

ACUTE TOXICITY SUMMARY

PERCHLOROETHYLENE

(ethylene tetrachloride, tetrachloroethylene)

CAS Registry Number: 127-18-4

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	12 mg/m³
<i>Critical effect(s)</i>	loss of normal coordination in addition to eye, nose and throat irritation, headache and light-headedness
<i>Hazard Index target(s)</i>	nervous system; eyes; respiratory system

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	C ₂ Cl ₄
<i>Molecular weight</i>	165.83
<i>Specific gravity</i>	1.6227 @ 20°C
<i>Boiling point</i>	121°C
<i>Melting point</i>	-19°C
<i>Vapor pressure</i>	18.47 mm Hg @ 25°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in alcohol, ether, chloroform, benzene and hexane; practically insoluble in water
<i>Odor threshold</i>	47 ppm (geometric mean) (AIHA, 1989)
<i>Description</i>	colorless, mildly sweet, chloroform-like odor
<i>Metabolites</i>	trichloroacetic acid, trichloroethanol (ATSDR, 1992)
<i>Conversion factor</i>	1 ppm = 6.78 mg/m ³ @ 25°C

III. Major Uses or Sources

Perchloroethylene (PCE) is widely used in the textile industry for dry-cleaning, processing, and finishing fabrics (HSDB, 1993). It is also used in the degreasing of metals and as a chemical intermediate in the synthesis of fluorocarbons. Electric transformers contain PCE as an insulating fluid and cooling gas.

IV. Acute Toxicity to Humans

PCE is an eye, skin, and respiratory irritant. The most sensitive endpoint of PCE toxicity is the central nervous system (Calabrese and Kenyon, 1991). Cardiac sensitization and arrhythmias have been reported following acute exposure to high concentrations of PCE (Reprotext, 1993).

Determination of Acute Toxicity Exposure Levels

Scientific Review Panel Draft - Do not cite or quote.

In one case report, pulmonary edema and coma followed a single exposure to an unknown concentration of PCE (Patel *et al.*, 1977). Hepatic necrosis and renal failure have been observed following inhalation exposure (Gosselin *et al.*, 1984). Symptoms associated with acute exposure to lower levels of PCE include tiredness, weakness, and nausea and vomiting (Reichert, 1983).

Four human volunteers exposed to 206-235 ppm (1,400-1,600 mg/m³) PCE for 2 hours acclimatized to the odor within minutes (Rowe *et al.*, 1952). All subjects reported eye irritation and congestion of the frontal sinuses after 20-30 minutes of exposure. Two of the four test subjects experienced dizziness. A separate group of 4 subjects exposed to 280 ppm (1,900 mg/m³) PCE for 2 hours reported light headedness and one subject reported nausea.

Human subjects exposed to 100 ppm (700 mg/m³) PCE for 7 hours exhibited CNS effects as indicated by an abnormal modified Romberg test (a test of position sense) and symptoms including headache and light-headedness (Stewart *et al.*, 1970). Symptoms were noted after the first 3 hours of exposure. Subjects exposed for 7 hours per day for 5 days reported decreased odor perception of PCE over the course of each exposure.

Mild and transient hepatitis was diagnosed in a worker found unconscious following a 30-minute exposure to an unknown concentration of PCE (Stewart, 1969). Elevated serum enzymes, which indicate impaired liver function, were observed in a worker rendered semicomatose by exposure to unknown levels of PCE for 3 hours (Stewart *et al.*, 1961). A simulation of the exposure conditions in the latter case report indicated that the average estimated concentration was at least 275 ppm (1,900 mg/m³) PCE.

Predisposing Conditions for Perchloroethylene Toxicity

Medical: Persons with skin, eye or respiratory conditions may be more sensitive to the effects of PCE exposure (Reprotext, 1993). Individuals with hypertension may be at increased risk of exhibiting elevated blood pressure following exposure to PCE.

Chemical: Interactions between PCE and trichloroethylene and ethyl alcohol, resulting in a potentiation of toxicity, have been reported (Reprotext, 1993).

V. Acute Toxicity to Laboratory Animals

The LC₅₀ for a 4-hour exposure to PCE is reported to be 5,200 ppm (35,000 mg/m³) in mice (Friberg *et al.*, 1953) and 4,000 ppm (27,000 mg/m³) in rats (Carpenter *et al.*, 1949). Rats exposed to 2,300 ppm (16,000 mg/m³) PCE for 4 hours exhibited ataxia and signs similar to those of ethanol intoxication (Goldberg *et al.*, 1964).

Enlarged livers were observed at necropsy in mice exposed continuously to 9, 37, 75, or 150 ppm (60, 250, 510, 1,000 mg/m³) PCE for 30 days (Kjellstrand *et al.*, 1984). Enlargement and vacuolization of hepatocytes was most pronounced in the mice exposed to 150 ppm PCE. In a

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

separate study, hepatocellular vacuolization was observed in mice at necropsy following a single 4-hour exposure to 200 ppm (1,400 mg/m³) PCE (Kylin *et al.*, 1963).

Mice exposed for a single 3-hour period to 50 ppm (340 mg/m³) PCE exhibited a significant decrease in pulmonary bactericidal activity (type unspecified) (Aranyi *et al.*, 1986). No significant changes were observed in pulmonary bactericidal activity and mortality in mice exposed to 25 ppm (170 mg/m³) PCE for a single 3-hour exposure or for five 3-hour exposures. Mortality was significantly increased in mice exposed to 50 ppm PCE and challenged with aerosolized streptococci when compared to controls.

VI. Reproductive or Developmental Toxicity

A single case-control study among women employed in dry cleaning operations indicates an increased risk of spontaneous abortion resulting from PCE exposure (Kyyronen *et al.*, 1989). However, this study is seriously limited by the small number of exposed women (247) and the lack of biological monitoring during the first trimester. No studies evaluating the reproductive performance of occupationally exposed men were located.

Pregnant mice exposed to 300 ppm (2,000 mg/m³) PCE for 7 hours per day on gestation days 6-15 exhibited increased fetal resorptions and other signs of fetotoxicity including decreased fetal body weight and delayed ossification of skull bones and sternebrae (Schwetz *et al.*, 1975). Pregnant rats similarly exposed on gestation days 6-15 exhibited a slight decrease in weight gain, but no statistically significant signs of fetotoxicity.

Male guinea pigs exposed to 1,600 ppm (11,000 mg/m³) PCE for 7 hours per day for 8 exposures over a 10 day period exhibited degenerative changes in the germinal epithelium of the testes (Rowe *et al.*, 1952).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 12 mg/m³(1.7 ppm)

<i>Study</i>	Stewart <i>et al.</i> , 1970
<i>Study population</i>	three human subjects
<i>Exposure method</i>	inhalation of 100 ppm (700 mg/m ³) PCE
<i>Critical effects</i>	CNS effects as indicated by an abnormal modified Romberg test and symptoms including headache, mild irritation of the eyes, nose and throat, and light-headedness
<i>LOAEL</i>	700 mg/m ³
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	3 h
<i>Extrapolated 1 hour concentration</i>	1200 mg/m ³ (700 ² mg/m ³ * 3 h = C ² * 1 h) (see Table 12 for information on “n”)

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	12 mg/m ³ (12,000 µg/m ³ ; 1.7 ppm)

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH of 150 ppm (1,017 mg/m³) based on acute inhalation toxicity data in humans but the level does not appear to be life-threatening based on the data cited.

VIII. References

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ACUTE TOXICITY SUMMARY

PHENOL

(carbolic acid, phenylic acid, phenyl hydroxide)

CAS Registry Number: 108-95-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **5,800 µg/m³**
Critical effect(s) irritation of the eyes, nose, and throat
Hazard Index target(s) Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	C ₆ H ₅ OH
<i>Molecular weight</i>	94.11
<i>Specific gravity</i>	1.0576 @ 20°C
<i>Boiling point</i>	181.75°C
<i>Melting point</i>	43° C
<i>Vapor pressure</i>	0.3513 mm Hg @ 25°C
<i>Flashpoint</i>	79°C (closed cup)
<i>Explosive limits</i>	upper = 8.6% (AIHA, 1992) lower = 1.7% (AIHA, 1992)
<i>Solubility</i>	very soluble in alcohol, carbon tetrachloride, acetic acid and liquid sulfur dioxide; soluble in chloroform, ethyl ether, carbon disulfide; slightly soluble in water and benzene
<i>Odor threshold</i>	0.060 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	medicinal, acid (AIHA, 1989)
<i>Metabolites</i>	o,p-hydroxylated products
<i>Description</i>	colorless to light pink
<i>Conversion factor</i>	1 ppm = 3.85 mg/m ³ @ 25°C

III. Major Uses or Sources

Phenol is obtained from coal tar and is widely used as a disinfectant for industrial and medical applications. It also serves as a chemical intermediate for phenolic resins and as a solvent for petroleum refining (HazardText, 1993). Approximately half of the US consumption is directly related to the housing and construction industries in applications such as germicidal paints and slimicides (HSDB, 1993).

IV. Acute Toxicity to Humans

Respiratory distress, pulmonary edema, cyanosis, muscular weakness, and loss of consciousness may be observed following inhalation exposure to phenol (Clayton and Clayton, 1982). Rapidly absorbed through the skin, phenol is corrosive and burns any tissue with which it comes in contact (Clayton and Clayton, 1982). Symptoms of acute phenol poisoning include headache, dizziness, photophobia, weakness, and difficulty breathing. Death from phenol poisoning is usually due to respiratory failure (Clayton and Clayton, 1982). It has been reported that ingestion of 4.8 g of pure phenol caused death within 10 minutes (HSDB, 1993). Ingestion may cause oral mucosal burns, nausea, vomiting, and severe abdominal pain. About 50% of the cases of acute overexposure to phenol are fatal (HSDB, 1993). The oral LD_{Lo} for adults is 14 g/kg with effects consisting of behavioral changes and cyanosis in addition to the previously described signs.

In a study designed to evaluate the absorption of phenol in the lungs and through the skin, eight volunteers were exposed either by face mask only or by skin only (accomplished by the use of a protective respirator) to up to 6.5 ppm phenol for 8 hours and their urinary excretion of phenol subsequently measured (Piotrowski, 1971). The concentrations of phenol to which the volunteers were exposed by face mask only were approximately 1.6-5.2 ppm. The exposures included two 30-minute breaks commencing at 2.5 and 5.5 hours after the start of exposure. The intent of this study was to determine whether urinary excretion of phenol could serve as an adequate biomarker of dermal and inhalation exposure. No mention of adverse effects in the volunteers was made. Therefore, a free-standing 8-hour NOAEL of 5.2 ppm can be determined from this study. A human irritancy threshold for phenol of 182.4 mg/m³ (47 ppm) was reported by Ruth (1986).

Predisposing Conditions for Phenol Toxicity

Medical: Individuals with skin, eye, respiratory, hepatic or renal diseases may be more susceptible to the toxic effects of phenol (Clayton and Clayton, 1982).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

The inhalation LC₅₀ values for an unspecified duration of exposure in rats and mice are reported as 316 mg/m³ (82 ppm) and 177 mg/m³ (46 ppm), respectively (RTECS, 1993). Smyth (1956) reported that rats survived an 8-hour inhalation exposure to saturated phenol vapors (approximately 323 ppm at 25°C).

A 5-minute RD₅₀ of 166 ppm was observed in mice (DeCeaurriz *et al.*, 1981). Kane *et al.* (1979) report a predictable qualitative correlation between a reduction in rate of respiration in experimental animals (RD₅₀) exposed to airborne sensory irritants, and the symptoms observed in humans exposed to the same irritants.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Deichmann *et al.* (1944) observed that guinea pigs exposed to concentrations of phenol between 25 and 50 ppm (96 and 200 mg/m³) 7 hours per day, five days per week, for four weeks displayed signs of respiratory difficulty and paralysis which affected primarily the hind quarters. Five of twelve animals exposed at this concentration died. At necropsy, extensive myocardial necrosis, lobular pneumonia, fatty degeneration of the liver, and hepatocellular necrosis were observed in all animals exposed at this level. Rabbits exposed at these same concentrations for 12 weeks did not exhibit any signs of discomfort, but showed similar findings at necropsy. No indications of toxicity were observed in rats during a 10-week exposure to the same concentrations. Necropsy findings in the rats were normal.

Based on data on species variation in the conjugation of phenol and its metabolite quinol, the metabolism of phenol by rats appears to be closer to that of humans than rabbits or guinea pigs. The percent glucuronide and sulphate conjugates of phenol and metabolite in test species administered phenol orally was compared to that of conjugates excreted by humans. The excretion of these conjugates by the rat was most similar to that observed in humans following phenol exposure (Capel *et al.*, 1972a,b).

Groups of 10 monkeys, 50 rats, and 100 mice were exposed to 0 or 5 ppm phenol continuously for 90 days (Sandage, 1961). Hematological parameters and kidney function tests were normal. Additionally, the author reported no significant pathological findings at necropsy.

VI. Reproductive or Developmental Toxicity

No adverse fetotoxic or teratogenic effects were found following treatment of pregnant rats with an intraperitoneal injection of phenol during gestation days 8-10 or 11-13 with up to 200 mg/kg (Minor and Becker, 1971). In rats, radiolabeled phenol was found to equilibrate between the maternal and embryonic serum in equivalent levels (Gray and Kavlock, 1990).

A dose-related reduction in fetal weight was observed following oral administration of 30, 60, and 120 mg/kg/day phenol to pregnant rats on days 6-15 of gestation (Jones-Price *et al.*, 1983). No teratogenic or fetotoxic effects were observed.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 1.5 ppm (5.8 mg/m³)

<i>Study</i>	Piotrowski, 1971
<i>Study population</i>	eight human volunteers
<i>Exposure method</i>	inhalation of phenol by face mask only
<i>Critical effects</i>	irritation of the eyes, nose, and throat
<i>LOAEL</i>	not determined in this study
<i>NOAEL</i>	5.2 ppm (free standing)
<i>Exposure duration</i>	8 hours
<i>Extrapolated 1 hour concentration</i>	15 ppm (5.2 ² ppm * 8 h) = C ² * 1 h)

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

	(see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	1.5 ppm (5.8 mg/m ³ ; 5,800 µg/m ³)

No adverse effects were reported in 8 volunteers exposed to 5.2 ppm for 8 hours. The study was designed to quantify dermal and respiratory absorption of phenol and not to detect mild irritation, but it contains the best available human acute inhalation exposure data. The irritation threshold of 47 ppm reported by Ruth (1986) does not contradict the determination of an 8-hour NOAEL of 5.2 ppm from this study.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

AIHA developed an ERPG-2 of 50 ppm (190 mg/m³) based on Flickinger (1976) where rats exposed for 8 hours to 900 mg/m³ (235 ppm) phenol exhibited in tremors (Flickinger, 1976). After 4 hours, ocular and nasal irritation with loss of coordination and muscular spasms were observed. However, the ERPG rationale incorrectly cites this study as reporting a 1-hour exposure of 312 ppm (1,200 mg/m³) in rats. The only acute inhalation exposure data included in the paper by Flickinger is exposure for 8 hours to 235 ppm as summarized above. No uncertainty factors or methods of extrapolating from a 4-hour exposure to an equivalent 1-hour exposure were reported by AIHA.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

AIHA developed an ERPG-3 of 200 ppm (770 mg/m³). Exposure of rats to 900 mg/m³ (235 ppm) phenol for four hours resulted in ocular and nasal irritation, slight loss of coordination and muscular spasms (Flickinger, 1976). The method used by AIHA (1992) for calculating the ERPG-3 value from the data was not reported. The rationale does include the observation that no reports of fatalities from inhalation have been reported in humans. No uncertainty factor is included for animal to human extrapolation.

NIOSH (1995) reports an IDLH of 250 ppm. It is based on animal inhalation toxicity data and on an analogy to cresol.

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Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

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Williams 1979

ACUTE TOXICITY SUMMARY

PHOSGENE

(carbon dichloride oxide; carbonyl chloride)

CAS Registry Number: 75-44-5

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	4 µg/m³
<i>Critical effect(s)</i>	minor damage to the lower airways
<i>Hazard Index target(s)</i>	Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	COCl ₂
<i>Molecular weight</i>	98.92
<i>Specific gravity</i>	1.381 @ 20°C
<i>Boiling point</i>	8.2°C @ 760 mm Hg
<i>Melting point</i>	-118°C
<i>Vapor pressure</i>	1215 mm Hg @ 20°C
<i>Explosive limits</i>	upper = unknown lower = unknown
<i>Solubility</i>	slightly soluble in water; soluble in benzene, glacial acetic acid, and most liquid hydrocarbons.
<i>Odor threshold</i>	0.9 ppm
<i>Odor description</i>	musty hay, green corn (Ruth, 1986)
<i>Metabolites</i>	spontaneously hydrolyzes to become HCl and CO ₂
<i>Description</i>	colorless gas
<i>Conversion factor</i>	1 ppm = 4 mg/m ³

III. Major Uses or Sources

Phosgene is highly chemically reactive and is used as an intermediate in carbonylation reactions in the preparation of many organic chemicals. It was formerly used as a potent chemical warfare “choking” agent. It is currently used in the production of aniline dyes. Occasionally, it is used in the manufacture of some insecticides, in the pharmaceutical industry, and in metallurgy (HSDB, 1994). In addition to its industrial uses, phosgene occurs as a breakdown product of chlorinated hydrocarbons such as tetrachloroethylene or carbon tetrachloride in the presence of short wavelength UV radiation (in heliarc welding of aluminum) or in the presence of hot iron and oxygen.

IV. Acute Toxicity to Humans

Much of the data on human exposures to phosgene comes from military experience, often with poorly characterized exposure conditions. Exposure to phosgene can lead to delayed pulmonary edema, cardiorespiratory arrest, and death (AIHA, 1989). The odor is not helpful in emergency situations since the odor threshold (0.9 ppm) is well above levels that may result in other toxic effects (Amoore and Hautala, 1983).

No evidence exists for a systemic action of inhaled phosgene; the vasculature of the lower respiratory tract appears to be the critical target. After initial exposure, irritation of the lower respiratory tract mucous membranes occurs due to acylation of biological macromolecules. This is followed by a severe reflex vasoconstriction in the lung 2-24 hours later (Arena and Drew, 1986). Hypovolemia with ensuing cardiac arrest may result from massive pulmonary edema. Because of its low water solubility, irritation to the eyes and upper respiratory tract are comparatively minor compared to the effects on the lower airways. The lowest concentration reported to cause throat irritation is 3 ppm (12 mg/m³) (Henderson and Haggard, 1943). Eye irritation occurs at 4 ppm (16 mg/m³), and 4.8 ppm causes cough (HSDB).

