CHRONIC TOXICITY SUMMARY

ACROLEIN

(2-propenal, acraldehyde, allyl aldehyde, acryl aldehyde)

CAS Registry Number: 107-02-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.02 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Histological changes in nasal epithelium in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless liquid/gas
Molecular formula	C_3H_40
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Vapor pressure	220 mm Hg @ 20°C
Solubility	Soluble in ethanol, diethyl ether, and up to 20% w/v in water
Conversion factor	1 ppm = 2.3 mg/m^3 @ 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 (IARC, 1985).

IV. Effects of Human Exposure

Information regarding the toxicity of acrolein to humans is scarce. Acrolein acts primarily as an irritant to the eyes and respiratory tract. The LOAEL for eye irritation is 0.06 ppm (0.14 mg/m^3) acrolein for five minutes (Darley *et al.*, 1960). In this study, 36 healthy human volunteers were exposed to 0.06 ppm (0.14 mg/m^3) for 5 minutes. 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. Subjects reported a significant incidence of eye irritation in a questionnaire following the exposure.

V. Effects of Animal Exposure

Male rats were exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3) (Kutzman, 1981). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests (PFT) included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lung were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed post-exposure for 6 days to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extrarespiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates and rhinitis, beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions was also observed. No lung lesions were observed in the 0.4 ppm group. The NOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

The concentration required for depression of the respiratory rate of mice by 50% (RD_{50}) during 15 minutes of acrolein exposure was estimated as 1.7 ppm (Kane *et al.*, 1979). These authors proposed that the highest concentration suitable for a human air quality standard was 0.001 x RD_{50}, or 0.002 ppm (0.005 mg/m^3).

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was dose-dependently impaired following exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

Leach and associates (1987) found histological changes in pulmonary epithelium and mucosa in rats exposed to 3 ppm acrolein 6 hours/day, 5 days/week, for 3 weeks. In this study, tests for pulmonary and systemic immune function revealed no significant differences between treated and control animals. Similarly, no difference was observed in survival from a bacterial challenge with *Listeria monocytogenes*, although this challenge was intravenous and not intratracheal, and may not have revealed the pulmonary macrophage impairment indicated by Astry and Jakab (1983).

Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy,

although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure.

Lyon and associates (1970) investigated the effects of repeated or continuous exposures of acrolein on rats, guinea pigs, dogs, and monkeys. Animals were exposed to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. In these studies, 2 monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea was observed in monkeys and dogs; 7 of the 9 monkeys also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchiopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs.

There are no reports of reproductive or developmental toxicity following exposure to acrolein. Kutzman *et al.* (1981) found no significant changes in embryo viability in rats exposed to 4.0 ppm acrolein throughout pregnancy. Similarly, sperm morphology was reportedly not affected at this level.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Kutzman *et al.*, 1981 (evaluated by U.S. EPA, 1995)
Study population	Fischer-344 rats (24 males per group)
Exposure method	Discontinuous whole-body inhalation exposure of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)
Critical effects	Histological lesions in the upper airways
LOAEL	0.4 ppm
NOAEL	Not observed (see below)
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	62 days
Average experimental exposure	0.071 ppm (0.16 mg/m^3)
Human equivalent concentration	0.0087 ppm (gas with extrathoracic respiratory effects, RGDR = 0.14 based on MV = 0.18 m^3/day, SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	10

Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factors	1
Cumulative uncertainty factor	1,000
Reference exposure level	9×10^{-6} ppm (0.009 ppb, 2×10^{-5} mg/m^3, 0.02 μg/m^3)

The LOAEL for nasal histological changes in mice was considered by U.S. EPA to be 0.4 ppm (0.92 mg/m^3). Only one rat showed slight metaplastic and inflammatory changes, which would be insufficient to demonstrate a statistically significant increase. The potentially slight effect, however, was accounted for by use of only an intermediate 3-fold LOAEL factor.

Significant strengths in the acrolein RfC include (1) the use of a well-conducted study with histopathological analysis and (2) the demonstration of consistent adverse effects among multiple studies of several species conducted by independent investigators.

Major areas of uncertainty are (1) the lack of adequate human exposure data, (2) limited reproductive toxicity data, (3) the absence of a NOAEL in the major study, and (4) the lack of chronic inhalation exposure studies.

VII. References

Astry CL, and Jakab GJ. 1983. The effects of acrolein exposure on pulmonary antibacterial defenses. Toxicol. Appl. Pharmacol. 67:49-54.

Darley EF, Middleton JT, and Garber MJ. 1960. Plant damage and eye irritation from ozone-hydrocarbon reactions. J. Agric. Food Chem. 8:483-485.

Feron VJ, and Kruysse A. 1977. Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. J. Toxicol. Environ. Health. 25:119-124.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM version). Denver, CO: Micromedex, Inc. (edition expires 7/31/95).

IARC. 1985. International Agency for Research on Cancer. IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans: allyl compounds, aldehydes, epoxides and peroxides. Vol 36. Lyon: IARC, pp. 133-161.

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

Kutzman RS. 1981. A subchronic inhalation study of Fischer 344 rats exposed to 0, 0.4, 1.4, or 4.0 ppm acrolein. Brookhaven National Laboratory, Upton, NY. National Toxicology Program: Interagency Agreement No. 222-Y01-ES-9-0043.

Leach CL, Hatoum NS, Ratajczak HV, and Gerhart JM. 1987. The pathologic and immunologic effects of inhaled acrolein in rats. Toxicol. Lett. 39:189-198.

Lyon JP, Jenkins LJ, Jones RA, Coon RA, and Siegel J. 1970. Repeated and continuous exposure of laboratory animals to acrolein. Toxicol. Appl. Pharmacol. 17:726732.

U.S. Environmental Protection Agency. 1995. Integrated Risk Information System (IRIS) database. Reference concentration (RfC) for acrolein.

