ACUTE TOXICITY SUMMARY

**1,4-DIOXANE**

*(diethylene oxide; p-dioxane; glycolethylene ether; tetrahydro-p-dioxin)*

**CAS Registry Number:  123-91-1**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **3,000 μg/m³** |
| *Critical effect(s)* | Nasal and eye irritation in healthy human volunteers |
| *Hazard Index target(s)* | Respiratory System; Eyes |

**II.     Physical and Chemical Properties  (ACGIH, 1991 except as noted)**

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_4H_8O_2$ |
| *Molecular weight* | 88.1 |
| *Density* | 1.0329 g/cm³ @ 20°C |
| *Boiling point* | 101.1°C @ 760 mm Hg |
| *Melting point* | 11.8°C |
| *Vapor pressure* | 29 mm Hg @ 20°C |
| *Flash point* | 12.22°C (closed cup) |
| *Explosive limits* | 2 - 22 % by volume in air |
| *Solubility* | soluble in water and most organic solvents |
| *Odor threshold* | 24 ppm (ACGIH, 1991); 1.8 ppm (Hellman and Small, 1974) |
| *Odor description* | ethereal odor (Buffler *et al.*, 1978) |
| *Metabolites* | hydroxyethoxyacetic acid (Braun and Young, 1977) |
| *Conversion factor* | 1 ppm = 3.6 mg/m³ |

**III.    Major Uses or Sources**

1,4 - Dioxane is used as a solvent for oils, resins, waxes, adhesives, cellulose esters and ethers.  It is also used as a stabilizer in chlorinated solvents (ACGIH, 1991).  As much as 90% of U.S. production of dioxane has been used to stabilize chlorinated solvents. As a stabilizer it is present as a few percent by volume.

**IV.    Acute Toxicity to Humans**

There are case reports of lethal hemorrhagic nephritis in workers exposed to unspecified high concentrations of 1,4-dioxane for several days (Barber, 1934; Johnstone, 1959).

1,4-Dioxane was irritating to the eyes, nasal passages, and the throat of adult volunteers following a 10-minute exposure to 1,600 ppm (Yant *et al.*, 1930). In this study, no control subjects were tested concomitantly. A similar study of 4-6 volunteers by Fairly *et al.* (1934) showed that inhalation exposure to a concentration of 1,000 ppm (3,600 mg/m³) for five minutes caused a warm sensation in the throat and chest, but no noticeable irritation. However, in a more recent study, four healthy adult male volunteers exposed in a chamber for 6 hours to 50 ppm (180 mg/m³) dioxane exhibited eye irritation and 2 of the 4 subjects reported olfactory fatigue after 4 and 5 hours (Young *et al.*, 1977).

*Predisposing Conditions for 1,4-Dioxane Toxicity*

**Medical**: Persons with preexisting skin, eye, respiratory, neurological, and liver and kidney conditions might be more sensitive (Reprotext, 1999).

**Chemical**: Unknown

## V.     Acute Toxicity to Laboratory Animals

Inhalation by guinea pigs and rats of 10,000 ppm (36,000 mg/m³) 1,4-dioxane for two 1.5-hour exposures was lethal (Fairley *et al.*, 1934). 1,4-Dioxane affects the rat central nervous system as measured by a significant decrease in avoidance behavior following a 4-hour exposure to 3,000 ppm (10,800 mg/m³) (Goldberg *et al.*, 1964). Nasal irritation was indicated by behavioral signs in guinea pigs exposed to 1,000 ppm (3,600 mg/m³) 1,4-dioxane for 4 hours (Yant *et al.*, 1930); behavioral signs of eye irritation were evident at concentrations of 2,000 ppm (7,200 mg/m³) 1,4-dioxane or greater. Slight hyperemia was observed in the lungs, large air passages, and the brain in the animals exhibiting mild irritation. No histological changes were noted in control animals (unexposed to 1,4-dioxane). The absence of pathological lesions in the brain and lungs in exposed animals 9-10 days after 1,4-dioxane exposure led the authors to conclude that the histological effects of dioxane exposure were transient at the concentrations and exposure duration tested.

Based on pharmacokinetic data, rats appear to be the most appropriate animal model for metabolism of 1,4-dioxane in humans (Young *et al.*, 1978). In a comparative toxicity study on rats, mice, guinea pigs, and rabbits, Fairley *et al.* (1934) showed that all species became drowsy after a 1.5 hour exposure to 1,000 ppm (3,600 mg/m³) 1,4-dioxane. In this study, guinea pigs were the most sensitive species to organ-specific histopathological lesions, which included: acute vascular congestion in the lungs, patchy cell degeneration and hemorrhage of the renal cortex, and hepatic necrosis. Schrenk and Yant (1936) showed that nasal irritation was evident in guinea pigs immediately following brief exposure to 1,000 ppm (3,600 mg/m³) 1,4-dioxane. No behavior indicative of eye irritation or lacrimation was observed at this concentration.

Drew *et al.* (1978) showed that a single 4-hour inhalation of 1,000 ppm (3,600 mg/m³) 1,4-dioxane by rats resulted in immediate elevation of serum glutamic-oxaloacetic transaminase activity. Alanine aminotransferase and ornithine carbamyl transaminase activities were elevated 24 hours following the 4-hour 1,000 ppm (3,600 mg/m³) exposure. The elevations of these hepatic enzymes indicated that 1,4-dioxane is hepatotoxic in rats.

## VI. Reproductive or Developmental Toxicity

Pregnant rats treated with 0, 0.25, 0.5, or 1.0 mL dioxane/kg body weight by gavage on days 6-15 of gestation showed no differences in the number of implanted fetuses, live fetuses, post-implantation loss, or major malformations. Slight maternal toxicity in the form of weight loss was observed at the 1.0 mL/kg dose (Giavini *et al.*, 1985). No data on human reproductive toxicity were available.

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

**Reference Exposure Level (protective against mild adverse effects):   0.8 ppm (3,000 μg/m³)**

| | |
|---|---|
| *Study* | Young *et al.*, 1977 |
| *Study population* | 4 healthy human male volunteers |
| *Exposure method* | chamber |
| *Critical effects* | subjective reports of eye irritation |
| *LOAEL* | 50 ppm |
| *NOAEL* | not reported |
| *Exposure duration* | 6 hours |
| *Extrapolation to 1 hour* | not used (see below) |
| *Extrapolated 1-hour concentration* | 50 ppm |
| *LOAEL uncertainty factor* | 6 (mild irritation) |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 60 |
| *Reference Exposure Level* | 0.8 ppm (3 mg/m³, 3,000 μg/m³) |

The volunteers complained of eye irritation throughout the exposure. Two of the subjects were not able to perceive the odor of dioxane after 4 and 5 hours exposure, respectively. A time-adjustment factor for the 6-hour exposure was not used since the individuals complained of eye irritation throughout the exposure.

## 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 1,4-dioxane of 500 ppm based on acute inhalation toxicity data in animals. NIOSH derived 30 minute $LC_{50}$s from several studies of cats, rats, mice and guinea pigs, then divided the lowest 30 minute $LC_{50}$ by 10 to determine an IDLH for humans. NIOSH stated that no relevant human data were available for the IDLH estimation.

## VII.    References

(ACGIH) American Conference of Governmental and Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Vol. I. Cincinnati: ACGIH; 1991. p. 512-515.

Barber H. Haemorrhagic nephritis and necrosis of the liver from dioxane poisoning. Guy's Hosp Rep 1934;84:267-280.

Braun WH, Young JD. Identification of hydroxyethoxyacetic acid as the major urinary metabolite of 1,4-dioxane in the rat. Fundam Appl Toxicol 1977;39:33-38.

Buffler PA, Wood SM, Suarez L, Kilian DJ. Mortality follow-up of workers exposed to 1,4-dioxane. J Occup Med 1978;20(4):255-259.

Drew RT, Patel JM, Lin FN. Changes in serum enzymes in rats after inhalation of organic solvents singly and in combination. Toxicol Appl Pharmacol 1978;45:809-819.

Fairley A, Linton EC, Forde-Moore AH. The toxicity to animals of 1,4-dioxan. J Hyg 1934;34:486-501.

Giavini E, Vismara C, Broccia ML. Teratogenesis study of dioxane in rats. Toxicol Lett 1985;26:85-88.

Goldberg ME, Johnson HE, Pozzani UC, Smyth HF Jr. Effect of repeated inhalation of vapors of industrial solvent on animal behavior. 1. Evaluation of nine solvent vapors on pole-climb performance. Am Ind Hyg Assoc J 1964;25:369-375.

Hellman TM, Small FH. Characterization of the odor properties of 101 petrochemicals using sensory methods. J Air Poll Cont Assoc 1974;24(10):979-982.

Johnstone RT. Death due to dioxane? AMA Arch Ind Health 1959;20:445-447.

Klimmer O. Beitrag zur toxikologischen Wirkung technischer Losungsmittel (German) [dissertation]. Wurzburg, Germany; 1937. [cited in: Spector WS. Handbook of toxicology. Vol I. Acute toxicities. Philadelphia (PA): Saunders Company; 1956. p. 334-5.]

(NIOSH) National Institute for Occupational Safety and Health. Pocket guide to chemical hazards. DHEW/NIOSH Pub. No. 93-114. Washington (DC): Government Printing Office; 1993.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Spector WS. Handbook of toxicology. Vol. I. Acute toxicities. Philadelphia (PA): Saunders Company; 1956. p. 334-335.

Schrenk HH, Tant WP. Toxicity of dioxan. J Ind Hyg Toxicol 1936;18:448-460.

Yant WP, Schrenk HH, Waite CP, Patty FA. Acute response of guinea pigs to vapors of some new commercial organic compounds. Pub Health Rep 1930;45:2023-2032.

Young JD, Braun WH, Gehring PJ. Dose-dependent fate of 1,4-dioxane in rats. J Toxicol Environ Health 1978;4:709-726.

Young JD, Braun WH, Rampy LW. Pharmacokinetics of 1,4-dioxane in humans. J Toxicol Environ Health 1977;3:507-520.

ACUTE TOXICITY SUMMARY

**EPICHLOROHYDRIN**

*(1-chloro-2,3-epoxy-propane)*

**CAS Registry Number**:  **106-89-8**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **1,300 µg/m³** |
| *Critical effect(s)* | eye and nasal irritation in human volunteers |
| *Hazard Index target(s)* | Eyes; Respiratory System |

**II.      Physical and Chemical Properties  (HSDB, 1994)**

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_3H_5ClO$ |
| *Molecular weight* | 92.5 |
| *Density* | 1.181 g/cm$^3$ @ 20°C |
| *Boiling point* | 117.9°C |
| *Melting point* | -25.6°C |
| *Vapor pressure* | 13 mm Hg @ 20°C |
| *Flash point* | 33.9°C |
| *Explosive limits* | 3.3% - 14.5 % by volume in air |
| *Solubility* | slightly soluble in water, soluble in most organic solvents |
| *Odor threshold* | 0.93 ppm (chloroform-like, irritating odor) |
| *Metabolites* | N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine |
| *Conversion factor* | 1 ppm = 4 mg/m³ |

**III.      Major Uses or Sources**

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins.  It is also used as a solvent and in the synthesis of glycerol.  Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994).

**IV.      Acute Toxicity to Humans**

Case reports of exposure to epichlorohydrin in the workplace, either through inhalation or dermal contact, describe symptoms including burning sensations of the nose and throat, chest congestion, running nose, eye tenderness, and headache followed by nausea, in addition to reddening and burning sensations of the exposed skin, which persist for several days to 2 months (Wexler, 1971, as cited in NIOSH, 1976).  Epichlorohydrin is a strong skin sensitizer following dermal contact (U.S.EPA, 1984).  Epichlorohydrin is a reactive epoxide and a known mutagen.

In vitro exposure of human lymphocytes to $10^{-11}$ to $10^{-4}$ M epichlorohydrin resulted in dose-dependent chromatid and chromosomal breaks (HSDB, 1994).

*Predisposing Conditions for Epichlorohydrin Toxicity*

**Medical**:          Asthmatics may be more sensitive to the irritant effects of inhaled epichlorohydrin.

**Chemical**:          Unknown

## V.      Acute Toxicity to Laboratory Animals

A six-hour exposure to epichlorohydrin with a 14-day follow-up showed the median lethal concentration to be 360 ppm (1,440 mg/m³) in rats (Laskin *et al*., 1980).  An LC$_{50}$ of 445 ppm (1,780 mg/m³) for four hours was reported for rabbits (HSDB, 1994).  An eight-hour exposure to 250 ppm (1,000 mg/m³) killed two-thirds of the rats exposed (sample size not given) (LeFaux, 1968).  A single subcutaneous injection of 75 mg/kg resulted in swelling of proximal renal tubular epithelium in male rats (Kluwe *et al*., 1983).

Deaths occurred in rats exposed chronically to a concentration of 68 ppm (272 mg/m³) epichlorohydrin for an unknown duration (IRIS, 1994).  Tumors induced by chronic epichlorohydrin exposure are typically local to the area of initial exposure (U.S.EPA, 1984).  Nasal carcinomas are among the tumors known to occur following epichlorohydrin exposure (U.S.EPA, 1984).

## VI.      Reproductive or Developmental Toxicity

Fetotoxicity and toxicity to dams were reported in mice exposed to 120 mg/kg/day epichlorohydrin via gavage during days 6-15 of gestation; however, no teratogenic effects were noted (Marks *et al*., 1982).  Teratology studies in rats and rabbits yielded negative results for embryotoxicity and teratogenicity (John *et al*., 1983a).

Maternal toxicity, as measured by a decrease in body weight and food consumption, was demonstrated in pregnant rats following exposure to 25 ppm (100 mg/m³) epichlorohydrin for 7 hours/day on days 6-18 of gestation (John *et al*., 1983a).  Additionally, exposure of male rats to 25 ppm for 5 days/week for 10 weeks resulted in a transient loss in fertility (John *et al*., 1983b).

Injury to epididymal tissue, testicular atrophy, and increases in the number of sperm with abnormal morphology have been observed in male rats exposed via single subcutaneous injection to 75 mg/kg epichlorohydrin (Kluwe *et al*., 1983).  Although animal studies indicate that male fertility is affected by exposure to high doses of epichlorohydrin, a human epidemiologic study showed no changes in male fertility rates among workers (HSDB, 1994).

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

**Reference Exposure Level (protective against mild adverse effects): 0.33 ppm (1,300 μg/m³)**

| | |
|---|---|
| *Study* | Wexler (1971) as cited in NIOSH, 1976 |
| *Study population* | occupationally exposed workers |
| *Exposure method* | during work-shifts (occupation not given) |
| *Critical effects* | irritation of eyes and nasal passages |
| *LOAEL* | 20 ppm |
| *NOAEL* | not reported |
| *Exposure duration* | 1 hour |
| *Extrapolated 1 hour concentration* | 20 ppm |
| *LOAEL uncertainty factor* | 6 (mild irritation) |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 60 |
| *Reference Exposure Level* | 0.33 ppm (1.3 mg/m³, 1,300 μg/m³) |

The Wexler (1971) study represents the only human data but it was not available for review. The report by NIOSH (1976), which reviewed the Wexler study, was therefore used as the basis for the REL.

**Level Protective Against Severe Adverse Effects**

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

Exposure of 8 rats for 6 hours/day, 5 days/week for 19 days to 17 ppm epichlorohydrin resulted in no pulmonary histopathological abnormalities as compared to controls (Gage, 1959). The ERPG documentation for epichlorohydrin (AIHA, 1992) erroneously refers to Laskin *et al*. (1980) as a teratology study instead of a carcinogenicity study. In addition, the extrapolation of sub-chronic animal exposures in the Gage study to acute human exposures involves considerable uncertainty that is not accounted for in the ERPG document. The ERPG-2 value of 20 ppm (76 mg/m³) is therefore poorly substantiated.

**Level Protective Against Life-threatening Effects**

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

Subacute exposures of rats and mice (5/sex) to 100 ppm epichlorohydrin 6 hours/day, 5 days/week, 9 exposures in 12 days, resulted in focal pneumonitis and inflammation and degeneration of nasal epithelium in addition to decreased weight gain (Quast *et al*., 1979a, b). Kidney toxicity was seen in the rats exposed to 100 ppm. No lethality was observed. It was concluded that acute exposure to 100 ppm would not cause fatality in humans. Thus AIHA (1992) selected 100 ppm (380 mg/m³) as the ERPG-3 for epichlorohydrin. This value can be considered a subchronic NOAEL for lethality in mice, but the lack of uncertainty factors for the extrapolation of animal to human exposures, in addition to those required for consideration of

sensitive individuals, dictate that this value should be reevaluated. The small sample sizes in the rodent studies, and the absence of peer-reviewed data used to derive the NOAEL, further weaken the scientific validity of this value. The ERPG-3 value is based on severe, non-lethal effects and not on lethality data. An inhalation $LC_{50}$ in mice of 2,998 mg/m³ for 2 hours is reported by the World Health Organization (1992).


## VIII.   References

(AIHA) American Industrial Hygiene Association. Emergency response planning guidelines for epichlorohydrin. Set 5. Akron: AIHA; 1992.

Gage JC. The toxicity of epichlorohydrin vapour. Br J Ind Med 1959;16:11-14.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

(IRIS) Integrated Risk Information System. U.S. Environmental Protection Agency, Washington (DC) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 10/31/94).

John JA, Gushow TS, Ayres JA, Hanley TR, Quast JF, Rao KS. Teratologic evaluation of inhaled epichlorohydrin and allyl chloride in rats and rabbits. Fundam Appl Toxicol 1983a;3:437-442.

John JA, Quast JF, Murray FJ, Calhoun LG, Staples RE. Inhalation toxicity of epichlorohydrin: effects on fertility in rats and rabbits. Toxicol Appl Pharmacol 1983b;68:415-423.

Kluwe WM, Gupta BN, Lamb JC. The comparative effects of 1,2-dibromo-3-chloropropane (DBCP) and its metabolites, 3-chloro-1,2-propanediol (alphachlorohydrin), and oxalic acid, on the urogenital system of male rats. Toxicol Appl Pharmacol 1983;70:67-86.

Laskin S, Sellakumar AR, Kuschner M, Nelson N, La Mendola S, Rusch GM, *et al*. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J Natl Cancer Inst 1980;65(4):751-757.

LeFaux R. Practical toxicology of plastics. London: Scripta Technica Ltd; 1968. p. 108.

Marks TA, Gerling FS, Staples RE. Teratogenic evaluation of epichlorohydrin in the mouse and rat and glycidol in the mouse. J Toxicol Environ Health 1982;9:87-96.

(NIOSH) National Institute for Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to epichlorohydrin. Cincinnati: DHEW (NIOSH); 1976;76-202.

Quast JF, Henck JW, Postma BJ, Schuetz DJ, McKenna MJ. Epichlorohydrin - subchronic studies. I. A 90-day inhalation study in laboratory rodents. Toxicology Research Laboratory, Dow Chemical, USA. Midland (MI); 1979a. (unpublished).

Quast JF, Lederer TS, Postma BJ, Schuetz DJ, John JA, McKenna MJ. Epichlorohydrin - subchronic studies II. A 12-day inhalation study in laboratory rodents. Toxicology Research Laboratory, Dow Chemical, USA. Midland (MI); 1979b. (unpublished).

Wexler B. [Determination of epichlorohydrin contamination in an industrial facility for the manufacturing of epoxy resins.] (Rum) Mater Plast (Bucharest) 1971;8:322-333.

U.S. Environmental Protection Agency. 1984. Health assessment for epichlorohydrin. EPA-600/8-83-032F, Washington (DC): U.S.EPA; 1979b.

World Health Organization. Chemical review: epichlorohydrin. In: Dangerous properties of industrial materials report. 1992;12(2):150-170.

ACUTE TOXICITY SUMMARY

**ETHYLENE GLYCOL MONOBUTYL ETHER**

*(2-butoxyethanol, butyl cellosolve, butyl glycol)*

**CAS Registry Number: 111-76-2**

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

*Inhalation reference exposure level*      **14,000 µg/m³**
*Critical effect(s)*                                       irritation
*Hazard Index target(s)*                          Respiratory System

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

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_6H_{14}O_2$ |
| *Molecular weight* | 118.20 |
| *Density* | 0.90 g/cm$^3$ @ 20°C |
| *Boiling point* | 171°C |
| *Melting point* | -70°C |
| *Vapor pressure* | 0.76 mm Hg @ 20°C |
| *Flashpoint* | unknown |
| *Explosive limits* | unknown |
| *Solubility* | soluble in water, acetone, benzene, carbon tetrachloride, ethyl ether; miscible with ketones, ethers, alcohols and halogenated hydrocarbons |
| *Odor threshold* | 0.10 ppm (geometric mean) (AIHA, 1989) |
| *Odor description* | sweet, ester-like, musty (AIHA, 1989) |
| *Metabolites* | butoxyacetic acid (Johanson *et al*., 1986) |
| *Conversion factor* | 1 ppm = 4.84 mg/m³ @ 25°C |

**III.      Major Uses or Sources**

Ethylene glycol monobutyl ether (EGBE) is used as a coupling agent to stabilize immiscible ingredients in metal cleaners, textile lubricants, and cutting oils (HSDB, 1994).  It is also used as a solvent for nitrocellulose resins, spray lacquers, enamels, and varnish removers.  EGBE is also found in hydraulic fluids.

## IV. Acute Toxicity to Humans

Two adult male volunteers were exposed to 113 ppm (550 mg/m³) EGBE for 4 hours. Eye, nose and throat irritation, taste disturbances, and headache and nausea were reported (Carpenter *et al.*, 1956). Erythrocyte osmotic fragility and urinalysis were normal in the subjects during and after exposure. In this study, 8-hour exposures at the same concentrations resulted in similar reports of discomfort.

Four volunteers were exposed either mouth-only or skin-only, by a mouthpiece or a respirator in a chamber, to 50 ppm EGBE for 2 hours (Johanson and Boman, 1991). Capillary blood samples were taken at regular intervals to determine rate of uptake from dermal and inhalation (mouth-only) exposure. The experiment was done under both normal and raised humidity conditions. The authors concluded that dermal uptake of EGBE from air is approximately four times greater than respiratory uptake. The authors also note that dermal uptake increased with air temperature and humidity.

Seven healthy male adults were exposed to 20 ppm (100 mg/m³) EGBE in a chamber experiment designed to assess pulmonary uptake and metabolism of EGBE. Butoxyacetic acid was the primary metabolite found in the urine (Johanson *et al.*, 1986). The authors report that 57% of the inhaled dose was absorbed in the respiratory tract. The authors report that none of the subjects complained or showed any adverse effects from exposure for 2 hours to 20 ppm EGBE.

Although increased erythrocyte fragility has been observed in rodents following exposure to EGBE (Carpenter *et al.*, 1956), recent studies found no increase in the fragility of human erythrocytes taken from normal and susceptible individuals (persons with hereditary spherocytosis or sickle cell disease and older persons) following a 4-hour incubation with butoxyacetic acid (Udden, 1994; Udden and Patton, 1994).

*Predisposing Conditions for EGBE Toxicity*

**Medical**:     Persons with preexisting neurological, blood or kidney conditions might be more sensitive (Reprotext, 1999).

**Chemical**:     Unknown

## V. Acute Toxicity to Laboratory Animals

A 7-hour $LC_{50}$ for mice was reported as 700 ppm (3,000 mg/m³) EGBE (Werner *et al.*, 1943). Severe hemoglobinuria was observed; hepatic focal necrosis and splenic lymphoid hyperplasia were noted at necropsy. An 8-hour $LC_{50}$ in rats was reported as 564 ppm (2,800 mg/m³) EGBE (Pozzani *et al.*, 1959).

No mortality or other clinical signs of toxicity were observed in 5 male and 5 female guinea pigs exposed to 691 or 633 ppm EGBE, respectively, for one hour (Nachreiner, 1994). Further, no signs of toxicity were observed during the 14-day post-exposure period or at necropsy.

