### ACUTE TOXICITY SUMMARY

**1,4-DIOXANE**

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

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

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

<table>
<thead>
<tr>
<th>Inhalation reference exposure level</th>
<th>3,000 µg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical effect(s)</td>
<td>Nasal and eye irritation in healthy human volunteers</td>
</tr>
<tr>
<td>Hazard Index target(s)</td>
<td>Respiratory System; Eyes</td>
</tr>
</tbody>
</table>

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

**Description**
- colorless liquid

**Molecular formula**  
- C₄H₈O₂

**Molecular weight**  
- 88.1

**Density**  
- 1.0329 g/cm³ @ 20°C

**Boiling point**  
- 101.1°C @ 760 mm Hg

**Melting point**  
- 11.8°C

**Vapor pressure**  
- 29 mm Hg @ 20°C

**Flash point**  
- 12.22°C (closed cup)

**Explosive limits**  
- 2 - 22 % by volume in air

**Solubility**  
- soluble in water and most organic solvents

**Odor threshold**  
- 24 ppm (ACGIH, 1991);
  - 1.8 ppm (Hellman and Small, 1974)

**Odor description**  
- ethereal odor (Buffler *et al.*, 1978)

**Metabolites**  
- hydroxyethoxyacetic acid (Braun and Young, 1977)

**Conversion factor**  
- 1 ppm = 3.6 mg/m³

#### III. Major Uses or Sources

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

#### IV. Acute Toxicity to Humans

There are case reports of lethal hemorrhagic nephritis in workers exposed to unspecified high concentrations of 1,4-dioxane for several days (Barber, 1934; Johnstone, 1959).
1,4-Dioxane was irritating to the eyes, nasal passages, and the throat of adult volunteers following a 10-minute exposure to 1,600 ppm (Yant et al., 1930). In this study, no control subjects were tested concomitantly. A similar study of 4-6 volunteers by Fairly et al. (1934) showed that inhalation exposure to a concentration of 1,000 ppm (3,600 mg/m³) for five minutes caused a warm sensation in the throat and chest, but no noticeable irritation. However, in a more recent study, four healthy adult male volunteers exposed in a chamber for 6 hours to 50 ppm (180 mg/m³) dioxane exhibited eye irritation and 2 of the 4 subjects reported olfactory fatigue after 4 and 5 hours (Young et al., 1977).

**Predisposing Conditions for 1,4-Dioxane Toxicity**

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

**Chemical:** Unknown

V. **Acute Toxicity to Laboratory Animals**

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

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

Drew et al. (1978) showed that a single 4-hour inhalation of 1,000 ppm (3,600 mg/m³) 1,4-dioxane by rats resulted in immediate elevation of serum glutamic-oxaloacetic transaminase activity. Alanine aminotransferase and ornithine carbamyl transaminase activities were elevated...
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

24 hours following the 4-hour 1,000 ppm (3,600 mg/m³) exposure. The elevations of these hepatic enzymes indicated that 1,4-dioxane is hepatotoxic in rats.

VI. Reproductive or Developmental Toxicity

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

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

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

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

Reference Exposure Level 0.8 ppm (3 mg/m³, 3,000 µg/m³)

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

Level Protective Against Severe Adverse Effects

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

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.
NIOSH (1995) lists a (revised) IDLH for 1,4-dioxane of 500 ppm based on acute inhalation toxicity data in animals. NIOSH derived 30 minute LC$_{50}$s from several studies of cats, rats, mice and guinea pigs, then divided the lowest 30 minute LC$_{50}$ by 10 to determine an IDLH for humans. NIOSH stated that no relevant human data were available for the IDLH estimation.

VII. References


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


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


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


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and

1/31/1999).


Yant WP, Schrenk HH, Waite CP, Patty FA. Acute response of guinea pigs to vapors of some

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

Young JD, Braun WH, Ramps LW. Pharmacokinetics of 1,4-dioxane in humans. J Toxicol
I. Acute Toxicity Summary (for a 1-hour exposure)

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

II. Physical and Chemical Properties (HSDB, 1994)

Description: colorless liquid
Molecular formula: C₃H₅ClO
Molecular weight: 92.5
Density: 1.181 g/cm³ @ 20°C
Boiling point: 117.9°C
Melting point: -25.6°C
Vapor pressure: 13 mm Hg @ 20°C
Flash point: 33.9°C
Explosive limits: 3.3% - 14.5 % by volume in air
Solubility: slightly soluble in water, soluble in most organic solvents
Odor threshold: 0.93 ppm (chloroform-like, irritating odor)
Metabolites: N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine
Conversion factor: 1 ppm = 4 mg/m³

III. Major Uses or Sources

Epichlorohydin 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 epichlorohydin 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). Epichlorohydin is a strong skin sensitizer following dermal contact
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

(U.S.EPA, 1984). Epichlorohydrin is a reactive epoxide and a known mutagen. In vitro exposure of human lymphocytes to $10^{-11}$ to $10^{-4}$M epichlorohydrin resulted in dose-dependent chromatid and chromosomal breaks (HSDB, 1994).

**Predisposing Conditions for Epichlorohydrin Toxicity**

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

**Chemical:**  Unknown

V. **Acute Toxicity to Laboratory Animals**

A six-hour exposure to epichlorohydrin with a 14-day follow-up showed the median lethal concentration to be 360 ppm (1,440 mg/m³) in rats (Laskin et al., 1980). An LC₅₀ of 445 ppm (1,780 mg/m³) for four hours was reported for rabbits (HSDB, 1994). An eight-hour exposure to 250 ppm (1,000 mg/m³) killed two-thirds of the rats exposed (sample size not given) (LeFaux, 1968). A single subcutaneous injection of 75 mg/kg resulted in swelling of proximal renal tubular epithelium in male rats (Kluwe et al., 1983).

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

VI. **Reproductive or Developmental Toxicity**

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

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

Injury to epididymal tissue, testicular atrophy, and increases in the number of sperm with abnormal morphology have been observed in male rats exposed via single subcutaneous injection to 75 mg/kg epichlorohydrin (Kluwe et al., 1983). Although animal studies indicate that male fertility is affected by exposure to high doses of epichlorohydrin, a human epidemiologic study showed no changes in male fertility rates among workers (HSDB, 1994).
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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

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

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

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

Level Protective Against Severe Adverse Effects

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

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

Level Protective Against Life-threatening Effects

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

Subacute exposures of rats and mice (5/sex) to 100 ppm epichlorohydrin 6 hours/day, 5 days/week, 9 exposures in 12 days, resulted in focal pneumonitis and inflammation and degeneration of nasal epithelium in addition to decreased weight gain (Quast et al., 1979a, b). Kidney toxicity was seen in the rats exposed to 100 ppm. No lethality was observed. It was concluded that acute exposure to 100 ppm would not cause fatality in humans. Thus AIHA
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

(1992) selected 100 ppm (380 mg/m³) as the ERPG-3 for epichlorohydrin. This value can be considered a subchronic NOAEL for lethality in mice, but the lack of uncertainty factors for the extrapolation of animal to human exposures, in addition to those required for consideration of sensitive individuals, dictate that this value should be reevaluated. The small sample sizes in the rodent studies, and the absence of peer-reviewed data used to derive the NOAEL, further weaken the scientific validity of this value. The ERPG-3 value is based on severe, non-lethal effects and not on lethality data. An inhalation LC₅₀ in mice of 2,998 mg/m³ for 2 hours is reported by the World Health Organization (1992).

VIII. References


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


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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

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


ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOBUTYL ETHER

(2-butoxyethanol, butyl cellosolve, butyl glycol)

CAS Registry Number: 111-76-2

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

*Inhalation reference exposure level* 14,000 μg/m³

*Critical effect(s)* irritation

*Hazard Index target(s)* Respiratory System

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

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>colorless liquid</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C₆H₁₄O₂</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>118.20</td>
</tr>
<tr>
<td>Density</td>
<td>0.90 g/cm³ @ 20°C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>171°C</td>
</tr>
<tr>
<td>Melting point</td>
<td>-70°C</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>0.76 mm Hg @ 20°C</td>
</tr>
<tr>
<td>Flashpoint</td>
<td>unknown</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>unknown</td>
</tr>
<tr>
<td>Solubility</td>
<td>soluble in water, acetone, benzene,</td>
</tr>
<tr>
<td></td>
<td>carbon tetrachloride, ethyl ether;</td>
</tr>
<tr>
<td></td>
<td>miscible with ketones, ethers,</td>
</tr>
<tr>
<td></td>
<td>alcohols and halogenated hydrocarbons</td>
</tr>
<tr>
<td>Odor threshold</td>
<td>0.10 ppm (geometric mean) (AIHA, 1989)</td>
</tr>
<tr>
<td>Odor description</td>
<td>sweet, ester-like, musty (AIHA, 1989)</td>
</tr>
<tr>
<td>Metabolites</td>
<td>butoxyacetic acid (Johanson <em>et al.</em>, 1986)</td>
</tr>
<tr>
<td>Conversion factor</td>
<td>1 ppm = 4.84 mg/m³ @ 25°C</td>
</tr>
</tbody>
</table>

III. Major Uses or Sources

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

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

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

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

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

Predisposing Conditions for EGBE Toxicity

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

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

A 7-hour LC50 for mice was reported as 700 ppm (3,000 mg/m³) EGBE (Werner et al., 1943). Severe hemoglobinuria was observed; hepatic focal necrosis and splenic lymphoid hyperplasia were noted at necropsy. An 8-hour LC50 in rats was reported as 564 ppm (2,800 mg/m³) EGBE (Pozzani et al., 1959).

