Triethylamine; CASRN 121-44-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Triethylamine

File First On-Line 04/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	04/01/1991
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Triethylamine
CASRN — 121-44-8

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Triethylamine
CASRN — 121-44-8
Last Revised — 04/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
No observed adverse effects **28-Week Rat Inhalation Study** **Lynch et al., 1990**	NOAEL: 1022.2 mg/cu.m (247 ppm) NOAEL(ADJ): 182.5 mg/cu.m NOAEL(HEC): 19.5 mg/cu/m LOAEL: None	3000	1	7E-3 mg/cu.m
Inflammation of the nasal passage **10-Day Rat Inhalation Study** **Virginia Chemicals, 1987**	NOAEL: None FEL: 4139 mg/cu.m (1000 ppm) FEL(ADJ): 739 mg/cu.m FEL(HEC): 79 mg/cu.m			

*Conversion Factors: MW = 101.19. Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = 247 ppm x 101.19/24.45 = 1022.2. NOAEL(ADJ) = 6 hours/24 hours x (5 days/7 days) = 182.5 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.107. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 19.5 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Lynch D.W., W.J. Moorman, T.R. Lewis, P. Stober, R. Hamlin, and R.L. Schueler. 1990. Subchronic inhalation of triethylamine vapor in Fisher-344 rats: Organ system toxicity. Toxicol. Indus. Health. 6(3/4): 403-414.

Virginia Chemicals. 1987. Pathologic findings in Fischer 344 rats exposed by inhalation to allylamine, ethylamine, diethylamine, and triethylamine with cover letter dated 042484. OTS # 308080. Doc # 86-870000813. Fiche # 0515251. (Animal data sheets from Dr. Dennis Lynch attached.)

In a subchronic study by Lynch et al. (1990), Fischer 344 rats (50/sex/group) inhaled 0, 25 ppm (103.4 mg/cu.m), or 247 ppm (1022.2 mg/cu.m) triethylamine (99% compound purity) vapors, 6 hours/day, 5 days/week, for 28 weeks. The duration adjusted values were 0, 18.5 mg/cu.m, or 182.5 mg/cu.m, respectively. Body weights were recorded at 2-week intervals. Animals were sacrificed at 30 days, 60 days, and at the end of the 28-week exposure period. Histopathologic examinations were conducted on all major organs including the lungs (following perfusion with formalin), nasal passages (at 5 levels), trachea, and eyes. Clinical parameters measured included BUN, ALT, AST, CPK, creatinine, hemoglobin, and RBC count. Electrocardiograms were performed in 20 (10/sex) rats of each group at the terminal sacrifice. Body weights were not affected by the exposure. Male lung weights were increased in a concentration-dependent manner, although the changes were not statistically significant or accompanied by any histopathology. No treatment-related effects on electrocardiography, hematology, or organ weights (other than lung) were noted. This study established a NOAEL of 247 ppm for inhalation exposure of rats to triethylamine. The NOAEL(HEC) for extrathoracic effects is 19.5 mg/cu.m.

Subsequent to the above study, the same authors conducted a supplementary inhalation study under the same conditions as above, but at a higher concentration (Virginia Chemicals, 1987). The authors exposed rats (5 males, 5 females) to 1000 ppm (4139 mg/cu.m) 6 hours/day for 10 days. The duration- adjusted concentration of triethylamine is 739 mg/cu.m. A minimum of 8 tissues were examined in each animal including the nasal cavity (a minimum of 2 sections were taken; personal communication with author) trachea, lung, heart, esophagus, kidney, and spleen. All 10 animals had at least moderate (grade 3) necrotizing inflammation of the nasal cavity.

Progression of effects deeper into the respiratory tract was indicated by the occurrence of squamous metaplasia (from slight to marked in severity) in the trachea in 7 of 10 animals. Moderate thymic atrophy was present in 7 of 10 animals. Keratitis (graded as slight) was noted in three animals. Two of the males and one of the females died after the seventh day of exposure. Lung effects (perivascular edema) was noted but only in the three animals that died. Although the cause of death is not indicated by the authors, the mortality may be related to the pulmonary edema observed and not due to systemic effects caused by the compound. Based on these effects 1000 ppm is considered a frank effect level. Dosimetrically adjusted for the extrathoracic region this value would become 79 mg/cu.m = FEL(HEC). Thus, the concentration response curve of triethylamine appears to rise abruptly, with frank effects occurring at levels only 4-fold above a no-effect level.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — A factor of 10 is used for the protection of sensitive human subpopulations. A factor of 3 is used for interspecies extrapolation as the concentrations were dosimetrically adjusted to humans. Factors of 10 each are applied for the use of a study of less than chronic length, and the lack of data on both developmental and reproductive effects, and of appropriate data in a second species.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Air exposure of humans to triethylamine has adverse ocular effects that are apparently reversible even after long-term exposures. Occupational studies and experimental settings have reported eye irritation, corneal swelling, and halo vision subsequent to short duration, high level exposure to triethylamine (Warren and Selchan, 1988). Akesson et al. (1988) reported that 4 of 5 volunteers exposed for 8 hours to 20 mg/cu.m triethylamine complained of a "blue haze" or "smoky vision" (subjective descriptions of visual effects). When exposed to 10 mg/cu.m for 8 hours, the same 5 volunteers reported no ocular effects. These ocular effects are apparently reversible as subjective symptoms reported by two volunteers exposed for 4 hours to 34 mg/cu.m triethylamine totally subsided by 4 to 4.5 hours after the exposure (Akesson et al., 1985). A limited study conducted by Akesson et al.(1986), suggests that there is no permanent ocular effects or progression of ocular toxicity from long-term exposure to triethylamine. In this occupational study, 19 workers in a polyurethane production plant were monitored over an 11-week period for signs of visual disturbances. Co-exposure of the workers in this study to another amine, dimethylethanolamine, was minimal (below 0.1 mg/cu.m). However, workers were also co-exposed to toluene diisocyanate (8 hour TWA of 0.001 - 0.048 mg/cu.m) and methylene diphenyl isocyanate (8 hour TWA of 0.001 -0.017 mg/cu.m). During this period, a total of 44