Rats were exposed to 867, 523, or 202 ppm EGBE for four hours (Dodd *et al.*, 1983). Exposure was lethal to all animals in the 867 ppm group and to 2/6 males and 3/6 females in the 523 ppm group. No deaths were observed in the 202 ppm EGBE exposure group. Rats exposed to 867 ppm exhibited loss of coordination and shallow breathing and had a red discharge around the urogenital area. Red-stained fluid in the urinary bladder and enlarged and discolored kidneys were observed at necropsy of the animals that died during or following exposure to 867 or 523 ppm EGBE.

Increased erythrocyte fragility was observed in rats exposed for 4 hours to 62 ppm (300 mg/m³) EGBE (Carpenter *et al.*, 1956). No significant increase in erythrocyte fragility was observed following a 4-hour exposure to 32 ppm (150 mg/m³) EGBE.

Corley *et al.* (1994) developed a physiologically based pharmacokinetic model to describe in rats and humans the disposition of EGBE and its major metabolite, 2-butoxyacetic acid (BAA); BAA is the agent that causes lysis of red blood cells. The model predicted that rats metabolize EGBE and eliminate BAA faster per kg body weight than humans do. The balance of the two processes in addition to physiological differences between species resulted in higher predicted peak blood concentrations for rats as well as total areas under the blood concentration (AUC) time curves for BAA. The species differences in kinetics coupled with the fact that human blood is significantly less susceptible than rat blood (and mouse blood and probably rabbit blood) to the hemolytic effects of BAA (Udden *et al.*, 1994a,b) indicate that there is less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard rat toxicity studies.

## VI.    Reproductive or Developmental Toxicity

No studies on the developmental and reproductive toxicity of EGBE in humans were located in the literature.

Pregnant rats were exposed to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-15 of gestation (Tyl *et al.*, 1984). A significant increase in the incidence of delayed skeletal ossification was observed in the offspring of rats exposed to 100 or 200 ppm EGBE. Maternal toxicity, as indicated by decreased body weight gain, decreased food consumption, and significantly decreased erythrocyte indices, was observed in rats exposed to 100 or 200 ppm EGBE. It is not clear whether the reported delayed ossification effects indicate distinct developmental toxicity since there was concurrent maternal toxicity (RCHAS, 1994).

The same study exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. Hematological parameters in the does were normal. However, rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem *et al.*, 1992). The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits. EGBE has not been listed as a developmental or reproductive toxicant under Proposition 65.

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

**Reference Exposure Level (protective against mild effects):     14,000 μg/m³**

| | |
|---|---|
| *Study* | Carpenter *et al*., 1956; Johanson *et al*., 1986 |
| *Study population* | human volunteers 2 in Carpenter; 7 in Johanson *et al*.) |
| *Exposure method* | inhalation of 113 ppm for 4 hours (2 men) in Carpenter *et al*. (1956); inhalation of 20 ppm in Johanson *et al*. (1986) |
| *Critical effects* | mucous membrane irritation of the nose and eyes |
| *LOAEL* | 113 ppm |
| *NOAEL* | 20 ppm for 2 hours |
| *Exposure duration* | 2 or 4 hours |
| *Equivalent 1-hour concentration* | 28 ppm $(20^2 * 2 \text{ hours} = C^2 * 1 \text{ hour}))$ |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty fctor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 10 |
| *Reference Exposure Level* | 2.8 ppm (14 mg/m³; 14,000 μg/m³) |

Two human volunteers were exposed to 113 ppm EGBE for 4 hours (Carpenter *et al*., 1956). Symptoms observed included nasal and ocular irritation, disagreeable metallic taste, and a slight increase in nasal mucus discharge.  The time to onset of symptoms was not specified; thus no time adjustment was made.  Volunteers exposed to 98 ppm for 8 hours with a 30-minute break and 3 volunteers exposed to 195 ppm for 8 hours showed similar symptoms.  The 3 exposed to the highest level agreed that it was too high for comfort.  In Johansen *et al*. (1986) 7 healthy adults were exposed to 20 ppm in a study designed to look at the toxicokinetics of EGBE.  The authors report that the subjects did not complain of adverse effects.  Thus, this level can be identified as a freestanding NOAEL.

**Level protective against severe adverse effects**

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

Tyl *et al*. (1984) exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation.  Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm.  The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits.  Rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem *et al*., 1992).  Hematologic parameters in the does were normal but there was evidence in their cages of hematuria.  Therefore, it is not clear if the reproductive and fetal toxicity were secondary to hematological effects.  No adverse effects to does or fetuses were

observed following exposure to 0, 25, 50 or 100 ppm EGBE. This study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal toxicity and embryotoxicity in rabbits. The pharmacokinetic model of Corley *et al*. (1994), as well as other evidence in humans and incubated human erythrocytes, indicates that that there is considerably less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard animal toxicity studies.

**Level Protective Against Life-threatening Effects**

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

Data on lethal effects of EGBE in species resistant to the hemolytic effects of EGBE were not available other than a 1-hour free-standing NOAEL of 633-691 ppm in guinea pigs (5 per sex) (Nachreiner, 1994). The only lethality study providing dose-response data had been conducted in mice (Werner *et al., 1*943). Both rats and mice have been shown to be sensitive to hemolysis following EGBE exposure. This effect is not observed in humans, including sensitive human subpopulations such as the elderly or those persons with sickle cell disease or hereditary spherocytosis (Udden and Patton, 1994; Udden, 1994). Therefore, the use of mouse lethality data may not accurately reflect the risk of potentially lethal effects in humans following EGBE exposure.

## VIII.   References

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 14

Carpenter CP, Pozzani UC, Weil CS, Nair JH, Keck GA, Smyth HF Jr. The toxicity of butyl cellosolve solvent. Arch Ind Health 1956;14:114-131.

Corley RA, Bormett GA, Ghanayem BI. Physiologically based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans.Toxicol Appl Pharmacol 1994;129(1):61-79

Crump KS and Co, Inc. Probit (Log-Normal) software for the IBM-PC. Ruston (LA); 1983.

Crump KS. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:854-871.

Dodd DE, Snellings WM, Maronpot RR, Ballantyne B. Ethylene glycol monobutyl ether: Acute, 9-day, and 90-day vapor inhalation studies in Fischer 344 rats. Toxicol Appl Pharmacol 1983;68:405-414.

Ghanayem BI, Ward S, Wall C. Effects of 1-butoxyethanol (BE) and its toxic metabolite, 2-butoxyacetic acid (BAA) on blood from various mammals in vivo and in vitro [abstract]. Toxicologist 1992;12, 282.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Johanson G, Boman A. Percutaneous absorption of 2-butoxyethanol vapour in human subjects. Br J Ind Med 1991;48:788-792.

Johanson G, Kronborg H, Naslund PH, Nordquist MB. Toxicokinetics of inhaled 2-butoxyethanol (ethylene glycol monobutyl ether) in man. Scand J Work Environ Health 1986;12:594-602.

Nachreiner DJ. Ethylene glycol butyl ether: Acute vapor inhalation toxicity study in guinea pigs. Project ID 94N1392. Export (PA):Bushy Run Research Center (BRRC), Union Carbide Corporation; 1994. Sponsored by the Chemical Manufacturers Association, Washington (DC).

Pozzani UC, Weil CS, Carpenter CP. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Ind Hyg Assoc (no volume #) 1959:364-369.

(RCHAS) Reproductive and Cancer Hazard Assessment Section. Memorandum on ethylene glycol monobutyl ether reproductive toxicity to George Alexeeff, Air Toxicology and Epidemiology Section (ATES) from Jim Donald, Reproductive Toxicology Unit. July 20, 1994.

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fischer LC. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 1984;57:47-68.

Udden MM. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: II. Resistance in red blood cells from humans with potential susceptibility. J Appl Toxicol 1994;14(2):97-102.

Udden MM, Patton CS. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: I. Sensitivity in rats and resistance in normal humans. J Appl Toxicol 1994;14(2):91-96.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.

ACUTE TOXICITY SUMMARY

**ETHYLENE GLYCOL MONOETHYL ETHER**

*(2-ethoxyethanol, Cellosolve)*

**CAS Registry Number: 110-80-5**

**I.      Acute Toxicity Summary (for a 6-hour exposure)**

| | |
|---|---|
| *Inhalation reference exposure level* | **370 µg/m³** |
| *Critical effect(s)* | specific skeletal defects |
| *Hazard Index target(s)* | Reproductive/developmental |

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

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_4H_{10}O_2$ |
| *Molecular weight* | 90.12 |
| *Density* | 0.931 g/cm³ @ 20°C |
| *Boiling point* | 135°C |
| *Melting point* | -70°C (solidifies) |
| *Vapor pressure* | 3.8 mm Hg @ 20°C (ACGIH, 1991) |
| *Flashpoint* | 44°C, closed cup |
| *Explosive limits* | upper = 15.6% |
| | lower = 1.7% |
| *Solubility* | miscible with water and organic solvents |
| *Odor threshold* | 2.7 ppm (geometric mean) (AIHA, 1989) |
| *Odor description* | sweet, fruity, ester-like (AIHA, 1989) |
| *Metabolites* | ethoxyacetic acid (Groeseneken *et al*., 1986) |
| *Conversion factor* | 1 ppm = 3.69 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Ethylene glycol monoethyl ether (EGEE) is used as a solvent for nitrocellulose, and natural and synthetic resins.  It is used in lacquers, varnish removers, and cleaning solutions and as an antifreeze in jet fuel.  EGEE is also used in the dyeing and printing of textiles.

**IV.    Acute Toxicity to Humans**

Investigators conducting an animal experiment on the acute toxicity of EGEE intentionally exposed themselves to 6,000 ppm EGEE for "a few seconds" and reported eye irritation and a "disagreeable odor" (Waite *et al*., 1930).

Reports of acute human toxicity following EGEE inhalation were not found in the literature. Cyanosis, pulmonary edema, and tonic-clonic spasms were reported in a woman who accidentally ingested approximately 40 ml EGEE (Reprotext, 1999).

Resting individuals exposed to EGEE retained 64% of the inhaled dose (Groeseneken *et al*., 1986). The main metabolite of EGEE detectable in the urine of exposed persons is ethoxyacetic acid (Veulemans *et al*., 1987).

The incidence of anemia and granulocytopenia was significantly increased in shipyard painters exposed to low levels (below the TLV of 5 ppm (20 mg/m³)) of EGEE for a mean of 8 years as compared to controls (Welch and Cullen, 1988). Concomitant exposure to lead and benzene may have occurred, but the authors report that the approximate exposure levels of these toxicants during the study period were negligible.

*Predisposing Conditions for EGEE Toxicity*

**Medical**:     Persons with preexisting eye, skin, kidney or blood conditions may be more sensitive (Reprotext, 1999).

**Chemical**:     Persons with concomitant exposure to ethylene glycol or other glycol ethers may be more sensitive to the effects of EGEE exposure (Reprotext, 1999) since ethoxyacetic acid is a common metabolite among glycol ethers.

## V.     Acute Toxicity to Laboratory Animals

A 7-hour $LC_{50}$ in mice of 1,820 ppm EGEE has been reported (Werner *et al*., 1943).

Four of six guinea pigs exposed to 6,000 ppm EGEE for 24-hours died; one of six guinea pigs exposed to 6,000 ppm EGEE for 8-hours died (Waite *et al*., 1930). One of six guinea pigs exposed to 1,000 ppm EGEE for either 16 or 24-hours died following exposure. Pulmonary edema, hyperemia in the kidneys, abdominal distention, and discoloration of the stomach contents were noted at necropsy of the above animals.

## VI.     Reproductive or Developmental Toxicity

EGEE is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard.

An increased prevalence of oligospermia and azoospermia and an increased odds ratio (OR 1.85; 95% CI = 0.6-5.6) for lower sperm count were observed in a study of shipyard painters exposed to a mean of 0.8 ppm EGEE for an average of 8 years compared to unexposed workers (Welch *et al*., 1988). Lower sperm count was also reported in workers exposed to a geometric mean air concentration of 6.6 ppm EGEE for at least one month (Ratcliffe *et al*., 1989).

Exposure of male rats by gavage to 936, 1,872, and 2,808 mg EGEE/kg/day for 5 consecutive days was reported to result in reversible impairment of testicular function as indicated by significantly decreased sperm counts and increased abnormal sperm morphology (Oudiz *et al.*, 1984).

Pregnant rats were exposed to 10, 50, and 250 ppm (40, 200, and 920 mg/m³) EGEE 6 hours per day on days 6-15 of gestation (Tinston *et al.*, 1983). Maternal toxicity as indicated by reduced hemoglobin, hematocrit, and mean cell volume in red blood cells was observed in rats exposed to 250 ppm EGEE. A significant reduction in the number of live fetuses was observed in rats exposed to 10 and 250 ppm, and a reduction in total litter weight was observed in rats exposed to 10 ppm and 50 ppm. Statistically significant pre-implantation loss was observed in all exposed groups and was statistically significant at 10 and 50 ppm EGEE. However, a dose-response relationship was not observed. Furthermore, since the first exposure to EGEE occurred on the expected day of implantation (gestational day 6), there was some question as to whether any increase in pre-implantation loss was exposure-related. Intergroup comparison showed significantly increased incidence of total minor skeletal defects in fetuses in the 250 ppm dose group; delayed ossification was the most common abnormality observed at this dose. Specific skeletal defects, including delayed ossification of the cervical vertebrae and sternebrae and the presence of extra ribs, were significantly increased in both the 50 and 250 ppm dose groups.

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

**Mild Adverse Effect Level**

Because the most sensitive effect observed is developmental toxicity, a severe adverse effect, and since this effect is observed at or below the threshold for a less serious effect, no mild adverse effect level is recommended.

**Reference Exposure Level for 6 hour exposure (protective against severe adverse effects): 0.1 ppm (370 µg/m³)**

Because of uncertainty in extrapolating from a repeated dose study to a one-hour concentration, for the reproductive/developmental endpoint we have chosen to use one day's exposure as the basis for the REL. Thus, the REL for EGEE is for a 6 hour exposure.

| | |
|---|---|
| *Study* | Tinston *et al.*, 1983; Doe, 1984 |
| *Study population* | pregnant rats |
| *Exposure method* | inhalation 6 hours per day on days 6-15 of gestation |
| *Critical effects* | specific skeletal defects, including delayed ossification of the cervical vertebrae and sternebrae and extra ribs |
| *LOAEL* | 50 ppm |
| *NOAEL* | 10 ppm |
| *Exposure duration* | 6 hours per day |
| *LOAEL uncertainty factor* | 1 |

| | |
|---|---|
| *Interspecies uncertainty factor* | 10 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 100 |
| *Reference Exposure Level* | 0.1 ppm (0.37 mg/m³; 370 µg/m³) |

**Level Protective Against Life-threatening Effects**

Mice were exposed to concentrations of 1,130-6,000 ppm EGEE for a single 7-hour exposure (Werner *et al*., 1943). Mortality during and up to 3 weeks following exposure was recorded.

The following data were used for benchmark calculation:

| | EGEE concentration (ppm) | | | | | | |
|---|---|---|---|---|---|---|---|
| 7-hour data | 1,130 | 1,580 | 1,740 | 1,830 | 2,210 | 2,800 | 5,500 |
| 1-hour equivalent | 2,990 | 4,180 | 4,604 | 4,842 | 5,847 | 7,408 | 14,552 |
| Mortality | 2/16 | 4/16 | 6/14 | 9/16 | 11/16 | 15/16 | 16/16 |

A benchmark dose approach employed a log-normal probit analysis (Crump, 1983) of 7-hour mouse lethality data from Werner *et al*. (1943). The 7-hour exposure concentrations were extrapolated to 1-hour exposure equivalents using the equation $C^n * T = K$, where $n = 2$. From the 1-hour data, the concentration associated with a 5% incidence of lethality ($ED_{05}$) was 3,307 ppm; the lower confidence limit (LCL) on this concentration [the $BC_{05}$] was 2,223 ppm. An uncertainty factor (UF) of 30 was applied to the $BC_{05}$ of 2,223 ppm (3 to account for interspecies variability and 10 for interindividual human variation).

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The final level protective against life-threatening effects for EGEE is therefore 74 ppm (270 mg/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% response rates are indicated below. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Comparison of benchmark concentrations (1% vs 5%)

| Response rate | MLE (ppm) | 95% LCL (ppm) |
|---|---|---|
| 1% | 2,766 | 1,635 |
| 5% | 3,307 | 2,223 |

**VIII. References**

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 564-566.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 18.

Crump KS and Co., Inc. Probit (Log-Normal) software for the IBM-PC. Ruston (LA); 1983.

Doe JE. Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. Environ Health Perspect 1984;57:33-41

Groeseneken H, Veulemans H, Masschelein R. Respiratory uptake and elimination of ethylene glycol monoethyl ether after experimental human exposure. Br J Ind Med 1986;43:544-549.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Oudiz DJ, Zenick H, Niewenhuis RJ, McGinnis PM. Male reproductive toxicity and recovery with acute ethoxyethanol exposure in rats. J Toxicol Environ Health 1984;13:763-775.

Ratcliffe JM, Schrader SM, Clapp DE, Halpern WE, Turner TW, Hornung RW. Semen quality in workers exposed to 2-ethoxyethanol. Br J Ind Med 1989;46:399-406.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Tinston DJ, Doe JE, Godley MJ, Head LK, Killick M, Litchfield MH, *et al*. Ethylene glycol monoethyl ether (EE): teratogenicity study in rats. Imperial Chemical Industries PLC. Report No. CTL/P/761 to Chemical Manufacturers Association 1983.

Veulemans H, Groeseneken D, Massachelein R, Van Vlem E. Field study of the urinary excretion of ethoxyacetic acid during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate. Scand J Work Environ Health 1987;13:239-242.

Waite CP, Patty FA, Yant WP. Acute response of guinea pigs to vapors of some new commercial organic compounds. Pub Health Rep 1930;45:1459-1466.

Welch LS, Cullen MR. Effect of exposure to ethylene glycol ethers on shipyard painters: III. Hematologic effects. Am J Ind Med 1988;14:527-536.

Welch LS, Schrader SM, Turner TW, Cullen MR. Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. Am J Ind Med 1988;14:509-526.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.

ACUTE TOXICITY SUMMARY

**ETHYLENE GLYCOL MONOETHYL ETHER ACETATE**

*(2-ethoxyethyl acetate, Cellosolve acetate)*

**CAS Registry Number: 111-15-9**

**I.      Acute Toxicity Summary (for a 6-hour exposure)**

| | |
|---|---|
| *Inhalation reference exposure level* | **140 μg/m³** |
| *Critical effect(s)* | developmental defects |
| *Hazard Index target(s)* | Reproductive/developmental; Nervous System |

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

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_6H_{12}O_3$ |
| *Molecular weight* | 132.2 |
| *Density* | 0.975 g/cm³ @ 20°C |
| *Boiling point* | 156°C |
| *Melting point* | -61.7°C |
| *Vapor pressure* | 2 mm Hg @ 20°C |
| *Flashpoint* | 49° C (ACGIH, 1991) |
| *Explosive limits* | upper = 12.7% |
| | lower = 1.7% |
| *Solubility* | soluble in water, alcohol, ether, acetone |
| *Odor threshold* | 0.060 ppm (geometric mean) (AIHA, 1989) |
| *Odor description* | mild, ester-like odor |
| *Metabolites* | ethylene glycol monoethyl ether, ethoxyacetic acid (Groesenken *et al.*, 1987) |
| *Conversion factor* | 1 ppm = 5.41 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Ethylene glycol monoethyl ether acetate (EGEEA) is used as a solvent for nitrocellulose, low viscosity cellulose, and resins (Doe, 1984).  It is also used as a solvent in coating applications for automobiles, coils, machinery and equipment, and metal furniture and appliances (NIOSH, 1991).

**IV.    Acute Toxicity to Humans**

Headaches, lethargy, sinus problems, nausea, and heartburn were reported by two silk screening workers following occupational exposures ranging from 0.5 to 3.9 ppm (3 to 21 mg/m³) EGEEA (Boiano, 1983).  Both workers reported that their symptoms improved when they were away

from work.  Dermal absorption and concomitant exposure to other organic solvents may have contributed to the observed symptoms.

It was reported in a human pharmacokinetic study that EGEEA was converted to ethylene glycol ethyl ether (EGEE) by plasma esterases and subsequently metabolized to ethoxyacetic acid (Groeseneken *et al*., 1987).  Ethoxyacetic acid, accounting for 22.2% of the absorbed dose, was found in the urine of EGEEA exposed subjects.

*Predisposing Conditions for EGEEA Toxicity*

**Medical**:     Persons with preexisting eye, respiratory, or neurologic conditions may be more sensitive to the effects of EGEEA exposure (Reprotext, 1999).

**Chemical**:     Persons with concurrent exposure to ethylene glycol monoethyl ether (EGEE) or to ethylene glycol may be more sensitive to the effects of EGEEA exposure because EGEE is a metabolite of EGEEA (Reprotext, 1999).

## V.     Acute Toxicity to Laboratory Animals

An 8-hour $LC_{50}$ in female rats is reported as 2,200 ppm (12,000 mg/m³) EGEEA (Pozzani *et al*., 1959).  However, the lethality data were generated using chemical mixtures, not EGEEA alone.

Hemoglobinuria and hematuria were observed in rabbits following a 4-hour exposure to 2,000 ppm (11,000 mg/m³) EGEEA (Truhaut *et al*., 1979).  No other signs of toxicity were noted either during a post-exposure observation period or at necropsy.

Osmotic fragility was compared in the erythrocytes of EGEEA exposed animals and unexposed animals (Carpenter *et al*., 1956).  The erythrocytes of rats exposed to 62 ppm (340 mg/m³) EGEEA for 4-hours exhibited increased osmotic fragility as compared to the erythrocytes of unexposed rats.  No increase in erythrocyte fragility was observed following a 4-hour exposure to 32 ppm (170 mg/m³) EGEEA.

## VI.     Reproductive or Developmental Toxicity

EGEEA is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard.

Tinston and colleagues (1983) exposed pregnant rabbits to 25, 100, or 400 ppm (140, 500, or 2,000 mg/m³) EGEEA 6 hours per day on days 6-18 of gestation.  Significant maternal toxicity, as indicated by decreased food consumption and body weight, and a significant reduction in hemoglobin concentration were observed in the rabbits exposed to 400 ppm EGEEA.  One fetus in the 25 ppm EGEEA exposed group had agenesis of the left kidney.  Right kidney agenesis was observed in one fetus in the 400 ppm EGEEA exposed group.  A review of the data is presented by Doe (1984).

In another study, embryotoxicity was observed following exposure of pregnant rats to 390 and 600 ppm (2,100 and 3,000 mg/m³) EGEEA 7 hours per day on days 7-15 of gestation (Nelson *et al*., 1984).  Decreased fetal body weight and a statistically significant increase in the incidence of heart, umbilicus, and rib malformations were observed in rats following maternal exposure to 130 ppm (700 mg/m³) EGEEA.  No significant maternal toxicity was noted.

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

### Mild Adverse Effect Level

Because the most sensitive effect observed is developmental toxicity, a severe adverse effect, and since this effect occurs at or below the threshold for a mild adverse effect, no mild adverse effect level is recommended.

