

## ACUTE TOXICITY SUMMARY

### 1,4-DIOXANE

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

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

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

<i>Inhalation reference exposure level</i>	<b>6,000 µg/m<sup>3</sup></b>
<i>Critical effect(s)</i>	Nasal and eye irritation in healthy human volunteers
<i>Hazard Index target(s)</i>	Respiratory System; Eyes

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

<i>Molecular formula</i>	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>
<i>Molecular weight</i>	88.1
<i>Specific gravity</i>	1.0329 @ 20°C
<i>Boiling point</i>	101.1°C @ 760 mm Hg
<i>Melting point</i>	11.8°C
<i>Vapor pressure</i>	29 mm Hg @ 20°C
<i>Flash point</i>	12.22°C (closed cup)
<i>Explosive limits</i>	2 - 22 % by volume in air
<i>Solubility</i>	soluble in water and most organic solvents
<i>Odor threshold</i>	24 ppm (ACGIH, 1991); 1.8 ppm (Hellman and Small, 1974)
<i>Description</i>	colorless gas with ethereal odor (Buffler <i>et al.</i> , 1978)
<i>Metabolites</i>	hydroxyethoxyacetic acid (Braun and Young, 1977)
<i>Conversion factor</i>	1 ppm = 3.6 mg/m <sup>3</sup>

#### 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).

#### 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 1600 ppm (Yant *et al.*, 1930). In this study, no control

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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/m<sup>3</sup>) 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/m<sup>3</sup>) 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:** Unknown

**Chemical:** Unknown

**V. Acute Toxicity to Laboratory Animals**

Inhalation by guinea pigs and rats of 10,000 ppm (36,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>) (Goldberg *et al.*, 1964). Nasal irritation was indicated by behavioral signs in guinea pigs exposed to 1,000 ppm (3,600 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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 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): 1.7 ppm (6,000 µg/m<sup>3</sup>)**

<i>Study</i>	Young <i>et al.</i> , 1977
<i>Study population</i>	4 healthy human male volunteers
<i>Exposure method</i>	chamber
<i>Critical effects</i>	subjective reports of eye irritation
<i>LOAEL</i>	50 ppm
<i>NOAEL</i>	not reported
<i>Exposure duration</i>	6 hours
<i>Extrapolation to 1 hour</i>	not used (see below)
<i>Extrapolated 1-hour concentration</i>	50 ppm
<i>LOAEL uncertainty factor</i>	3 (mild irritation)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	30
<i>Reference Exposure Level</i>	1.7 ppm (6 mg/m <sup>3</sup> , 6,000 µg/m <sup>3</sup> )

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<sub>50</sub>s from several studies of cats, rats, mice and guinea pigs, then divided the lowest 30 minute LC<sub>50</sub> by 10 to determine an IDLH for humans. NIOSH stated that no relevant human data were available for the IDLH estimation.

## VII. References

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## 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* **2,700 µg/m<sup>3</sup>**  
*Critical effect(s)* eye and nasal irritation in human volunteers  
*Hazard Index target(s)* Eyes; Respiratory System

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

<i>Molecular formula</i>	C <sub>3</sub> H <sub>5</sub> ClO
<i>Molecular weight</i>	92.5
<i>Specific gravity</i>	1.181 @ 20°C
<i>Boiling point</i>	117.9°C
<i>Melting point</i>	-25.6°C
<i>Vapor pressure</i>	13 mm Hg @ 20°C
<i>Flash point</i>	33.9°C
<i>Explosive limits</i>	3.3% - 14.5 % by volume in air
<i>Solubility</i>	slightly soluble in water, soluble in most organic solvents
<i>Odor threshold</i>	0.93 ppm (chloroform-like, irritating odor)
<i>Metabolites</i>	N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine
<i>Description</i>	colorless gas
<i>Conversion factor</i>	1 ppm = 4 mg/m <sup>3</sup>

#### 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

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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 (1440 mg/m<sup>3</sup>) in rats (Laskin *et al.*, 1980). An LC<sub>50</sub> of 445 ppm (1780 mg/m<sup>3</sup>) for four hours was reported for rabbits (HSDB, 1994). An eight-hour exposure to 250 ppm (1,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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): 0.67 ppm (2,700 µg/m<sup>3</sup>)**

<i>Study</i>	Wexler (1971) as cited in NIOSH, 1976
<i>Study population</i>	occupationally exposed workers
<i>Exposure method</i>	during workshifts (occupation not given)
<i>Critical effects</i>	irritation of eyes and nasal passages
<i>LOAEL</i>	20 ppm
<i>NOAEL</i>	not reported
<i>Exposure duration</i>	1 hour
<i>Extrapolated 1 hour concentration</i>	20 ppm
<i>LOAEL uncertainty factor</i>	3 (mild irritation)
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	30
<i>Reference Exposure Level</i>	0.67 ppm (2.7 mg/m <sup>3</sup> , 2,700 µg/m <sup>3</sup> )

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/m<sup>3</sup>) 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

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(1992) selected 100 ppm (380 mg/m<sup>3</sup>) 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<sub>50</sub> in mice of 2998 mg/m<sup>3</sup> for 2 hours is reported by the World Health Organization (1992).

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Fcrump  
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)**

<i>Inhalation reference exposure level</i>	<b>12,000 µg/m<sup>3</sup></b>
<i>Critical effect(s)</i>	reduced gravid uterine weight, reduction in total fetuses, fewer viable fetuses, increased maternal deaths, increased spontaneous abortions, and decreased body weight in rabbits
<i>Hazard Index target(s)</i>	Reproductive/developmental; Eyes; Respiratory System

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

<i>Molecular formula</i>	C <sub>6</sub> H <sub>14</sub> O <sub>2</sub>
<i>Molecular weight</i>	118.20
<i>Specific gravity</i>	0.90 @ 20°C
<i>Boiling point</i>	171°C
<i>Melting point</i>	-70°C
<i>Vapor pressure</i>	0.76 mm Hg @ 20°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in water, acetone, benzene, carbon tetrachloride, ethyl ether; miscible with ketones, ethers, alcohols and halogenated hydrocarbons
<i>Odor threshold</i>	0.10 ppm (geometric mean) (AIHA, 1989)
<i>Description</i>	colorless liquid; sweet, ester-like, musty (AIHA, 1989)
<i>Metabolites</i>	butoxyacetic acid (Johanson <i>et al.</i> , 1986)
<i>Conversion factor</i>	1 ppm = 4.84 mg/m <sup>3</sup> @ 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/m<sup>3</sup>) 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.

Butoxyacetic acid was the primary metabolite found in the urine of adult male volunteers exposed to 20 ppm (100 mg/m<sup>3</sup>) EGBE for 2 hours (Johanson *et al.*, 1986). The authors report that 57% of the inhaled dose was absorbed in the respiratory tract.

