Appendix C

Acute Toxicity Summaries

ACUTE TOXICITY SUMMARY

ACROLEIN

CAS Registry Number: 107-02-8

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

Inhalation reference exposure level   **0.19 μg/m³**
Critical effect(s)   eye irritation in healthy human volunteers
Hazard Index Target(s)   Eyes; Respiratory System

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

Description   colorless liquid
Molecular formula C_3H_4O
Molecular weight   56.1
Density   0.843 g/cm^3 @ 20°C
Boiling point   53°C
Melting point   -87°C
Vapor pressure   220 mm Hg @ 20°C
Flashpoint   -26°C
Explosive limits   2.8% - 31% by volume
Solubility   soluble in ethanol, diethyl ether, and up to
                          20% w/v in water
Odor threshold   0.5 ppm
Metabolites   glycidaldehyde, acrylic acid
Conversion factor   1 ppm in air = 2.3 mg/m³ @ 25° C

III.   **Major Uses or Sources**

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water-treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein.

IV.   **Acute Toxicity to Humans**

Exposure to 1 ppm (2.3 mg/m³) for 5 minutes causes lacrimation and irritation of the eyes, nose, and throat (IARC: Fassett, 1962). At a concentration of 7 mg/m³, acrolein causes severe lacrimation and irritation of the mucous membranes of the respiratory tract (Prentiss, 1937). A 10-minute exposure to 350 mg/m³ acrolein was lethal (Prentiss, 1937). A case report of respiratory failure and death in individuals exposed to vapors from overheated frying pans containing fat and food items implicated acrolein as the principal toxicant (Gosselin *et al*. 1979).

The lowest observed adverse effect level (LOAEL) for eye irritation in healthy human volunteers is exposure to 0.14 mg/m³ (0.06 ppm) acrolein for five minutes (Darley *et al.*, 1960).

Prolonged treatment of cancer patients with cyclophosphamide can result in hemorrhagic cystitis. The bladder toxicity is due to the formation of acrolein as a metabolite and may be prevented by co-administration of 2-mercaptoethane sulfonate (Brock *et al.*, 1979).

There is inadequate direct evidence for carcinogenicity of acrolein in experimental animals or in humans (IARC, 1985). However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats. Therefore, acrolein has been designated a Group C substance, with possible human carcinogenic potential (U.S.EPA, 1987).

Predisposing Conditions for Acrolein Toxicity

Medical: Persons with pre-existing eye, skin, respiratory, allergic, asthmatic or heart diseases might be at increased risk due to acrolein exposure. Individuals with cystic fibrosis or asthma should be excluded from acrolein exposure (Reprotext, 1999).

Chemical: Cancer patients treated with cyclophosphamide could be at increased risk because acrolein is a metabolite of cyclophosphamide (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The LC_{50} for inhalation of acrolein in rats is 300 mg/m³ for a 30-minute exposure (Fassett, 1963). An LC_{50} of 152 mg/m³ is reported in mice for a 6-hour exposure (Philippin *et al.*, 1970). An LC_{50} of 58 mg/m³ for a four-hour exposure is reported for hamsters (Kruysse, 1971). No mortality was observed in 8 rats exposed to 100 mg/m³ acrolein for 30 minutes, although heavy lacrimation and nasal secretion were reported (NTIS, 1981). An initial 35% decrease in liver alkaline phosphatase (AP) activity, followed by a 200% increase in AP activity over controls, was seen in rats exposed to 10 mg/m³ for 24 hours (NTIS, 1981). In guinea pigs, exposure to 39.6 mg/m³ for 1 hour resulted in no changes in respiratory rate, minute volume, or airway resistance (NTIS, 1981).

Roemer *et al.* (1993) exposed Male Sprague Dawley rats by inhalation to 0, 0.2 or 0.6 ppm acrolein for 6 h per day on one or three successive days. Nasal and tracheal epithelial and free lung cells were analyzed for proliferative responses using 5-bromodeoxyuridine (BrdU) labeling to identify DNA synthesizing cells. A single exposure to acrolein increased the DNA synthesizing cells 3-fold. After three exposures the increase was distinctly lower. All sites analyzed showed approximately the same concentration/response pattern. Since significant changes in cell proliferation were detected at 0.2 ppm acrolein, it is a LOAEL for this experiment.

Acrolein depletes glutathione (GSH) and other free thiol groups both in vitro and in vivo (WHO, 1992). Exposure of rats to a concentration of 11.4 mg/m³ for 3 hours caused irreversible depletion of GSH in the nasal mucosa. In addition, ^{14}C-labeled acrolein has been shown to bind irreversibly to sulfhydryl groups on cytochrome P450 in rats (WHO, 1992). The binding of

acrolein to sulfhydryl groups is localized to the area of contact (e.g., nasal membranes or lung epithelium), and is not a systemic effect (WHO, 1992).

VI.   Reproductive or Developmental Toxicity

In rats, acrolein can induce teratogenic and embryotoxic effects when administered directly into the amniotic fluid, or when added to cultured rat embryos (ReproText, 1999; Slott and Hales, 1986). Additionally, acrolein injected into chicken embryos resulted in embryotoxicity and some teratogenic effects at moderate to high doses (0.001-0.1 mg/egg) (Chhibber and Gilani, 1986). However, intravenous exposure to 3 mg/kg in pregnant rabbits showed no developmental effects in the offspring (WHO, 1992). Based on this latter study, the World Health Organization (1992) concluded that human exposure to acrolein was unlikely to affect the developing embryo.

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

Reference Exposure Level (protective against mild adverse effects):   0.09 ppb (0.19 μg/m³)

Study	Darley *et al*., 1960
Study population	36 healthy human volunteers
Exposure method	5 minute exposures to 0.06 ppm; carbon-filter respirators worn during exposure
Critical effects	subjective reports of eye irritation
LOAEL	0.06 ppm
NOAEL	not observed
Exposure duration	5 minutes
Extrapolation to 1 hour	$C^n * T = K$, where n = 1 (Ten Berge *et al*., 1986)
Extrapolated 1 hour concentration	0.005 ppm (5 ppb)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	0.09 ppb (0.19 μg/m³)

Only volunteers without a prior history of chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. There is significant uncertainty in this calculation because of the lack of a NOAEL and the short exposure duration (5 min) in the study.

Level Protective Against Severe Adverse Effects

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

Forty-six human subjects (21 male and 25 female) were exposed to 0.3 ppm (0.69 mg/m³) acrolein for 1 hour (Weber-Tschopp *et al*., 1977). Effects included significant irritation of the eyes, nose, and throat. A decrease in respiratory rate of 10% was evident in 47% of the subjects

after 10 minutes of exposure. Based on this information the National Academy of Sciences decided that the previous EEGL of 0.2 ppm was not sufficiently protective, and it was changed to 0.05 ppm (0.115 mg/m³). The NAS-EEGL for acrolein was determined by an expert panel and the details governing the selection of a margin of safety are not presented by NAS. Lack of data on 1-hour exposures of humans to lower concentrations of acrolein prevented NAS from deriving a definitive EEGL for a 1-hour exposure. Therefore, no recommendation can be made.

Level Protective Against Life-threatening Effects

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

LC_{50} data in mice, guinea pigs, rabbits, and rats ranged from 8-25 ppm (18.4 - 57.5 mg/m³) acrolein (Carpenter *et al*., 1949; Pattle and Cullumbine, 1956; Kruysse, 1971). Based on these animal lethality studies, a value of 3 ppm (6.9 mg/m³) was chosen by AIHA as the life-threatening level (AIHA, 1989). The methodology employed by AIHA to develop the margin of safety for the ERPG-3 for acrolein is not presented in the ERPG document. NIOSH (1995) lists a revised IDLH of 2 ppm based on several reports of acute inhalation toxicity in healthy humans for exposure periods of 10 minutes or less to 1.8-8 ppm acrolein. There is no formal protocol for its derivation and no consideration of sensitive subpopulations. Therefore, no recommendation can be made for a level protective against life-threatening effects.

VIII.   References

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ACUTE TOXICITY SUMMARY

ACRYLIC ACID

CAS Registry Number: 79-10-7

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

Inhalation reference exposure level	**6,000 μg/m³**
Critical effect(s)	nasal irritation
Hazard Index target(s)	Respiratory System; Eyes

II.   Physical and Chemical Properties (HSDB, 1994)

Description	colorless liquid
Molecular formula	$C_3H_4O_2$
Molecular weight	72.06
Density	1.0497 g/cm^3 @ 20°C (liquid)
Boiling point	141°C
Melting point	14°C
Vapor pressure	52 mm Hg @ 20°C
Flashpoint	54°C, open cup
Explosive limits	unknown
Solubility	soluble in benzene and acetone; miscible with water, alcohol and several ethers.
Odor threshold	0.06 ppm-1.0 ppm
Odor description	acrid, irritating
Metabolites	carbon dioxide and a short chain fatty acid (possibly 3-hydroxypropionic acid)
Conversion factor	1 ppm in air = 2.95 mg/m³

III.   Major Uses and Sources

The most common industrial production process is the oxidation of acrolein, which is then further oxidized to acrylic acid. Acrylic acid is used in the manufacture of plastics, molding powder for signs, construction units, decorative emblems and insignias, emulsion in polymers, paint formulations, leather finishing and paint coatings.

IV.   Acute Toxicity to Humans

Acrylic acid vapors have been reported to cause nasal and eye irritation in workers, although no concentrations were given in these reports (ACGIH 1986, 1991). Contact with the liquid may produce skin and eye burns and blindness.

Predisposing Conditions for Acrylic Acid Toxicity

Medical: Persons with severe uncorrected vision or chronic lung disease may be at increased risk for the adverse effects of acrylic acid (HSDB, 1994).

Chemical: Acrylic acid is a skin sensitizing agent as determined by the guinea pig maximization test, but not by the Draize test (ACGIH, 1991). This finding may indicate a sensitizing potential of acrylic acid in humans.

## V.	Acute Toxicity to Laboratory Animals

Inhalation exposure of rats to 2,000 ppm (6,000 mg/m³) acrylic acid for 4 hours resulted in no mortality (Carpenter *et al*., 1974). All animals (6) died at twice this concentration (4,000 ppm). An inhalation LC_{50} of 1,200 ppm (3,500 mg/m³) acrylic acid was determined for rats exposed for 4 hours (Majka *et al*., 1974).

In rats exposed to acrylic acid aerosol for 30 minutes, the LC50 is 8,612 ppm (25,400 mg/m³) and the LC_{01} is 1,203 ppm (3,550 mg/m³) (Hagan, 1988). For a 60-minute exposure the LC_{50} is 3,750 ppm (11,100 mg/m³) and the LC_{01} is 2,180 ppm (6,430 mg/m³); for a 2-hour exposure, the LC_{50} is 2,502 ppm (7,381 mg/m³) and the LC_{01} is 928 ppm (2,740 mg/m³). Treatment related signs of toxicity included eye squinting, lacrimation, rhinorrhea, salivation, gasping, difficulty in breathing and corneal opacities. In addition to these signs, following the 2-hour exposure, rales, loss of righting reflex, ataxia, lethargy and prostration were reported. Rats exposed to acrylic acid vapors ranging from 928 to 2,142 ppm (2,740 to 6,319 mg/m³) for 60 minutes showed signs similar to the animals exposed at the same concentrations of aerosol. However, unlike the aerosol, recovery was more rapid and no deaths occurred following exposure to vapors.

A single 5-hour exposure to 6,000 ppm (18,000 mg/m³) acrylic acid in rats produced nasal and eye irritation, respiratory difficulties, unresponsiveness and death in 1 of 4 animals (Gage, 1970). An autopsy revealed lung hemorrhage and degeneration of the liver and kidney tubules. Four 6-hour exposures to 1,500 ppm (4,400 mg/m³) in 8 animals produced nasal discharge, lethargy, weight loss and congested kidneys. Nasal irritation, lethargy and reduced weight gain were observed after twenty 6-hour exposures at 300 ppm (900 mg/m³). Histopathological examination showed no damage to tissues. No toxic signs were observed in 8 rats exposed 20 times to 80 ppm (240 mg/m³) for 6 hours.

Histologic examinations were performed in ten rats and ten mice exposed to acrylic acid vapor 6 hours per day, 5 days per week for 2 weeks at 25, 75, and 225 ppm (74, 220, and 664 mg/m³) (Miller *et al*., 1981). At 25 ppm, very slight olfactory tissue effects (unspecified) were observed in mice. Slight focal degeneration of the olfactory tissue without metaplasia was found in mice at 75 ppm. No adverse effects were noted in rats at this dose. Labored breathing and apparent nasal irritation during exposure occurred in mice exposed to 225 ppm. Slight focal squamous metaplasia of the olfactory epithelium was observed in both rats and mice at this concentration. The investigators noted that since rodents are obligate nasal breathers, irritation of the nasal mucosa was likely to be pronounced in these animals. Majka *et al*. (1974) observed that exposure of rats to 240 ppm (710 mg/m³) acrylic acid, 4 hours per day for 5 weeks resulted in

reduced body weight gain, increased reticulocyte count, and irritation with irreversible changes to the skin and eyes.

The instillation of 0.5 ml of a 1% solution of acrylic acid caused severe irritation and corneal burns in the eyes of rabbits (Union Carbide Corp., 1977).

VI.   Reproductive or Developmental Effects

Four groups of 5 female rats were injected intraperitoneally with 2.5, 4.7, or 8 mg/kg body weight acrylic acid three times on days 5, 10, and 15 of gestation (Singh *et al*., 1972). Skin abnormalities (hemangiomas) were observed in the offspring of animals from the two highest dose groups. Skeletal abnormalities and embryotoxicity were observed in the litter from the highest dose group.

DePass *et al*. (1983) conducted a one-generation reproduction study in rats. Animals were exposed to doses ranging from 83 to 750 mg/kg/day acrylic acid in the drinking water throughout gestation and lactation. No statistically significant changes in reproductive indices were observed.

Pregnant rats were exposed via inhalation to concentrations of acrylic acid ranging from 40 to 360 ppm (120-1,060 mg/m³) on days 6 through 15 of gestation (Klimisch *et al*., 1983). Decreased body weight and feed consumption were observed in the dams exposed to 120 or 360 ppm acrylic acid. No embryotoxic or teratogenic effects were observed.

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

Reference Exposure Level (protective against mild adverse effects):
                                             2 ppm (6,000 μg/m³)

Study	Gage, 1970
Study population	groups of 4-8 rats
Exposure method	inhalation
Critical effects	nasal irritation
LOAEL	300 ppm
NOAEL	80 ppm
Exposure duration	6 hours/day (on 20 occasions)
Extrapolation to 1 hour	$C^n * T = K$, where $n = 2$
	(ten Berge *et al*., 1986)
Extrapolated 1 hour concentration	200 ppm (80^2ppm $* 6$ h $= C^2 * 1$ h)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	2 ppm (6 mg/m³; 6,000 μg/m³)

Level Protective Against Severe Adverse Effects

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

Slight focal degeneration of the olfactory tissue was observed in mice exposed to 75 ppm (225 mg/m³) acrylic acid, 6 hours per day for 10 days (Miller *et al*., 1981). An ERPG-2 of 50 ppm (150 mg/m³) was recommended based on this study (AIHA, 1991). The AIHA document stated that strong odors and slight eye irritation may be present at this level but that escape would not be impaired. The document incorrectly states that no effects were seen at 75 ppm. Because no safety factors were used in the derivation of this value, it should be reevaluated. Therefore, no recommendation can be made.

Level Protective Against Life-threatening Effects

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

NIOSH does not list an IDLH for acrylic acid. An acute inhalation study in rats determined a 1-hour LC_{01} of 2,180 ppm (6,430 mg/m³) acrylic acid aerosol (Hagan, 1988). In addition, no deaths were observed in rats exposed for 6 hours per day for 4 days to 1,500 ppm (4,400 mg/m³) acrylic acid (Gage, 1970). AIHA (1991) derived an ERPG-3 value of 763 ppm (2,250 mg/m³). Because the ERPG-3 value was based on a personal communication (Hagan, 1988) with little supporting documentation, no recommendation can be made.

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ACUTE TOXICITY SUMMARY

AMMONIA

(anhydrous ammonia, aqueous ammonia)

CAS Registry Number: 7664-41-7

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

Inhalation reference exposure level **3,200 μg/m³**
Critical effect(s) eye and respiratory irritation
Hazard Index target(s) Eyes; Respiratory System

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

Description	colorless gas
Molecular formula	NH_3
Molecular weight	17.03
Density	0.695 g/L @ 25°C
Boiling point	-33.5°C
Melting point	-77.7°C
Vapor pressure	6,460 mm Hg @
Flashpoint	unknown
Explosive limits	unknown
Solubility	very soluble in water, alcohol and ether
Odor threshold	17 ppm (geometric mean) (AIHA, 1989)
Odor description	sharp and very irritating
Metabolites	unknown
Conversion factor	1 ppm = 0.71 mg/m³ @ 25°C

III. Major Uses or Sources

Ammonia is a strongly alkaline chemical which is widely used in industry as a feed stock for nitrogen based chemicals such as fertilizers, plastics and explosives (ATSDR, 1990). Nationwide, ammonia is the third most common chemical to be released accidentally (U.S.EPA, 1989). Among hazardous material incidents such as intentional and threatened releases, those involving ammonia are the sixth most common. The volatility of ammonia, along with its common method of storage as large quantities under pressure, results in a potential for release of large amounts of ammonia gas (NRC, 1987).

IV.   Acute Toxicity to Humans

Ammonia vapors cause irritation of the eyes and respiratory tract. Higher concentrations cause conjunctivitis, laryngitis, and pulmonary edema, possibly accompanied by a feeling of suffocation (OSHA, 1989). Contact with the skin causes burns and blistering. The eye is especially sensitive to alkali burns. Ammonia combines with moisture in the eyes and mucous membranes to form ammonium hydroxide. Ammonium hydroxide causes saponification and liquefaction of the exposed, moist epithelial surfaces of the eye and can easily penetrate the cornea and damage the iris and the lens (CCOHS, 1988; Way *et al*., 1992). Damage to the iris may eventually lead to cataracts (CCOHS, 1988). Inhalation exposure to ammonia may result in an increase in systemic arterial blood pressure (Zitnik *et al*., 1969). Exposure can also cause a decrease in minute ventilation volume (Cole *et al*., 1977). Ammonia gas is especially irritating to upper respiratory passages, which prompts exposed victims to attempt escape from the fumes as quickly as possible. MacEwen and Vernot (1972) described pulmonary edema as the most frequent cause of death in humans exposed to ammonia.

Silverman and coworkers (1949) exposed 7 volunteers to 500 ppm (355 mg/m³) ammonia for 30 minutes using an oral-nasal mask. Symptoms due to ammonia inhalation varied widely among the 7 subjects. All seven subjects experienced upper respiratory irritation, which was graded as severe in 2 subjects. Only 2 subjects were able to continue nasal breathing throughout the 30 minute exposure. Reactions included irritation of the nose and throat, hypoesthesia of the exposed skin, and lacrimation. In two subjects, the nasopharyngeal irritation persisted for 24 hours after the exposure. One of the 7 subjects was only exposed to ammonia for 15 minutes rather than the full 30 minutes. The reason for this deviation in the exposure regimen was not given. In a previous experiment, brief exposure to 1,000 ppm reportedly resulted in immediate coughing in human subjects.

Ferguson and coworkers (1977) used six human subjects to demonstrate that a tolerance to ammonia exposure of 100 ppm (71 mg/m³) can be developed with a two-to-three week inurement period during which volunteers were exposed to lesser concentrations. The results tended to support the belief that persons with no recent history of ammonia exposure are more sensitive to the irritating effects than those who are acclimated to the noxious gas.