### Reference Exposure Level for a 6 hour exposure (protective against severe adverse effects): 140 µg/m³

Because of the uncertainty of extrapolating from a repeated dose study to a one-hour concentration, for the reproductive/developmental endpoint, we have chosen to use one-day's exposure as the basis for the REL. Thus, for EGEEA the REL is for a 6-hour exposure.

| | |
|---|---|
| *Study* | Tinston *et al*., 1983 |
| *Study population* | pregnant rabbits |
| *Exposure method* | inhalation of 25, 100, or 400 ppm 6 hours per day on days 6-29 of gestation. |
| *Critical effects* | developmental defects |
| *LOAEL* | 25 ppm |
| *NOAEL* | not observed |
| *Exposure duration* | 6 hours |
| *LOAEL uncertainty factor* | 10 |
| *Interspecies uncertainty factor* | 10 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 1,000 |
| *Reference Exposure Level* | 0.025 ppm (0.14 mg/m³; 140 µg/m³) |

Significantly decreased fetal weights and increased incidence of skeletal defects were observed following exposure to 100 or 400 ppm EGEEA.  Maternal toxicity as indicated by a dose-related decrease in food consumption was observed in all exposed groups.  Kidney agenesis was observed in one fetus from both the 25 ppm and 400 ppm EGEEA exposure groups.  Thus, the LOAEL for developmental effects was 25 ppm.

### Level Protective Against Life-threatening Effects

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

NIOSH (1995) lists a (revised) IDLH of 500 ppm for 2-ethoxyethyl acetate, based on acute inhalation toxicity (specifically lethality) data in animals (Pozzani *et al*., 1959; Smyth *et al*., 1941; Truhaut *et al*., 1979), but states that it may be a conservative value due to the lack of relevant acute inhalation toxicity data for workers.

## VIII.   References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 567-568.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 18.

Boiano JM. Health hazard evaluation determination report: Downing Displays, Incorporated, Cincinnati (OH). NIOSH Report No. HETA 1983;82-330-1252. Cincinnati (OH): US Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health; 1983. [cited in NIOSH, 1991.]

Carpenter CP, Pozzani UC, Weil CS, Nair JH III, Keck GA, Smyth HF Jr. The toxicity of butyl Cellosolve solvent. Arch Ind Health 1956;14:114-131.

Doe JE. Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. Environ Health Perspect 1984;57:33-44.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. Ethoxyacetic acid: a metabolite of ethylene glycol monoethyl ether acetate in man. Br J Ind Med 1987;44:488-493.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex Inc.; 1994. (Edition expires 4/30/94).

(NIOSH) National Institute for Occupational Safety and Health. Criteria for a recommended standard. Occupational exposure to ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates. Cincinnati (OH): US Department of Health and Human Services, Public Health Service, Centers for Disease Control, NIOSH, Division of Standards for Development and Technology Transfer; 1991.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

Nelson BK, Setzer JV, Brightwell WS, Mathinos PR, Kuczuk MH, Weaver TE, Goad PT. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. Environ Health Perspect 1984;57:261-271.

Pozzani UC, Weil CS, Carpenter CP. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single oral dose data. Ind Hyg J 1959:364-369.

Reprotext® System. Dabney B.J, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Smyth HF Jr, Seaton J, Fischer L. The single dose toxicity of some glycols and derivatives. J Ind Hyg Toxicol 1941;23:259-268

Ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J Hazard Mater 1983;13:301-309.

Tinston DJ, Doe JE, Killick ME, Thomas MR. Ethylene glycol monoethyl ether acetate (EEAc): inhalation teratogenicity study in rabbits. Imperial Chemical Industries PLC, Report No. CTL/P/840 to Chemical Manufacturers Association, 1983 [cited in Doe, 1984].

Truhaut R, Dutertre-Catella H, Phu-Lich N, Huyen VN. Comparative toxicological study of ethylglycol acetate and butylglycol acetate. Toxicol Appl Pharmacol 1979;51:117-127.

ACUTE TOXICITY SUMMARY

**ETHYLENE GLYCOL MONOMETHYL ETHER**

*(2-methoxyethanol, 1-hydroxy-2-methoxyethane, methyl cellosolve)*

**CAS Registry Number: 109-86-4**

**I.    Acute Toxicity Summary (for a 6-hour exposure)**

| | |
|---|---|
| *Inhalation reference exposure level* | **93 μg/m³** |
| *Critical effect(s)* | teratogenic effects |
| *Hazard Index target(s)* | Reproductive/developmental |

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

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_3H_8O_2$ |
| *Molecular weight* | 76.09 |
| *Density* | 0.965 g/cm³ @ 20°C |
| *Boiling point* | 125°C |
| *Melting point* | -85.1°C |
| *Vapor pressure* | 6.2 mm Hg @ 20°C |
| *Flashpoint* | 41.7° C (closed cup) (ACGIH, 1991) |
| *Explosive limits* | upper = 19.8% (ACGIH, 1991) |
| | lower = 2.5% (ACGIH, 1991) |
| *Solubility* | miscible with water, alcohol, benzene, ether, acetone |
| *Odor threshold* | 2.3 ppm (Amoore and Hautala, 1983) |
| *Odor description* | mild ethereal odor |
| *Metabolites* | methoxyacetic acid, carbon dioxide (Miller *et al.*, 1983) |
| *Conversion factor* | 1 ppm = 3.1 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Ethylene glycol monomethyl ether (EGME) is used as a solvent for cellulose acetate and resins (HSDB, 1994).  It is also used in dyeing leather and in the manufacture of photographic film. EGME is used as an antifreeze in jet fuels.  Quick drying varnishes, enamels, nails polishes and wood stains may also contain EGME.

**IV.    Acute Toxicity to Humans**

Acute overexposure to EGME may cause irritation of the eyes, nose, and throat, drowsiness, dizziness, headache, nausea, vomiting, disorientation, and loss of consciousness (HSDB, 1994). Fatigue and hematologic effects including decreased white and red blood cell counts, and decreased hemoglobin, hematocrit and platelet levels, were observed in a microfilm manufacturing worker following daily inhalation exposure for approximately 9 months to a mean concentration of 35 ppm EGME and substantial but unquantified dermal exposure (Cohen,

1984).  Concomitant exposure to methyl ethyl ketone and propylene glycol monomethyl ether was also reported.

Retention of EGME was reported to be 76% in seven male volunteers who inhaled 5 ppm EGME for 4 hours (Groeseneken *et al.*, 1989).  The average elimination half-life was 77 hours.  The majority (85%) of the inhaled dose was metabolized to methoxyacetic acid.

*Predisposing Conditions for EGME Toxicity*

**Medical**:    Persons with eye, neurologic, or hematologic conditions may be more sensitive to the effects of EGME exposure (Reprotext, 1999).

**Chemical**:    Persons exposed to other bone marrow suppressants or substances affecting the nervous system may be more sensitive to the effects of EGME exposure (Reprotext, 1999).

## V.    Acute Toxicity to Laboratory Animals

A 7-hour $LC_{50}$ in mice of 1,480 ppm (4,736 mg/m³) was reported (Werner *et al.*, 1943).  Rats were exposed to 100, 300, or 1,000 ppm (320, 960, or 3,200 mg/m³) EGME for 6 hours per day for 9 days (Miller *et al.*, 1981).  Reduced bone marrow cellularity, severe degeneration and necrosis of the germinal epithelium in the testes, and severe lymphoid depletion in the cortex of the thymus were observed at necropsy following exposure to 1,000 ppm (3,200 mg/m³) EGME.  Red and white blood cell counts and hemoglobin levels were significantly reduced in female rats exposed to 300 or 1,000 ppm, and in male rats exposed to 100, 300, or 1,000 ppm EGME.

Methoxyacetic acid and carbon dioxide were the main metabolites measured in the urine, feces and exhaled air of male rats following oral exposure to EGME (Miller *et al.*, 1983).  The majority of the metabolites were recovered in the urine, with smaller amounts in the exhaled air and feces.

## VI.    Reproductive or Developmental Toxicity

EGME is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard with male reproductive toxicity and developmental endpoints.

Hanley and colleagues (1984) exposed pregnant rats and rabbits to 3, 10, or 50 ppm (9.6, 32, or 160 mg/m³) EGME for 6 hours per day on days 6-15 (rats) or 6-18 (rabbits) of gestation.  Pregnant mice were exposed to 10 or 50 ppm (32 or 160 mg/m³) EGME for 6 hours per day on days 6-15 of gestation.  A statistically significant increase in the incidence of skeletal variations was observed in rats and mice following maternal exposure to 50 ppm EGME.  Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights were observed in rabbits following maternal exposure to 50 ppm EGME.  In rabbits, a significant increase in the rate of fetal resorption was observed in the 10 ppm exposure group.  Thus 10 ppm was considered a LOAEL for increased resorptions and 3 ppm a NOAEL.  Although the authors

attribute the statistical significance of this effect to an unusually low rate of resorptions in controls compared to historical controls, historical control data were not presented.

Maternal toxicity as indicated by decreased body weight gain was observed in all three species exposed to 50 ppm. Pregnant rats exposed to EGME exhibited statistically significant lower mean hemoglobin levels and packed cell volumes at all 3 exposure levels. Thus 3 ppm was selected as a LOAEL for these 2 hematologic effects. A NOAEL was not identified. A lower mean red blood cell count was observed in rat dams exposed to 50 ppm EGME.

In another study, male rats were exposed to 30, 100, and 300 ppm (96, 320, and 960 mg/m³) EGME for 6 hours per day, 5 days per week for 13 weeks before mating with unexposed female rats (Rao *et al*., 1983). A decrease in fertility, body and testes weights, and an increase in the incidence of gross and microscopic testicular and epididymal lesions were observed in the male rats exposed to 300 ppm (960 mg/m³). Complete resorption of all fetuses was observed in the unexposed females mated with the males exposed to 300 ppm EGME. A male reproductive NOAEL of 100 ppm (320 mg/m³) EGME was observed.

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

Level Protective against Mild Adverse Effects: Because the most sensitive effect observed is developmental toxicity, a severe adverse effect, and since this effect is observed at or below the threshold for a less serious effect, no mild adverse effect level is recommended.

**Reference Exposure Level for 6 hr exposure (Protective Against Severe Adverse Effects): 0.03 ppm (93 μg/m³)**

| | |
|---|---|
| *Study* | Hanley *et al*., 1984 |
| *Study population* | pregnant rabbits |
| *Exposure method* | inhalation of 3, 10, or 50 ppm EGME 6 hours per day on days 6-15 of gestation |
| *Critical effects* | gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights |
| *LOAEL* | 10 ppm |
| *NOAEL* | 3 ppm |
| *Exposure duration* | 6 hours |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty factor* | 10 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 100 |
| *Reference Exposure Level* | 0.03 ppm (0.093 mg/m³; 93 μg/m³) |

Pregnant rabbits were exposed to 3, 10, or 50 ppm EGME 6 hours per day on days 6-18 of gestation (Hanley *et al*., 1984). Maternal toxicity, as indicated by decreased body weight gain, was observed only in rabbits exposed to 50 ppm EGME. The authors report that the hematologic parameters of EGME exposed rabbits were not altered at any dose. Gross soft tissue and skeletal

teratogenic effects and significantly decreased fetal body weight were observed in rabbits following maternal exposure to 50 ppm EGME. Statistically significant increases in fetal resorption rates were observed following maternal exposure to 10 or 50 ppm EGME. A NOAEL of 3 ppm for increased resorptions was used to develop the REL. An uncertainty factor of 100 was applied to account for inter- and intraspecies differences. Dividing this by 100 gives a level protective against severe adverse effects for a 6 hour exposure of 0.03 ppm ($0.093$ mg/m$^3$; 93 $\mu$g/m$^3$).

**Level Protective Against Life-threatening Effects**

Mice were exposed to EGME at concentrations of 930 to 6,800 ppm for a single 7-hour exposure (Werner *et al*., 1943). The mortality during exposure and up to three weeks following were recorded. The NOAEL was 930 ppm and was extrapolated from 7-hour to 1-hour exposure using a modification of Haber's equation, $C^n * T = K$, where n = 2. An uncertainty factor (UF) of 100 was applied to the time-adjusted NOAEL of 2,461 ppm to account for interspecies variability and individual human variation. The final 1-hour level protective against life-threatening effects for EGME is 25 ppm. (A benchmark dose approach (Crump, 1984; Crump and Howe, 1983) could not be employed because log-normal probit analysis of the lethality data was shown to be too heterogeneous.)

NIOSH (1995) lists an IDLH of 200 ppm derived by multiplying the current NIOSH REL of 0.1 ppm by 2,000, an assigned protection factor for respirators.

## VIII.   References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 913-921.

Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds for compounds with threshold limit values and volatilities for 24 industrial chemicals in air and water dilution. J Appl Toxicol 1983;3(6):272-290.

Cohen R. Reversible subacute ethylene glycol monomethyl ether toxicity associated with microfilm production. A case report. Am J Ind Med 1984;6:441-446.

Crump KS. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:854-871.

Crump KS, Howe R. Probit-A computer program to extrapolate quantile animal toxicological data to low doses. Ruston (LA): KS Crump & Company Inc.; 1983.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. Experimental human exposure to ethylene glycol monomethyl ether. Int Arch Occup Environ Health 1989;61:243-7.

Hanley TR Jr, Yano BL, Nitschke KD, John JA. Comparison of the teratogenic potential of inhaled ethylene glycol monomethyl ether in rats, mice, and rabbits. Toxicol Appl Pharmacol 1984;75:409-422.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Miller RR, Ayres JA, Calhoun LL, Young JT, McKenna MJ. Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mice. Toxicol Appl Pharmacol 1981;61:368-377.

Miller RR, Hermann EA, Largvardt PW, McKenna MJ, Schwetz BA. Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. Toxicol Appl Pharmacol 1983;67:229-237.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

Rao KS, Cobel-Geard SR, Young JT, Hanley TR Jr, Hayes WC, John JA. Ethylene glycol monomethyl ether. II. Reproductive and dominant lethal studies in rats. Fundam Appl Toxicol 1983;3:80-85.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J Hazard Mater 1983;13:301-309.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.

ACUTE TOXICITY SUMMARY

**FORMALDEHYDE**

*(methanal, oxomethane, oxymethylene, methylene oxide,
formic aldehyde, methyl aldehyde)*

**CAS Registry Number: 50-00-0**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **94 μg/m³** |
| *Critical effect(s)* | eye irritation |
| *Hazard Index target(s)* | Eyes; Respiratory System; Immune System |

**II.     Physical and Chemical Properties (HSDB, 1993)**

| | |
|---|---|
| *Description* | colorless gas |
| *Molecular formula* | $CH_2O$ |
| *Molecular weight* | 30.03 |
| *Density* | 0.815 g/L @ -20°C |
| *Boiling point* | -19.5°C |
| *Melting point* | -92°C |
| *Vapor pressure* | 3883 mm Hg @ 25°C (Howard, 1989) |
| *Flashpoint* | 300° C or 573°F |
| *Explosive limits* | upper = 73% |
| | lower = 7% |
| *Solubility* | soluble in water, alcohol, ether, other polar solvents |
| *Odor threshold* | 0.05-0.5 ppm |
| *Odor description* | very pungent odor; straw-like |
| *Metabolites* | formic acid |
| *Conversion factor* | 1 ppm = 1.24 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Formaldehyde is used in the manufacture of melamine, polyacetal, and phenolic resins.  It is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids.  Mobile home interiors and pressed wood furniture are two other common sources of formaldehyde exposure.

**IV.    Acute Toxicity to Humans**

Exposure to moderate levels of formaldehyde (1-3 ppm) can result in eye and upper respiratory tract irritation (Weber-Tschoppe *et al*., 1977; Kulle *et al*., 1987).  Feinman (1988) states that

most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs.  High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984).

A few human case studies report severe pulmonary symptoms.  A medical intern with known atopy and exposure to formaldehyde over a period of 1 week developed dyspnea, chest tightness, and edema, following a final 2 hour exposure to high concentrations of formaldehyde (Porter, 1975).  Five workers exposed to high concentrations of formaldehyde from urea-formaldehyde foam insulation experienced intolerable eye and upper respiratory tract irritation, choking, marked dyspnea, and nasal obstruction (Solomons and Cochrane, 1984).  However, the concentration of formaldehyde and the contribution of other airborne chemicals were unknown in both of the reports.

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects (Harving *et al*., 1990; Kulle *et al*., 1987; Sheppard *et al*., 1984; Witek *et al*., 1986; Witek *et al*., 1987; Schachter *et al*., 1986; Schachter *et al*., 1987; Sauder *et al*., 1986; Sauder *et al*., 1987; Frigas *et al*., 1984; Uba *et al*., 1989; Akbar-Khanzadeh *et al*., 1994).  Short exercise sessions during exposure on a bicycle ergometer were included in some of the studies.  Concentrations of formaldehyde in the human exposure studies ranged as high as 3 ppm for up to 3 hours.  The major findings in these studies were mild to moderate eye and upper respiratory tract irritation, typical of mild discomfort from formaldehyde exposure.

In a human irritation study by Weber-Tschoppe *et al*. (1977), 33 subjects were exposed to formaldehyde at concentrations ranging from 0.03-3.2 ppm (0.04-4.0 mg/m³) for 35 minutes.  Thresholds were 1.2 ppm (1.5 mg/m³) for eye and nose irritation, 1.7 ppm (2.1 mg/m³) for eye blinking, and 2.1 ppm (2.6 mg/m³) for throat irritation.

Kulle *et al*. (1987) exposed nonasthmatic humans to up to 3.0 ppm (3.7 mg/m³) formaldehyde in a controlled environmental chamber for 3 hours.  Significant dose-response relationships were seen with odor and eye irritation.  At 0.5 ppm for 3 hours, none of 9 subjects had eye irritation.  At 1.0 ppm, 3 of 19 subjects reported mild eye irritation and one experienced moderate irritation.  At 2.0 ppm, 6 subjects reported mild and 4 reported moderate eye irritation.  Nasal flow resistance was increased at 3.0 ppm but not at 2.0 ppm (2.5 mg/m³).  There were no significant decrements in pulmonary function nor increases in methacholine induced bronchial reactivity as a result of 3-hour exposures to 0.5-3.0 ppm (0.6-3.7 mg/m³) formaldehyde at rest or at exercise, including 24 hours post exposure.

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m³ formaldehyde for 2 hours (Pazdrak *et al*., 1993).  Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure.  Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in nasal lavage fluid 4 and 18 hours after exposure.  No differences were found between patients with skin sensitization and healthy subjects.

In a study by Green *et al*. (1987), volunteer asthmatic and normal subjects exposed to formaldehyde developed clinically significant decrements in pulmonary function.  Exposure to 3 ppm formaldehyde for 1 hour resulted in clinically significant reductions of $FEV_1$ (defined as > 20% or more) and $FEV_1/FVC$ (ratio 70% or less) in 5 individuals in the study (2 of 16 asthmatics, 2 of 22 normal subjects, and one clinically normal subject with hyperactive airways).  Of these individuals, 3 had reductions of $FEV_1$ of 20% or more during exposure.  One of 22 asthmatics had a greater than 20% reduction in $FEV_1$ (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation $[V_E]$ = 30-40 l/min), which, according to the authors, was low enough to prevent exercise-induced bronchospasm.  One of 22 normal subjects also exhibited a greater than 20% clinically significant reduction in $FEV_1$ (-24.4%) and in $FEV_1/FVC$, which occurred at 47 minutes into exposure to 3 ppm formaldehyde.  These reductions occurred following a second 15 minute heavy exercise session ($V_E$ = 60-70 l/min) near the end of the 1 hour exposure period.  A third asymptomatic "normal" subject with hyperactive airways had a clinically significant reduction of $FEV_1$ (-20.5%) at 17 minutes, following the first heavy exercise session.  This subject exhibited occult airway hyperactivity and was excluded from analysis with the other exposure groups due to his respiratory condition.  Subjects exhibiting reductions in $FEV_1$ of greater than 20% following exposure also exhibited $FEV_1/FVC$ ratios of less than 70%.  However, none of the subjects in the study exhibited a clinically significant reduction of 50% or greater in airway conductance ($SG_{aw}$) during exposure to 3 ppm formaldehyde.  Other than mild nose and throat irritation, no severe respiratory signs and symptoms were apparently reported.

Sim and Pattle (1957) exposed twelve men to 17.3 mg/m³ (13.9 ppm) formaldehyde for 30 minutes.  This concentration caused "considerable nasal and eye irritation when they first entered the chamber; but despite the continued mild lacrimation for some period of time, there was no marked response (pulmonary or cardiovascular) to the exposure."  The eye irritation was not severe, according to the authors, and resolved after 10 minutes in the chamber.

Kriebel and associates (1993) studied 24 physical therapy students dissecting cadavers for 3 h per week for 10 weeks. Measured formaldehyde exposures in the breathing zone ranged from 0.49 to 0.93 ppm (geometric mean ± SD = 0.73 ± 1.22).  There was a pronounced increase in irritant symptoms over the duration of the each laboratory period, but this effect was stronger at the beginning of the study period.  Peak expiratory flow (PEF) declined over the 10 week study by an average of 10 L/min (statistically significant trend in random-effects regression models).  Fourteen weeks after ceasing exposures, the group mean baseline PEF had returned to the pre-exposure level.  Mean PEF decreased over each laboratory period, although this effect was less noticeable over the course of the semester.

Rhinitis and a wide range of asthma-like conditions can result from exposure to formaldehyde.  Some studies have reported that workers exposed to low concentrations may develop severe prolonged asthma attacks after prior exposure; this suggests that they may have become sensitized (Feinman, 1988).  However, there is little evidence to suggest that formaldehyde exposure can result in sensitization through IgE- and IgG-mediated mechanisms (Chang and Gershwin, 1992; Heck *et al*., 1990; Bardana and Montanaro, 1987).

Formaldehyde provocation of human subjects, occupationally exposed to formaldehyde and suffering from asthma-like symptoms such as wheezing, shortness of breath, or rhinitis, occasionally resulted in pulmonary function decrements (2 to 33% response rate) consistent with immediate, delayed, or both immediate and delayed bronchoconstriction (Nordman *et al*., 1985; Burge *et al*., 1985; Henrick and Lane, 1977; Wallenstein *et al*., 1978). While some of the concentrations of formaldehyde that elicited a positive response following provocation tests (6 to 20.7 ppm) were quite high, the authors suggested that formaldehyde-induced bronchial hyperreactivity is due to specific sensitization to the gas. However, no study was able to detect antibodies to formaldehyde which would prove that sensitization to formaldehyde occurs through an immunologic pathway.

In controlled studies with asthmatics from urea-formaldehyde insulated homes, formaldehyde concentrations equal to or greater than those found in indoor environments have not resulted in hematologic or immunologic abnormalities. These tests include: blood count and differential, erythrocyte sedimentation rate; lymphocyte subpopulations (E-rosetting, T3, T4, T8, B73.1, Fc receptor positive lymphocytes and large granular lymphocytes); lymphocyte response to phytohemagglutinin and formalin-treated red blood cells; serum antibody against the Thomsen-Friedenrich RBC antigen and against formalin-RBC; and natural killer, interferon-boosted natural killer, and antibody-dependent cell-mediated cytotoxicity (Pross *et al*., 1987). In addition, nearly all exposure studies on patients with asthma have failed to demonstrate that exposure to formaldehyde results in onset or aggravation of the patients' asthmatic symptoms (Harving *et al*., 1990; Sheppard *et al*., 1984).

The binding of formaldehyde to endogenous proteins creates haptens which can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher *et al.*, 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher *et al.* (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

The effects of formaldehyde on asthmatics appear to be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief durations exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and $FEV_1$) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m$^3$) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

Dermal contact with formaldehyde may result in an erythematous or eczematous dermatitis reaction on exposed areas (Feinman, 1988). Dermal sensitization can result.

Gorski et al (1992) evaluated the production of active oxygen species by neutrophils in 18 persons exposed to 0.5 mg/m³ formaldehyde for 2 hours. All 13 subjects who had allergic contact dermatitis (tested positive to formaldehyde in skin patch) exhibited significantly higher chemiluminescence of granulocytes isolated from whole blood 30 minutes and 24 hours post-exposure than the individuals who were not formaldehyde sensitive. Thus, the immune cellular response of skin-sensitized individuals to an inhalation exposure to formaldehyde indicates increased production of active oxygen species. The significance of this result is unclear but may have repercussions for toxicological effects mediated by active oxygen species.