ACRYLONITRILE

(acrylonitrile monomer, cyanoethylene, propenenitrile, 2-propenenitrile, VCN, vinyl cyanide)

CAS number: 107-13-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**2 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Degeneration and inflammation of nasal epithelium in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Clear, colorless to pale yellow liquid (technical grades)
Molecular formula	C_3H_3N
Molecular weight	53.1
Density	0.81 g/cm^3 @ 25°C
Boiling point	77.3 ^{o}C
Melting point	-82 ^{o}C
Vapor pressure	100 mm Hg @ 23°C
Solubility	Soluble in isopropanol, ethanol, ether acetone and benzene
Conversion factor	1 ppm = 2.17 mg/m^3 @25 ^{o}C

III. Major Uses or Sources

Acrylonitrile is produced commercially by propylene ammoxidation, in which propylene, ammonia and air are reacted by catalyst in a fluidized bed. Acrylonitrile is used primarily as a co-monomer in the production of acrylic and modacrylic fibers. Uses include the production of plastics, surface coatings, nitrile elastomers, barrier resins, and adhesives. It is also a chemical intermediate in the synthesis of various antioxidants, pharmaceuticals, dyes, and surface active agents. Formerly, acrylonitrile was used as a fumigant for food commodities, flour milling and bakery food processing equipment (HSDB, 1994).

IV. Effects of Human Exposure

Many occupational epidemiology studies have investigated retrospectively the morbidity and mortality of acrylonitrile exposed workers. An increased incidence of lung cancer was associated with acrylonitrile exposure. No significant excess mortality has been observed for any noncarcinogenic endpoint. One early cross-sectional study (Wilson *et al.*, 1948) observed multiple deleterious effects in synthetic rubber manufacturing workers acutely exposed (20 to 45 minutes) to various concentrations of acrylonitrile (16 to 100 ppm, 34.7 to 217 mg/m^3). Mucous membrane irritation, headaches, nausea, feelings of apprehension and nervous irritability were observed in the majority of workers. Other less common symptoms observed included low grade anemia, leukocytosis, kidney irritation, and mild jaundice. These effects were reported to subside with cessation of exposure. Human volunteers exposed for a single 8 hour period to acrylonitrile vapors exhibited no deleterious CNS effects at concentrations ranging from 5.4 to 10.9 mg/m^3 (2.4 to 5.0 ppm) (Jakubowski *et al.*, 1987).

A cross-sectional study (Sakurai *et al.*, 1978) found no statistically significant increases in adverse health effects in chronically exposed workers (minimum 5 years) employed at 6 acrylic fiber factories (n=102 exposed, n=62 matched controls). Mean acrylonitrile levels ranged from 0.1 to 4.2 ppm (0.2 to 9.1 mg/m^3) as determined by personal sampling. Though not statistically significant, slight increases in reddening of the conjunctiva and pharynx were seen in workers from the plant with the highest mean levels (4.2 ppm arithmetic mean). However, this study has limitations, including small sample size and examiner bias (the medical examiner was not blind to exposure status). The time-weighted average exposure of the group occupationally exposed to 4.2 ppm (9.1 mg/m^3) acrylonitrile can be calculated as: TWA = 9.1 mg/m^3 x (10/20)m^3/day x 5 days/7 days = 3 mg/m^3. This level is comparable to the LOAEL(HEC) derived by the U.S. EPA.

V. Effects of Animal Exposure

Quast *et al.* (1980) exposed Sprague-Dawley rats (100/sex/ concentration) 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20, or 80 ppm acylonitrile vapors (0, 43, or 174 mg/m^3). A statistically significant increase in mortality was observed in the first year among 80 ppm exposed rats (male and female). Additionally, the 80 ppm exposed group had a significant decrease in mean body weight. Two tissues, the nasal respiratory epithelium and the brain, exhibited treatment-related adverse effects due to acrylonitrile exposure.

Proliferative changes in the brain glial cells (i.e., tumors and early proliferation suggestive of tumors) were significantly increased in the 20 ppm (8/100) and 80 ppm (20/100) females versus female controls (0/100), and in the 80 ppm males (22/99) versus male controls (0/100). Noncarcinogenic, extrarespiratory effects were observed in the nasal turbinate epithelium at both exposure concentrations, 20 and 80 ppm, but were statistically significant only in the 80 ppm exposed rats. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory epithelium were observed at either concentration.

Maltoni and associates exposed Sprague-Dawley rats (30/sex/concentration) to 0, 5, 10, 20 or 40 ppm acrylonitrile vapor for 5 days/week over 52 weeks, and at 60 ppm for 4 to 7 days, 5

days/week for 104 weeks (Maltoni *et al.*, 1977; Maltoni *et al.*, 1988). Histopathologic examinations were performed, including on lungs, brain, kidney, and liver. No noncarcinogenic effects were reported.

One developmental study exposed rats to acrylonitrile vapors at 0, 40, or 80 ppm (duration adjusted concentrations of 0, 15.4, and 31 mg/m^3, respectively) for 6 hours/day during gestational days 6 to 15. In the 80 ppm exposed group, significant increases in fetal malformations were observed including short tail, missing vertebrae, short trunk, omphalocoele and hemivertebra (Murray *et al.*, 1978). No difference in implantations, live fetuses or resorptions were seen in the exposed (40 and 80 ppm) versus the control group. Maternal toxicity was observed as decreased body weight at both exposure levels. This study identified a developmental NOAEL of 15.5 mg/m^3 with a LOAEL of 31 mg/m^3 (with maternal toxicity).

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Quast *et al.*, 1980 (evaluated by U.S. EPA, 1994)
Study population	Sprague-Dawley rats (100/sex/concentration)
Exposure method	Discontinuous whole-body inhalation exposures (0, 20 or 80 ppm)
Critical effects	Degeneration and inflammation of nasal respiratory epithelium, hyperplasia of mucous secreting cells
LOAEL	20 ppm
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	3.6 ppm for LOAEL group (20 x 6/24 x 5/7)
Human equivalent concentration	0.9 ppm (gas with extrathoracic respiratory effects, RGDR = 0.25 based on MV = 0.33 m^3/day, SA(ET) = 11.6 cm^2)
Exposure duration	2 years
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	10 (lack of inhalation bioassay in second species and lack of reproductive data for inhalation exposures when oral study showed adverse reproductive effects)
Cumulative uncertainty factor	1,000
Inhalation reference exposure level	0.0009 ppm (0.9 ppb; 0.002 mg/m^3; 2 µg/m^3)

Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to 0, 20 or 80 ppm acrylonitrile (0, 43, and 174 mg/m^3, respectively). Significant degenerative

and inflammatory changes were observed in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm). This treatment-related irritation of the nasal mucosa appeared in the 20 ppm exposed male rats as either epithelial hyperplasia of the nasal turbinates, or as hyperplasia of the mucous secreting cells. In the 20 ppm exposed females it appeared as either focal inflammation in the nasal turbinates or flattening of the respiratory epithelium of the nasal turbinates. In 80 ppm exposed rats the effects were more severe, including suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment related effects in the olfactory epithelium, trachea or lower respiratory system were observed at either concentration. This study identified a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory tract of 20 ppm (43 mg/m^3).