Verberk (1977) exposed sixteen subjects, eight previously exposed and eight naive, for two hours to ammonia in concentrations of 50, 80, 110, and 140 ppm (36, 57, 78, 99 mg/m³). The naive group could not tolerate 140 ppm for two hours and had several complaints during exposure to 110 ppm for 1 hour. None of the subjects in the study demonstrated a decrease in measured pulmonary function tests, including vital capacity, forced expiratory volume (1 second), and forced inspiratory volume (1 second), following ammonia exposure. The results showed a greater sensitivity to ammonia exposure for the naive group for responses of smell, eye irritation, cough, general discomfort, headache, and irritation of the chest. At the end of the initial 30 minutes of the 2-hour exposure period, nuisance level smell, eyes, nose, or throat irritation, or cough urge were reported by 7 of 16 (44%), 9 of 16 (56%), 12 of 16 (75%), or 15 of 16 (94%) individuals at concentrations of 50, 80, 110, or 140 ppm, respectively.

MacEwen *et al*. (1970) exposed groups of 5 and 6 human subjects to respective ammonia concentrations of 30 and 50 ppm (21 and 36 mg/m³). The volunteers subjectively rated irritation for the 10-minute exposures. No moderate or higher irritation was discerned by the group at the lower exposure level; however, 4 of the 6 subjects rated the 10 minute exposure at 50 ppm as causing moderate irritation.

The Industrial Bio-Test Laboratories (1973) evaluated ten human subjects for the irritation threshold of ammonia from exposures to ammonia gas at four different concentrations: 32, 50, 72, and 134 ppm (23, 36, 51, and 95 mg/m³). Irritation was taken to be any annoyance to the eyes, nose, mouth, throat, or chest which persisted throughout the 5-minute exposure period. At 72 ppm three subjects experienced eye irritation, two had nasal irritation, and three had throat irritation. At 134 ppm, five of the ten subjects experienced lacrimation and eye irritation, seven complained of nasal irritation, eight had throat irritation, and one experienced chest irritation. The authors only used 5-minute exposure durations; and it is possible that irritation symptoms could have developed with longer exposure durations at the lower exposures. The authors discounted the significance of nasal dryness reported at the two lowest levels.

Douglas and Coe (1987) determined a lachrymatory threshold of 55 ppm for ammonia following approximately 15 second exposures of volunteers via tight-fitting goggles. The threshold for bronchoconstriction, determined as a 20% increase in airway resistance, was slightly higher at 85 ppm following 10 breaths of ammonia via mouthpiece.

Estimates of odor thresholds for ammonia vary from 0.04-103 ppm (0.03-73 mg/m³) (Ferguson *et al*., 1977; Henderson and Haggard, 1943; Ruth, 1986). Near the odor threshold, persons exposed to ammonia can experience annoyance and believe the odor to be a nuisance. Exposure to ammonia may result in an exacerbation of preexisting asthma. Shim and Williams (1986) surveyed 60 patients with a history of asthma worsened by certain odors. Nearly 80% of these patients claimed to have an exacerbation of asthma following exposure to household cleaners containing ammonia.

Predisposing Conditions for Ammonia Toxicity

Medical: Persons with asthma and other respiratory ailments including underlying cardiopulmonary disease (Shim and Williams, 1986) and persons with no tolerance, developed from recent exposures to ammonia (Ferguson *et al*. 1977), may be more susceptible to the toxic effects of ammonia.

Chemical: Chronic high dose aspirin therapy and therapy with valproic acid elevate blood ammonia levels (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

The pulmonary lesions observed following acute, potentially lethal, inhalation of ammonia are similar in man and experimental animals (Withers, 1986; Payne *et al*., 1990). Male rats and mice were determined to be more sensitive to the lethal effects of ammonia than the females of either species (Appelman *et al*., 1982; Stupfel *et al*., 1971).

Several animal lethality studies published dose-response data from which the MLE_{05} (maximum likelihood estimate corresponding to 5% lethality) and BC_{05} (benchmark dose at the 95% lower confidence interval of the MLE_{05}) could be determined (see Table 1).

Table 1. Animal Lethality Effective and Benchmark Dose Levels for Ammonia

Reference	Species	Time (min)	MLE_{05} (ppm)	BC_{05} (ppm)
MacEwen & Vernot (1972)	rat	60	5,999	4,908
MacEwen & Vernot (1972)	mouse	60	4,006	3,406
Kapeghian *et al*. (1982)	mouse	60	3,664	3,366
Appelman *et al*. (1982)	rat	(10)*	11,862	9,950
Appelman *et al*. (1982)	rat	(20)*	13,010	10,206
Appelman *et al*. (1982)	rat	(40)*	11,137	4,881
Silver and McGrath (1948)	mouse	(10)*	2,846	2,298

* *Exposure time was adjusted to 60 min using a modification of Haber's Law to facilitate comparisons of MLE_{05} and BC_{05} values. Exponent n = 2 was determined, based on Appelman et al. (1982) rat lethality data, by varying the term in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983).*

Appelman *et al*. (1982) observed signs of restlessness, wet noses and nasal discharge in rats immediately after the start of inhalation exposure to ammonia. Mouth breathing and dyspnea occurred soon after the start of exposure. Eye discharge began about 30 minutes into the exposure, and signs of eye irritation after 60 minutes of exposure. Dose versus exposure time varied from 7,000 ppm (4,970 mg/m³) for 60 minutes to 26,850 ppm (19,064 mg/m³) for 10 minutes.

VI.   Reproductive or Developmental Toxicity

There are no confirmed studies which show conclusively that reproductive or developmental toxicity can be linked experimentally or epidemiologically to ammonia exposure (Reprotext, 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):   3,200 $\mu g/m^3$

Study	Industrial Biotest Laboratories, 1973; MacEwen *et al.*, 1970; Silverman *et al.*, 1949; Verberk, 1977
Study population	humans
Exposure method	inhalation
Critical effects	eye and respiratory irritation
LOAEL	varied (see Section IV of text)
NOAEL	varied (see Section IV of text)
Exposure duration	varied (see Section IV of text)
Extrapolated 1 hour concentration	13.6 ppm (BC_{05})
LOAEL uncertainty factor	not needed in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Reference Exposure Level	4.5 ppm (3.2 mg/m³; 3,200 $\mu g/m^3$)

The exposure concentrations from the 4 studies were adjusted to 1-hour durations using the formula $C^n \times T = K$ (Table 2). The value for the exponent n was empirically derived from the preceding data sets. The value of n (in the formula $C^n \times T = K$) was sequentially varied for the log-normal probit relationship analysis. Using a chi-square analysis, a value of n = 4.6 was found to be the best fit.

The REL was calculated by a benchmark concentration (BC) approach using a log-normal probit analysis (Crump and Howe, 1983; Crump. 1984). The 95% lower confidence limit of the concentration expected to produce a response rate of 5% is defined as the BC_{05}. The maximum likelihood estimate for a 5% response was 20.1 ppm and the 95% LCL on this value (BC_{05}) for ammonia from this analysis was 13.6 ppm.

Response rate	MLE (ppm)	95% LCL (ppm)
1%	13.4	7.8
5%	20.1	13.6 (BC_{05})

An uncertainty factor (UF) of 3 was used to account for intraspecies variation in the human population. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Table 2. Ammonia, Human Irritation, 60 Minute Exposures (adjusted), ppm

Study Concentration	32	30	50	50	72	50	80	134	110	140	500
Exposure Time (min.)	5	10	5	10	5	120	120	5	60	60	30
60 min. adjusted Concentration	19	20	29	34	42	43	69	78	95	120	430
Response	0/10	0/5	0/10	4/6	3/10	7/16	9/16	8/10	12/16	15/16	7/7
Study	2	3	2	3	2	1	1	2	1	1	4

Table adapted from: (1) Verberk, 1977; (2) Industrial Biotest Laboratories, 1973; (3) MacEwen et al., 1970; (4) and Silverman et al., 1949. The two lowest concentrations were combined for the log-probit analysis since this improved the fit of the data.

Level Protective Against Severe Adverse Effects

Exposure to 140 ppm (99.4 mg/m³) ammonia was considered 'unbearable' resulting in termination of exposure by all of 8 non-expert student volunteers after 30 to 75 minutes (Verberk, 1977). These exposures were tolerated for the full 2-hour exposure period by all 8 expert volunteers who were familiar with irritant vapors. Based on these findings in which ammonia inhalation resulted in a subjective response of panic or the need in naive subjects to take shelter, a 2-hour NOAEL of 110 ppm and a 30-minute LOAEL of 140 ppm were noted. Short exposures to ammonia did not result in increased nasal resistance of atopic subjects when compared to nonatopic subjects (McLean *et al*., 1979). The non-expert group was considered to be more like the general public in their response. The final value to protect against severe adverse effects from ammonia exposure is thus 110 ppm (78 mg/m³).

Level Protective Against Life-threatening Effects

Kapeghian *et al*. (1982) determined a 1-hour LC_{50} of 4,230 ppm and a 1-hour no observed lethality level of 3,440 ppm in male mice. The MLE_{05} and BC_{05} were estimated as 3,664 and 3,366 ppm (Table 1), respectively. The report by Kapeghian *et al*. (1982) provides one of the most detailed exposure and monitoring methods used for ammonia among the various animal lethality reports reviewed. In addition, a sensitive experimental animal species was used for the experiments (MacEwen & Vernot, 1972). An uncertainty factor of 1 was applied to account for animal to human extrapolation since (1) the BC accounts for some degree of variation and (2) OEHHA's comparison of human irritation thresholds with concentrations lethal to mice suggests humans are not more susceptible than mice to ammonia toxicity. That is, in examining the Verberk (1977) study and comparing it to the mouse lethality study, additional uncertainty factors to the mouse study results in a concentration below the Verberk (1977) human study. A factor of 10 was applied to account for individual human variation. The cumulative uncertainty factor was 10. The resulting level for ammonia to protect against life-threatening effects is 340 ppm (240 mg/m³).

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IX. Graphic Representation of Benchmark Concentration Determination
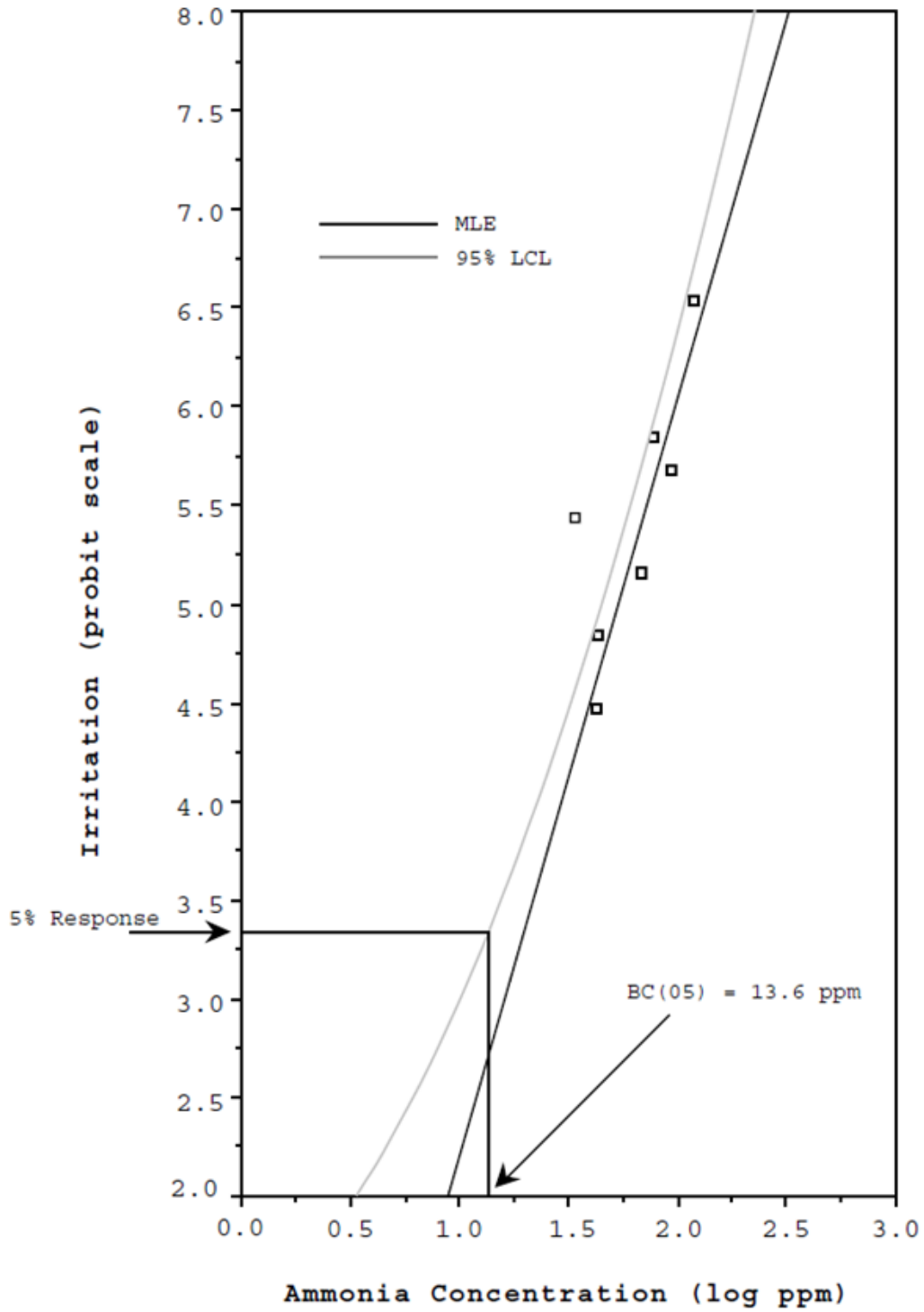
ACUTE TOXICITY SUMMARY

ARSENIC AND INORGANIC ARSENIC COMPOUNDS

Molecular formula	Molecular weight	Percent As by weight	Synonyms	CAS Registry Number
As	74.92	100%	arsenic black, metallic arsenic	7440-38-2
As_2O_3	197.82	75.7%	arsenious acid, crude arsenic, white arsenic	1327-53-3
$AsCl_3$	181.28	41.3%	arsenic butter, trichloroarsine, arsenious chloride	7784-34-1
As_2O_5	229.82	65.2%	arsenic anhydride, arsenic oxide, arsenic acid anhydride	1303-28-2
$AsH_3Na_2O_4$	185.91	40.3%	arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	7778-43-0
$AsHNaO_2$	130.92	57.2%	arsenous acid disodium salt, arsenious acid sodium salt	7784-46-5

I.   Acute Toxicity Summary (for a 4-hour exposure)

Inhalation reference exposure level **0.19 μg As/m³**
Critical effect(s)   decreased fetal weight in mice
Hazard Index target(s)   Reproductive/developmental

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

Description   yellow, black or gray solid
Density   As: 5.727 g/cm³ @ 14°C
                                 $AsCl_3$: 2.16 g/cm³ @ 25°C
Boiling point   613°C (sublimes) (ACGIH, 1991)
Melting point   sublimes (see boiling point)
Vapor pressure   760 mm Hg @ 372° C
Flashpoint   not applicable
Explosive limits   not applicable
Solubility   soluble in nitric acid, insoluble in water (salts and
                                 oxides are soluble in water)
Odor threshold   not applicable
Odor description   not applicable

Metabolites	dimethylarsinic acid, methylarsonic acid
Conversion factor	not applicable for As;
	$AsCl_3$: 1 ppm = 7.41 mg/m³

III. Major Uses or Sources

Arsenic is ubiquitous and is found in small amounts in soils and water throughout the world and also in foods, particularly seafood (NIOSH, 1976). Ore refining processes, including the smelting of copper and lead, are the major sources of release of arsenic dust and inorganic arsenic compounds. Arsenic trioxide is the form of inorganic arsenic most commonly produced. It is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds (Kirk-Othmer, 1978).

Pesticides constitute the largest single use (50%) of arsenic compounds (HSDB, 1993). The major arsenic herbicides manufactured are monosodium methyl arsonate (MSMA), disodium methyl arsonate (DSMA), and dimethyl arsenic acid (cacodylic acid). Inorganic arsenic compounds are also used as herbicides (arsenite), insecticides (calcium and other arsenates), or rodenticides (sulfides) (ACGIH, 1991). Arsenic trichloride, for example, is used mainly as a chemical intermediate in the production of insecticides, but has other applications in the ceramics and pharmaceutical industries (HSDB, 1993). Arsenic is used as a pesticide to treat tobacco; thus, cigarette smoke is another common source of exposure (U.S.EPA, 1984).

Arsenic-based wood preservatives constitute the next largest use (40%) of arsenic compounds (HSDB, 1993). Arsenic pentoxide is used in the manufacturing of colored glass and as an insecticide and soil fumigant, but its major use is in formulated wood preservatives (HSDB, 1993).

The glass and electronic industries are also consumers of arsenic compounds. In the manufacture of semiconductors, elemental arsenic is alloyed with gallium and other heavy metals (HSDB, 1993). Several arsenic compounds are used in the production of colored glass.

The highly toxic trivalent arsenic compounds, such as arsenic trioxide, are typically introduced into the environment as a result of industrial processes including the smelting of metal ores. Pentavalent arsenic compounds are generally considered to be less toxic and are most frequently found naturally.

IV. Acute Toxicity to Humans

The relative toxicity of arsenic compounds decreases as follows: arsine(III) > organo-arsine derivatives > arsenites(III) > arsenoxides(III) > arsenates (V) > pentavalent organic compounds (V) > arsonium metals (I) > metallic arsenic (0), where the Roman numeral indicates the oxidation state (HSDB, 1993).

Acute inhalation exposure may result in severe irritation of the mucous membranes of the upper and lower respiratory tract with symptoms of cough, dyspnea, and chest pain (Friberg *et al*., 1986). These may be followed by garlicky breath and gastrointestinal symptoms including

vomiting and diarrhea (HSDB, 1993). Signs of acute poisoning are dermatitis, nasal mucosal irritation, laryngitis, mild bronchitis, and conjunctivitis (Friberg *et al*., 1986). The acute toxic symptoms of trivalent arsenic poisoning are due to severe inflammation of the mucous membranes and increased permeability of the capillaries (HSDB, 1993). Inorganic arsenic compounds are easily absorbed through the skin; the trivalent is more rapidly absorbed than the pentavalent (Reprotext, 1999).

Ingestion of 2 g of As_2O_3 was fatal to an adult male (Levin-Scherz *et al*., 1987). Populations on the southern coast of Taiwan, chronically exposed to variable high concentrations of arsenic (0.10-1.81 ppm) in deep-well water used for drinking, exhibit an endemic peripheral vascular disorder named "blackfoot disease" (Yu *et al*., 1984). This condition results in gangrene of the extremities, especially the feet.

Predisposing Conditions for Arsenic Toxicity

Medical: Persons with skin or respiratory conditions, including allergies, may be more sensitive to the toxic effects of arsenic (HSDB, 1993).

Chemical: Persons with higher than normal intakes of arsenic, including smokers and fish and shellfish eaters, may be more sensitive to toxic effects following arsenic exposure (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

The LC_{Lo} for $AsCl_3$ in the cat for a 20 minute inhalation exposure is 100 ppm (740 mg/m³) (Flury, 1921). In the mouse, the LC_{Lo} of $AsCl_3$ for a 10 minute exposure is 338 ppm (2500 mg/m³) (Flury, 1931).

Mortality in mice challenged with aerosolized streptococci following a 3-hour exposure to 123-940 μg As/m³ (in an arsenic trioxide aerosol) increased in a dose-related manner with increasing concentrations of As_2O_3 (Aranyi *et al*., 1985). Pulmonary bactericidal activity (type unspecified) was significantly decreased in all mice exposed for a single 3-hour period to concentrations greater than 123 μg As/m³. No adverse effects were observed following a single 3-hour exposure to 123 μg As/m³.