Inhalation of 50 ppm (200 mg/m³) may be rapidly fatal (HSDB, 1994). Phosgene acylates biological molecules easily, thus altering biological membrane integrity and protein structure. Hours after initial exposure, phosgene is hydrolyzed to HCl and CO₂; the former causes increased irritation to mucosal surfaces.

Predisposing Conditions for Phosgene Toxicity

Medical: Individuals with congestive heart failure may be particularly susceptible to phosgene-induced pulmonary edema.

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

An LC₅₀ of 5.1 ppm (20.4 mg/m³) for 30 minutes is reported in mice, and an LC₅₀ of 60-70 ppm (240-280 mg/m³) for 15 minutes is reported in dogs (HSDB, 1994).

Exposure of rats to 1 ppm for 4 hours caused excess fluid and fibrin to occur in alveolar spaces immediately following exposure (Currie *et al.*, 1985). Pulmonary edema was also observed in guinea pigs exposed to 0.9 ppm phosgene for 5 hours (Cameron *et al.*, 1942). Exposure to phosgene at 0.2 ppm for 4 hours caused pulmonary edema in rats, mice, and hamsters, while guinea pigs and rabbits showed similar signs at 0.5 ppm and above (Hatch *et al.*, 1986). Exposure of rats to 5 ppm for 10 minutes resulted in pulmonary edema, while exposure to 0.15 ppm for 5.5 hours resulted in increased protein in pulmonary lavage fluid (Diller *et al.*, 1985).

Diller and colleagues (1985) exposed rats to various concentrations of phosgene from 0.1 to 5 ppm for time periods of 10 to 500 minutes. Rats exposed to 0.1 ppm phosgene for 4 hours

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

showed histological changes in the lung, whereas no effects were seen after exposure for 1 hour. The histologic changes included highly vacuolated “foamy cells” in the air compartment from the terminal bronchioles to the alveolar ducts and broadening alveolar septae due to cellular elements in the septae and to edematous changes in the interstitia. When compared to measurements of bronchoalveolar lavage fluid protein content, the histological changes were more sensitive indicators of cellular damage due to phosgene. These histological changes indicate oxidative damage to the alveolar region of the lung. Continued damage may result in permeability changes in the pulmonary vascular endothelium, a precursor to pulmonary edema (Pritchard, 1982).

Pulmonary natural killer cell activity was suppressed in rats exposed to 0.5 or 1.0 ppm phosgene for 4 hours (Burleson and Keyes, 1989). Exposure to 0.1 ppm had no significant effect.

Male Sprague-Dawley rats inhaled 0, 0.125, 0.25, 0.5, or 1.0 ppm phosgene for 4 hours (Currie *et al.*, 1987a). Rats exposed to 0.5 ppm or greater had significantly increased lung weight (wet and dry). Lavage fluid protein was increased at 0.25 ppm and greater. No effects were noted at 0.125 ppm.

Intracellular ATP levels in rats were diminished and non-protein sulfhydryl groups and associated antioxidant enzymes were increased in lung tissue following acute phosgene exposure (Currie *et al.*, 1985; Currie *et al.*, 1987b; Jaskot *et al.*, 1991).

Female CD-1 mice inhaled 0.1, 0.15, 0.25, or 0.5 ppm phosgene for 4 hours (Illing *et al.*, 1988). No changes in body weight, liver weight, or cytochrome P450 levels were noted at any concentration. Exposures to 0.15 ppm or greater significantly increased phenobarbital-induced sleeping time.

VI. Reproductive or Developmental Toxicity

No evidence exists to suggest that maternal phosgene exposure directly affects reproduction or fetal development.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 4 $\mu\text{g}/\text{m}^3$

<i>Study</i>	Diller <i>et al.</i> , 1985
<i>Study population</i>	14 rats
<i>Exposure method</i>	inhalation (for 10 to 500 minutes)
<i>Critical effects</i>	histologic changes in the lungs
<i>LOAEL</i>	0.1 ppm for 4 hours
<i>NOAEL</i>	0.1 ppm (0.4 mg/m^3) for 1 hour
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	0.1 ppm
<i>LOAEL uncertainty factor</i>	1

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	1 ppb (4 µg/m ³)

The 0.1 ppm 1-hour NOAEL and 4-hour LOAEL is generally consistent with the findings of a number of other studies. Burlison and Keyes (1989) observed a 4-hour rat NOAEL of 0.1 ppm for suppression of pulmonary natural killer cell activity. Jaskot *et al.* (1991) reported a 4 hour rat LOAEL of 0.1 ppm for elevated activities of several pulmonary enzymes. Hatch *et al.* (1986) and Currie *et al.* (1987a) noted 4-hour rat NOAELs of 0.1 ppm and 0.125 ppm, respectively, for increased lavage fluid protein. Illing and associates (1988) observed a 4 hour mouse NOAEL of 0.1 ppm for increased phenobarbital-induced sleeping time.

Level Protective Against Severe Adverse Effects

Exposure of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, and 2 goats to 0.2 ppm phosgene for 5 hours per day for 5 days resulted in no deaths and in minimal pulmonary edema in the majority of the animals (Cameron and Foss, 1941; Cameron *et al.*, 1942). In a few animals (1 rat, 1 mouse, 1 rabbit, and 3 guinea pigs) massive pulmonary edema was noted. The NRC (1986) proposed an EEGL of 0.2 ppm (0.8 mg/m³) and the AIHA (1989) proposed an ERPG-2 level of 0.2 ppm. The EEGL value includes extrapolation from 5-hour data assuming an exponent (n) of 1 for the equation $C^n * t = k$ (Rinehart and Hatch, 1964). Additional uncertainty factors (to account for differences between animals and humans, for approximation of a NOAEL, and for consideration of sensitive individuals) were not included. Hatch *et al.* (1986) reported pulmonary edema in several laboratory species after 4-hour exposures to 0.2 ppm phosgene, indicating that a lower value would be required to protect the general public.

Gross *et al.* (1965) reported that the lowest exposure level of phosgene, which produced moderate pneumonitis in rats, was 0.8 ppm. We will consider this level of 0.8 ppm for 1 hour as a NOAEL for severe pneumonitis, a severe adverse effect. Applying an interspecies uncertainty factor of 10 and an intraspecies uncertainty factor of 10 results in a cumulative uncertainty factor of 100 and a level protective against severe adverse effects for 1 hour of 8 ppb (32 µg/m³). As indicated above, this lower value is needed to provide protection for the general public.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Rats exposed to 1.7 ppm phosgene for 2 hours had mild to severe pneumonitis 2 days following exposure (Rinehart and Hatch, 1964; Gross *et al.*, 1965). Exposure of rats to 0.5 ppm for 2 hours resulted in changes in alveolar epithelium leading to decreased diffusing capacity of the lungs (Gross *et al.*, 1965). The AIHA (1989) concluded that a 1-hour exposure to phosgene below 1.0 ppm (4 mg/m³) is not life-threatening. NIOSH (1995) lists an IDLH of 2 ppm. A 30-minute

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

LC₅₀ in mice of 5.1 ppm (HSDB, 1994) suggests that levels lower than 2 ppm are required to protect the general public from life-threatening effects.

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ACUTE TOXICITY SUMMARY

PROPYLENE OXIDE

(1,2-propylene oxide, methyl ethylene oxide, propene oxide)

CAS Registry Number: 75-56-9

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	6,100 µg/m³
<i>Critical effect(s)</i>	dyspnea in mice
<i>Hazard Index target(s)</i>	Eyes; Respiratory System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	C ₃ H ₆ O
<i>Molecular weight</i>	58.08
<i>Specific gravity</i>	0.83 @ 20°C
<i>Boiling point</i>	34.23°C
<i>Melting point</i>	-112.13°C
<i>Vapor pressure</i>	445 mm Hg @ 20°C
<i>Flashpoint</i>	-19.44°C, closed cup
<i>Explosive limits</i>	2.8% - 37%
<i>Solubility</i>	soluble in water, miscible in acetone, benzene, carbon tetrachloride, methanol, ether
<i>Odor threshold</i>	35 ppm (geometric mean) (AIHA, 1989)
<i>Description</i>	colorless, sweet (AIHA, 1989)
<i>Conversion factor</i>	1 ppm = 2.38 mg/m ³ @ 25°C

III. Major Uses or Sources

Propylene oxide is used as a fumigant such as in the sterilization of packaged foods. It is also used as a chemical intermediate in the production of propylene glycol and glycol ethers and as a solvent. Propylene oxide is used in the preparation of surfactants and oil demulsifiers.

IV. Acute Toxicity to Humans

Propylene oxide is a primary irritant of the eyes and of the upper and lower respiratory tracts (HSDB, 1994). Mild CNS depression, indicated by incoordination, ataxia, and depression, are also reported effects of propylene oxide exposure.

In a case-report, an accidental 15-minute human exposure to 1,400-1,500 mg/l (5.9×10^5 - 6.3×10^5 ppm) propylene oxide vapor was reported to result in irritation of the eyes and a

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

burning sensation behind the sternum (Beljaev *et al.*, 1971). Late onset symptoms included headache, asthenia, and diarrhea. Recovery was reported to be complete the following day.

Predisposing Conditions for Propylene Oxide Toxicity

Medical: Persons with existing eye, respiratory, or neurological conditions may be more sensitive to the toxic effects of propylene oxide exposure (Reprotext, 1994).

Chemical: Persons consuming large quantities of foods fumigated with propylene oxide may be more sensitive to toxic effects following inhalation exposure to propylene oxide (Reprotext, 1994).

V. Acute Toxicity to Laboratory Animals

The 4-hour LC₅₀s for mice and rats are reported as 1,740 and 4,000 ppm (4,100 and 9,500 mg/m³) propylene oxide, respectively (Jacobsen *et al.*, 1956). The LD₅₀ for propylene oxide administered by stomach tube is reported as 1,140 mg/kg in rats and 690 mg/kg in guinea pigs (Smyth *et al.*, 1941).

Rats (5 of each sex) were exposed to 1,277, 2,970, 3,794, and 3,900 ppm (3,040, 7,070, 9,030, and 9,300 mg/m³) propylene oxide for 4 hours (NTP, 1985). Dyspnea and red nasal discharge, followed by death, were observed in animals in the three highest exposure groups.

In the same experiment, ten mice (5 of each sex) were exposed to 387, 859, 1,102, 1,277, and 2,970 ppm (920, 2,040, 2,600, 3,040, and 7,070 mg/m³) propylene oxide for 4 hours. Dyspnea was observed in all exposed groups. Narcosis was observed in those mice exposed to 1,102 or 1,277 ppm propylene oxide. Lacrimation was observed in mice exposed to 1,277 ppm propylene oxide. Treatment-related lethality was observed in the three highest exposure groups. While deaths were not observed following exposure to 859 ppm, one female mouse died 6 days following exposure to 387 ppm. The authors suggest that the death observed at 387 ppm was not treatment related. No gross pathologic effects were observed in any of the exposed mice at necropsy.

No studies of the metabolism of propylene oxide were located. Epichlorohydrin, structurally similar to propylene oxide, was found to be readily absorbed in the gastrointestinal and respiratory tracts (USEPA, 1987). By analogy to other structurally similar compounds, propylene oxide is likely to be distributed to the kidneys, liver, pancreas, adrenal glands, and spleen. Glutathione conjugates and carbon dioxide are likely metabolites to be found in the urine and expired air of animals exposed to propylene oxide.

VI. Reproductive or Developmental Toxicity

Female rats exposed to 500 ppm (1,200 mg/m³) propylene oxide 7 hours per day, 5 days per week for three weeks prior to mating exhibited a significant reduction in the number of corpora

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

lutea, implants, and live fetuses compared to rats exposed from days 7-16 or 1-16 of gestation (Hardin *et al.*, 1983). Fetal effects included a significant reduction in fetal body weight and crown-rump length; wavy ribs and reduced skeletal ossification were also noted in propylene oxide exposed litters. Maternal toxicity, indicated by a statistically significant decrease in body weight gain and increased kidney weight, was observed. The same study exposed rabbits in a similar manner to the same concentration; no significant reproductive or developmental effects were observed.

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 2.6 ppm (6.1 mg/m³)

<i>Study</i>	National Toxicology Program, 1985
<i>Study population</i>	10 mice (5 per sex)
<i>Exposure method</i>	inhalation in a chamber
<i>Critical effects</i>	dyspnea (1 death 6 days post exposure)
<i>LOAEL</i>	387 ppm
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	4 hours
<i>Extrapolated 1-hour concentration</i>	774 ppm (387 ² ppm * 4 h = C ² * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	3
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	300
<i>Reference Exposure Level</i>	2.6 ppm (6.1 mg/m ³ ; 6,100 µg/m ³)

Mice (five of each sex) were exposed to 387 ppm or 859 ppm propylene oxide for 4 hours. Dyspnea was observed in all exposed groups. No gross abnormalities were noted at necropsy. The LOAEL for dyspnea (in this case considered an irritant, mild adverse effect) is 387 ppm propylene oxide. (One female mouse died 6 days following exposure to 387 ppm propylene oxide. Because no deaths were observed in the 859 ppm exposure group, it is plausible that the observed death was not treatment related.)

NTP (1985) reports that propylene oxide acts as an irritant only at the site of administration, the nose in this case. Therefore, the dyspnea reflects nasal irritation, a mild effect. Necropsy findings in the NTP study of animals following both acute and chronic exposures support this assumption.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a revised IDLH for propylene oxide of 400 ppm based on acute inhalation toxicity/lethality data in mice and dogs. The dog 4-hour LC_{LO} is 2,005 ppm and the mouse 4-hour LC₅₀ is 1,740 ppm (Jacobson *et al.* 1956). This value of 400 ppm appears low for a level protective against life-threatening effects based on the case report of complete recovery from a 600,000 ppm exposure for 15 minutes (Beljaev *et al.*, 1971).

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ACUTE TOXICITY SUMMARY

SELENIUM AND COMPOUNDS

Molecular formula	Molecular weight	Synonyms	CAS Registry Number
Se	78.96	elemental selenium	7782-49-2
SeO ₂	110.96	selenium dioxide, selenium oxide	7446-08-4
SeS	111.02	selenium sulfide, sulfur selenide	7446-34-6
H ₂ Se	80.98	hydrogen selenide, selenium hydride	7783-07-5
Na ₂ SeO ₄	188.94	sodium selenate, selenic acid disodium salt	13410-01-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **3 µg/m³**
Critical effect(s) signs of eye and respiratory irritation in guinea pigs during exposure. (Difficulty in breathing and inactivity were observed after the exposure.)
Hazard Index target(s) Eyes; Respiratory System

II. Physical and Chemical Properties for Elemental Se (HSDB, 1994 except as noted)

Specific gravity 4.26-4.81 @ 25°C
Boiling point 690°C
Melting point 170-217°C
Vapor pressure 0.001 mm Hg @ 20°C
Flashpoint not applicable
Explosive limits not applicable
Solubility (Se⁰ crystal) insoluble in water and alcohol; slightly soluble in carbon disulfide; soluble in ether (ACGIH, 1993)
Odor threshold (Se⁰) not applicable
 (H₂Se) 0.3 ppm (AIHA, 1989)
Description (Se⁰) odorless. Grey crystals
 (H₂Se) garlic odor (AIHA, 1989)
Metabolites trimethylselenonium (Palmer *et al.*, 1970)
Conversion factor (Se⁰) not applicable;
 (H₂Se) 1 ppm = 3.31 mg/m³ @ 25°C

III. Major Uses or Sources

Selenium occurs in four distinct valence forms: selenates (6+), selenite (4+), selenides (2-), and elemental (0) (Amdur *et al.*, 1991). Selenite (4+) compounds and elemental selenium are believed to be of low toxicity because of their insolubility in biological media. Selenates are more acutely toxic due to their greater solubility.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

The most acutely toxic selenium compound reported is hydrogen selenide (H₂Se). Hydrogen selenide is formed by the reaction of acids or water with metal selenides or by the contact of nascent hydrogen with soluble selenium compounds (Clayton and Clayton, 1982). Hydrogen selenide has no reported commercial use.

Selenium compounds are used as a decolorizing agent in the glass industry, as a vulcanizing agent in the rubber industry, in insecticides, and in photoelectric cells. Selenium compounds are also found in the toning baths used in photography and xerography. Selenium sulfide (SeS) is used in shampoos as an antidandruff agent. Up to 90% of the selenium content in ambient air is emitted during the burning of fossil fuels (Kut and Sarikaya, 1981).

The most widely used selenium compound in industry is selenium dioxide (SeO₂) (HSDB, 1994). It is produced by the oxidation of Se with nitric acid followed by evaporation or by burning Se in oxygen.

Selenium is an essential trace element in many species, including humans (Amdur *et al.*, 1991). However, the dose differential between acute toxicity and chronic deficiency is slight. While the lower limit for acute oral selenium toxicity is reported to be 200 µg Se/day in humans, the “normal” oral intake is reported as 70 µg Se/day, and the oral level associated with disease due to chronic deficiency is 20 µg Se/day.

IV. Acute Toxicity to Humans

Eye, nose and throat irritation and headaches were reported by workers briefly exposed to high, but unquantitated, concentrations of selenium fume (Clinton, 1947). One worker reported delayed symptoms of sore throat and dyspnea 8-12 hours following exposure.

In a review of the literature and a report of five cases, Buchan (1947) reported that signs of acute intoxication following exposure to 0.21 ppm (0.7 mg/m³) H₂Se included irritation of the respiratory tract, severe bronchitis, bronchial pneumonia, and pulmonary edema. This report reflects occupational exposure; the exact duration of exposure was not specified. In another report, workers accidentally exposed to selenium oxide reported initial symptoms of bronchospasms, irritation of the upper respiratory passages, violent coughing, and gagging with nausea and vomiting (Wilson, 1962). Late onset symptoms observed 2 or more hours following exposure included fever, chills, headache, and dyspnea. Symptoms of bronchitis persisted for four days.

Predisposing Conditions for Selenium Toxicity

Medical: Persons with eye, skin, or respiratory conditions may be more sensitive to the effects of exposure to Se and its compounds (Reprotext, 1994).

Chemical: Persons exposed to multiple selenium compounds over time may be more sensitive to the effects of additional Se exposure (Reprotext, 1994).

V. Acute Toxicity to Laboratory Animals

The 2-hour LC₅₀ in guinea pigs is 3.6 ppm (12 mg/m³) H₂Se (Dudley and Miller, 1941). No increase in mortality was observed in rabbits and guinea pigs exposed to 33 mg/m³ Se dust for 4 hours every other day for 8 days (total duration of exposure of 16 hours) (Hall *et al.*, 1951). Moderate interstitial pneumonitis and congestion of the lungs was noted in both species at necropsy. A 10% mortality rate was observed in rats exposed to the same concentration of Se dust for a total of 8 hours; mild pneumonitis was noted at necropsy.