Significant strengths in the acrylonitrile REL include (1) the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis and (2) the demonstration of a dose-response relationship.

Major uncertainties are (1) the lack of adequate human exposure data and (2) the lack of a NOAEL.

VII. References

HSDB. 1994. Hazardous Substances Data Bank. TOMES® Vol. 20. Denver, CO: Micromedex, Inc.

Jakubowski M, Linhart I, Pielas G, and Kopecky J. 1987. 2-Cyanoethylmercapturic acid (CEMA) in the urine as a possible indicator of exposure to acrylonitrile. Br. J. Ind. Med. 44:834-840.

Maltoni C, Ciliberti A, and Di Maio V. 1977. Carcinogenicity bioassays on rats of acrylonitrile administered by inhalation and by ingestion. Med. Lav. 68(6):401-411.

Maltoni C, Ciliberti A, Cotti G, and Perino G. 1988. Long-term carcinogenicity bioassays on acrylonitrile administered by inhalation and by ingestion to Sprague-Dawley rats. Ann. NY Acad. Sci. 534:179-202.

Murray FJ, Schwetz BA, Nitschke KD, John JA, Norris JM, and Gehring PJ. 1978. Teratogenicity of acrylonitrile given to rats by gavage or by inhalation. Food Cosmet. Toxicol. 16(6):547-552.

Quast JF, Schwetz DJ, Balmer MF, Gunshow TS, Park CN, and McKenna MJ. 1980. A two-year toxicity and oncogenicity study with acrylonitrile following inhalation exposure of rats. Toxicology Research Laboratory. Midland, MI: Dow Chemical Co.

Sakurai H, Onodera T, Utsunomiya T, Minakuchi H, Iwai H, and Matsumura H. 1978. Health effects of acrylonitrile in acrylic fibre factories. Br. J. Ind. Med. 35:219-225.

U.S. EPA 1994. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS) Database. Reference concentration (RfC) for acrylonitrile.

Wilson RH, Hough GV, McCormick WE. 1948. Medical problems encountered in the manufacture of American-made rubber. Ind. Med. 17:199-207.

CHRONIC TOXICITY SUMMARY

ARSENIC AND ARSENIC COMPOUNDS

Molecular Formula	Synonyms	Molecular Weight	% As by Weight	CAS Reg. No.
As	Arsenic black, metallic arsenic	74.92	100%	7440-38-2
As_2O_3	Arsenious acid, crude arsenic, white arsenic	197.82	75.7%	1327-53-3
As_2O_5	Arsenic anhydride, arsenic oxide, arsenic oxide anhydride	229.82	41.3%	1303-28-2
$AsH_3Na_2O_4$	Arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	185.91	40.3%	7778-43-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.03 µg As/m^3**
Oral reference exposure level	**0.0003 mg/kg bw-day** (based on U.S. EPA RfD)
Critical effect(s)	Decreased fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations in mice
Hazard index target(s)	Development (teratogenicity); cardiovascular system; nervous system

II. Physical and Chemical Properties (For metallic arsenic except as noted) (from HSDB, 1995, except as noted)

Description	As: Yellow, black or gray solid As_2O_3: White solid
Molecular formula	See above
Molecular weight	See above
Density	As: 5.727 g/cm^3 @ 14°C As_2O_3: 3.74 g/cm^3
Boiling point	613° C (sublimes) (ACGIH, 1992)
Melting point	As: 817°C @ 28 atm As_2O_3: 312.3°C
Vapor pressure	1 mm Hg @ 372° C
Solubility	As: soluble in nitric acid; insoluble in water Oxides: soluble in water

	Salts: soluble in water)
Conversion factor	Not applicable

III. Major Uses or Sources

Ore refining processes, including the smelting of copper and lead, are the major sources by which arsenic dust and inorganic arsenic compounds are released (Grayson, 1978). Arsenic trioxide (As_2O_3) is the most commonly produced form of arsenic. As_2O_3 is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds.

IV. Effects of Human Exposure

Smelter workers, exposed to concentrations of arsenic up to 7 mg As/m^3, showed an increased incidence in nasal septal perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (Lundgren, 1954; as cited in U.S. EPA, 1984).

In a case-control study, copper smelter workers (n=47) exposed to arsenic for 8-40 years (plus 50 unexposed controls matched for age, medical history, and occupation) were examined by electromyography and for nerve conduction velocity in the arms and legs (Blom *et al.*, 1985). The workers were found to have a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocities in three peripheral nerves (upper and lower extremities). Slightly reduced nerve conduction velocity in 2 or more peripheral nerves was reported as “more common” among arsenic exposed workers. Minor neurological and electromyographic abnormalities were also found among exposed workers. Occupational exposure levels were estimated to be 0.05-0.5 mg As/m^3, with As_2O_3 the predominant chemical form. Except for three arsenic exposed workers who had long-term exposure to lead, exposure to other heavy metals was insignificant.

The smelter workers described by Blom *et al.* (1985) (number of controls reduced to 48) were further examined for prevalence of Raynaud’s phenomenon and for vasospastic tendency by measurement of finger systolic pressure at 10°C and/or 15°C relative to that at 30°C (FSP%) (Lagerkvist *et al.*, 1986). The FSP% was found to covary with the duration of exposure to arsenic and the prevalence of Raynaud’s phenomenon was significantly increased among exposed workers. Daily arsenic uptake was estimated at less than 300 μg/day and was confirmed with urinary excretion data.