A single intratracheal instillation of 17 mg As_2O_3/kg in rats resulted in multifocal interstitial pneumonia and focal proliferative bronchiolitis and alveolitis observed at necropsy 14 days post-exposure (Webb *et al*., 1986). The authors suggest (but do not confirm) that As_2O_3 induced an acute fibrogenic response.

VI.   Reproductive or Developmental Toxicity

Arsenic is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. The oxidation state of arsenic determines the teratogenic potential of its inorganic compounds; trivalent (III) arsenic

compounds possess greater teratogenic potential than pentavalent (V) compounds. In hamsters, a single maternal intravenous injection of 20 mg/kg sodium arsenate (V) ($AsH_3Na_2O_4$) on gestation day 8 was lethal to 44% of all embryos (Willhite and Ferm, 1984). A smaller dose (10 mg/kg) of sodium arsenite (III) ($AsHNaO_2$) administered in the same manner resulted in 90% embryonic lethality.

Fetal malformations, including exencephaly, resulted from an intravenous injection of $AsH_3Na_2O_4$ (V) into pregnant hamsters on gestation day eight (Ferm and Carpenter, 1968). The reproductive NOAEL in this experiment was 5 mg/kg. A significant reduction in fetal body weight, but no malformations were observed following a maternal dose of 5 mg/kg $AsHNaO_2$ (III) by the same route on gestation day eleven or twelve (Harrison and Hood, 1981).

A significant increase in pre-implantation mortality followed exposure of pregnant rats to aerosolized As_2O_3 at 1 mg/m³ for 5 months; no maternal toxicity was observed (Kamkin, 1982). At the LOAEL, 0.3 mg/m³, slightly elevated pre-implantation lethality was observed. The validity of this report cannot be evaluated, however, because key experimental details were not reported

Pregnant mice were exposed to 0.26, 2.9, or 28.5 mg/m³ As_2O_3 for four hours per day on days 9-12 of gestation (Nagymajtenyi *et al*., 1985). A significant dose-related decrease in fetal weight was observed in the offspring of exposed dams. Dose-related increases in hepatocellular chromosomal damage were observed in all exposed groups; in the highest dose group the chromosomal damage was statistically significantly different from the control. The percent of dead fetuses per dose group also increased in a dose-related manner. Maternal toxicity was not reported

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to As_2O_3 at a concentration of 40 mg/m³ for 48 hours (Kamil'dzhanov, 1982). Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggests that long term exposure of sperm may occur *in vivo* following acute exposure to As (Danielsson, 1984).

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

Mild Adverse Effect Level

Because the most sensitive endpoint found in the literature was reproductive toxicity which is a potentially disabling, severe adverse effect, a discomfort or mild adverse effect level is not recommended.

Reference Exposure Level for a 4 hour exposure (protective against severe adverse effects):
0.19 µg As/m³

Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

Because of the uncertainty of extrapolating from repeated dose studies to a one-hour concentration, for the reproductive endpoint we have chosen to use one-day's exposure regimen as a basis for the REL. Thus, for arsenic, this REL is for a 4-hour exposure.

Study	Nagymajtenyi *et al*., 1985
Study population	pregnant mice
Exposure method	maternal inhalation exposure for 4 hours on gestation days 9, 10, 11, and 12
Critical effects	decreased fetal weight
LOAEL	0.26 mg/m³ As_2O_3 (0.19 mg As/m³)
NOAEL	not determined in this study
Exposure duration	4 hours per day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Reference Exposure Level	0.00019 mg As/m³ (0.19 µg As/m³)

Level Protective Against Life-threatening Effects

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

NIOSH lists a revised IDLH of 5 mg/m³ on the NIOSH web site (http://www.cdc.gov/niosh), which is derived from an oral lethality study of calcium arsenate in dogs.

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ACUTE TOXICITY SUMMARY

ARSINE

(arsenic hydride, arsenic trihydride, hydrogen arsenide)

CAS Registry Number: 7784-42-1

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

Inhalation reference exposure level	**160 μg/m³**
Critical effect(s)	hemolysis of red blood cells
Hazard Index target(s)	Hematologic

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

Description	colorless gas
Molecular formula	AsH_3
Molecular weight	77.93
Density	2.695 g/L @ 25°C
Boiling point	-55°C
Melting point	-117°C
Vapor pressure	11,000 mm Hg @ 25°C
Flashpoint	not applicable
Explosive limits	upper = 78 % by volume in air (NIOSH Pocket Guide, 1993) lower = 5.1 % by volume in air (NIOSH Pocket Guide, 1993)
Solubility	soluble in chloroform and benzene, slightly soluble in water, ethyl alcohol and in alkalis
Odor threshold	0.5 ppm (NJ Hazardous Substance Fact Sheets, 1993)
Odor description	garlic (AIHA, 1989)
Metabolites	oxidation to As^{3+}, As_2O_3 (Landrigan *et al.*, 1982)
Conversion factor	1 ppm = 3.19 mg/m³ @ 25°C

III.   Major Uses or Sources (HSDB, 1993)

Processes such as smelting, galvanizing, soldering, and etching, that require the treatment of metal with strong acids, are possible sources of arsine gas. Acid treatment of metals contaminated with arsenic can result in the release of arsine gas. Arsine is used to provide arsenic as a dopant in the semiconductor industry. Combustion of fossil fuels may produce arsine gas.

## IV.	Acute Toxicity to Humans

Numerous case reports of accidental arsine poisoning exist in the literature, but reliable estimates of concentrations following acute human intoxication do not exist. This is due in large part to the insidious nature of arsine toxicity - arsine is a colorless gas, has a mild odor at low concentrations, produces no mucous membrane irritation, and usually results in delayed symptoms of toxicity (Klimecki and Carter, 1995). In mammalian systems, arsine primarily targets the erythrocyte and causes hemolysis and methemoglobinemia with acute exposure (NRC, 1984). Jaundice, hemoglobinuria, anuria, hepatic and renal damage, anoxia, and anemia are secondary effects resulting from hemolysis. Before the advent of dialysis, there were no reports of patients surviving if renal failure developed (Buchanan, 1962). Other acute symptoms reported include headache, weakness, dizziness, dyspnea, nausea, vomiting, diarrhea, and abdominal cramping (Klimecki and Carter, 1995). Central and peripheral nervous systems may be affected by acute arsine exposure, leading to agitation, disorientation, hallucinations, psychopathologic abnormalities, and peripheral nerve degeneration (Klimecki and Carter, 1995; Frank, 1976). The psychopathologic and peripheral abnormalities are thought to be secondary to the conversion of arsine to arsenate or arsenite. The first signs and symptoms of toxicity, hemoglobinuria and/or nausea, are usually delayed 2 to 24 hours following exposure (Kleinfeld, 1980).

A case report documents hemolytic anemia, hematuria, and renal failure following intermittent exposure to arsine gas over 2.5 hours (Parish *et al*., 1979). Symptoms of gastrointestinal distress, headache, and malaise were also reported following this exposure. The concentration of arsine gas sampled 3 days after exposure was 0.1 ppm (0.3 mg/m³), but the concentration at the time of poisoning was unknown. Another typical accidental poisoning resulted when 2 men were exposed to arsine gas in a metal smelting works (Coles *et al*., 1969). Symptoms included nausea, vomiting, red urine, generalized aching, shivering, epigastric pain, and jaundice. However, the more severely affected worker developed symptoms within 1 hour of exposure while the other did not develop symptoms for 24 hours. The more severely affected worker developed acute renal failure that required peritoneal dialysis.

In an occupational study, the highest average concentration of arsine recorded in a battery formation area of a battery manufacturing plant was 20.6 µg/m³ (0.006 ppm) (Landrigan *et al*., 1982). Elevated levels of urinary arsenic were observed in some workers but effects on the hematopoietic system were apparently not examined.

A study by Williams *et al*. (1981) collected personal and area air samples after 2 workers exhibited symptoms of arsine poisoning while restoring a large 19th century painting. Symptoms included headaches, nausea, weakness, vomiting, and red urine. The blank-corrected air concentration of arsine ranged from 0.010 to 0.067 mg/m³. While these concentrations are below the OSHA PEL 8-hour TWA of 0.2 mg/m³, the results may indicate that these workers are sensitive responders or that humans in general may be more sensitive to the effects of arsine than experimental animals. However, the air samples may not represent the actual concentration of arsine that caused the symptoms of poisoning in the workers since the workplace air was not analyzed for arsine until after symptoms were reported. The study also notes that 'appreciable concentrations' of lead and arsenic were found in the workplace air.

Predisposing Conditions for Arsine Gas Toxicity

Medical: Persons with renal disease and hematologic disorders such as glucose-6-phosphatase deficiency or sickle cell anemia may be at higher risk for adverse effects following arsine gas exposure (Reprotext, 1999).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

LC_{50} values reported by Gates (1946) are as follows: 120-210 ppm (380-670 mg/m³) for 10 minutes in rats, 110 ppm (350 mg/m³) for 30 minutes in dogs (equivalent to 190 ppm (610 mg/m³) for 10 minutes), and 200-300 ppm (640-960 mg/m³) for 10 minutes in rabbits. An LC_{50} in mice was reported as 31 ppm (99 mg/m³) for a 50-minute exposure (Levvy, 1947). The survival time of the fatalities (4 days) was reported to be more or less independent of exposure concentration (2500 mg/m³ to 25 mg/m³) and exposure duration.

The study by Levvy (1947) varied exposure durations for each given concentration of arsine. Because the mortality data were not presented in conventional form by the standard LC_{50} method, the data were normalized to a 1-hour exposure using Haber's equation ($C^n \times T = K$). The exponent "n" of 1.8 was determined by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. Only 54 data points were used to estimate the exponent n because these points were of sufficient duration ($\geq$ 5 minutes) and resulted in the best chi-square fit for the line and obvious heterogeneity (Table 1).

Table 1. Selected mice mortality results from Levvy (1947) and the 1-hour adjusted concentration using Haber's equation ($C^n \times T = K$, where n = 1.8).

Concentration (ppm)	Exposure Duration (min)	Mortality (no. died/total)	1-Hour Adjusted Concentration (ppm)
157*	10	30/30	58
	5	28/30	39
	2.5	17/30	27
	1.7	0/30	22
78.4*	15	21/30	36
	9	10/30	27
31.4	70	30/30	34
	50	15/30	28

* Shaded rows include data used for determination of the ED_{05} and BD_{05}

Craig and Frye (1988) reported a 4-hour LC_{50} of 42.6 ppm in rats. However, when the rats were separated by sex for statistical purposes, there was slightly greater mortality among females than males (38.9 ppm LC_{50} for females vs. 46.8 ppm LC_{50} for males). No abnormalities were seen at necropsy except red discharge from nose, mouth, and genitalia at the higher concentrations. A

concentration-related suppression of body weight gain was observed during the first week of the 14-day post-observation period.

The most comprehensive arsine lethality study was undertaken by IRDC (1985). LC_{50}'s of 240, 178, and 45 ppm were determined in rats (10 rats/sex/group) for 30 minute, 1 hour, and 4 hour exposures, respectively. Deaths generally occurred within 3 days following 30 minute exposure to arsine. As in the previous study (Craig and Frye, 1988), there was slightly greater mortality in females than males. Adverse effects noted during exposure included dyspnea, while effects noted post-exposure included a concentration-related increase in hematuria, dark material around the head or the anogenital area, and pallor of ears, eyes, and feet. The higher concentrations resulted in weight loss immediately following exposure, suppressed weight gain during the first week, and compensatory weight gains during the second week post-exposure. Necropsy on animals that died showed red, yellow or orange fluid in the bladder, stomach, or intestine, and discoloration of the kidneys, lungs, and liver.

Data in the IRDC (1985) report were used to determine the exponent "n" in the equation $C^n \times T = K$. This was done by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The value of "n" for extrapolation to 1-hour exposure was dependent on exposure duration. For extrapolation from 30 minutes to 1-hour exposure, n = 2.2; for extrapolation from 4-hours to 1-hour exposure, n = 1.0.

Table 2 contains the studies which provided adequate raw mortality data from which a maximum likelihood estimate corresponding to 5% lethality (MLE_{05}) and benchmark dose at the 95% lower confidence interval of the MLE_{05} and MLE_{01} (BD_{05} and BD_{01}, respectively) could be determined.

Table 2. Animal Lethality Benchmark Dose Determinations in ppm for Arsine

Reference	Species	Exposure Time (min)	LC_{50} 60 min[1]	MLE_{05} 60 min[1]	BD_{05} 60 min[1]	BD_{01} 60 min[1]
IRDC, 1985	rat	30	175	120	105	86
	rat	60	178	112	88	66
	rat	240	181	118	101	80
Craig and Frye, 1988	rat	240	170	125	102	84
Levvy, 1947	mice	varied[2]	29	20	16	13

[1] Exposure time was extrapolated to 60 minutes, if needed, using a modification of Haber's equation ($C^n * T = K$). For rats, n = 2.2 for extrapolation from 30 minutes to 1-hour, or n = 1.0 for extrapolation from 4 hours to 1-hour; for mice, n = 1.8.

[2] Lethality data for 5 exposure durations were pooled and normalized to a 1-hour exposure using the equation $C^n \times T = K$ (see Table 1).

In other experimental animal studies, a reduction in hematocrit as a function of arsine concentration was observed in mice following a 1-hour exposure (Peterson and Bhattacharyya, 1985). A LOAEL of 9 ppm (29 mg/m³) and a NOAEL of 5 ppm (16 mg/m³) were reported.

The demarcation between the NOAEL and LOAEL for this non-lethal effect was well defined, not only among the exposure groups (5 ppm vs. 9 ppm), but also among individual mice in each exposure group (Peterson, 1990). Hematologic recovery of the surviving mice was gradual but nearly complete within 11 days after exposure (Peterson and Bhattacharyya, 1985). The study also reported a NOAEL of 15 ppm (100% survival) and LOAEL of 26 ppm (100% lethality) for lethality. Therefore, the NOAEL/LOAEL approach for determination of a severe adverse effect level for arsine is appropriate.

A subchronic study in male and female rats and female mice (Fowler *et al*., 1988) supports the sharp demarcation in dose-response noted by Peterson and Bhattacharyya (1985). All treatment groups exposed to arsine (6 hr/day, 5 days/week) at concentrations of 10 ppm and above showed 100 percent mortality within 4 days while those exposed to 5 ppm or less showed no mortality or overt signs of toxicity. Other effects observed included a dose-related increase in spleen weight and a slight increase in liver weight. Blood samples taken at necropsy showed a slight dose-related decrease in hematocrit and a marked dose-related increase in the activity of red blood cell ALAD (δ-aminolevulinic acid dehydratase).

In a 90 day study, male and female mice were exposed to 0, 0.025, 0.5, and 2.5 ppm arsine gas for 6 hours/day, 5 days/week (Blair *et al*., 1990). After 5, 15, and 90 days, blood was collected for hematologic analysis. Exposure to 2.5 ppm had significant effects on all hematological parameters for nearly the entire exposure period, while 0.5 ppm caused only a few significant changes in hematological parameters at day 90 of exposure (decreased hemoglobin in males and increased MCV in females). Exposure to 0.025 ppm was without effect.

VI.   Reproductive or Developmental Toxicity

In an unpublished study, workers in one semiconductor plant were reported to have a 39% rate of miscarriage, almost twice the national average (Sanger, 1987). Workers were exposed to unidentified levels of arsine gas, but other possible exposures were not identified.

A developmental toxicity study exposed pregnant rats and mice to 0.025, 0.5, or 2.5 ppm (0.079, 1.5, or 7.9 mg/m³) arsine for 6 hours per day on gestation days 6 through 15 (Morrissey *et al*., 1990). The rats exposed to 2.5 ppm exhibited a significant increase in fetal body weight, but no other endpoints of developmental toxicity were observed. The incidence of malformations observed in arsine exposed mice at 0.025 ppm (exencephaly) and at 2.5 ppm (unfused eyelids) was not significantly different from control mice.

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

Mild Adverse Effect Level

Because lysis of red blood cells is considered a severe adverse effect, and since this effect occurs
at or <u>below</u> the threshold for discomfort (a mild adverse effect), there is no mild adverse effect
level currently recommended for arsine.

Reference Exposure Level (protective against severe adverse effects): 0.05 ppm (160 µg/m³)

Study	Peterson and Bhattacharyya, 1985; Peterson, 1990
Study population	mice
Exposure method	inhalation
Critical effects	lysis of red blood cells
LOAEL	9 ppm (29 mg/m³)
NOAEL	5 ppm (16 mg/m³)
Exposure duration	1 hour
Extrapolated 1 hour concentration	5 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	0.05 ppm (0.16 mg/m³; 160 µg/m³)

Level Protective Against Life-threatening Effects

The work by Craig and Frye (1988) and IRDC (1985) provide recent, well-conducted rat
lethality studies from which to derive a life threatening level for arsine from human data using
the standard benchmark dose approach. However, the results by Levvy (1947) indicate that mice
are at least 5-fold more sensitive to the lethal effects of arsine than rats (see Table 2). This
finding is supported by the recent study by Peterson and Bhattacharyya (1985), which observed a
1-hour NOAEL and LOAEL for lethality of 15 and 26 ppm, respectively. Therefore, the level
for arsine is based on mouse lethality data obtained from Levvy (1947). Based on probit analysis
of data by Levvy (1947), a BD_{05} of 16 ppm was determined in mice for 1-hour exposure to
arsine. An uncertainty factor of 3 was applied to the BC_{05} to account for interspecies differences
because the BD_{05} likely accounts for some degree of variation and an uncertainty factor of 10
was applied to account for increased susceptibility of sensitive human individuals.

Level protective against life-threatening effects = BC/(UF)

The total uncertainty factor was 30. Incorporation of these factors results in a level protective
against life-threatening effects for arsine of 0.537 ppm (1.712 mg/m³) for 1-hour exposure.

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ACUTE TOXICITY SUMMARY

BENZENE

(benzol; benzole; cyclohexatriene)

CAS Registry Number: 71-43-2

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

Inhalation reference exposure level	**1,300 µg/m³**
Critical effect(s)	Reproductive/developmental toxicity
Hazard Index target(s)	Reproductive/developmental; Immune System; Hematologic System;

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

Description	colorless liquid
Molecular formula	C_6H_6
Molecular weight	78.1
Density	0.879 g/cm^3 @ 25°C
Boiling point	80.1°C
Melting point	5.5°C
Vapor pressure	100 mm Hg @ 26.1°C
Flashpoint	-11°C
Explosive limits	upper = 8.0% by volume in air
	lower = 1.4% by volume in air
Solubility	soluble in ethanol, chloroform, ether, carbon disulfide, acetone, oils, and glacial acetic acid; slightly soluble in water
Odor threshold	0.875 ppm (2.8 mg/m³) (Haley, 1977)
Odor description	sweet
Metabolites	hydroquinone, quinone, catechol, phenol
Conversion factor	1 ppm = 3.24 mg/m³

III.   Major Uses or Sources

Benzene has been widely used as a multipurpose organic solvent. This use is now discouraged due to its high toxicity. Present uses include benzene as a raw material in the synthesis of styrene, phenol, cyclohexane, aniline, and alkyl benzenes and in the manufacture of various plastics, resins, and detergents. Synthesis of many pesticides and pharmaceuticals also involves benzene as a chemical intermediate (HSDB, 1994). Benzene is emitted in large quantities from refineries and petroleum storage facilities. The tire industry and shoe factories use benzene extensively. Annual demand in the U.S. was estimated to be 6 million tons in 1990 (HSDB, 1994).