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:** Unknown

**Chemical:** Unknown

#### **V. Acute Toxicity to Laboratory Animals**

A 7-hour LC<sub>50</sub> for mice was reported as 700 ppm (3,000 mg/m<sup>3</sup>) EGBE (Werner *et al.*, 1943). Severe hemoglobinuria was observed; hepatic focal necrosis and splenic lymphoid hyperplasia were noted at necropsy. An 8-hour LC<sub>50</sub> in rats was reported as 564 ppm (2,800 mg/m<sup>3</sup>) 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

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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/m<sup>3</sup>) EGBE (Carpenter *et al.*, 1956). No significant increase in erythrocyte fragility was observed following a 4-hour exposure to 32 ppm (150 mg/m<sup>3</sup>) EGBE.

## **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)**

### **Mild Adverse Effect Level**

The most sensitive effect observed is developmental toxicity, a severe adverse effect, and it is observed at or below the threshold for a mild adverse effect. Therefore, no mild adverse effect level is recommended.

**Reference Exposure Level (protective against severe adverse effects): 12,000 µg/m<sup>3</sup>**

<i>Study</i>	Tyl <i>et al.</i> , 1984
<i>Study population</i>	pregnant rabbits
<i>Exposure method</i>	inhalation of 0, 25, 50, 100, or 200 ppm in a chamber
<i>Critical effects</i>	reduced gravid uterine weight, reduction in total fetuses, fewer viable fetuses, increased maternal deaths, increased spontaneous abortions, and decreased body weight
<i>LOAEL</i>	200 ppm
<i>NOAEL</i>	100 ppm
<i>Exposure duration</i>	6 hours per day, days 6-18 of gestation
<i>Equivalent 1-hour concentration</i>	245 ppm (100 <sup>2</sup> ppm * 6 hours = C <sup>2</sup> * 1 hour) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	not required
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	2.5 ppm (12 mg/m <sup>3</sup> ; 12,000 µg/m <sup>3</sup> )

Hematologic parameters in the does were normal. Therefore, reproductive and fetal toxicity were not 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.

In a companion study, pregnant rats were exposed to 25, 50, 100, or 200 ppm EGBE for 6 hours per day on days 6-15 of gestation. 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 (480 or 960 mg/m<sup>3</sup>) EGBE. A significantly increased incidence of delayed skeletal ossification was observed following maternal exposure to 100 or 200 ppm EGBE. No maternal toxicity or developmental toxicity was observed following exposure to 25 or 50 ppm (120 or 240 mg/m<sup>3</sup>) EGBE. The rats displayed significant hematological effects which are not observed in humans exposed to EGBE. It is believed that these effects contributed to the adverse developmental outcomes above. Because the critical physiological effects in rats are not observed in humans, the rat data were not used in the derivation of the REL for EGBE.

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). Since rabbits, like humans, do not appear to be susceptible to EGBE-induced hemolysis, the Tyl *et al.* study, which used rabbits, was used as the basis for the REL.

Human irritation data for EGBE identify NOAELs and LOAELs that are not protective of the potential reproductive toxicity described above. Two human volunteers were exposed to

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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. This study identifies a LOAEL for mucous membrane irritation of 113 ppm. An REL resulting from this study, including a margin of safety of 30 (10 for sensitive individuals and 3 for a LOAEL for mild irritation), would be 3.8 ppm.

In another human study, 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). No adverse effects were reported. This study indicates a 2-hour free-standing NOAEL for throat irritation of 50 ppm. The free-standing NOAEL reported by Johanson and Boman (1991) was not used as the basis for the REL because the method of exposure was mouth-only and thus excluded nasal and eye irritant effects.

### **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.* 1943). 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.

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## ACUTE TOXICITY SUMMARY

### ETHYLENE GLYCOL MONOETHYL ETHER

*(2-ethoxyethanol, Cellosolve)*

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

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

*Inhalation reference exposure level*    **880 µg/m<sup>3</sup>**  
*Critical effect(s)*                            specific skeletal defects  
*Hazard Index target(s)*                    Reproductive/developmental

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

<i>Molecular formula</i>	C <sub>4</sub> H <sub>10</sub> O <sub>2</sub>
<i>Molecular weight</i>	90.12
<i>Specific gravity</i>	0.931 @ 20°C
<i>Boiling point</i>	135°C
<i>Melting point</i>	-70°C (solidifies)
<i>Vapor pressure</i>	3.8 mm Hg @ 20°C (ACGIH, 1991)
<i>Flashpoint</i>	44°C, closed cup
<i>Explosive limits</i>	upper = 15.6% lower = 1.7%
<i>Solubility</i>	miscible with water and organic solvents
<i>Odor threshold</i>	2.7 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sweet, fruity, ester-like (AIHA, 1989)
<i>Metabolites</i>	ethoxyacetic acid (Groeseneken <i>et al.</i> , 1986)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 3.69 mg/m <sup>3</sup> @ 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).

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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, 1994).

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/m<sup>3</sup>)) 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:** Men with low sperm counts may be more sensitive to the adverse male reproductive effects of EGEE exposure (Reprotext, 1994).

**Chemical:** Persons with concomitant exposure to ethylene glycol or other glycol ethers may be more sensitive to the effects of EGEE exposure since ethoxyacetic acid is a common metabolite among glycol ethers (Reprotext, 1994).

## **V. Acute Toxicity to Laboratory Animals**

A 7-hour LC<sub>50</sub> 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).

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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/m<sup>3</sup>) 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 sternbrae 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 (protective against severe adverse effects): 0.24 ppm (880 µg/m<sup>3</sup>)**

<i>Study</i>	Tinston <i>et al.</i> , 1983; Doe, 1984
<i>Study population</i>	pregnant rats
<i>Exposure method</i>	inhalation 6 hours per day on days 6-15 of gestation
<i>Critical effects</i>	specific skeletal defects, including delayed ossification of the cervical vertebrae and sternbrae and extra ribs
<i>LOAEL</i>	50 ppm
<i>NOAEL</i>	10 ppm
<i>Exposure duration</i>	6 hours per day
<i>Extrapolated 1 hour concentration</i>	24 ppm (10 <sup>2</sup> ppm* 6 h = C <sup>2</sup> * 1 h ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10

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<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	0.24 ppm (0.88 mg/m <sup>3</sup> ; 880 µg/m <sup>3</sup> )

**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<sub>05</sub>) was 3,307 ppm; the lower confidence limit (LCL) on this concentration [the BC<sub>05</sub>] was 2,223 ppm. An uncertainty factor (UF) of 30 was applied to the BC<sub>05</sub> of 2,223 ppm (3 to account for interspecies variability and 10 for interindividual human variation).