Hyperpigmentation and hyperkeratinization were observed in workers exposed to 0.4-1 mg/m^3 inorganic arsenic for 2 or more years (Perry *et al.*, 1948).

Dermatitis and irritation of the mucous membranes have been observed in arsenic exposed workers (Vallee *et al.*, 1960).

Chronic exposure to arsenic has been associated with decreased birth weight and an increased rate of spontaneous abortion in female smelter workers. However, this association is confounded by the presence of other toxicants in the smelting process, including lead (Nordstrom *et al.*, 1979).

Hepatic fatty infiltration, central necrosis, and cirrhosis were observed in two patients who ingested As_2O_3 (1% in Fowler's solution) for three or more years (Morris *et al.*, 1974). Daily consumption of 0.13 mg As/kg in contaminated well water resulted in the chronic poisoning and death of four children; at autopsy, myocardial infarction and arterial thickening were noted (Zaldívar and Guillier, 1977).

Anemia and leukopenia have been reported in infants ingesting approximately 3.5 mg As/day in contaminated milk over a period of 33 days (Hammamoto, 1955; as cited in ATSDR, 1989).

Premature birth and subsequent neonatal death was reported in a single individual following ingestion of arsenic (Lugo *et al.*, 1969).

V. Effects of Animal Exposure

Changes in host resistance from inhalation exposure to As_2O_3 aerosol were examined in female CD1 mice using a streptococcus infectivity model and an assay for pulmonary bactericidal activity (Aranyi *et al.*, 1985; Aranyi *et al.*, 1981). Mice (100-200/group) were exposed to As_2O_3 aerosol (or filtered air) for 3 hours/day, 5 days/week, for 1, 5 or 20 days. Aerosol exposed and control mice were then combined before challenge with *Streptococcus zoopidemicus* aerosol (4-8 replicate exposures). Statistically significant increases in mortality ($p < 0.05$) were observed in mice exposed (1) once to 271, 496, and 940 μg As/m^3, (2) 5 times to 519 μg As/m^3, and (3) 20 times to 505 μg As/m^3. Multiple exposures at a given exposure level did not correlate with increased mortality, suggesting an adaptation mechanism. Single exposure did, however, show a dose-response for increased mortality with increasing level of arsenic exposure. Bactericidal activity was evaluated by measuring the ratio of viable bacteria count to radioactive count in the lung 3 hours after infection with ^{35}S-labeled *Klebsiella pneumoniae*. A single exposure to 271, 496, and 940 μg As/m^3, but not 123 μg As/m^3, resulted in significantly decreased bactericidal activity. Five exposures to 519 μg As/m^3 and twenty exposures to both 245 and 505 μg As/m^3 resulted in decreased bactericidal activity.

Female albino rats (20/group) were exposed to 0, 1.3, 4.9, or 60.7 μg As_2O_3/m^3 as aerosol continuously for 3 months (Rozenshtein, 1970). Decreased whole blood sulfhydryl group content, histological changes in the brain, bronchi, and liver, changes in conditioned reflexes, and changes in chronaxy ratio were observed in both the high- and mid-dose groups. Among animals in the high dose group, eosinophilia, decreased blood cholinesterase activity, decreased serum sulfhydryl content, and increased blood pyruvic acid were observed. No significant changes were observed in the low-dose group.

Male mice (8-10/group) were exposed to 0, 0.5, 2.0, or 10.0 ppm sodium arsenite in drinking water for 3 weeks followed by a 28 day recovery period (Blakley *et al.*, 1980). The primary

immune response of the spleen (as indicated by changes in IgM-production assayed by plaque-formation) was suppressed at all dose levels. The secondary immune response was also suppressed at all dose levels as indicated by a decrease in the number of IgG producing cells.

Male Sprague-Dawley rats (7-28/group) were exposed to 0, 40, 85, or 125 ppm sodium arsenate in drinking water for 6 weeks (Brown *et al.*, 1976). Rats from all arsenic exposed groups showed increased relative kidney weights, decreased renal mitochondrial respiration, and ultrastructural changes to the kidney.

Male ddY mice (number not stated) received 0, 3, or 10 mg As_2O_3/kg/day orally for 14 days and were examined for changes in concentrations of monoamine-related substances in various brain regions and for changes in locomotor activity (Itoh *et al.*, 1990). Locomotor activity was increased in the low-dose group and decreased in the high-dose group. Several monoamine-related compounds were altered in both dose groups in the cerebral cortex, hippocampus, hypothalamus, and corpus striatum.

Male and female Wistar rats (7-10/group) were treated from age 2 to 60 days by oral gavage with daily administration of 0 or 5 mg As/kg body weight (as sodium arsenate) (Nagaraja and Desiraju, 1993; Nagaraja and Desiraju, 1994). After 160 days, body weights, brain weights, and food consumption were decreased in the arsenic exposed group. Acetylcholinesterase (AChE) and GAD activity and GABA levels were decreased in the hypothalamus, brain stem, and cerebellum during the exposure period; all but AChE activity returned to normal during the post-exposure period. Changes in operant conditioning were also observed among the exposed animals.

Female Holtzman rats (>5/group) were treated with 0, 100, 500, 1000, 2000, or 5000 ppm As_2O_3 in feed for 15 days (Wagstaff, 1978). Hexibarbitone sleeping time was altered in all arsenic exposed groups. Body weight and feed consumption were decreased among animals in the groups exposed to ≥ 500 ppm As_2O_3. Clinical signs of toxicity observed among arsenic exposed animals included roughened hair, diarrhea, and decreased physical activity.

Male Sprague-Dawley rats and C57 black mice (12/group) were treated with 0, 20, 40, or 85 ppm sodium arsenate in drinking water for up to 6 weeks (Woods and Fowler, 1978). Among arsenic exposed rats, heme synthetase activity was decreased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, hepatic ALA synthetase activity was decreased and urinary uroporphyrin and coproporphyrin were increased. Among exposed mice, heme synthetase activity was decreased and uroporphyrinogen I synthetase activity was increased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, urinary uroporphyrin and coproporphyrin were increased.