incidences of "blue haze" were reported by 4 of 4 workers exposed to high TWA concentrations (13 mg/cu.m, range 4 to 24 mg/cu.m) over the 11-week period. The symptoms observed in these four workers were consistent with reversible corneal edema. No instances of visual disturbances were reported six other workers exposed to a TWA of 5 mg/cu.m (range 1 to 9 mg/cu.m). Further detailed medical examination of all 19 workers did not reveal any sign of permanent eye disease; the average duration of employment for these 19 workers was 9.7 years with a range of 4 to 11 years. Systemic effects were not evaluated in any of these studies. In summary, the ocular toxicity observed with triethylamine is most likely not due to a specific property of the chemical, but rather to the alkaline nature of aliphatic amines. Judging from these studies, ocular toxicity is a sensitive effect in humans, with minimal effects occurring at around 10 mg/cu.m. Although this subjective effect of "blue haze" is not possible to evaluate in animals, the Virginia Chemicals (1987) study did note keratitis in 3 of 10 exposed animals. The final RfC (0.007 mg/cu.m) is well below the level at which minimal effects are documented to occur in humans (10 mg/cu.m).

Groups of male albino rats (15-20/group) were exposed to either air (controls), 0.16, 1.71, or 13.01 mg/cu.m 97% pure triethylamine vapors for 3 months by Tkachev (1971). Based on descriptions in the study, an exposure duration of 22 hours/day is assumed and the duration-adjusted values become 0, 0.15, 1.57, or 11.92 mg/cu.m. Physiologic parameters were monitored at 10-day intervals during the exposures. Monitored parameters not affected by amine exposure included weight gain, hemoglobin concentration, and prothrombin clotting time. Whole blood cholinesterase activity was increased significantly ($p=0.05$) in the 1.71 mg/cu.m group at 80 days of exposure. In the 13.01 mg/cu.m exposure group, this effect was observed much earlier, at the first 10-day period, and again at 90 days of exposure. Hematological effects noted were also concentration-dependent with significant increases in erythrocyte fragility occurring at 60 exposure days in both the 1.71 mg/cu.m and the 13.01 mg/cu.m groups. This effect was observed again in the highest exposure group at 70 exposure days. Chronaxie (a measure of nerve excitability) was similarly altered in a concentration-dependent manner. No effects different from the controls were recorded for the lowest exposure group (0.16 mg/cu.m) for either blood cholinesterase, hematology, or chronaxie. Pathology was reported as occurring in the internal organs in response to the highest concentrations of triethylamine although specific details were given only for the lungs. In this organ, thickening of the interalveolar walls and mucous accumulation in the alveolar spaces were reported. Based on the moderate nature and intermittency of the effects described, 1.71 mg/cu.m is judged as a NOAEL, for respiratory effects (HEC) = 1.46 mg/cu.m. The NOAEL(HEC) was also calculated for a gas:extrarespiratory effect assuming periodicity was attained; NOAEL(HEC) = 1.57 mg/cu.m. This study is ambiguous in reporting procedures, exposure durations, and pathologies. The methodology of exposure is not characterized nor are any data actually shown in the report. These deficiencies preclude this report being a principal study for RfC development.