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

The final level protective against life-threatening effects for EGEE is therefore 74 ppm (270 mg/m<sup>3</sup>). 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

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## 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 1-hour exposure)

*Inhalation reference exposure level*    **330 µg/m<sup>3</sup>**  
*Critical effect(s)*                            developmental defects  
*Hazard Index target(s)*                    Reproductive/developmental; Nervous System

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

<i>Molecular formula</i>	C <sub>6</sub> H <sub>12</sub> O <sub>3</sub>
<i>Molecular weight</i>	132.2
<i>Specific gravity</i>	0.975 @ 20°C
<i>Boiling point</i>	156°C
<i>Melting point</i>	-61.7°C
<i>Vapor pressure</i>	2 mm Hg @ 20°C
<i>Flashpoint</i>	49° C (ACGIH, 1991)
<i>Explosive limits</i>	upper = 12.7% lower = 1.7%
<i>Solubility</i>	soluble in water, alcohol, ether, acetone
<i>Odor threshold</i>	0.060 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	mild, ester-like odor
<i>Metabolites</i>	ethylene glycol monoethyl ether, ethoxyacetic acid (Groesenken <i>et al.</i> , 1987)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 5.41 mg/m <sup>3</sup> @ 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/m<sup>3</sup>) EGEEA (Boiano, 1983). Both workers reported that their symptoms improved when they were away

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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 neurologic conditions may be more sensitive to the effects of EGEEA exposure (Reprotext, 1994).

**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, 1994).

**V. Acute Toxicity to Laboratory Animals**

An 8-hour LC<sub>50</sub> in female rats is reported as 2,200 ppm (12,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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).

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In another study, embryotoxicity was observed following exposure of pregnant rats to 390 and 600 ppm (2,100 and 3,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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 (protective against severe adverse effects): 330 µg/m<sup>3</sup>**

<i>Study</i>	Tinston <i>et al.</i> , 1983
<i>Study population</i>	pregnant rabbits
<i>Exposure method</i>	inhalation of 25, 100, or 400 ppm 6 hours per day on days 6-29 of gestation.
<i>Critical effects</i>	developmental defects
<i>LOAEL</i>	25 ppm
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	6 hours
<i>Extrapolation to 1 hour</i>	$C^n * T = K$ , where $n = 2$ (Ten Berge <i>et al.</i> , 1986)
<i>Extrapolated 1 hour concentration</i>	61 ppm ( $25^2 \text{ ppm} * 6 \text{ h} = C^2 * 1 \text{ h}$ ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	1,000
<i>Reference Exposure Level</i>	0.061 ppm (0.33 mg/m <sup>3</sup> ; 330 µg/m <sup>3</sup> )

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.

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NIOSH (1995) lists a (revised) IDLH of 500 ppm for 2ethoxyethyl 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.

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## 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 1-hour exposure)

*Inhalation reference exposure level* **23 µg/m<sup>3</sup>**  
*Critical effect(s)* anemia  
*Hazard Index target(s)* Hematologic System

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

<i>Molecular formula</i>	C <sub>3</sub> H <sub>8</sub> O <sub>2</sub>
<i>Molecular weight</i>	76.09
<i>Specific gravity</i>	0.965 @ 20°C
<i>Boiling point</i>	125°C
<i>Melting point</i>	-85.1°C
<i>Vapor pressure</i>	6.2 mm Hg @ 20°C
<i>Flashpoint</i>	41.7° C (closed cup) (ACGIH, 1991)
<i>Explosive limits</i>	upper = 19.8% (ACGIH, 1991) lower = 2.5% (ACGIH, 1991)
<i>Solubility</i>	miscible with water, alcohol, benzene, ether, acetone
<i>Odor threshold</i>	2.3 ppm (Amoore and Hautala, 1983)
<i>Odor description</i>	mild ethereal odor
<i>Metabolites</i>	methoxyacetic acid, carbon dioxide (Miller <i>et al.</i> , 1983)
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 3.1 mg/m <sup>3</sup> @ 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

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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, 1994).

**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, 1994).

**V. Acute Toxicity to Laboratory Animals**

A 7-hour LC<sub>50</sub> in mice of 1,480 ppm (4,736 mg/m<sup>3</sup>) was reported (Werner *et al.*, 1943). Rats were exposed to 100, 300, or 1,000 ppm (320, 960, or 3,200 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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

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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/m<sup>3</sup>) 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/m<sup>3</sup>). 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/m<sup>3</sup>) EGME was observed.

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

**Reference Exposure Level (protective against mild adverse effects): 0.007 ppm (23 µg/m<sup>3</sup>)**

<i>Study</i>	Hanley <i>et al.</i> , 1984
<i>Study population</i>	pregnant rats
<i>Exposure method</i>	inhalation of 3, 10, or 50 ppm EGME 6 hours per day on days 6-15 of gestation
<i>Critical effects</i>	decrease in mean hemoglobin content and packed red blood cell volume
<i>LOAEL</i>	3 ppm
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	6 hours
<i>Extrapolation to 1 hour</i>	$C^n * T = K$ , where $n = 2$ (Ten Berge <i>et al.</i> , 1986)
<i>Extrapolated 1 hour concentration</i>	7 ppm ( $3^2 \text{ ppm} * 6 \text{ h} = C^2 * 1 \text{ h}$ ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	1,000
<i>Reference Exposure Level</i>	0.007 ppm (0.023 mg/m <sup>3</sup> ; 23 µg/m <sup>3</sup> )

**Level Protective Against Severe Adverse Effects**

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. The 6-hour exposure was extrapolated to a 1-hour exposure equivalent using the equation  $C^n * T = K$ , where  $n = 2$  resulting in a 1 hour NOAEL estimate of 7.3 ppm. Dividing this by 100 gives a level protective against severe adverse effects of 0.07 ppm (0.23 mg/m<sup>3</sup>; 230 µg/m<sup>3</sup>).

### **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 2461 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.

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## 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)

<i>Inhalation reference exposure level</i>	<b>310 µg/m<sup>3</sup></b>
<i>Critical effect(s)</i>	eye irritation
<i>Hazard Index target(s)</i>	Eyes; Respiratory System; Immune System

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

<i>Molecular formula</i>	CH <sub>2</sub> O
<i>Molecular weight</i>	30.03
<i>Description</i>	colorless gas
<i>Specific gravity</i>	0.815 @ -20°C
<i>Boiling point</i>	-19.5°C
<i>Melting point</i>	-92°C
<i>Vapor density</i>	1.08 mm Hg @ 25°C
<i>Flashpoint</i>	300° C or 573°F
<i>Explosive limits</i>	upper = 73% lower = 7%
<i>Solubility</i>	soluble in water, alcohol, ether, other polar solvents
<i>Odor threshold</i>	0.05-0.5 ppm
<i>Odor description</i>	very pungent odor; straw-like
<i>Metabolites</i>	formic acid
<i>Conversion factor</i>	1 ppm = 1.24 mg/m <sup>3</sup> @ 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

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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/m<sup>3</sup>) for 35 minutes. Thresholds were 1.2 ppm (1.5 mg/m<sup>3</sup>) for eye and nose irritation, 1.7 ppm (2.1 mg/m<sup>3</sup>) for eye blinking, and 2.1 ppm (2.6 mg/m<sup>3</sup>) for throat irritation.