No mortality or other clinical signs of toxicity were observed in 5 male and 5 female guinea pigs exposed to 691 or 633 ppm EGBE, respectively, for one hour (Nachreiner, 1994). Further, no signs of toxicity were observed during the 14-day post-exposure period or at necropsy.
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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

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

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

VI. Reproductive or Developmental Toxicity

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

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

The same study exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. Hematological parameters in the does were normal. However, rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem et al., 1992). The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in

C - 112- Ethylene Glycol Monobutyl Ether
rabbits. EGBE has not been listed as a developmental or reproductive toxicant under Proposition 65.

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Carpenter et al., 1956; Johanson et al., 1986</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>human volunteers 2 in Carpenter; 7 in Johanson et al.)</td>
</tr>
<tr>
<td>Exposure method</td>
<td>inhalation of 113 ppm for 4 hours (2 men) in Carpenter et al. (1956); inhalation of 20 ppm in Johanson et al. (1986)</td>
</tr>
<tr>
<td>Critical effects</td>
<td>mucous membrane irritation of the nose and eyes</td>
</tr>
<tr>
<td>LOAEL</td>
<td>113 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>20 ppm for 2 hours</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>2 or 4 hours</td>
</tr>
<tr>
<td>Equivalent 1-hour concentration</td>
<td>28 ppm (20² * 2 hours = C² * 1 hour))</td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>2.8 ppm (14 mg/m³; 14,000 µg/m³)</td>
</tr>
</tbody>
</table>

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

Level protective against severe adverse effects

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

Tyl et al. (1984) exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits. Rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of

C - 113- Ethylene Glycol Monobutyl Ether
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

EGBE (Ghanayem et al., 1992). Hematologic parameters in the does were normal but there was evidence in their cages of hematuria. Therefore, it is not clear if the reproductive and fetal toxicity were secondary to hematological effects. No adverse effects to does or fetuses were observed following exposure to 0, 25, 50 or 100 ppm EGBE. This study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal toxicity and embryotoxicity in rabbits. The pharmacokinetic model of Corley et al. (1994), as well as other evidence in humans and incubated human erythrocytes, indicates that there is considerably less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard animal toxicity studies.

**Level Protective Against Life-threatening Effects**

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

Data on lethal effects of EGBE in species resistant to the hemolytic effects of EGBE were not available other than a 1-hour free-standing NOAEL of 633-691 ppm in guinea pigs (5 per sex) (Nachreiner, 1994). The only lethality study providing dose-response data had been conducted in mice (Werner et al., 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.

**VIII. References**


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


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


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


C - 115- Ethylene Glycol Monobutyl Ether
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOETHYL ETHER

(2-ethoxyethanol, Cellosolve)

CAS Registry Number: 110-80-5

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

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

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

Description colorless liquid
Molecular formula C₄H₁₀O₂
Molecular weight 90.12
Density 0.931 g/cm³ @ 20°C
Boiling point 135°C
Melting point -70°C (solidifies)
Vapor pressure 3.8 mm Hg @ 20°C (ACGIH, 1991)
Flashpoint 44°C, closed cup
Explosive limits upper = 15.6%
lower = 1.7%
Solubility miscible with water and organic solvents
Odor threshold 2.7 ppm (geometric mean) (AIHA, 1989)
Odor description sweet, fruity, ester-like (AIHA, 1989)
Metabolites ethoxyacetic acid (Groeseneken et al., 1986)
Conversion factor 1 ppm = 3.69 mg/m³ @ 25°C

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans

Investigators conducting an animal experiment on the acute toxicity of EGEE intentionally exposed themselves to 6,000 ppm EGEE for “a few seconds” and reported eye irritation and a “disagreeable odor” (Waite et al., 1930).
Determining of Acute Reference Exposure Levels for Airborne Toxicants

March 1999

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

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

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

Predisposing Conditions for EGEE Toxicity

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

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

V. Acute Toxicity to Laboratory Animals

A 7-hour LC₅₀ in mice of 1,820 ppm EGEE has been reported (Werner et al., 1943).

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

VI. Reproductive or Developmental Toxicity

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

An increased prevalence of oligospermia and azoospermia and an increased odds ratio (OR 1.85; 95% CI = 0.6-5.6) for lower sperm count were observed in a study of shipyard painters exposed to a mean of 0.8 ppm EGEE for an average of 8 years compared to unexposed workers (Welch et al., 1988). Lower sperm count was also reported in workers exposed to a geometric mean air concentration of 6.6 ppm EGEE for at least one month (Ratcliffe et al., 1989).
Exposure of male rats by gavage to 936, 1,872, and 2,808 mg EGEE/kg/day for 5 consecutive days was reported to result in reversible impairment of testicular function as indicated by significantly decreased sperm counts and increased abnormal sperm morphology (Oudiz et al., 1984).

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

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

Mild Adverse Effect Level

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

Reference Exposure Level for 6 hour exposure (protective against severe adverse effects):

0.1 ppm (370 μg/m³)

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

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

LOAEL | 50 ppm
NOAEL | 10 ppm
Exposure duration | 6 hours per day
Determination of Acute Reference Exposure Levels for Airborne Toxicants  
March 1999

<table>
<thead>
<tr>
<th>LOAEL uncertainty factor</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>100</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>0.1 ppm (0.37 mg/m³; 370 µg/m³)</td>
</tr>
</tbody>
</table>

**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:

<table>
<thead>
<tr>
<th>EGEE concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,130</td>
</tr>
<tr>
<td>2,990</td>
</tr>
<tr>
<td>2/16</td>
</tr>
</tbody>
</table>

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 \( C^n \times T = K \), where \( n = 2 \). From the 1-hour data, the concentration associated with a 5% incidence of lethality \( \text{ED}_{05} \) was 3,307 ppm; the lower confidence limit (LCL) on this concentration \( \text{BC}_{05} \) was 2,223 ppm. An uncertainty factor (UF) of 30 was applied to the \( \text{BC}_{05} \) of 2,223 ppm (3 to account for interspecies variability and 10 for interindividual human variation).

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/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% response rates are indicated below. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

**Comparison of benchmark concentrations (1% vs 5%)**

<table>
<thead>
<tr>
<th>Response rate</th>
<th>MLE (ppm)</th>
<th>95% LCL (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>2,766</td>
<td>1,635</td>
</tr>
<tr>
<td>5%</td>
<td>3,307</td>
<td>2,223</td>
</tr>
</tbody>
</table>

**VIII. References**

C - 119 - Ethylene Glycol Monoethyl Ether
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


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

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


C - 120 - Ethylene Glycol Monoethyl Ether
ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOETHYL ETHER ACETATE

(2-ethoxyethyl acetate, Cellosolve acetate)

CAS Registry Number: 111-15-9

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

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

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

Description colorless liquid
Molecular formula C₆H₁₂O₃
Molecular weight 132.2
Density 0.975 g/cm³ @ 20°C
Boiling point 156°C
Melting point -61.7°C
Vapor pressure 2 mm Hg @ 20°C
Flashpoint 49°C (ACGIH, 1991)
Explosive limits upper = 12.7%
lower = 1.7%
Solubility soluble in water, alcohol, ether, acetone
Odor threshold 0.060 ppm (geometric mean) (AIHA, 1989)
Odor description mild, ester-like odor
Metabolites ethylene glycol monoethyl ether, ethoxyacetic acid
(Groesenken et al., 1987)
Conversion factor 1 ppm = 5.41 mg/m³ @ 25°C

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans

Headaches, lethargy, sinus problems, nausea, and heartburn were reported by two silk screening workers following occupational exposures ranging from 0.5 to 3.9 ppm (3 to 21 mg/m³) EGEEA (Boiano, 1983). Both workers reported that their symptoms improved when they were away
from work. Dermal absorption and concomitant exposure to other organic solvents may have contributed to the observed symptoms.