*Predisposing Conditions for Formaldehyde Toxicity*

**Medical:** Persons with eye, skin, respiratory, or allergic conditions (especially asthma) may be more sensitive to the effects of formaldehyde (Reprotext, 1999). Asthmatics sensitized to formaldehyde may be more sensitive to formaldehyde at low concentrations than non-sensitized individuals.

**Chemical**: Formaldehyde reacts with hydrochloric acid to form bis-chloroacetyl ether, a carcinogen (Reprotext, 1993).

## V. Acute Toxicity to Laboratory Animals

In 72 rats exposed to approximately 600-1,700 mg/m³ (500-1,400 ppm) formaldehyde vapor for 30 minutes the $LC_{50}$ was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950). The first deaths did not occur until 6 hours after cessation of exposure. Respiratory difficulty lasted several days after exposure and the last of 49 rats died after 15 days of purulent bronchitis and diffuse bronchopneumonia. Three weeks following exposure, histological examinations of the 23 surviving animals revealed bronchitis, pulmonary microhemorrhages, and edema. No changes were seen in other organs.

A multispecies study by Salem and Cullumbine (1960) showed that a 10-hr exposure to 15.4 ppm (19 mg/m³) formaldehyde vapor killed 3/5 rabbits, 8/20 guinea pigs, and 17/50 mice. The report stated that formaldehyde exposure resulted in delayed lethality.

Alarie (1981) determined the 10 minute $LC_{50}$ for formaldehyde in mice to be 2,162 ppm (95% confidence interval, 1,687-2,770 ppm). The post-exposure observation period was 3 hours. From the concentration mortality graph provided in the report, an $MLE_{05}$ and $BC_{05}$ of 1,440 ppm and 778 ppm, respectively, could be estimated for a 10 minute formaldehyde exposure. However, as indicated in the previous reports, delayed deaths occur with formaldehyde which suggests that the 3-hour post-exposure observation period used in this study may not have been long enough.

In other lethality studies, Nagornyi *et al*. (1979) determined a 4 hour formaldehyde $LC_{50}$ in rats and mice to be 588 mg/m³ (474 ppm) and 505 mg/m³ (407 ppm), respectively.  However, the raw data for this study were not included in the report.  Horton *et al*. (1963) observed that 2 hour exposure of mice to 0.9 mg/l (900 mg/m³) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but 2 hour exposure to 0.14 mg/l (140 mg/m³) did not produce signs of "substantial distress."  In a lethality study by Carpenter *et al*. (1946), 250 ppm formaldehyde for 4 hours resulted in deaths of 2-4 out of 6 albino rats (actual number of deaths not specified) and exposure to 125 ppm formaldehyde for 4 hours resulted in deaths of 0-1 out of 6 albino rats.

Swiecechowski *et al*. (1993) exposed groups of five to seven guinea pigs to 0.86, 3.4, 9.4, or 31.1 ppm (1.1, 4.2, 11.6, or 38.6 mg/m³) formaldehyde for 2 hr, or to 0.11, 0.31, 0.59, or 1.05 ppm (0.14, 0.38, 0.73, 1.30 mg/m³) formaldehyde for 8 hours.  An 8-hour exposure to $\geq$ 0.3 ppm ($\geq$ 0.4 mg/m³) formaldehyde was sufficient to produce a significant increase in airway reactivity.  Similar effects occurred after > 9 ppm (> 11 mg/m³) formaldehyde for the 2-hour exposure group.  Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine (or carbachol) *ex vivo*.  No inflammation or epithelial damage was seen up to 4 days post exposure.  The researchers suggest that duration of exposure is important to the induction of airway hyperreactivity and that prolonged (8-hour), low-level exposures may generate abnormal physiologic responses in the airways not detectable after acute (2-hour) exposures.

Male F-344 rats, 7-9 weeks old, were exposed to 0.5, 2, 6 or 15 ppm formaldehyde for 6 hours per day for 1 to 4 days (Monteiro-Riviere and Popp, 1986). Effects noted in the rat nasal respiratory epithelium with 0.5 or 2 ppm were limited to altered cilia with occasional wing-like projections on the ends of the ciliary shafts. Effects noted at 6 ppm for 1 day were autophagic vacuoles in some basal cells, neutrophils in the basal and suprabasal layers, and hypertrophy of goblet and ciliated cells. Loss of microvilli in ciliated cells was noted at all exposure concentrations.

Rats were exposed to 0, 5, 10 or 20 ppm formaldehyde for 3 hours per day on 2 consecutive days (Boja *et al*., 1985).  Decreased motor activity and neurochemical changes in dopamine and 5-hydroxytryptamine neurons were reported.

## VI.    Reproductive or Developmental Toxicity

There are no studies that conclusively show adverse reproductive or developmental effects in animals exposed to formaldehyde (Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988).  In humans there are few data on the association of teratogenicity or adverse reproductive effects with formaldehyde exposure.  Existing data do not suggest that formaldehyde, by any route, produces significant teratogenic or reproductive effects (Reprotext, Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988).

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

**Reference Exposure Level (protective against mild adverse effects):   94 µg/m³**

| | |
|---|---|
| *Study* | Kulle *et al*. (1987) |
| *Study population* | 19 nonasthmatic, nonsmoking human subjects |
| *Exposure method* | 0.5-3.0 ppm |
| *Critical effects* | mild and moderate eye irritation |
| *LOAEL* | 1 ppm |
| *NOAEL* | 0.5 ppm |
| *Benchmark concentration* | 0.44 ppm ($BC_{05}$) |
| *Exposure duration* | 3 hours |
| *Extrapolated 1 hour concentration* | 0.76 ppm $(0.44^2 \text{ ppm}* 3 \text{ h} = C^2 * 1 \text{ h})$ |
| | (see Table 12 for information on "n") |
| *LOAEL uncertainty factor* | not required in BC approach |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 10 |
| *Reference Exposure Level* | 0.076 ppm (0.094 mg/m³; 94 µg/m³) |

The recommended REL was estimated by a benchmark concentration ($BC_{05}$) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983).  The $BC_{05}$ is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%.  The resulting $BC_{05}$ from this analysis was 0.44 ppm (0.53 mg/m³) formaldehyde.  This value was adjusted to a 1-hour duration using the formula $C^n * T = K$ , where n = 2 (AICE, 1989), resulting in a value of 0.74 ppm.  An uncertainty factor (UF) of 10 was used to account for individual variation.  Generally an uncertainty factor of 3 would be used with the $BC_{05}$ for intraindividual variability, since the $BC_{05}$ accounts for some degree of individual variation.  However, information from the literature indicates a wide variability in response to formaldehyde irritancy including reports of irritation (NIOSH HHE reports 1981-1996; Liu et al. 1991; Horvath et al, 1985) or cellular changes associated with irritation and an immune response at levels below the one-hour extrapolated $BC_{05}$ (Pazdrak et al, 1993; Gorski et al, 1992).  For these reasons, we used an uncertainty factor of 10 to account for intraindividual variability in the human population.

$$REL = BC_{05}/(UF)$$

The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for response rates of 1% and 5% are compared below.  For a graphical representation of the derivation of the REL, refer to section IX.

The study reported by Pazdrak and associates (1993) was not selected as the key study because lack of information on the method used to estimate exposure concentrations and additional limitations in reporting data reduce the level of confidence in this study.  The study adds weight, however, to the REL and to the conclusion that low-level exposures  may cause adverse health effects.

Table 1. Comparison of benchmark concentration calculations (1% vs 5%)

| Response rate | MLE (ppm) | 95% LCL (ppm) |
|---|---|---|
| 1% | 0.50 | 0.25 |
| 5% | 0.72 | 0.44 |

**Level Protective Against Severe Adverse Effects**

Based on the results of Green *et al.* (1987), an acute LOAEL of 3 ppm formaldehyde in asthmatics for a duration of 17 minutes (immediately following moderate exercise for 15 minutes) was determined. The researchers felt that, when examined along with the other 3 studies in the series (Kulle *et al.*, 1987; Sauder *et al.*, 1987; Sauder *et al.*, 1986), this study represented a threshold where protective mechanisms of the respiratory tract were beginning to be overwhelmed. Only Green *et al.* (1987) identified 5 out of 39 asthmatic and healthy subjects as having clinically significant decrements in $FEV_1$ (defined as > 10%). However, 3 of these 5 subjects (out of 39 asthmatic and healthy subjects) responded with a 20% or greater decrease in $FEV_1$, which is considered a severe adverse effect for acute toxicity exposure. The dose of formaldehyde necessary to produce pulmonary deficits in the Green *et al.* study is consistent with the dose necessary to produce pulmonary deficits in asthmatics or workers in other, less reliable reports (Hendrick *et al.*, 1982; Burge *et al.*, 1985; Nordman *et al.*, 1985).

Because the LOAEL actually represents a threshold for pulmonary effects in asthmatics due to formaldehyde inhalation, and because exercise during exposure was required to observe pulmonary deficits, the LOAEL was considered to be a NOAEL and no uncertainty factor was applied. Note that in Sauder *et al.* (1987) no asthmatic subjects experienced significant bronchoconstriction (> 10% decrease in $FEV_1$) when exposed to 3 ppm formaldehyde at rest for 3 hours. The 3 ppm value was adjusted to a 1-hour exposure, using a modification of Haber's equation, $C^n * T = K$ , where n = 2 for extrapolation from a shorter duration to 1 hour. The exponent n = 2 was based on findings in the AICE Guidelines (AICE, 1989). The resulting level protective against severe adverse effects is 1.6 ppm for 1-hour exposure to formaldehyde.

**Level Protective Against Life-threatening Effects**

Alarie (1981) estimated a 10 minute $LC_{50}$ for formaldehyde in mice of 2,162 ppm (95% confidence interval = 1,687-2,770 ppm). The post-exposure observation period was 3 hours. Formaldehyde exposure to 250 ppm (310 mg/m³) for 4 hours killed 4/6 rats within a 14 day observation period (Carpenter *et al., 1*946). Among 72 rats exposed to 600-1,700 mg/m³ formaldehyde vapor for 30 minutes the $LC_{50}$ was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950).

Of the lethality studies summarized above, the study by Alarie (1981) best presents mortality data for the determination of a $BC_{05}$ with an adequate post-exposure period. The major limitation of this study was the short post-exposure observation period of 3 hours. Given the paucity of exposure data resulting in potentially lethal effects, this study currently represents the best estimate for the development of a life-threatening level for formaldehyde. A $BED_{05}$ (which

represents an experimental threshold for lethality) of 778 ppm (965 mg/m³) for a 130 minute exposure was estimated from the data (Crump, 1984; Crump and Howe, 1983), but a $BC_{05}$ could not be determined due to lack of data. The $BED_{05}$ was adjusted for a 1-hour exposure using a modification of Haber's equation $C^n * T = K$, where n = 2 for extrapolation from a shorter duration to a 1-hour level, resulting in a value of 318 ppm (400 mg/m³). The exponent n = 2 was based on findings in the AICE Guidelines (AICE, 1989). Uncertainty factors applied to the 1-hour $BC_{05}$ were 3-fold to account for interspecies differences and 10-fold for increased susceptibility of sensitive human individuals. The cumulative uncertainty factor was thus 30, which results in an estimated level protective against life-threatening effects of 11 ppm (13 mg/m³) for a 1-hour exposure to formaldehyde.

NIOSH (1995) lists a (revised) IDLH for formaldehyde of 20 ppm based on several reports of acute inhalation toxicity data, mainly in workers. Thus there is no consideration of sensitive subpopulations.

## VIII.  References

Akbar-Khanzadeh F, Vaquerano MU, Akbar-Khanzadeh M, Bisesi MS. Formaldehyde exposure, acute pulmonary response, and exposure control options in a gross anatomy laboratory. Am J Ind Med 1994;26:61-75.

Alarie Y. Toxicological evaluation of airborne chemical irritants and allergens using respiratory reflex reactions. In: Leong BKJ, editor. Proceedings of the Inhalation Toxicology and Technology Symposium. Kalamazoo (MI), October 23-24, 1980. Ann Arbor (MI): Ann Arbor Science Inc; 1981. p. 207-231.

(AICE) American Institute of Chemical Engineers. Guidelines for chemical process quantitative risk analysis. New York (NY): Center for Chemical Process Safety of the American Institute of Chemical Engineers; 1989. p. 148-159.

Bardana EJ, Montanaro A. The formaldehyde fiasco: A review of the scientific data. Immunol Allergy Pract 1987;9(1):11-24.

Boja JW, Nielsen JA, Foldvary E, Truitt EB Jr. Acute low-level formaldehyde behavioural and neurochemical toxicity in the rat. Prog Neuropsychopharmacol Biol Psychiatry 1985;9(5-6):671-674.

Burge PS, Harries MG, Lam WK, O'Brien IM, Patchett PA. Occupational asthma due to formaldehyde. Thorax 1985;40(4):255-260.

Carpenter CP, Smyth HF Jr. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 1946;23:259-268.

Chang CC, Gershwin ME. Perspectives on formaldehyde toxicity: Separating fact from fantasy. Regul Toxicol Pharmacol 1992;16:150-160.

Crump KS. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:854-871.

Crump KS, Howe R. Probit-A computer program to extrapolate quantile animal toxicological data to low doses. Ruston (LA): Crump KS & Company, Inc; 1983.

Feinman SE, editor. Formaldehyde sensitivity and toxicity. Boca Raton (FL): CRC Press Inc; 1988.

Frigas E, Filley WV, Reed CE. Bronchial challenge with formaldehyde gas: lack of bronchoconstriction in 13 patients suspected of having formaldehyde-induced asthma. Mayo Clin Proc 1984;59:295-299.

Gorski P, Tarkowski M, Krakowiak A, Kiec-Swierczynska M.  Neutrophil chemiluminescence following exposure to formaldehyde in healthy subjects and in patients with contact dermatitis. Allergol Immunopathol 1992;20(1):20-23.

Green DJ, Sauder LR, Kulle TJ, Bascom R. Acute response to 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. Am Rev Respir Dis 1987;135:1261-1266.

Harving H, Korsgaard J, Pederson OF, Mølhave L, Dahl R. Pulmonary function and bronchial reactivity in asthmatics during low-level formaldehyde exposure. Lung 1990;168:15-21.

Horvath EP, Anderson H, Pierce WE, Hanrahan L, Wendlick J. The effects of formaldehyde on the mucus membranes and lungs in an industrial population. Submitted to US Department of Labor for proposed rulemaking for exposure to formaldehyde (50 FR 50412, December 10, 1985).

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1993. (Edition expires 11/31/93).

Heck HD, Casanova M, Starr TB. Formaldehyde toxicity - new understanding. CRC Crit Rev Toxicol 1990;20(6):397-426.

Henrick DJ, Lane DJ. Occupational formalin asthma. Br J Ind Med 1977;34:11-18.

Horton AW, Tye R, Stemmer KL. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J Natl Cancer Inst 1963;30(1):31-43.

Howard P. Handbook of fate and exposure data for organic chemicals. Vol. 1. Lewis Publishers; 1989.

Kriebel D, Sama SR, Cocanour B. Reversible pulmonary responses to formaldehyde. A study of clinical anatomy students. Am Rev Respir Dis 1993;148(6 Pt 1):1509-1515.

Kulle JT, Sauder LR, Hebel JR, Green D, Chatham MD. Formaldehyde dose-response in healthy nonsmokers. J Air Pollution Control Assoc 1987;37:919-924.

Monteiro-Riviere NA, Popp JA. Ultrastructural evaluation of acute nasal toxicity in the rat respiratory epithelium in response to formaldehyde gas. Fundam Appl Toxicol 1986;6(2):251-262.

Nagornyi PA, Sudakova ZhA, Shohablenko SM. General toxic and allergic effects of formaldehyde. Gig Tr Prof Zabol 1979;1:27-30. [Chem Abs 1979;90:133606g.]

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

(NIOSH) National Institute for Occupational Safety and Health.  Health Hazard Evaluations: Formaldehyde.  CDROM for 1981-1989 and 1990-1996

Nordman H, Keskinen H, Tuppurainen M. Formaldehyde asthma - rare and overlooked? J Allergy Clin Immunol 1985;75:91-99.

Pazdrak K, Gorski P, Krakowiak A, Ruta U. Changes in nasal lavage fluid due to formaldehyde inhalation. Int Arch Occup Environ Health 1993;64(7):515-519

Porter JAH. Acute respiratory distress following formalin inhalation. Lancet 1975;1:603-604.

Pross HF, Day JH, Clark RH, Lees REM. Immunologic studies of subjects with asthma exposed to formaldehyde and urea-formaldehyde foam insulation (UFFI) off products. J Allergy Clin Immunol 1987;79:797-810.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1993.

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Salem H, Cullumbine H. Inhalation toxicities of some aldehydes. Toxicol Appl Pharmacol 1960;2:183-187.

Sauder LR, Chatham MD, Green DJ, Kulle TJ. Acute pulmonary response to formaldehyde exposure in healthy nonsmokers. J Occup Med 1986;28(6):420-424.

Sauder LR, Green DJ, Chatham MD, Kulle TJ. Acute pulmonary response of asthmatics to 3.0 ppm formaldehyde. Toxicol Ind Health 1987;3:569-578.

Schachter NE, Witek TJ Jr, Brody DJ, Tosun T, Beck GJ, Leaderer BP. A study of respiratory effects from exposure to 2.0 ppm formaldehyde in occupationally exposed workers. Environ Res 1987;44:188-205.

Schachter NE, Witek TJ Jr, Tosun T, Leaderer BP, Beck GJ. A study of respiratory effects from exposure to 2 ppm formaldehyde in healthy subjects. Arch Environ Health 1986;41(4):229-239.

Shepard's catalog of teratogenic agents (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1993.

Sheppard D, Eschenbacher W, Epstein J. Lack of bronchomotor response to up to 3 ppm formaldehyde in subjects with asthma. Environ Res 1984;35:133-139.

Skog E. A toxicological investigation of lower aliphatic aldehydes. Acta Pharmacol Toxicol 1950;6:299-318.

Sim VM, Pattle RE. Effect of possible smog irritants on human subjects. J Am Med Assoc 1957;165:1908-1913.

Solomons K, Cochrane JWC. Formaldehyde toxicity: Part 1. Occupational exposure and a report of 5 cases. S Afr Med J 1984;66:101-102.

Swiecechowski AL, Long KJ, Miller ML, Leikauf GD. Formaldehyde-induced airway hyperreactivity *in vivo* and *ex vivo* in guinea pigs. Environ Res 1993;61:185-199.

Thrasher JD, Wojdani A, Cheung G, Heuser G. Evidence for formaldehyde antibodies and altered cellularity immunity in subjects to formaldehyde in mobile homes. Arch Environ Health 1987;42:347-350.

Thrasher JD, Broughton A, Madison R. Immune activation and autoantibodies in humans with long-term inhalation exposure to formaldehyde. Arch Environ Health 1990;45:217-223.

Uba G, Pachorek D, Bernstein J, Garabrant DH, Balmes JR, Wright WE, Amar RB. Prospective study of respiratory effects of formaldehyde among healthy and asthmatic medical students. Am J Ind Med 1989;15:91-101.

Wallenstein G, Rebohle E, Bergmann I, Voight U, Schneider WD. Berufliche Erkrankungen des Atmungsorgans durch chemische Stoffe mit potentieller Allergenwirkung [Occupational diseases of the respiratory system due to chemical substances with potential allergen effects]. Dtsch Gesundheitsw 1978;33(24):1119-1123.

Weber-Tschopp A, Fisher T, Granjean E. Irritating effects of formaldehyde on men. Int Occup Environ Health 1977;39:207-218.

Witek TJ Jr, Schachter NE, Tosun T, Beck GJ, Leaderer BP. An evaluation of respiratory effects following exposure to 2.0 ppm formaldehyde in asthmatics: lung function, symptoms, and airway reactivity. Arch Environ Health 1987;42(4):230-237.

Witek TJ Jr, Schachter NE, Tarik T, Leaderer BP, Beck GJ. Controlled human studies on the pulmonary effects of indoor air pollution: experiences with sulfur dioxide and formaldehyde. Environ Int 1986;12:129-135.

**IX.  Graphic Representation of Benchmark Concentration Determination**

ACUTE TOXICITY SUMMARY

# HYDROGEN CHLORIDE

*(hydrogen chloride, anhydrous hydrogen chloride, muriatic acid)*

**CAS Registry Number: 7647-01-1**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **2,100 µg/m³** |
| *Critical effect(s)* | upper respiratory symptoms |
| *Hazard Index target(s)* | Respiratory System; Eyes |

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

| | |
|---|---|
| *Description* | colorless gas |
| *Molecular formula* | HCl |
| *Molecular weight* | 36.46 |
| *Density* | 1.49 g/L @ 25°C |
| *Boiling point* | -84.9°C |
| *Melting point* | -114.8°C |
| *Flashpoint* | not applicable |
| *Explosive limits* | unknown |
| *Solubility* | soluble in water, alcohol, benzene, ether; insoluble in hydrocarbons |
| *Odor threshold* | 0.26-10.0 ppm (AIHA, 1989a) |
| *Odor description* | sharp, irritating (AIHA, 1989a) |
| *Metabolites* | not applicable |
| *Conversion factor* | 1 ppm = 1.49 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Hydrogen chloride (HCl) is used in the manufacture of vinyl chloride, fertilizers, dyes, artificial silk, and pigments for paints.  It is also used in electroplating, soap refining, and leather tanning.  Other consumers of HCl include the photographic, textile and rubber industries (HSDB, 1994).  Hydrogen chloride is produced in large quantities during combustion of most materials and especially chlorine-containing materials.  Thus, HCl is a major product formed during the thermal decomposition of polyvinyl chloride, a commonly used plastic polymer (Burleigh-Flayer *et al*., 1985).  It is also released in large quantities during the test firing of some rocket and missile engines (Wohlslagel *et al*., 1976).

## IV.　　Acute Toxicity to Humans

Inhalation exposure to high concentrations of HCl fumes may result in coughing, choking sensation, burning of the respiratory tract, and pulmonary edema (Proctor *et al.*, 1991). Dental erosion has been reported in workers chronically exposed to low levels of gaseous hydrogen chloride (Finkel, 1983). Reactive Airway Dysfunction Syndrome (RADS; acute, irritant-induced asthma) was reported in three male police officers (36-45 years old) who responded to a roadside chemical spill (Promisloff *et al.*, 1990). Other reports of RADS include individual occupational cases (Boulet, 1988; Turlo and Broder, 1989).

Young adult asthmatic subjects (18-25 years, 5 of each sex) were exposed by a half-face mask to filtered air, 0.8 ppm HCl, and 1.8 ppm HCl during three separate 45-minute exposures (Stevens *et al.*, 1992). The exposure protocol included two 15-minute exercise periods separated by a 15-minute rest period. Tests of pulmonary function included forced expiratory volume in 1 second, forced expiratory volume, maximal flow at 50% and 75% of expired vital capacity, and total respiratory resistance and peak flow. Nasal work of breathing was also measured pre- and post exposure. No significant changes in these parameters were observed following exposure to HCl at 0.8 or 1.8 ppm. There was no exposure-related increases in severity of upper respiratory, lower respiratory, or other symptoms reported by participants. Because exposure occurred by half-face mask, effects on the ocular mucosae were not addressed.

*Predisposing Conditions for HCl Toxicity*

**Medical**:　　Persons with preexisting skin, eye, gastrointestinal tract (including ulcers) or respiratory conditions or underlying cardiopulmonary disease may be more sensitive to the effects of HCl exposure (Reprotext, 1999).