Administration of 3.7 mg As_2O_3/kg/day to rhesus monkeys for 12 months did not result in any neurologic change detectable by an EEG (Heywood and Sortwell, 1979). Two of the 7 animals exposed to this concentration died before the conclusion of the 52 week period. Of the surviving animals, two were retained for a 52 week recovery period after which they were sacrificed and necropsied. No significant changes in organ weights or gross appearance were noted.

Pregnant CFLP mice (8-11 females/group) were exposed to As_2O_3 for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg As_2O_3/m^3 (~0.2, 2.2, and 21.6 mg As/m^3 (Nagymajtényi *et al.*, 1985). A significant decrease in fetal weight was observed in all the dose groups, with a 3, 9, and 29% reduction in average fetal weight with increasing dose groups. Significantly increased fetal malformations were observed only in the highest dose group; delayed ossification was the primary defect.

Rats exposed to 1 μg As_2O_3/m^3 (0.76 μg As/m^3) for 5 months showed increased preimplantation mortality and delayed ossification in fetuses (Kamkin, 1982). Experimental detail was not presented, thus limiting the usefulness of this study.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to 32.4 mg As_2O_3/m^3 for 48 hours (Kamil'dzhanov, 1982). Similarly, motility was decreased after (1) a 120 hour exposure to 7.95 mg/m^3, (2) a 252 hour exposure to 1.45 mg/m^3, and (3) an 800 hour exposure to 0.36 mg/m^3.

Male and female Charles River CD mice (10/group) were treated with 0 or 5 ppm arsenite in drinking water continuously through 3 generations (Schroeder and Mitchener, 1971). Endpoints examined included the interval between litters, the age at first litter, the ratio of males to females, the number of runts, stillborn offspring, failures to breed, and congenital abnormalities. The study showed an alteration in the number of small litters in the arsenic exposed group.

Female CD-1 mice (8-15/group) were treated by oral gavage with 0, 20, 40, or 45 mg sodium arsenite/kg on a single day of gestation between days 8 and 15 (Baxley *et al.*, 1981). Maternal mortality, fetal malformations, and increased prenatal death were observed among animals treated with 40 and 45 mg sodium arsenite/kg.

Pregnant golden hamsters (>10/group) were treated by oral gavage with a single administration of 0, 20, or 25 mg/kg sodium arsenite on one of gestational days 8-12 (Hood and Harrison, 1982). Prenatal mortality was increased among animals receiving 25 mg/kg on gestational days 8 and 12 and fetal weights were decreased among animals receiving 25 mg/kg on gestational day 12. One dam died following administration of 20 mg/kg.

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 suggested that long term exposure of sperm to arsenic may occur *in vivo* following acute exposure (Danielsson *et al.*, 1984).

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Chronic Reference Exposure Level

Study	Nagymajtényi et al., 1985
Study population	CFLP mice (8-11/group)
Exposure method	Discontinuous inhalation exposure
Critical effects	Reduction in fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations
LOAEL	200 μg As/m^3
NOAEL	Not observed
Exposure continuity	4 hr/day
Exposure duration	4 days (gestational days 9-12)
Average experimental exposure	33 μg As/m^3 for LOAEL group (200 x 4/24)
Human equivalent concentration	33 μg As/m^3 for LOAEL group (particle with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	10 (since USEPA severity level > 5)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.03 μg As/m^3

Reports of human inhalation exposure to arsenic compounds, primarily epidemiological studies of smelter workers, indicate that adverse health effects occur as a result of chronic exposure. Among the targets of arsenic toxicity are the respiratory system (Lundgren, 1954), the circulatory system (Lagerkvist *et al.*, 1986), the skin (Perry *et al.*, 1948), the nervous system (Blom *et al.*, 1985), and the reproductive system (Nordstrom *et al.*, 1979). Occupational exposure levels associated with these effects ranged from 50 to 7000 μg As/m^3. These epidemiological studies suffer, however, from confounding as a result of potential exposure to other compounds, which limits their usefulness in the development of the chronic REL.

Studies in experimental animals show that inhalation exposure to arsenic compounds can produce immunological suppression, developmental defects, and histological or biochemical effects on the nervous system and lung, thus providing supportive evidence of the types of toxicity observed in humans. Among the inhalation studies, the lowest adverse effect level (LOAEL) was quite consistent:

245 μg As/m^3 for decreased bactericidal activity in mice (Aranyi *et al.*, 1985);
200 μg As/m^3 for decreased fetal weight in mice (Nagymajtényi *et al.*, 1985); and
270 μg As/m^3 for decreased sperm motility in rats (Kamil'dzhanov, 1982).

A single study showed effects occurring at 4.9 μg As_2O_3/m^3 (Rozenshtein, 1970), however, lack of detail with respect to endpoints and experimental design limits this study's usefulness. A significant dose-related reduction in fetal weight and increased incidences of intrauterine growth

retardation, skeletal malformations, and hepatocellular chromosomal aberrations were observed in mice following maternal inhalation exposure to 200 μg As/m^3 (260 μg As_2O_3/m^3) for 4 hours on gestation days 9, 10, 11, and 12 ($p<0.05$) (Nagymajtényi *et al.*, 1985). The most sensitive effect, decreased fetal weight, was observed at 200 μg As/m^3, so 200 μg As/m^3 was taken as a LOAEL. Maternal toxicity data were not reported.

The weight decrement of 3% might not be biologically significant if the loss is generally distributed. If it were specific, it could be. In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant.

Route-to-route conversion of the LOAEL in the key study indicates that this chronic REL should also be protective of adverse effects that have been observed in studies with oral exposures, either in food or drinking water. Since adverse health effects have been reported among workers exposed to levels near 50 μg As/m^3, use of the human data would produce a chronic REL near that derived using animal data. The chronic REL from animal data should, therefore, be protective of potential adverse health effects from human exposures.

The major strength of the REL is the identification of a LOAEL that is supported by data from other studies. The major uncertainties are the lack of adequate human data, the lack of a NOAEL observation, the lack of comprehensive, long-term, multiple-dose, multiple-species studies, and the possibly marginal significance of the findings in the low dose group in the Nagymajtényi *et al.* (1985) study.