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

**Predisposing Conditions for EGEEA Toxicity**

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

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

**V. Acute Toxicity to Laboratory Animals**

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

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

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

**VI. Reproductive or Developmental Toxicity**

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

Tinston and colleagues (1983) exposed pregnant rabbits to 25, 100, or 400 ppm (140, 500, or 2,000 mg/m³) EGEEA 6 hours per day on days 6-18 of gestation. Significant maternal toxicity, as indicated by decreased food consumption and body weight, and a significant reduction in hemoglobin concentration were observed in the rabbits exposed to 400 ppm EGEEA. One fetus in the 25 ppm EGEEA exposed group had agenesis of the left kidney. Right kidney agenesis was observed in one fetus in the 400 ppm EGEEA exposed group. A review of the data is presented by Doe (1984).
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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

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

**Mild Adverse Effect Level**

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

**Reference Exposure Level for a 6 hour exposure (protective against severe adverse effects):**

\[ 140 \mu g/m^3 \]

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

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

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

**Level Protective Against Life-threatening Effects**
No recommendation is made due to the limitations of the database.

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

VIII. References


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


C - 125 - Ethylene Glycol Monoethyl Ether Acetate


ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOMETHYL ETHER

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

CAS Registry Number: 109-86-4

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

\[ \text{Inhalation reference exposure level} \quad 93 \, \mu g/m^3 \]

\[ \text{Critical effect(s)} \quad \text{teratogenic effects} \]

\[ \text{Hazard Index target(s)} \quad \text{Reproductive/developmental} \]

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

- **Description**: colorless liquid
- **Molecular formula**: C\(_3\)H\(_8\)O\(_2\)
- **Molecular weight**: 76.09
- **Density**: 0.965 g/cm\(^3\) @ 20°C
- **Boiling point**: 125°C
- **Melting point**: -85.1°C
- **Vapor pressure**: 6.2 mm Hg @ 20°C
- **Flashpoint**: 41.7°C (closed cup) (ACGIH, 1991)
- **Explosive limits**
  - upper = 19.8% (ACGIH, 1991)
  - lower = 2.5% (ACGIH, 1991)
- **Solubility**: miscible with water, alcohol, benzene, ether, acetone
- **Odor threshold**: 2.3 ppm (Amoore and Hautala, 1983)
- **Odor description**: mild ethereal odor
- **Metabolites**: methoxyacetic acid, carbon dioxide (Miller et al., 1983)
- **Conversion factor**: 1 ppm = 3.1 mg/m\(^3\) @ 25°C

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans

Acute overexposure to EGME may cause irritation of the eyes, nose, and throat, drowsiness, dizziness, headache, nausea, vomiting, disorientation, and loss of consciousness (HSDB, 1994). Fatigue and hematologic effects including decreased white and red blood cell counts, and decreased hemoglobin, hematocrit and platelet levels, were observed in a microfilm manufacturing worker following daily inhalation exposure for approximately 9 months to a mean concentration...
of 35 ppm EGME and substantial but unquantified dermal exposure (Cohen, 1984). Concomitant exposure to methyl ethyl ketone and propylene glycol monomethyl ether was also reported.

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

**Predisposing Conditions for EGME Toxicity**

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

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

V. Acute Toxicity to Laboratory Animals

A 7-hour LC$_{50}$ in mice of 1,480 ppm (4,736 mg/m$^3$) was reported (Werner et al., 1943). Rats were exposed to 100, 300, or 1,000 ppm (320, 960, or 3,200 mg/m$^3$) 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$^3$) 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$^3$) 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$^3$) EGME for 6 hours per day on days 6-15 of gestation. A statistically significant increase in the incidence of skeletal variations was observed in rats and mice following maternal exposure to 50 ppm EGME. Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights were observed in rabbits following maternal exposure to 50 ppm EGME. In rabbits, a significant increase in the rate of fetal resorption was observed in the 10 ppm exposure group. Thus 10 ppm was considered a LOAEL for increased resorptions and 3 ppm a NOAEL. Although the authors
attribute the statistical significance of this effect to an unusually low rate of resorptions in controls compared to historical controls, historical control data were not presented.

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

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

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

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

Reference Exposure Level for 6 hr exposure (Protective Against Severe Adverse Effects):

\[
0.03 \text{ ppm (93 } \mu \text{g/m}^3) 
\]

<table>
<thead>
<tr>
<th>Study</th>
<th>Hanley et al., 1984</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>pregnant rabbits</td>
</tr>
<tr>
<td>Exposure method</td>
<td>inhalation of 3, 10, or 50 ppm EGME 6 hours per day on days 6-15 of gestation</td>
</tr>
<tr>
<td>Critical effects</td>
<td>gross soft tissue and skeletal teratogenic effects and  significantly decreased fetal body weights</td>
</tr>
<tr>
<td>LOAEL</td>
<td>10 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>6 hours</td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
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<tr>
<td>Interspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>100</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>0.03 ppm (0.093 mg/m³; 93 } \mu \text{g/m}^3)</td>
</tr>
</tbody>
</table>

Pregnant rabbits were exposed to 3, 10, or 50 ppm EGME 6 hours per day on days 6-18 of gestation (Hanley et al., 1984). Maternal toxicity, as indicated by decreased body weight gain, was observed only in rabbits exposed to 50 ppm EGME. The authors report that the hematologic...
parameters of EGME exposed rabbits were not altered at any dose. Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weight were observed in rabbits following maternal exposure to 50 ppm EGME. Statistically significant increases in fetal resorption rates were observed following maternal exposure to 10 or 50 ppm EGME. A NOAEL of 3 ppm for increased resorptions was used to develop the REL. An uncertainty factor of 100 was applied to account for inter- and intraspecies differences. Dividing this by 100 gives a level protective against severe adverse effects for a 6 hour exposure of 0.03 ppm (0.093 mg/m³; 93 µg/m³).

**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, \( C^n \times T = K \), where \( n = 2 \). An uncertainty factor (UF) of 100 was applied to the time-adjusted NOAEL of 2,461 ppm to account for interspecies variability and individual human variation. The final 1-hour level protective against life-threatening effects for EGME is 25 ppm. (A benchmark dose approach (Crump, 1984; Crump and Howe, 1983) could not be employed because log-normal probit analysis of the lethality data was shown to be too heterogeneous.)

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

**VIII. References**


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

ACUTE TOXICITY SUMMARY

FORMALDEHYDE

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

CAS Registry Number: 50-00-0

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

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

II. Physical and Chemical Properties (HSDB, 1993)

Description: colorless gas
Molecular formula: CH₂O
Molecular weight: 30.03
Density: 0.815 g/L @ -20°C
Boiling point: -19.5°C
Melting point: -92°C
Vapor pressure: 3883 mm Hg @ 25°C (Howard, 1989)
Flashpoint: 300° C or 573°F
Explosive limits: upper = 73% lower = 7%
Solubility: soluble in water, alcohol, ether, other polar solvents
Odor threshold: 0.05-0.5 ppm
Odor description: very pungent odor; straw-like
Metabolites: formic acid
Conversion factor: 1 ppm = 1.24 mg/m³ @ 25°C

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans
Exposure to moderate levels of formaldehyde (1-3 ppm) can result in eye and upper respiratory tract irritation (Weber-Tschoppe et al., 1977; Kulle et al., 1987). Feinman (1988) states that most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs. High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984).

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

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

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

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

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m³ formaldehyde for 2 hours (Pazdrak et al., 1993). Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure. Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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 FEV₁ (defined as > 20% or more) and FEV₁/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 FEV₁ of 20% or more during exposure. One of 22 asthmatics had a greater than 20% reduction in FEV₁ (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation [Vₑ] = 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 FEV₁ (-24.4%) and in FEV₁/FVC, which occurred at 47 minutes into exposure to 3 ppm formaldehyde. These reductions occurred following a second 15 minute heavy exercise session (Vₑ = 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 FEV₁ (-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 FEV₁ of greater than 20% following exposure also exhibited FEV₁/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 (SGₐw) during exposure to 3 ppm formaldehyde. Other than mild nose and throat irritation, no severe respiratory signs and symptoms were apparently reported.

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

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

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

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

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

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

The effects of formaldehyde on asthmatics appear to be dependent on previous, repeated exposure to formaldehyde. Burge et al. (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief durations exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV₁) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m³) formaldehyde (Nordman et al., 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde.
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not
occupationally exposed to formaldehyde, Sheppard et al. (1984) found that a 10-minute challenge
with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in
airway resistance or thoracic gas volume.

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

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

_Predisposing Conditions for Formaldehyde Toxicity_

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

**Chemical:** Formaldehyde reacts with hydrochloric acid to form bis-chloroacetylether, a
carcinogen (Reprotox, 1993).

**V. Acute Toxicity to Laboratory Animals**

In 72 rats exposed to approximately 600-1,700 mg/m³ (500-1,400 ppm) formaldehyde vapor for
30 minutes the LC₅₀ was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950). The first deaths did
not occur until 6 hours after cessation of exposure. Respiratory difficulty lasted several days after
exposure and the last of 49 rats died after 15 days of purulent bronchitis and diffuse
bronchopneumonia. Three weeks following exposure, histological examinations of the 23
surviving animals revealed bronchitis, pulmonary microhemorrhages, and edema. No changes
were seen in other organs.