Kulle *et al.* (1987) exposed nonasthmatic humans to up to 3.0 ppm (3.7 mg/m<sup>3</sup>) 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/m<sup>3</sup>). 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/m<sup>3</sup>) 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/m<sup>3</sup> 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

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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<sub>1</sub> (defined as > 20% or more) and FEV<sub>1</sub>/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<sub>1</sub> of 20% or more during exposure. One of 22 asthmatics had a greater than 20% reduction in FEV<sub>1</sub> (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation [V<sub>E</sub>] = 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<sub>1</sub> (-24.4%) and in FEV<sub>1</sub>/FVC, which occurred at 47 minutes into exposure to 3 ppm formaldehyde. These reductions occurred following a second 15 minute heavy exercise session (V<sub>E</sub> = 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<sub>1</sub> (-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<sub>1</sub> of greater than 20% following exposure also exhibited FEV<sub>1</sub>/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<sub>aw</sub>) 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/m<sup>3</sup> (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

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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 appears 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<sub>1</sub>) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m<sup>3</sup>) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde

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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.

*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, 1993). 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/m<sup>3</sup> (500-1,400 ppm) formaldehyde vapor for 30 minutes the LC<sub>50</sub> was found to be 1,000 mg/m<sup>3</sup> (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/m<sup>3</sup>) 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<sub>50</sub> 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<sub>05</sub> and BC<sub>05</sub> 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<sub>50</sub> in rats and mice to be 588 mg/m<sup>3</sup> (474 ppm) and 505 mg/m<sup>3</sup> (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/m<sup>3</sup>) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but 2 hour exposure to 0.14 mg/l (140 mg/m<sup>3</sup>) did not

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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/m<sup>3</sup>) 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/m<sup>3</sup>) formaldehyde for 8 hours. An 8-hour exposure to  $\geq 0.3$  ppm ( $\geq 0.4$  mg/m<sup>3</sup>) formaldehyde was sufficient to produce a significant increase in airway reactivity. Similar effects occurred after  $> 9$  ppm ( $> 11$  mg/m<sup>3</sup>) 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 (Reprotex, 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): 310  $\mu\text{g}/\text{m}^3$**

*Study*

Kulle *et al.* (1987)

*Study population*

19 nonasthmatic, nonsmoking human subjects

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<i>Exposure method</i>	0.5-3.0 ppm
<i>Critical effects</i>	mild and moderate eye irritation
<i>LOAEL</i>	1 ppm
<i>NOAEL</i>	0.5 ppm
<i>Benchmark concentration</i>	0.44 ppm (BC <sub>05</sub> )
<i>Exposure duration</i>	3 hours
<i>Extrapolated 1 hour concentration</i>	0.76 ppm (0.44 <sup>2</sup> ppm* 3 h = C <sup>2</sup> * 1 h ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	not required in BC approach
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Reference Exposure Level</i>	0.25 ppm (0.31 mg/m <sup>3</sup> ; 310 µg/m <sup>3</sup> )

The recommended REL was estimated by a benchmark concentration (BC<sub>05</sub>) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983). The BC<sub>05</sub> is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC<sub>05</sub> from this analysis was 0.44 ppm (0.53 mg/m<sup>3</sup>) formaldehyde. This value was adjusted to a 1-hour duration using the formula C<sup>n</sup> \* T = K, where n = 2 (AICE, 1989), resulting in a value of 0.74 ppm. An uncertainty factor (UF) of 3 was used to account for individual variation, since the BC<sub>05</sub> accounts for some degree of individual variation.

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

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 errors and 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 exposures above 310 µg/m<sup>3</sup> 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**

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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<sub>1</sub> (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<sub>1</sub>, 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<sub>1</sub>) 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,  $C^n \times T = K$ , 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<sub>50</sub> 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/m<sup>3</sup>) for 4 hours killed 4/6 rats within a 14 day observation period (Carpenter *et al.* 1946). Among 72 rats exposed to 600-1,700 mg/m<sup>3</sup> formaldehyde vapor for 30 minutes the LC<sub>50</sub> was found to be 1,000 mg/m<sup>3</sup> (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<sub>05</sub> 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<sub>05</sub> (which represents an experimental threshold for lethality) of 778 ppm (965 mg/m<sup>3</sup>) for a 130 minute exposure was estimated from the data (Crump, 1984; Crump and Howe, 1983), but a BC<sub>05</sub> could not be determined due to lack of data. The BED<sub>05</sub> was adjusted for a 1-hour exposure using a modification of Haber's equation  $C^n \times T = K$ , where  $n = 2$  for extrapolation from a shorter duration to a 1 -hour level, resulting in a value of 318 ppm (400 mg/m<sup>3</sup>). The exponent  $n = 2$  was based on findings in the AICE Guidelines (AICE, 1989). Uncertainty factors applied to the 1-hour BC<sub>05</sub> 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,

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which results in an estimated level protective against life-threatening effects of 11 ppm (13 mg/m<sup>3</sup>) 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.

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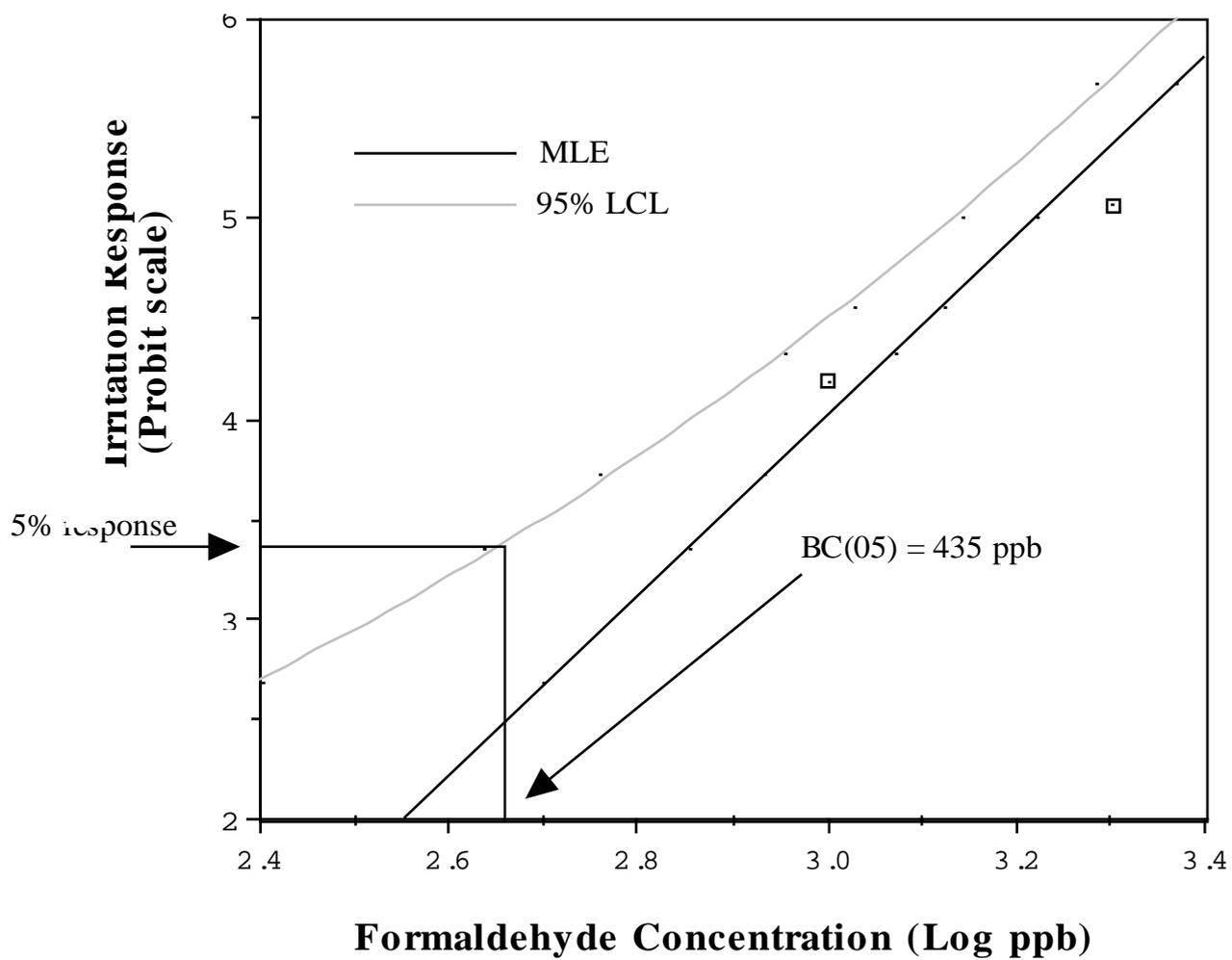
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## ACUTE TOXICITY SUMMARY