**Chemical**:　　Persons also exposed to formaldehyde might be at increased risk for developing cancer (Reprotext, 1999).

## V.　　Acute Toxicity to Laboratory Animals

A single baboon exposed for 5-minutes to 16,570 ppm (24,690 mg/m³) HCl was dyspneic until death 18 days following exposure (Kaplan *et al.*, 1985). Pneumonia, pulmonary edema, tracheitis, and epithelial erosion were noted at autopsy. Baboons exposed for 15-minutes to 500, 5,000 or 10,000 ppm (750, 7,500, or 15,000 mg/m³) HCl exhibited a concentration-related increase in respiratory rate and minute volume (Kaplan *et al.*, 1988). A marked decrease in arterial blood oxygenation was observed in baboons exposed to 5,000 or 10,000 ppm. Pulmonary function parameters measured 3 days and 3 months following exposure were not significantly different from pre-exposure measurements. However, the animals were anesthetized with Ketamine which could reduce airway resistance and bronchospasm (Bovill *et al., 1*971). Histopathologic examination performed 12 months post-exposure (Kaplan *et al., 1*993a) found pulmonary hemorrhage, edema, fibrosis, and bronchiolitis in the medial right lung of one of three animals exposed to 10,000 ppm. In another of the three animals zonal atelectasis and focal multiple hemorrhages were observed in the right lung. In each of the three animals exposed to 5,000 ppm and examined, focal, patchy hemorrhages were observed.

A 30-minute $LC_{50}$ in rats and mice is reported as 5,666 ppm (8,442 mg/m³) and 2,142 ppm (3,192 mg/m³) HCl aerosol, respectively (Darmer *et al*., 1974). Alveolar emphysema, atelectasis, and pulmonary edema were noted at necropsy of animals that died either during or within 7 days following exposure. Bloody nasal discharge, indicative of purulent bronchitis, was observed in animals of both species surviving the exposure.

A 1-hour $LC_{50}$ of 2,810 ppm in rats was reported by Hartzell and colleagues (1985). Rats were exposed to concentrations of HCl ranging from 1,793-4,854 ppm HCl for one hour and the mortality following exposure was recorded over a 14-day observation period. Hartzell *et al*. also reported $LC_{50}$s of 15,900 ppm, 8,370 ppm, 6,920 ppm, 5,920 ppm and 3,715 ppm, for rats exposed for 5 minutes, 10 minutes, 15 minutes, 22.5 minutes, and 30 minutes, respectively.

A decrease in respiratory rate was observed in guinea pigs exposed to 320 ppm (480 mg/m³) HCl for 6-minutes and to 680 ppm (1,010 mg/m³) HCl for less than 1-minute (Burleigh-Flayer *et al*., 1985). The $RD_{50}$ is the concentration of a chemical in air that is associated with a 50% decrease in respiratory rate, and is used as a measure of irritancy. The $RD_{50}$ in animals has a predictable relationship to irritation in man (Kane *et al*., 1979). The $RD_{50}$ in mice was reported as 309 ppm (460 mg/m³) for a 10-minute exposure (Kane *et al*., 1979).

In addition to respiratory irritation, HCl exerts ocular effects. Corneal opacities were observed in guinea pigs following a 30-minute exposure to HCl concentrations of 680 ppm (1,010 mg/m³ ; 1 of 4), 1,040 ppm (1,550 mg/m³; 4 of 6) and 1,380 ppm (5 of 5), but not 320 ppm (480 mg/m³ ). Cloudy corneas were also reported 90 days post-exposure by Kaplan *et al*. (1993b) in guinea pigs exposed for 15 minutes to 4,200 ppm, but not at 500 ppm (Burleigh-Flayer *et al*., 1985). Coughing, frothing at the mouth, excess salivation, and blinking and rubbing of the eyes were observed in baboons following a 5-minute exposure to 810 ppm (1,210 mg/m³) HCl (Kaplan *et al*., 1985). No signs of irritation were observed following a 5-minute exposure to 190 ppm (280 mg/m³) HCl.

In another study conducted in exercising guinea pigs (Malek and Alarie, 1989), a concentration of 107 ppm for 30 minutes was irritating and a concentration of 140 ppm was incapacitating at 16.5 minutes.

## VI. Reproductive or Developmental Toxicity

The reproductive hazard of hydrogen chloride to humans is unknown (Reprotext, 1999). Few studies on the reproductive effects of HCl exposure were found in the literature. Maternal exposure to a high concentration of a strong acid could result in metabolic acidosis and subsequent fetal acidemia which has been linked with low Apgar scores, neonatal death, and seizures. However, there is no evidence linking HCl exposure to fetal acidemia (Reprotext, 1999).

Pregnant rats exposed to 300 ppm (450 mg/m³) HCl for 1 hour on the 9th day of gestation exhibited signs of severe dyspnea and cyanosis (Pavlova, 1976; 1978). The exposure was lethal to one-third of the exposed rats (number of rats exposed not reported). Increased mortality was

also observed in the progeny of the exposed rats compared to that of controls.  The author implies that organ functional abnormalities in the progeny resulted from *in utero* exposure.  However, the lack of key experimental details and the ambiguity of organ function tests make this conclusion difficult to validate.

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

**Reference Exposure Level (protective against mild adverse effects):   1.4 ppm (2,100 µg/m³)**

| | |
|---|---|
| *Study* | Stevens *et al*., 1992 |
| *Study population* | 10 asthmatics aged 18-25 |
| *Exposure method* | inhalation via half face mask to 0.8 or 1.8 ppm HCl |
| *Critical effects* | upper respiratory system symptoms of sore throat;  nasal discharge |
| *LOAEL* | not observed |
| *NOAEL* | 1.8 ppm |
| *Exposure duration* | 45 minutes |
| *Extrapolated 1 hour concentration* | 1.4 ppm $(1.8^1 \text{ ppm} * 0.75 \text{ h} = C^1 * 1 \text{ h})$ (see Table 12 for information on "n") |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 1 |
| *Cumulative uncertainty factor* | 1 |
| *Reference Exposure Level* | 1.4 ppm (2.1 mg/m³; 2,100 µg/m³) |

No significant effects on pulmonary function (forced expiratory volume in one second, forced expiratory volume, maximal flow at 50% and 75% of expired vital capacity, and total respiratory resistance and peak flow) or nasal work of breathing were observed in asthmatics aged 18-25 years exposed via half-face mask to 0.8 or 1.8 ppm HCl for 45 minutes, including 30 minutes of exercise.  Additionally, there was no association between HCl exposure and upper respiratory symptoms of sore throat and nasal discharge.  There was no association between HCl exposure and lower respiratory symptoms of cough, chest pain, burning, dyspnea and wheezing.  The lack of effects on the pulmonary functions measured is not surprising because of the extreme water-solubility of HCl.  The high water solubility of HCl supports upper airway effects as the most sensitive target endpoint since the HCl would dissolve there.  While the animal studies summarized in this document suggest that HCl does penetrate and affect the lower respiratory system, this would be expected to occur mostly at higher concentrations of HCl.

**Level Protective Against Severe Adverse Effects**

The $RD_{50}$ in mice for a 10-minute exposure to HCl is reported as 309 ppm (460 mg/m³).  NRC applied an uncertainty factor of 10 to the $RD_{50}$ to account for interspecies differences yielding a 1-hour EEGL of 31 ppm.  The EEGL was further reduced to 20 ppm (29.8 mg/m³) because "of the paucity of human data."

A 1-hour SPEGL (Short-term Public Emergency Planning Level) of 1 ppm is also recommended by NRC. The rationale states "...in connection with community exposure during space shuttle launches, the Committee recommends lower concentrations, to avoid adverse effects that might occur in a more sensitive population..." (NRC, 1987). While it appears that no supporting data are cited to justify the value, the SPEGL essentially incorporates an additional 20-fold safety factor to protect sensitive subpopulations and is an excessively low value, lower than the acute REL recommended to protect against mild adverse effects. However, since the development of the SPEGL, that relied largely on expert judgment since the database was poor (NRC, 1987), the Stevens *et al*. (1992) human study has become available, in addition to a number of additional animal studies. For this reason, we recommend the EEGL of 20 ppm as a level protective against severe adverse effects. The levels should be reevaluated when more data become available.

**Level Protective Against Life-threatening Effects**

Groups of 6 rats were exposed to the following concentrations of HCl for a single 1-hour period: 1,793, 2,281, 2,600, 4,277, 4,460, and 4,854 ppm (Hartzell *et al*., 1985). Mortality during and up to 14 days following exposure was reported.

Rat Mortality Data from Hartzell *et al*., 1985

| HCl Concentration (ppm) | 1,793 | 2,281 | 2,600 | 4,277 | 4,460 | 4,854 |
|---|---|---|---|---|---|---|
| Mortality | 0/6 | 3/6 | 1/6 | 7/8 | 6/6 | 6/6 |

The rat study was chosen since it was considered to be of greatest quality based on the number of doses and time points tested. Furthermore, Kaplan *et al*. (1987 and 1993b) suggest fairly similar lethality responses between baboons and rats for HCl exposure. A benchmark dose approach was employed using a log-normal probit analysis (Crump, 1983) of 60-minute lethality data from Hartzell *et al*. (1985). The concentration associated with a 5% incidence of lethality ($ED_{05}$) was 1,772 ppm; the lower 95% confidence limit (LCL) on this concentration [the $BC_{05}$] was 1,271 ppm. A total uncertainty factor of 30 was applied to the $BC_{05}$ of 1,271 ppm to account for interspecies variability (3) and individual variation (10) in response.

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The final level protective against life-threatening effects for HCl is therefore 42 ppm (63 mg/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% response rates are compared below. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Comparison of benchmark calculations (1% vs 5%)

| Response rate | MLE (ppm) | 95% LCL (ppm) |
|---|---|---|
| 1% | 1,464 | 946 |

| 5% | 1,772 | 1,271 |
|---|---|---|

## VIII.    References

(AIHA) American Industrial Hygiene Association. Emergency response planning guidelines. Hydrogen chloride. Akron (OH): AIHA; 1989.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989a. p. 20

Boulet L-P. Increases in airway responsiveness following acute exposure to respiratory incidents: Reactive airway dysfunction syndrome or occupational asthma? Chest 1988; 94: 476-481.

Bovill JG, Clarke RSJ, Davis EA, Dundee JW. Some cardiovascular effects of ketamine in man. Br J Pharmacol 1971;41:411P-412P.

Burleigh-Flayer H, Wong KL, Alarie Y. Evaluation of the pulmonary effects of HCl using $CO_2$ challenges in guinea pigs. Fundam Appl Toxicol 1985;5:978-985.

Crump KS & Co., Inc. Probit (Log-Normal) software for the IBM-PC. Ruston (LA); 1983.

Darmer KI, Kinkead ER, Di Pasquale LC. Acute toxicity in rats and mice exposed to hydrogen chloride gas and aerosol. Am Ind Hyg Assoc J 1974;35:623-631.

Finkel AJ, editor. Hamilton and Hardy's industrial toxicology. Boston: John Wright, PSG Inc.; 1983. p. 179.

Hartzell GE, Packham SC, Grand AF, Switzer WG. Modeling of toxicological effects of fire gases: III. Quantification of post-exposure lethality of rats from exposure to HCl atmospheres. J Fire Sci 1985;3:195-207.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Henderson Y, Haggard HW. Noxious gases. New York: Reinhold Publishing Corp; 1943. p. 126.

(IRIS) Integrated Risk Information System. US Environmental Protection Agency, Washington (DC) (CD-ROM Version). Denver (CO): Micromedex Inc.; 1994. (Edition expires 4/30/94).

Kane LE, Barrow CS, Alarie Y. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am Ind Hyg Assoc J 1979;40:207-229.

Kaplan HL, Grand AF, Switzer WG, Mitchell DS, Rogers WR, Hartzell GE. Effects of combustion gases on escape performance of the baboon and rat. J Fire Sci 1985;3:228-244.

Kaplan HL, Anzueto A, Switzer WG, Hinderer RK. Effects of hydrogen chloride on respiratory response and pulmonary function of the baboon. J Toxicol Environ Health 1988;23:473-493.

Kaplan HL, Switzer WG, Hinderer RK, Anzueto A. A study on the acute and long-term effects of hydrogen chloride on respiratory response and pulmonary function and morphology in the baboon. J Fire Sci 1993a; 11: 459-484.

Kaplan HL, Switzer WG, Hinderer RK, Anzueto A. Studies of the effects of hydrogen chloride and polyvinyl chloride (PVC) smoke in rodents. J Fire Sci 1993b; 11: 512-552.

(NRC) National Research Council. Committee on Toxicology. Emergency and continuous exposure limits for selected airborne contaminants. Vol. 7. Washington (DC): National Academy Press; 1987. p. 17-30.

Pavlova TE. [Disorders in the development of offspring following exposure of rats to hydrogen chloride] [Russian]. Biull Eksp Biol Med 1976;82:866-868.

Pavlova TE. Disturbance of development of the progeny of rats exposed to hydrogen chloride. Bull Exp Biol Med 1978;2:1078-1081.

Proctor NH, Hughes JP, Hathaway GJ, Fischman ML, editors. Proctor and Hughes' chemical hazards of the workplace. 3rd ed. New York: Van Nostrand Reinhold; 1991. p. 322.

Promisloff RA, Lenchner GS, Phan A, Cichelli AV. Reactive airway dysfunction syndrome in three police officers following a roadside chemical spill. Chest 1990;98:928-929.

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Stevens B, Koenig JQ, Rebolledo V, Hanley QS, Covert DS. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. J Occup Med 1992;34(9):923-929.

Ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J Hazard Mater 1983;13:301-309.

Turlo SM, Broder I. Irritant-induced occupational asthma. Chest 1989; 96: 297-300.

Wohlslagel J, Di Pasquale LC, Vernot EH. Toxicity of solid rocket motor exhaust of HCl, HF, and alumina on rodents. J Combust Toxicol 1976;3:61-70.

ACUTE TOXICITY SUMMARY

# HYDROGEN CYANIDE

*(formonitrile; hydrogen cyanide; prussic acid)*

**CAS Registry Number: 74-90-8**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **340 µg/m³** |
| *Critical effect(s)* | loss of coordination and loss of consciousness, due to cellular hypoxia of the central nervous system |
| *Hazard Index target(s)* | Nervous System |

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

| | |
|---|---|
| *Description* | colorless gas |
| *Molecular formula* | HCN |
| *Molecular weight* | 27.03 |
| *Density* | 1.1 g/L @ 25°C |
| *Boiling point* | 25.6°C |
| *Melting point* | -13.4°C |
| *Vapor pressure* | 630 mm Hg @ 20°C |
| *Flashpoint* | -17.8°C (closed cup) |
| *Explosive limits* | upper = 40% by volume in air |
| | lower = 5.6% by volume in air |
| *Solubility* | miscible in water, alcohol, slightly soluble in ether |
| *Odor threshold* | 0.58 ppm (w/w) (Amoore and Hautala, 1983) |
| *Odor description* | faint, bitter almond odor |
| *Metabolites* | thiocyanate, 2-aminothiazo-line-4-carboxylic acid, cyanocobalamin (Vitamin B12) (Ansell and Lewis, 1970) |
| *Conversion factor* | 1 ppm = 1.13 mg/m³ |

## III.	Major Uses or Sources

Hydrogen cyanide (HCN) is used in a variety of syntheses, including the production of adiponitrile (for nylon), methyl methacrylate, sodium cyanide, cyanuric chloride, chelating agents, pharmaceuticals, and other specialty chemicals.  Manufacturing activities producing HCN include electroplating, metal mining, metallurgy, and metal cleaning processes.  Additionally, HCN has some insecticide and fungicide applications (ATSDR, 1993).  Fires involving some nitrogen-containing polymers, often found in fibers used in fabrics, upholstery covers, and padding, also produce HCN (Tsuchiya and Sumi, 1977).

Another common source of HCN is cigarette smoke. Levels in inhaled mainstream cigarette smoke range from 10 to 400 μg per cigarette and decrease to levels ranging from 0.06 to 108 μg in secondary or sidestream smoke (Fiksel *et al*., 1981).

## IV.    Acute Toxicity to Humans

Cyanide toxicity results from cytochrome oxidase inhibition which prevents cellular utilization of oxygen. The respiratory, cardiovascular, and central nervous systems are the primary target organs of acute cyanide toxicity. Acute effects from inhalation of HCN are characterized by altered sense of smell, headache, tachypnea, nausea, loss of coordination, loss of consciousness, palpitations, convulsions, respiratory distress, and asphyxiation (Chandra *et al*., 1980; Blanc *et al*., 1985; Peden *et al*., 1986; ATSDR, 1993). Eye or dermal contact with liquid HCN, a weak acid, may cause some mild local irritation (Anon., 1970). However, dermal and ocular absorption leading to systemic effects is clearly more cause for concern than possible local irritation. Even though the signs and symptoms of HCN poisoning are recognized, the acute dose-response relationship has not been well defined.

Lethality data from case report studies exist, but specific exposure concentrations are often lacking. As reported by McNamara (1976), several commonly reported inhalation values given as human toxicity data (Kobert, 1912; Henderson and Haggard, 1927; Flury and Zernick, 1931; Dudley *et al*., 1942; Moore and Gates, 1946; Fassett, 1963) may actually be based on pre-1920 animal data. One estimate of the average fatal inhaled dose for humans, 546 ppm (617 mg/m³), is based on minimal human data and relies on multiple unsubstantiated assumptions including: (1) human susceptibility to HCN is similar to the relatively resistant monkey and goat, and (2) animal data, such as breathing rates, can be substituted for human parameters (McNamara, 1976).

In an accidental human poisoning, a workman collapsed 3 minutes after entering a tank for inspection and cleaning (Bonsall, 1984). The workman was exposed for an additional 3 minutes before being fitted with a breathing apparatus and taken to a hospital, where he later recovered. Later analysis of the tank revealed an HCN concentration of 500 mg/m³ (442 ppm). In a fatal human poisoning, a workman cleaning the bottom of a silver plating tank was found unconscious by workmates (Singh *et al*., 1989). The duration of exposure was unknown but subsequent analysis of the air in the tank revealed a concentration of 200 ppm HCN.

The onset and progression of severe health effects are similar among humans and experimental animals (ATSDR, 1993, Ballantyne, 1987; Wexler *et al*., 1947, Purser *et al*., 1984). These effects are hyperventilation, followed by loss of consciousness, depressed respiration, and bradycardia.

Blanc *et al*. (1985) studied 36 former workers who had been exposed to HCN in a silver-reclaiming facility. A significant dose-response trend was observed between proximity of work to the CN⁻ source and prevalence of symptoms consistent with CN⁻ toxicity including headache, dizziness, nausea or vomiting, dyspnea, and syncope (unconsciousness). A 24-hour time-weighted average air concentration of 15 ppm was recorded 1 day after the plant had been closed because of a death from cyanide exposure. Due to poor hygienic conditions at the plant, dermal

and oral exposure also occurred.  The researchers considered the time-weighted average of 15 ppm to be a low estimate of the occupational exposure due to multiple potential routes of exposure and the retrospective analysis of the air concentration.

*Predisposing Conditions for HCN Toxicity*

**Medical:**     Individuals with some motor neuron diseases, such as amyotrophic lateral sclerosis, have a decreased ability to convert cyanide to thiocyanate and may be predisposed to HCN toxicity (Kato *et al*., 1985).  Individuals with Leber's hereditary optic atrophy, a rare neuroopthalmologic condition, may have low activity of the enzyme rhodanese, an enzyme responsible for converting cyanide to thiocyanate (Wilson, 1983).

Up to 20% to 40% of the population cannot detect the bitter almond odor of cyanide and may therefore be at greater risk for toxicity following exposure (Brown and Robinette, 1967).

**Chemical:**     Individuals taking megadoses of ascorbic acid may diminish the availability of cysteine, an amino acid important in the detoxification of cyanide, thus increasing susceptibility to HCN poisoning (Basu, 1983).

## V.     Acute Toxicity to Laboratory Animals

The progression of severe health effects is similar among humans and experimental animals (ATSDR, 1993, Kulig and Ballantyne, 1993; Curry, 1992; Ballantyne, 1987; Wexler *et al*., 1947, Purser *et al*., 1984).  These effects are characterized by hyperventilation, followed by loss of coordination and consciousness, depressed respiration, bradycardia, convulsions, asphyxiation, and respiratory failure.

In work by Purser (1984), 4 monkeys exposed to 60 ppm HCN developed electroencephalogram (EEG) patterns characteristic of early onset of CNS depression (increased slow wave [delta] activity and decreased fast wave [beta] activity) and increased respiratory rate near the end of the 30 minute exposure period.  While both results are indicative of early onset of cellular hypoxia, none of the monkeys lost consciousness.  However, with exposures to 80 ppm and above, incapacitation (semi-conscious state with loss of muscle tone) did result within 30 minutes (Purser *et al*., 1984).

Time-to-incapacitation, as a function of HCN concentration, has been measured in mice (Sakurai, 1989), rats (Hartzell *et al*., 1985), monkeys (Purser *et al*., 1984; Purser, 1984), and goats (Barcroft, 1931).  The tests used by Barcroft (1931) and Purser *et al*. (1984) essentially defined incapacitation as a semi-conscious state with loss of muscle tone, whereas Sakurai (1989) and Hartzell *et al*. (1985) defined incapacitation as complete loss of consciousness.  A linear relationship between gas concentration and mean incapacitation time can be shown as:

$$C = (a/t) + b$$

where $C$ = gas concentration (ppm), $t$ = incapacitation time (min), and $a$, $b$ = coefficients for HCN gas.

The HCN concentration producing a mean incapacitation time of 30 minutes, using the equation $C = (a/t) + b$, is shown in Table 1.

Table 1. Tabulation of modeling constants for use in the equation $C = (a/t) + b$ for various experimental animal species and determination of HCN concentration resulting in incapacitation following 30 minute exposure to HCN.

| Reference | Species | $a$ (slope) | $b$ (y-intercept) | Concentration (ppm)[1] |
|---|---|---|---|---|
| Sakurai (1989) | mouse | 491 | 25 | 42 |
| Hartzell *et al.* (1985) | rat | 698 | 92 | 115 |
| Purser *et al.* (1984) | monkey | 685 | 66 | 89 |
| Barcroft (1931) | goat | 885 | 152 | 182 |

[1] Concentration of HCN producing a mean incapacitation time of 30 minutes.

While the above equation can estimate the mean time-to-incapacitation for a given concentration of HCN, it cannot provide a NOAEL for incapacitation. However, the coefficient $b$ (y-intercept) could be viewed as the concentration of HCN below which incapacitation will not occur in normal experimental animals.

In mice, Sakurai (1989) has shown that exposure to HCN concentrations of approximately 150 ppm and above results in incapacitation and apnea at about the same time, within 5 minutes. However, exposures to lower HCN concentrations (approximately 150 ppm or less) result in incapacitation in about one-third the time required to cause apnea. This latter situation is observed when incapacitation occurs at 10 minutes or later into exposure to HCN.

Rats inhaling 64 ppm HCN were incapacitated after a mean duration of 35 minutes, while those inhaling 184 ppm HCN were incapacitated after a mean of 5 minutes (Chaturvedi *et al.*, 1995). Blood cyanate levels did not predict incapacitation onset, since the blood cyanate at incapacitation following 184 ppm HCN inhalation was half that seen upon incapacitation following 64 ppm HCN inhalation.

In rats, Levin *et al.* (1987) observed that incapacitating levels were approximately 65% of lethal levels for exposure durations ranging from 1 to 10 minutes. Also in rats, Hartzell *et al.* (1985) observed that time-to-lethality was about 2 to 6-fold greater for a given concentration of HCN that produces incapacitation within 1 to 21 minutes. For exposures that produced mean incapacitation times of 10.9 and 21.0 minutes (165 and 127 ppm, respectively), the mean time-to-lethality was 3- to 4-fold greater. Purser *et al.* (1984) noted that a monkey exposed to 147 ppm HCN was incapacitated at 8 minutes and developed apnea at 27 minutes, a 3.4 fold difference. Other monkeys exposed to similar or lower levels of HCN did not develop apnea.

Therefore, there is a clear (though steep) dose-response effect for HCN exposure resulting in incapacitation (a severe adverse effect) followed by apnea (a life-threatening effect) and death.