IV.   Acute Toxicity to Humans

Deaths from acute exposure to benzene are often related to physical exertion and release of epinephrine with subsequent cardiac failure. Frequently, the person trying to rescue a collapsed victim will die during the effort of lifting the unconscious person (HSDB, 1994). Anesthesia may develop at concentrations above 3,000 ppm (9,600 mg/m³) (Reprotext, 1993). At exposures of greater than 1,000 ppm (3,200 mg/m³) (duration unspecified), CNS symptoms include giddiness, euphoria, nausea, and headaches; heightened cardiac sensitivity to epinephrine-induced arrhythmias may develop (Snyder, 1987). These effects may be accompanied by symptoms of mild irritation to the eyes and mucous membranes. Acute hemorrhagic pneumonitis is highly likely if benzene is aspirated into the lung (HSDB, 1994). Respiratory tract inflammation, pulmonary hemorrhages, renal congestion, and cerebral edema have been observed at autopsy in cases of acute benzene poisoning (IARC, 1987). In these cases, blood levels of 2 mg/ml benzene were not associated with hematological changes (Winek and Collom, 1971).

Systemic poisoning by benzene can occasionally result in neuroretinal edema and in retinal and conjunctival hemorrhage (Grant, 1986). Additionally, petechial hemorrhages of the brain, pleura, pericardium, urinary tract, mucous membranes, and skin may occur in cases of fatal, acute benzene poisoning (Haley, 1977).

Major concerns of systemic benzene toxicity include aplastic anemia and acute myelogenous leukemia (IARC, 1987; Reprotext, 1993). Both of these conditions are typically seen in the chronic and subchronic exposures, but may be of concern following acute exposures as well. Myeloid and erythroid components of the bone-marrow are specific targets of benzene toxicity, which leads to aplastic anemia (IARC, 1982).

In men and women exposed to benzene for 4 hours, 46.9% of the inhaled dose was absorbed. Of this absorbed fraction, 30.1% was retained and 16.8% was excreted unchanged in the expired air (Nomiyama and Nomiyama, 1974). Most of the catechol and phenol metabolites are excreted within 24 hours in the urine, while hydroquinone requires 48 hours (Teisinger *et al*., 1952).

Exposure at the odor threshold (0.875 ppm or 2.8 mg/m³) for a brief duration is reported to enhance the electropotential of the brain (Haley, 1977).

Predisposing Conditions for Benzene Toxicity

Medical: People with existing hematologic disorders and cellular anemias may be more sensitive to the acute toxicity of benzene to the bone-marrow (Reprotext 1993, 1999). People with heart conditions may also be at increased risk for cardiac arrhythmias induced by exposure to high levels of benzene. Administration of epinephrine is known to potentiate the cardiac toxicity of benzene (Reprotext, 1993).

Females may be more sensitive to benzene toxicity than males due to higher average body fat content, which serves as a storage reservoir for the chemical

(Reprotext, 1993). Similarly, obese individuals of either sex may be more sensitive to benzene toxicity.

Chemical: Previous acute exposure to toluene inhibits benzene metabolism to toxic metabolites, and may reduce toxicity (Reprotext, 1993). Consumption of ethanol potentiates the bone-marrow toxicity of inhaled benzene in mice (Baarson *et al.*, 1982).

V. Acute Toxicity to Laboratory Animals

The oral LD_{50} in rats is reported to be 3.4 g/kg in young rats and 4.9 g/kg in older rats (Kimura *et al.*, 1971). Mortality was observed in 2 out of 10 rats exposed to 33,000 mg/m³ (10,300 ppm) for 12.5-30 minutes daily for either 1 or 12 days (IARC, 1982). A 4-hour LC_{50} of 13,700 ppm (43,800 mg/m³) was reported in female rats (IARC, 1982). An LC_{Lo} of 45,000 ppm (144,000 mg/m³) is reported in rabbits (RTECS, 1994). In mice, an LC_{50} of 9,800 ppm (31,400 mg/m³) is reported (RTECS, 1994). Leukopenia has been demonstrated to occur in rabbits exposed to 240 ppm (767 mg/m³) for 10 hours/day for 2 weeks (IARC, 1982).

Brief inhalation of air saturated with benzene vapor (concentration unknown) resulted in ventricular extrasystole in cats and primates, with periods of ventricular tachycardia that occasionally terminated in ventricular fibrillation (Clayton and Clayton, 1981).

An attempt by Nielsen and Alarie (1982) to determine the inhalation RD_{50} for benzene was not successful. These investigators showed that inhalation of 5,800 ppm (18,800 mg/m³) benzene in mice caused an increase in respiratory rate beginning at 5 minutes following onset of exposure. They speculated that the stimulation of respiratory rate resulted from the action of benzene on the central nervous system. In this study, benzene was not irritating to the upper airways of the animals.

The pharmacokinetics of benzene in the rat reportedly follows a 2-compartment model. The rapid phase has an elimination half-life ($t_{1/2}$) of 0.7 hours, and the $t_{1/2}$ for the longer phase is 13.1 hours (Rickert *et al.*, 1979). The long elimination half-life for benzene is due to the formation of catechol, quinone, and hydroquinone in the bone marrow. These reactive metabolites are not readily excreted, and are cytotoxic to the germinal cells in the bone marrow (Greenlee *et al.*, 1981). A 3-compartment model was fitted to human data on benzene disposition and bone-marrow metabolism (Watanabe *et al.*, 1994). The general relationship between cumulative quantity of metabolites produced and inhalation concentration was not linear, but was S-shaped, inflecting upward at low concentrations, and saturating at high concentrations.

Mice, particularly the DBA/2 strain, are more sensitive to myelotoxicity from benzene than are rats or rabbits (IARC, 1982). Colony-forming unit cells (CFUs; leukocyte precursors) were depleted in bone-marrow cultures taken from mice exposed to 4,610 ppm (14,950 mg/m³) benzene for 8 hours. Recovery of CFUs was noted 7 days after exposure (IARC, 1982).

In addition to myelotoxicity, acute exposure to benzene may disrupt erythropoiesis and result in genotoxicity. Erythropoiesis, as measured by uptake of radiolabeled iron in the bone-marrow,

has been shown to be inhibited by subcutaneous injection of 10 mmol/kg benzene in mice (Bolcsak and Nerland, 1983).

Results from subacute exposures further illustrate the hematotoxic effects of benzene and the potential for immunotoxicity. Inhalation of 103 ppm (334 mg/m³) benzene for 6 hours/day for 7 days by mice caused decreased spleen and marrow cellularities and decreased spleen weights (Green *et al*., 1981). Benzene inhalation at concentrations of 0, 10, 30, 100, and 300 ppm (0, 32.4, 97.3, 324, and 973 mg/m³) for 6 hours/day for 5 days resulted in a decreased host-resistance to bacterial infection by <u>Lysteria</u> <u>monocytogenes</u> (Rosenthal and Snyder, 1985). The numbers of <u>L.</u> <u>monocytogenes</u> bacteria isolated from the spleen were increased in a dose-dependent manner on day 4 of infection. The total numbers of T- and B-lymphocytes in the spleen and the proliferative ability of the splenic lymphocytes were decreased in a dose-dependent manner by benzene exposures of 30 ppm (97.3 mg/m³) or greater. In this study, no decrement in host resistance or immune response was observed at 10 ppm (32 mg/m³) benzene. Later studies in mice have also shown that exposure to 10 ppm for a subacute duration does not significantly alter hematological parameters in blood, spleen, thymus, or bone marrow (Farris *et al*., 1996; 1997).

Farris *et al*. (1997) reported the hematological consequences of benzene inhalation in B6C3F1 mice exposed to 1, 5, 10, 100, and 200 ppm benzene for 6 hr/day, 5 days/week for 1, 2, 4, or 8 weeks and a recovery group. There were no significant effects on hematopoietic parameters from exposure to 10 ppm benzene or less. Thus 10 ppm was a NOAEL for 1 week of exposure (and longer). Exposure to 100 and 200 ppm benzene reduced the number of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters. Replication of primitive progenitor cells in the bone marrow was increased during the exposure period as a compensation for the cytotoxicity. At 200 ppm, the primitive progenitor cells maintained an increased percentage of cells in S-phase through 25 days of recovery compared with controls.

Inhalation of 3 ppm (9.6 mg/m³) benzene for 6 hours by rats resulted in a significant increase over controls in the frequency of sister chromatid exchanges in peripheral blood lymphocytes (Erexson *et al*., 1986).

Evans *et al*. (1981) observed an increase in active behavior in the form of eating and grooming in mice following exposure to 300 ppm (960 mg/m³) benzene for 6 hours.

VI.   Reproductive or Developmental Toxicity

Coate *et al*. (1984) exposed groups of 40 female rats to 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, or 324 mg/m³) benzene for 6 hours/day during days 6-15 of gestation. In this study, teratologic evaluations and fetotoxic measurements were done on the fetuses. A significant decrease was noted in the body weights of fetuses from dams exposed to 100 ppm (324 mg/m³). No effects were observed at a concentration of 40 ppm (129.6 mg/m³).

Keller and Snyder (1986) reported that exposure of pregnant mice to concentrations as low as 5 ppm (16 mg/m³) benzene on days 6-15 of gestation (6 hr/day) resulted in bone-marrow

hematopoietic changes in the offspring that persisted into adulthood. However, the hematopoietic effects (e.g., bimodal changes in erythroid colony-forming cells) in the above study were of uncertain clinical significance. In a similar, later study, Keller and Snyder (1988) found that exposure of mice in utero to 20 ppm (64 mg/m³) benzene on days 6-15 of gestation resulted in neonatal suppression of erythropoietic precursor cells and persistent, enhanced granulopoiesis. This effect was considered significant bone-marrow toxicity by the authors. No hematotoxicity was seen in this study at 10 ppm (32 mg/m³).

An exposure of 500 ppm (1,600 mg/m³) benzene through days 6-15 of gestation was teratogenic in rats while 50 ppm (160 mg/m³) resulted in reduced fetal weights on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (Kuna and Kapp, 1981). An earlier study by Murray *et al*. (1979) showed that inhalation of 500 ppm benzene for 7 hours/day on days 6-15 and days 6-18 of gestation in mice and rabbits, respectively, induced minor skeletal variations.

Tatrai *et al*. (1980) demonstrated decreased fetal body weights and elevated liver weights in rats exposed throughout gestation to 150 mg/m³ (47 ppm).

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

Level protective against mild adverse effects: While benzene exposure results in decreased immune response and hematopoietic effects in laboratory animals following 5 day exposures, it was problematic to extrapolate from these repeated dose studies for these endpoints. Thus, no level protective against mild adverse effects for one-hour is being recommended. The REL is based on developmental toxicity, a severe adverse effect.

Reference Exposure Level for a 6-hour exposure (Level Protective Against Severe Adverse Effects): 1,300 μg/m³

Because of the uncertainty of extrapolating from repeated exposures to a one-hour concentration, we have chosen to use a single day exposure in the reproductive studies with no time extrapolation as an REL. In the case of benzene, the REL is for a 6-hour exposure.

Study	Coate *et al*., 1984; (supported by Kuna and Kapp, 1981; Keller and Snyder, 1988)
Study population	pregnant female rats
Exposure method	inhalation of 0, 1, 10, 40, or 100 ppm
Critical effects	decreased fetal body weights
LOAEL	100 ppm
NOAEL	40 ppm
Exposure duration	6 hours per day (for 5 days)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10

       Cumulative uncertainty factor   100
       Reference Exposure Level   0.4 ppm (1.3 mg/m³; 1,300 µg/m³)

Pregnant female rats (40 per group) were exposed for 6 hours/day on days 6-15 of gestation to benzene concentrations of 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, and 324 mg/m³) (Coate *et al*., 1984). The mean fetal weights from the females treated with 100 ppm benzene were significantly decreased ($p < 0.05$) compared to controls. No teratogenic, fetotoxic, or maternally toxic effects were observed in rats exposed to 40 ppm (129.6 mg/m³) benzene or less. The 40 ppm (129.6 mg/m³) concentration is considered a NOAEL for reduced fetal weight. The value of 40 ppm for a 6-hour exposure was extrapolated to a 1-hour exposure using the equation $C^n * T = k$, where $n = 2$. The resulting 100 ppm extrapolated value was used to determine the level protective against severe adverse effects using uncertainty factors of 10 for intraspecies and 10 for interspecies variation. The level protective against severe adverse effects for benzene is therefore 1.0 ppm or 3.24 mg/m³.

Kuna and Kapp (1981) found direct teratogenic effects measured as decreased crown-rump length, exencephaly, and angulated ribs in rats when pregnant females were exposed 6 hours/day during days 6-15 of gestation to a concentration of 500 ppm. In this study, a concentration of 50 ppm during gestation resulted in lower fetal weights measured on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (32 mg/m³). Keller and Snyder (1988) reported a NOAEL of 10 ppm for developmental hematopoietic effects in mice. The highest reported NOAEL (i.e., 40 ppm) consistent with reported LOAEL values was chosen for the derivation of the Reference Exposure Level (severe adverse effect level, in this case) for benzene.

Level Protective Against Life-threatening Effects

Svirbely *et al*. (1943) exposed mice for 7 hours to various benzene concentrations. They determined a NOAEL (0/18 animals) for lethality of 4,980 ppm and a LOAEL (3/18 animals) of 7,490 ppm. A benchmark concentration derived (BC_{05}) using a log-normal model with these data is 5,650 ppm (MLE = 6,550 ppm). A life-threatening level was calculated using these data with an uncertainty factor of 30 (10 for individual variability, and 3 for interspecies uncertainty using the BC_{05} as the starting point for the calculation). The level protective against life-threatening effects is therefore 5,650 ppm ÷ 30 = 190 ppm (620 mg/m³).

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ACUTE TOXICITY SUMMARY

BENZYL CHLORIDE

(α-chlorotoluene, chloromethylbenzene, tolyl chloride)

CAS Registry Number: 100-44-7

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

Inhalation reference exposure level	**240 μg/m³**
Critical effect(s)	eye and nose irritation in rats and mice
Hazard Index target(s)	Eyes; Respiratory System

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

Description	colorless to slightly yellow liquid
Molecular formula	C_7H_7Cl
Molecular weight	126.58
Density	1.1 g/cm^3 @ 20°C
Boiling point	179° C
Melting point	-43 to -48°C
Vapor pressure	1 mm Hg @ 22°C
Flashpoint	67°C, closed cup; 74°C, open cup
Explosive limits	upper = unknown
	lower = 1.1% by volume in air
Solubility	insoluble in water; miscible with most organic solvents
Odor threshold	0.041 ppm (240 μg/m³) (geometric mean) (AIHA, 1989)
Odor description	pungent (AIHA, 1989)
Metabolites	benzyl mercapturic acid, benzoic acid
Conversion factor	1 ppm = 5.2 mg/m³ @ 25°C

III.   Major Uses or Sources

Benzyl chloride is a chemical intermediate in the manufacture of dyes, plasticizers, lubricants, gasoline additives, pharmaceuticals, tanning agents, and quaternary ammonium compounds (HSDB, 1994). Benzyl chloride can react with water or steam to produce corrosive and toxic fumes. It reacts vigorously with oxidizing materials, decomposes rapidly, and liberates heat and hydrochloric acid when exposed to all common metals, except lead and nickel. When heated, it may form phosgene (Hazardtext, 1993).

IV. Acute Toxicity to Humans

Benzyl chloride is extremely irritating to the eyes, nose, and throat, is a potent lacrimator, and is capable of causing pulmonary edema (Smyth, 1956). Exposure to 31 ppm (160 mg/m³) benzyl chloride for 5 minutes was reported to be unbearably irritating to the eyes and respiratory tract; a 5-minute exposure to 1.2-1.5 ppm (6-8 mg/m³) benzyl chloride resulted in "slight conjunctivitis" (Mikhailova, 1983). Skin burns or irritation may result from direct contact with vapors or liquid (Meditext, 1993).

Human volunteers exposed to benzyl chloride vapor for a single breath reported that the odor was perceptible at 8 ppm (42 mg/m³), very unpleasant at 17 ppm (88 mg/m³), painfully strong at 37 ppm (190 mg/m³), and intolerable at 79 ppm (410 mg/m³) (Katz and Talbert, 1930).

Occupational exposure to 2 ppm (10 mg/m³) benzyl chloride was reported to result in neurological symptoms and liver dysfunction; these effects most likely reflect chronic exposure, although the duration of exposure was not reported (Mikhailova, 1983). Little or no information was reported on the number of workers examined in the original studies cited, on the range of exposure, or on possible concomitant exposures.

Predisposing Conditions for Benzyl Chloride Toxicity

Medical: Those individuals with preexisting eye, skin, allergic, liver or kidney disease or preexisting respiratory conditions including underlying cardiopulmonary disease may be more sensitive to the effects of benzyl chloride exposure (Reprotext, 1999).

Chemical: Persons exposed to other irritants might be more sensitive (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The 2-hour LC_{50} for benzyl chloride is reported as 0.39 mg/l (80 ppm) and 0.74 mg/l (150 ppm) in mice and rats, respectively (Mikhailova, 1965). The same study reports that rats and mice exposed to concentrations exceeding 0.1 mg/l (20 ppm) benzyl chloride for 2 hours exhibited irritation of the eyes, nose, and throat and decreased respiratory rate. Two cats exposed for 8 hours per day for 6 days to 95 ppm (500 mg/m³) benzyl chloride exhibited eye and respiratory irritation and decreased appetite (Wolf, 1912).

VI. Reproductive or Developmental Toxicity

No adverse reproductive effects were observed in rats administered 50 or 100 mg/kg/day benzyl chloride orally on days 6-15 of gestation (Skowronski and Abdel-Rahman, 1986). A non-statistically significant increase in sternebral defects was observed in the 100 mg/kg/day exposure group. No maternal toxicity was observed.

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

Reference Exposure Level (protective against mild adverse effects):   46 ppb (240 μg/m³)

Study	Mikhailova, 1965
Study population	rats and mice
Exposure method	inhalation chamber
Critical effects	signs of irritation of eyes and nasal passages; decreased respiratory rate
LOAEL	20 ppm
NOAEL	not observed
Exposure duration	2 hours
Extrapolated 1 hr concentration	28 ppm ($20^2 * 2$ h $= C^2 * 1$ h) (see Table 12 for information on "n")
LOAEL uncertainty factor	6
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	600
Reference exposure level	46 ppb (240 μg/m³)

An animal study was used for the derivation of the REL because the available human data (Smyth, 1956; Mikhailova, 1983; Katz and Talbert, 1930) were not adequate for the determination of this level; the original human data were anecdotal and the exposure conditions were not well defined.

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 lists an IDLH of 10 ppm. However, NIOSH admits: "Very little data are available on the acute effects of exposure to benzyl chloride." NIOSH also states: "ACGIH (1971) reported that in 1 minute an exposure to 16 ppm is intolerable to man (Flury and Zernik, 1931). ILO (1972) reported that 20 ppm will render the atmosphere irrespirable in 1 minute. ILO (1971) reported that 50 to 100 mg/m³ (10 to 19 ppm) immediately causes weeping and twitching of the eyelids, while 160 mg/m³ (30 ppm) causes effects that are intolerable to the eyes and nasal mucous membranes. Based on this data, an IDLH of 10 ppm is assumed in order to avoid difficulties in escape in the event of respirator failure." The level makes no allowance for sensitive individuals and therefore can not be recommended for use for the general public.