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

Alarie (1981) determined the 10 minute LC₅₀ 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 MLEₗ₀ and BCₗ₀ 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 LC₅₀ in rats and mice to be 588 mg/m³ (474 ppm) and 505 mg/m³ (407 ppm), respectively. However, the raw data for this study were not included in the report. Horton et al. (1963) observed that 2 hour exposure of mice to 0.9 mg/l (900 mg/m³) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but 2 hour exposure to 0.14 mg/l (140 mg/m³) did not produce signs of “substantial distress.” In a lethality study by Carpenter et al. (1946), 250 ppm formaldehyde for 4 hours resulted in deaths of 2-4 out of 6 albino rats (actual number of deaths not specified) and exposure to 125 ppm formaldehyde for 4 hours resulted in deaths of 0-1 out of 6 albino rats.

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

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

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

### VI. Reproductive or Developmental Toxicity

There are no studies that conclusively show adverse reproductive or developmental effects in animals exposed to formaldehyde (Shepard’s Catalog of Teratogenic Agents, 1993; Feinman, 1988). In humans there are few data on the association of teratogenicity or adverse reproductive effects with formaldehyde exposure. Existing data do not suggest that formaldehyde, by any route, produces significant teratogenic or reproductive effects (Reprotext, Shepard’s Catalog of Teratogenic Agents, 1993; Feinman, 1988).
VII. Derivation of Acute Reference Exposure Level and Other Severity Levels
(for a 1-hour exposure)

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Kulle et al. (1987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>19 nonasthmatic, nonsmoking human subjects</td>
</tr>
<tr>
<td>Exposure method</td>
<td>0.5-3.0 ppm</td>
</tr>
<tr>
<td>Critical effects</td>
<td>mild and moderate eye irritation</td>
</tr>
<tr>
<td>LOAEL</td>
<td>1 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>0.5 ppm</td>
</tr>
<tr>
<td>Benchmark concentration</td>
<td>0.44 ppm (BC₀₅)</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>3 hours</td>
</tr>
<tr>
<td>Extrapolated 1 hour concentration</td>
<td>0.76 ppm (0.44² ppm* 3 h = C² * 1 h )</td>
</tr>
<tr>
<td>(see Table 12 for information on “n”)</td>
<td></td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
<td>not required in BC approach</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>0.076 ppm (0.094 mg/m³; 94 μg/m³)</td>
</tr>
</tbody>
</table>

The recommended REL was estimated by a benchmark concentration (BC₀₅) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983). The BC₀₅ is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC₀₅ from this analysis was 0.44 ppm (0.53 mg/m³) formaldehyde. This value was adjusted to a 1-hour duration using the formula Cⁿ * T = K, where n = 2 (AICE, 1989), resulting in a value of 0.74 ppm. An uncertainty factor (UF) of 10 was used to account for individual variation. Generally an uncertainty factor of 3 would be used with the BC₀₅ for intraindividual variability, since the BC₀₅ accounts for some degree of individual variation. However, information from the literature indicates a wide variability in response to formaldehyde irritancy including reports of irritation (NIOSH HHE reports 1981-1996; Liu et al. 1991; Horvath et al, 1985) or cellular changes associated with irritation and an immune response at levels below the one-hour extrapolated BC₀₅ (Pazdrak et al, 1993; Gorski et al, 1992). For these reasons, we used an uncertainty factor of 10 to account for intraindividual variability in the human population.

REL = BC₀₅/(UF)

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

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

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

<table>
<thead>
<tr>
<th>Response rate</th>
<th>MLE (ppm)</th>
<th>95% LCL (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>5%</td>
<td>0.72</td>
<td>0.44</td>
</tr>
</tbody>
</table>

**Level Protective Against Severe Adverse Effects**

Based on the results of Green *et al.* (1987), an acute LOAEL of 3 ppm formaldehyde in asthmatics for a duration of 17 minutes (immediately following moderate exercise for 15 minutes) was determined. The researchers felt that, when examined along with the other 3 studies in the series (Kulle *et al*., 1987; Sauder *et al*., 1987; Sauder *et al*., 1986), this study represented a threshold where protective mechanisms of the respiratory tract were beginning to be overwhelmed. Only Green *et al.* (1987) identified 5 out of 39 asthmatic and healthy subjects as having clinically significant decrements in FEV1 (defined as > 10%). However, 3 of these 5 subjects (out of 39 asthmatic and healthy subjects) responded with a 20% or greater decrease in FEV1, 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 FEV1) 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 LC50 for formaldehyde in mice of 2,162 ppm (95% confidence interval = 1,687-2,770 ppm). The post-exposure observation period was 3 hours. Formaldehyde exposure to 250 ppm (310 mg/m³) for 4 hours killed 4/6 rats within a 14 day observation period (Carpenter *et al*., 1946). Among 72 rats exposed to 600-1,700 mg/m³ formaldehyde vapor for 30 minutes the LC50 was found to be 1,000 mg/m³ (800 ppm) (Skog, 1950).
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

Of the lethality studies summarized above, the study by Alarie (1981) best presents mortality data for the determination of a BC_{05} with an adequate post-exposure period. The major limitation of this study was the short post-exposure observation period of 3 hours. Given the paucity of exposure data resulting in potentially lethal effects, this study currently represents the best estimate for the development of a life-threatening level for formaldehyde. A BED_{05} (which represents an experimental threshold for lethality) of 778 ppm (965 mg/m³) for a 130 minute exposure was estimated from the data (Crump, 1984; Crump and Howe, 1983), but a BC_{05} could not be determined due to lack of data. The BED_{05} was adjusted for a 1-hour exposure using a modification of Haber’s equation C^n x T = K, where n = 2 for extrapolation from a shorter duration to a 1-hour level, resulting in a value of 318 ppm (400 mg/m³). The exponent n = 2 was based on findings in the AICE Guidelines (AICE, 1989). Uncertainty factors applied to the 1-hour BC_{05} were 3-fold to account for interspecies differences and 10-fold for increased susceptibility of sensitive human individuals. The cumulative uncertainty factor was thus 30, which results in an estimated level protective against life-threatening effects of 11 ppm (13 mg/m³) for a 1-hour exposure to formaldehyde.

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

VIII. References


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


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


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


Wallenstein G, Rebohle E, Bergmann I, Voight U, Schneider WD. Berufliche Erkrankungen des Atmungsorgans durch chemische Stoffe mit potentiell allergenwirkung [Occupational diseases...
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

of the respiratory system due to chemical substances with potential allergen effects]. Dtsch Gesundheitsw 1978;33(24):1119-1123.


IX. Graphic Representation of Benchmark Concentration Determination
BC(05) = 435 ppb

MLE
95% LCL

Formaldehyde Concentration (Log ppb)

Irritation Response (Probit scale)

5% response

BC(05) = 435 ppb
ACUTE TOXICITY SUMMARY

HYDROGEN CHLORIDE

(hydrogen chloride, anhydrous hydrogen chloride, muriatic acid)

CAS Registry Number: 7647-01-1

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

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

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

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>HCl</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>36.46</td>
</tr>
<tr>
<td>Density</td>
<td>1.49 g/L @ 25°C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>-84.9°C</td>
</tr>
<tr>
<td>Melting point</td>
<td>-114.8°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>soluble in water, alcohol, benzene, ether; insoluble in hydrocarbons</td>
</tr>
<tr>
<td>Odor threshold</td>
<td>0.26-10.0 ppm (AIHA, 1989a)</td>
</tr>
<tr>
<td>Odor description</td>
<td>sharp, irritating (AIHA, 1989a)</td>
</tr>
<tr>
<td>Conversion factor</td>
<td>1 ppm = 1.49 mg/m³ @ 25°C</td>
</tr>
</tbody>
</table>

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).
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

IV. Acute Toxicity to Humans

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

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

Predisposing Conditions for HCl Toxicity

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

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

V. Acute Toxicity to Laboratory Animals

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

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

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

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

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

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

VI. Reproductive or Developmental Toxicity

The reproductive hazard of hydrogen chloride to humans is unknown (Reprotext, 1999). Few studies on the reproductive effects of HCl exposure were found in the literature. Maternal exposure to a high concentration of a strong acid could result in metabolic acidosis and subsequent fetal acidemia which has been linked with low Apgar scores, neonatal death, and seizures. However, there is no evidence linking HCl exposure to fetal acidemia (Reprotext, 1999).
Pregnant rats exposed to 300 ppm (450 mg/m³) HCl for 1 hour on the 9th day of gestation exhibited signs of severe dyspnea and cyanosis (Pavlova, 1976; 1978). The exposure was lethal to one-third of the exposed rats (number of rats exposed not reported). Increased mortality was also observed in the progeny of the exposed rats compared to that of controls. The author implies that organ functional abnormalities in the progeny resulted from in utero exposure. However, the lack of key experimental details and the ambiguity of organ function tests make this conclusion difficult to validate.