Derivation of U.S. EPA Oral Reference Dose (RfD)

Study	Tseng *et al.*, 1968; Tseng, 1977
Study population	>40,000 residentially exposed individuals
Exposure method	Drinking water (residential exposures)
Critical effects	Hyperpigmentation, keratosis, and possible vascular complications
LOAEL	0.17 mg/L (0.014 mg/kg-day)
NOAEL	0.009 mg/L (0.0008 mg/kg-day)
Exposure continuity	Not applicable
Exposure duration	Lifetime
Average exposure	0.006 mg/kg-day for LOAEL group
Human equivalent concentration	0.006 mg/kg-day for LOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Oral reference exposure level	0.0003 mg/kg bw-day

*Conversion Factors: NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentrations from 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy *et al.*, 1989).

NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg-day.

The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L.

LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg-day.

The oral REL is the U.S. EPA's oral Reference Dose (RfD) (U.S. EPA, 1996). The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, one report indicates that it may not be strictly due to arsenic exposure (Lu, 1990).

The data in Tseng *et al.* (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL. The control group described in Tseng *et al.* (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This exposure of this group is considered a NOAEL. The arithmetic mean of the arsenic

concentration in the wells used by the individuals in the NOAEL group is 9 µg/L (range: 1-17 µg/L) (Abernathy *et al.*, 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 µg/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy *et al.* (1989), the NOAEL and LOAEL doses for both food and water are as follows:

LOAEL - [170 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 14 µg/kg/day;
NOAEL - [9 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 0.8 µg/kg/day.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7).

This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on humans exposed to arsenic. This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 mg/L and at the low dose is 5 mg/L (Cebrian *et al.*, 1983; Figure 2 and Table 1) or 7 mg/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below an average water consumption of 3 L/day was assumed by USEPA. No data are given on the arsenic exposure from food or the body weight of the participants (therefore 55 kg was assumed). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study were more than 20 years old (Figure 1). Exposure estimates (water only) are:

high dose - 410 mg/L x 3 L/day x (1/55 kg) = 22 mg/kg/day;
low dose - 5-7 mg/L x 3 L/day x (1/55 kg) = 0.3-0.4 mg/kg/day.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng *et al.* (1968) control group, but the dose is lower (0.4 vs. 0.8 mg/kg/day). The Southwick *et al.* (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16%) (Southwick *et al.*, 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic. Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance. Table 3 (Southwick *et al.*, 1983) shows the annual arsenic exposure from

drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are >5 years, and dose groups are ranges of exposure. Exposure estimates (water only) are:

dosed group - 152.4 mg/year x 1 year/365 days x (1/70) kg = 6 µg/kg/day;
control group - 24.2 mg/year x 1 year/365 days x (1/70) kg = 0.9 µg/kg/day.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian *et al.* (1983) study. The incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh *et al.* (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng *et al.* (1968) and Hindmarsh *et al.* (1977) studies. The dosed group may or may not be a LOAEL, since it is does not report statistically significant effects when compared to the control. This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh *et al.*, 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups. The exact doses are not given in the Hindmarsh *et al.* (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 µg/L, respectively. Figure 1 (Hindmarsh *et al.*, 1977) shows that the average arsenic concentration of the low-dose wells is about 25 µg/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated. Exposure estimates (water only) are:

low - 25 µg/L x 2 L/day x (1/70) kg = 0.7 µg/kg/day;
mid - 70 µg/L x 2 L/day x (1/70) kg = 2 µg/kg/day; and
high - 680 µg/L x 2 L/day x (1/70) kg = 19 µg/kg/day.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick *et al.* (1983) studies.

The responses at the mid-dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses. As discussed previously there is no way of knowing whether the low doses in the Cebrian *et al.* (1983), Southwick *et al.* (1983), and Hindmarsh *et al.* (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the U.S.EPA felt comfortable in assigning the low doses in these studies as NOAELs. The Tseng (1977) and Tseng *et al.* (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people less than 20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

1) Tseng (1977):	NOAEL = 0.0008;	LOAEL = 0.014
2) Cebrian *et al.* (1983):	NOAEL = 0.0004;	LOAEL = 0.022
3) Southwick *et al.* (1983):	NOAEL = 0.0009;	LOAEL = none (equivocal effects at 0.006)
4) Hindmarsh *et al.* (1977):	NOAEL = 0.0007;	LOAEL = 0.019 (equivocal effects at 0.002)

There was not a clear consensus among U.S. EPA scientists on the oral RfD. Applying the U.S. EPA's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 µg/kg/day. However, the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the U.S. EPA Work Group as it becomes available.

The U.S. EPA used an Uncertainty Factor (UF) of 3 to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the oral RfD as: Study - Medium; Data Base - Medium; and RfD - Medium. Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian *et al.* (1983) study. The U.S. studies are too small in number to resolve several issues. However, the data base does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

VII. References

ACGIH. 1992. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the threshold limit values and biological exposure indices. Sixth edition. Cincinnati, OH: ACGIH.

Abernathy CO, Marcus W, Chen C, Gibb H, and White P. 1989. Office of Drinking Water, Office of Research and Development, U.S. EPA. Memorandum to O. Cook, Office of Drinking Water, U.S. EPA and P. Preuss, Office of Regulatory Support and Scientific Management, U.S. EPA. Report on Arsenic (As) Work Group Meetings. February 23.

Aranyi C, Bradof JN, Fenters JD, Graham JA, and Miller FJ. 1981. Effects of inhalation of arsenic trioxide aerosols in the pulmonary defenses of mice. In: International Conference. Heavy

Metals in the Environment. Commission of the European Communities and the World Health Organization. pp. 450-453.

Aranyi C, Bradof JN, O'Shea WJ, Graham JA, and Miller FJ. 1985. Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. J. Toxicol. Environ. Health 15:163-172.

ATSDR. 1989. Agency for Toxic Substances and Disease Registry. US Public Health Service. Toxicological profile for arsenic. Prepared by Life Systems, Inc. under contract No. 68-02-4228.

Baxley MN, Hood RD, Vedel GC, Harrison WP, and Szczech GM. 1981. Prenatal toxicity of orally administered sodium arsenite in mice. Bull. Environ. Contam. Toxicol. 26:749-756.