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ACUTE TOXICITY SUMMARY

CARBON DISULFIDE

(carbon bisulfide, carbon sulfide, dithiocarbonic anhydride)

CAS Registry Number: 75-15-0

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

Inhalation reference exposure level   **6,200 µg/m³**
Critical effect(s)   significant reductions in fetal body weight
Hazard Index target(s)   Reproductive/developmental; Nervous System

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

Description	colorless to faintly yellow liquid
Molecular formula	CS_2
Molecular weight	76.14
Density	1.2632 g/cm^3 @ 20° C
Boiling point	46.5°C at 760 mm Hg
Melting point	-11.5°C
Vapor pressure	297 mm Hg @ 20°C
Flashpoint	-30°C (closed cup) (AIHA, 1992)
Explosive limits:	upper = 50% (AIHA, 1992) lower = 1.25%
Solubility	soluble in chloroform, alcohol, ether, benzene, slightly soluble in water
Odor threshold	0.1-0.2 ppm (ACGIH, 1991)
Odor description	Commercially pure CS_2 has a sweetish aromatic odor; industrial grade CS_2 has a rotten cabbage or radish odor (Coppock *et al.*, 1981).

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Metabolites	inorganic sulfates such as thiourea
Conversion factor	1 ppm = 3.11 mg/m³@ 25°C

III.   Major Uses or Sources (HSDB, 1993)

The most prominent industrial use of CS_2 is in the production of viscose rayon fibers; it is also used in the production of carbon tetrachloride and cellophane. Carbon disulfide is used as a solvent for rubber, sulfur, oils, resins, and waxes, and has been used for soil fumigation and insect control in stored grain. Industrial processes that produce carbon disulfide as a by-product include coal blast furnaces and oil refining.

IV.   Acute Toxicity to Humans

CS_2 is primarily a neurotoxic poison; symptoms indicate both central nervous system (CNS) and peripheral nervous system (PNS) damage. Acute inhalation toxicity, after accidental exposure to very high concentrations, is usually characterized by excitation followed by sulfocarbonic inebriation, similar to drunkenness, and narcosis with extinction of cornea and tendon reflexes (Teisinger, 1971; Bashore and Staley, 1938). Death may occur due to respiratory depression. Recovery from acute exposure may result in motor agitation and disorientation. Other symptoms of acute inhalation toxicity are headache, nausea, garlicky breath, vomiting, dizziness, fatigue, abdominal pain, weak pulse, and palpitations (HSDB, 1993). Hallucinations of sight, smell, hearing, and taste have also been reported following massive vapor exposures. However, many case reports of so-called "acute" poisonings were actually acute exposure and acute onset of symptoms superimposed on chronic inhalation exposure (Gordy and Trumper, 1938). Therefore, it is unknown whether all of the effects described above are due entirely to acute exposure to CS_2. Eye and mucous membrane irritation are also reported as symptoms of acute CS_2 exposure (HSDB, 1993). However, experimental exposure to the pure gas has not resulted in this effect (Beauchamp *et al*., 1983; Du Pont, 1981). It is likely that the irritant effects attributed to CS_2 are due to its combustion products (carbonyl sulfide [COS] and sulfur dioxide [SO_2]) when it burns or to hydrogen sulfide, a known eye and mucous membrane irritant commonly found in workplace air with CS_2 in viscose rayon facilities (Beauchamp *et al*., 1983; Bashore and Staley, 1938; Spyker *et al*., 1982).

Chronic, subchronic, and, in some cases, subacute inhalation exposure to relatively low concentrations of CS_2 have resulted in severe CNS and PNS effects with sequelae different from those seen with acute exposure. The vast majority of the published literature on CS_2 exposure describes long-term or occupational toxicity rather than acute toxicity. Vigliani (1954) reported that viscose rayon workers developed severe CS_2 toxicity from 4-5 hour daily exposures to 1-2 mg/l (322-643 ppm) for as little as 2 months. Symptoms included polyneuritis, psychosis, gastric disturbances, headaches, vertigo, impotence, tremors, sleep disturbances, and myopathy. Concentrations of 0.40 to 0.50 mg/l (129-161 ppm) caused toxicity after 1 or more years of work, while exposure to 0.15-0.20 mg/l (48-64 ppm) did not result in cases of toxicity. Paluch (1948) reported that viscose rayon workers occupationally exposed to 283-370 ppm CS_2 (daily exposure duration unknown) developed serious CNS and PNS effects such as severe headaches, paresthesia of the upper and lower extremities, marked polyneuritis, and neurotic/psychotic behavior. However, one worker exposed to this level of CS_2 for only 8 days experienced severe headaches, psychotic behavior, and optical hallucinations.

Because of improvements in technology and hygienic conditions in viscose rayon factories in developed countries, there have been few, if any, recent reports of acute or chronic toxicity due to occupational exposure from these countries (Teisinger, 1971).

Spyker *et al*. (1982) reported an exposure that occurred following an accidental spill in which a railroad tank car that was leaking CS_2 caught fire. Twenty-seven people, mainly first responders (police and firefighters), were subsequently admitted to a hospital due to exposure. Symptoms included (in order of frequency) headache, dizziness, nausea, burning of throat, lips, or skin,

shortness of breath or chest pain, impotence, and vomiting. No significant changes were observed in FEV_1, FVC, or diffusing capacity and all subjective complaints were transient. However, changes in slow (i.e., not rushed or forced) vital capacity and arterial partial pressure of oxygen were observed, which suggest mild inflammation in small airways. Airborne CS_2 levels of 20 ppm were measured at a nearby undisclosed site during transfer of the chemical to an intact railroad tank car. While the effects reported may have been due to CS_2, it is likely that some or all the effects, particularly the throat, skin, and pulmonary irritation, were due to combustion products such as SO_2 and COS (Spyker *et al*., 1982; Beauchamp *et al*., 1983).

Predisposing Conditions for Carbon Disulfide Toxicity

Medical: Persons with disorders of the central nervous system, eyes, cardiovascular system, kidneys, and liver may be more sensitive to CS_2 (Reprotext, 1999). Persons taking disulfiram (Antabuse) may be more sensitive to CS_2 (Brugnone et al, 1992; Caroldi et al, 1994) since disulfiram is metabolized to CS_2.

Chemical: Human subjects exposed for 6 hours to 10 ppm (30 mg/m³) CS_2 exhibited an inhibition of oxidative N-demethylation (Mack *et al*., 1974). In persons using drugs such as analgesics, hypnotics, antidiabetics, and anticonvulsants, which are metabolized by oxidative N-demethylation, critical elevations in the plasma levels of these agents may be observed following exposure to CS_2. Persons exposed to other neurotoxicants may be at increased risk during carbon disulfide exposure (Reprotext, 1999).

V.   Acute Toxicity to Laboratory Animals

Izmerov (1982) reports a 2 hour LC_{50} of 10,000 mg/m³ (3,215 ppm) in mice. Kuljak *et al*. (1974) reports that an "average" lethal concentration (LC_m) of 4,500 ppm over 30 minutes resulted in 17 deaths out of 30 mice. Exposure to 3,000 ppm for 30 minutes/day for 3 days resulted in 21 deaths out of 30 mice. An unpublished report (PPG Industries, 1978) observed a 1-hour LC_{50} of 15,500 ppm in rats. Intraperitoneal injection of 400 mg/kg CS_2 in male guinea pigs resulted in the death of 3 of the 4 test animals within 24 hours (Divincenzo and Krasavage, 1974).

In an unpublished study, exposure of 6 rats to 3,000 ppm CS_2 for 4 hours resulted in no deaths during the exposure or during the 14 day post-exposure observation period (DuPont, 1966). Adverse effects during exposure included tachypnea, ptosis (drooping of eyelids), incoordination, chromodacyorrhea (red fluid emanating from the eyes), and gasping. Weight loss, hyperexcitability, and dyspnea were noted 24 hours post-exposure. Exposure of 6 rats to 3,500 ppm for 4 hours resulted in death of all animals during exposure or before 2 hours post-exposure. Adverse effects similar to the ones previously mentioned were noted, in addition to salivation, aimless wandering, and prostration. Autopsy of 2 rats revealed pleural effusion, dark red and edematous lungs, petechial lung hemorrhages, and pulmonary hyperemia. Changes in other organs were seen but not reported. In another acute inhalation study by the same laboratory, head-only exposure of rats (4 per group) to 1,660, 8,760, 35,100, or 81,100 ppm CS_2

for 10 minutes did not result in significant respiratory rate depression or overt clinical signs of toxicity (DuPont, 1981). Therefore, CS_2 was not considered by the investigators to be a direct-acting respiratory irritant.

In a range finding portion for a reproductive/developmental toxicity study, 6 pregnant rabbits were exposed to 3,000 ppm CS_2 for 6 hours on day 6 of gestation (PAI, 1991). Four of 6 animals died during exposure and the other 2 were moribund at the end of exposure and were euthanized. No gross lesions were observed but the rabbits exhibited tremors, labored breathing, and apparent anoxia. The 4 animals that died during exposure did not struggle or convulse prior to death. Pregnant rabbits exposed daily (6 hours/day on gestation days 6-18) to 1,000 ppm CS_2 showed only occasional transient signs of toxicity, including ataxia, tremors, and decreased food consumption. Rabbits exposed to 600 ppm or lower showed no signs of exposure-related effects.

Several subchronic studies have reported acute effects in experimental animals soon after initiation of exposure. Wilmarth *et al*. (1993) observed a narcotic-like stupor in rats during 10-hour exposure to 600 or 800 ppm CS_2. Eight-hour exposure of dogs to 404 ppm resulted in drowsiness, stumbling, staggering, and tremors immediately after leaving the exposure chamber (Lewey *et al*., 1941). Exposure of cats to a nominal concentration of 8-10 mg/l (2,560-3,210 ppm) for 2-3 hours resulted in restlessness and excitement early in the exposure; apathy, and occasionally coma, occurred later (Ferraro *et al*., 1941). Other signs of CS_2 toxicity during exposure were salivation, dyspnea, tremors, and muscular jerks. Vomiting was seen occasionally but convulsions were observed in only one instance.

VI.   Reproductive or Developmental Toxicity

Carbon disulfide is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard with male, female, and developmental endpoints. No teratogenic effects were observed in rats and rabbits exposed to 40 ppm (120 mg/m³) CS_2 for 6 hours per day on days 1-19 or 1-24 of gestation, respectively (Hardin *et al*., 1981). The U.S.EPA NOAEL, from which the Proposition 65 NOAEL for developmental endpoints was adopted, is based on these data (IRIS, 1994).

In a reproductive toxicity study, groups of 15 female rats were exposed to 125, 250, and 500 ppm carbon disulfide 6 hours per day from 14 days prior to mating through day 19 of gestation (CMA, 1993). A concurrent control group of 24 female rats was included in the study. The dams were allowed to deliver normally and both pups and dams were observed through day 21 of lactation. Signs of irritation (clear fluid around the eyes and reddening around the nose) were observed in dams immediately following exposure to 500 ppm. A slight decrease in food consumption was observed between days 15-20 of gestation in dams exposed to 500 ppm. Difficulty with delivery (dystocia) was observed in 2 dams and total litter loss was observed in 3 dams from the 500 ppm group. Increased pup mortality, decreased pup viability, and decreased mean litter size were also observed in this group.

In another study, pregnant rats (17-22 per exposure group; 40 controls) were exposed to 0, 100, 200, 400, or 800 ppm carbon disulfide 6 hours per day on days 6-20 of gestation (Saillenfait *et al*., 1989). A statistically significant reduction in maternal body weight gain was observed in rats

exposed to 400 or 800 ppm carbon disulfide. Fetal body weights were also statistically significantly reduced in these exposure groups. A statistically significant increase in the incidence of unossified sternebrae was observed at 800 ppm. An increase in the incidence of club foot at 400 and 800 ppm was not statistically significant.

In a developmental toxicity study conducted by PAI (1991), pregnant rabbits in groups of 24 were exposed to 0, 60, 100, 300, 600, or 1,200 ppm carbon disulfide 6 hours per day on days 6-18 of gestation. In dams exposed to 1,200 ppm, statistically significant decreases in maternal weight gain and clinical signs of toxicity including ataxia, low food consumption, labored respiration, wheezing, tremors, and abortion with bloody excretion involving the death of two animals, were observed. No exposure-related signs of maternal toxicity were observed in does of the other dose groups. In this study, post implantation loss had a significantly higher incidence in does exposed to 600 or 1,200 ppm. Total resorption was observed in 2/22 and 14/21 litters of the 600 ppm and 1,200 ppm exposure groups, respectively. Mean fetal body weight was significantly reduced in the 600 and 1200 ppm exposure groups. In the 1,200 ppm group, the total incidence of skeletal and visceral malformations was significantly increased; however, no single malformation accounted for this increase. In the lower dose groups, significant increases in skeletal malformations were observed in the incidences of rudimentary 13th ribs, extra ribs, extrathoracic vertebrae, or hypoplastic pubis. The malformations in the lower dose groups did not appear to be dose-related and were within the range of historical control data presented by the authors.

In a multigenerational reproductive study, pregnant rats (F_0) inhaled 0.03-200 mg/m³ (0.01-60 ppm) CS_2 for 8 hours per day for the duration of gestation (Tabacova $et\ al.$, 1983). When the healthy pregnant female offspring of the F_0 rats (F_1) were exposed to CS_2 during gestation at levels identical to their prenatal exposure, the progeny of F_1 (F_2) had significantly more malformations than the F_1 generation or the progeny of unexposed rats. For example, exposure at 0.03 mg/m³ was non-teratogenic in the F_1 generation yet had teratogenic effects on the F_2 generation. At the highest level of exposure (200 mg/m³), 38% of the first generation (F_1) exhibited some malformations and 53% of the progeny of this generation (F_2) were malformed while no malformations were observed in controls. The LOAEL for teratogenic effects in the first generation was 100 mg/m³ (30 ppm). Teratogenic endpoints observed in a dose dependent manner within the same generation included gross malformations such as club foot and hypognathia, and CNS abnormalities such as hydrocephalus and microcephalus, in addition to decreased levels of hepatic aniline hydroxylase and aminopyrine N-demethylase. The purity of the CS_2 was not reported, nor was the method of air sampling. It is not clear from the paper if concentrations were measured from the input lines and whether there was potential condensation on fur, cage walls, or food. The study design and the toxicological endpoints observed may be valid, but the dose levels may not have been adequately determined.

Male rats exposed to approximately 610 ppm (1,900 mg/m³) CS_2 for 6 hours per day, 5 days per week for 10 weeks resulted in significant changes in copulatory behavior by the fourth week and reduction in sperm counts by the seventh week (Zenick $et\ al.$, 1984). Caudal epididymal sperm counts were not depressed and the testes appeared histologically normal. These findings suggest that CS_2 does not exert a direct effect on the testes, but may instead interfere with sperm

transport and ejaculation. No significant adverse effects on male rat reproductive parameters were observed following 1 week of exposure to 610 ppm CS_2.

Few reproductive studies exist of human CS_2 exposures. Studies of rayon worker groups suggest that occupational exposure to carbon disulfide may result in reproductive abnormalities. In a cross-sectional study, the rate of spontaneous abortion in women employed in the viscose rayon industry was found to be elevated compared to the rate among women employed in other industrial production, excluding paper products or chemical factories (Hemminki and Niemi, 1982). In this study, women whose husbands worked in the viscose rayon industry also had increased rates of spontaneous abortion. However, this study was exploratory in nature and has yet to be validated.

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

Mild Adverse Effect Level

Because the most sensitive endpoint found in the literature was developmental toxicity, a potentially disabling effect, there is no mild adverse effect level available for CS_2.

Reference Exposure Level for a 6 hour exposure (protective against severe adverse effects):
2.0 ppm (6,200 µg/m³)

Study	Saillenfait *et al*., 1989
Study population	pregnant rats
Exposure method	inhalation of 0, 100, 200, 400, and 800 ppm on days 6-20 of gestation
Critical effects	significant reductions in fetal body weight
LOAEL	400 ppm
NOAEL	200 ppm
Exposure duration	6 hours
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	2.0 ppm (6.2 mg/m³; 6,200 µg/m³)

Level Protective Against Life-threatening Effects

Animal data suggest that subchronic exposure to 1,000 ppm or less does not result in life-threatening effects while exposure to 3,000 ppm or more for several hours can be lethal. However, the experimental animal lethality studies do not provide enough data for a reliable 1-hour life threatening level. Kuljak *et al*. (1974) reported a 30 minute LC_m of approximately 4,500 ppm in mice. However, since the methods used were relatively primitive and the resulting LC_m does not agree with any other animal exposure data, this study was not considered for life threatening level determination. The studies by DuPont (1966, 1981) observed a steep dose-

response for lethality in rats following 4-hour exposure to 3,000 (0% lethality) or 3,500 ppm (100% lethality) CS_2. However, 10 minute exposure of rats to 81,100 ppm did not result in any observable effects. A 1-hour LC_{50} of 15,500 ppm in rats is reported, but no other information is provided (PPG Industries, 1978). In pregnant rabbits, 3,000 ppm for 6 hours produced high mortality while exposure to 1,000 ppm during gestation (6 hours/day) produced little or no effects. Because of the steep dose-response curve for lethality and the lack of lethality data approximating 1 hour of exposure, the life threatening level is based on high-level human occupational exposures to CS_2 that may result in non-lethal effects. These effects were considered comparable to a NOAEL for lethality.

Vigliani (1954) reported that occupational exposure to 322-643 ppm CS_2 4-5 hours/day may result in severe CNS effects such as polyneuritis, psychosis, gastric disturbances, headaches, vertigo, impotence, tremors, sleep disturbances, and myopathy within 2 months. However, no life-threatening effects were reported. Therefore, exposure to 643 ppm for 5 hours, the highest reported human exposure, represents a free-standing NOAEL for life threatening level effects (lethality) in humans. An equivalent 1-hour exposure concentration was estimated from the 5-hour NOAEL using the equation $C^n \times T = K$, where $n = 2$, resulting in a 1-hour level of 1,438 ppm. An uncertainty factor of 10 was applied to account for sensitive individuals. The resulting level protective against life-threatening effects of 144 ppm (448 mg /m³) is appropriately health protective, based on occupational studies (Paluch, 1948; Vigliani, 1954; Toyama and Sukurai, 1967) for a 1-hour exposure to CS_2.

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ACUTE TOXICITY SUMMARY

CARBON MONOXIDE

(carbon monoxide)

CAS Registry Number: 630-08-0

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

Inhalation reference exposure level	**23 mg/m³**
Critical effect(s)	angina in persons with known cardiovascular diseases who are exercising heavily
Hazard Index target(s)	Cardiovascular System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless gas
Molecular formula	CO
Molecular weight	28.01
Density	1.25 g/L @ 0°C
Boiling point	-191.5°C
Melting point	-205°C
Vapor pressure	>760 mm Hg @ 20°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in benzene, ethyl acetate, chloroform, acetic acid
Odor threshold	not applicable
Odor description	odorless
Metabolites	unknown
Conversion factor	1 ppm = 1.15 mg/m³ @ 25°C

III. Major Uses or Sources

Carbon monoxide (CO) is formed during the incomplete combustion of organic substances including gasoline, diesel, natural gas, wood, coal, tobacco, and other vegetation. The California Air Resources Board (CARB) Staff Report (1989) estimated that approximately 70% of the CO present in California urban atmospheres was due to emissions from mobile sources. Solid waste combustion, agricultural burning, and various industrial processes accounted for most of the remaining urban CO.

IV.   Acute Toxicity to Humans

The severity of symptoms due to CO exposure increases with the blood carboxyhemoglobin
(COHb) level. The first signs of CO exposure include mild headache and breathlessness with
moderate exercise (HSDB, 1994). Continued exposure may lead to more severe headache,
irritability, impaired judgment and memory, and rapid onset of fatigue (Winter and Miller,
1976). Persons with existing cardiovascular conditions, such as angina pectoris, are likely to be
more sensitive to the effects of CO exposure. Earlier onset of angina was reported in exercising
subjects with coronary heart disease exposed to 100 ppm (120 mg/m³) carbon monoxide
(resulting in 2.9% blood COHb level) (Kleinman *et al*., 1989).