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Stevens et al., 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>10 asthmatics aged 18-25</td>
</tr>
<tr>
<td>Exposure method</td>
<td>Inhalation via half face mask to 0.8 or 1.8 ppm HCl</td>
</tr>
<tr>
<td>Critical effects</td>
<td>Upper respiratory system symptoms of sore throat; nasal discharge</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Not observed</td>
</tr>
<tr>
<td>NOAEL</td>
<td>1.8 ppm</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Extrapolated 1 hour concentration</td>
<td>1.4 ppm (1.8 ppm × 0.75 h = C₁ × 1 h) (see Table 12 for information on “n”)</td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>1.4 ppm (2.1 mg/m³; 2,100 µg/m³)</td>
</tr>
</tbody>
</table>

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

Level Protective Against Severe Adverse Effects
The RD$_{50}$ in mice for a 10-minute exposure to HCl is reported as 309 ppm (460 mg/m$^3$). NRC applied an uncertainty factor of 10 to the RD$_{50}$ to account for interspecies differences yielding a 1-hour EEGL of 31 ppm. The EEGL was further reduced to 20 ppm (29.8 mg/m$^3$) because “of the paucity of human data.”

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

**Level Protective Against Life-threatening Effects**

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

<table>
<thead>
<tr>
<th>HCl Concentration (ppm)</th>
<th>1,793</th>
<th>2,281</th>
<th>2,600</th>
<th>4,277</th>
<th>4,460</th>
<th>4,854</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0/6</td>
<td>3/6</td>
<td>1/6</td>
<td>7/8</td>
<td>6/6</td>
<td>6/6</td>
</tr>
</tbody>
</table>

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$_{50}$) was 1,772 ppm; the lower 95% confidence limit (LCL) on this concentration [the BC$_{05}$] was 1,271 ppm. A total uncertainty factor of 30 was applied to the BC$_{05}$ of 1,271 ppm to account for interspecies variability (3) and individual variation (10) in response.

\[
\text{level protective against life-threatening effects} = \frac{\text{BC}_{05}}{(\text{UF})}
\]

The final level protective against life-threatening effects for HCl is therefore 42 ppm (63 mg/m$^3$). 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%)
<table>
<thead>
<tr>
<th>Response rate</th>
<th>MLE (ppm)</th>
<th>95% LCL (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>1,464</td>
<td>946</td>
</tr>
<tr>
<td>5%</td>
<td>1,772</td>
<td>1,271</td>
</tr>
</tbody>
</table>

C - 151 - Hydrogen Chloride
VIII. References


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


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


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


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March 1999

ACUTE TOXICITY SUMMARY

HYDROGEN CYANIDE
(formonitrile; hydrogen cyanide; prussic acid)

CAS Registry Number: 74-90-8

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

Inhalation reference exposure level

340 μg/m³

Critical effect(s)

loss of coordination and loss of consciousness, due to cellular hypoxia of the central nervous system

Hazard Index target(s)

Nervous System

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

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

Conversion factor

1 ppm = 1.13 mg/m³

III. Major Uses or Sources

Hydrogen cyanide (HCN) is used in a variety of syntheses, including the production of adiponitrile (for nylon), methyl methacrylate, sodium cyanide, cyanuric chloride, chelating agents, pharmaceuticals, and other specialty chemicals. Manufacturing activities producing HCN include electroplating, metal mining, metallurgy, and metal cleaning processes. Additionally, HCN has some insecticide and fungicide applications (ATSDR, 1993). Fires involving some nitrogen-containing polymers, often found in fibers used in fabrics, upholstery covers, and padding, also produce HCN (Tsuchiya and Sumi, 1977).
Another common source of HCN is cigarette smoke. Levels in inhaled mainstream cigarette smoke range from 10 to 400 µg per cigarette and decrease to levels ranging from 0.06 to 108 µg in secondary or sidestream smoke (Fiksel et al., 1981).

**IV. Acute Toxicity to Humans**

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

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

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

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

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

**Predisposing Conditions for HCN Toxicity**

**Medical:** Individuals with some motor neuron diseases, such as amyotrophic lateral sclerosis, have a decreased ability to convert cyanide to thiocyanate and may be predisposed to HCN toxicity (Kato et al., 1985). Individuals with Leber’s hereditary optic atrophy, a rare 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:

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

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

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>$a$ (slope)</th>
<th>$b$ (y-intercept)</th>
<th>Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakurai (1989)</td>
<td>mouse</td>
<td>491</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Hartzell et al. (1985)</td>
<td>rat</td>
<td>698</td>
<td>92</td>
<td>115</td>
</tr>
<tr>
<td>Purser et al. (1984)</td>
<td>monkey</td>
<td>685</td>
<td>66</td>
<td>89</td>
</tr>
<tr>
<td>Barcroft (1931)</td>
<td>goat</td>
<td>885</td>
<td>152</td>
<td>182</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Numerous citations were located in the literature that contained LC$_{50}$ determinations for HCN at various exposure durations in experimental animals, but many of the studies did not include the raw mortality data from which to estimate an MLE$_{0.05}$ (maximum likelihood estimate corresponding to 5% lethality) and BC$_{0.05}$ (benchmark dose at the 95% lower confidence interval of the MLE$_{0.05}$). These citations and their respective LC$_{50}$s are shown in Table 2.

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

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

---

1. LC$_{50}$ determinations for exposure durations of less than 5 minutes were not included in the table.
2. Not reported
3. Mean time to death (± SD) at 450 ppm HCN
4. Not applicable, time to death experiment
Determination of Acute Reference Exposure Levels for Airborne Toxicants  
March 1999

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

Groups of 10 rats inhaled hydrogen cyanide for 30 minutes and were observed over the next 24 hours (Lynch, 1975). Deaths noted occurred within 1 hour of exposure. No deaths were reported following exposure to 60 or 68 mg/m$^3$. Some but not all rats survived exposure to HCN at concentrations between 90 and 166 mg/m$^3$. There were no survivors following exposure to 168 or 192 mg/m$^3$.

Table 3. Animal Lethality Benchmark Dose Determinations for Hydrogen Cyanide

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

$^1$ Exposure durations of less than 5 minutes were not included in the table.

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

$^3$ Not applicable

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

One mortality study reported an inhalation NOAEL of 16 ppm (18.1 mg/m$^3$) for rats and mice exposed for 16 hours (Weedon et al., 1940). Of the four experimental HCN concentrations...
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

(1,000, 250, 63, and 16 ppm, or 1,130, 282, 71, and 18 mg/m³, respectively), only 16 ppm produced no distress (excitement, loss of coordination, or respiratory difficulties) throughout the exposure period. However, no other physiological indicators or measures of toxicity were used. Necropsy revealed lung and coronary artery changes in one of the two rats exposed to 16 ppm HCN.

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

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

VI. Reproductive or Developmental Toxicity

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

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

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

Mild Adverse Effect Level

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

Reference Exposure Level (protective against severe adverse effects): 340 μg/m³
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

<table>
<thead>
<tr>
<th>Study</th>
<th>Purser, 1984; Purser et al., 1984</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>4 cynomolgus monkeys</td>
</tr>
<tr>
<td>Exposure method</td>
<td>inhalation</td>
</tr>
<tr>
<td>Critical effects</td>
<td>CNS depression/incapacitation</td>
</tr>
<tr>
<td>LOAEL</td>
<td>80 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>60 ppm (68 mg/m³)</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Extrapolated 1 hour concentration</td>
<td>30 ppm (60 ppm * 0.5 h = C₁ * 1 h)</td>
</tr>
</tbody>
</table>

(see Table 12 for information on “n”)

| LOAEL uncertainty factor | 1 |
| Interspecies uncertainty factor | 10 |
| Intraspecies uncertainty factor | 10 |
| Cumulative uncertainty factor | 100 |

Reference Exposure Level
0.30 ppm (0.34 mg/m³; 340 µg/m³)

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

**Level Protective Against Life-threatening Effects**

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

\[
\text{level protective against life-threatening effects} = \frac{\text{BC₀₅}}{(\text{UF})}
\]

Incorporation of these factors (cumulative uncertainty factors = 30) yielded a level protective against life-threatening effects of 1.1 ppm (1.2 mg/m³) for a 1-hour HCN exposure.
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

ACUTE TOXICITY SUMMARY

HYDROGEN FLUORIDE

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

CAS Registry Number: 7664-39-3

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

*Inhalation reference exposure level* 240 µg/m³

*Critical effect(s)* irritation to the eyes, nose, and throat

*Hazard Index target(s)* Respiratory System; Eyes

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

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

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans

Hydrogen fluoride, an inorganic acid of fluorine, can cause both severe burns and systemic toxicity. Hydrogen fluoride produces dehydration and corrosion of tissues mediated by free hydrogen ions. In addition, the dissociated fluoride ion, F⁻, also produces severe toxicity. The
fluoride ion complexes certain bivalent cations, primarily calcium and magnesium, to form insoluble salts. This interferes with the calcium metabolism in the underlying soft and bony tissues and results in cell destruction and severe pain. With severe HF burns, systemic toxicity may also result; hypocalcemia and hypomagnesemia are the most common manifestations (Bertolini, 1992).