Blakley BR, Sisodia CS, and Mukkur TK. 1980. The effect of methylmercury, tetraethyl lead and sodium arsenite on the humoral immune response in mice. Toxicol. Appl. Pharmacol. 52:245-254.

Blom S, Lagerkvist B, and Linderholm H. 1985. Arsenic exposure to smelter workers. Scand. J. Work Environ. Health 11:265-269.

Brown MM, Rhyne BC, Goyer RA, and Fowler BA. 1976. Intracellular effects of chronic arsenic administration on renal proximal tubule cells. J. Toxicol. Environ. Health 1:505-514.

Cebrian ME, Albores A, Aguilar M, and Blakely E. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicol. 2: 121-133.

Danielsson BRG, Dencker L, Lindgren A, and Tjalve H. 1984. Accumulation of toxic metals in male reproductive organs. Arch. Toxicol. Suppl, 7:177-180.

Grayson M. (ed.) 1978. Kirk-Othmer Encyclopedia of Chemical Technology. Third ed. New York, NY: John Wiley and Son, pp. 247-251.

Hammamoto E. 1955. Infant arsenic poisoning by powdered milk. Japanese Medical Journal, 1649:2-12 [cited in ATSDR, 1989].

Heywood R, and Sortwell RJ. 1979. Arsenic intoxication in the rhesus monkey. Toxicol. Lett. 3:137-144.

Hindmarsh JT, McLetchie OR, Hefferman LPM *et al.* 1977. Electromyographic abnormalities in chronic environmental arsenicalism. J. Anal. Toxicol. 1:270-276.

Hogue CJ, Buehler JW, Strauss LT, and Smith JC. 1987. Overview of the National Infant Mortality Surveillance (NIMS) project - design, methods, results. Public Health Rep. 102(2):126-138.

Hood RD, and Harrison WP. 1982. Effects of prenatal arsenite exposure in the hamster. Bull. Environ. Contam. Toxicol. 29:671-678.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Itoh T, Zhang YF, Murai S, Saito H, Nagahama H, Miyate H, Saito Y, and Abe E. 1990. The effect of arsenic trioxide on brain monoamine metabolism and locomotor activity of mice. Toxicol. Lett. 54:345-353.

Kamil'dzhanov AX. 1982. Hygienic basis for the maximum permissible concentration of the arsenic trioxide in the ambient air. Gig. Sanit. 2:74-75.

Kamkin AB. 1982. For a revision of the maximum permissible concentration of arsenic trioxide in the ambient air of inhabited areas. Gig. Sanit. 1:6-9.

Lagerkvist B, Linderholm H, and Nordberg GG. 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. Environ. Res. 39:465-474.

Lu FJ. 1990. Blackfoot disease: arsenic or humic acid? Lancet 336(8707):115-116.

Lugo G, Cassady G, and Palmisano P. 1969. Acute maternal arsenic intoxication with neonatal death. Am. J. Dis. Child. 117:328-330.

Lundgren KD. 1954. [Damage to respiratory organs in workers in a smelting plant]. Nor. Hyg. Tidskr. 3:66-82 [cited in U.S. EPA, 1984].

Morris JS, Schmid M, Newman S, Scheuer PJ, and Sherlock S. 1974. Arsenic and noncirrhotic portal hypertension. Gastroenterology, 64:86-94.

Nagaraja TN, and Desiraju T. 1993. Regional alterations in the levels of brain biogenic amines, glutamate, GABA, and GAD activity due to chronic consumption of inorganic arsenic in developing and adult rats. Bull. Environ. Contam. Toxicol. 50:100-107.

Nagaraja TN, and Desiraju T. 1994. Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. Hum. Exp. Toxicol. 13:353-356.

Nagymajtényi L, Selypes A, and Berencsi G. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J. Appl. Toxicol. 5:61-63.

Nordstrom S, Beckman L, and Nordenson I. 1979. Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90:291-296.

Perry K, Bowler RG, Buckell HM, Druett HA, and Scilling RSF. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. II. Clinical and environmental investigations. Br. J. Ind. Med. 5:6-15.

Rees DC, and Hattis D. 1994. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third ed. AW Hayes (ed.). New York: Raven.

Rozenshtein IS. 1970. [Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere]. Gig. Sanit. 35:16-21.

Schroeder HA, and Mitchener M. 1971. Toxic effects of trace elements on reproduction of mice and rats. Arch Environ. Health 23:102-106.

Southwick JW, Western AE, Beck MM, *et al.* 1983. An epidemiological study of arsenic in drinking water in Millard County, Utah. In: Arsenic: Industrial, Biomedical, Environmental Perpsectives. Lederer WH, and Fensterheim RJ, eds. New York: Van Nostrand Reinhold Co., pp. 210-225.

Tseng WP. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19:109-119.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS, and Yeh S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40:453-463.

U.S. EPA 1984. United States Environmental Protection Agency. Health Assessment Document for Inorganic Arsenic. EPA-600/8-83-012F. Final Report. U.S. EPA Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment. Research Triangle Park, NC: U.S. EPA. pp. 5-20.

U.S. Environmental Protection Agency. 1996. Integrated Risk Information System (IRIS) Database.

Vallee BL, Ulmer DD, and Wacker WEC. 1960. Arsenic toxicology and biochemistry. Arch. Ind. Health, 21:132-151.

Wagstaff DJ. 1978. Alteration of hepatic detoxification enzyme activity by dietary arsenic trioxide. Food Cosmet. Toxicol. 16:423-426.

Woods JS, and Fowler BA. 1978. Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. Toxicol. Appl. Pharmacol. 43:361-371.

Zaldívar R, and Guillier A. 1977. Environmental and clinical investigations on endemic chronic arsenic poisoning in infants and children. Zentralbl. Bakt. Hyg. 1 Abt. Orig. B 165:226-234.