In another study, men with confirmed coronary artery disease and stable exertional angina were
exposed to air with or without one of two levels of CO for 1 hour while at rest. They then
exercised until the onset of angina (Allred *et al*., 1989). A 4.2% decrease in time to angina
compared to control exercise periods ($p = 0.03$; 95% CI = 0.4-8.74) was observed following a 1-
hour exposure to a mean concentration of 117 ppm (135 mg/m³) CO (resulting in 2% blood
COHb level). Similarly, a 1-hour exposure to a mean concentration of 253 ppm (291 mg/m³) CO
resulted in 4% blood COHb level and a 7.1% decrease in time to onset of angina compared to
control exercise periods ($p = 0.002$; 95% CI = 5.18-14.46).

The California Ambient Air Quality Standard (CAAQS) for CO is based on the conclusion of the
California Air Resources Board (CARB) (1982, 1989) that "exposure to carbon monoxide has
been clearly demonstrated to cause aggravation of angina and other cardiovascular diseases.
Carbon monoxide exerts its effect primarily by binding to hemoglobin and forming
carboxyhemoglobin (COHb), thereby reducing the oxygen-carrying capacity of the blood. These
effects are considered to be adverse and have been shown to occur at COHb levels in the range
of 2.0 to 3.0 percent COHb." Aronow (1981) reported that the lowest demonstrated effect level
for aggravation of angina was as low as 2% COHb.

In double blinded exposures (Benignus *et al*., 1987), 18 nonsmoking, young men at rest were
exposed to high levels of CO in order to elevate COHb to levels of 15-20% in 3-5 minutes,
followed by continued exposure to 232 ppm CO in order to maintain a constant COHb level for a
total of 130 minutes, which resulted in COHb values of 16-23% (average = 19%). These values
did not produce significantly more symptoms such as headache, dizziness, and nausea (as
reported in open-ended questioning of the subjects) than in the control group (n = 23) exposed to
air. The authors theorized that neurological symptoms reported for similar levels of COHb in the
discussion of CO poisoning in medical standard references (cited in Benignus *et al*., 1987) may
have resulted (1) from CO exposure in combination with exposure to other substance(s), (2) from
stress, or (3) from higher COHb levels before the initial blood sample to measure COHb was
taken.

Predisposing Conditions for Carbon Monoxide Toxicity

Medical: Persons with cardiovascular disease, including those with angina, persons with chronic obstructive pulmonary disease, persons with anemia, and fetuses may be more sensitive to the adverse effects of carbon monoxide exposure (CARB, 1982). The fetuses of pregnant women, especially those mothers exercising vigorously, may be especially vulnerable due to the much higher affinity of fetal hemoglobin for CO compared to adult hemoglobin.

Chemical: Persons exposed to methylene chloride are more sensitive to the effects of CO exposure because CO is a metabolite of methylene chloride. Smokers will experience an additional burden of COHb since their carboxyhemoglobin levels are already elevated by smoking.

V.   Acute Toxicity to Laboratory Animals

Four-hour LC_{50}s for rats, mice, and guinea pigs are 1,807, 2,444, and 5,718 ppm (2,078, 2,811, and 6,576 mg/m³) CO, respectively (Rose *et al*., 1970). The lowest reported lethal concentration in dogs (the level at which one dog in the group died) was 4,000 ppm (4,600 mg/m³) CO for a 46-minute exposure (RTECS, 1994).

Anesthetized, open-chested dogs were exposed for 2 hours to air or to 100 ppm (120 mg/m³) CO (Aronow *et al*., 1979). Postexposure blood COHb levels were 6.5%. Electrical shocks of varying amplitude were applied to the myocardium to induce ventricular fibrillation. A decrease in the ventricular fibrillation threshold was observed in CO-exposed dogs compared to controls.

A dose-dependent decrement in performance was observed in maze running in rats following a 30-minute exposure to 2,000, 3,000, 3,500, or 4,000 ppm (2,300, 3,500, 4,030, or 4,600 mg/m³) CO (Annau, 1987). As exposure concentration increased, a greater proportion of rats failed to reach the goal and there was a decrease in goal directed behavior. The authors compare these results to lethargy and confusion observed in human victims following smoke inhalation.

VI.   Reproductive or Developmental Toxicity

Carbon monoxide is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause developmental toxicity.

A prospective study of pregnancy outcomes reported an increased risk of fetal neurologic disorders following maternal CO poisoning. This resulted in blood COHb levels of 21% or greater with symptoms including, but not limited to, disorientation, depressed sensorium, limited and inappropriate response to simple commands, and coma (Koren *et al*., 1991).

Pregnant rats were exposed to 150 ppm (170 mg/m³) CO continuously for the duration of gestation (Fechter and Annau, 1980). The offspring of the CO exposed rats exhibited decreased

birth weights and decreased growth rates prior to weaning. Behavioral testing revealed decreased performance on negative geotaxis (performing a 180° turn to face the top of an incline plane) and homing (orientation by the rat pup towards its home cage) tests in offspring of CO-exposed rats compared to controls.

Pregnant mice were exposed to 65, 125, 250, or 500 ppm (75, 144, 290, or 580 mg/m³) CO continuously on days 7-18 of gestation (Singh and Scott, 1984). A significant increase in fetal mortality was observed following maternal exposure to 500 ppm CO. A significant decrease in fetal body weight was observed following maternal exposure to CO at concentrations of 125 ppm or greater. Delayed ossification was observed in all dose groups but was not statistically significant or dose-dependent. No significant developmental effects were observed following maternal exposure to 65 ppm CO.

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

Level Protective Against mild adverse effects)

Because angina is a severe effect, there is no level protective against mild adverse effects.

Reference Exposure Level (level protective against severe adverse effects) :**20 ppm (23 mg/m³)**

Study	Aronow, 1981
Study population	humans
Exposure method	inhalation
Critical effects	aggravation of angina and other cardiovascular diseases
LOAEL	2% carboxyhemoglobin in blood
NOAEL	1.1%-1.3% carboxyhemoglobin in blood (corresponds to 20 ppm CO, calculated toxicokinetically)
Exposure duration	1 hour
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	20 ppm (23 mg/m³, 23,000 µg/m³)

Level Protective Against Life-threatening Effects

The NRC (1984) selected an EEGL of 400 ppm (460 mg/m³). The NRC document states that 400 ppm (460 mg/m³) was determined as the concentration of CO to which a 1-hour exposure would result in a carboxyhemoglobin (COHb) level of less than 10% in resting individuals. The committee cautions that sensitive individuals, such as persons with angina or heart disease, should not be exposed to concentrations approaching the EEGL as they may incur serious adverse health effects. The Coburn model (Coburn *et al*., 1965) estimates that only at a low ventilation rate (e.g., 5 liters/ min) would a 1-hour exposure to 400 ppm CO result in a COHb of less than 10%. At a ventilation rate of 15 liters/min, the same exposure would be expected to result in 16% COHb (Shusterman, 1994). The NRC (1984) acknowledged that at the EEGL of 400 ppm physical activity might increase the COHb to 20% or higher by 1 hour. The exposure level of 400 ppm may not protect sensitive subpopulations, since persons with cardiovascular disease would experience serious health effects such as angina pectoris (Aronow, 1981; Allred *et al*., 1989). According to NRC (1984), "It must also be stressed that, in people with atherosclerosis, the danger of myocardial infarction, angina pectoris, or even sudden death might be increased by exposure to CO." The EEGL of 400 ppm is recommended as the level protective against life-threatening effects with a cautionary note that people with heart disease, as noted by NRC, may not be protected. In addition, the NRC notes that the EEGL is derived for resting individuals. Individuals engaged in activities other than resting will achieve a higher COHb level and will beat increased risk.

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ACUTE TOXICITY SUMMARY

CARBON TETRACHLORIDE

(carbon chloride; carbon tet; freon 10; halon-104; methane tetrachloride; necatrine; tetrachlorocarbon; tetrachloromethane; tetraform; tetrasol; univerm)

CAS Registry Number: 56-23-5

I.   Acute Toxicity Summary (for a 7-hour exposure)

Inhalation reference exposure level	**1,900 μg/m³**
Critical effect(s)	toxicity to the developing fetus
Hazard Index target(s)	Reproductive/developmental; Nervous System; Alimentary Tract

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

Description	colorless liquid
Molecular formula	CCl_4
Molecular weight	153.24
Density	1.59 g/cm^3 @ 20°C
Boiling point	76.54°C
Melting point	-23°C
Vapor pressure	91.3 mm Hg @ 20°C
Flashpoint	critical temperature = 283.1°C
Explosive limits	not found
Solubility	soluble in acetone, ethanol, benzene, carbon disulfide; moderately soluble in water
Odor threshold	96 ppm (604 mg/m³) (Amoore and Hautala, 1983)
Odor description	sweet, chloroform-like odor
Metabolites	chloroform; carbene radical, carbon monoxide (Ahr *et al.*, 1980)
Conversion factor	1 ppm = 6.3 mg/m³

III.   Major Uses or Sources

Carbon tetrachloride is used as a solvent for the recovery of tin in tin-plating waste and in the manufacture of semiconductors. It is also used in petrol additives, refrigerants, metal degreasing, and as a catalyst in the production of polymers. Carbon tetrachloride is also used as a chemical intermediate in the production of fluorocarbons and pesticides (HSDB, 1994).

IV. Acute Toxicity to Humans

Hepatotoxicity is the most sensitive and best studied toxic endpoint for CCl_4 exposure (Andrews and Snyder, 1991). The human data on hepatic effects of CCl_4 are based on numerous clinical case reports with poorly defined exposure conditions. The hepatotoxic effects, which may occur more readily in persons regularly consuming alcohol, are often reversible over the course of several weeks (Fry *et al*., 1959).

Bioactivation of CCl_4 into reactive metabolites by hepatic cytochrome P-450 enzymes results in hepatic centrilobular degeneration and necrosis (Andrews and Snyder, 1991). After a single dose of CCl_4, evidence of centrilobular necrosis is visible within 12 hours and obvious necrosis occurs by 24 hours. If no further injury occurs, the lesions begin to repair after 24 hours, and may be restored to normal after 14 days recovery. A reduction of P450 activity in the liver also occurs and is due to irreversible binding by reactive metabolites and subsequent inhibition of the P450 enzymes that metabolize CCl_4 (Andrews and Snyder, 1991).

Mucosal irritation and CNS effects have also been reported following CCl_4 exposure. In one of the first controlled human studies on the effects of CCl_4, Davis (1934) observed headaches, nausea, and vomiting in subjects exposed to 317 ppm (1,997 mg/m³) for 30 minutes. Stewart *et al*. (1961) exposed 6 human volunteers to 49 ppm (309 mg/m³) CCl_4 for 70 minutes, or to 10-11 ppm (63-69 mg/m³) CCl_4 for 3 hours. The subjects reported no irritation to the eyes or respiratory tract. A Romberg test and a heel to toe test (tests of central nervous system function) were normal in these subjects immediately following exposure, but one individual had elevated urine urobilinogen levels 7 days following exposure. The magnitude of the elevation of urinary urobilinogen was not given. Two of 4 individuals exposed to 49 ppm (309 mg/m³) CCl_4 also exhibited decreased serum iron, although in one the decrease was still within the normal range.

Predisposing Conditions for CCl4 Toxicity

Medical: Individuals with compromised liver function may be more susceptible to CCl_4-induced hepatotoxicity.

Chemical: Co-exposure to ethanol, acetone, or isopropanol is known to potentiate the toxicity of carbon tetrachloride (Charbonneau *et al*., 1986; Cornish and Adefuin, 1966). Exposure to other chlorinated compounds, such as chlordecone, also potentiates the toxicity of CCl_4 (Curtis *et al*., 1979).

V. Acute Toxicity to Laboratory Animals

A concentration of 7,300 ppm (45,990 mg/m³) CCl_4 was reported to be lethal to 1 out of 10 rats after a single, 2-hour exposure (Adams *et al*., 1952). In this study, one rat out of 30 died after a 10-hour exposure to 3,000 ppm (18,900 mg/m³). Delayed effects from these exposures included weight loss, abnormal behavior and appearance, and additional mortality. Rats surviving these exposures exhibited liver injury evidenced by serum phosphatase, increased prothrombin clotting time, fatty degeneration, and enlargement of the liver.

A 4-hour inhalation exposure to 250 ppm (1,575 mg/m³) CCl_4 resulted in increased serum glutamic-oxalacetic transaminase (SGOT) activity in rats, indicative of hepatic damage (Cornish and Block, 1960). Exposure of these rats to a concentration of 100 ppm for 4 hours did not result in changes in SGOT activity.

Kim and coworkers (1990) showed that administration of a range of concentrations from 10 mg/kg to 1,000 mg/kg CCl_4 by gavage to rats resulted in a dose-dependent increase in serum levels of hepatic enzymes, decrease in hepatic cytochrome P-450 activity, and an increase in centrilobular lesions in the liver. In this study, 10 mg/kg was the LOAEL for hepatocellular changes and elevated serum enzymes. At low doses, the hepatocellular effects of CCl_4 are reversible, while at higher doses necrosis and irreversible damage occur (Gerhard *et al*., 1970).

In addition to its hepatocellular toxicity, CCl_4 also has been shown to affect the immune system. Mice exposed orally to 500 mg/kg CCl_4 exhibited suppressed T-cell dependent immune responses as measured by decreased splenic antibody forming cells. These mice also had elevated plasma interleukin-2 and transforming growth factor-β1 measured 24 and 48 hours after exposure (Delaney *et al*., 1994). However, a previous study showed that hepatotoxicity from CCl_4 occurs at much lower concentrations than does toxicity to the immune system (Smialowitz *et al*., 1991).

A physiologically-based pharmacokinetic model for carbon tetrachloride has been developed in the rat (Paustenbach *et al*., 1988). In this model, it was estimated that 60% of inhaled CCl_4 is metabolized, and that 96% of the metabolized CCl_4 forms biological adducts which degrade slowly with a half-life of 24 hours. The remaining 4% of the metabolized CCl_4 becomes CO_2.

VI.   Reproductive or Developmental Toxicity

No studies were available on the reproductive effects of CCl_4 in humans. Significant decreases in fetal body weight, crown-rump length, and ossification of sternebrae were observed in rats exposed to 300 ppm (1,890 mg/m³) CCl_4 on days 6-15 gestation (Schwetz *et al*., 1974). High doses (0.3 ml/100 g body weight) of CCl_4 injected intraventricularly caused marked histologic injury to the chorionic epithelium of the placenta in rats (Tsirel'nikov and Tsirel'nikova, 1976). Carbon tetrachloride has not been listed as a developmental toxicant under Proposition 65.

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

Mild Adverse Effect Level

Because the most sensitive endpoint found in the inhalation toxicity literature was developmental toxicity, a potentially disabling effect, there is no mild adverse effect level available for CCl_4.

Determination of Acute Reference Exposure Levels for Airborne Toxicants
March 1999

Reference Exposure Level (protective against severe adverse effects for a 7 hour exposure):
$$0.3 \text{ ppm } (1,900 \text{ } \mu g/m^3)$$

Because of the uncertainty in extrapolating from repeated dose studies to a one-hour concentration, for the reproductive/developmental endpoint, we have chosen to use a single day exposure as the basis for the REL. Thus, the REL for CCl_4 is for a 7 hour exposure.

Study	Schwetz *et al*. (1974)
Study population	pregnant rats
Exposure method	inhalation exposure to 0, 300, or 1,000 ppm for 7 hours/day on days 6-15 of gestation
Critical effects	fetal growth retardation (decreased crown-rump length and body weight)
LOAEL	300 ppm
NOAEL	not determined in this study
Exposure duration	7 hours/day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Reference Exposure Level	0.3 ppm (1.9 mg/m³; 1,900 µg/m³)

Level Protective Against Life-threatening Effects

Rats (5-30 per group, males and females) were exposed to single concentrations of CCl_4 for durations varying from 6 minutes to 10 hours (Adams *et al*., 1952). Concentrations used ranged from 3,000 to 19,000 ppm (45,990 to 119,700 mg/m³) CCl_4. Mortality was measured for several weeks following the exposure.

1-Hour Mortality Data in Rats from CCl_4 Inhalation

Concentration (ppm x 10^3)	7.3	8.4	9.4	10.8	12.0	12.0	15.4	17.8	19.0	24.0
Response	0/20	0/20	1/10	1/10	3/10	4/10	7/10	8/10	9/19	20/20

Adams et al. (1952)

A benchmark dose approach used a log-normal probit analysis (Crump, 1983) of rat lethality data from Adams *et al*. (1952). Exposure durations from 1-4 hours were included in the analysis. Concentrations of CCl_4 were adjusted to approximate equivalent 1-hour concentrations using the equation $C^n * T = K$, where n = 2.8 (ten Berge *et al*., 1986). The concentration associated with a 5% incidence of lethality was 8,557 ppm (53,909 mg/m³); the benchmark concentration (BC_{05}) for this response, the 95% lower confidence limit on this concentration, was 7,010 ppm (44,163 mg/m³). An uncertainty factor (UF) of 3 was applied to the BC_{05} to account for

interspecies variation since the BC_{05} accounts for some degree of individual variation and a UF of 10 was used to account for human individual variability. The total UF was 30.

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

The level protective against life-threatening effects for CCl_4 is therefore 234 ppm (1,470 mg/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for 1% and 5% response rates are compared below. Refer to section IX of this toxicity summary for the graphic representation of benchmark concentration derivation.

Response rate	MLE (ppm)	95% LCL (ppm)
1%	6,646	4,976
5%	8,557	7,010

NIOSH (1995) lists a revised IDLH of 200 ppm based on acute inhalation toxicity in humans.

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ACUTE TOXICITY SUMMARY

CHLORINE

(bertholite)

CAS Registry Number: 7782-50-5

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

Inhalation reference exposure level   **210 μg/m³**
Critical effect(s)   throat irritation
Hazard Index target(s)   Respiratory System; Eyes

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

Description	yellow/green gas
Molecular formula	Cl_2
Molecular weight	70.9
Density	2.9 g/L
Boiling point	-34.6°C
Melting point	-101°C
Vapor pressure	5 atm @ 10.3°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	slightly soluble in water
Odor threshold	0.2 ppm
Odor description	bleachy, pungent odor (Ruth, 1986)
Metabolites	N-chloro-derivatives of biomolecules; reacts with water to form hypochlorous acid, hydrochloric acid
Conversion factor	1 ppm = 2.9 mg/m³

Chlorine, although non-combustible by itself, reacts explosively with many chemicals including: acetylene, acetaldehyde, alcohols, alkyl isothiourea, salts, ammonia, benzene, t-butanol, carbon disulfide, diborane, diethyl ether, and glycerin.

III.   Major Uses or Sources

Chlorine is used in the manufacture of rubber and plastics, pesticides, and other chlorinated hydrocarbons. It is also extensively used to bleach woodpulp and paper and is used as chlorinated lyme in the bleaching of all kinds of fabrics. It is used in the cleaning of dairy equipment and as a disinfectant in laundries and dishwater. It is also used in odor control and as a demulsifying agent in the treatment of water. When acid is mixed with household bleach (a dilute solution of sodium hypochlorite) in an attempt to increase the cleaning power of bleach, chlorine gas is released. Internationally, chlorine gas is the major source of toxic release incidents (Davis *et al*., 1989).

IV.   Acute Toxicity to Humans

Chlorine exposure in the range of 3-6 ppm (9-17 mg/m³) results in stinging or burning sensations from irritation and corrosion of mucous membranes including the eyes, skin, and the respiratory system (Baxter *et al*., 1989; Wither and Lees, 1985). In high concentrations, inhalation may result in necrosis of the tracheal and bronchial epithelium as well as in pulmonary edema. Delayed pulmonary edema may also develop up to 24 hours following acute exposure. Death at high exposure is mainly from respiratory failure or cardiac arrest due to toxic pulmonary edema. Bronchopneumonia may be a common and potentially lethal complication of pulmonary edema.