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

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

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

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

Lund et al. (1997) investigated eye and airway symptoms and lung function (forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)) during and after a one hour exposure to hydrogen fluoride. Twenty healthy male volunteers were exposed in a chamber to constant HF concentrations that ranged from 0.2 to 5.2 mg/m³. (Such concentrations occur among potroom workers in the primary aluminum industry, according to the authors.) The volunteers were asked to report itching or soreness of the eyes and upper airways and to grade these subjective responses on a scale from 1 to 5 with a standardized questionnaire. Lower airway symptoms of chest tightness and soreness, coughing, expectoration, and wheezing were similarly reported and graded by the volunteers. For the purposes of analysis the authors grouped the subjects into exposure groups of 0.2-0.6 mg/m³ (low), 0.7-2.4 mg/m³ (medium), and 2.5-5.2 mg/m³ (high). Lower airway scores were not significantly different for any concentration range. The upper airway and total symptom score was significantly increased (p<0.05) at the end of exposure for the highest exposure range (2.5-5.2 mg/m³, n=7) and for all exposures considered as a single group (0.2-5.2 mg/m³, n=23). The total symptom score was also significantly increased at the end of exposure for the lowest concentration range (0.2-0.6 mg/m³, n=9), although individual scores for eye irritation, upper respiratory irritation, and lower respiratory irritation were not significantly different comparing before and after exposure. Almost all the symptoms
had disappeared four hours after the end of exposure. Symptom scores from the upper airways were significantly correlated with the HF concentration (r = 0.62, p = 0.002), the change in plasma fluoride concentration (delta C) (r = 0.51, p = 0.01), and the maximum plasma fluoride concentration (Cmax) (r = 0.42, p = 0.05). A significant correlation was found between total symptom score for airways and the HF concentration (p = 0.009). No significant changes occurred in FEV1 following exposure at any concentration. A statistically significant decrease in FVC (-0.02 L, 95% CI -0.5 to 0.06) was found in the group exposed at the lowest concentration range (0.2-0.6 mg/m³, n = 9). However, no dose-response relationship was evident and no lower airway symptoms were reported. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL for upper airway irritation.

**Predisposing Conditions for HF Toxicity**

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

**Chemical:** Unknown

**V. Acute Toxicity to Laboratory Animals**

In a study of the lethal effects of HF in mice, Higgins _et al._ (1972) determined a 5-minute LC50 of 6,427 ppm (5,334 mg/m³) while no lethality was observed after exposure to 2,430 ppm (2,017 mg/m³). The authors observed pulmonary edema in varying degrees of severity in most of the exposed mice. Pulmonary hemorrhage was a common finding in animals that died during, or shortly after, exposure to concentrations above the LC50 value. Higgins and colleagues also exposed rats to high concentrations of HF for 5-minute periods. Exposure of rats to 12,440 ppm (10,325 mg/m³) HF resulted in 10% mortality and exposure to 25,690 ppm (21,323 mg/m³) resulted in 100% mortality.

Wohlslagel and colleagues (1976) exposed rats and mice to HF for 60 minute durations. The 1-hour LC50 in mice, the most sensitive species, was 342 ppm (284 mg/m³), while no lethality was observed at 263 ppm (218 mg/m³). An exposure of 1,087 ppm (902 mg/m³) resulted in no lethality in rats, while 100% mortality was observed at 1,765 ppm (1,464 mg/m³). Wohlslagel _et al._ (1976) noted symptoms in both rats and mice which included eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of exposed skin.

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

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

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

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

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

Self-reported upper airway and eye irritation occurred after one hour of exposure to HF at 0.2-0.6 mg/m³ with 4/9 subjects reporting low symptom scores. However, the scored symptoms were not statistically significantly different comparing before-exposure reported symptoms to after-exposure reported symptoms until concentrations exceeded 2.5 mg/m³. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL. While there were no changes in FEV₁, there was a slight decrease in FVC after exposure at the medium concentration range. However, OEHHA staff did not consider the changes in FVC to be significant adverse effects since there was no dose-response relationship and they were unaccompanied by changes in FEV₁ (see Section 3.2.1.1 in main text).

Level Protective Against Severe Adverse Effects

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

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

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

Level Protective Against Life-threatening Effects

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

In contrast to the qualitative estimate of the ERPG-3, the benchmark dose (BD) approach is presented below as a quantitative derivation. Wohlslagel et al. (1976) exposed mice to varying concentrations of HF for 60-minute intervals. The 1-hour LC₅₀ value was determined to be 342 ppm (284 mg/m³) in mice. With these data, an exposure level was calculated by a BD approach using a log-normal probit analysis (Crump, 1983). The 95% LCL of the concentration expected to produce a response (in this case, lethality) rate of 5% was defined as the benchmark concentration (BC₅₀). The resulting BC₅₀ from this analysis was 204 ppm (170 mg/m³). A UF of 3 was applied to account for animal to human (interspecies) extrapolation since use of the BC accounts for some degree of variation and a UF of 10 to account for human individual variation (intraspecies extrapolation).

level protective against life-threatening effects = BC/(UF)
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

The resulting value is 6.8 ppm (5.6 mg/m³). Based on comparison with the available literature on human studies, discussed above, this value appears to be an overly protective life-threatening effect level even for sensitive subpopulations. The appropriate level is probably between 7 and 50 ppm. Since neither value appears to be entirely appropriate, we chose a single point estimate within the range of these values, the geometric mean, or 19 ppm (15.5 mg/m³), as the level protective against life-threatening effects.

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

Comparison of 1% and 5% mortality rates for HF

<table>
<thead>
<tr>
<th>Response rate</th>
<th>MLE (ppm)</th>
<th>95% LCL (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>216</td>
<td>166</td>
</tr>
<tr>
<td>5%</td>
<td>247</td>
<td>204</td>
</tr>
</tbody>
</table>

VIII. References


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


Higgins EA, Fiorca V, Thomas AA, Davis HV. Acute toxicity of brief exposures to HF, HCl, NO₂, and HCN with and without CO. Fire Technol 1972;8:120-130.


ACUTE TOXICITY SUMMARY

HYDROGEN SELENIDE

(hydrogen selenide, selenium hydride)

CAS Registry Number: 7783-07-5

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

Inhalation reference exposure level  5 μg/m³

Critical effect(s)  signs of eye and respiratory irritation in guinea pigs during exposure. (Difficulty in breathing and inactivity were observed after the exposure.)

Hazard Index target(s)  Eyes; Respiratory System

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

Description  gas

Molecular formula  H₂S

Molecular weight  80.98

Density  3.31 g/L @ 25°C

Boiling point  -41.3°C

Melting point  -65.73°C

Flashpoint  not applicable

Explosive limits  not applicable

Solubility  soluble in water, carbonyl chloride and carbon disulfide

Odor threshold  0.3 ppm (AIHA, 1989)

Odor description  garlic odor (AIHA, 1989)

Metabolites  trimethylselenonium (Palmer et al., 1970)

Conversion factor  1 ppm = 3.31 mg/m³ @ 25°C

III. Major Uses or Sources

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

The most acutely toxic selenium compound reported is hydrogen selenide (H₂Se). Hydrogen selenide is formed by the reaction of acids or water with metal selenides or by the contact of nascent hydrogen with soluble selenium compounds (Clayton and Clayton, 1982). Hydrogen selenide has no reported commercial use.
Selenium compounds are used as a decolorizing agent in the glass industry, as a vulcanizing agent in the rubber industry, in insecticides, and in photoelectric cells. Selenium compounds are also found in the toning baths used in photography and xerography. Selenium sulfide (SeS) is used in shampoos as an antidandruff agent. Up to 90% of the selenium content in ambient air is emitted during the burning of fossil fuels (Kut and Sarikaya, 1981).

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

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

IV. Acute Toxicity to Humans

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

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

Predisposing Conditions for Selenium Toxicity

Medical: Persons with preexisting eye, skin, or respiratory conditions (including allergies) may be more sensitive to the effects of exposure to H₂Se (Reprotext, 1999).

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

V. Acute Toxicity to Laboratory Animals
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

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

Signs of nasal and ocular irritation, including nasal discharge and pawing of the eyes and nose, were observed in guinea pigs exposed to 0.9-57 ppm (3-190 mg/m³) H₂Se for 60-minutes (Dudley and Miller, 1937). Decreased activity, marked difficulty in breathing, and decreased food intake were noted in those animals surviving the exposure. No significant increase in mortality as compared to controls was observed in guinea pigs exposed to 3 mg/m³ H₂Se for 1 hour. (Three of the 32 control animals died during the 30 day observation period following exposure while 1 of 16 animals exposed to either 3 or 4 mg/m³H₂Se died during the observation period).