Signs of nasal and ocular irritation, including nasal discharge and pawing of the eyes and nose, were observed in guinea pigs exposed to 0.9-57 ppm (3-190 mg/m³) H₂Se for 60-minutes (Dudley and Miller, 1937). Decreased activity, marked difficulty in breathing, and decreased food intake were noted in those animals surviving the exposure. No significant increase in mortality as compared to controls was observed in guinea pigs exposed to 3 mg/m³ H₂Se for 1 hour. (Three of the 32 control animals died during the 30 day observation period following exposure while 1 of 16 animals exposed to either 3 or 4 mg/m³ H₂Se died during the observation period).

No histological changes or other signs of toxicity were observed in rats following a 1-hour exposure to 1,607, 4,499, or 8,034 ppm (7,200, 20,000, or 36,000 mg/m³) dimethylselenide vapor (equivalent to 5,200, 15,000, or 26,000 mg Se/m³) (Al-Bayati *et al.*, 1992).

Microorganisms in the soil and plant products can methylate selenium to form dimethylselenide and, subsequently, dimethylselenide has been shown to be released as a vapor from acidic soil.

Rats were exposed to 2.6 mg/m³ Se⁰ for 10 minutes and sacrificed 4 hours later; 57% of the Se deposited in the lungs had been absorbed into the blood (Medinsky *et al.*, 1981). The single largest fraction of the excreted Se (20-28%) was found in the urine.

VI. Reproductive or Developmental Toxicity

Female Japanese rectifier workers known to be exposed to selenium reported irregular menstrual bleeding (Nagaii, 1959). The original article was not available for review and no additional information was reported in the secondary source (Friberg *et al.*, 1986). No other reports of human reproductive or developmental toxicity following exposure to Se were available.

A dose-dependent increase in fetal malformations was observed following a single oral administration of 90, 100, or 110 mg/kg sodium selenate (Na₂SeO₄) to pregnant hamsters on the 8th day of gestation (Ferm *et al.*, 1990). A significant decrease in fetal body weight and crown-rump length were observed following a single maternal oral dose of 110 mg/kg Na₂SeO₄. Maternal toxicity, as indicated by a significant weight loss, was observed following a single oral dose of 110 mg/kg Na₂SeO₄; approximately 30% of the dams in this group died following administration of the dose.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Dose-dependent injury to the testes of male rats was observed following a 90-day intraperitoneal administration of 2, 6, or 10 mg/day selenium dioxide (SeO₂) (Chowdhury and Venkatakrishna-Bhatt, 1983). Statistically significant decreases in relative testes weight, seminiferous tubular diameter, and Leydig cell population were observed following exposure to 6 or 10 mg SeO₂/day. Significant testicular degeneration and testicular atrophy were observed following administration of the higher dose.

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 3 µg Se/m³

<i>Study</i>	Dudley and Miller, 1937; Dudley and Miller, 1941
<i>Study population</i>	groups of 16 guinea pigs; 32 controls
<i>Exposure method</i>	inhalation in a chamber
<i>Critical effects</i>	signs of eye and respiratory irritation, with persistent coughing after exposure, for several days.
<i>LOAEL</i>	0.9 ppm (3 mg/m ³)
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	0.9 ppm (3 mg/m ³)
<i>LOAEL uncertainty factor</i>	10 (see below)
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	1000
<i>Reference Exposure Level</i>	0.0009 ppm; 0.003 mg/m ³ ; 3 µg/m ³

Guinea pigs exposed to 0.9 ppm (3 mg/m³) H₂Se for 1 hour exhibited acute eye and nasal irritation (indicated by pawing of the nose and eyes) during the exposure and marked difficulty breathing and decreased activity following the exposure. The range of exposure concentrations was 0.9-57 ppm (3-190 mg/m³) and a 30 day observation period followed the exposure. Nearly 100% of the animals were dead within 30 days of exposure to concentrations of H₂Se of 6 ppm (20 mg/m³) and greater. No increase in mortality was observed in animals exposed to 3 or 4 mg/m³ H₂Se compared to control animals. The LOAEL for irritant effects is 0.9 ppm (3 mg/m³) H₂Se. The signs reported by the authors indicate that the irritation experience by the animals was at least moderate and may have approached a severe level. For this reason, the uncertainty factor for the LOAEL was maintained at 10 instead of 3.

Dudley and Miller (1941) exposed guinea pigs to hydrogen selenide for periods of 2, 4, or 8 hours. The 8-hour exposure resulted in 8/16 (50%) mortality in the animals when exposed to a concentration of 1 mg/m³. The dose-response is very steep for hydrogen selenide.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Since H₂Se is reported to be the most acutely toxic selenium compound (Amdur *et al.*, 1991), this level is considered to be protective against adverse effects from other selenium compounds as well. Use of this value for some selenium compounds will overestimate health risks.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists an IDLH of 1 mg Se/m³ based on acute toxicity data in animals. “This may be a conservative value for selenium compounds in general since it is based on sodium selenite, which is orders of magnitude more toxic than many other selenium compounds. Further, this may also be a conservative value due to the lack of relevant acute toxicity data for workers.” Due to the uncertainty this value can not be recommended.

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ACUTE TOXICITY SUMMARY

SODIUM HYDROXIDE

(caustic soda, caustic flake, white caustic, soda lye, lye, sodium hydrate)

CAS Registry Number: 1310-93-2

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation Reference Exposure Level</i>	5 µg/m³
<i>Critical effect(s)</i>	subjective complaints of eye, skin, and respiratory irritation in occupationally exposed workers
<i>Hazard Index target(s)</i>	Eyes; Skin; Respiratory System

II. Physical and Chemical Properties (HSDB, 1993)

<i>Molecular formula</i>	NaOH
<i>Molecular weight</i>	40.01
<i>Specific gravity</i>	2.13 at 25°C
<i>Boiling point</i>	1390°C
<i>Melting point</i>	318.4°C
<i>Vapor pressure</i>	1 mm Hg @ 739°C
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	soluble in water, alcohol and glycerine
<i>Odor threshold</i>	not applicable
<i>Description</i>	colorless, odorless
<i>Metabolites</i>	not applicable
<i>Conversion factor</i>	not applicable (when dust)

III. Major Uses and Sources

Sodium hydroxide (NaOH) is produced primarily by the electrolysis of sodium chloride solutions and also from sodium carbonate. Sodium hydroxide is used in the manufacture of chemicals, rayon, soap and detergents, pulp and paper, petroleum products, cellophane, textiles and explosives, in etching and electroplating, in metal descaling, and in batteries.

IV. Acute Toxicity to Humans

Sodium hydroxide is a strong irritant and has a marked corrosive action on all body tissues regardless of the route of exposure (Reprotext, 1993). It is also more irritating than equivalent amounts of strong acid.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Controlled dermal exposures with concentrated sodium hydroxide have resulted in intercellular edema, erythema, decomposition of keratin material, and destruction of the epidermis (NIOSH, 1975). There may be a latency period between dermal contact and the onset of a sensation of irritation or burning. Exposure to sodium hydroxide mist may cause multiple small burns and temporary hair loss.

Sodium hydroxide in contact with the eyes can result in ulceration, perforation, and opacification of the cornea, leading to blindness (Grant, 1986; NIOSH, 1975).

Oral ingestion of sodium hydroxide can result in burns to the lips, tongue, oral mucosa, and esophagus (Medical Management, 1993). Sodium hydroxide has been implicated in the production of esophageal cancer at the site of esophageal strictures resulting from accidental ingestion (Appelqvist *et al.*, 1980). These cancers are believed to be the consequence of scar formation and tissue destruction rather than from a direct carcinogenic effect of sodium hydroxide (NIOSH, 1975).

The effects of inhalation exposure to sodium hydroxide have not been reliably studied. Some cases of acute respiratory symptoms following exposure with nose and throat irritation, chest pains, and shortness of breath have been reported (NIOSH, 1974). In an unreferenced comment, Patty (1949) remarked that exposure to 2 mg /m³ NaOH in air is noticeably, but not excessively, irritating. Ott *et al.* (1977) stated that workers exposed to sodium hydroxide levels estimated to range from 0.5 to 2 mg/m³ time-weighted average (TWA) experienced nasal, skin, and, to a lesser extent, respiratory irritation. The duration of exposure prior to development of symptoms was not mentioned. Also, the 8-hour TWA concentrations are based on a one-time measurement. Workers exposed to 0.01 to 0.7 mg/m³ heated sodium hydroxide, in addition to other solvents, experienced upper respiratory tract irritation (Hervin and Cohen, 1973). Heating may increase the toxicity of sodium hydroxide (NRC, 1984).

Case reports exist in the literature of irreversible obstructive lung disease following chronic occupational exposure as well as after a one-time, high-level exposure to sodium hydroxide (Hansen and Isager, 1991; Rubin *et al.*, 1992).

Predisposing Conditions for Sodium Hydroxide Toxicity

Medical: Persons with skin, eye or respiratory conditions may be more sensitive to the effects of sodium hydroxide. Persons with glaucoma should not work around mists or aerosols of sodium hydroxide since it can raise eye pressure (Reprotext, 1993).

Chemical: Persons exposed simultaneously to ammonium chloride, other irritants, or alkalis may be more sensitive to the effects of sodium hydroxide (Dluhos *et al.*, 1969).

V. Acute Toxicity to Laboratory Animals

Application of sodium hydroxide to the skin of rats and mice has produced severe irritation leading to necrosis and death (NIOSH, 1975). Topical ocular application of sodium hydroxide in rabbits has resulted in ulceration, perforation, and corneal necrosis (NIOSH, 1975; Grant, 1986). Corneal opacification, vascularization, and an increase in intraocular pressure have also been observed. Species differences in the degree of irritancy and recovery after eye application have been noted (Grant, 1986). The eyes of monkeys are less sensitive to sodium hydroxide and recover more completely than rabbits' eyes.

In rats exposed by inhalation to an unknown concentration of sodium hydroxide produced from an aerosolized 40% solution for 30 minutes twice daily for 2.5 months, lung examination revealed alveolar wall thickening with cell proliferation and congestion (Dluhos *et al.*, 1969). Ulceration and flattening of the bronchial epithelium and proliferation of lymphadenoid tissue were also reported. Undescribed, isolated tumors were observed in 3 of 10 animals. In another study, inhalation exposure twice weekly for one month to an aerosol produced from a 40% sodium hydroxide solution resulted in the deaths of all 27 rats, predominantly from bronchopneumonia (Vyskocil *et al.*, 1966). Exposure to an aerosol produced from a 20% solution of sodium hydroxide produced dilatation and destruction of alveolar septae. Although no effects were observed in the group exposed to a 10% solution, in rats exposed to aerosolized 5% sodium hydroxide, bronchial dilatation and mucus membrane degeneration were observed, which suggest a poor dose-response relationship in this study.

VI. Reproductive or Developmental Effects

No studies are available regarding the reproductive or developmental effects of sodium hydroxide in humans.

Sodium hydroxide injected into the amniotic fluid of rats at 0.001 M on day 13 of gestation was not teratogenic but was slightly embryotoxic (Dostal, 1973).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.005 mg/m³ (5 µg/m³)

<i>Study</i>	Ott <i>et al.</i> , 1977
<i>Study population</i>	291 workers in sodium hydroxide production
<i>Exposure methods</i>	occupational exposure
<i>Critical effects</i>	subjective reports of mild to moderate-severe irritation of the eyes and skin; mild respiratory irritation
<i>LOAEL</i>	0.5 mg/m ³
<i>NOAEL</i>	not reported
<i>Exposure duration</i>	8-hour time-weighted average

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>Extrapolation to 1 hour</i>	not used
<i>LOAEL uncertainty factor</i>	10 (see below)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	0.005 mg/m ³ (5 µg/m ³)

Uncertainty factors were applied to the lowest concentration at which symptoms were reported (0.5 mg/m³). The reported irritation was mild to moderate-severe, which indicates that the irritation was beyond mild irritation. For this reason, an uncertainty factor of 10 was used to estimate a NOAEL from the observed LOAEL. Because sodium hydroxide aerosols can readily undergo reaction with carbon dioxide to form sodium carbonate, a standard for sodium carbonate should also be developed (Cooper *et al.*, 1979).

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

In an unreferenced comment, Patty (1949) stated that exposure to 2 mg/m³ sodium hydroxide in air would cause noticeable, but not excessive respiratory irritation. Exposure to sodium hydroxide estimated to be as high as 2 mg/m³ TWA caused nasal and skin irritation, especially in areas of the plant where temperatures were higher (Ott *et al.*, 1977).

The NRC (1984) used their expert judgment in determining an EEGL of 2 mg/m³, therefore it does not follow OEHHA's methodology. No margin of safety was applied in the derivation of the 1-hour EEGL.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH of 10 mg/m³. It is based on Ott *et al.* (1977). Workers exposed to 2 to 8 mg/m³ "caustic dust" experienced irritation of the respiratory system. NIOSH states that "This may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations above 8 mg/m³."

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ACUTE TOXICITY SUMMARY

STYRENE

(vinyl benzene; phenylethylene; cinnamene; styrol; vinylbenzol)

CAS Registry Number: 100-42-5

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **22,000 µg/m³**
Critical effect(s) eye and upper respiratory irritation
Hazard Index target(s) Eyes; Respiratory System;
Reproductive/developmental

II. Physical and Chemical Properties (Vainio and Hietanen, 1987 except as noted)

<i>Molecular formula</i>	C ₈ H ₈
<i>Molecular weight</i>	104.14
<i>Specific gravity</i>	0.902 @ 20°C
<i>Boiling point</i>	145.2°C
<i>Melting point</i>	-30.6°C
<i>Vapor pressure</i>	6.45 mm Hg @ 25°C
<i>Flashpoint</i>	31°C (closed cup) (ATSDR, 1992)
<i>Explosive limits</i>	upper = 6.1% by volume in air lower = 1.1% by volume in air (ATSDR, 1992)
<i>Solubility</i>	soluble in ethanol, ether, acetone, benzene, and petroleum ether; sparingly soluble in water
<i>Odor threshold</i>	1.36 mg/m ³ (0.32 ppm) (Amoore and Hautala, 1983)
<i>Odor Description</i>	sweet, sharp odor (Amoore and Hautala, 1983)
<i>Metabolites</i>	styrene 7,8-oxide, styrene glycol, mandelic acids, phenylglyoxylic acids (Leibman and Ortiz, 1970; Sedivec <i>et al.</i> , 1984)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 4.2 mg/m ³

III. Major Uses or Sources

Styrene is produced by the dehydrogenation of ethylbenzene in the presence of polymerization inhibitors (Vainio and Hietanen, 1987). It is used in the plastics industry as a solvent for synthetic rubber and resins, as a starting material in the manufacture of emulsifying agents, in the manufacture of synthetic rubber and polystyrene, and in the production of propylene oxide (Vainio and Hietanen, 1987).

IV. Acute Toxicity to Humans

Styrene may irritate the eyes and mucous membranes and may be toxic to the central nervous system (IARC, 1979). Immediate eye and throat irritation, increased nasal mucus secretion, listlessness, impairment of balance, and drowsiness followed by unsteadiness, muscle weakness, and depression were reported in a study of 2 human volunteers exposed to 800 ppm (3,360 mg/m³) styrene for 4 hours (Carpenter *et al.*, 1944). Other symptoms include a feeling of being “lightheaded” or “drunk” (Lorimer *et al.*, 1976).

In an exposure chamber study, volunteer subjects complained of an objectionably strong odor when exposed to 200-400 ppm (840-1,680 mg/m³) styrene; exposure to 60 ppm (252 mg/m³) resulted in detectable odor but no irritation (Wolf *et al.*, 1956). The duration of exposure and number of subjects were not specified. Investigators at a fiberglass plant could not withstand more than 1-2 minute exposure to concentrations of 500-800 ppm styrene (Götell *et al.*, 1972). However, workers exposed to this concentration of styrene for hours complained of only mild to moderate complaints of irritation, suggesting that tolerance may have developed.

Stewart *et al.* (1968) found eye and throat irritation in 3 out of 6 volunteers exposed to 99 ppm (416 mg/m³) styrene for 20 minutes. No symptoms were reported in 3 subjects after exposure to 51 ppm for 1 hour. Exposure of these subjects to 376 ppm (1,579 mg/m³) styrene for 25 minutes resulted in nausea, significant discomfort, and an abnormal Romberg test, indicative of cerebellar dysfunction. Significant decrements were noted in 3/5 subjects in other tests of coordination and manual dexterity at 50 minutes. Exposure to 216 ppm or less for up to 1-hour did not cause measurable impairment of coordination and balance.

The neurotoxic effects mediated by styrene consist of slowing in sensory, but not motor, nerve conduction velocity and CNS depression (Cherry and Gautrin, 1990). Reaction time was significantly impaired in 12 males exposed to 350 ppm (1,470 mg/m³) styrene for 30 minutes, whereas no significant impairment was observed at 250 ppm (1,050 mg/m³) or lower (Gamberale and Hultengren, 1974). In this study, no effects on perceptual speed or manual dexterity were detected. In another study of 12 workers exposed during the workday to 110 mg/m³ (26 ppm), Edling and Ekberg (1985) measured reaction time before and after work and found no significant differences. Other non-CNS symptoms were reported in a neuropsychiatric questionnaire completed by the subjects.

Abnormal electroencephalograms were correlated with urinary levels of the styrene metabolite, mandelic acid, of 700 mg/l or higher in workers exposed to styrene (Harkonen *et al.*, 1978).

Consumption of ethanol has been shown to decrease formation of the metabolites mandelic and phenylglyoxylic acid in human volunteers exposed to 420 mg/m³ (100 ppm) styrene for 8 hours (Cerny *et al.*, 1990). Lowered levels of these metabolites have been associated with a reduced risk of CNS disturbances in volunteer workers (Cherry and Gautrin, 1990). Co-exposure to inhaled acetone was reported to alter cytochrome-P450 enzymes as measured by altered urinary steroid metabolites and glucaric acid in workers who consumed moderate amounts of alcohol

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

(Dolara *et al.*, 1983). However, the clinical significance of the presence of these compounds in the urine is unknown.

Styrene is bioactivated to styrene 7,8-oxide, a reactive metabolite which binds to tissue proteins, acts as a hapten, and elicits contact allergy in some individuals (Sjoberg *et al.*, 1984). Analyses of styrene oxide adducts bound to human serum albumin have been used as biomarkers for exposure to styrene (Rappaport *et al.*, 1993). In a study comparing 9 styrene-exposed workers with 24 healthy controls, hematocrit, blood lead levels, and delta-aminolevulinic acid dehydratase (ALA-D) levels were measured (Fujita *et al.*, 1987). The workers were exposed to at least 210 mg/m³ (50 ppm) styrene for 7 days. Styrene oxide was shown to inhibit the formation of ALA-D, an important enzyme in heme biosynthesis, in these workers. Styrene oxide is also known to bind covalently to DNA *in vitro* (Hemminki and Hesso, 1984).