The odor threshold is not an adequate warning sign for overexposure to chlorine since the sense of smell rapidly accommodates at low concentrations, near the ACGIH 8-hour TLV of 0.5 ppm (1.45 mg/m³) (Reprotext, 1999).

Anglen (1981) showed that exposure of "up to" 29 volunteer subjects to chlorine resulted in concentration- and time-dependent severity of irritation to the eyes and throat. In this study, volunteers were exposed for 4 or 8 hours to chlorine concentrations of 0, 0.5, 1.0, and 2.0 (4 hour exposures only) ppm. Severity of irritation was subjectively measured by questionnaires from the subjects every 15-60 minutes, and was divided into 5 categories, which ranged from barely perceptible to clearly objectionable. A consistent, statistically significant increase in throat irritation in subjects exposed to 1.0 ppm chlorine began at 1 hour into exposure. Consistent throat irritation was not observed in subjects during a 4-hour exposure to 0.5 ppm. However, 0.5 ppm chlorine produced throat irritation and an urge to cough after a 4-hour exposure (Anglen *et al*., 1980). A statistically significant decrease in group mean FEV_1 (-15.3%) was observed following 8-hour exposure to 1.0 ppm chlorine.

D'Alessandro *et al*. (1996) studied 10 subjects, five with and five without airway hyperresponsiveness (HR) after exposure to 1.0 ppm chlorine and five persons, all with HR, to 0.4 ppm chlorine for 1 hour by mouth-breathing facial mask. After inhalation of 1.0 ppm, there was a significant fall in FEV_1 immediately following exposure among both normal and HR subjects. The fall was greater among the HR subjects compared with the normals (p = 0.04). Specific airway resistance (SR_{aw}) increased to a greater degree among the HR group compared with normal subjects (p = 0.04). Among all 10 subjects, the proportional change in FEV_1 after exposure to 1.0 ppm chlorine correlated with baseline reactivity (Spearman rank correlation r = 0.64, p < 0.05). At 24-h follow-up, there were no significant chlorine-related pulmonary function deficits. After 0.4 ppm chlorine inhalation by the 5 persons with HR, there was no significant pulmonary function effect. These data indicated that persons with hyperreactive airways manifest a clinically significant, exaggerated airway response to chlorine at 1.0 ppm, but not at 0.4 ppm.

Rotman *et al*. (1983) studied clinically significant changes in pulmonary function tests (PFTs) following controlled chlorine exposures. Using a group of 9 volunteers (8 normal volunteers plus 1 volunteer with allergic rhinitis), data were collected on several PFTs following 4- and 8-hour exposures to 0, 0.5, and 1.0 ppm (0, 1.45, and 2.9 mg/m³) chlorine. The subject with allergic rhinitis was excluded from the final group mean statistical analysis due to the severity of his response to chlorine exposure. Although 8-hour exposure to 1 ppm chlorine resulted in

clinically significant decreases in FEV_1 (4 subjects) and clinically significant increases in specific airway resistance (SR_{aw}) (4 subjects), there were no reports of respiratory distress among the normal subjects (Rotman *et al*., 1983; Rotman, 1994). The NOAEL for a clinically significant increase (100%) in SR_{aw} and clinically significant decrease (20%) in FEV_1 was 1 ppm for a 4-hour exposure.

The subject with allergic rhinitis developed shortness of breath and wheezing following 4-hour exposure to 1 ppm chlorine and left the exposure chamber due to development of shortness of breath and wheezing (Rotman *et al*., 1983). Pulmonary function tests showed that this subject had a clinically significant increase in pulmonary SR_{aw} and a clinically significant decrease in FEV_1 when compared to sham exposure of 8 healthy subjects and when compared to the subject's own sham control values. The subject also had compromised lung function relative to the 8 healthy subjects during sham exposures. The pulmonary tests under sham control conditions also showed that exposure of the sensitive subject to 0.5 ppm chlorine for 8 hours, but not 4 hours, resulted in a clinically significant, greater than 100% increase in SR_{aw} and clinically significant, greater than 20% decrease in FEV_1. However, no clinical symptoms and no apparent indication of bronchoconstriction were reported at this concentration.

The Rotman study is supported by two earlier human studies, which suggest that some test subjects develop respiratory distress at similar concentrations of chlorine. In a study by Rupp and Henschler (1967), the concentration of chlorine was gradually increased from 0 to 1.3 ppm over a 50 minute period. One subject developed shortness of breath and a severe headache following exposure to 1.0 to 1.3 ppm chlorine for 35 to 50 minutes. NIOSH (1976) suggested that this subject was sensitive to the irritant effects of chlorine. In a study by Beck (1959), 1 out of 10 subjects judged a 20 minute exposure to 1 ppm chlorine as unbearable due to sensory skin and conjunctival irritation, headache, and slight respiratory distress. It was not indicated in the study if this was a "sensitive" individual and it was unclear if clinical symptoms indicative of bronchoconstriction had actually occurred.

In another human exposure study, 6-8 healthy 'expert' volunteers (people familiar with irritant gases and laboratory exposure situations) easily tolerated exposure to 0.5, 1, and 2 ppm chlorine for 2 hours (Joosting and Verberk, 1975). Exposure of 3 expert volunteers to 4 ppm chlorine for 2 hours was considered a limit, due mainly to throat irritation. One of the 3 volunteers actually left the exposure chamber after 75 minutes, but it was unclear if this was due to throat irritation. However, no significant changes in ventilatory capacity (VC, FEV, and FIV) were noted at any concentration following exposure. The researchers considered 4 ppm to be unbearable for non-informed (non-expert) healthy subjects.

In a human poisoning case, a young male with a questionable history of asthma was exposed to 0.05 ounce/1,000 ft^3 ($^1/_{20}$ ounce per 1,000 cubic feet (equivalent to 19 ppm)) of chlorine for several minutes (Monto and Woodall, 1944). Immediately following exposure, the patient did not complain of any unusual irritation or shortness of breath. Several hours later, however, the subject was hospitalized with dyspnea and wheezing, with rales over the chest area. The diagnosis was pulmonary edema. The patient's past history included one questionable asthmatic attack in which he was subsequently told that he was sensitive to dust.
Predisposing Conditions for Chlorine Toxicity

Medical: Persons with skin, eye, respiratory, cardiovascular or neurologic conditions and smokers may be more sensitive to chlorine (Reprotext, 1999). Persons who are sensitive to irritants, such as those with RADS, may react strongly to chlorine.

Chemical: Smokers may be more sensitive to the effects of chlorine gas (Das and Blanc, 1993).

V.   Acute Toxicity to Laboratory Animals

One of the most comprehensive acute lethality studies for chlorine was performed by Zwart and Woutersen (1988). Lethality data were collected for 4 exposure durations (5, 10, 30, and 60 minutes) in rats and 2 exposure durations (10 and 30 minutes) in mice. Clinical observations during exposure included restlessness, eye irritation, dyspnea, and nasal discharge. Nearly all rats that died during the course of the investigation did so during exposure or up to 1 week after exposure. However, many mice died during the second week post-exposure, which suggested that these delayed deaths were the result of secondary infection (Zwart and Woutersen, 1988). Post-mortem examination noted swollen lungs and increased lung weights in exposed rats and mice, indicative of pulmonary edema.

For studies that published adequate lethality data, the LC_{50}, MLE_{05} (maximum likelihood estimate corresponding to 5% lethality), BD_{05}, and BD_{01} (benchmark dose at the 95% lower confidence interval of the MLE_{05} and MLE_{01}, respectively) were determined by log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) and are shown in Table 1.

Table 1. Animal Lethality Benchmark Dose Determinations in ppm for Chlorine

Reference	Species	Exposure Time (min)	LC_{50} 60 min[1]	MLE_{05} 60 min[1]	BD_{05} 60 min[1]	BD_{01} 60 min[1]
MacEwen & Vernot, 1972	rat	60	294	233	197	169
	mouse	60	134	102	73	58
Zwart & Woutersen, 1988	rat	60	483	383	311	265
	mouse	30	285	164	-[2]	-[2]
	mouse	varied[3]	816	494	363	265
Schlagbauer & Hensc., 1967	mouse	30	105	76	54	43
Underhill, 1920	dog	30	500	228	111	66

[1] *Exposure time was extrapolated to 60 minutes using a modification of Haber's equation ($C^n * T = K$) where n = 2.8 for rats and 1.3 for mice.*

[2] *The 30 minute mouse lethality data were insufficient for benchmark dose determination.*

[3] *Lethality data for 2 durations (10 and 30 minutes) were pooled and normalized to a 1-hour exposure using the equation $C^n * T = K$, where n = 1.3.*

The values in Table 1 were extrapolated to equivalent 60-minute exposures, where needed, using a modification of Haber's equation, $C^n * T = K$. The exponent "n" was determined from the lethality data provided by Zwart and Woutersen (1988) for each species by varying the term n in

a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The lethality data for chlorine indicate that the exponent is dependent on exposure duration ("n" increases with increasing exposure time). The rat data provide an $n = 2.8$ for extrapolation from 30 minute to 1 hour exposures. However, for exposures of 5-10 minutes in duration, the rat data indicate that $n = 1$ for extrapolation to 1-hour exposure. Extrapolation of the 10 and 30 minute mouse lethality data to 1-hour provides an $n = 1.3$.

The lethality data by Zwart and Woutersen (1988) probably provide the most accurate estimation of the BD_{05} for acute chlorine exposure. Inspection of the values in Table 1 suggests that mice are more sensitive to the lethal effects of chlorine. However, the 30-minute mouse data generated by the Zwart and Woutersen (1988) study were not usable for determining low dose lethality, as the variability of the dose-response slope was too high. By extrapolating the 10- and 30-minute mouse lethality data to 1-hour and pooling the values, a benchmark dose can be estimated from the mouse data (see Table 1). Calculating the BD_{05} by this method for mice results in a value similar to that determined for rats using data by the same authors.

Zwart and Woutersen (1988) determined lethality values higher than previous studies. However, the authors felt that the earlier studies were deficient, partly due to high fluctuations in chlorine concentration at each dose.

In other acute animal studies, a dose-response study for chlorine exposure in rabbits was performed by Barrow and Smith (1975). While the number of rabbits per group was not included in the report for all dose levels, a 30-minute LOAEL (500 ppm) and NOAEL (250 ppm) for lethality were determined. The study also identified a non-lethal, 30-minute LOAEL and NOAEL of 100 and 50 ppm, respectively, for severe pulmonary function changes and development of pulmonary edema.

Exposure of rats and mice to 9-11 ppm for 6 hours produced severe lesions in specific locations in both olfactory and respiratory epithelia of the nasal passages with a widespread loss of cilia (Jiang *et al*., 1983).

In order to develop an animal model of the asthma-like abnormality known as reactive airways dysfunction syndrome (RADS; acute, irritant-induced asthma), Demnati *et al*. (1995) evaluated the effects of exposure to various levels of chlorine on airway mucosa and lung parenchyma. Seventy-four Sprague-Dawley rats were exposed to air (controls) or to 50, 100, 200, 500, and 1,500 ppm of chlorine for 2 to 10 minutes. Histological assessment was performed at 1, 3, 6, 12, 24, and 72 hours after exposure. Exposure to 500 ppm did not induce significant histological changes. Exposure to 1,500 ppm for 2 minutes induced perivascular edema and the appearance of focal mild inflammation, whereas exposure to 1,500 ppm for 10 minutes caused profound histological changes, including airspace and interstitial edema associated with bronchial epithelial sloughing at 1 hour; decreased edema and the appearance of mucosal polymorphonuclear leukocytes at 6 to 24 hours (maximal at 12 hours); and epithelial regeneration, manifested by hyperplasia and goblet cell metaplasia, at 72 hours. Demnati *et al*. (1995) concluded that acute exposure to chlorine at 1500 ppm for 10 minutes induces significant airway mucosal abnormalities that vary over a short period of time.

Winternitz et al. (1920) report severe lung edema and desquamation of the trachea and bronchial epithelium in dogs exposed to chlorine gas at lethal concentrations (concentration not reported). Bronchial constriction from the irritant properties was noted.

VI.   Reproductive or Developmental Toxicity

No information is available on reproductive toxicity of chlorine in humans. Meier *et al*. (1985) determined that chlorine, predominantly in the form of hypochlorite, causes sperm head abnormalities when given in the drinking water at 4 mg/kg per day in mice. However, these effects were observed after three weeks exposure but were not present after five weeks.

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

Reference Exposure Level (protective against mild adverse effects):

$$\text{0.07 ppm (210 µg/m}^3\text{)}$$

Study	Anglen, 1981
Study population	29 adult volunteers
Exposure method	inhalation of 1.0 ppm chlorine for up to 8 hr
Critical effects	itching or burning of the throat
LOAEL	not determined
NOAEL	1 ppm
Exposure duration	30 minutes
Extrapolated 1 hour concentration	0.71 ppm (1^2ppm $* 0.5$ h $= C^2 * 1$ h)
	(see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.07 ppm (0.21 mg/m³; 210 µg/m³)

A published value of 3.5 for "n" is based on animal lethality data for chlorine (Ten Berge *et al*., 1986). However, in this case, a value of 2 for "n" appears to be more appropriate based on graphic representation of the human throat irritation data in the Anglen study.

Level Protective Against Severe Adverse Effects

In the D'Alessandro *et al*. (1996) study, after inhalation of 1.0 ppm chlorine for 1 hour, there was a significant fall in FEV_1 among subjects with hyperreactive airways. After 0.4 ppm chlorine inhalation by the 5 persons with hyperreactive airways, there was no significant effect on pulmonary function. The data indicated that persons with hyperreactive airways, a sensitive subpopulation, manifest a clinically significant, exaggerated airway response to chlorine at 1.0 ppm, but not at 0.4 ppm. Since the exposure was for 1 hour in a sensitive population, no time adjustment or uncertainty factor is applied. Thus 0.4 ppm (1.2 mg/m³) is a level protective against severe adverse effects for chlorine. (The sensitive individual in the study by Rotman *et*

al. (1983) and less reliable evidence for respiratory distress in sensitive individuals from 3 other studies (Rupp and Henschler, 1967; Beck, 1959; Monto and Woodall, 1940) resulted in a severe adverse effect level of 1 ppm after time extrapolation from 4 hours to 1 hour. The D'Alessandro *et al*. (1996) study tested sensitive subjects. The overall uncertainty was lower, thus it was selected as the key study.)

Level Protective Against Life-threatening Effects

The comprehensive chlorine lethality study conducted in rats and mice by Zwart and Woutersen (1988) provides the best data for estimation of the life threatening level. The results suggested that the "n" for the equation $C^n \times T = K$ is dependent on exposure duration. However, the 1-hour lethality data for rats were sufficient for determining a BD_{05}. Data from earlier lethality studies in the literature (see Table 1) produced lower LD_{50}s and BDs than those produced by Zwart and Woutersen (1988). The researchers felt that continuous monitoring of the chlorine gas concentration to keep the concentration extremely stable during exposure produced higher, but more accurate, values. Based on probit analysis of the data, a BC_{05} of 311 ppm was determined in rats for 1-hour exposure to chlorine. Uncertainty factors of 3 to account for interspecies differences and 10 to account for the increased susceptibility of sensitive human individuals were applied to the BC_{05}.

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

The total uncertainty factor was 30. Incorporation of these factors resulted in a level protective against life-threatening effects of 10 ppm (29 mg/m³) for 1-hour exposure to chlorine.

NIOSH (1995) reports a (revised) IDLH for chlorine of 10 ppm based on acute inhalation toxicity data in humans.

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ACUTE TOXICITY SUMMARY

CHLOROFORM

(trichloromethane, formyl trichloride, methenyl trichloride, methyl trichloride)

CAS Registry Number: 67-66-3

I.   Acute Toxicity Summary (for a 7-hour exposure)

Inhalation reference exposure level	**150 μg/m³**
Critical effect(s)	histological changes in the nasal epithelium
Hazard Index target(s)	Respiratory System; Nervous System; Reproductive/developmental

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

Description	colorless liquid
Molecular formula	$CHCl_3$
Molecular weight	119.49
Density	1.483 g/cm^3 @ 20°C
Boiling point	61°C
Melting point	-63.5°C
Vapor pressure	200 mm Hg @ 25°C
Flashpoint	not applicable; non-flammable liquid, vapor will burn at high temperatures
Explosive limits	not applicable
Solubility	soluble in water, carbon tetrachloride, carbon disulfide, alcohols, benzene, ethers, oils
Odor threshold	192 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, suffocating (AIHA, 1989)
Metabolites	carbon dioxide, phosgene
Conversion factor	1 ppm = 4.88 mg/m³ @ 25°C

III.   Major Uses or Sources

Chloroform ($CHCl_3$) is used in industry and laboratory settings as a solvent for adhesives, pesticides, fats, oils, and rubbers. It is also used as a chemical intermediate for fluorocarbon 22, dyes, pesticides, and tribromomethane. It is produced as a byproduct of water and sewage chlorination. Chloroform is also produced in large quantities as a byproduct of wood pulp chlorination in the production of paper products.

IV.   Acute Toxicity to Humans

In humans, pulmonary excretion was found to be the major means of elimination following a single oral dose of 0.5 or 1.0 g $CHCl_3$ (Fry *et al*., 1972). Up to 68% of the unchanged $CHCl_3$ and up to 50.6% of the metabolite carbon dioxide were found in the expired air within eight hours of administration. Chloroform in the urine accounted for less than 1% of the oral dose.

Signs of acute $CHCl_3$ toxicity include fainting, vomiting, dizziness, salivation, fatigue, headache, respiratory depression, and coma (IRIS, 1993). Few reports were found in the literature on the acute toxicity of $CHCl_3$ to humans in chamber studies. However, a number of case reports exist stemming from its use an anesthetic.

Cardiac arrhythmia, brachycardia, and cardiac arrest resulting in death have been reported following the use of $CHCl_3$ as an anesthetic in concentrations of approximately 8,000 to 22,500 ppm (39,000 to 110,000 mg/m³) (Payne, 1981). Severe liver and kidney damage were noted in an adult male following fatal suicidal ingestion of approximately 6 ounces of $CHCl_3$ (Piersol *et al*., 1933).

The incidence of liver enlargement and jaundice was increased in workers exposed to 2-204 ppm (10-995 mg/m³) $CHCl_3$ for at least one year (Bomski *et al*., 1967). Jaundice was reported in 31 workers occupationally exposed to 14-400 ppm (68-1,952 mg/m³) $CHCl_3$ for 6 months or less (Phoon *et al*., 1983).

Predisposing Conditions for Chloroform Toxicity

Medical: Persons with skin, eye, respiratory, liver, kidney or neurological conditions may be more sensitive to the effects of chloroform (Reprotext, 1999).

Chemical: Epinephrine (e.g., in bronchodilators) may potentiate the cardiac effects of chloroform exposure (Reprotext, 1999). Concurrent exposure to barbiturates has been shown to increase chloroform toxicity by induction of liver cytochrome P-450 activity (Cornish *et al*., 1973). The potentiation of chloroform-induced hepatotoxicity and nephrotoxicity by various alcohols and ketones is well documented (Cowlen *et al*., 1984; Iijima *et al*., 1983; Brown and Hewitt, 1984.)

V.   Acute Toxicity to Laboratory Animals

Beagle dogs exposed to 14,500 ppm (70,800 mg/m³) $CHCl_3$ survived an average of 202 minutes (Von Oettingen *et al*., 1949). The oral LD_{50} in male and female adult Sprague-Dawley rats is reported as 908 mg $CHCl_3$/kg and 1,117 mg $CHCl_3$/kg, respectively (Chu *et al*., 1980).