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

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

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

VI. Reproductive or Developmental Toxicity

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

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

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

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

Reference Exposure Level (protective against mild adverse effects): 5 \( \mu \text{g/m}^3 \)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dudley and Miller, 1937; Dudley and Miller, 1941</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>groups of 16 guinea pigs; 32 controls</td>
</tr>
<tr>
<td>Exposure method</td>
<td>inhalation in a chamber</td>
</tr>
<tr>
<td>Critical effects</td>
<td>signs of eye and respiratory irritation, with persistent coughing after exposure, for several days.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOAEL</th>
<th>0.9 ppm (3 mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>not observed</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>1 hour</td>
</tr>
<tr>
<td>Extrapolated 1 hour concentration</td>
<td>0.9 ppm (3 mg/m³)</td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
<td>6</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>600</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>0.0015 ppm (0.005 mg/m³; 5 ( \mu \text{g/m}^3 ))</td>
</tr>
</tbody>
</table>

Guinea pigs exposed to 0.9 ppm (3 mg/m³) \( \text{H}_2\text{Se} \) for 1 hour exhibited acute eye and nasal irritation (indicated by pawing of the nose and eyes) during the exposure and marked difficulty breathing and decreased activity following the exposure. The range of exposure concentrations was 0.9-57 ppm (3-190 mg/m³) and a 30 day observation period followed the exposure. Nearly 100% of the animals were dead within 30 days of exposure to concentrations of \( \text{H}_2\text{Se} \) of 6 ppm (20 mg/m³) and greater. No increase in mortality was observed in animals exposed to 3 or 4 mg/m³ \( \text{H}_2\text{Se} \) compared to control animals. The LOAEL for irritant effects is 0.9 ppm (3 mg/m³) \( \text{H}_2\text{Se} \). The signs reported by the authors indicate that the irritation experience by the animals was at least moderate and may have approached a severe level.

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

Since \( \text{H}_2\text{Se} \) is reported to be the most acutely toxic selenium compound (Amdur et al., 1991), this level is considered to be protective against adverse effects from other selenium compounds as well. Use of this value for some selenium compounds will overestimate health risks. Thus, its use should be restricted to evaluating emissions of hydrogen selenide. OEHHA will continue to evaluate the literature for other selenium compounds for the development of RELs for selenium salts.
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

Level Protective Against Severe Adverse Effects

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

Level Protective Against Life-threatening Effects

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

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

VIII. References


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


ACUTE TOXICITY SUMMARY

HYDROGEN SULFIDE

(sulfur hydride; sulfuretted hydrogen)

CAS Registry Number: 7783-06-4

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

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

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

Description colorless gas
Molecular formula H₂S
Molecular weight 34.08
Density 1.39 g/L @ 25°C
Boiling point -60.7°C
Melting point unknown
Vapor pressure 1 atm @ -60.4°C
Flash point 26°C
Explosive limits upper = 4.3% by volume in air
lower = 46% by volume in air
Solubility soluble in water, hydrocarbon solvents, ether, and ethanol
Odor threshold 0.0081 ppm (Amoore and Hautala, 1983)
Odor description resembles rotten eggs
Metabolites bisulfite (HSO₃⁻), thiosulfate (S₂O₃²⁻)
(Baxter and Van Reen, 1958)
Conversion factor 1 ppm = 1.4 mg/m³ @ 25°C

II. Major Uses or Sources

Hydrogen sulfide (H₂S) is used as a reagent and an intermediate in the preparation of other reduced sulfur compounds. It is also a by-product of desulfurization processes in the oil and gas industries and rayon production, sewage treatment, and leather tanning (Ammann, 1986).
IV. Acute Toxicity to Humans

Hydrogen sulfide is an extremely hazardous gas (ACGIH, 1992). Hydrogen sulfide exposure is reported to be the most common cause of sudden death in the workplace (NIOSH, 1977). The mortality in acute hydrogen sulfide intoxications has been reported to be 2.8% (Arnold et al., 1985) to 6% (WHO, 1981). While severe intoxication is especially of concern when exposure occurs in confined spaces, an accidental release of hydrogen sulfide into the air surrounding industrial facilities can cause very serious effects. For example, at Poza Rica, Mexico 320 people were hospitalized and 22 died (WHO, 1981). An inhalation LC₅₀ of 600 and 800 ppm (840 and 1,120 mg/m³) for 30 and 5 minutes, respectively, is reported (Hazardtext, 1994). A lethal exposure was documented for a worker exposed to approximately 600 ppm H₂S for 5-15 minutes (Simson and Simpson, 1971). Inhalation of 1,000 ppm (1,400 mg/m³) is reported to cause immediate respiratory arrest (ACGIH, 1992). Concentrations greater than 200 ppm (280 mg/m³) H₂S 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 H₂S toxicity, cellular hypoxia caused by inhibition of cytochrome oxidase, is similar to that for cyanide and can be treated by induction of methemoglobin or with hyperbaric oxygen (Elovaara et al., 1978; Hsu et al., 1987).

At concentrations exceeding 50 ppm (70 mg/m³), olfactory fatigue prevents detection of H₂S odor. Exposure to 100-150 ppm (140-210 mg/m³) for several hours causes local irritation (Haggard, 1925). Exposure to 50 ppm for 1 hour causes conjunctivitis with ocular pain, lacrimation, and photophobia; this can progress to keratoconjunctivitis and vesculation of the corneal epithelium (ACGIH, 1992). Bhambhani and Singh (1991) showed that 16 healthy subjects exposed to 5 ppm (7 mg/m³) H₂S under conditions of moderate exercise exhibited impaired lactate and oxygen uptake in the blood. Bhambhani and Singh (1985) reported that exposure of 42 individuals to 2.5 to 5 ppm (3.5 to 7 mg/m³) H₂S caused coughing and throat irritation after 15 minutes.

In another study, ten asthmatic volunteers were exposed to 2 ppm H₂S 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 FEV₁ were reported. Although individual values for specific airway resistance (SRₐw) were not reported, the difference following exposure ranged from -5.95% to +137.78%. The decrease in specific airway conductance, SGₐw, ranged from -57.7% to +28.9%. The increase in mean SRₐw and the decrease in mean SGₐw were not statistically significant. However, significantly increased airway resistance and decreased airway conductance were noted in two of ten asthmatic subjects which may be biologically significant.

Hydrogen sulfide is noted for its strong and offensive odor. Based on a review of 26 studies, the average odor detection threshold ranged from 0.00007 to 1.4 ppm (Amoore, 1985). The geometric mean of these studies is 0.008 ppm. In general, olfactory sensitivities decrease by a factor of 2 for each 22 years of age above 20 (Venstrom and Amoore, 1968); the above geometric mean is based on the average age of 40.
For hydrogen sulfide, concentrations that substantially exceed the odor threshold result in the annoying and discomforting physiological symptoms of headache or nausea (Amoore, 1985; Reynolds and Kauper 1985). The perceived intensity of the odor of hydrogen sulfide depends on the longevity of the concentration, and the intensity increases 20% for each doubling concentration (Amoore, 1985). Several studies have been conducted to establish the ratio of discomforting annoyance threshold to detection threshold for unpleasant odors (Winneke, 1975; Winneke and Kastka, 1977; Hellman and Small, 1974; Adams et al., 1968; and NCASI, 1971). The geometric mean for these studies is 5, indicating that when an unpleasant odor reaches an average concentration of 5 times its detection threshold, the odor will result in annoying discomfort. Applying the 5-fold multiplier to the mean detectable level, 0.008 ppm, results in a mean annoyance threshold of 0.04 ppm. At the current California Ambient Air Quality Standard (CAAQS) of 0.03 ppm, the level would be detectable by 83% of the population and would be discomforting to 40% of the population. These estimates have been substantiated by odor complaints and reports of nausea and headache (Reynolds and Kauper 1985) at 0.03 ppm H2S exposures from geyser emissions. The World Health Organization (WHO) reports that in order to avoid substantial complaints about odor annoyance among the exposed population, hydrogen sulfide concentrations should not be allowed to exceed 0.005 ppm (7 μg/m³), with a 30-minute averaging time (WHO, 1981; National Research Council, 1979; Lindvall, 1970).

**Predisposing Conditions for Hydrogen Sulfide Toxicity**

**Medical:** Unknown

**Chemical:** Ethanol has been shown to potentiate the effects of H₂S by shortening the mean time-to-unconsciousness in mice exposed to 800 ppm (1,120 mg/m³) H₂S (Beck et al., 1979).

V. Acute Toxicity to Laboratory Animals

A median lethal concentration (LC₅₀) in rats exposed to H₂S for 4 hours was estimated as 440 ppm (616 mg/m³) (Tansy et al., 1981). An inhalation LCₐ₀ of 444 ppm for an unspecified duration is reported in rats, and a lethal concentration of 673 ppm (942 mg/m³) for 1 hour is reported in mice (RTECS, 1994). In another study, mortality was significantly higher for male rats (30%), compared to females (20%), over a range of exposure times and concentrations (Prior et al., 1988). A concentration of 1,000 ppm (1,400 mg/m³) caused respiratory arrest and death in dogs after 15-20 minutes (Haggard and Henderson, 1922). Inhalation of 100 ppm (140 mg/m³) for 2 hours resulted in altered leucine incorporation into brain proteins in mice (Elovaara et al., 1978). Kosmider et al. (1967) reported abnormal electrocardiograms in rabbits exposed to 100 mg/m³ (71 ppm) H₂S for 1.5 hours.