### HYDROCHLORIC ACID

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

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

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

<i>Inhalation reference exposure level</i>	<b>2,100 µg/m<sup>3</sup></b>
<i>Critical effect(s)</i>	upper respiratory symptoms
<i>Hazard Index target(s)</i>	Respiratory System; Eyes

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

<i>Molecular formula</i>	HCl
<i>Molecular weight</i>	36.46
<i>Specific gravity</i>	1.05 @ 15°C
<i>Boiling point</i>	-84.9°C (HCl gas)
<i>Melting point</i>	-114.8°C (HCl gas)
<i>Vapor pressure</i>	760 mm Hg @ -84.3°C
<i>Flashpoint</i>	unknown
<i>Explosive limits</i>	unknown
<i>Solubility</i>	soluble in water, alcohol, benzene, ether; insoluble in hydrocarbons
<i>Odor threshold</i>	0.26-10.0 ppm (AIHA, 1989a)
<i>Odor description</i>	sharp, irritating (AIHA, 1989a)
<i>Metabolites</i>	not applicable
<i>Description</i>	colorless gas
<i>Conversion factor</i>	1 ppm = 1.49 mg/m <sup>3</sup> @ 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) 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 respiratory conditions may be more sensitive to the effects of HCl exposure (Reprotext, 1994).

**Chemical:** Unknown

#### **V. Acute Toxicity to Laboratory Animals**

A single baboon exposed for 5-minutes to 16,570 ppm (24,690 mg/m<sup>3</sup>) 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/m<sup>3</sup>) 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.* 1971). Histopathologic examination performed 12 months post-exposure (Kaplan *et al.* 1993a) 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 lobe. In each of the three animals exposed to 5,000 ppm and examined, focal, patchy hemorrhages were observed.

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A 30-minute LC<sub>50</sub> in rats and mice is reported as 5,666 ppm (8,442 mg/m<sup>3</sup>) and 2,142 ppm (3,192 mg/m<sup>3</sup>) 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<sub>50</sub> 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<sub>50s</sub> 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/m<sup>3</sup>) HCl for 6-minutes and to 680 ppm (1,010 mg/m<sup>3</sup>) HCl for less than 1-minute (Burleigh-Flayer *et al.*, 1985). The RD<sub>50</sub> in mice was reported as 309 ppm (460 mg/m<sup>3</sup>) 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/m<sup>3</sup>; 1 of 4), 1,040 ppm (1,550 mg/m<sup>3</sup>; 4 of 6) and 1,380 ppm (5 of 5), but not 320 ppm (480 mg/m<sup>3</sup>). 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/m<sup>3</sup>) HCl (Kaplan *et al.*, 1985). No signs of irritation were observed following a 5-minute exposure to 190 ppm (280 mg/m<sup>3</sup>) 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, 1994). 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, 1994).

Pregnant rats exposed to 300 ppm (450 mg/m<sup>3</sup>) 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.

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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/m<sup>3</sup>)**

<i>Study</i>	Stevens <i>et al.</i> , 1992
<i>Study population</i>	10 asthmatics aged 18-25
<i>Exposure method</i>	inhalation via half face mask to 0.8 or 1.8 ppm HCl
<i>Critical effects</i>	upper respiratory system symptoms of sore throat; nasal discharge
<i>LOAEL</i>	not observed
<i>NOAEL</i>	1.8 ppm
<i>Exposure duration</i>	45 minutes
<i>Extrapolated 1 hour concentration</i>	1.4 ppm (1.8 <sup>1</sup> ppm * 0.75 h = C <sup>1</sup> * 1 h) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	1
<i>Reference Exposure Level</i>	1.4 ppm (2.1 mg/m <sup>3</sup> ; 2,100 µg/m <sup>3</sup> )

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 or 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 supports upper airway effects as the most sensitive target endpoint. 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.

**Level Protective Against Severe Adverse Effects**

The RD<sub>50</sub> in mice for a 10-minute exposure to HCl is reported as 309 ppm (460 mg/m<sup>3</sup>). NRC applied an uncertainty factor of 10 to the RD<sub>50</sub> to account for interspecies differences yielding a 1-hour EEGl of 31 ppm. The EEGl was further reduced to 20 ppm (29.8 mg/m<sup>3</sup>) 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

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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. However, since the development of the SPEGL, 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 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<sub>05</sub>) was 1,772 ppm; the lower 95% confidence limit (LCL) on this concentration [the BC<sub>05</sub>] was 1,271 ppm. A total uncertainty factor of 30 was applied to the BC<sub>05</sub> of 1,271 ppm to account for interspecies variability (3) and individual variation (10) in response.

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

The final level protective against life-threatening effects for HCl is therefore 42 ppm (63 mg/m<sup>3</sup>). 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

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## 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)

<i>Inhalation reference exposure level</i>	<b>340 <math>\mu\text{g}/\text{m}^3</math></b>
<i>Critical effect(s)</i>	loss of coordination and loss of consciousness, due to cellular hypoxia of the central nervous system
<i>Hazard Index target(s)</i>	Nervous System

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

<i>Molecular formula</i>	HCN
<i>Molecular weight</i>	27.03
<i>Specific gravity</i>	0.688 @ 20°C
<i>Boiling point</i>	25.6°C
<i>Melting point</i>	-13.4°C
<i>Vapor pressure</i>	630 mm Hg @ 20°C
<i>Flashpoint</i>	-17.8°C (closed cup)
<i>Explosive limits</i>	upper = 40% by volume in air lower = 5.6% by volume in air
<i>Solubility</i>	miscible in water, alcohol, slightly soluble in ether
<i>Odor threshold</i>	0.58 ppm (w/w) (Amoore and Hautala, 1983)
<i>Odor description</i>	faint, bitter almond odor
<i>Metabolites</i>	thiocyanate, 2-aminothiazo-line-4-carboxylic acid, cyanocobalamin (Vitamin B12) (Ansell and Lewis, 1970)
<i>Description</i>	colorless
<i>Conversion factor</i>	1 ppm = 1.13 $\text{mg}/\text{m}^3$

#### 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).

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Another common source of HCN is cigarette smoke. Levels in inhaled mainstream cigarette smoke range from 10 to 400  $\mu\text{g}$  per cigarette and decrease to levels ranging from 0.06 to 108  $\mu\text{g}$  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  $\text{mg}/\text{m}^3$ ), 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  $\text{mg}/\text{m}^3$  (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  $\text{CN}^-$  source and prevalence of symptoms consistent with  $\text{CN}^-$  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

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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 neuroophthalmologic 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:

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

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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) <sup>1</sup>
Sakurai (1989)	mouse	491	25	42
Hartzell <i>et al.</i> (1985)	rat	698	92	115
Purser <i>et al.</i> (1984)	monkey	685	66	89
Barcroft (1931)	goat	885	152	182

<sup>1</sup> 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.