Two subjects with occupational asthma due to prior exposure to styrene were exposed to 15 ppm (63 mg/m³) styrene in a chamber (Moscato *et al.* (1987). Immediate bronchoconstriction was observed in both subjects while a late rash was also observed in one of the subjects.

Predisposing Conditions for Styrene Toxicity

Medical: Asthmatics may be more sensitive to adverse pulmonary effects from styrene exposure (Moscato *et al.*, 1987).

Chemical: Ethanol consumption and acetone inhalation may inhibit the metabolism and clearance of styrene (Cerny *et al.*, 1990; Dolara *et al.*, 1983; Elovaara *et al.*, 1990).

V. Acute Toxicity to Laboratory Animals

The irritant and central nervous system (CNS) depressant effects of styrene in humans are consistent with the acute effects observed in experimental animals (Bond, 1989).

Bonnet *et al.* (1979; 1982) determined a 6 hour LC₅₀ in rats and mice of 4,618 ppm (95% confidence interval, 4,399-4,894 ppm) and 2,429 ppm (95% confidence interval, 2,353-2,530 ppm), respectively. Shugeav (1969) also determined the LC₅₀ in rats and mice. In rats the 4 hour LC₅₀ was 2,810 ppm (95% confidence interval, 2,452-3,214 ppm), and in mice the 2 hour LC₅₀ was 5,000 ppm (95% confidence interval, 4,238-5,905 ppm). Jeager *et al.* (1974) estimated the 4 hour LC₅₀ in rats to be 2,700 ppm. In other acute lethality studies, 2 of 6 rabbits died following 4 hour exposure to 4,000 ppm styrene (Union Carbide Corp., 1957).

Lundberg *et al.* (1986) could not determine an LC₅₀ in rats because the concentrations required for lethality in a 4 hour exposure exceeded the vapor saturation point. No animals died as a result of a 4 hour exposure to 7,904 ppm styrene while 4/10 rats died when exposure at this concentration was extended to 8 hours.

Inhalation of 1,300 ppm (6,000 mg/m³) by rats and guinea pigs resulted in immediate irritation and lacrymation (Spencer *et al.*, 1942). No deaths occurred from exposure to 10,000 ppm

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

styrene for 1 hour. However, exposure to this concentration for 3 hours resulted in 100% mortality in both species. This concentration of styrene was the highest that the researchers could attain at room temperature without the chemical condensing out of the atmosphere. At 5,000 ppm, a 100% survival rate was observed following exposure of rats and guinea pigs for 2 and 3 hours, respectively. One-hundred percent mortality was observed at this concentration in both species following 8 hour exposure. Immediate deaths were due to CNS depression. However, delayed deaths occurred due to pulmonary edema and hemorrhage which frequently developed as a result of styrene's acute lung irritant action.

In a study by Morgan *et al.* (1993a), B6C3F1 mice (36 mice/sex/dose) were exposed to 125, 250, or 500 ppm styrene 6 hours/day for 3 days. Seven of 72 mice died or were terminated moribund following one 6 hour exposure to 500 ppm. Necropsy of dead or dying mice revealed livers engorged with blood. Severe congestion and necrosis of the liver was observed under microscopic examination. Exposure to both 250 and 500 ppm styrene was associated with progressive degenerative and necrotic hepatocellular changes after one 6 hour exposure. There were no significant histologic lesions in mice exposed to 125 ppm styrene. While the liver was identified as the major target organ in mice, the authors indicated that styrene's CNS depressant action also likely contributed to the overall toxicity. Another inhalation study by this research group determined that B6C3F1 mice are more sensitive to styrene induced hepatotoxicity than other common mouse strains, and that kidney toxicity was not seen in any strain of mice investigated following styrene exposure (Morgan *et al.*, 1993b).

Morgan *et al.* (1995) conducted additional studies to investigate mouse strain and gender differences in susceptibility to hepatotoxicity caused by repeated exposure to styrene at concentrations that do not cause metabolic saturation. Male and female B6C3F1 and Swiss mice (8 weeks old) were exposed to 0, 150, or 200 ppm styrene for 6 hr/day, 5 days/week, for up to 2 weeks. Changes in body and liver weights, serum enzyme levels, liver histopathology, and total liver glutathione (GSH) were evaluated after 2, 3, 5, and 10 exposures (six mice/sex/strain/time point/concentration). Serum alanine aminotransferase (ALT) and sorbitol dehydrogenase (SDH) levels were significantly elevated only in female B6C3F1 mice after 3 exposures to 200 ppm styrene; enzyme levels had returned to control levels when measured after 5 and 10 exposures. Degeneration and coagulative necrosis of centrilobular hepatocytes were observed in female B6C3F1 mice exposed 2, 3, and 5 days to 150 or 200 ppm styrene; incidences of these lesions were greater in the 200 ppm than in the 150 ppm dose group. After 10 days of exposure to 150 or 200 ppm styrene, hepatocellular lesions had resolved, although a residual chronic inflammation was present in livers of most female B6C3F1 mice.

The acute inhalation toxicity adverse effects in mice do not appear to be consistent with adverse effects seen in humans and other animal species. In research by Mendrala *et al.* (1993) and a review by Sumner and Fennell (1994), comparison of the metabolic fate of styrene and its toxic metabolite, styrene oxide, in mice, rats, and humans showed that mice are more sensitive than rats and humans to the hepatotoxic effects of styrene. Based on P450 enzyme kinetics (the primary enzymes responsible for metabolizing styrene to styrene oxide) and the relative liver and body size, the mouse had the greatest capacity to form styrene oxide from styrene. In mice exposed to relatively low levels of styrene (250 to 500 ppm), the blood concentration of the

metabolite styrene oxide rises steeply, potentially resulting in hepatotoxicity and mortality. This metabolic phenomenon does not occur in rats or humans. In addition, hepatotoxicity has not been reported for rats, and there have not been epidemiological findings of hepatotoxicity in humans exposed to styrene.

Sumner *et al.* (1997) compared the metabolism and hepatotoxicity (mice only) of styrene in male B6C3F1 mice, CD-1 mice, and F344 rats to evaluate mechanisms of toxicity. Rats and mice were exposed to 250 ppm styrene for 6 h/day for 1 to 5 days. Mortality and increased serum ALT activity were observed in mice but not in rats. Hepatotoxicity in B6C3F1 mice was characterized by severe centrilobular congestion after one exposure followed by acute centrilobular necrosis. Hepatotoxicity was delayed by 1 day in CD-1 mice, and the increase in ALT and degree of necrosis were less than in B6C3F1 mice. After exposure to (unlabeled) styrene for 0, 2, or 4 days, rats and mice were exposed to [7-¹⁴C]-styrene (60 µCi/mmol) for 6 h. Most styrene-derived radioactivity was excreted in urine; the time-course indicated that rats and CD-1 mice eliminated radioactivity at a faster rate than B6C3F1 mice following a single 250 ppm exposure, consistent with a greater extent of liver injury for B6C3F1 mice. The elimination rate following 3 or 5 days of exposure was similar for rats and the two mouse strains. After three exposures, the total radioactivity eliminated was elevated over that measured for one exposure for both mouse strains. An increased excretion of metabolites on multiple exposure is consistent with the absence of ongoing acute necrosis following 4 to 5 daily exposures. The data indicate that an induction in styrene metabolism occurs after multiple exposures.

Pretreatment of rats with acetone potentiated pulmonary toxicity, measured by decreased lung glutathione and cytochrome-P450 activity following inhalation of 2,100 mg/m³ styrene vapor 5 hours/day for 3 days (Elovaara *et al.*, 1990).

Styrene has been shown to suppress antibody responses and to enhance hypersensitivity responses in mice after multiple administrations of 20 mg/kg for 5 days (Dogra *et al.*, 1989).

VI. Reproductive or Developmental Toxicity

There is no direct evidence for human reproductive or developmental toxicity from styrene exposure.

Murray *et al.* (1978) found no teratogenesis or reproductive impairment in rats or rabbits inhaling styrene concentrations up to 600 ppm (2,520 mg/m³) throughout critical days of gestation. Decreased maternal body weight gain was observed in rats but not rabbits. Other studies in rodents have supported this finding (Daston *et al.*, 1991; Srivastava *et al.*, 1989). A comprehensive review on the subject could find no evidence for reproductive and developmental toxicity in experimental animals or humans (Brown, 1991). Likewise, a review of epidemiological studies could find no evidence of reproductive health effects in women due to occupational exposure to styrene (Lindbohm, 1993).

Kishi *et al.* (1995) exposed pregnant Wistar rats via inhalation to 0, 50, or 300 ppm styrene for 6 h/day during gestation days 7 to 21. Offspring were evaluated in several neurobehavioral tests.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Initial results with a few litters showed significant dose-dependent effects in tests performed pre-weaning (surface righting, pivoting locomotion, and bar holding) and in tests performed post-weaning (motor coordination, open-field behavior, and motor activity). Exposure to 50 ppm styrene caused disturbances in motor coordination and delayed some motor and reflex developments, and 300 ppm led to changes in open-field behavior, increases in spontaneous activity, and delay in neurobehavioral developments. Exposure of dams to styrene did not clearly affect the learning behavior of the offspring. Age played a role in the differences in styrene's effects on neurobehavioral function. At 120 days after birth only subtle effects were found in both open-field behavior and motor-coordination function when compared with control rats.

Exposure of rats and rabbits to the reactive metabolite, styrene oxide, at 100 ppm throughout gestation resulted in reproductive and developmental toxicity, as well as maternal toxicity (Sikov *et al.*, 1986).

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 5.1 ppm (22,000 µg/m³)

<i>Study</i>	Stewart <i>et al.</i> , 1968
<i>Study population</i>	three human volunteers
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	eye and throat irritation
<i>LOAEL</i>	99 ppm (for 20 minutes)
<i>NOAEL</i>	51 ppm
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	51 ppm
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	5.1 ppm (22 mg/m ³ ; 22,000 µg/m ³)

Level Protective Against Severe Adverse Effects

Human subjects exposed to 376 ppm styrene for 25 minutes developed significant decrements in coordination and manual dexterity as well as nausea and discomfort (Stewart *et al.*, 1968). These effects were not observed in subjects exposed to 216 ppm for 1 hour. An uncertainty factor of 10 was applied to the 1-hour NOAEL of 216 ppm to account for increased susceptibility of sensitive human individuals. The resulting level protective against severe adverse effect is 22 ppm (91 mg/m³) for a 1-hour exposure to styrene. However, sensitized individuals may be unable to tolerate exposure to styrene at detectable levels (Moscatto *et al.*, 1987; Hayes *et al.*, 1991). Therefore, these individuals may not be protected by the severe adverse effect level developed for styrene in this document.

Level Protective Against Life-threatening Effects

Spencer *et al.* (1942) observed a NOAEL for lethality in rats and guinea pigs of approximately 10,000 ppm for a 1-hour exposure. This was consistent with the lack of mortality observed following exposure for 2- to 3-hours at 5,000 ppm. The LOAEL for lethality was 10,000 ppm for a 3-hour exposure. Although more recent lethality studies in rats exist (Lundberg *et al.* 1986), the Spencer *et al.* (1942) report was the only study that was known to include a post-exposure observation period (2-4 weeks) long enough to observe delayed mortality due to pulmonary injury. The lethal hepatic effect observed in mice following exposure to styrene is inconsistent with that seen in humans for acute exposures via inhalation. Therefore, a life-threatening level based on mouse exposure data does not appear to be appropriate. Uncertainty factors of 10 each were applied to the NOAEL (10,000 ppm) to account for interspecies differences and increased susceptibility of sensitive human individuals. The total uncertainty factor incorporated was 100, resulting in a level of 100 ppm (420 mg/m³) protective against life-threatening effects for a 1-hour exposure to styrene.

NIOSH (1995) reports an IDLH of 700 ppm based on acute inhalation toxicity in human workers. There is no allowance made for sensitive individuals.

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Conversion factor

H₂SO₄: 1 ppm = 4.08 mg/m³

III. Major Uses or Sources

Sulfates, including sulfuric acid, are produced in ambient air through oxidation of the SO₂ and SO₃ formed from fuel combustion (CARB, 1976). Atmospheric ammonia reacts with sulfuric acid to form the ammonium salts (NH₄)₂SO₄ and (NH₄)HSO₄. Sodium sulfate occurs near marine sources. Sulfuric acid is a strong acid used as an intermediate for linear alkylbenzene sulfonation surfactants used in dyes. It is used in petroleum refining; for the nitration of explosives; in the manufacture of nitrocellulose; in caprolactam manufacturing; and as a drying agent for chlorine and nitric acid.

IV. Acute Toxicity to Humans

The hydrogen ion content of the acid sulfate exposure provides a stimulus for bronchoconstriction, especially in asthmatics (Balmes *et al.*, 1989). Consequently, sulfuric acid is the most potent of the sulfates in producing airway responses, followed by (NH₄)HSO₄ and (NH₄)₂SO₄ (Schlesinger and Graham, 1992; Schlesinger *et al.*, 1992; Schlesinger and Chen, 1994). A comparison of sulfate aerosols on carbachol-induced bronchoconstriction in healthy humans confirmed the above relative potencies (Utell *et al.*, 1982). This Appendix also contains an acute toxicity summary for sulfuric acid.

Utell *et al.* (1983) found that exposure of asthmatics to 450 µg/m³ sulfates as H₂SO₄, but not (NH₄)HSO₄, for 16 minutes resulted in decreased airway conductance (SGaw). In this study, exposure to 1,000 µg/m³ of either type of sulfate resulted in decreased SGaw and decreased forced expiratory volume in one second. Utell *et al.* (1982) reported that in normal volunteers a single exposure of 0.45 mg/m³ for 4 hours resulted in increased bronchoconstriction 24 hours later.

Concomitant exposures to other pollutants in industrial areas, including SO₂, ozone, and metallic aerosols can add to or potentiate the irritancy of H₂SO₄ (Amdur, 1989). This is of particular concern for asthmatic individuals, who may be more sensitive than non-asthmatics to the irritant effects of H₂SO₄.

Amdur *et al.* (1952) demonstrated that the lowest exposure detected by odor, taste, or irritation was 1 mg/m³ H₂SO₄. The same experiment showed that a 30% increase in airway resistance in healthy individuals occurred following a 15-minute exposure to 0.35 mg/m³ H₂SO₄. Avol and associates (1979) found no significant effects on pulmonary function in groups of 6 normal or asthmatic volunteers exposed for 2 hours to 0.1 mg/m³ (NH₄)₂SO₄, 85 µg/m³ (NH₄)HSO₄, or 75 µg/m³ H₂SO₄. In contrast, adolescent asthmatics exposed to 0.068 mg/m³ H₂SO₄ for 40 minutes exhibited pulmonary changes as measured by a 6% decrease from pre-exposure control (Koenig *et al.*, 1989). Avol and associates (1990) were unable to reproduce this observation by Koenig *et al.* (1989) of statistically significant respiratory dysfunction in a group of young asthmatics exposed to H₂SO₄ aerosol at concentrations near 100 µg/m³ (30 min at rest and 10 min at moderate exercise).

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Normal and asthmatic subjects exposed for 2 hours to 0.075 mg/m³ ferric sulfate (0.055 mg/m³ SO₄²⁻) showed no significant decrements in pulmonary function tests when compared to average pre-exposure values (Kleinman *et al.*, 1981).

Predisposing Conditions for Sulfate Toxicity

Medical: The young may be more sensitive than adults to lethal effects, based on guinea pig LC₅₀ values (Amdur, 1952). Some asthmatics are more sensitive to pulmonary irritation produced by exposure to sulfuric acid.

Chemical: Exposure to ozone may increase the irritant effects of sulfate exposure (Amdur, 1989).

Other: Factors increasing the irritancy of sulfates include (1) adding steam to sulfuric acid mist; (2) high humidity in general; (3) large particle size (> 10 μm) (Sim and Pattle, 1957); and (4) concomitant exposure to other pollutants from automobile exhaust (SO₂, ozone, and metallic aerosols) (Amdur, 1989).

V. Acute Toxicity to Laboratory Animals

The LC₅₀ value for H₂SO₄ in young guinea pigs is 18 mg/m³ and in adult guinea pigs 50 mg/m³ for an 8-hour exposure (Amdur, 1952). The LC₅₀ for H₂SO₄ in rats is 1,402 mg/m³ for a one-hour exposure (RTECS, 1993).

Sulfuric acid was more potent than either ammonium bisulfate or ferric sulfate in slowing particle clearance from the lungs of rats following a single 4-hour exposure to 3.5 mg/m³ (Phalen *et al.*, 1980).

Schlesinger *et al.* (1990) showed that daily one hour exposures for five days to 250 μg/m³ H₂SO₄ caused a decrease in prostaglandins E₂, F_{2α}, and thromboxane B₂ in lavage fluid from rabbit lungs. Similarly, a single 3-hour exposure to 75 μg/m³ H₂SO₄ resulted in decreased superoxide production and tumor necrosis factor in stimulated alveolar macrophages in rabbits (Schlesinger *et al.*, 1992). A single 3-hr exposure (300 μg/m³) to guinea pigs to fine (0.3 μm) diameter and ultrafine (0.04 μm) diameter H₂SO₄ caused an increase in lactate dehydrogenase, β-glucuronidase, and total protein in lung lavage fluid (Chen *et al.* 1992). Together, these results indicate localized compromises in macrophage function and development of airway responsiveness in the alveolar region of the lung.

VI. Reproductive or Developmental Toxicity

There are no studies that conclusively show reproductive or developmental toxicity linked to sulfate exposure.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 120 µg/m³

<i>Study</i>	Utell <i>et al.</i> (1983)
<i>Study population</i>	17 human asthmatics
<i>Exposure method</i>	inhalation of 100, 450 or 1000 µg/m ³ H ₂ SO ₄ aerosol
<i>Critical effects</i>	decrease in airway conductance
<i>LOAEL</i>	1,000 µg/m ³ sulfate as H ₂ SO ₄
<i>NOAEL</i>	450 µg/m ³ sulfate
<i>Exposure duration</i>	16 min
<i>Extrapolated 1 hour concentration</i>	120 µg/m ³ (C ⁿ * T = K, where n =1)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	120 µg/m ³

The 24-hour California ambient air standard for sulfates is 25 µg/m³. From the supporting document (CARB Staff Report, May 4, 1976), this number was derived mainly from a study by Amdur *et al.* (1952) and five CHESS (Community Health and Surveillance System) studies (dated 1972 and discussed by Shy *et al.*, 1973 and USEPA, 1974). According to the document, the CAAQS for sulfate of 25 µg/m³, 24-hour average, is approximately midway between a lower bound of 10 µg/m³ for 24 hours recommended from the CHESS data and the upper bound of 33 µg/m³ for 24 hours extrapolated from industrial experience with sulfuric acid mist. In Amdur's study the human exposure was for 15 minutes and it is unclear how the number derived remained unchanged after extrapolation to the 24-hour average. Due to this uncertainty, the CAAQS for sulfate did not appear appropriate for derivation of the 1-hour REL. However, if the standard of 25 µg/m³ for 24 hours is time extrapolated to 1 hour using Cⁿ x t = K, where n=2, a one hour value of 120 µg/m³ is also obtained. Thus the REL is 120 µg/m³.