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

C - 182 - Hydrogen Sulfide
(p<0.05) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1-hour post-exposure compared to controls. A NOAEL of 10 ppm was identified in this study for effects on lung mitochondrial cytochrome c oxidase activity.

VI. Reproductive or Developmental Toxicity

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

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

Reference Exposure Level (protective against mild adverse effects): 42 μg/m³
(California Ambient Air Quality Standard)

| Study | California State Department of Public Health, 1969; CARB, 1984; Reynolds and Kamper, 1985; Amoore, 1985 |
| Study population | panel of 16 people; general population |
| Exposure method | inhalation of increasing concentrations of H₂S |
| Critical effects | headache, nausea |
| LOAEL | 0.012-0.069 ppm (range of odor threshold) |
| NOAEL | ≤ 0.01 ppm |

C - 183 - Hydrogen Sulfide
Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

Exposure duration not stated (tested until odor detected)

Extrapolated 1 hour concentration 0.012-0.069 ppm (geometric mean = 0.03 ppm)
(1 hour = minimum duration for an air standard)

LOAEL uncertainty factor not used

Interspecies uncertainty factor 1

Intraspecies uncertainty factor 1

Cumulative uncertainty factor 1

Reference Exposure Level 0.03 ppm (0.042 mg/m³; 42 μg/m³)

The 1-hour California Ambient Air Quality Standard (AAQS) for hydrogen sulfide was originally based on an olfactory perception study by the California State Department of Public Health (1969). Sixteen individuals were each exposed to increasing concentrations of H₂S until his or her odor threshold was reached. The range of the odor thresholds was 0.012-0.069 ppm, and the geometric mean was 0.029 ppm (geometric standard deviation = 0.005 ppm). The mean odor threshold (rounded to 0.03 ppm) was selected as the AAQS for H₂S. However, others have reported that the odor threshold is as low as 0.0081 ppm (Amoore and Hautala, 1983). In 1984 CARB reviewed the AAQS for H₂S and found that the standard was necessary not only to reduce odors, but also to reduce the physiological symptoms of headache and nausea. (CARB, 1984). Furthermore, Amoore (1985) conducted a study that estimated 40% of the population would find 0.03 ppm (0.042 mg/m³) to be an objectionable concentration. In public testimony before the ARB it was stated that some people reported headaches and other symptoms at the standard (Reynolds and Kamper, 1985). Thus this recommended level protective against mild adverse effects may be need to be reexamined as more data become available.

Level Protective Against Severe Adverse Effects

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

An ERPG-2 of 30 ppm (AIHA, 1991) was based on experimental data showing that exposure of rats to 45 ppm (63 mg/m³) H₂S for 4 hours resulted in no deaths (Rogers and Ferin, 1981). In addition, rabbits exposed to 71 ppm (100 mg/m³) H₂S for 1.5 hours developed cardiac irregularities, measured by electrocardiogram, and decreased myocardial ATP phosphorylase (Kosmider et al., 1967). The rationale for the margin of safety used for the ERPG-2 is not presented.

Level Protective Against Life-threatening Effects

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

The AIHA ERPG-3 for hydrogen sulfide of 100 ppm (AIHA, 1991) was based on case reports of conjunctivitis, respiratory irritation, and unconsciousness in humans exposed to estimated concentrations of 200-300 ppm (280-420 mg/m³) H₂S for 20 minutes to 1 hour (Ahlborg, 1951; Yant, 1930). In addition, a 1-hour LC₅₀ of 712 ppm (997 mg/m³) in rats is cited (CIIT, 1983). The case reports cited in the ERPG document are inadequate to establish acute exposure levels in humans because the concentrations and durations of exposure are only estimates. In addition,
there are no LC$_{50}$ data in the CIIT (1983) report. Rats (5 female and 5 male) exposed to H$_2$S concentrations ranging from 400-600 ppm (560-840 mg/m$^3$) 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$^3$) for only 35 minutes or less died, which suggests that primates are more sensitive to the lethal effect of H$_2$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.

VII. References


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


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


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999


Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

ACUTE TOXICITY SUMMARY

ISOPROPYL ALCOHOL

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

CAS Registry Number: 67-63-0

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

Inhalation reference exposure level 3,200 μg/m³
Critical effect(s) irritation of the eyes, nose and throat.
Hazard Index target(s) Eyes; Respiratory System

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

Description colorless liquid
Molecular formula C₃H₈O
Molecular weight 60.09
Density 0.78505 g/cm³ @ 20°C
Boiling point 82.5°C @ 760 mm Hg
Melting point -88.5°C
Vapor pressure 44.0 mm Hg @ 25°C
Flashpoint 11.7°C (closed cup)
Explosive limits upper = 12.0%
lower = 2.0%
Solubility soluble in benzene, miscible with most organic solvents,
slightly soluble in water, alcohol, and acetone
Odor threshold 19 ppm (geometric mean) (AIHA, 1989)
Odor description sharp (AIHA, 1989)
Metabolites acetone
Conversion factor 1 ppm = 2.45 mg/m³ @ 25°C

III. Major Uses or Sources

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

IV. Acute Toxicity to Humans

Symptoms of acute poisoning include dizziness, incoordination, headache, and confusion. Vomiting,
hematemesis, diarrhea, and hypotension may occur following ingestion of large quantities of isopropyl alcohol. Late manifestations include aspiration pneumonia and kidney and
liver dysfunction (Reprotox, 1993). The oral LOAEL for isopropyl alcohol is reported as 233 mg/kg (RTECS, 1993).
Irritation of the mucous membranes of the upper respiratory tract may occur following inhalation of isopropyl alcohol. Ten human subjects were exposed for 3-5 minutes to 400 or 800 ppm (1,000 or 2,000 mg/m³) isopropyl alcohol (Nelson et al., 1943). Exposure to 400 ppm isopropyl alcohol produced mild irritation of the eyes, nose, and throat. When exposed to 800 ppm the majority of the subjects declared the atmosphere unsuitable for a prolonged exposure. The subjects indicated, however, that prolonged exposure to 200 ppm would not be objectionable.

Predisposing Conditions for Isopropyl Alcohol Toxicity

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

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

V. Acute Toxicity to Laboratory Animals

A 4-hour rat LC₅₀ of 16,000 ppm (39,000 mg/m³) isopropyl alcohol is reported (Carpenter et al., 1949). Reduced ciliary activity and epithelial damage in the nasal mucosa of guinea pigs were observed following a 24-hour exposure to 400 ppm (1,000 mg/m³) isopropanol. Complete recovery from the exposure occurred within 2 weeks. Exposure at 5,500 ppm (13,000 mg/m³) resulted in similar damage requiring more than two weeks for complete recovery (Ohashi et al., 1988). A 10-minute RD₅₀ of 17,693 ppm (43,000 mg/m³) for mice has been reported (Kane at al., 1980).

VI. Reproductive or Developmental Toxicity

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Nelson et al., 1943</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>ten human subjects</td>
</tr>
<tr>
<td>Exposure method</td>
<td>400 ppm for 3-5 minutes</td>
</tr>
<tr>
<td>Critical effects</td>
<td>mild irritation of the eyes, nose and throat</td>
</tr>
<tr>
<td>LOAEL</td>
<td>400 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>200 ppm (implied)</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>4 minutes</td>
</tr>
<tr>
<td>Extrapolated 1 hour concentration</td>
<td>13 ppm (200^1 ppm * 0.067 h = C^1 * 1 h)</td>
</tr>
<tr>
<td>LOAEL uncertainty factor</td>
<td>1</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>1</td>
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<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Reference Exposure Level</td>
<td>1.3 ppm (3.2 mg/m³; 3,200 mg/m³)</td>
</tr>
</tbody>
</table>

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

Level Protective Against Severe Adverse Effects

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

A TLV-TWA of 400 ppm is reported by ACGIH (1991) based on findings by Nelson et al. (1943); the NRC-EEGL of 400 ppm is based on the TLV (NRC, 1984). However, the reported 3-5-minute exposure to 400 ppm was not extrapolated to a 1-hour equivalent by NRC. Using the...
Determination of Acute Reference Exposure Levels for Airborne Toxicants  
March 1999

equation \( C^n * T = K \), where \( n = 1 \), the equivalent 1-hour exposure is 20 ppm. This is consistent with our use of the animal studies. In addition, the recent data described above (Gill et al., 1995) were not available to ACGIH or NRC when determining these values.

**Level Protective Against Life-threatening Effects**

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

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

**VIII. References**


C - 192 - Isopropyl Alcohol