Numerous citations were located in the literature that contained $LC_{50}$ determinations for HCN at various exposure durations in experimental animals, but many of the studies did not include the raw mortality data from which to estimate an $MLE_{05}$ (maximum likelihood estimate corresponding to 5% lethality) and $BC_{05}$ (benchmark dose at the 95% lower confidence interval of the $MLE_{05}$)  These citations and their respective $LC_{50}$s are shown in Table 2.

Table 2.  Experimental Animal $LC_{50}$s for Hydrogen Cyanide

| Reference | Species | Exposure Time (min)[1] | $LC_{50}$ ppm (95% Confidence Interval) | Post-exposure Time |
|---|---|---|---|---|
| Ballantyne (1983) | rat | 5 | 436 (329-585) | NR[2] |
| | | 30 | 153 (141-171) | NR |
| | | 60 | 140 (127-154) | NR |
| | rabbit | 5 | 362 (284-405) | NR |
| | | 35 | 184 (136-244) | NR |
| Ballantyne (1984) | rat | 30 | 133 | NR |
| Levin et al. (1987) | rat | 5 | 570 (460-710) | 24 hr |
| | | 10 | 290 (250-340) | 24 hr |
| | | 20 | 170 (160-180) | 24 hr |
| | | 30 | 110 (95-130) | 24 hr |
| | | 30 | 160 (140-180) | none |
| | | 60 | 90 | 24 hr |
| Moore & Gates (1946) | mouse | 10 | 204 | NR |
| | | 30 | 165 | NR |
| | rabbit | 10 | 283 | NR |
| Esposito & Alarie (1988) | mouse | 30 | 177 (157 -199) | 10 min |
| Hartzell et al. (1985) | rat | 30 | 170 | NA[4] |
| Smith et al. (1976) | rat | $7.9 \pm 2.0$[3] | 450 | NA[4] |

[1]  $LC_{50}$ determinations for exposure durations of less than 5 minutes were not included in the table.
[2]  Not reported
[3]  Mean time to death ($\pm$ SD) at 450 ppm HCN
[4]  Not applicable, time to death experiment

Table 3 contains the studies which provided adequate data from which an $MLE_{05}$ and $BC_{05}$ could be determined. The $MLE_{05}$ and $BC_{05}$ in Table 3 were extrapolated to 60- minute exposure using a modification of Haber's equation, $C^n * T = K$, where n = 1. The value of n = 1 was based on the lethality studies of Levin *et al*. (1995) and Sato *et al*. (1955) for extrapolation from exposure durations of less than 1 hour to 1-hour exposure. An exponent n = 2.7 was determined by ten Berge *et al*. (1986) based on lethality data from Barcroft (1931). However, the Barcroft study used static HCN exposure conditions based mainly on nominal concentration estimates; the HCN concentration decreased during exposure and sampling of the HCN concentration was apparently not done on a consistent basis.

Groups of 10 rats inhaled hydrogen cyanide for 30 minutes and were observed over the next 24 hours (Lynch, 1975). Deaths noted occurred within 1 hour of exposure. No deaths were reported following exposure to 60 or 68 mg/m³. Some but not all rats survived exposure to HCN at concentrations between 90 and 166 mg/m³. There were no survivors following exposure to 168 or 192 mg/m³.

Table 3. Animal Lethality Benchmark Dose Determinations for Hydrogen Cyanide

| Reference | Species | Exposure Time (min)[1] | $MLE_{05}$ (ppm) 60 min[2] | $BC_{05}$ (ppm) 60 min[2] | Post-exposure Time |
|---|---|---|---|---|---|
| Lynch (1975) | rat | 30 | 35 | 29 | 24-hr |
| Bhattacharya *et al*. (1991) | mouse | 30 | 337 | 169 | 24 hr |
| Matijak-Shaper *et al*. (1982) | mouse | 30 | 51 | 25 | 10 min |
| Sato *et al*. (1955) | mouse | varied | 35 | 26 | NA[3] |
| Higgins *et al*. (1972) | mouse | 5 | 19 | 16 | 7 days |
|  | rat | 5 | 28 | 24 | 7 days |
| Levin *et al*. (1985) | rat | 30 | 87 | 73 | none |

[1] Exposure durations of less than 5 minutes were not included in the table.
[2] Exposure time was extrapolated to 60 minutes using a modification of Haber's equation ($C^n * T = K$), where n = 1.
[3] Not applicable

Experimental animals incapacitated and brought near death during HCN exposure can appear to recover quickly following cessation of exposure (Purser *et al*., 1984). However, while most deaths occur during the exposure period, Levin *et al*. (1987) noted that deaths of additional experimental animals may occur within 24 hours of exposure. Therefore, $LC_{50}$ studies without a post-exposure period may overestimate the exposure necessary to cause death. Similarly, time to death studies (Hartzell *et al*., 1985; Smith *et al*., 1976; Sato *et al*., 1955) may also overestimate the concentration of HCN necessary to produce death.

One mortality study reported an inhalation NOAEL of 16 ppm (18.1 mg/m³) for rats and mice exposed for 16 hours (Weedon *et al*., 1940). Of the four experimental HCN concentrations (1,000, 250, 63, and 16 ppm, or 1,130, 282, 71, and 18 mg/m³, respectively), only 16 ppm

produced no distress (excitement, loss of coordination, or respiratory difficulties) throughout the exposure period.  However, no other physiological indicators or measures of toxicity were used.  Necropsy revealed lung and coronary artery changes in one of the two rats exposed to 16 ppm HCN.

Continuous exposure of rabbits to 0.5 ppm HCN (0.57 mg/m³), for either 1 or 4 weeks, produced no microscopically detectable morphological changes in the lung parenchyma, pulmonary arteries, coronary arteries, or aorta (Hugod, 1979; 1981).

Due to the lipophilic nature of HCN, dermal absorption during exposure to high atmospheric concentrations of HCN can occur.  Moore and Gates (1946) exposed mice, cats, and dogs to body-only exposure to HCN gas, which resulted in 10 minute lethality at concentrations of 20,000 mg/m³ (17,700 ppm), 50,000 mg/m³ (44,250 ppm) and 100,000 mg/m³ (88,500 ppm), respectively.  Dermal exposure through whole body or shaved region exposures of guinea pigs, rabbits, and dogs also resulted in systemic signs and symptoms of HCN poisoning (Walton and Witherspoon, 1926; Fairley *et al.*, 1934).

## VI.     Reproductive or Developmental Toxicity

No information is available regarding developmental and reproductive effects in humans for any route of exposure to HCN.  Also, no animal studies utilizing inhalation or dermal exposure have been reported for either HCN or cyanide salts.

Certain plants, such as cassava, contain naturally occurring cyanide compounds, cyanogenic glycosides, that produce HCN when hydrolyzed.  Hamsters fed a cassava diet exhibited adverse effects, such as stunted growth and decreased ossification (Frakes *et al.*, 1986).  However, rats fed cassava or cassava supplemented with potassium cyanide failed to display this toxicity (Tewe and Maner, 1981).  Furthermore, no reproductive or developmental effects were reported in hamsters fed cassava during gestation (Frakes *et al.*, 1986).

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

**Mild Adverse Effect Level**

The most sensitive, measurable endpoints, loss of coordination and consciousness, are potentially disabling (severe adverse effects).  Acute symptoms of HCN toxicity which may qualify as mild adverse effects, such as headache, dizziness, and nausea or vomiting, have been described in humans (ATSDR, 1993; Blanc *et al.*, 1985).  Flury and Zernik (1931) described similar symptoms in humans following exposure to 45 ppm.  However, no adequate acute dose-response trends can be determined from these data to develop a mild adverse effect level.

**Reference Exposure Level (protective against severe adverse effects):  340 μg/m³**

   *Study*           Purser, 1984; Purser *et al.*, 1984

| | |
|---|---|
| *Study population* | 4 cynomolgus monkeys |
| *Exposure method* | inhalation |
| *Critical effects* | CNS depression/incapacitation |
| *LOAEL* | 80 ppm |
| *NOAEL* | 60 ppm (68 mg/m³) |
| *Exposure duration* | 30 minutes |
| *Extrapolated 1 hour concentration* | 30 ppm $(60^1 \text{ppm} * 0.5 \text{ h} = C^1 * 1 \text{ h})$ |
| | (see Table 12 for information on "n") |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty factor* | 10 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 100 |
| *Reference Exposure Level* | 0.30 ppm (0.34 mg/m³; 340 µg/m³) |

This value of 0.30 ppm protective against severe adverse effects is consistent with the conclusion of a review by Kaplan and Hartzell (1984), which determined that HCN exhibits a steep dose-response effect with incapacitating doses of HCN about one-third to one-half of those required to effect death (see below).

**Level Protective Against Life-threatening Effects**

From Table 3, the best estimate of the $BC_{05}$ is 66.1 mg/m³ for 30 minute exposures and is derived from the Lynch (1975) data. This study included 9 exposure groups, 10 animals per group, and an adequate post-exposure observation period (24 hours), which made the data superior to that of other data presented in Table 3. Uncertainty factors of 3 to account for interspecies differences and 10 to account for increased susceptibility of sensitive human individuals were applied to the 60 minute BC05 (33 ppm).

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

Incorporation of these factors (cumulative uncertainty factors = 30) yielded a level protective against life-threatening effects of 1.1 ppm (1.2 mg/m³) for a 1-hour HCN exposure.

## VIII.   References

Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air water dilution. J Appl Toxicol 1983;3:272-290.

Anonymous. Hydrogen cyanide. Am Ind Hyg Assoc J 1970;31:116-119.

Ansell M, Lewis FAS. A review of cyanide concentrations found in human organs: A survey of literature concerning cyanide metabolism, 'normal', non-fatal and fatal body cyanide levels. J Forensic Med 1970;17:148-155.

ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological profile for cyanide. TP-92/09. Atlanta: U.S. Department of Health and Human Services; 1993.

Ballantyne B. The influence of exposure route and species on the acute lethal toxicity and tissue concentrations of cyanide. In: Hayes AW, Schnell RC, Miya TS, editors. Developments in the science and practice of toxicology. Amsterdam, The Netherlands: Elsevier Science Publishers BV; 1983. p. 583-586.

Ballantyne B. Relative toxicity of carbon monoxide and hydrogen cyanide in combined atmospheres [abstract]. Toxicologist 1984;4:69.

Ballantyne B. Toxicology of cyanides. In: Ballantyne B, Marrs T, editors. Clinical and experimental toxicology of cyanides. Bristol: Wright; 1987. p. 41-126.

Barcroft J. The toxicity of atmospheres containing hydrocyanic acid gas. J Hyg 1931;31(1):1-34.

Basu TK. High-dose ascorbic acid decreases detoxification of cyanide derived from amygdalin (laetrile): studies in guinea pigs. Can J Physiol Pharmacol 1983;61:1426-1430.

Bhattacharya R, Vijayaraghavan R. Cyanide intoxication in mice through different routes and its prophylaxis by $\alpha$-ketoglutarate. Biomed Environ Sci 1991;4:452-459.

Blanc P, Hogan M, Mallin K, Hryhorczuk D, Hessl S, Bernard B. Cyanide intoxication among silver-reclaiming workers. JAMA 1985;253:367-371.

Bonsall J. Survival without sequelae following exposure to 500 mg/m³ of hydrogen cyanide. Human Toxicol 1984;3:57-60.

Brown KS, Robinette RR. No simple pattern of inheritance in ability to smell solutions of cyanide. Nature (London) 1967;215:406-408.

Chandra H, Gupta BN, Bhargave SH, Clerk SH, Mahendra PN. Chronic cyanide exposure - a biochemical and industrial hygiene study. J Anal Toxicol 1980;4:161-165.

Chaturvedi AK, Sanders DC, Endecott BR, Ritter RM. Exposures to carbon monoxide, hydrogen cyanide and their mixtures: interrelationship between gas exposure concentration, time to incapacitation, carboxyhemoglobin and blood cyanide in rats. J Appl Toxicol 1995;15(5):357-363.

Curry SC. Hydrogen cyanide and inorganic cyanide salts. In: Sullivan J, Krieger G, editors. Hazardous materials toxicology, clinical principles of environmental health. Baltimore (MD): Williams and Wilkins; 1992. p. 698-710.

Dudley HC, Sweeney TR, Miller JW. Toxicology of acrylonitrile (vinyl cyanide). II. Studies of effects of daily inhalation. J Ind Hyg Toxicol 1942;24:255-258.

Esposito FM, Alarie Y. Inhalation toxicity of carbon monoxide and hydrogen cyanide gases released during the thermal decomposition of polymers. J Fire Sci 1988;6(3):195-242.

Fairley A, Linton EC, Wild FE. The absorption of hydrocyanic acid vapour through the skin: with notes on other matters relating to acute cyanide poisoning. J Hyg 1934;34(3):283-294.

Fassett DW. Cyanides and nitriles. In: Patty, FA, editor. Industrial hygiene and toxicology. Chapter XLIV. Vol. II. 2nd ed. New York (NY): Interscience Publishers; 1963.

Fiskel J, Cooper C, Eschenroeder A. Exposure and risk assessment for cyanide. EPA/440/4-85/008. NTIS PB85-220572. Springfield (VA) NTIS; 1981.

Flury F, Zernik F. [Hydrogen cyanide]. In: [Noxious Gases--Vapors, Mist, Smoke- and Dust Particles]. Berlin: Verlag von Julius Springer; 1931. p. 340-493.

Frakes RA, Sharma RP, Willhite CC, Gomez G. Effect of cyanogenic glycosides and protein content in cassava diets on hamster prenatal development. Fundam Appl Toxicol 1986;7:191-198.

Hartzell GE, Priest DN, Switzer WG. Modeling of toxicological effects of fire gases: II. Mathematical modeling of intoxication of rats by carbon monoxide and hydrogen cyanide. J Fire Sci 1985;3:115-128.

Henderson Y, Haggard HW. Noxious gases and the principles of respiration influencing their action. New York: The Chemical Catalog Co., Inc.; 1927. p. 110-112.

Higgins EA, Fiorca V, Thomas AA, Davis HV. Acute toxicity of brief exposures to HF, HCl, NO$_2$ and HCN with and without CO. Fire Technol 1972;8:120-130.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Hugod C. Effect of exposure to 0.5 ppm hydrogen cyanide singly or combined with 200 ppm carbon monoxide and/or 5 ppm nitric oxide on coronary arteries, aorta, pulmonary artery, and lungs in the rabbit. Int Arch Occup Environ Health 1979;44:13-23.

Hugod C. Myocardial morphology in rabbits exposed to various gas-phase constituents of tobacco smoke. Artherosclerosis 1981;40:181-190.

Kaplan HL, Hartzell GE. Modeling of toxicological effects of fire gases: I. Incapacitating effects of narcotic fire gases. J Fire Sci 1984;2:286-305.

Kato T, Kameyama M, Nakamura S, Inada M, Sugiyama H. Cyanide metabolism in motor neuron disease. Acta Neurol Scand 1985;72:151-156.

Kobert R. Kompendium der Praktischen Toxikologie zum Gebrauche für Ärzte, Studierende und Medizinalbeamte. Stuttgart, Germany: Ferdinand Enke (publisher); 1912.

Kulig KW, Ballantyne B. Cyanide toxicity. Am Family Physician 1993;48(1):107-114.

Levin BC, Gurman JL, Paabo M, Baier L, Holt T. Toxicological effects of different time exposures to the fire gases: carbon monoxide or hydrogen cyanide or to carbon monoxide combined with hydrogen cyanide or carbon dioxide. 9th Joint Panel Meeting of the UJNR Panel on Fire Research and Safety, May, 1987. U.S. Department of Commerce; 1987. p. 368-385.

Levin BC, Braun E, Navarro M, Paabo M. Further development of the N-gas mathematical model: An approach for predicting the toxic potency of complex combustion mixtures. In: Nelson GL, editor. Fire and polymers II: Materials and tests for hazard prevention. ACS Symposium Series No. 599. American Chemical Society; 1985. p. 293-311.

Lynch RD. On the non-existence of synergism between inhaled hydrogen cyanide and carbon monoxide. Fire Research Note No. 1035. Borehamwood, Hertfordshire, WD6 2BL, England: Fire Research Station; 1975.

Matijak-Schaper M, Alarie Y. Toxicity of carbon monoxide, hydrogen cyanide and low oxygen. J Combust Toxicol 1982;9:21-61.

McNamara BP. Estimates of the toxicity of hydrocyanic acid vapors in man. Edgewood Arsenal Technical Report. EB-TR-78023. Edgewood (MD): Dept of the Army; 1976.

Moore S, Gates M. Hydrogen cyanide and cyanogen chloride. In: Summary Technical Report of Division 9, NDRC, Volume 1: Chemical warfare agents and related chemical problems, Parts I-II, PB-158 508; 1946. p.7-16.

Peden NR, Taha A, McSorley PD, Bryden GT, Murdoch IB, Anderson JM. Industrial exposure to hydrogen cyanide: implications for treatment. BMJ 1986;293:538.

Purser DA. A bioassay model for testing the incapacitating effects of exposure to combustion product atmospheres using cynomolgus monkeys. J Fire Sci 1984;2:20-36.

Purser DA, Grimshaw P, Berrill KR. Intoxication by cyanide in fires: a study in monkeys using polyacrylonitrile. Arch Environ Health 1984;39(6):394-400.

Sakurai T. Toxic gas tests with several pure and mixed gases using mice. J Fire Sci 1989;7(1):22-77.

Sato T, Fukuyama T, Yamada M. The study of allowable concentration of hydrogen cyanide in air. Bull Inst Publ Health (Jap) 1955;4(4):3-5.

Singh BM, Coles N, Lewis P, Braithwaite RA, Nattrass M, FitzGerald MG. The metabolic effects of fatal cyanide poisoning. Postgrad Med J 1989;65:923-925.

Smith PW, Crane CR, Sanders DC, Abbott JK, Endecott B. Effects of exposure to carbon monoxide and hydrogen cyanide. In: Physiological and toxicological aspects of combustion products: International Symposium. Washington (DC): National Academy of Sciences; 1976. p. 75-84.

ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systematically acting vapours and gases. J Hazard Mater 1986;13:301-309.

Tewe OO, Maner JH. Long-term and carry-over effect of dietary inorganic cyanide (KCN) in the life cycle performance and metabolism of rats. Toxicol Appl Pharmacol 1981;58:1-7.

Tsuchiya Y, Sumi K. Thermal decomposition products of polyacrylonitrile. J Appl Polym Sci 1977;21:975-980.

Walton DC, Witherspoon MG. Skin absorption of certain gases. J Pharmacol Exp Ther 1926;26:315-324.

Weedon FR, Hartzell A, Setterstrom C. Toxicity of ammonia, chlorine, hydrogen cyanide, hydrogen sulphide, and sulphur dioxide gases. V. Ann Contri Boyce Thompson Inst 1940;11:365-385.

Wexler J, Whittenberger J, Dumke P. The effect of cyanide on the electrocardiogram of man. Am Heart J 1947;34:163-173.

Wilson J. Cyanide in human disease: a review of clinical and laboratory evidence. Fundam Appl Toxicol 1983;3:397-399.

ACUTE TOXICITY SUMMARY

**HYDROGEN FLUORIDE**

*(hydrofluoric acid (aqueous solution); hydrogen fluoride (gas))*

**CAS Registry Number: 7664-39-3**

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

*Inhalation reference exposure level*   **240 μg/m³**
*Critical effect(s)*                    irritation to the eyes, nose, and throat
*Hazard Index target(s)*                Respiratory System; Eyes

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

| | |
|---|---|
| *Description* | colorless liquid or gas |
| *Molecular formula* | HF |
| *Molecular weight* | 20.01 |
| *Density* | 0.818 g/L @ 25°C (gas) |
| *Boiling point* | 19.51°C |
| *Melting point* | -83.55°C |
| *Vapor pressure* | 760 mm Hg @ 19.5°C |
| *Flashpoint* | not applicable |
| *Explosive limits* | not applicable |
| *Solubility* | soluble in water and alcohol |
| *Odor threshold* | 0.042 ppm (geometric mean) (Amoore and Hautala, 1983) |
| *Odor Description* | strong, irritating odor |
| *Metabolites* | F⁻ (fluoride) |
| *Conversion factor* | 1 ppm = 0.83 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949).  This acid is used in the glass etching, electronic, and chemical industries (Bertolini, 1992).  These industries use HF in the manufacture of such things as metal cans, plastics, refrigerant chemicals, inorganic chemicals, soaps and detergents, high octane gasoline, and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991).

**IV.    Acute Toxicity to Humans**

Hydrogen fluoride, an inorganic acid of fluorine, can cause both severe burns and systemic toxicity.  Hydrogen fluoride produces dehydration and corrosion of tissues mediated by free hydrogen ions.  In addition, the dissociated fluoride ion, F⁻, also produces severe toxicity.  The fluoride ion complexes certain bivalent cations, primarily calcium and magnesium, to form

insoluble salts. This interferes with the calcium metabolism in the underlying soft and bony tissues and results in cell destruction and severe pain. With severe HF burns, systemic toxicity may also result; hypocalcemia and hypomagnesemia are the most common manifestations (Bertolini, 1992).

Inhalation of HF causes coughing, choking, and chills lasting 1-2 hours after exposure; following an asymptomatic period of 1-2 days, pulmonary edema can occur with cough, chest tightness, rales, and cyanosis (Dreisbach and Robertson, 1987). Fatalities from HF inhalation may be due to pulmonary edema (ATSDR, 1993) and bronchial pneumonia (Dreisbach and Robertson, 1987). Acute aspiration of HF following facial splashes can cause bronchiolar ulceration, pulmonary hemorrhage and edema, and death (ATSDR, 1993).

Dermal exposures have resulted in death when as little as 2.5% of the body surface has come into contact with HF (Bertolini, 1992; Dreisbach and Robertson, 1987).

Largent (1961) describes the effects on 5 human volunteers of low-level HF exposures lasting 6 hours a day for 10-50 days. Each subject received a range of overlapping concentrations. The lowest concentration, 1.42 ppm (1.18 mg/m³), produced no noticeable effects in one individual. Concentrations ranging from 2.59 to 4.74 ppm (2.15-3.93 mg/m³) caused slight irritation of the face, nose and eyes, in addition to facial erythema apparently during the exposures. At 3.39 ppm (2.81 mg/m³) "...an upper respiratory cold made the nasal passages hyper-irritable for a short time, and during this period burning in the nose produced by HF was the source of considerable discomfort" (Largent, 1961).

Wing *et al*. (1991) noted that hydrofluoric acid, in the form of a mist, can cause severe irritation of the eyes and respiratory tract, resulting in intense lacrimation, sore throat, cough, lower airway inflammation, and possible airway edema.

Lund *et al*. (1997) investigated eye and airway symptoms and lung function (forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC)) during and after a one hour exposure to hydrogen fluoride. Twenty healthy male volunteers were exposed in a chamber to constant HF concentrations that ranged from 0.2 to 5.2 mg/m³. ( Such concentrations occur among potroom workers in the primary aluminum industry, according to the authors.) The volunteers were asked to report itching or soreness of the eyes and upper airways and to grade these subjective responses on a scale from 1 to 5 with a standardized questionnaire. Lower airway symptoms of chest tightness and soreness, coughing, expectoration, and wheezing were similarly reported and graded by the volunteers. For the purposes of analysis the authors grouped the subjects into exposure groups of 0.2-0.6 mg/m³ (low), 0.7-2.4 mg/m³ (medium), and 2.5-5.2 mg/m³ (high). Lower airway scores were not significantly different for any concentration range. The upper airway and total symptom score was significantly increased ($p<0.05$) at the end of exposure for the highest exposure range (2.5-5.2 mg/m³, n=7) and for all exposures considered as a single group (0.2-5.2 mg/m³, n=23). The total symptom score was also significantly increased at the end of exposure for the lowest concentration range (0.2-0.6 mg/m³, n=9), although individual scores for eye irritation, upper respiratory irritation, and lower respiratory irritation were not significantly different comparing before and after exposure. Almost all the symptoms had disappeared four hours after the end of exposure. Symptom scores

from the upper airways were significantly correlated with the HF concentration (r = 0.62, p = 0.002), the change in plasma fluoride concentration (delta C) (r = 0.51, p = 0.01), and the maximum plasma fluoride concentration (Cmax) (r = 0.42, p = 0.05). A significant correlation was found between total symptom score for airways and the HF concentration (p = 0.009). No significant changes occurred in $FEV_1$ following exposure at any concentration. A statistically significant decrease in FVC (-0.02 L, 95% CI -0.5 to 0.06) was found in the group exposed at the lowest concentration range (0.2-0.6 mg/m³, n = 9). However, no dose-response relationship was evident and no lower airway symptoms were reported. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL for upper airway irritation.