The 24-hour California ambient standard for particulate matter with a diameter at or below 10 microns (PM₁₀) is 50 µg/m³.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database. (NIOSH (1995) lists an IDLH of 15 mg/m³ for sulfuric acid.)

Determination of Acute Toxicity Exposure Levels
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ACUTE TOXICITY SUMMARY

SULFUR DIOXIDE

(sulfur oxide; sulfurous anhydride; sulfurous oxide)

CAS Registry Number: 7446-09-5

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	660 $\mu\text{g}/\text{m}^3$
<i>Critical effect(s)</i>	impairment of airway function, especially in asthmatics
<i>Hazard Index target(s)</i>	Respiratory system

II. Physical and Chemical Properties (from HSDB, 1994 except as noted)

<i>Molecular formula</i>	SO ₂
<i>Molecular weight</i>	64.1 g/mol
<i>Specific gravity</i>	2.927 @ 20°C
<i>Boiling point</i>	-10°C
<i>Melting point</i>	-72.7°C
<i>Vapor pressure</i>	2432 mm Hg @ 20°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in water, ethanol, chloroform, ether, acetic acid
<i>Odor threshold</i>	0.62 - 1.2 ppm (Ryazanov, 1961)
<i>Odor description</i>	pungent, irritating odor
<i>Metabolites</i>	sulfate (SO ₄ ²⁻) salts
<i>Description</i>	colorless vapor
<i>Conversion factor</i>	1 ppm = 2.62 mg/m ³ @ 25°C

III. Major Uses or Sources

Sulfur dioxide is a product of combustion from coal and other fuel burning. In addition, there are many natural sources of atmospheric SO₂, including volcanoes and marine and terrestrial biogenic emissions (CARB, 1983). The decay of biologic materials containing sulfur results in the release of reduced sulfur compounds which are oxidized to SO₂ and other sulfur oxides (CARB, 1983). Anthropogenic sources of sulfur dioxide in ambient air include oil refineries, power plants and automobiles.

IV. Acute Toxicity to Humans

A thorough review of the scientific and epidemiological literature regarding the acute toxicity of sulfur dioxide (SO₂) to animals and humans can be found in the Recommendation for the one-hour Ambient Air Quality Standard for sulfur dioxide (OEHHA, 1994). Several of the most sensitive studies considered in the development of the California Ambient Air Quality Standard (CARB, 1983) for SO₂ are described below.

Increased airway resistance (S_{Raw}) in asthmatics following exposure to SO₂ has been frequently reported. Horstman *et al.* (1986) exposed 27 adults with mild asthma to 0, 0.25, 0.5, 1.0, and 2.0 ppm (0, 0.66, 1.31, 2.62, and 5.24 mg/m³) SO₂ for 10 minutes of moderate exercise. The exposure concentrations required for a 100% increase in S_{Raw} varied considerably in the study group, from less than 0.5 ppm (1.31 mg/m³) to greater than 2.0 ppm (5.24 mg/m³). The median concentration to which these subjects responded with a 100% increase in S_{Raw} was 0.75 ppm (1.97 mg/m³).

Linn *et al.* (1983) reported that moderate to severe asthmatics with a ventilation rate of approximately 48 L/minute exhibited increased S_{Raw} of 120% when exposed to 0.4 ppm (1.05 mg/m³) SO₂ for 5 minutes.

A study on the acute effects of SO₂ on S_{Raw} was conducted by Linn *et al.* (1987). Included in this study were mild, moderate, and severe asthmatics, atopic individuals, and normal subjects. These subjects were exposed to 0, 0.2, 0.4, or 0.6 ppm (0, 0.52, 1.05, or 2.1 mg/m³) SO₂ for 1 hour. Analysis of the Linn data by OEHHA scientists showed that statistically significant increases in S_{Raw} and respiratory symptoms were present in atopic individuals exposed to 0.6 ppm for 15-55 minutes, and in moderate to severe asthmatic individuals at 0.4 ppm after 55 minutes. Mild asthmatics were the only group that showed a significant increase in S_{Raw} and respiratory symptoms at 0.2 ppm. OEHHA staff also analyzed data from the most sensitive 30 percent of the subjects studied by Linn *et al.* (1987), and found that asthmatics, atopics, and normal subjects all exhibited statistically significantly increased S_{Raw} after exposure to 0.2 ppm. However, at this concentration, the changes in S_{Raw} were not considered clinically significant, since they were not accompanied by respiratory symptoms. Of these groups, asthmatics were the most sensitive to the effects of SO₂ on S_{Raw}.

Male volunteers with mild asthma were exposed to 0.0, 0.25, 0.5, or 1.0 ppm SO₂ for 75 minutes (Roger *et al.*, 1985). Each exposure included three 10 minute moderate treadmill exercise periods. Specific airway resistance was not significantly increased after exercise with 0.25 ppm SO₂ compared to clean air exposure, but was significantly increased with 0.5 and 1.0 ppm SO₂.

A study by Bethel *et al.* (1985) showed that asthmatics exposed for 15 minutes to 0.25 ppm SO₂ had significantly increased S_{Raw}. However, exposure in this study was via mouthpiece and may have resulted in a greater dose than similar concentrations in chamber exposures. Furthermore, the results of Bethel *et al.* could not be reproduced at higher exposures and workloads.

Fourteen healthy non-smokers (7 men and 7 women), between 20 and 46 years old, were exposed for 30 minutes to filtered air while free breathing and to 2.0 ppm SO₂ with either free breathing,

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

forced oral, or forced nasal breathing with continuous exercise (Bedi and Horvath, 1989). Lack of changes in pulmonary function tests including airway resistance indicated that 2.0 ppm SO₂ did not adversely affect normal subjects.

Predisposing Conditions for Sulfur Dioxide Toxicity

Medical: Asthmatics are more sensitive to the irritant effects of SO₂ than non-asthmatics, especially when exercising or when in cold, dry air (Koenig *et al.*, 1982; Bethel *et al.*, 1984). Some allergic or atopic individuals may also be more sensitive to SO₂ irritation (Linn *et al.*, 1987).

Chemical: Co-exposures to other irritants such as sulfuric acid, nitrogen dioxide, and ozone may potentiate the irritant effects of SO₂ on pulmonary function in asthmatics (OEHHA, 1994). In animals, co-exposure to ozone has been shown to increase the irritancy of SO₂ and to increase airway responsiveness (Amdur *et al.*, 1978).

V. Acute Toxicity to Laboratory Animals

Due to the abundance of clinical data collected using human asthmatics, animal data were not used as the basis for the 1-hour Ambient Air Quality Standard for SO₂.

VI. Reproductive or Developmental Toxicity

Reports of reproductive effects in the human workplace have involved mixed exposures, and are not definitive. Some data in rats indicate that SO₂ affects the estrous cycle, increases the incidence of fetal resorptions, and impairs fetal development at concentrations as low as 4.97 mg/m³ (Reprotext, 1993).

VII. Derivation of Acute Toxicity Exposure Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 660 µg/m³

<i>Study</i>	multiple studies as cited in OEHHA, 1994
<i>Study population</i>	multiple studies of healthy, asthmatic and atopic volunteers
<i>Exposure method</i>	controlled inhalation exposures with or without exercise
<i>Critical effects</i>	adverse respiratory effects, bronchoconstriction
<i>LOAEL</i>	0.4 ppm for 5 minutes (Linn <i>et al.</i> , 1983) 0.4 ppm for 60 minutes (Linn <i>et al.</i> , 1987) 0.5 ppm for 75 minutes (Roger <i>et al.</i> , 1985)
<i>NOAEL</i>	0.25 ppm for 75 minutes (Roger <i>et al.</i> , 1985)
<i>Exposure duration</i>	0.2 ppm for 60 minutes (Linn <i>et al.</i> , 1987) varied

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>Equivalent 1 hour concentration</i>	0.25 ppm (consensus value from multiple studies)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	0.25 ppm (250 ppb; 0.66 mg/m ³ ; 660 µg/m ³) (California Ambient Air Quality Standard)

After reviewing several studies on controlled human data on acute exposures of normal, asthmatic, and atopic individuals to low concentrations of SO₂ (0.25 - 2.0 ppm), OEHHA staff concluded that exposure to 0.25 ppm, the California Ambient Air Quality Standard (CAAQS) for SO₂, would not result in discomforting respiratory effects in sensitive individuals for a period of 1-hour. The CAAQS for SO₂ aims to protect sensitive individuals (i.e., exercising asthmatics) from lower respiratory effects of acute exposure. The procedures used to derive the CAAQS were not identical to those in this report. However, based on a thorough review of the literature, OEHHA staff concluded that an exposure concentration of 0.25 ppm SO₂ for 1 hour is comparable to a NOAEL in sensitive individuals. This level is felt to protect asthmatic individuals because adverse effects are consistently observed only at higher concentrations under conditions of moderate exercise (ventilation rates of > 40 L/minute) and there is an inconsistency in response to SO₂ exposure at lower concentrations.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Asthmatics exposed via a mouthpiece to 5 ppm SO₂ for 10 minutes required bronchodilator therapy because of bronchoconstriction resulting from the exposure (Sheppard *et al.*, 1980). The Sheppard *et al.* (1980) study was a mouthpiece study, and therefore most likely resulted in a greater inhaled dose of SO₂ than in chamber studies. The AIHA (1992) developed an ERPG-2 of 3 ppm (7.86 mg/m³) and stated that exposures above 3 ppm are likely to cause bronchoconstriction of varying severity in a significant portion of the population. This could impair the ability to take protective action. There is therefore no margin of safety included for protection of these individuals from severe effects, a serious shortcoming.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Many reports show that asthmatics exposed to SO₂ at low concentrations (0.37-5 ppm) exhibit bronchoconstriction (Amdur, 1974; Bell *et al.*, 1977; Bethel *et al.*, 1983, 1984; Koenig *et al.*, 1980, 1982; Linn *et al.*, 1977, 1983, 1984; Sheppard *et al.*, 1980, 1981). In its selection of an ERPG-3 for SO₂ of 15 ppm (39.3 mg/m³), the AIHA (1992) acknowledges that the bronchoconstriction observed in asthmatics could be potentially life-threatening, but does not include specific information about the adoption of the 15 ppm value. The ERPG-3 is based on estimation of lethality in asthmatics exposed to SO₂ for 1-hour. Although the ERPG document

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

correctly considers asthmatics as a sensitive subpopulation for this level, the specific rationale used to develop a margin of safety for the ERPG-3 is not presented, a serious shortcoming.

NIOSH (1995) lists an IDLH for sulfur dioxide of 100 ppm. It is based on the statement by AIHA (1955) that 50 to 100 ppm is considered the maximum concentration for exposures of 0.5 to 1 hour (Henderson and Haggard, 1943).

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ACUTE TOXICOLOGY SUMMARY

SULFURIC ACID AND OLEUM

Molecular formula	Molecular weight	Synonyms	CAS Registry Number
H ₂ SO ₄	98.1	sulfuric acid; dithionic acid; pyrosulphuric acid	7664-93-9
SO ₃	80.07	sulfur trioxide	7446-71-9
H ₂ SO ₄ + SO ₃		oleum	8014-95-7

I. Acute Toxicity Exposure Levels (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	120 µg/m³
<i>Critical effect(s)</i>	small changes in airway function tests, especially in asthmatics
<i>Hazard Index target(s)</i>	Respiratory System

II. Physical and Chemical Properties (HSDB, 1994)

<i>Molecular formula</i>	H ₂ SO ₄ (sulfuric acid) H ₂ SO ₄ + SO ₃ (oleum)
<i>Molecular weight</i>	98.1 g/mol (sulfuric acid)
<i>Specific gravity</i>	1.84 (sulfuric acid) 1.91-1.97 @ 15°C (oleum)
<i>Boiling point</i>	315-388°C
<i>Melting point</i>	10.4°C
<i>Vapor pressure</i>	0.001 mm Hg @ 20°C
<i>Solubility</i>	soluble in water
<i>Odor threshold</i>	1 mg/m ³
<i>Metabolites</i>	SO ₄ ²⁻ , neutral sulfur
<i>Color</i>	colorless
<i>Conversion factor</i>	1 ppm = 4.08 mg/m ³

Description of oleum

Oleum is supersaturated anhydrous H₂SO₄ with varying concentrations of free sulfur trioxide (SO₃). Upon contact with atmospheric moisture, SO₃ is rapidly converted to H₂SO₄ mist. Exposure to sulfur trioxide is, therefore, equivalent to exposure to H₂SO₄.

III. Major Uses or Sources

Sulfuric acid is a strong acid used as an intermediate for linear alkylbenzene sulfonation surfactants used in dyes; in petroleum refining; for the nitration of explosives; in the manufacture

of nitrocellulose; in caprolactam manufacturing; and as a drying agent for chlorine and nitric acid.

IV. Acute Toxicity to Humans

The irritant properties of H₂SO₄ account for its acute as well as its chronic effects. Two properties of concentrated H₂SO₄, its acidity and its hygroscopic potential, make it particularly corrosive as compared to diluted H₂SO₄ to the skin, eyes and respiratory tract. In splash accidents involving H₂SO₄, the heat, liberated by dilution of the concentrated acid with water, can add thermal burn to the chemical injury caused by the acid itself. Sulfuric acid exposure results in irritation of the tracheobronchial tree, which leads to bronchoconstriction and altered lung function. Sim and Pattle (1957) reported that in healthy volunteers a range of exposures, from 2.9 to 39 mg/m³, resulted in coughing, bronchoconstriction, and rales. In this study, H₂SO₄ mists of 20.8 mg/m³ were nearly intolerable to the volunteers exposed for 30 minutes. Wet mists were also more potent inducers of irritation than dry mists at the same exposure levels.

Delayed effects of sulfuric acid exposure may be seen in some individuals. Utell *et al.* (1983) reported that in normal volunteers a single exposure to 0.45 mg/m³ for 4 hours resulted in increased bronchoconstriction 24 hours later. Concomitant exposures to other pollutants in industrial areas, including SO₂, ozone, and metallic aerosols, can add to, or potentiate the irritancy of H₂SO₄ (Amdur, 1989). This is of particular concern for asthmatic individuals, who may be more sensitive than non-asthmatics to the irritant effects of H₂SO₄. In human asthmatic subjects, exposure to 450 µg/m³ sulfuric acid for 16 minutes decreased airway conductance but the magnitude of the decrease was not clinically significant (Utell *et al.*, 1984).

Dental erosion has been reported in battery plant workers exposed chronically to sulfuric acid mist at 0.8 mg/m³ for several months (Malcolm and Paul, 1961). Dose-dependent dental erosion has also been described in workers exposed to an average concentration of 0.23 mg/m³ for at least 4 months (Gamble *et al.*, 1984).

A report of acute respiratory distress syndrome (ARDS) in a 23 year-old worker exposed to unknown high concentrations of sulfuric acid for over 30 minutes showed parenchymal opacities on roentgenogram and deficits in lung function that resolved within 6 weeks of treatment (Knapp *et al.*, 1991).

Predisposing Conditions for Sulfuric Acid Toxicity

Medical: The young may be more sensitive than adults to the lethal effects based on guinea pig LC₅₀ values (Amdur, 1952a). Asthmatics are more sensitive to the pulmonary irritation produced by exposure to sulfuric acid.

Chemical: Factors increasing the irritancy of sulfuric acid include: 1) adding steam to sulfuric acid mist; 2) high humidity in general; 3) large particle size (> 10 microns) (Sim and Pattle, 1957); and 4) concomitant exposure to other pollutants from automobile exhaust (SO₂, ozone, and metallic aerosols) (Amdur, 1989).

V. Acute Toxicity in Laboratory Animals

The LC₅₀ in young guinea pigs is 18 mg/m³ and in old guinea pigs is 50 mg/m³ for an 8-hour exposure (Amdur 1952a). The LC₅₀ in rats is 1,402 mg/m³ for a one-hour exposure (RTECS, 1994).

Schlesinger *et al.* (1990) showed that daily one hour exposures for five days to 250 µg/m³ H₂SO₄ caused a decrease in prostaglandins E₂, F_{2a}, and thromboxane B₂ in lavage fluid from rabbit lungs. Donkeys exposed to 102-106 µg/m³ H₂SO₄ for 1 hr/day, 5 days/wk, over 6 months developed significant impairment of normal bronchial clearance, with sustained effects for up to 3 months after cessation of treatment (Schlesinger *et al.*, 1978). Exposure of monkeys to 2.43-4.79 mg/m³ sulfuric acid for 78 weeks resulted in adverse histological changes in lung parenchymal tissue. In addition, decreased blood oxygenation was observed (Alarie *et al.*, 1973).

Five squirrel monkeys exposed to 2.6 mg/m³ sulfuric acid for 1 hour exhibited significant (11%) increases in total respiratory system resistance compared with 5 sham-exposed monkeys, although no overt clinical signs of coughing, wheezing, or blinking were observed (Kleinman and Hackney, 1978).

VI. Reproductive or Developmental Toxicity

There are no confirmed studies that conclusively show reproductive or developmental toxicity linked to sulfuric acid exposure.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 120 µg/m³ (30 ppb)

<i>Study</i>	Utell <i>et al.</i> , 1984
<i>Study population</i>	17 human asthmatics
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	small changes in airway function especially in asthmatics
<i>LOAEL</i>	1,000 µg/m ³
<i>NOAEL</i>	450 µg/m ³ (112 ppb)
<i>Exposure duration</i>	16 minutes
<i>Extrapolated 1 hour concentration</i>	120 µg/m ³ (C ¹ * 1 hr = 450 ¹ µg/m ³ * 16/60 hr)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	120 µg/m ³ (30 ppb)

Determination of Acute Toxicity Exposure Levels

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The lowest observed effect level (considered a NOAEL) for a 16-minute exposure resulting in decreased airway conductance in human asthmatic subjects was $450 \mu\text{g}/\text{m}^3$ (112 ppb) sulfuric acid. The REL of $120 \mu\text{g}/\text{m}^3$ for a 1-hour exposure was derived using the formula $C^n * T = K$, where $n = 1$. The 24-hour California ambient air standard for sulfates is $25 \mu\text{g}/\text{m}^3$, and the 24-hour California ambient standard for particulate matter with a diameter at or below 10 microns (PM_{10}) is $50 \mu\text{g}/\text{m}^3$.