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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<sub>50</sub> 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<sub>05</sub> (maximum likelihood estimate corresponding to 5% lethality) and BC<sub>05</sub> (benchmark dose at the 95% lower confidence interval of the MLE<sub>05</sub>) These citations and their respective LC<sub>50</sub>s are shown in Table 2.

Table 2. Experimental Animal LC<sub>50</sub>s for Hydrogen Cyanide

Reference	Species	Exposure Time (min) <sup>1</sup>	LC <sub>50</sub> ppm (95% Confidence Interval)	Post-exposure Time
Ballantyne (1983)	rat	5	436 (329-585)	NR <sup>2</sup>
		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 <i>et al.</i> (1985)	rat	30	170	NA <sup>4</sup>
Smith <i>et al.</i> (1976)	rat	7.9 ± 2.0 <sup>3</sup>	450	NA <sup>4</sup>

<sup>1</sup> LC<sub>50</sub> determinations for exposure durations of less than 5 minutes were not included in the table.

<sup>2</sup> Not reported

<sup>3</sup> Mean time to death (± SD) at 450 ppm HCN

<sup>4</sup> Not applicable, time to death experiment

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Table 3 contains the studies which provided adequate data from which an MLE<sub>05</sub> and BC<sub>05</sub> could be determined. The MLE<sub>05</sub> and BC<sub>05</sub> 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/m<sup>3</sup>. Some but not all rats survived exposure to HCN at concentrations between 90 and 166 mg/m<sup>3</sup>. There were no survivors following exposure to 168 or 192 mg/m<sup>3</sup>.

Table 3. Animal Lethality Benchmark Dose Determinations for Hydrogen Cyanide

Reference	Species	Exposure Time (min) <sup>1</sup>	MLE <sub>05</sub> (ppm) 60 min <sup>2</sup>	BC <sub>05</sub> (ppm) 60 min <sup>2</sup>	Post-exposure Time
Lynch (1975)	rat	30	35	29	24-hr
Bhattacharya <i>et al.</i> (1991)	mouse	30	337	169	24 hr
Matijak-Shaper <i>et al.</i> (1982)	mouse	30	51	25	10 min
Sato <i>et al.</i> (1955)	mouse	varied	35	26	NA <sup>3</sup>
Higgins <i>et al.</i> (1972)	mouse	5	19	16	7 days
	rat	5	28	24	7 days
Levin <i>et al.</i> (1985)	rat	30	87	73	none

<sup>1</sup> Exposure durations of less than 5 minutes were not included in the table.

<sup>2</sup> Exposure time was extrapolated to 60 minutes using a modification of Haber's equation ( $C^n * T = K$ ), where  $n = 1$ .

<sup>3</sup> 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<sub>50</sub> 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/m<sup>3</sup>) for rats and mice exposed for 16 hours (Weedon *et al.*, 1940). Of the four experimental HCN concentrations

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(1,000, 250, 63, and 16 ppm, or 1,130, 282, 71, and 18 mg/m<sup>3</sup>, 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/m<sup>3</sup>), 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/m<sup>3</sup> (17,700 ppm), 50,000 mg/m<sup>3</sup> (44,250 ppm) and 100,000 mg/m<sup>3</sup> (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/m<sup>3</sup>**

<i>Study</i>	Purser, 1984; Purser <i>et al.</i> , 1984
<i>Study population</i>	4 cynomolgus monkeys
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	CNS depression/incapacitation
<i>LOAEL</i>	80 ppm
<i>NOAEL</i>	60 ppm (68 mg/m <sup>3</sup> )
<i>Exposure duration</i>	30 minutes
<i>Extrapolated 1 hour concentration</i>	30 ppm (60 <sup>1</sup> ppm* 0.5 h = C <sup>1</sup> * 1 h ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Reference Exposure Level</i>	0.30 ppm (0.34 mg/m <sup>3</sup> ; 340 µg/m <sup>3</sup> )

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<sub>05</sub> is 66.1 mg/m<sup>3</sup> 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 BC<sub>05</sub> (33 ppm).

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

Incorporation of these factors (cumulative uncertainty factors = 30) yielded a level protective against life-threatening effects of 1.1 ppm (1.2 mg/m<sup>3</sup>) for a 1-hour HCN exposure.

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## 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/m<sup>3</sup>**  
*Critical effect(s)*                            irritation to the eyes, nose, and throat  
*Hazard Index target(s)*                      Eyes; Respiratory System

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

<i>Molecular formula</i>	HF
<i>Molecular weight</i>	20.01
<i>Specific gravity</i>	0.991 @ 20°C
<i>Boiling point</i>	19.51°C
<i>Melting point</i>	83.55°C
<i>Vapor pressure</i>	400 mm Hg @ 2.5°C
<i>Flashpoint</i>	not applicable
<i>Explosive limits</i>	not applicable
<i>Solubility</i>	soluble in water and alcohol
<i>Odor threshold</i>	0.042 ppm (geometric mean) (Amoore and Hautala, 1983)
<i>Odor Description</i>	strong, irritating odor
<i>Metabolites</i>	F <sup>-</sup> (fluoride)
<i>Color</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 0.83 mg/m <sup>3</sup> @ 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

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hydrogen ions. In addition, the dissociated fluoride ion, F<sup>-</sup>, 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/m<sup>3</sup>), produced no noticeable effects in one individual. Concentrations ranging from 2.59 to 4.74 ppm (2.15-3.93 mg/m<sup>3</sup>) 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/m<sup>3</sup>) “..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<sub>1</sub>) and forced vital capacity (FVC)) during and after a one hour exposure to HF. Twenty healthy male volunteers were exposed in a chamber to constant HF concentrations that ranged from 0.2 to 5.2 mg/m<sup>3</sup> (concentrations that occur among potroom workers in the primary aluminum industry, according to the authors). Subjects were asked to report itching or soreness of the eyes and upper airways and to grade them 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. For the purposes of analysis the authors grouped the subjects into exposure groups of 0.2-0.6 mg/m<sup>3</sup>, 0.7-2.4 mg/m<sup>3</sup>, and 2.5-5.2 mg/m<sup>3</sup>. Lower airway scores were not significant for any concentration range. The upper airway and total symptom score was significant (p<0.05) at the end of exposure for the highest exposure range (2.5-5.2 mg/m<sup>3</sup>, n=7) and for all exposures considered as a single group (0.2-5.2 mg/m<sup>3</sup>, 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/m<sup>3</sup>, n=9). Almost all the symptoms had disappeared four hours after the end of exposure. Symptom scores from the upper airways were

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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 (C<sub>max</sub>) ( $r = 0.42$ ,  $p = 0.05$ ). A significant correlation was found between total symptom score for airways and the HF concentration ( $p = 0.009$ ). No significant changes occurred in FEV<sub>1</sub> 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/m<sup>3</sup>,  $n = 9$ ). However, no dose-response relationship was evident and no lower airway symptoms were reported.