*Predisposing Conditions for HF Toxicity*

**Medical**: People with underlying cardiopulmonary disease may be more at risk from the irritating properties of HF at high concentrations on the lower airway.

**Chemical**: Unknown

## V.     Acute Toxicity to Laboratory Animals

In a study of the lethal effects of HF in mice, Higgins *et al*. (1972) determined a 5-minute $LC_{50}$ of 6,427 ppm (5,334 mg/m³) while no lethality was observed after exposure to 2,430 ppm (2,017 mg/m³). The authors observed pulmonary edema in varying degrees of severity in most of the exposed mice. Pulmonary hemorrhage was a common finding in animals that died during, or shortly after, exposure to concentrations above the $LC_{50}$ value. Higgins and colleagues also exposed rats to high concentrations of HF for 5-minute periods. Exposure of rats to 12,440 ppm (10,325 mg/m³) HF resulted in 10% mortality and exposure to 25,690 ppm (21,323 mg/m³) resulted in 100% mortality.

Wohlslagel and colleagues (1976) exposed rats and mice to HF for 60 minute durations. The 1-hour $LC_{50}$ in mice, the most sensitive species, was 342 ppm (284 mg/m³), while no lethality was observed at 263 ppm (218 mg/m³). An exposure of 1,087 ppm (902 mg/m³) resulted in no lethality in rats, while 100% mortality was observed at 1,765 ppm (1,464 mg/m³). Wohlslagel *et al*. (1976) noted symptoms in both rats and mice which included eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of exposed skin.

Rosenholtz *et al*. (1963) showed that rats and guinea pigs exhibited dose- and duration-dependent toxic effects from exposure to concentrations as low as 103 ppm (85 mg/m³) for 60 minutes. At this concentration, HF produced signs of irritation in rats, including pawing of the eyes and blinking. No histological damage to nasal or pulmonary epithelium, liver, or kidney was observed upon necropsy at this concentration. The signs resolved shortly after removal of the animals from the exposure chamber. Exposure to a concentration of 126 ppm (104 mg/m³) resulted in general discomfort, pawing at the nose, and tearing from the eyes. Most of the signs were mild and lasted for a few hours after exposure. Consequently, it was concluded that 103 ppm (85 mg/m³) represented a NOAEL for severe or disabling effects.

## VI.    Reproductive or Developmental Toxicity

There are no data available which describe reproductive effects in humans or animals, resulting from acute inhalation exposure to HF.  Exposure of female rats to HF at 0.2 mg/m³ (0.24 ppm) was reported to be embryotoxic and teratogenic (Kenchenko and Saripova, 1974).  The original study was not available for review.

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

**Reference Exposure Level (protective against mild adverse effects):  0.3 ppm (240 μg/m³)**

| | |
|---|---|
| *Study* | Lund *et al*. (1997) |
| *Study population* | 20 healthy, male volunteers |
| *Exposure method* | inhalation of 0.2 to 5.2 mg/m³ HF (range) in an exposure chamber |
| *Critical effects* | upper respiratory tract membrane irritation |
| *LOAEL* | 2.5-5.2 mg/m³ |
| *NOAEL* | 0.7-2.4 mg/m³ |
| *Exposure duration* | 1 hour |
| *Extrapolated 1 hour concentration* | 2.4 mg/m³ (3 ppm) |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 10 |
| *Reference Exposure Level* | 0.24 mg/m³ (240 μg/m³; 0.3 ppm) |

Self-reported upper airway and eye irritation occurred after one hour of exposure to HF at 0.2-0.6 mg/m³ with 4/9 subjects reporting low symptom scores.  However, the scored symptoms were not statistically significantly different comparing before-exposure reported symptoms to after-exposure reported symptoms until concentrations exceeded 2.5 mg/m³. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL.  While there were no changes in $FEV_1$, there was a slight decrease in FVC after exposure at the medium concentration range.  However, OEHHA staff did not consider the changes in FVC to be significant adverse effects since there was no dose-response relationship and they were unaccompanied by changes in $FEV_1$ (see Section 3.2.1.1 in main text).

**Level Protective Against Severe Adverse Effects**

Following a 60-minute exposure to 103 ppm (85 mg/m³) HF, rats exhibited signs of mild irritation that resolved shortly after removal from exposure (Rosenholtz *et al*., 1963).  Higher concentrations produced increasingly severe responses that persisted for hours after exposure. The 103 ppm (85 mg/m³) exposure was considered a NOAEL for severe effects.  Application of an uncertainty factor of 100 to account for interspecies and individual (human intraspecies) variation results in a level protective against severe adverse effects of 1.0 ppm (0.85 mg/m³).

The ERPG-2 for HF (20 ppm) is based on a report by Machle and Evans (1940) that workmen were exposed to HF in the range of 13-26 ppm (11-22 mg/m³) over a period of 9 years.  The ERPG document also considered the animal lethality data from Machle *et al*. (1934) for development of the ERPG-2.  The studies that form the basis for the ERPG-2 for HF are inappropriate.  The study on workers by Machle and Evans (1940) did not examine irritation, kidney, liver, or lung function, but only skeletal fluorosis.  In addition, the animal lethality data from Machle *et al*. (1934) is inappropriate for use as a basis for the ERPG-2, which is intended to protect nearly all individuals from serious or irreversible health effects.  For these reasons, the ERPG-2 was rejected for use as a severe adverse effect level.

In comparison with the severe adverse effect level for HF, an alternative analysis yielded a level of 2 ppm that is protective against severe effects from a single 1-hour exposure to HF (Alexeeff *et al*., 1993).  The results in this published paper provide support for the 1 ppm value calculated above to be protective against severe adverse effects.

**Level Protective Against Life-threatening Effects**

The ERPG-3 value for HF of 50 ppm (AIHA, 1992) is based on essentially two reports. The first, Machle *et al*. (1934), indicated that no deaths in rabbits or guinea pigs were observed following 30-minute exposures to 1,220 ppm (1,013 mg/m³) HF.  The second report, an unpublished communication in the ERPG document, describes dangerous serum fluoride concentrations in humans exposed to 50 ppm (41.5 mg/m³) HF (Smith, 1988). However, the unpublished personal communication from Smith (1988) is not described in the ERPG documentation in sufficient detail for evaluation.  There are some data indicating that mice and rats may be more sensitive to the acute lethal effects of HF than rabbits and guinea pigs (Wohlslagel *et al*., 1976). We did not choose to use the ERPG-3 as the level protective against life-threatening effects because of the inadequate explanation in the ERPG documentation.

In contrast to the qualitative estimate of the ERPG-3, the benchmark dose (BD) approach is presented below as a quantitative derivation.  Wohlslagel *et al*. (1976) exposed mice to varying concentrations of HF for 60-minute intervals.  The 1-hour $LC_{50}$ value was determined to be 342 ppm (284 mg/m³) in mice.  With these data, an exposure level was calculated by a BD approach using a log-normal probit analysis (Crump, 1983).  The 95% LCL of the concentration expected to produce a response (in this case, lethality) rate of 5% was defined as the benchmark concentration ($BC_{05}$).  The resulting $BC_{05}$ from this analysis was 204 ppm (170 mg/m³).  A UF of 3 was applied to account for animal to human (interspecies) extrapolation since use of the BC accounts for some degree of variation and a UF of 10 to account for human individual variation (intraspecies extrapolation).

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The resulting value is 6.8 ppm (5.6 mg/m³).  Based on comparison with the available literature on human studies, discussed above, this value appears to be an overly protective life-threatening effect level even for sensitive subpopulations.  The appropriate level is probably between 7 and 50 ppm.  Since neither value appears to be entirely appropriate, we chose a single point estimate

within the range of these values, the geometric mean, or 19 ppm (15.5 mg/m³), as the level protective against life-threatening effects.

The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% mortality rates are compared below.

Comparison of 1% and 5% mortality rates for HF

| Response rate | MLE (ppm) | 95% LCL (ppm) |
|---|---|---|
| 1% | 216 | 166 |
| 5% | 247 | 204 |

## VIII.   References

(ATSDR) Agency for Toxic Substances and Disease Registry. Toxicological profile for fluorides, hydrogen fluoride, and fluorine (F). Atlanta (GA): ATSDR; 1993.

Alexeeff GV, Lewis DC, Ragle NL. Estimation of potential health effects from acute exposure to hydrogen fluoride using a "benchmark dose" approach. Risk Anal 1993;13(1):63-69.

(AIHA) American Industrial Hygiene Association. Emergency response planning guidelines for hydrogen fluoride. Set 2. Akron (OH): AIHA; 1992.

Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983;3(6):272-290.

Bertolini JC. Hydrofluoric acid: A review of toxicity. J Emerg Med 1992;10:163-168.

Braun J, Stob H, Zober A. Intoxication following the inhalation of hydrogen fluoride. Arch Toxicol 1984;56:50-54.

Crump KS & Co, Inc. Probit (Log-Normal) software for the IBM-PC. Ruston (LA); 1983.

Dreisbach RH, Robertson WO. Fluorine, hydrogen fluoride, and derivatives. In: Handbook of poisoning: prevention, diagnosis, and treatment. 12th ed. Norwalk (CT): Appleton and Lange; 1987.

Fairhall L. Industrial toxicology. Baltimore (MD): Williams and Wilkins; 1949 [cited in Smyth, 1956].

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Higgins EA, Fiorca V, Thomas AA, Davis HV. Acute toxicity of brief exposures to HF, HCl, $NO_2$, and HCN with and without CO. Fire Technol 1972;8:120-130.

Jenkins GN, Venkateswarlu P, Zipkin I. Physiological effects of small doses of fluoride. In: Fluorides and human health. Geneva: World Health Organisation; 1970. p. 173.

Kenchenko VG, Saripova NP. Vopy Eksp Klin Ter Profil Prom Intoksikatsi: 1974;160-164. [cited in ReproRisk Vol 21. Denver (CO): Micromedex, Inc; 1994.]

Largent EJ, Fluorosis: The health aspects of fluorine compounds. Columbus (OH): Ohio State University Press; 1961.

Lund K, Ekstrand J, Boe J, Sostrand P, Kongerud J. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. Occup Environ Med 1997;54:32-37.

Machle W, Evans EE. Exposure to fluorine in industry. J Ind Hyg Toxicol 1940;22:213-217. [cited in AIHA, 1992.]

Machle W, Thamann F, Kitzmiller K, Cholak J. The effects of the inhalation of hydrogen fluoride. I. The response following exposure to high concentrations. J Ind Hyg 1934;16(2):129-145.

National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard for occupational exposure to hydrogen fluoride. Washington (DC): US Government Printing Office; 1976.

Rosenholtz MJ, Carson TR, Weeks MH, Wilinski F, Ford D, Oberst F. A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. Ind Hyg J 1963;24:253-261.

Smith FA. 1988. Written communication to AIHA ERPG Review Committee. AIHA, 475 Wolf Ledges Pkwy., Akron, OH 44311-1087. [cited in AIHA, 1992.]

Smyth HF Jr. Improved communication - hygienic standards for daily inhalation. Am Ind Hyg Assoc J 1956;17:129-185.

(U.S.EPA) United States Environmental Protection Agency. Interim methods for development of inhalation Reference Concentrations. Office of Research and Development. EPA/600/8-90//066A. Washington (DC): U.S.EPA; 1990.

Wing JS, Brender JD, Sanderson LM, Perrotta DM, Beauchamp RA. Acute health effects in a community after a release of hydrofluoric acid. Arch Environ Health 1991;46(3):155-160.

Wohlslagel J, DiPasquale LC, Vernot EH. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J Combust Toxicol 1976;3:61-70.

ACUTE TOXICITY SUMMARY

**Hydrogen Selenide**

*(hydrogen selenide, selenium hydride)*

CAS Registry Number:  7783-07-5

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

| | |
|---|---|
| *Inhalation reference exposure level* | **5 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 (HSDB, 1994 except as noted)**

| | |
|---|---|
| *Description* | gas |
| *Molecular formula* | $H_2S$ |
| *Molecular weight* | 80.98 |
| *Density* | 3.31 g/L @ 25°C |
| *Boiling point* | -41.3°C |
| *Melting point* | -65.73°C |
| *Flashpoint* | not applicable |
| *Explosive limits* | not applicable |
| *Solubility* | soluble in water, carbonyl chloride and carbon disulfide |
| *Odor threshold* | 0.3 ppm  (AIHA, 1989) |
| *Odor description* | garlic odor (AIHA, 1989) |
| *Metabolites* | trimethylselenonium (Palmer *et al.*, 1970) |
| *Conversion factor* | 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.

The most acutely toxic selenium compound reported is hydrogen selenide ($H_2Se$).  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 ($SeO_2$) (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) $H_2Se$ 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 preexisting eye, skin, or respiratory conditions (including allergies) may be more sensitive to the effects of exposure to $H_2Se$ (Reprotext, 1999).

**Chemical**:    Persons exposed to multiple selenium compounds over time may be more sensitive to the effects of additional Se exposure (Reprotext, 1999).

## V.    Acute Toxicity to Laboratory Animals

The 2-hour $LC_{50}$ in guinea pigs is 3.6 ppm (12 mg/m³) $H_2Se$ (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) $H_2Se$ 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 $H_2Se$ 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 $H_2Se$ 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 $Se^0$ 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 ($Na_2SeO_4$) 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 $Na_2SeO_4$. Maternal toxicity, as indicated by a significant weight loss, was observed following a single oral dose of 110 mg/kg $Na_2SeO_4$; approximately 30% of the dams in this group died following administration of the dose.

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 ($SeO_2$) (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 $SeO_2$/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):    5 μg/m³**

|  |  |
|---|---|
| *Study* | Dudley and Miller, 1937; Dudley and Miller, 1941 |
| *Study population* | groups of 16 guinea pigs; 32 controls |
| *Exposure method* | inhalation in a chamber |
| *Critical effects* | signs of eye and respiratory irritation, with persistent coughing after exposure, for several days. |
| *LOAEL* | 0.9 ppm (3 mg/m³) |
| *NOAEL* | not observed |
| *Exposure duration* | 1 hour |
| *Extrapolated 1 hour concentration* | 0.9 ppm (3 mg/m³) |
| *LOAEL uncertainty factor* | 6 |
| *Interspecies uncertainty factor* | 10 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 600 |
| *Reference Exposure Level* | 0.0015 ppm (0.005 mg/m³; 5 μg/m³) |

Guinea pigs exposed to 0.9 ppm (3 mg/m³) $H_2Se$ 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 $H_2Se$ of 6 ppm (20 mg/m³) and greater.  No increase in mortality was observed in animals exposed to 3 or 4 mg/m³ $H_2Se$ compared to control animals.  The LOAEL for irritant effects is 0.9 ppm (3 mg/m³) $H_2Se$.  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.

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.

Since $H_2Se$ 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.  Thus, its use should be restricted to evaluating emissions of hydrogen selenide.  OEHHA will continue to evaluate the literature for other selenium compounds for the development of RELs for selenium salts.

**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 cannot be recommended.

## VIII.   References

Al-Bayati MA, Raabe OG, Teague SV. Effect of inhaled dimethylselenide in the Fischer 344 male rat. J Toxicol Environ Health 1992;37:549-557.

Amdur MO, Doull J, Klaassen CD, editors. Casarett and Doull's Toxicology. 4th ed. New York: Pergamon Press; 1991. p. 658-660.

(ACGIH) American Conference of Governmental Industrial Hygienists . Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 1354-1360.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 20.

Buchan RF. Industrial selenosis: a review of the literature, report of five cases and a general bibliography. Occup Med 1947;3:439-456.

Chowdhury AR, Venkatakrishna-Bhatt H. Effect of selenium dioxide on the testes of the rat. Indian J Physiol Pharmacol 1983;27:237-240.

Clayton GD, Clayton FE, editors. Patty's industrial hygiene and toxicology. 3rd ed. Revised. Vol. II. Toxicology. New York (NY): John Wiley Sons; 1982. p. 2133.

Clinton M Jr. Selenium fume exposure. J Ind Hyg Toxicol 1947;29:225.

Dudley HC, Miller JW. Toxicology of selenium. IV. Effects of exposure to hydrogen selenide. US Public Health Rep 1937;52:1217-1231.

Dudley HC, Miller JW. Toxicology of selenium. VI. Effects of subacute exposure to hydrogen selenide. J Ind Hyg Toxicol 1941;23:470-477.

Ferm VH, Hanlon DP, Willhite CC, Choy WN, Book SA.  Embryotoxicity and dose-response relationships of selenium in hamsters. Reproductive Toxicol 1990;4(3):183-190.

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Friberg L, Nordberg GF, Vouk VB, editors. Handbook on the toxicology of metals. Vol II. Specific metals. 2nd ed. New York: Elsevier; 1986. p. 482-520.

Hall RH, Leskin S, Frank P, Maynard EA, Hodge HC. Preliminary observations on toxicity of elemental selenium. Arch Ind Hyg Occup Med 1951;4:458-464.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 7/31/94).

Kut D, Sarikaya Y. Determination of selenium in atmospheric particulate material of Ankara and its possible sources. J Radioanal Chem 1981;62:161-170. [cited in Friberg *et al*., 1986.]

Medinsky MA, Cuddihy RG, McClellan RO. Systemic absorption of selenious acid and elemental selenium aerosols in rats. J Toxicol Environ Health 1981;8:917-928.

Nagaii I. Igaku Kenkyu 1959;29:1505-1532 (Japanese). [cited in Friberg *et al*., 1986.]

NIOSH. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

Palmer IS, Gunsalus RP, Halverson AW, Olson OE. Trimethylselenonium ion as a general excretory product from selenium metabolism in the rat. Biochim Biophys Acta 1970;208:260-266.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Wilson HM. Selenium oxide poisoning. N Carolina Med J 1962;23:73-75.

ACUTE TOXICITY SUMMARY

## HYDROGEN SULFIDE

*(sulfur hydride; sulfuretted hydrogen)*

**CAS Registry Number: 7783-06-4**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **42 µg/m³** |
| *Critical effect(s)* | Headache, nausea, physiological responses to odor |
| *Hazard Index target(s)* | CNS |

**II.     Physical and Chemical Properties (AIHA, 1991 except as noted)**

| | |
|---|---|
| *Description* | colorless gas |
| *Molecular formula* | $H_2S$ |
| *Molecular weight* | 34.08 |
| *Density* | 1.39 g/L @ 25°C |
| *Boiling point* | -60.7°C |
| *Melting point* | unknown |
| *Vapor pressure* | 1 atm @ -60.4°C |
| *Flash point* | 26°C |
| *Explosive limits* | upper = 4.3% by volume in air |
| | lower = 46% by volume in air |
| *Solubility* | soluble in water, hydrocarbon solvents, ether, and ethanol |
| *Odor threshold* | 0.0081 ppm (Amoore and Hautala, 1983) |
| *Odor description* | resembles rotten eggs |
| *Metabolites* | bisulfite ($HSO_3$), thiosulfate ($S_2O_3^{2-}$) (Baxter and Van Reen, 1958) |
| *Conversion factor* | 1 ppm = 1.4 mg/m³ @ 25°C |

**II.     Major Uses or Sources**

Hydrogen sulfide ($H_2S$) is used as a reagent and an intermediate in the preparation of other reduced sulfur compounds.  It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986).

## IV.    Acute Toxicity to Humans

Hydrogen sulfide is an extremely hazardous gas (ACGIH, 1992).  Hydrogen sulfide exposure is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977).  The mortality in acute hydrogen sulfide intoxications has been reported to be 2.8% (Arnold *et al.*, 1985) to 6% (WHO, 1981).  While severe intoxication is especially of concern when exposure occurs in confined spaces, an accidental release of hydrogen sulfide into the air surrounding industrial facilities can cause very serious effects.  For example, at Poza Rica, Mexico 320 people were hospitalized and 22 died (WHO, 1981).  An inhalation $LC_{Lo}$ of 600 and 800 ppm (840 and 1,120 mg/m³) for 30 and 5 minutes, respectively, is reported (Hazardtext, 1994).  A lethal exposure was documented for a worker exposed to approximately 600 ppm $H_2S$ for 5-15 minutes (Simson and Simpson, 1971).  Inhalation of 1,000 ppm (1,400 mg/m³) is reported to cause immediate respiratory arrest (ACGIH, 1992).  Concentrations greater than 200 ppm (280 mg/m³) $H_2S$ are reported to cause direct irritant effects on exposed surfaces and can cause pulmonary edema following longer exposures (Spiers and Finnegan, 1986).  The mechanism of $H_2S$ toxicity, cellular hypoxia caused by inhibition of cytochrome oxidase, is similar to that for cyanide and can be treated by induction of methemoglobin or with hyperbaric oxygen (Elovaara *et al.*, 1978; Hsu *et al.*, 1987).

At concentrations exceeding 50 ppm (70 mg/m³), olfactory fatigue prevents detection of $H_2S$ odor.  Exposure to 100-150 ppm (140-210 mg/m³) for several hours causes local irritation (Haggard, 1925).  Exposure to 50 ppm for 1 hour causes conjunctivitis with ocular pain, lacrimation, and photophobia; this can progress to keratoconjunctivitis and vesiculation of the corneal epithelium (ACGIH, 1992).  Bhambhani and Singh (1991) showed that 16 healthy subjects exposed to 5 ppm (7 mg/m³) $H_2S$ under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood.  Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m³) $H_2S$ caused coughing and throat irritation after 15 minutes.

In another study, ten asthmatic volunteers were exposed to 2 ppm $H_2S$ for 30 minutes and pulmonary function was tested (Jappinen *et al.*, 1990).  All subjects reported detecting "very unpleasant" odor but "rapidly became accustomed to it."  Three subjects reported headache following exposure.  No significant changes in mean FVC or $FEV_1$ were reported.  Although individual values for specific airway resistance ($SR_{aw}$) were not reported, the difference following exposure ranged from -5.95% to +137.78%.  The decrease in specific airway conductance, $SG_{aw}$, ranged from -57.7% to +28.9%.  The increase in mean $SR_{aw}$ and the decrease in mean $SG_{aw}$ were not statistically significant.  However, significantly increased airway resistance and decreased airway conductance were noted in two of ten asthmatic subjects which may be biologically significant.

Hydrogen sulfide is noted for its strong and offensive odor.  Based on a review of 26 studies, the average odor detection threshold ranged from 0.00007 to 1.4 ppm (Amoore, 1985).  The geometric mean of these studies is 0.008 ppm.  In general, olfactory sensitivities decrease by a factor of 2 for each 22 years of age above 20 (Venstrom and Amoore, 1968); the above geometric mean is based on the average age of 40.

For hydrogen sulfide, concentrations that substantially exceed the odor threshold result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1985). The perceived intensity of the odor of hydrogen sulfide depends on the longevity of the concentration, and the intensity increases 20% for each doubling concentration (Amoore, 1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winneke, 1975; Winneke and Kastka, 1977; Hellman and Small, 1974; Adams *et al.,* 1968; and NCASI, 1971). The geometric mean for these studies is 5, indicating that when an unpleasant odor reaches an average concentration of 5 times its detection threshold, the odor will result in annoying discomfort. Applying the 5-fold multiplier to the mean detectable level, 0.008 ppm, results in a mean annoyance threshold of 0.04 ppm. At the current California Ambient Air Quality Standard (CAAQS) of 0.03 ppm, the level would be detectable by 83% of the population and would be discomforting to 40% of the population. These estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper 1985) at 0.03 ppm H2S exposures from geyser emissions. The World Health Organization (WHO) reports that in order to avoid substantial complaints about odor annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (7 $\mu g/m^3$), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970).