Level Protective Against Severe Adverse Effects

The National Research Council (NRC, 1986) derived a 60-minute EEGL (Emergency Exposure Guidance Level) of $1 \text{ mg}/\text{m}^3$ for sulfuric acid. Exposure of humans to $5 \text{ mg}/\text{m}^3 \text{ H}_2\text{SO}_4$ for 15 minutes was tolerable to the subjects. Monkeys, exposed to $4.8 \text{ mg}/\text{m}^3$ continuously over a 78 week period, showed some respiratory changes. Similar changes were seen in this study at a concentration of $2.4 \text{ mg}/\text{m}^3$, but were not included by NAS in the EEGL document. Adjusting these results for time of exposure yielded an acceptable human exposure of $1 \text{ mg}/\text{m}^3$ for 60 minutes. The AIHA (1989) ERPG-2 level of $10 \text{ mg}/\text{m}^3$ does not consider LC_{50} data in guinea pigs of $18 \text{ mg}/\text{m}^3$ (Amdur *et al.*, 1952a). Furthermore, the ERPG document relies heavily on older studies that are either unpublished or poorly presented (Sim and Pattle 1957). Thus, although the EEGL 60-minute value of $1 \text{ mg}/\text{m}^3$ did not include respiratory changes in monkeys exposed to $2.4 \text{ mg}/\text{m}^3$, this value is health protective based on a thorough review of the literature.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Exposure of healthy, human subjects for 30 minutes to $20.8 \text{ mg}/\text{m}^3 \text{ H}_2\text{SO}_4$ was almost intolerable, causing coughing, bronchoconstriction and rales. LC_{50} values in young guinea pigs are reported to be $18 \text{ mg}/\text{m}^3$, and $50 \text{ mg}/\text{m}^3$ for older guinea pigs (Amdur *et al.*, 1952a). Based on these results, the AIHA has set an ERPG-3 value for a 1 hour exposure of $30 \text{ mg}/\text{m}^3$ as protective against the lethal effects of H_2SO_4 . The ERPG-3 value may be inappropriately high based on the guinea pig 8-hour LC_{50} values (Amdur *et al.*, 1952a). Silbaugh *et al.* (1981) also reported 22% mortality of guinea pigs exposed to $24.3 \text{ mg}/\text{m}^3 \text{ H}_2\text{SO}_4$ for 35 minutes. Consequently, this level cannot be recommended as the level protective against life-threatening effects.

NIOSH (1995) lists a revised IDLH for sulfuric acid of $15 \text{ mg}/\text{m}^3$ based on acute inhalation toxicity data in humans (Amdur *et al.* 1952b) and animals (Amdur *et al.* 1952a; Treon *et al.* 1950). NIOSH states: "This may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations above $5 \text{ mg}/\text{m}^3$." This value would also not take into account sensitive human subpopulations.

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ACUTE TOXICITY SUMMARY

TOLUENE

(methyl benzene, methyl benzol, phenyl methane, toluol)

CAS Registry Number: 108-88-3

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **37,000 µg/m³**
Critical effect(s) headache, dizziness, slight eye and nose irritation
Hazard Index target(s) Nervous System; Eyes; Respiratory System;
Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Molecular formula</i>	C ₇ H ₈
<i>Molecular weight</i>	92.13
<i>Specific gravity</i>	0.861 @ 25°C (Low <i>et al</i> , 1988)
<i>Boiling point</i>	111°C
<i>Melting point</i>	-95°C
<i>Vapor pressure</i>	28.1 mm Hg @ 25°C (USEPA, 1984)
<i>Flashpoint</i>	4° C, closed cup
<i>Explosive limits</i>	upper = 7% lower = 1.27%
<i>Solubility</i>	miscible in organic solvents
<i>Odor threshold</i>	1.6 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sour, burnt (AIHA, 1989)
<i>Metabolites</i>	hippuric acid
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 3.75 mg/m ³ @ 25°C

III. Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations. It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitors, adhesives, and solvent based cleaning agents. Toluene is also used in printing operations, leather tanning, and chemical processes. Benzene and other polycyclic aromatic hydrocarbons (PAHs) are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene exposure.

IV. Acute Toxicity to Humans

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Dysfunction of the central nervous system and narcosis are the major effects of acute exposure to toluene (ATSDR, 1989). Irritation of the skin, eye, and respiratory tract can also result. Inhalational abuse of toluene with high level exposure for long periods of time has produced progressive and irreversible changes in brain structure and function (Spencer and Schaumberg, 1985).

Two separate workplace incidents involving acute inhalation exposure to toluene in several workers resulted in effects of euphoria, drunkenness, dizziness, nausea, confusion, incoordination, drowsiness, and loss of consciousness (Longley *et al.*, 1967). The toluene concentrations were estimated at 10,000 to 30,000 ppm (40,000 to 110,000 mg/m³) although no actual measurements were made. No long-term follow-up of the exposed workers was conducted.

Reaction time and perceptual speed were studied in 12 young male subjects exposed by inhalation to toluene concentrations ranging from 100 to 700 ppm (400 to 3,000 mg/m³), each for a 20-minute interval (Gamberale and Hultengren, 1972). Statistically significant impaired reaction time was apparent following exposure to 300 ppm (1,000 mg/m³) toluene. A statistically significant impairment in perceptual speed was observed at 700 ppm toluene. No effects were observed at 100 ppm.

Two groups of middle aged workers, one with previous occupational exposure to solvents and one without, were exposed once to 100 ppm (400 mg/m³) of toluene for 6.5 hours (Baelum *et al.*, 1985). Fatigue, sleepiness, a feeling of intoxication, and eye, nose and throat irritation were reported. Decrements in manual dexterity, color discrimination, and accuracy in visual perception were also observed. Greater sensitivity to toluene was noted for those subjects with previous solvent exposure.

Nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 10 to 100 ppm (40 mg/m³ to 400 mg/m³) for 6 hours (Andersen *et al.*, 1983). Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 100 ppm. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 100 ppm. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 10 and 40 ppm.

A battery of neurobehavioral and performance tests was conducted among 42 young men and women exposed by inhalation for 7 hours to 0, 75, and 150 ppm (0, 280, and 560 mg/m³) toluene (Echeverria *et al.*, 1989). Statistically significant decrements in visual short term memory, visual perception, and psychomotor skills were observed at 150 ppm compared to control exposures. A dose-dependent increase in subjective symptoms of headache and eye irritation was also observed.

Wilson (1943) reported that workers exposed to concentrations of commercial toluene ranging from 50 to 200 ppm (200 to 750 mg/m³) for periods of 1 to 3 weeks experienced headaches,

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

lassitude, and loss of appetite. At 200 to 500 ppm (750 to 2,000 mg/m³), symptoms of nausea, bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss were also observed. Exposure to 500 to 1,500 ppm (2,000 to 5,600 mg/m³) resulted in palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time. Red blood cell counts were decreased and there were 2 cases of aplastic anemia. The hematologic effects were most likely caused by benzene impurities (ACGIH, 1986).

Three volunteer subjects exposed by inhalation to toluene concentrations ranging from 50 to 100 ppm (200 to 400 mg/m³), 8 hours per day, 2 times per week over 8 weeks experienced fatigue, drowsiness, and headaches (von Oettingen *et al.*, 1942). At 200 to 800 ppm (750 to 3,000 mg/m³), symptoms of muscular weakness, confusion, impaired coordination, paresthesia, and nausea were also reported. After exposure to 800 ppm, all 3 subjects reported considerable after-effects (severe nervousness, muscular fatigue, and insomnia) lasting several days.

Predisposing Conditions for Toluene Toxicity

Medical: Since toluene is metabolized by the liver, persons with liver disease may be sensitive to its acute effects (ATSDR, 1993). Persons with neurologic disease may also be at increased risk for adverse effects resulting from exposure to toluene.

Chemical: Because salicylates and alcohol competitively inhibit toluene metabolism, concurrent use of these substances may increase susceptibility to toluene toxicity (ATSDR, 1993).

V. Acute Toxicity to Laboratory Animals

The 1-hour LC₅₀ for toluene in the rat is 26,700 ppm (100,000 mg/m³) (Pryor *et al.*, 1978). The 6-hour LC₅₀s in rats and mice are 4,618 ppm (17,320 mg/m³) and 6,949 ppm (26,060 mg/m³), respectively (Bonnet *et al.*, 1982). The 8-hour LC₅₀ is 5,300 ppm (19,900 mg/m³) in the mouse (Svirbely *et al.*, 1943).

Attention deficits and impairment of visual-motor abilities were observed in 6 macaque monkeys exposed by inhalation for 50 minutes to 2,000-4,500 ppm (7,500-17,000 mg/m³) toluene (Taylor and Evans, 1985). Expired carbon dioxide increased in a dose-dependent manner from 100 to 3,000 ppm (400 to 11,000 mg/m³). The investigators stated that changes in expired carbon dioxide may provide evidence of combined behavioral, respiratory, sensory, and metabolic effects.

Dose-dependent decreases in behavioral performance and central nervous system depression were observed in mice and rats exposed by inhalation to toluene at concentrations ranging from 2,600 to 12,000 ppm (9,800 to 45,000 mg/m³) for up to 3 hours (Bruckner and Peterson, 1981). Younger animals were more susceptible to toluene toxicity and mice were more sensitive than rats of the same age.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Kishi *et al.* (1988) used the shock avoidance response test to study behavioral effects in rats. Inhalation exposure to 125 ppm (469 mg/m³) toluene for 20 minutes resulted in a considerable decrease in the effective avoidance response rate.

Hearing loss was observed in rats after exposure to 1,000 ppm (4,000 mg/m³) toluene, 14 hours per day for 2 weeks (Pryor *et al.*, 1984).

VI. Reproductive or Developmental Effects

Toluene is listed under the California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. Most of the information concerning the adverse developmental effects of toluene in humans comes from case reports among children of deliberate toluene “sniffers.” Children whose mothers had inhaled large quantities of toluene during pregnancy were found to have microencephaly, facial and limb abnormalities, attention deficits, hyperactivity, developmental delay with greater language impairment, and growth retardation (Hersch *et al.*, 1985; Hersch, 1989). Multiple solvent and/or other substance abuse may have contributed to the observed abnormalities. Growth retardation, craniofacial abnormalities, and hyperchloremic acidosis were observed in the children of women with severe renal tubular acidosis induced by chronic paint sniffing (Goodwin, 1988). Preterm delivery, perinatal death, and growth retardation were significantly increased among 21 newborns exposed to toluene as a result of maternal inhalation abuse (Wilkins-Haug and Gabow, 1991). A case-referent study of women occupationally exposed to organic solvents, including toluene, reported increased incidences of urogenital, gastrointestinal, and cardiac anomalies in their children (McDonald *et al.*, 1987). Although toluene was considered to be the most likely teratogenic agent, concurrent exposures to other developmental toxicants make this conclusion difficult to support.

There are several animal studies of varying quality on the reproductive and developmental toxicity of toluene. A complete review of the developmental toxicology of toluene is available (Donald *et al.*, 1991). Selected studies are summarized below.

Shigeta *et al.* (1982) reported statistically significant increases in the number of fetal resorptions observed in the offspring of mice exposed by inhalation to 100 ppm (400 mg/m³) toluene for 6 hours per day on days 1-17 of gestation. Exposure at 1,000 ppm (4,000 mg/m³) resulted in a statistically significant increase in the incidence of extra ribs.

A statistically insignificant increased incidence of extra ribs was observed in rats exposed by inhalation to 1,000 mg/m³ toluene for 24 hours per day on days 7-14 of gestation (Tatrai *et al.*, 1980). Fused sternbrae and extra ribs were observed in rats exposed to 400 ppm (1,500 mg/m³) toluene for 24 hours per day on days 9-14 of gestation (Hudak and Ungvary, 1978). Skeletal retardation was observed in rats exposed to 266 ppm (1,000 mg/m³) toluene for 8 hours per day on days 1-21 of gestation and to 400 ppm (1,500 mg/m³) 24 hours per day on days 1-8. This same group exposed mice to 400 ppm (1,500 mg/m³) or to 133 ppm (500 mg/m³) toluene for 24 hours per day on days 6-13 of gestation. All dams died at the higher dose and a statistically significant decrease in fetal weight was observed at the lower dose.

Skeletal retardations were observed in the offspring of pregnant rabbits exposed by inhalation to concentrations of toluene ranging from 30 to 300 ppm (100 to 1,000 mg/m³), 6 hours per day on days 6-18 of gestation (Klimisch *et al.*, 1992). These results were not dose-dependent and were not reproduced in two additional groups of rabbits exposed to 100 and 500 ppm (400 and 2,000 mg/m³) toluene.

A statistically significant increase in the number of animals showing a 13/13 rib profile (which is considered normal) was observed in mice exposed to 400 ppm (1,500 mg/m³) toluene, 7 hours per day on days 7-16 of gestation (Courtney *et al.*, 1986). An increased number of resorptions was observed in mice exposed to 400 ppm toluene on days 6-15 of gestation (Gleich and Hofman, 1983); the daily exposure duration was not specified.

These preceding animal studies support the association between toluene exposure and effects on somatic development of the fetus. However, the value of these studies is limited by issues such as unknown or unconventional exposure durations, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and purity of toluene used (Donald *et al.*, 1991).

The best available study relating toluene exposure and retardation of somatic development is one in which adult rats of 2 generations were exposed for 6 hours per day to 0, 100, 500 or 2,000 ppm (0, 375, 1,875, or 7,500 mg/m³) toluene during an 80-day pre-mating period and a 15 day mating period (IRDC, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. Exposure at this level to the male parent only did not result in any adverse effects. The NOAEL for fetotoxic effects in this study was 500 ppm.

In a recent teratogenicity study by inhalation, Ono *et al.* (1995) exposed pregnant Sprague-Dawley rats to 600 or 2000 ppm toluene for 6 h/day from day 7 to day 17 of pregnancy. The control group inhaled "conditioned" clean air. Maternal exposure to 2000 ppm caused significant toxic effects such as body weight suppression in dams and offspring, high fetal mortality, and embryonic growth retardation. However, no external, internal, or skeletal anomalies were observed in the fetuses of any treated group. In addition, there were no differences in the results of pre- and post-weaning behavioral tests of the offspring. No changes which could be related to toluene were apparent in the 600 ppm group. Thus 600 ppm is a NOAEL in this study.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 9.8 ppm (37,000 µg/m³)

<i>Study</i>	Andersen <i>et al.</i> , 1983
<i>Study population</i>	16 young, healthy males

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>Exposure method</i>	inhalation
<i>Critical effects</i>	impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication and slight eye and nose irritation
<i>LOAEL</i>	100 ppm
<i>NOAEL</i>	40 ppm
<i>Exposure duration</i>	6 hours
<i>Extrapolated 1 hour concentration</i>	98 ppm ($40^2 \text{ ppm} \cdot 6 \text{ h} = C^2 \cdot 1 \text{ h}$) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	9.8 ppm (37 mg/m ³ ; 37,000 µg/m ³)

Level Protective Against Severe Adverse Effects

In a 2-generation study, adult rats were exposed for 6 hours per day to 0, 100, 500, or 2,000 ppm (0, 375, 1875, or 7,500 mg/m³) toluene during an 80-day pre-mating period and a 15 day mating period (International Research and Development Corporation, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weight of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. The NOAEL for fetotoxic effects in this study was 500 ppm. The NOAEL reported in the study, a chronic exposure study, was in the same concentration range as the LOAELs reported in other acute exposure studies addressing reproductive and developmental toxicity, summarized above. However, because the IRDC study was judged to be methodologically the most sound of all the studies considered for this endpoint (Donald *et al.*, 1991), it was chosen as the basis for the severe adverse effect level. An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability. The 6-hour exposure was extrapolated to 1 hour using the formula $C^n \cdot T = K$ where $n = 2$. This yields a 1-hour level protective against severe adverse effects of 12.3 ppm (46 mg/m³).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH for toluene of 500 ppm. According to NIOSH, “It has been reported that extreme fatigue, mental confusion, exhilaration, nausea, headache and dizziness resulted from exposures to 600 ppm by the end of 3 hours [von Oettingen *et al.* 1942]. In addition, the following observations have been made: some workers will tolerate concentrations ranging up to 200 ppm for 6 to 8 hours daily with no demonstrable ill effects; 200 to 500 ppm for 6 to 8 hours will cause tiredness and lassitude in most workers; and concentrations over 500 ppm for 1 to 3 hours are definitely dangerous and will cause symptoms attributable to depression of the central nervous system and the bone marrow [Wilson 1943]. It has also been reported that

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

exposure to concentrations greater than 4,000 ppm for more than 5 minutes might limit self rescue ability [ANSI 1973]. After 20 minutes, exposures to concentrations at 300, 500, or 700 ppm resulted in significant increases in reaction times; a significant decrease in perceptual speed resulted after a 20-minute exposure to 700 ppm [Gamberale and Hultengren 1972]. The revised IDLH for toluene is 500 ppm based on acute inhalation toxicity data in humans [Gamberale and Hultengren 1972; von Oettingen *et al.* 1942; Wilson 1943].” Based on its documentation, the IDLH of 500 ppm, designed for a 30 minute exposure, does not appear to be low enough to protect the general public, especially sensitive individuals, from life-threatening effects for 1 hour. Therefore, no recommendation for a level protective against life-threatening effects is made at this time.

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ACUTE TOXICITY SUMMARY

TRIETHYLAMINE

(diethylaminoethane; ethanamine; N,N-diethylethanamine)

CAS Registry Number: 121-44-8

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **2,800 µg/m³**
Critical effect(s) visual disturbances and ocular irritation in
healthy human volunteers
Hazard Index target(s) Nervous System; Eyes

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

<i>Molecular formula</i>	C ₆ H ₁₅ N
<i>Molecular weight</i>	101.9 g/mol
<i>Description</i>	colorless liquid
<i>Specific gravity</i>	0.726 @ 25°C
<i>Boiling point</i>	89.3°C
<i>Melting point</i>	-115°C
<i>Vapor pressure</i>	400 mm Hg @ 31.5°C
<i>Flashpoint</i>	-6.7°C
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in water above 18.7°C; very soluble in acetone, benzene and chloroform
<i>Odor threshold</i>	0.36 - 1.12 mg/m ³
<i>Odor description</i>	fishy odor
<i>Metabolites</i>	acetaldehyde, ammonia and urea
<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).

IV. Acute Toxicity to Humans

Vapors of TEA may cause irritation of the mucous membranes resulting in lacrimation, conjunctivitis, corneal edema, cough and respiratory distress (Albrecht and Stephenson, 1988).