*Predisposing Conditions for HF Toxicity*

**Medical:** Unknown

**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<sub>50</sub> of 6,427 ppm (5,334 mg/m<sup>3</sup>) while no lethality was observed after exposure to 2,430 ppm (2,017 mg/m<sup>3</sup>). 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<sub>50</sub> 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/m<sup>3</sup>) HF resulted in 10% mortality and exposure to 25,690 ppm (21,323 mg/m<sup>3</sup>) resulted in 100% mortality.

Wohlslagel and colleagues (1976) exposed rats and mice to HF for 60 minute durations. The 1-hour LC<sub>50</sub> in mice, the most sensitive species, was 342 ppm (284 mg/m<sup>3</sup>), while no lethality was observed at 263 ppm (218 mg/m<sup>3</sup>). An exposure of 1,087 ppm (902 mg/m<sup>3</sup>) resulted in no lethality in rats, while 100% mortality was observed at 1,765 ppm (1,464 mg/m<sup>3</sup>). 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup>) 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/m<sup>3</sup> (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): 0.24 mg/m<sup>3</sup> (240 µg/m<sup>3</sup>)**

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

Self-reported upper airway and eye irritation occurred after one hour of exposure to HF at 0.2-0.6 mg/m<sup>3</sup>, with 4/6 subjects reporting low symptom scores. However, symptoms were not increased following exposure at the next concentration range, 0.7-2.4 mg/m<sup>3</sup>. The 0.7-2.4 mg/m<sup>3</sup> range was considered to be a NOAEL and the range of 2.5-5.2 mg/m<sup>3</sup> was deemed to be a LOAEL since 3/7 subjects in the latter group reported high upper airway symptom scores while 0/7 in the former group reported high upper airway symptom scores. While there were no changes in FEV<sub>1</sub>, there was a slight decrease in FVC after exposure at this concentration range. However, OEHHHA 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<sub>1</sub> (see Section 3.2.1.1 in Technical Support Document).

### Level Protective Against Severe Adverse Effects

Following a 60-minute exposure to 103 ppm (85 mg/m<sup>3</sup>) 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/m<sup>3</sup>) exposure was considered a NOAEL for severe effects. Application of

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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/m<sup>3</sup>).

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/m<sup>3</sup>) 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).

### **Level Protective Against Life-threatening Effects**

The ERPG-3 value for HF of 50 ppm (AIHA, 1992) is based on the observation by Machle *et al.* (1934) that no deaths in rabbits or guinea pigs were observed following 30-minute exposures to 1,220 ppm (1,013 mg/m<sup>3</sup>) HF. An unpublished communication in the ERPG document describes dangerous serum fluoride concentrations in humans exposed to 50 ppm (41.5 mg/m<sup>3</sup>) HF (Smith, 1988). Mice and rats may be more sensitive to the acute lethal effects of HF than rabbits and guinea pigs (Wohlslagel *et al.*, 1976). In addition, the unpublished personal communication from Smith (1988) is not described in sufficient detail for evaluation. Therefore, the ERPG-3 for HF was thought to overestimate the life-threatening level.

In contrast to the ERPG-3, the benchmark dose (BD) approach is presented as a quantitative derivation. Wohlslagel *et al.* (1976) exposed mice to varying concentrations of HF for 60-minute intervals. The 1-hour LC<sub>50</sub> value was determined to be 342 ppm (284 mg/m<sup>3</sup>) 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<sub>05</sub>). The resulting BC<sub>05</sub> from this analysis was 204 ppm (170 mg/m<sup>3</sup>). 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).

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

The resulting value is 6.8 ppm (5.6 mg/m<sup>3</sup>). Based on comparison with the available literature on human studies, discussed above, this value appears to be an underestimate of a life-threatening effect level even for sensitive subpopulations. The level is thought to be between 7 and 50 ppm. Since neither value appears to be entirely appropriate, a single point estimate within the range of

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these values, the geometric mean, or 19 ppm (15.5 mg/m<sup>3</sup>), is chosen 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. For a graphical representation of the derivation of the REL, refer to section IX.

Comparison of 1% and 5% mortality rates for HF

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

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## ACUTE TOXICITY SUMMARY

### HYDROGEN SULFIDE

*(sulfur hydride; sulfuretted hydrogen)*

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

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

<i>Inhalation reference exposure level</i>	<b>140 µg/m<sup>3</sup></b>
<i>Critical effect(s)</i>	airway function changes, especially in asthmatics
<i>Hazard Index target(s)</i>	Respiratory System

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

<i>Molecular formula</i>	H <sub>2</sub> S
<i>Molecular weight</i>	34.08
<i>Specific gravity</i>	1.189 @ 15°C (air = 1)
<i>Boiling point</i>	-60.7°C
<i>Melting point</i>	unknown
<i>Vapor pressure</i>	1 atm @ -60.4°C
<i>Flash point</i>	26°C
<i>Explosive limits</i>	upper = 4.3% by volume in air lower = 46% by volume in air
<i>Solubility</i>	soluble in water, hydrocarbon solvents, ether, and ethanol
<i>Odor threshold</i>	0.0081 ppm (Amoore and Hautala, 1983)
<i>Odor description</i>	resembles rotten eggs
<i>Metabolites</i>	bisulfite (HSO <sub>3</sub> ), thiosulfate (S <sub>2</sub> O <sub>3</sub> <sup>2-</sup> ) (Baxter and Van Reen, 1958)
<i>Description</i>	colorless gas
<i>Conversion factor</i>	1 ppm = 1.4 mg/m <sup>3</sup> @ 25°C

#### II. Major Uses or Sources

Hydrogen sulfide (H<sub>2</sub>S) 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**

H<sub>2</sub>S exposure is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977). An inhalation LC<sub>Lo</sub> of 600 and 800 ppm (840 and 1,120 mg/m<sup>3</sup>) for 30 and 5 minutes, respectively, is reported (Hazardtext, 1994). A lethal exposure was documented for a worker exposed to approximately 600 ppm H<sub>2</sub>S for 5-15 minutes (Simson and Simpson, 1971). Inhalation of 1,000 ppm (1,400 mg/m<sup>3</sup>) is reported to cause immediate respiratory arrest (ACGIH, 1992). Concentrations greater than 200 ppm (280 mg/m<sup>3</sup>) H<sub>2</sub>S 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<sub>2</sub>S 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/m<sup>3</sup>), olfactory fatigue prevents detection of H<sub>2</sub>S odor. Exposure to 100-150 ppm (140-210 mg/m<sup>3</sup>) 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/m<sup>3</sup>) H<sub>2</sub>S 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/m<sup>3</sup>) H<sub>2</sub>S caused coughing and throat irritation after 15 minutes.

