson *et al.* (1986) showed symptoms at 12-13 mg/m³ TEA, which is equivalent to 4.5 mg/m³ continuous exposure. (Other tasks were at 4-5 mg/m³ TEA or 1.6 mg/m³ continuous exposure.) Selection of a LOAEL UF of 3 (26% incidence of a reversible effect), a subchronic UF of 1 since the workers had been employed for 9.7 years (range = 4-11), and an intraspecies UF of 10 results in an estimated REL of 200 µg/m³ based on human data. These workers experienced some short-term peak exposures to TEA and were also exposed to dimethylethanolamine (<0.1 mg/m³), toluene diisocyanate, and methylene diphenyl isocyanate.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the triethylamine REL are the observation of a NOAEL in a controlled exposure experiment and finding of the same adverse effect, eye irritation, in humans and animals. The major weaknesses are the minimal amount of adequate human health effects information, the lack of dose-response data in a single experiment, and the lack of long-term exposure data.

VIII. Potential for Differential Impacts on Children's Health

There is no direct evidence in the literature to quantify a differential effect of TEA in infants and children. However, it is a respiratory irritant and thus has the potential to exacerbate asthma. In addition, other alkylamines are known to be associated with occupational asthma (Bernstein *et al.*, 1999). There is some concern that TEA could have a similar effect.

IX. References

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