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Headache, nausea, and faintness may also be observed following TEA exposure (Albrecht and Stephenson, 1988).

Two volunteers exposed to 4.35 ppm (18 mg/m³) TEA for 8 hours, experienced visual disturbances (hazy vision and halo perception); corneal edema was observed in these individuals (Akesson *et al.*, 1985). The ocular effects were transient, and resolved within hours of the exposure. Similar symptoms were reported by workers exposed over an 11-week period to 2.90 ppm (12-13 mg/m³) TEA (Akesson *et al.*, 1986). However, eye examinations performed in these workers were normal, without signs of corneal edema.

Predisposing Conditions for Triethylamine Toxicity

Medical: Unknown

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

Lethality studies in several animal species are relatively consistent: (1) exposure to 1,000 ppm for 4 hours was lethal to 1 of 3 guinea pigs (Carpenter *et al.*, 1948), (2) exposure to 1,425 ppm for 2 hours was lethal to an unspecified percentage of mice (Izmerov *et al.*, 1982); and (3) exposure to 1,000 ppm for 4 hours was lethal to 1 of 6 rats (Smyth *et al.*, 1951). The acute oral LD₅₀ is 460 and 546 mg TEA/kg in rats and mice, respectively (RTECS, 1993).

No significant gross or histological changes were observed in male and female rats exposed for 6 hours/day, 5 days/week for 28 weeks to TEA concentrations up to 247 ppm (1,023 mg/m³) (Lynch *et al.*, 1990). However, degeneration of heart muscle, hepatocellular necrosis, and pulmonary edema were observed in rabbits following exposure to 100 ppm (414 mg/m³) TEA for 7 hours/day, 5 days/week, for 6 weeks (Brieger and Hodes, 1951). Exposure of rabbits to 50 ppm (207 mg/m³) TEA for 5 days/week for 6 weeks caused corneal edema and erosions. Pulmonary irritation in these rabbits was evidenced by peribronchial lymphocyte infiltration and slight hepatic parenchymal degeneration.

VI. Reproductive or Developmental Toxicity

Triethylamine is highly teratogenic to chick embryos. The ED₅₀ for embryotoxicity and unspecified external malformations is 0.9 µmol/egg (Korhonen *et al.*, 1983).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 2,800 µg/m³

Study

Study population

Akesson *et al.*, 1985; Akesson *et al.*, 1988

two healthy human volunteers

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>Exposure method</i>	8 hour exposures to 10 or 20 mg/m ³ TEA
<i>Critical effects</i>	visual disturbances, eye irritation, and transient corneal edema
<i>LOAEL</i>	20 mg/m ³
<i>NOAEL</i>	10 mg/m ³
<i>Exposure duration</i>	8 hours
<i>Equivalent 1 hour concentration</i>	28 mg/m ³ ($C^2 * 1 \text{ hr} = [10 \text{ mg/m}^3]^2 * 8 \text{ hrs}$)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	2.8 mg/m ³ (2,800 µg/m ³ ; 0.68 ppm; 680 ppb)

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) has developed a 30-minute IDLH value of 200 ppm (830 mg/m³). The value is based on three animal lethality studies: (1) a 4 hour LC₃₃ of 1000 ppm for guinea pigs (Carpenter *et al.*, 1948), (2) a 2 hour LC₁₀ of 1425 ppm for mice (Izmerov *et al.*, 1982); and (3) a 4 hour LC₃₃ of 1000 ppm for rats (Smyth *et al.*, 1951). Using duration extrapolation to 30 minutes and a ten-fold uncertainty factor, the three data sets yielded values of 200 to 228 ppm.

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ACUTE TOXICITY SUMMARY

VANADIUM PENTOXIDE

(divanadium pentoxide, vanadic anhydride, vanadium oxide)

CAS Registry Number: 1314-62-1

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	30 µg/m³
<i>Critical effect(s)</i>	coughing, increased mucus production in healthy human volunteers
<i>Hazard Index target(s)</i>	Respiratory System; Eyes

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	V ₂ O ₅
<i>Molecular weight</i>	181.88 g/mol
<i>Specific gravity</i>	3.357 @ 18°C
<i>Boiling point</i>	1750°C
<i>Melting point</i>	690°C
<i>Vapor pressure</i>	0 mm Hg @ 20°C
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	soluble in acetone, concentrated acid and alkali; slightly soluble in water; insoluble in alcohol
<i>Odor threshold</i>	not applicable
<i>Metabolites</i>	none reported (Friberg <i>et al.</i> , 1986)
<i>Description</i>	yellow to rust-brown solid (ACGIH, 1986)
<i>Conversion factor</i>	not applicable

III. Major Uses or Sources

Vanadium pentoxide (V₂O₅) is used as a catalyst in oxidation reactions in the production of sulfuric acid and plastics (Friberg *et al.*, 1986). It is also used as a mordant in dyeing, and as a component of photographic developer (Sax, 1984). In the manufacture of glass, it is used as a depolarizer and inhibitor of UV light. V₂O₅ is also released by the combustion of fossil fuels which contain small amounts of vanadium (NAS, 1974).

IV. Acute Toxicity to Humans

Inhalation of V₂O₅ fumes, released during the production of V₂O₅ and during boiler cleaning, may result in irritation of the eyes and respiratory tract and in bronchospasm (Friberg *et al.*, 1986). The onset of symptoms occurs 1-6 days after exposure. Subsequent exposures to V₂O₅

Determination of Acute Toxicity Exposure Levels

Scientific Review Panel Draft - Do not cite or quote.

may result in increased severity of symptoms, most likely a result of sensitization (Zenz *et al.*, 1962). The eye irritation threshold is reported to be 0.5 mg/m³ (Reprotex, 1994). The respiratory irritation threshold is reported to be below that of ocular irritation (Grant, 1986).

High level acute exposures may result in CNS effects including paralysis, respiratory depression, convulsions, and death (Reprotex, 1994).

Workers exposed to 0.1-0.3 mg/m³ V₂O₅ for a minimum of 6 months reported symptoms of eye, nose, and throat irritation and exhibited signs of pharyngeal infection, green tongue and wheezing or rales (Lewis, 1959).

Predisposing Conditions for Vanadium Pentoxide Toxicity

Medical: Persons with skin, eye, or respiratory conditions such as chronic bronchitis or asthma may be more sensitive to the toxic effects of V₂O₅ (Reprotex, 1994).

Chemical: Persons exposed simultaneously to phthalic anhydride and V₂O₅ may be at greater risk for exacerbation of asthma. Persons exposed to other vanadium compounds may be more sensitive to the effects of V₂O₅ exposure (Reprotex, 1994).

V. Acute Toxicity to Laboratory Animals

Exposure to V₂O₅ at a concentration of 500 mg/m³ for 23 minutes was found to be lethal in cats (Heimberger, 1929). Gastroenteritis, pneumonitis, and pulmonary edema were observed at autopsy. An LC_{LO} of 205 mg/m³ V₂O₅ for a 7-hour exposure was reported for rabbits (Sjoberg, 1950). Autopsy results revealed marked tracheitis, bronchopneumonia, and pulmonary edema. In this same study, rabbits exposed to 20-40 mg/m³ V₂O₅ for 1 hour per day for "several months" (exact duration not specified) exhibited chronic rhinitis and tracheitis, emphysema and patches of lung atelectasis with bronchopneumonia.

Sixteen adult, male cynomolgus monkeys were acutely exposed by whole-body inhalation of V₂O₅ dust (0.5 mg or 5.0 mg/m³) at 1 week intervals (Knecht *et al.*, 1985). Pulmonary function tests were performed one day after each inhalation exposure, and inflammation was studied by cytologic analysis of lower respiratory tract cells by bronchoalveolar lavage (BAL). Pre-exposure comparisons were used in place of controls. Reduction in air-flow in central and peripheral airways was noted without any change in parenchymal function. V₂O₅ dust exposures led to a significant increase in the total cell counts recovered from the lungs by BAL, including very large increases in absolute number and relative percentage of polymorphonuclear leukocytes (PMN).

Rats (200-250 g) were intratracheally administered vanadium compounds or vehicle (as a control) (Pierce *et al.*, 1996). The soluble vanadium compounds NaVO₃ and VOSO₄ induced rapid and intense pulmonary inflammation and inflammatory cytokine mRNA expression while the less soluble V₂O₅ was much less potent. Significant neutrophil influx was noted 24 hours after V₂O₅ exposure and persisted for several days. Analysis of lavage fluid, BAL cells, and lung

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

suggested rapid clearance of the V₂O₅ from the lung surface and accumulation in BAL cells and lung tissue.

VI. Reproductive or Developmental Toxicity

No studies of reproductive toxicity in humans were available (Reprotext, 1994).

Pregnant mice injected with a total dose of 28 µg V₂O₅ (delivered as 0.15 ml of a 1.0 mM V₂O₅ solution) on the eighth day of gestation exhibited a significant increase in number of fetuses with delayed skeletal ossification as compared to controls (Wide, 1984). Additionally, six of the exposed fetuses had “broken spinal cords”.

Pregnant Wistar rats were administered V₂O₅ by intraperitoneal injections on days 6-15 (3 mg/kg/day) or 9-12 (5 mg/kg/day) of gestation (Zhang *et al.*, 1993a). Single doses (5 mg/kg/day) were also given on days 9, 10, or 11. Decreased maternal weight gain was noted. Effects observed included decreased weight gain, increased fetal mortality, decreased fetal weight, delayed bone ossification, subcutaneous hemorrhage, and dilation of lateral ventricles and renal pelvis. The greatest effects were noted from exposures on day 10. In a second study, pregnant Wistar rats were administered 0.33, 1, or 3 mg/kg-day over days 6-15 of gestation (Zhang *et al.*, 1993b). Adverse effects similar to that reported in the companion paper (Zhang *et al.*, 1993a) were noted in the two higher dose groups but not in the low dose group.

Effects of vanadium pentoxide treatment on male mouse reproductive function were investigated (Altamirano-Lozano *et al.*, 1996). Sperm count, motility, and morphology were adversely affected, and decreased fertility rate was reported.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 30 µg/m³

<i>Study</i>	Zenz and Berg, 1967
<i>Study population</i>	two healthy human volunteers
<i>Exposure method</i>	8 hour exposures to 0.1 mg/m ³ V ₂ O ₅
<i>Critical effects</i>	subjective reports of increased respiratory mucus production that was cleared by coughing.
<i>LOAEL</i>	0.25 mg/m ³ V ₂ O ₅
<i>NOAEL/LOEL</i>	0.1 mg/m ³ V ₂ O ₅
<i>Exposure duration</i>	8 hours
<i>Equivalent 1 hour concentration</i>	0.3 mg/m ³ (C ² * 1 hr = [0.1 mg/m ³] ² * 8 hrs)
<i>LOAEL uncertainty factor</i>	1 (effect observed was not adverse)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	0.03 mg/m ³ (30 µg/m ³)

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

A NIOSH-IDLH of 35 mg/m³ has been presented, but the method for deriving this value was not reported (NIOSH, 1995).

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ACUTE TOXICITY SUMMARY

VINYL CHLORIDE

(chloroethene; chloroethylene; vinyl chloride monomer; VC; VCM)

CAS Registry Number: 75-01-4

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	180,000 µg/m³
<i>Critical effect(s)</i>	mild headache and dryness of eyes and nose in healthy human volunteers
<i>Hazard Index target(s)</i>	Eyes; Nervous System; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	C ₂ H ₃ Cl
<i>Molecular weight</i>	62.5 g/mol
<i>Description</i>	colorless gas
<i>Specific gravity</i>	0.91 @ 20°C
<i>Boiling point</i>	-13°C
<i>Melting point</i>	-153.8°C
<i>Vapor pressure</i>	2660 mm Hg @ 25°C
<i>Flashpoint</i>	-77.8°C (open cup) (ACGIH, 1991)
<i>Explosive limits</i>	4 to 22% by volume in air (ACGIH, 1991)
<i>Solubility</i>	soluble in alcohol, ethyl ether, carbon tetrachloride, benzene
<i>Odor threshold</i>	3,000 ppm (Amoore and Hautala, 1983)
<i>Metabolites</i>	chloroethylene oxide, chloroacetic acid (Antweiler, 1976)
<i>Conversion factor</i>	1 ppm = 2.56 mg/m ³ @ 25°C

III. Major Uses or Sources

The chief use of vinyl chloride (VC) is in the production of polyvinyl chloride (PVC) resins used for plastic piping and conduit (IARC, 1979). It is also used in the manufacture of methyl chloroform. Vinyl chloride was used as a propellant until 1974 when this use was banned due to its demonstrated carcinogenicity. The main toxicological concern for vinyl chloride is from exposure to the monomer rather than the polymerized forms (i.e., PVC). Thermal decomposition of VC produces hydrogen chloride, carbon monoxide, and traces of phosgene (ACGIH, 1991).

IV. Acute Toxicity to Humans

The primary acute physiological effect of VC inhalation is CNS depression (Holmberg, 1984). Anesthesia may occur at high concentrations (7,000 - 10,000 ppm) for short durations in both animals and humans (Purchase *et al.*, 1987).

In two accidental human poisonings, workers became incapacitated when exposed to high concentrations of VC gas (Anon., 1953). Following removal from exposure, one of the workers experienced tightness of the chest, nausea, abdominal pain, and headache. Before VC's relationship with certain forms of cancer was established, workers in at least one polyvinyl chloride manufacturing facility reportedly inhaled VC fumes for its euphoric effect, sometimes to the point of unconsciousness (Klein, 1976). Danziger (1960) reported a worker death associated with exposure to high concentrations of VC. Autopsy revealed cyanosis, local burns of the conjunctiva and cornea, congestion of internal organs (especially lung and kidneys), and failure of blood to clot.

Suciu *et al.* (1975) reported that factory workers exposed to high concentrations of VC experienced euphoria, giddiness, somnolence and, in some cases, narcosis. Yearly average concentrations reported at this factory were between 98 and 2,298 mg/m³ (38 to 898 ppm).

Two male volunteers exposed to 25,000 ppm (64,000 mg/m³) VC for 3 minutes reported the odor as pleasant, but became dizzy and disoriented to the space and size of surrounding objects. The men also reported a burning sensation on the soles of their feet (Patty *et al.*, 1930).

In a controlled exposure, 6 adult volunteers (3 male, 3 female) were exposed to varying concentrations up to 20,000 ppm (51,200 mg/m³) of VC via an oral-nasal mask (Lester *et al.*, 1963). The 5 minute exposures took place twice each day and were separated by 6-hour periods for 3 successive days. No CNS effects were reported at 4,000 ppm (10,240 mg/m³). Exposure to 12,000 ppm (30,720 mg/m³) resulted in complaints of dizziness and reeling in 2 subjects. A clear dose-response was observed in this study, but statistical comparisons were not made by the authors.

In a chamber exposure, human volunteers were exposed to 59, 261, 491, or 493 ppm VC for up to 7.5 hours (excluding a 0.5-hour lunch period) (Baretta *et al.*, 1969). The subjects exposed to either 59 or 261 ppm VC reported no untoward effects. However, 2 of 7 subjects exposed to 491 ppm for 3.5 hours and 2 of 4 subjects exposed to 493 ppm for 7.5 hours reported mild headache and dryness of eyes and nose.

Vinyl chloride is known to cause "vinyl chloride disease" upon repeated exposures in workers. This multisystem disorder consists of Raynaud's phenomenon, acro-osteolysis, thrombocytopenia, splenomegaly, portal fibrosis, and hepatic and pulmonary dysfunction (IARC, 1979). This disease is likely an immune complex disorder from the adsorption of VC or a metabolite onto tissue proteins and is unlikely to occur following single acute exposure (Ward *et al.*, 1976).

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Differences in genetic susceptibility to hepatotoxicity of vinyl chloride have been described (Huang *et al.*, 1997). Vinyl chloride is metabolized by cytochrome P450 2E1 (CYP2E1) to form the toxic electrophilic metabolites, chloroethylene oxide and chloroacetaldehyde. These metabolites are detoxified by glutathione S-transferases (GSTs). A total of 251 workers from polyvinyl chloride plants were categorized into high or low exposure groups based on air exposure monitoring. Serum alanine aminotransferase (ALT) was used as an indicator of liver function. CYP2E1, GST theta, and GST mu were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) on peripheral white blood cell DNA. For the low vinyl chloride exposure group, positive GST theta (odds ratio = 3.8, 95% CI 1.2-14.5) but not CYP2E1 was associated with abnormal ALT levels in serum. For the high exposure group, a c2c2 CYP2E1 genotype was associated with an increased risk of abnormal ALT (odds ratio = 5.4, 95% CI 0.7-35.1), while a positive GST theta was associated with significantly reduced risk of abnormal ALT (odds ratio = 0.3, 95% CI 0.1-0.9).

Predisposing Conditions for Vinyl Chloride Toxicity

Medical: Inherited cytochrome P450 and glutathione S-transferase alleles may affect individual susceptibility (Huang *et al.*, 1997).

Chemical: Inducers of hepatic cytochrome-P450 enzymes, such as phenobarbital, potentiate the hepatotoxic effects of inhaled VC in rats (IARC, 1979; Jaeger *et al.*, 1974; Kappus *et al.*, 1975). Liver damage was measured by the release of alanine alpha-ketoglutarate, SGOT, and SGPT enzymes.

Ethanol co-administration with VC resulted in greater toxicity to pregnant mice, rats, or rabbits than exposure to VC alone (John *et al.*, 1981).

V. Acute Toxicity to Laboratory Animals

A lethality study was carried out by Prodan *et al.* (1975) in which mice, rats, guinea pigs, and rabbits were exposed to VC for 2 hours. Deaths were due to respiratory failure. Animals that were still alive at the end of exposure recovered quickly following removal from the gas. However, no post-exposure observation period was included in the study to investigate possible delayed mortality. Table 1 below shows the LC₅₀, MLE₀₅ (maximum likelihood estimate expected to produce a response rate of 5%), BC₀₅ and BC₀₁ (benchmark concentration at the 95% lower confidence interval of the 5% and 1% lethality level, respectively) as determined by log normal probit analysis (Crump, 1984; Crump and Howe, 1983).

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

Table 1. Animal lethality benchmark concentration estimates from Prodan *et al.* (1975) for 2-hour vinyl chloride exposure

Species	LC ₅₀ (mg/m ³ x 10 ³)	MLE ₀₅ (mg/m ³ x 10 ³)	BC ₀₅ (mg/m ³ x 10 ³)	BC ₀₁ (mg/m ³ x 10 ³)
mouse	299	253	246	227
rat ¹	(394)	(329)	(292)	(260)
guinea pig	591	527	453	410
rabbit	600	545	466	424

¹ Log normal probit analysis indicates the data points for rats resulted in an unacceptable fit.