In another study, ten asthmatic volunteers were exposed to 2 ppm H<sub>2</sub>S 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<sub>1</sub> were reported. Although individual values for specific airway resistance (SR<sub>aw</sub>) were not reported, the difference following exposure ranged from -5.95% to +137.78%. The decrease in specific airway conductance, SG<sub>aw</sub>, ranged from -57.7% to +28.9%. The increase in mean SR<sub>aw</sub> and the decrease in mean SG<sub>aw</sub> were not statistically significant.

#### *Predisposing Conditions for Hydrogen Sulfide Toxicity*

**Medical:** Unknown

**Chemical:** Ethanol has been shown to potentiate the effects of H<sub>2</sub>S by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m<sup>3</sup>) H<sub>2</sub>S (Beck *et al.*, 1979).

#### **V. Acute Toxicity to Laboratory Animals**

A median lethal concentration (LC<sub>50</sub>) in rats exposed to H<sub>2</sub>S for 4 hours was estimated as 440 ppm (616 mg/m<sup>3</sup>) (Tansy *et al.*, 1981). An inhalation LC<sub>Lo</sub> of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m<sup>3</sup>) for 1 hour is

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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/m<sup>3</sup>) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m<sup>3</sup>) 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/m<sup>3</sup> (71 ppm) H<sub>2</sub>S for 1.5 hours.

## VI. Reproductive or Developmental Toxicity

There are no reports of reproductive or developmental toxicity resulting from hydrogen sulfide exposure.

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

### Reference Exposure Level (protective against mild adverse effects): 140 µg/m<sup>3</sup>

<i>Study</i>	Jappinen <i>et al.</i> , 1990
<i>Study population</i>	ten asthmatic volunteers (7 females, 3 males)
<i>Exposure method</i>	2 ppm H <sub>2</sub> S
<i>Critical effects</i>	significantly increased airway resistance and decreased airway conductance in 2 of 10 subjects
<i>LOAEL</i>	2 ppm
<i>NOAEL</i>	not observed
<i>Exposure duration</i>	30 minutes
<i>Extrapolated 1 hour concentration</i>	1 ppm (2 <sup>1</sup> ppm* 0.5 h = C <sup>1</sup> * 1 h ) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	1
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	0.1 ppm (0.14 mg/m <sup>3</sup> ; 140 µg/m <sup>3</sup> )

Although the increase in mean SR<sub>aw</sub> and the decrease in mean SG<sub>aw</sub> were not statistically significant in this study, significantly increased airway resistance and decreased airway conductance were noted in two of ten asthmatic subjects. An uncertainty factor of 10 was applied since a NOAEL was not identified in the study. An uncertainty factor for sensitive individuals of 1 was applied since the study was conducted in asthmatic subjects. An equivalent 1-hour REL of 0.1 ppm (0.14 mg/m<sup>3</sup>) was extrapolated from the 30-minute value using the equation C<sup>n</sup> x T = K, where n = 1.

The 1-hour California Ambient Air Quality Standard (AAQS) for hydrogen sulfide is based on an olfactory perception study by the California State Department of Health (1969). Sixteen

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individuals were exposed to increasing concentrations of H<sub>2</sub>S until the odor threshold was reached. The range of the odor thresholds was 0.012-0.069 ppm, and the geometric mean was 0.029 ppm. The mean odor threshold (0.03 ppm) was selected as the AAQS for H<sub>2</sub>S. In 1984 CARB reviewed the AAQS for H<sub>2</sub>S and found it adequate for the protection of public health, including protection against odor annoyance (CARB, 1984). However, Amoores (1985) conducted a study that estimated 40% of the population would find 0.03 ppm (0.042 mg/m<sup>3</sup>) to be an objectionable concentration.

### **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/m<sup>3</sup>) H<sub>2</sub>S for 4 hours resulted in no deaths (Rogers and Ferin, 1981). In addition, rabbits exposed to 71 ppm (100 mg/m<sup>3</sup>) H<sub>2</sub>S 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.

An 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/m<sup>3</sup>) H<sub>2</sub>S for 20 minutes to 1 hour (Ahlborg, 1951; Yant, 1930). In addition, a 1-hour LC<sub>50</sub> of 712 ppm (997 mg/m<sup>3</sup>) 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<sub>50</sub> data in the CIIT (1983) report. Rats (5 female and 5 male) exposed to H<sub>2</sub>S concentrations ranging from 400-600 ppm (560-840 mg/m<sup>3</sup>) 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/m<sup>3</sup>) for only 35 minutes or less died, which suggests that primates are more sensitive to the lethal effect of H<sub>2</sub>S 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.

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## 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/m<sup>3</sup>**  
*Critical effect(s)* irritation of the eyes, nose and throat.  
*Hazard Index target(s)* Eyes; Respiratory System

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

<i>Molecular formula</i>	C <sub>3</sub> H <sub>8</sub> O
<i>Molecular weight</i>	60.09
<i>Specific gravity</i>	0.78505 @ 20°C
<i>Boiling point</i>	82.5°C @ 760 mm Hg
<i>Melting point</i>	-88.5°C
<i>Vapor pressure</i>	44.0 mm Hg @ 25°C
<i>Flashpoint</i>	11.7°C (closed cup)
<i>Explosive limits</i>	upper = 12.0% lower = 2.0%
<i>Solubility</i>	soluble in benzene, miscible with most organic solvents, slightly soluble in water, alcohol, and acetone
<i>Odor threshold</i>	19 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sharp (AIHA, 1989)
<i>Metabolites</i>	acetone
<i>Description</i>	colorless liquid
<i>Conversion factor</i>	1 ppm = 2.45 mg/m <sup>3</sup> @ 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

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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/m<sup>3</sup>) 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, 1993).

**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, 1993).

**V. Acute Toxicity to Laboratory Animals**

A 4-hour rat LC<sub>Lo</sub> of 16,000 ppm (39,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>) isopropanol. Complete recovery from the exposure occurred within 2 weeks. Exposure at 5,500 ppm (13,000 mg/m<sup>3</sup>) resulted in similar damage requiring more than two weeks for complete recovery (Ohashi *et al.*, 1988). A 10-minute RD<sub>50</sub> of 17,693 ppm (43,000 mg/m<sup>3</sup>) for mice has been reported (Kane et 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/m<sup>3</sup>) 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/m<sup>3</sup>)**

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

Ten human subjects, exposed for 3-5 minutes to 400 ppm (1,000 mg/m<sup>3</sup>) 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/m<sup>3</sup>).

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

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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/m<sup>3</sup>). The IDLH is based strictly on safety considerations and is 10% of the lower explosive limit of 2%.

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