*Predisposing Conditions for Hydrogen Sulfide Toxicity*

**Medical**:     Unknown

**Chemical**:     Ethanol has been shown to potentiate the effects of $H_2S$ by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m³) $H_2S$ (Beck *et al.*, 1979).

## V.     Acute Toxicity to Laboratory Animals

A median lethal concentration ($LC_{50}$) in rats exposed to $H_2S$ for 4 hours was estimated as 440 ppm (616 mg/m³) (Tansy *et al.*, 1981). An inhalation $LC_{Lo}$ of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m³) for 1 hour is reported in mice (RTECS, 1994). In another study, mortality was significantly higher for male rats (30%), compared to females (20%), over a range of exposure times and concentrations (Prior *et al*., 1988). A concentration of 1,000 ppm (1,400 mg/m³) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m³) for 2 hours resulted in altered leucine incorporation into brain proteins in mice (Elovaara *et al*., 1978). Kosmider *et al*. (1967) reported abnormal electrocardiograms in rabbits exposed to 100 mg/m³ (71 ppm) $H_2S$ for 1.5 hours.

Khan *et al*. (1990) exposed groups of 12 male Fischer 344 rats to 0, 10, 50, 200, 400, or 500-700 ppm hydrogen sulfide for 4 hours. Four rats from each group were sacrificed at 1, 24, or 48 hours post-exposure. Cytochrome c oxidase activity in lung mitochondria was significantly (p<0.05) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1-hour post-

exposure compared to controls.  A NOAEL of 10 ppm was identified in this study for effects on lung mitochondrial cytochrome c oxidase activity.

## VI.      Reproductive or Developmental Toxicity

Xu *et al*. (1998) conducted a retrospective epidemiological study in a large petrochemical complex in Beijing, China in order to assess the possible association between petrochemical exposure and spontaneous abortion.  The facility consisted of 17 major production plants which are divided into separate workshops, allowing for the assessment of exposure to specific chemicals.  Married women (n = 2853), who were 20-44 years of age, had never smoked, and who reported at least one pregnancy during employment at the plant, participated in the study.  According to their employment record, about 57% of these workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy.  There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals compared with those working in nonchemical plants.  Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to petrochemicals was consistently associated with an increased risk of spontaneous abortion (overall odds ratio (OR) = 2.7 (95% confidence interval (95% CI) = 1.8 to 3.9) after adjusting for potential confounders).  When the analysis was performed with the exposure information obtained from the women' interview responses for (self reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI = 2.0 to 4.0).  The analysis was repeated by excluding those 452 women who provided inconsistent reports between recalled exposure and work history, and a comparable risk of spontaneous abortion (OR 2.9; 95% CI 2.0 to 4.4) was found.  In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals.  There were 106 women (3.7% of the study population) exposed only to hydrogen sulfide, and the results for hydrogen sulphide (OR 2.3; 95% CI = 1.2 to 4.4) were significant.  No hydrogen sulfide exposure concentration 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):  42 µg/m³**
(California Ambient Air Quality Standard)

|  |  |
|---|---|
| *Study* | California State Department of Public Health, 1969; CARB, 1984; Reynolds and Kamper, 1985; Amoore, 1985 |
| *Study population* | panel of 16 people; general population |
| *Exposure method* | inhalation of increasing concentrations of $H_2S$ |
| *Critical effects* | headache, nausea |
| *LOAEL* | 0.012-0.069 ppm (range of odor threshold) |
| *NOAEL* | ≤ 0.01 ppm |
| *Exposure duration* | not stated (tested until odor detected) |
| *Extrapolated 1 hour concentration* | 0.012-0.069 ppm (geometric mean = 0.03 ppm) |

|                                 | (1 hour = minimum duration for an air standard) |
| ------------------------------- | --------------------------------------------- |
| *LOAEL uncertainty factor*      | not used                                      |
| *Interspecies uncertainty factor* | 1                                           |
| *Intraspecies uncertainty factor* | 1                                           |
| *Cumulative uncertainty factor* | 1                                             |
| *Reference Exposure Level*      | 0.03 ppm (0.042 mg/m³; 42 µg/m³)              |

The 1-hour California Ambient Air Quality Standard (AAQS) for hydrogen sulfide was originally based on an olfactory perception study by the California State Department of Public Health (1969). Sixteen individuals were each exposed to increasing concentrations of $H_2S$ until his or her odor threshold was reached. The range of the odor thresholds was 0.012-0.069 ppm, and the geometric mean was 0.029 ppm (geometric standard deviation = 0.005 ppm). The mean odor threshold (rounded to 0.03 ppm) was selected as the AAQS for $H_2S$. However, others have reported that the odor threshold is as low as 0.0081 ppm (Amoore and Hautala, 1983). In 1984 CARB reviewed the AAQS for $H_2S$ and found that the standard was necessary not only to reduce odors, but also to reduce the physiological symptoms of headache and nausea. (CARB, 1984). Furthermore, Amoore (1985) conducted a study that estimated 40% of the population would find 0.03 ppm (0.042 mg/m³) to be an objectionable concentration. In public testimony before the ARB it was stated that some people reported headaches and other symptoms at the standard (Reynolds and Kamper, 1985). Thus this recommended level protective against mild adverse effects may be need to be reexamined as more data become available.

**Level Protective Against Severe Adverse Effects**

No recommendation can be made due to the limitations of the database.

An ERPG-2 of 30 ppm (AIHA, 1991) was based on experimental data showing that exposure of rats to 45 ppm (63 mg/m³) $H_2S$ for 4 hours resulted in no deaths (Rogers and Ferin, 1981). In addition, rabbits exposed to 71 ppm (100 mg/m³) $H_2S$ for 1.5 hours developed cardiac irregularities, measured by electrocardiogram, and decreased myocardial ATP phosphorylase (Kosmider *et al.*, 1967). The rationale for the margin of safety used for the ERPG-2 is not presented.

**Level Protective Against Life-threatening Effects**

No recommendation can be made due to the limitations of the database.

The AIHA ERPG-3 for hydrogen sulfide of 100 ppm (AIHA, 1991) was based on case reports of conjunctivitis, respiratory irritation, and unconsciousness in humans exposed to estimated concentrations of 200-300 ppm (280-420 mg/m³) $H_2S$ for 20 minutes to 1 hour (Ahlborg, 1951; Yant, 1930). In addition, a 1-hour $LC_{50}$ of 712 ppm (997 mg/m³) in rats is cited (CIIT, 1983). The case reports cited in the ERPG document are inadequate to establish acute exposure levels in humans because the concentrations and durations of exposure are only estimates. In addition, there are no $LC_{50}$ data in the CIIT (1983) report. Rats (5 female and 5 male) exposed to $H_2S$ concentrations ranging from 400-600 ppm (560-840 mg/m³) for 4 hours showed dose-dependent lethality rates ranging from 30% - 100% (Tansy *et al.*, 1981). On the other hand, two of three

rhesus monkeys exposed to a concentration of 500 ppm (700 mg/m³) for only 35 minutes or less died, which suggests that primates are more sensitive to the lethal effect of $H_2S$ than rats (Lund and Wieland, 1966). The rationale for the margin of safety used for the ERPG-3 was not presented.

NIOSH (1995) reports a (revised) IDLH for hydrogen sulfide of 100 ppm based on acute inhalation toxicity data in humans and animals, but the values from animals appear to be more heavily weighted than the human data in the selection of the IDLH.

## VII.    References

Adams DF, Young FA, Lahr RA. Evaluation of odor perception threshold test facility. TAPPI 1968;51(13):62A-67A.

Ahlborg G. Hydrogen sulfide poisoning in shale oil industry. AMA Arch Ind Hyg Occup Med 1951;3:247-266. [cited in: AIHA; 1991.]

Alberta Health. Report on $H_2S$ Toxicity. Alberta Health 1990.

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Vol II. Cincinnati: ACGIH; 1991. p. 786-788.

(AIHA) American Industrial Hygiene Association. Emergency response planning guideline for hydrogen sulfide. Set 6. Akron: AIHA; 1991.

Ammann HM. A new look at physiologic respiratory response to $H_2S$ poisoning. J Hazard Mater 1986;13:369-374.

Amoore JE. The perception of hydrogen sulfide odor in relation to setting an ambient standard. California Air Resources Board Contract A4-046-33. April 1985.

Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983;3(6):272-290.

Arnold IM, Dufresne RM, Alleyne BC, Stuart PJ. Health implications of occupational exposures to hydrogen sulfide. J Occup Med 1985;27:373-376.

Baxter CF, Van Reen R. Some aspects of sulfide oxidation by rat-liver preparations. Biochim Biophys Acta 1958;28:567-573.

Beck JF, Cormier F, Donini JC. The combined toxicity of ethanol and hydrogen sulfide. Toxicol Lett 1979;311-313.

Bhambhani Y, Singh M. Effects of hydrogen sulphide on selected metabolic and cardio-respiratory variables during rest and exercise. Report submitted to Alberta Worker's Health and Safety and Compensation. June, 1985. [cited by Alberta Health; 1990.]

Bhambhani Y, Singh M. Physiological effects of hydrogen sulfide inhalation during exercise in healthy men. J Appl Physiol 1991;71:1872-1877.

California Air Resources Board. Report of the committee regarding the review of the AAQS for hydrogen sulfide. Memorandum from CARB to G. Duffy, 1984.

California State Department of Public Health. Recommended Ambient Air Quality Standards. (Statewide standards applicable to all California Air Basins). 1969;HS-3.

(CIIT) Chemical Industry Institute of Toxicology. Ninety day vapor inhalation toxicity study of $H_2S$ in Fischer-344 rats. Docket #22063. Research Triangle Park (NC): Chemical Industry Institute of Toxicology; 1983.

Elovaara E, Tossavainen A, Savolainen H. Effects of subclinical hydrogen sulfide intoxication on mouse brain protein metabolism. Exp Neurol 1978;62:93-98.

Haggard HAW. The toxicology of hydrogen sulphide. J Ind Hyg 1925;7:113-121.

Haggard HW, Henderson Y. The influence of hydrogen sulfide on respiration. Am J Physiol 1922;61:289-297.

HAZARDTEXT™. Hall AH, Rumack BH, editors. Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Hellman TM, Small FH. Characterization of the odor properties of 101 petrochemicals using sensory methods. J Air Pollut Control Assoc 1974;24:979-982.

Hsu P, Li HW, Lin Y. Acute hydrogen sulfide poisoning treated with hyperbaric oxygen. J Hyperbaric Med 1987;2(4):215-221.

Jappinen P, Vilka V, Marttila O, Haahtela T. Exposure to hydrogen sulfide and respiratory function. Br J Ind Med 1990;47:824-828.

Khan AA, Schuler MM, Prior MG *et al*. (1990) Effects of hydrogen sulfide exposure on lung mitochondrial respiratory chain enzymes in rats. Toxicol Appl Pharmacol 103: 482-490.

Kosmider S, Rogala E, Pacholek A. Electrocardiographic and histochemical studies of the heart muscle in acute experimental hydrogen sulfide poisoning. Arch Immunol Ther Exp 1967;15:731-740.

Lindvall T On sensory evaluation of odorous air pollutant intensities. Nord Hyg Tidskr 1970;Suppl 2:1-181.

Lund OE, Wieland H. Pathologic-anatomic findings in experimental hydrogen sulfide poisoning: A study on rhesus monkeys. Int Arch Gewerbepathol Gewerbehyg 1966;22:46-54.

NCASI. Evaluation of the use of humans in measuring the effectiveness of odor control technology at the source. Atmospheric Quality Improvement Technical Bulletin No. 56. New York: National Council of Paper Industry for Air and Steam Improvement; 1971.

(NIOSH) National Institute for Occupational Safety and Health. Criteria for a recommended standard...Occupational exposure to hydrogen sulfide, DHEW (NIOSH) #77-158. Cincinnati (OH): National Institute for Occupational Safety and Health; 1977.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

National Research Council. Hydrogen sulfide. Baltimore: University Park Press: 1979.

Prior MG, Sharma AK, Yong S, Lopez A. Concentration-time interactions in hydrogen sulphide toxicity. Can J Vet Res 1988;52:375-379.

Reynolds R L, Kamper RL. Review of the State of California Ambient Air Quality Standard for Hydrogen Sulfide ($H_2S$). Lakeport (CA): Lake County Air Quality Management District; 1984.

(RTECS®) Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health, Cincinnati (OH) (CD-ROM version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Rogers RE, Ferin J. Effect of hydrogen sulfide on bacterial inactivation in the rat lung. Arch Environ Health 1981;36:261-264. [cited in AIHA, 1991.]

Simson RE, Simpson GR. Fatal hydrogen sulphide poisoning associated with industrial waste exposure. Med J Austral 1971;2:331-334.

Spiers M, Finnegan OC. Near death due to inhalation of slurry tank gases. Ulster Med Soc 1986;55(2):181-183.

Tansy MF, Kendall FM, Fantasia J, Landlin WE, Oberly R, Sherman W. Acute and subchronic toxicity of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J Toxicol Environ Health 1981;8(1-2):71-88.

Venstrom P, Amoore JE. Olfactory threshold in relation to age, sex or smoking. J Food Sci 1968;33:264-265.

Winkler K. Zur Diskussion Gestellt Imissionsgrenzwerte Zur Vehrinderung von. Geruchsbelastigungan Wasser Luft Betrieb 1975;19:411.

Winneke G, Kastka J. Odor pollution and odor annoyance reactions in industrial areas of the Rhine-Ruhr region. In: Olfaction and Taste VI. J Le Magnen, P MacLeod, editors. pp. 471-479. London: Information Retrieved; 1977.

(WHO) World Health Organization. Hydrogen sulfide. Environmental Health Criteria No. 19. Geneva: WHO; 1981.

Xu X, Cho SI, Sammel M, You L, Cui S, Huang Y, *et al*. Association of petrochemical exposure with spontaneous abortion. Occup Environ Med 1998;55(1):31-36.

Yant WP. Hydrogen sulphide in industry: Occurrence, effects, and treatment. Am J Publ Health 1930;20:598-608.

ACUTE TOXICITY SUMMARY

**ISOPROPYL ALCOHOL**

*(isopropanol, 2-propanol, dimethylcarbinol, propyl alcohol)*

**CAS Registry Number: 67-63-0**

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

| | |
|---|---|
| *Inhalation reference exposure level* | **3,200 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)**

| | |
|---|---|
| *Description* | colorless liquid |
| *Molecular formula* | $C_3H_8O$ |
| *Molecular weight* | 60.09 |
| *Density* | 0.78505 g/cm$^3$ @ 20°C |
| *Boiling point* | 82.5°C @ 760 mm Hg |
| *Melting point* | -88.5°C |
| *Vapor pressure* | 44.0 mm Hg @ 25°C |
| *Flashpoint* | 11.7°C (closed cup) |
| *Explosive limits* | upper = 12.0% |
| | lower = 2.0% |
| *Solubility* | soluble in benzene, miscible with most organic solvents, slightly soluble in water, alcohol, and acetone |
| *Odor threshold* | 19 ppm (geometric mean) (AIHA, 1989) |
| *Odor description* | sharp (AIHA, 1989) |
| *Metabolites* | acetone |
| *Conversion factor* | 1 ppm = 2.45 mg/m³ @ 25°C |

**III.    Major Uses or Sources**

Isopropyl alcohol has wide use in consumer products such as mild skin disinfectants and astringents.  It is also used as a solvent for cellulose nitrate.

**IV.    Acute Toxicity to Humans**

Symptoms of acute poisoning include dizziness, incoordination, headache, and confusion. Vomiting, hematemesis, diarrhea, and hypotension may occur following ingestion of large quantities of isopropyl alcohol.  Late manifestations include aspiration pneumonia and kidney and liver dysfunction (Reprotext, 1993).  The oral LOAEL for isopropyl alcohol is reported as 233 mg/kg (RTECS, 1993).

Irritation of the mucous membranes of the upper respiratory tract may occur following inhalation of isopropyl alcohol. Ten human subjects were exposed for 3-5 minutes to 400 or 800 ppm (1,000 or 2,000 mg/m³) isopropyl alcohol (Nelson *et al*., 1943). Exposure to 400 ppm isopropyl alcohol produced mild irritation of the eyes, nose, and throat. When exposed to 800 ppm the majority of the subjects declared the atmosphere unsuitable for a prolonged exposure. The subjects indicated, however, that prolonged exposure to 200 ppm would not be objectionable.

*Predisposing Conditions for Isopropyl Alcohol Toxicity*

**Medical**:    Persons with eye, skin, respiratory or neurological conditions and diabetics may be more sensitive to the toxic effects of isopropyl alcohol (Reprotext, 1999).

**Chemical**:    Individuals exposed to acetone, carbon tetrachloride, or n-hexane may be at increased risk for adverse effects when exposed simultaneously to isopropyl alcohol (Reprotext, 1999).

## V.    Acute Toxicity to Laboratory Animals

A 4-hour rat $LC_{Lo}$ of 16,000 ppm (39,000 mg/m³) isopropyl alcohol is reported (Carpenter *et al*., 1949). Reduced ciliary activity and epithelial damage in the nasal mucosa of guinea pigs were observed following a 24-hour exposure to 400 ppm (1,000 mg/m³) isopropanol. Complete recovery from the exposure occurred within 2 weeks. Exposure at 5,500 ppm (13,000 mg/m³) resulted in similar damage requiring more than two weeks for complete recovery (Ohashi *et al*., 1988). A 10-minute $RD_{50}$ of 17,693 ppm (43,000 mg/m³) for mice has been reported (Kane at al., 1980).

## VI.    Reproductive or Developmental Toxicity

No human reproductive studies and only a limited number of animal studies on the effects of isopropyl alcohol were available. Pregnant rats exposed to 3,500, 7,000, and 10,000 ppm (8,600, 17,000, and 25,000 mg/m³) isopropanol for 7 hours per day on days 1-19 of gestation exhibited signs of maternal toxicity, indicated by retarded weight gain, following exposure to 7,000 ppm or greater. Signs of narcosis were observed in the dams exposed to 10,000 ppm. Fetal weight was reduced in all three exposed groups in a dose-dependent manner; increased skeletal and visceral malformations were observed following exposure to 7,000 ppm (Nelson *et al*., 1988).

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

**Reference Exposure Level (protective against mild adverse effects)   1.3 ppm (3,200 µg/m³)**

| | |
|---|---|
| *Study* | Nelson *et al*., 1943 |
| *Study population* | ten human subjects |
| *Exposure method* | 400 ppm for 3-5 minutes |
| *Critical effects* | mild irritation of the eyes, nose and throat |
| *LOAEL* | 400 ppm |
| *NOAEL* | 200 ppm (implied) |
| *Exposure duration* | 4 minutes |
| *Extrapolated 1 hour concentration* | 13 ppm $(200^1 \text{ppm} * 0.067\,\text{h} = C^1 * 1\,\text{h})$ |
| | (see Table 12 for information on "n") |
| *LOAEL uncertainty factor* | 1 |
| *Interspecies uncertainty factor* | 1 |
| *Intraspecies uncertainty factor* | 10 |
| *Cumulative uncertainty factor* | 10 |
| *Reference Exposure Level* | 1.3 ppm (3.2 mg/m³; 3,200 µg/m³) |

Ten human subjects, exposed for 3-5 minutes to 400 ppm (1,000 mg/m³) isopropyl alcohol, reported mild irritation of the eyes, nose and throat.  The study indicates a 4 minute LOAEL of 400 ppm.  The subjects indicated that exposure to 200 ppm would be tolerable, which implies a NOAEL of 200 ppm.  This 4 minute NOAEL was time adjusted to 1 hour.  An uncertainty factor of 10 was applied to the 200 ppm NOAEL to account for the susceptibility of sensitive individuals.

### Level Protective Against Severe Adverse Effects

Rats were exposed for 6 hours to 0, 500, 1,500, 5,000, or 10,000 ppm isopropyl alcohol (Gill *et al*., 1995).  Signs of narcosis and concentration-related decreases in motor activity were observed in rats exposed to 5,000 or 10,000 ppm.  Slight but statistically significant decreases in motor activity were observed in male, but not female, rats exposed to 1,500 ppm isopropyl alcohol.  No adverse effects were observed in rats exposed to 500 ppm isopropyl alcohol.  Narcosis during isopropanol exposure at 1,500 and 5,000 ppm was also noted in a chronic inhalation study by Burleigh-Flayer *et al*. (1994).  A 6-hour NOAEL of 500 ppm is defined from this study.  An uncertainty factor of 10 was applied to account for interspecies differences.  An additional uncertainty factor of 10 was applied to account for sensitive individuals.  An equivalent 1-hour exposure concentration was estimated from the reported 6-hour NOAEL using the equation $C^n * T = K$, where n = 2.  The resulting level protective against severe adverse effects is 12 ppm (29 mg/m³).

A TLV-TWA of 400 ppm is reported by ACGIH (1991) based on findings by Nelson *et al*. (1943); the NRC-EEGL of 400 ppm is based on the TLV (NRC, 1984).  However, the reported 3-5-minute exposure to 400 ppm was not extrapolated to a 1-hour equivalent by NRC.  Using the equation $C^n * T = K$, where n = 1, the equivalent 1-hour exposure is 20 ppm.  This is consistent

with our use of the animal studies.  In addition, the recent data described above (Gill *et al*., 1995) were not available to ACGIH or NRC when determining these values.

**Level Protective Against Life-threatening Effects**

No recommendation can be made due to the limitations of the database.

NIOSH (1995) lists an IDLH of 2,000 ppm (4,900 mg/m³).  The IDLH is based strictly on safety considerations and is 10% of the lower explosive limit of 2%.

## VIII.   References

American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 828-830.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 21.

Burleigh-Flayer HD, Gill MW, Strother DE, Masten LW, McKee RH, Tyler TR, Gardiner TH. Isopropanol 13-week vapor inhalation study in rats and mice with neurotoxicity evaluation in rats.  Fundam Appl Toxicol 1994; 23:421-428.

Carpenter CP, Smyth HF Jr, Pozzani UC. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 1949;31(6):343-346.

Gill MW, Burleigh-Flayer HD, Strother DE, Masten LW, McKee RH, Tyler TR, Gardiner TH. Isopropanol: Acute vapor inhalation neurotoxicity study in rats. J Appl Toxicol 1995;15(2):77-84.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1993. (Edition expires 11/31/93).

Kane LE, Dombroske R, Alarie Y. Evaluation of sensory irritation from some common industrial solvents. Am Ind Hyg Assoc J 1980;41:451-455.

(NRC) National Research Council. Committee on Toxicology. Emergency and continuous exposure limits for selected airborne contaminants. Vol 2. Washington (DC): National Academy Press; 1984.

Nelson BK, Brightwell WS, MacKenzie-Taylor DR, Khan A, Burg JR, Weigel WW. Teratogenicity of n-propanol and isopropanol administered at high inhalation concentrations to rats. Food Chem Toxicol 1988;26(3):247-254.

Nelson KW, Ege JF Jr, Ross M, Woodman LE, Silverman L. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 1943;25(7):282-285.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

Ohashi Y, Nakai Y, Koshimo H, Esaki Y, Ikeoka H, Horiguchi S, *et al*. Toxicity of isopropyl alcohol exposure in the nasal mucociliary system in the guinea pig. Environ Res 1988;46:25-38.

(RTECS) Registry of the Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health, Cincinnati (OH) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1993. (Edition expires 11/31/93).

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Smyth HF Jr. Improved communication--Hygienic standards for daily inhalation. Am Ind Hyg Assoc Q 1956;17(2):129-185.