Hepatocellular necrosis was observed in adult female mice following a single 4-hour exposure to 200 ppm (976 mg/m³) $CHCl_3$ (Kylin *et al*., 1963). Hepatic fatty infiltration was noted following a single 4-hour exposure to 100 ppm (488 mg/m³) $CHCl_3$. Some studies report that chloroform renal toxicity is gender-dependent, while hepatotoxicity is similar in both sexes (Smith *et al*., 1983 and 1984; Hill *et al*., 1975; Pohl *et al*., 1984; Taylor *et al*., 1974).

Cytochrome P-450-mediated metabolism of $CHCl_3$ in the liver and kidneys has been demonstrated to produce phosgene in rats (Pohl *et al*., 1979). Hepatotoxicity following chloroform exposure is thought to be due largely to phosgene and other reactive $CHCl_3$ metabolites. Metabolism of $CHCl_3$ to phosgene is also responsible for the nephrotoxicity of $CHCl_3$ (Bailie *et al*., 1984).

Male rats were exposed to 1, 3, 10, 30, 100, or 300 ppm $CHCl_3$ 6 hours per day for 7 days (Mery *et al*., 1994). Statistically significant, concentration-dependent, bony proliferation was observed in the ethmoid turbinates of rats exposed to 10 ppm $CHCl_3$ or greater. Cellular hypertrophy and proliferation in the nasal pharyngeal and olfactory mucosal regions were also increased in a concentration dependent manner in rats exposed to 10 ppm $CHCl_3$ or greater. No adverse effects were observed following exposure to 3 ppm (15 mg/m³) $CHCl_3$.

VI.   Reproductive or Developmental Toxicity

Pregnant rats were exposed to 30, 100, or 300 ppm (150, 500, or 1,500 mg/m³) $CHCl_3$ for 7 hours per day on days 6-15 of gestation (Schwetz *et al*., 1974). A significant increase in the number of fetal resorptions and a decrease in fetal body weights and crown-rump lengths were observed in those animals exposed to 300 ppm $CHCl_3$. Following maternal exposure to 100 ppm $CHCl_3$, fetuses exhibited a significant increase in malformations including acaudia, imperforate anus, missing ribs and delayed sternal ossification. An increase in the incidence of wavy ribs and delayed skull ossification, as well as reduced fetal crown-rump length, were observed following maternal exposure to 30 ppm $CHCl_3$. Maternal toxicity was observed in all three exposure groups.

The incidence of abnormal sperm was significantly increased in male mice exposed to 400 ppm (1,952 mg/m³) $CHCl_3$ for 4 hours/day for 5 days (Land *et al*., 1981).

Chloroform has not been listed as a developmental or reproductive toxicant under Proposition 65.

VII.   Derivation of Acute Reference Exposure Level and Other Severity Levels

Reference Exposure Level (level protective against severe adverse effects; estimated for 7 hour exposure):   **0.03 ppm (150 μg/m³)**

Study	Schwetz et al (1974)
Study population	pregnant rats
Exposure method	inhalation exposures to 30, 100, 300 ppm for 7 h/d, days 6-15 of gestation
Critical Effect	fetotoxicity
LOAEL	30 ppm
NOAEL	not determined
Exposure duration	7 hours/day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Reference Exposure Level (7 *h*)	0.03 ppm (0.15 mg/m³; 150 μg/m³)

The study by Schwetz *et al*. (1974) is the only published developmental toxicity study of chloroform. Exposure of pregnant rats to 30 ppm (150 mg/m³) $CHCl_3$ for 7 hours per day on days 6-15 of gestation resulted in fetotoxicity as indicated by decreased crown-rump length and increased incidences of wavy ribs and skeletal ossification defects. Maternal toxicity was also observed. An abstract by Dilley *et al*. (1977) indicates an absence of teratological effects in rats exposed to 20,000 mg/m³ $CHCl_3$ on days 7-14 of gestation. The data from this study were not available for review, therefore, the Schwetz *et al*. study is used in developing the severe adverse effect level for chloroform. A NOAEL was estimated from the reported LOAEL using an uncertainty factor of 10. An additional uncertainty factor of 100 was applied to account for inter- and intraspecies differences. The level protective against severe adverse effects for a 7 hour exposure is estimated as 0.03 ppm (0.15 mg/m³).

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 based on acute inhalation toxicity in humans but the selection of the level is somewhat arbitrary and the IDLH does not make allowance for sensitive individuals.

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ACUTE TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

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

Inhalation reference exposure level   **29 µg/m³**
Critical effect(s)   mild respiratory irritation
Hazard Index target(s)   Respiratory System; Eyes

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

Description   colorless to faint yellow liquid
Molecular formula CCl_3NO_2
Molecular weight   164.4
Density   1.65 g/cm³ @ 20°C
Boiling point   112.4°C
Melting point   -64°C
Vapor pressure   5.7 mm Hg @ 0°C
Flashpoint   not applicable
Explosive limits: upper = not applicable
                              lower = not applicable
Solubility   0.16 g/100 mL water; miscible in benzene,
                                absolute alcohol, and carbon disulfide
Odor threshold   1.1 ppm (7.3 mg/m³)

Odor description   pungent, sweet, irritating odor resembling flypaper
                                (Prentiss, 1937)
Metabolites   unknown; photodegrades into phosgene
Conversion factor   1 ppm = 6.72 mg/m³ @ 25°C

III.   Major uses or sources

Chloropicrin is used as a fumigant for warehouses, cereals and grains. It is also a soil
insecticide, and is added in trace amounts as a warning agent in odorless gases such as methyl
bromide. Previously, it was used as a chemical warfare agent by the military because of its
strong irritancy and potency in inducing lacrimation.

IV.   Acute Toxicity to Humans

Data on the effects of chloropicrin on humans were collected post-World War I. The symptomatology in humans following an exposure to 50 mg/m³ for 1 hour includes intolerable irritation to the eyes and upper respiratory tract (Prentiss, 1937). The probable oral lethal dose in humans is between 5 and 50 mg/kg (HSDB, 1994). Inhalation of 2,000 ppm (13,340 mg/m³) for 10 minutes is reported to be lethal (HSDB, 1994). Lethality was also reported following a 10 minute exposure to 2.0 mg/L (2,000 mg/m³) chloropicrin (Prentiss, 1937). Death is due to acute effects on the upper and lower airways. Chloropicrin affects the medium and small bronchi primarily, but also injures the alveoli, resulting in pulmonary edema, which is often the cause of lethality (Clayton and Clayton, 1982; Gonmori *et al*., 1987). Flury and Zernik (1931) reported that exposure to a concentration of 26.8 mg/m³ (4 ppm) chloropicrin for a few seconds renders a person unfit for military action, although no clinical details were provided. Exposure to 1 ppm (6.7 mg/m³) chloropicrin causes immediate lacrimation and eye irritation (Grant, 1986). Systemically, chloropicrin reacts with sulfhydryl groups on hemoglobin to interfere with oxygen transport.

Predisposing Conditions for Chloropicrin Toxicity

Chemical: Persons with preexisting eye, skin, respiratory, or asthmatic conditions might be more sensitive (Reprotext, 1999).

Medical: Individuals with a high level of carboxyhemoglobin (e.g., smokers) may be more susceptible to the effects of chloropicrin on oxygen transport. Persons with underlying cardiopulmonary disease may be more sensitive to the irritant effects on the lung. Persons exposed to other lacrimators or irritants or with prevoius exposure to chloropicrin might be more sensitive (Reprotext, 1999).

V.   Acute Toxicity in Laboratory Animals

In guinea pigs and cats the inhalation LC_{Lo} is 800 mg/m³ for 20 min (HSDB, 1994). For rats, the LC_{50} is 96 mg/m³ for 4 hours, and the LC_{50} for mice is 9.9 ppm (66 mg/m³) for 4 hours (HSDB, 1994).

The RD_{50} is the concentration of a chemical in air which is associated with a 50% decrease in respiratory rate. The RD_{50} in animals has a predictable relationship to irritation in man (Kane *et al*., 1979). The RD_{50} in mice for chloropicrin is 53-60 mg/m³ (8-9 ppm) (Kane *et al*., 1979; TeSlaa *et al*., 1986). Chloropicrin exposure at the RD_{50} concentration caused lesions in both the upper and lower respiratory tract in mice (Buckley *et al*., 1984).

Lambert and Jackson (1920) reported on the pathology of chloropicrin poisoning in the dog. Concentrations of 900 to 1000 mg/m³ for 30 minutes killed more than half the dogs. Extreme lung edema, severe necrosis of the bronchi, congestion of the lung and dilatation of the heart were observed at necropsy. These authors described lethal concentrations in several different species (no sample size reported) to range from 370 (in the cat) to 740 mg/m³ (in the dog) for 30 minutes.

VI.   Reproductive or Developmental Toxicity

No animal studies or human exposures indicate that chloropicrin is embryotoxic or teratogenic.

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

Reference Exposure Level (protective against mild adverse effects):   4.4 ppb (29 μg/m³)

Study	Kane *et al*., 1979
Study population	mice
Exposure method	inhalation
Critical effects	decrease in respiratory rate by 50% (RD_{50})
LOAEL (RD_{50})	7.98 ppm (54 mg/m³) (RD_{50})
RD_{05}	0.79 ppm (5.3 mg/m³)
Exposure duration	10 minutes
Extrapolated 1 hour concentration	132 ppb (0.89 mg/m³)
	(0.79ppm * 1/6 h = C * 1 h)
	(see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Reference Exposure Level	4.4 ppb (0.029 mg/m³; 29 μg/m³)

In mice exposed for 10 minutes to 7.98 ppm chloropicrin, a decrease in respiratory rate by 50% (RD_{50}) was observed. Using the regression equation ($y = 9.54 + 44.87$ Log x) presented by Kane *et al*. (1979), the concentration associated with a 5% reduction in respiratory rate in mice (RD_{05}) was estimated to be 0.79 ppm. This is similar to the BC_{05}; an interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 10 were applied to the RD_{05}. The resulting REL is 4.4 ppb.

Level Protective Against Severe Adverse Effects

Eye irritation and lacrimation were observed in humans exposed to chloropicrin at 0.3 ppm (2 mg/m³) or higher for 10 minutes (Prentiss, 1937). AIHA (1993) determined an EPRG-2 of 0.2 ppm (1.3 mg/m³). The intent of the ERPG-2 level is to protect against painful eye irritation and lacrimation. However, the safety factor used to derive this level was not specified. Smyth (1956) stated that exposure to 4 ppm (27 mg/m³) for 2 minutes will "incapacitate a man." Adjusting the concentration for the 2-minute exposure to an equivalent concentration for a 1-hour exposure using the formula $C^n * T = K$, where n = 1, yields a value of 0.13 ppm (0.9 mg/m³). Dividing by a UF of 10 to account for sensitive individuals in the human population results in a level protective against severe adverse effects of 13 ppb (90 μg/m³).

Level Protective Against Life-threatening Effects

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

Exposure of mice to 336 mg/m³ (50 ppm) chloropicrin for 15 minutes caused death after 10 days (Clayton and Clayton, 1982). Brief exposures to 27 mg/m³ (4 ppm) chloropicrin may cause severe respiratory irritation in addition to vertigo, fatigue, gastrointestinal cramps, and diarrhea in humans (Fairhall, 1949). Application of the standard safety factors (1,000) to the value reported by Clayton and Clayton (1982), and time extrapolation to a 1-hour exposure would yield a concentration for a life threatening level that is lower than the EPRG-3 level of 3.0 ppm (20 mg/m³) recommended by AIHA (1992). NIOSH (1995) lists an IDLH of 2 ppm based on acute inhalation toxicity data in workers and animals. NIOSH also mentions that 4 ppm for a few seconds renders a worker unfit for activity. The IDLH makes no allowance for sensitive individuals.

VIII.   References

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ACUTE TOXICITY SUMMARY

METALLIC COPPER AND COPPER COMPOUNDS

Molecular formula	Molecular weight	Synonyms	CAS Registry Number
Cu	63.55	copper	7440-50-8
CuO	79.54	cupric oxide, copper oxide, copper (I) oxide	1317-38-0
CuSO$_4$	159.60	copper sulfate, blue vitrol, copper (II) sulfate, cupric sulfate, blue copper, blue stone	7758-98-7

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

Inhalation reference exposure level   **100 μg/m³**
Critical effect(s)   respiratory system defense mechanism
Hazard Index target(s)   Respiratory System

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

Description   reddish metal
Density   8.94 g/cm^3 @ 25°C
Boiling point   2595°C
Melting point   1083°C
Vapor pressure   1 mm Hg @ 1628°C
Flashpoint   not applicable
Explosive limits   not applicable
Solubility   soluble in nitric acid; very slightly soluble in
                          hydrochloric acid and ammonium hydroxide
Odor threshold   not applicable
Odor description   odorless
Metabolites   no data found
Conversion factor   not applicable

III.   Major Uses or Sources

Copper (Cu) is a widely used structural metal, particularly where high electrical and thermal conductivity are needed (ATSDR, 1990). Copper fumes are generated in copper and brass foundries, in smelters, and in the welding of copper-containing metals. Copper compounds are found in fungicides and other agricultural products, ceramics, and pyrotechnics. Airborne sources of copper include combustion of fuels and other materials containing copper.

Copper sulfate (CuSO$_4$), the most common copper salt, is used as a fungicide, as a component of electroplating solutions, as a chemical intermediate for other copper salts in dyes, and in the tanning of leather (ATSDR, 1990).

Copper oxide (CuO) is another common copper salt. It is used in insecticides, fungicides, and catalysts (HSDB, 1994). CuO is also used in fuel additives, cement, and wood preservatives.

IV.   Acute Toxicity to Humans

Following occupational exposures to copper dust, commonly reported reactions include metallic or sweet taste, upper respiratory tract irritation, and nausea (Whitman, 1962). An unpublished letter regarding occupational exposure to copper fumes reported that levels of 0.02-0.40 mg/m³ copper did not "cause complaints" while exposure to 1.0-3.0 mg/m³ copper for "short periods of time" resulted in a "sweet taste in the mouth" but no nausea (Whitman, 1957).

Inhalation exposure to copper fumes, usually from welding or smelting operations, may result in "metal fume fever." This condition results in headache, dryness of the mouth and throat, chills, fever, and muscle aches, usually beginning 4-8 hours after exposure to the oxides of various metals, including copper. Symptoms and signs spontaneously subside within 24-36 hours (ATSDR, 1990; Seaton and Morgan, 1984). Symptoms consistent with metal fume fever were reported by workers in a facility with airborne copper dust at concentrations of 0.03-0.12 mg/m³ (Gleason, 1968). Upper respiratory irritation has been reported, in addition to symptoms consistent with metal fume fever (fever, dyspnea, chills, headache, nausea, myalgia, cough, shortness of breath, a sweet metallic taste, and vomiting), in factory workers exposed to copper fumes for 1 to 10 hours as a result of cutting pipes known to contain copper (Armstrong *et al.*, 1983). The sweet taste experienced by workers from the Whitman (1957) report above is consistent with the onset of symptoms of metal fume fever.

Factory workers exposed to copper dust, CuO, and several other copper salts reported symptoms of eye, nose, and throat irritation, anorexia, and nausea (Askergren and Mellgren, 1975; Suciu *et al.*, 1981). Occasional diarrhea was also reported by these workers.

Predisposing Conditions for Copper and Copper Compound Toxicity

Medical: Persons with Wilson's disease, a genetic disorder affecting copper homeostasis, may be more sensitive to the effects of copper exposure (Schroeder *et al.*, 1966; ATSDR, 1990). Persons with glucose-6-phosphate dehydrogenase deficiency, anemic, allergic, liver or kidney conditions moght be more sensitive (Reprotext, 1999). Infants and children less than 1-year of age may be more sensitive to the effects of copper exposure because homeostatic mechanisms for clearing copper from the body are not yet developed

Chemical: Persons exposed to molybdenum might be less sensitive to copper, since molybdewnum is antagonistic to copper toxicity (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

Rats were dosed by intratracheal instillation with 2.5, 5, 10, 20, 30, 50, and 100 mg Cu/rat and pulmonary clearance of CuO was measured over time (Hirano *et al*., 1993). The CuO particles were cleared from the lung with a half-time of 37 hours.

A 54% and 70% increase in mortality in male and female mice, respectively, over controls was observed following challenge with aerosolized streptococci after a 3-hour exposure to 0.56 mg/m³ Cu as $CuSO_4$ (Drummond *et al*., 1986). Pulmonary bactericidal activity was not measured for this exposure group.

The effects of copper sulfate (and other metal sulfate) aerosols on respiratory defense mechanisms were studied in male hamsters (Skornik and Brain, 1983). Pulmonary macrophage phagocytic rates were measured by determining the in vivo uptake of radioactive colloidal gold 1, 24, or 48 hours after a single 4-hour inhalation exposure to 0, 0.3, 3.2, 4.0, 5.8 and 7.1 mg Cu/m³. When hamsters were exposed for 4 h to greater than or equal to 3.2 mg Cu/m³, macrophage endocytosis was significantly reduced 1 h after exposure compared with that in unexposed control animals. The reduction was dose-dependent. At 24 h after exposures to the higher concentrations of Cu the percent of gold ingested by pulmonary macrophages remained depressed but less than at 1 hour. (By 48 h, the rate of macrophage endocytosis in hamsters returned to control levels except in hamsters exposed to 3.2 and 5.8 mg Cu/m³.)

VI. Reproductive or Developmental Toxicity

Copper is known to be spermicidal (U.S.EPA, 1987). Copper absorbed from copper intrauterine loops or wires has been shown to prevent mammalian embryogenesis. Conversely, terata have been observed in the offspring of experimental animals deficient in dietary copper.

Inhibited spermatogenesis and testicular atrophy were observed in male rats exposed to 0.1-1.0 mg/m³ CuO (Ginoian, 1976). The same study also reported that the number of fetuses was reduced in a dose-related manner in females exposed to CuO. Because the original article was not available for review, key experimental details, including duration of exposure, are unknown.

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

Reference Exposure Level (protective against mild adverse effects):   100 µg/m³

Study	ACGIH, 1991; Gleason, 1968; Whitman, 1957, 1962
Study population	workers
Exposure method	inhalation
Critical effects	metal fume fever
LOAEL	unkown
NOAEL	1 mg Cu/m³
Exposure duration	unknown

Extrapolated 1 hour concentration	no extrapolation
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.1 mg Cu/m³ (100 µg/m³)

The ACGIH-TLV is based on an unpublished letter which reported that exposure to 1 - 3 mg/m^3 copper fume for "short periods" resulted in a "sweet taste in the mouth" and that exposure to 0.02 - 0.4 mg/m^3 did not result in any symptoms (Whitman, 1957). However, it was not clear from the letter if or how actual copper levels were measured. Another author reported that symptoms of metal fume fever were observed in workers exposed for an unspecified number of weeks to 0.03 - 0.12 mg/m^3 copper dust (Gleason, 1968). The latter exposure was not designed to determine the level of copper responsible for the symptoms; it was meant to justify the implementation of exhaust controls. Therefore, the air samples were not directly compared to worker exposure or worker symptoms.

The current REL is based on the ACGIH-TLV of 1 mg/m^3 copper dust. The TLV of 1 mg/m^3 is a NOAEL based on the report of Whitman (1957) indicating that exposure to copper dust was detectable by taste but that no other symptoms occurred following exposure to 1 - 3 mg/m^3 for an unknown duration. An uncertainty factor of 10 was applied to the NOAEL to account for variability in individual response. No time extrapolation was applied because the duration of exposure was not clearly specified by either of the available reports. Because of the limitations of the existing data, reevaluation of the REL for copper is recommended when better methods or data are available.

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 100 mg/m³ but it is based on studies of lethality by the oral route in animals and man.

VIII. References

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