Exposure of rats, mice and guinea pigs to 100,000 ppm VC (5 animals/species) resulted in increased motor activity at 10 minutes but progressed to muscular incoordination, unsteady gait and pronounced tremor in all species 15 minutes into the exposure (Mastromatteo *et al.*, 1960). Rats and mice became unconscious at 25 minutes while guinea pigs remained conscious during the entire 30 minute exposure period. At 200,000 and 300,000 ppm VC, rats and mice exhibited muscular incoordination at 2 and 1 minutes, respectively, following initiation of exposure. Guinea pigs were slightly more tolerant of the CNS depressant effects at these concentrations. Deaths in mice, rats and guinea pigs occurred at 200,000 ppm and above, 300,000 ppm and 400,000 ppm, respectively.

Exposure to 5,000 and 10,000 ppm vinyl chloride for 8 hours did not produce signs of CNS depression in guinea pigs (Patty *et al.*, 1930). Inhalation of 25,000 ppm (64,000 mg/m³) (sample size unspecified) resulted in motor ataxia and unsteadiness by 5 minutes, deep narcosis without convulsions or twitching by 90 minutes, and death by respiratory paralysis by 6 hours. Gross pathological changes included congestion and edema in the lungs, and hyperemia in the liver and kidneys. Guinea pigs exposed to 100,000 ppm developed complete loss of coordination and incomplete narcosis 2 minutes into exposure.

Lester *et al.* (1963) showed that rats exposed to 50,000 ppm (128,000 mg/m³) VC for 2 hours exhibited moderate intoxication with loss of the righting reflex. Loss of the corneal reflex was apparent following a 2-hour exposure to 100,000 ppm (256,000 mg/m³). Exposure of these rats to 100,000 ppm (256,000 mg/m³) for two 8-hour periods resulted in mortality from a “pneumonic process.”

Tatrai and Ungvary (1981) exposed mice, rats and rabbits to 1500 ppm VC for up to 24 hours. Rats and rabbits were unaffected, but 90% of mice died following 12 hours of exposure and 100% of mice died following 24 hours of exposure. Pathological examination of mice revealed hemorrhages and vasodilatation in the lungs, suggestive of pulmonary edema.

Dermal exposure of monkeys to gaseous VC indicated that absorption of VC across the intact skin is very limited (Hefner *et al.*, 1975).

Rhesus monkeys eliminate VC at approximately half the rate of mice and rats (Buchter *et al.*, 1980). Rodents may therefore be less sensitive than primates to systemic VC toxicity.

VI. Reproductive or Developmental Toxicity

In a review of the epidemiological data, Hemminki and Vineis (1985) concluded that there was inadequate evidence of increased teratogenesis in humans exposed to VC.

Animal studies have also failed to show significant association between VC exposure and teratogenesis. In rats, exposure to VC at a concentration of 1,500 ppm (3,840 mg/m³) for 24 hours/day during all three trimesters of pregnancy did not result in an increased incidence of birth defects (13-28 rats per group) (Ungvary *et al.*, 1978). Pharmacokinetic studies showed that VC crossed the placental barrier of these rats, and was present in fetal blood.

John *et al.* (1981) showed that exposure of pregnant mice, rats or rabbits to 500 ppm (1,280 mg/m³) VC for 7 hours/day during organogenesis did not result in teratogenicity or embryotoxicity. Inhalation of 2,500 ppm (6,400 mg/m³) caused slight ossification changes in the offspring and maternal mortality in the mice. Co-administration of 15% ethanol in drinking water resulted in maternal toxicity, but no elevation in fetal effects above that seen for ethanol exposure alone.

Male mice exposed to 30,000 ppm (76,800 mg/m³) VC 6 hours/day for 5 days were mated to control females, with no resultant increase in spontaneous abortions (Purchase, 1975). However, Bi *et al.* (1985) showed that inhalation exposure of male rats to 100 ppm VC for 6 hours/day, 6 days/week for 3 months resulted in significant damage to seminiferous tubules compared to controls ($p < 0.05$).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 180,000 µg/m³

<i>Study</i>	Baretta <i>et al.</i> , 1969
<i>Study population</i>	4-8 healthy human volunteers
<i>Exposure method</i>	(1) 7.5 hour exposures to 261 ppm VC (2) 3.5 hour exposures to 491 ppm VC (3) 7.5 hour exposures to 493 ppm VC
<i>Critical effects</i>	subjective reports of mild headaches and dryness of eyes and nose (groups 2 and 3); no effects reported by group 1
<i>LOAEL</i>	3.5 to 7.5 hour exposure to 491 or 493 ppm
<i>NOAEL</i>	7.5 hour exposure to 261 ppm
<i>Exposure duration</i>	7.5 hours
<i>Equivalent 1 hour concentration</i>	715 ppm ($C^2 * 1 \text{ hr} = [261 \text{ ppm}]^2 * 7.5 \text{ hrs}$)

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	72 ppm (180 mg/m ³ , 180,000 µg/m ³)

Level Protective Against Severe Adverse Effects

Exposure of guinea pigs to 10,000 ppm VC for 8 hours did not produce signs of CNS depression (Patty *et al.*, 1930). Exposure to 25,000 ppm produced motor ataxia and unsteadiness within 5 minutes and unconsciousness in 90 minutes. Exposure to 100,000 ppm produced motor ataxia within 2 minutes in guinea pigs (Patty *et al.*, 1930) and motor ataxia with a pronounced tremor within 15 minutes in rats and mice (Mastromatteo *et al.*, 1960). Higher concentrations of VC (200,000 and 300,000 ppm) reduced the onset of CNS depression to 1 to 2 minutes following initiation of exposure (Mastromatteo *et al.*, 1960).

Based on the results of Patty *et al.* (1930), the NOAEL for motor ataxia, or muscular incoordination, in guinea pigs was 10,000 ppm for 8-hour exposure. The LOAEL was 25,000 ppm, which resulted in motor ataxia within 5 minutes and unconsciousness in 90 minutes. The NOAEL was adjusted to a 1-hour exposure by the formula $C^n \times T = K$ (where “n” = 2), which resulted in a concentration of 28,282 ppm VC. Applying uncertainty factors of 10 each to account for interspecies differences and increased susceptibility of sensitive human individuals results in a final value of 280 ppm (720 mg/m³) VC for a level protective against serious adverse effects.

Level Protective Against Life-threatening Effects

Log-normal analysis of lethality data for mice, guinea pigs, and rabbits (Prodan *et al.*, 1975) yielded BC₀₅ estimates of 246,000, 453,000, and 466,000 mg/m³, respectively. Mastromatteo *et al.* (1960) reported 30-minute no-observed-lethality levels of 100,000, 300,000, and 400,000 ppm, respectively, for mice, rats and guinea pigs.

The study by Prodan *et al.* (1975) provides data from which to derive an estimate for VC using the benchmark concentration approach. The BC₀₅ of the most sensitive species, the mouse, was adjusted to a 1-hour equivalent exposure using the equation $C^n \times T = K$, where “n” = 2. Uncertainty factors of 3 and 10 were applied to the adjusted BC₀₅ of 348,000 mg/m³ (136,000 ppm) to account for interspecies differences and increased susceptibility of sensitive human individuals, respectively. The resultant level protective against life-threatening effects is thus 4,500 ppm (12,000 mg/m³).

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ACUTE TOXICITY SUMMARY

XYLENES

(technical xylene (o-, m-, p-), xylol)
(o-xylene, ortho-xylene, 1,2-dimethylbenzene, 2-xylene)
(m-xylene, meta-xylene, 1,3-dimethylbenzene, 3-xylene)
(p-xylene, para-xylene, 1,4-dimethylbenzene, 4-xylene)

CAS Registry Numbers: 1330-20-7 (technical), 95-47-6 (o-), 108-38-3 (m-), 106-42-3 (p-)

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level **2,200 µg/m³**
Critical effect(s) eye irritation in healthy human volunteers
Hazard Index target(s) Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

<i>Molecular formula</i>	C ₈ H ₁₀
<i>Molecular weight</i>	106.2 g/mol
<i>Specific gravity</i>	0.881 (o-); 0.860 (m-); 0.861 (p-) @ 20°C
<i>Boiling point</i>	144.4°C (o-); 139.1°C (m-); 138.4°C (p-)
<i>Melting point</i>	-25°C (o-); -47.87°C (m-); 13.3°C (p-)
<i>Vapor pressure</i>	6.6 (o-); 8.39 (m-); 8.87 (p-) mm Hg at 25°C
<i>Flashpoint</i>	17.2°C (o-); 25°C (m-); 25°C (p-) (closed cup)
<i>Explosive limits</i>	unknown
<i>Solubility</i>	insoluble in water; soluble in ethanol, acetone, ether
<i>Odor threshold</i>	1 ppm (Carpenter <i>et al.</i> , 1975)
<i>Metabolites</i>	methylbenzoic acids
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 4.34 mg/m ³ @ 25°C

III. Major Uses or Sources

As nonexplosive aromatic hydrocarbons, mixtures of the three (technical xylene) isomers are heavily used in the chemical industry and in the petroleum industry as a solvent and gasoline “antiknock” additives. Of the three isomers, p-xylene is produced in the highest quantities in the U.S. for use in the synthesis of terephthalic acid for polymer fibers such as mylar and dacron (HSDB, 1994). However, m-xylene is the most abundant isomer in the environment (Silverman and Schatz, 1991).

IV. Acute Toxicity to Humans

Despite its structural similarity to benzene, xylene does not influence hematopoiesis. The principal systemic effects of acute xylene exposure are on the central nervous system (CNS) but it is also a respiratory irritant. Nelson *et al.* (1943) exposed 10 healthy human volunteers for periods of 3 to 5 minutes to estimated concentrations of 100 or 200 ppm technical grade xylene. The subjects reported eye, nose, and throat irritation at 200 ppm but not at 100 ppm. Exposure of sedentary or exercising subjects to a 10-minute peak concentration of 400 ppm (1,736 mg/m³) resulted in significantly increased uncontrolled body sway in these subjects. Exposure to 200 ppm (868 mg/m³) xylene for up to 5 hours did not result in CNS disturbances measured by increased body sway (Laine *et al.*, 1993). Riihimaki and Savolainen (1980) reported that a single 5-minute exposure to 400 ppm xylene (isomeric form unknown) resulted in lightheadedness and inebriation similar to alcohol intoxication. Deleterious effects on EEG, reaction time, body balance, and manual dexterity were found in 8 healthy volunteers following exposure to 100 ppm (434 mg/m³) m-xylene for 6 hours/day for 6 days (Savolainen *et al.*, 1980). Exposure of 15 volunteers to 100 ppm technical xylene mixed with 20% ethylbenzene for 70 minutes, including 30 minutes of exercise, resulted in significant impairments in short-term memory and other CNS performance tests (Gamberale *et al.*, 1978). Because ethylbenzene may have contributed to the CNS effects, definitive conclusions about the effects of xylene cannot be drawn from this study.

Nine healthy male volunteers were exposed to 200 ppm m-xylene 4 hours a day, with or without exercise for 10 minutes at the beginning of each session (Savolainen *et al.*, 1985). There were no changes in reaction times, but average and maximal body sway were decreased in a concentration-dependent manner. Exercise had a sway reducing effect. Male volunteers were exposed to 200 ppm m-xylene vapor for 4 hours a day, either sedentary or with 10 minutes periods of exercise twice a day (Savolainen *et al.*, 1984). The body balance of the subjects was impaired in the anteroposterior direction. Nine healthy male students were exposed to 200 ppm m-xylene for 4 hours per day at 6-day intervals over 6 consecutive weeks (Savolainen *et al.*, 1982). Body sway tended to decrease with exposure. Only minor electroencephalographic effects were noted on 4 hour exposures to 200 ppm m-xylene exposure, and no other adverse effects were noted (Seppalainen *et al.*, 1991).

Five volunteers were exposed to 40 ppm xylene for 7 hours/day, 3 consecutive days/week in an inhalation chamber. There was an 11-day break between each 3-day session (Mergler and Beauvais, 1992). Individual differences in olfactory perception thresholds for toluene were noted, but there was no effect of exposure duration.

Predisposing Conditions for Xylene Toxicity

Medical: Unknown

Chemical: In rats, exposure to 300 ppm (1302 mg/m³) m-xylene mixed with 600 ppm methyl ethyl ketone (MEK) for 6 hours resulted in synergistic effects on liver enzyme induction and glutathione depletion compared to MEK exposure alone (Liira *et al.*, 1991). Xylene may therefore accelerate the metabolism and clearance of some

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

other xenobiotics. However, in the presence of MEK, xylene metabolism was strongly inhibited; this was accompanied by elevation of xylene concentrations in blood and fat. Thus, exposure to xylene in the presence of other solvents may result in increased toxicity.

V. Acute Toxicity to Animals

Six-hour inhalation LC₅₀ values in mice for each xylene isomer are: 4,595, 5,267, and 3,907 ppm (19,942, 22,859, 16,956 mg/m³) for o-, m-, and p- xylene, respectively (Bonnet *et al.*, 1979). A 4-hour LC₅₀ for mixed xylenes was estimated as 6,700 ppm (29,078 mg/m³) in rats; and a 2-hour LC₅₀ was calculated as 9,500 ppm (41,230 mg/m³) in cats (Carpenter *et al.*, 1975).

An increase in liver weight and cytochrome P450 (P450) content was observed in rats exposed to 1,600 ppm (6,944 mg/m³) p-xylene for 6 hours (Simmons *et al.*, 1991). Rats exposed for 6-hours to 300 ppm (1,302 mg/m³) m-xylene showed increased specific liver P450 enzyme activity and depleted liver glutathione concentrations. These effects were enhanced by simultaneous exposure to 600 ppm MEK (Liira *et al.*, 1991).

Pulmonary effects following exposure to 300 ppm (1,302 mg/m³) p-xylene for 6 hours include microsomal membrane damage and decreased lung P450 enzyme content (Silverman and Schatz, 1991). The destruction of rat lung but not liver P450 enzymes by p-xylene has been described by Patel *et al.* (1978), and has been attributed to the formation of a toxic aldehyde metabolite of p-xylene. Single 6-hr exposures of rats to m-xylene caused inhibition of aryl hydrocarbon hydroxylase and CYP2B1 activities in the lung but not the liver (Foy *et al.*, 1996).

VI. Reproductive or Developmental Toxicity

Exposure of pregnant rats for 6 hours/day on days 4-20 of gestation to 200 ppm (868 mg/m³) technical (mixed) xylene resulted in significantly increased incidence of delayed ossification of the skull in the offspring (Hass and Jakobsen, 1993). The rat pups exposed prenatally to 200 ppm xylene displayed significantly decreased motor performance during adolescence. However, a study using p-xylene showed no significant embryotoxic or developmental effects on the CNS as measured by acoustic startle response in rats following exposure to 7,000 mg/m³ (1,613 ppm) throughout gestation (Rosen *et al.*, 1986).

All three isomers of xylene cause maternal toxicity and are fetotoxic but not teratogenic at near lethal concentrations in rats (Hudak and Ungvary, 1978; Ungvary *et al.*, 1980). Ungvary and Tatrai (1985) showed that exposure of both rats and mice to technical xylene as well as specific isomers resulted in fetotoxic effects such as fetal weight loss and delayed skeletal ossification. Of the 3 isomers, p-xylene exposure is the most toxic to the fetus, since it results in the least maternal toxicity and the greatest fetotoxicity (Barlow and Sullivan, 1982); m-xylene has been shown to cause the greatest maternal toxicity (Hood and Ottley, 1985).

Persistence of neurobehavioral effects was noted in offspring of female rats (Mol:WIST) exposed to 500 ppm technical xylene for 6 hours per day on days 7-20 of prenatal development. The dose

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

was not maternally toxic and did not decrease viability of offspring. Learning and memory abilities with spatial navigation on a water maze were impaired at 16, 28 and 55 weeks of age. However, differences were not significant at 55 weeks. The authors suggested these results were compatible with two different conclusions: 1) the effect was partly reversible over a long time period, or 2) practice at solving the problem led to compensation over unresolved neurotoxic effects (Hass *et al.*, 1997). Rats of the same strain (Mol: WIST) exposed prenatally to the same regimen did not show any differences from control rats in synaptosomal cytosolic calcium concentration (Edelfors *et al.*, 1996).

**VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)**

Reference Exposure Level (protective against mild adverse effects): 2,200 µg/m³

<i>Study</i>	Nelson <i>et al.</i> , 1943
<i>Study population</i>	10 healthy human volunteers
<i>Exposure method</i>	3 minute exposures to 100 or 200 ppm xylene (technical grade)
<i>Critical effects</i>	subjective reports of eye, nose, and throat irritation
<i>LOAEL</i>	200 ppm
<i>NOAEL</i>	100 ppm
<i>Exposure duration</i>	3 minutes
<i>Equivalent 1 hour concentration</i>	5 ppm ($C^1 * 60 \text{ min} = 100 \text{ ppm}^1 * 3 \text{ min}$)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	0.5 ppm (500 ppb, 2.2 mg/m ³ , 2,200 µg/m ³)

With the exception of inconsistently observed developmental endpoints, this is the lowest reported human health effect for xylene. A significant area of uncertainty arising from the Nelson *et al.* (1943) study is the use of estimated rather than measured exposure concentrations.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

The NAS Committee on Toxicology (NRC, 1984) reviewed the toxicological literature for xylene and determined that the CNS was the main target for xylene toxicity. The Committee concluded that the CNS disturbances in humans (Ogata *et al.*, 1970; Gamberale *et al.*, 1978) were reversible and were similar to those produced by alkyl benzenes and other related compounds. Irritation of the eyes and mucous membranes (Carpenter *et al.*, 1975; Nelson *et al.*, 1943) was considered, but the purpose of the EEGL is to protect against CNS toxicity in military personnel. Based on these findings, the Committee recommended a NAS-EEGL of 200 ppm

Determination of Acute Toxicity Exposure Levels
Scientific Review Panel Draft - Do not cite or quote.

(870 mg/m³). However, it is not clear that an adequate margin of safety is incorporated into this EEGL for use for the general public.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The IDLH is 900 ppm, based on animal LC₅₀ and LC₁₀ estimates divided by a 10-fold uncertainty factor (NIOSH, 1995). The data cited include several 4 hour studies: (1) an 8,000 ppm m-xylene LC₁₀ for rats (Smyth *et al.*, 1962); (2) a 4,550 ppm rat LC₅₀ for p-xylene (Harper *et al.* 1977); and (3) a 5,000 ppm rat LC₅₀ for xylenes (NPIRI, 1974). The IDLH appears to be based on the Harper *et al.* (1977) data with an extrapolated 30-minute LC₅₀ estimate of 9,100 ppm.

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