Groups of rabbits (6/group, sex not specified) were whole body exposed to vapors of triethylamine (purity not stated) at either 48 ppm (199 mg/cu.m; duration adjusted = 41.4 mg/cu.m) or 100 ppm (414 mg/cu.m; duration adjusted = 86.2 mg/cu.m), 7 hours/day, 5 days/week for a period of 6 weeks (Breiger and Hodes, 1951). This exposure was repeated such that a total of 12 animals/ group were exposed. Although a detailed listing of endpoints examined is not presented, results from blood examinations, blood pressure determinations, as well as pathological examination of the lungs, eyes, kidneys, and heart are described. No deaths occurred during the exposures. Histopathology of the lungs from animals exposed to 100 ppm showed evidence of irritation including edema, moderate peribronchitis, vascular thickening, and edema. Lung tissue from the 48 ppm exposed groups showed only focal areas of lymphocytic infiltration and a slight thickening of vascular walls, indicating less irritation than at the higher concentration. Hepatic pathology was also exposure-related with cell degeneration and necrosis occurring in animals exposed to the higher concentration and only slight cellular degeneration occurring in the 48 ppm exposure animals. In the high exposure animals, kidney and heart pathology (cellular degeneration and necrosis) were both reported. Eye lesions, described as corneal edema and multiple punctate erosions of the corneal epithelium, were reported at 48 ppm. Based on the pathologies occurring both in internal and external (eyes) organs, 48 ppm is considered as a LOAEL in this study, (HEC) for extrarespiratory effects (eyes) = 41.4 mg/cu.m. For the lung effects, LOAEL(HEC) = 16.56 mg/cu.m. This study is deficient in reporting specifics such as incidences of pathologies, the purity of the triethylamine, whether the kidneys were examined in the 48 ppm exposure group, and in citing whether the ocular changes were reversible. There were apparently no controls in this study. These deficiencies preclude use of this study in deriving an RfC.

In a chronic 3-generation reproductive study, rats (10/sex/group) drank tap water containing 0, 2, or 200 ppm triethylamine (Davison et al., 1965). The third litters of each generation were used for composing the next generation. No specific details were available on the mating procedures. In the third generation of the 200-ppm group, the dose was increased to 500 ppm triethylamine since no apparent effects occurred at 200 ppm through two generations. No symptoms were observed during the 2-year study except in the 500-ppm group which showed a 5% decrease in weight and a 26% decrease in water consumption compared to controls. Mortality was excessive (numbers not given) in both exposed and control animals presumably due to chronic respiratory disease that appeared unrelated to chemical exposure. The condition is blamed for the observed decrease in the number of litters produced in the second generation at all dose levels, including controls. No other treatment-related effects were reported. No further details could be obtained from examination of the study documentation. Due to lack of reproductive end-points measured (apparently only litter size) and information on developmental effects, interpretation of this study is extremely limited.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Low
RfC -- Low

Medium confidence is placed in the principal studies. A concentration- response was evident, although a LOAEL could not be identified and a second species was not used. Low confidence is placed in the database as there exists only a single reproductive/developmental study, which is by the oral route and is therefore not useful for inhalation risk assessment. No chronic studies exist for this compound. A low confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 11/15/1990, 12/20/1990

Verification Date — 12/20/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for triethylamine conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Triethylamine
CASRN — 121-44-8

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. Bibliography

Substance Name — Triethylamine
CASRN — 121-44-8

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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Akesson, B., M. Bengtsson, and I. Floren. 1986. Visual disturbances after industrial triethylamine exposure. Int. Arch. Occup. Environ. Health. 57: 297-302.

Akesson, B., S. Skerfving, and L. Mattiasson. 1988. Experimental study on the metabolism of triethylamine in man. Br. J. Ind. Med. 45: 262-268.

Breiger, H. and W.A. Hodes. 1951. Toxic effects of exposure to vapors of aliphatic amines. A.M.A. Arch. Ind. Hyg. Occup. Med. 3(3): 287-291.

Davison, R.R., D.W. Hood, and B. McMullen. 1965. Toxicity of triethylamine to lbino rats. Prepared for the Office of Saline Water through Texas A&M University (final report reference 65-4F; Office of Saline Water Contract No. 14-01-0001-282). OTS # 303940. Doc # 86-870000536. Fiche # 0513614.

Lynch, D.W., W.J. Moorman, T.R. Lewis, P. Stober, R. Hamlin, and R.L. Schueler. 1990. Subchronic inhalation of triethylamine vapor in Fisher-344 rats: Organ system toxicity. Toxicol. Indus. Health. 6(3/4): 403-414.

Tkachev, P.G. 1971. Hygienic evaluation of the effects of low concentrations of aliphatic ethylamines on inhalation. Hyg. Sanit. 36 (7-9): 334-338. (page numbers for translation).

Virginia Chemicals. 1987. Pathologic findings in Fischer 344 rats exposed by inhalation to allylamine, ethylamine, diethylamine, and triethylamine with cover letter dated 042484. OTS # 308080. Doc # 86-870000813. Fiche # 0515251. (Animal data sheets from Dr. Dennis Lynch attached.)

Warren, D.W. and D.F. Selchan. 1988. An industrial hygiene appraisal of triethylamine and dimethylamine exposure limits in the foundry industry. Am. Ind. Hyg. Assoc. J. 49(12): 630-634.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Triethylamine
CASRN — 121-44-8

Date	Section	Description
04/01/1991	I.B.	Inhalation RfC summary on-line
10/28/2003	I.B.6	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Triethylamine
CASRN — 121-44-8
Last Revised — 04/01/1991

- 121-44-8

- Ethanamine, N,N-diethyl-
- (DIETHYLAMINO)ETHANE
- ETHANAMINE, N,N-DIETHYL-
- HSDB 896
- N,N-DIETHYLETHANAMINE
- Triaethylamin [German]
- Triethylamine
- Trietilamina [Italian]
- Trietilamina [Spanish]
- UN 1296