CHRONIC TOXICITY SUMMARY

BERYLLIUM and BERYLLIUM COMPOUNDS

(beryllium-9; glucinium; glucinum; beryllium metallic)
CAS Registry Number: 7440-41-7

(beryllium oxide; beryllia; beryllium monoxide)
CAS Registry Number: 1304-56-9

(beryllium hydroxide; beryllium hydrate; beryllium dihydroxide)
CAS Registry Number: 13327-32-7

(beryllium sulfate; sulfuric acid; beryllium salt)
CAS Registry Number: 13510-49-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.001 µg Be/m^3**
Critical effect(s)	Berylliosis in non-occupationally exposed humans
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties Summary (ATSDR, 1993)

Description	Solid gray, hexagonal structure	White light, amorphous powder	White amorphous powder or crystalline	Colorless tetragonal crystals
Molecular formula	Be	BeO	$Be(OH)_2$	$BeSO_4$
Molecular weight	9.012	25.01	43.03	105.07
Vapor pressure	10 mm Hg at 1860 ^oC	No data	No data	No data
Solubility	Insoluble in water; metal soluble in dilute acid and alkali, oxide and hydroxide species soluble in concentrated acid and alkali			
Conversion factor	Not applicable			

III. Major Uses and Sources

Beryllium is a metallic element mined from bertrandite and beryl mineral ores. As the lightest structural metal, beryllium is used in the space, aircraft and nuclear industries in a variety of components including air craft disc brakes, x-ray transmission windows, vehicle optics, nuclear reactor neutron reflectors, fuel containers, precision instruments, rocket propellants, navigational

systems, heat shields, and mirrors. In addition to the 4 species listed, there are at least 13 other beryllium containing compounds including other salts, ores and alloys.

Beryllium alloys, especially the hardest alloy beryllium copper, are used in electrical equipment, precision instruments, springs, valves, non-sparking tools, and in molds for injection-molded plastics for automotive, industrial and consumer applications. Beryllium oxide is used in high-technology ceramics, electronic heat sinks, electrical insulators, crucibles, thermocouple tubing, and laser structural components. Other beryllium compounds, containing chloride, nitrate, fluoride and sulfate, are utilized as chemical reagents or generated from the refining of beryllium-containing ores.

Beryllium is naturally emitted into the atmosphere by windblown dusts and volcanic particles. However, the major emission source is the combustion of coal and fuel oil, which releases beryllium-containing particulates and ash. Other beryllium-releasing industrial processes include ore processing, metal fabrication, beryllium oxide production, and municipal waste incineration (ATSDR, 1993). Beryllium also occurs in tobacco smoke.

IV. Effects of Human Exposure

The respiratory tract is the major target organ system in humans following the inhalation of beryllium. The common symptoms of chronic beryllium disease include shortness of breath upon exertion, weight loss, cough, fatigue, chest pain, anorexia, and overall weakness. Most studies reporting adverse respiratory effects in humans involve the occupational exposure to beryllium. Exposure to soluble beryllium compounds is associated with acute beryllium pneumonitis (Eisenbud *et al.*, 1948). Exposure to both soluble or insoluble beryllium compounds may result in obstructive and restrictive diseases of the lung, called chronic beryllium disease (berylliosis) (Cotes *et al.*, 1983; Johnson, 1983; Infante *et al.*, 1980; Kriebel *et al.*, 1988a; Metzner and Lieben, 1961). Overall, the total number of beryllium-related disease cases has declined since the adoption of industrial standards (Eisenbud and Lisson, 1983; ATSDR, 1993).

Historically, beryllium pneumonitis has been associated with occupational concentrations over 0.1 mg Be/m^3, primarily as beryllium sulfate or beryllium fluoride (Eisenbud *et al.*, 1948). But the atmospheric concentrations related to chronic beryllium disease have been more difficult to define, in part due to the lack of individual exposure estimates, especially in the studies derived from the berylliosis case registries (Infante *et al.*, 1980; Lieben and Metzner, 1959). However, Infante and associates (1980) reported significantly increased mortality due to non-neoplastic respiratory disease in beryllium-exposed workers, and noted one case of chronic berylliosis in a worker following 7 years exposure to $\leq$ 2 µg Be/m^3. In a 30-year follow-up study of 146 beryllium-exposed workers, Cotes *et al.* (1983) identified seven cases of chronic beryllium related disease (146 workers examined). All the cases were exposed to beryllium oxide or hydroxide, but in a wide range of retrospectively estimated doses (over 3000 samples from 1952 to 1960). The estimated average daily exposure did not exceed 2 µg/m^3 for the ten site/process classifications, but 318 samples did exceed 2 µg Be/m^3 (and 20 samples were greater than 25 µg Be/m^3). No atmospheric samples were available after 1963, even though the exposure occurred

through 1973. The LOAEL for occupationally-induced berylliosis observed in this study was estimated from uncertain exposure data to be less than 2 µg Be/m^3.

One cross-sectional study (Kriebel *et al.*, 1988a; Kriebel *et al.*, 1988b) estimated beryllium exposure levels for 309 workers originally surveyed in 1977, with a median duration of exposure of 17 years (range 2 to 39 years). Historic plant beryllium levels were estimated to be as high as 100 µg Be/m^3, and, even as late as 1975, some job classifications exceeded 10 µg Be/m^3. The workers' median cumulative exposure was 65 µg Be/m^3-years (range 0.1 to 4400 µg Be/m^3-years); the median lifetime exposure estimate was 4.3 µg/m^3 (range 0.01 to 150 µg/m^3). Spirometric measurement of pulmonary function, chest x-rays, and arterial blood gas measurements were collected. Decrements in lung function, as defined by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), were associated with cumulative exposure up to 20 years prior to the health survey, even in workers with no radiographic abnormalities. Differences in alveolar-arterial oxygen gradient were associated with cumulative exposure in the 10 years prior to the study. These endpoints give a LOAEL of 39 µg/m^3-years (geometric mean cumulative exposure) for decrements in pulmonary function and changes in arterial blood gases.

Non-occupational beryllium-related chronic disease has been reported in individuals residing in the vicinity of beryllium manufacturing industries (Eisenbud *et al.*, 1949; Metzner and Lieben, 1961). An early cross-sectional study (Eisenbud *et al.*, 1949) described 11 cases of non-occupational berylliosis after examining (x-ray and clinical) approximately 10,000 residents near a beryllium fabrication facility. Ten of the cases resided within 3/4 mile of the plant (up to 7 years duration), and five cases resided within 1/4 mile. The authors approximated a 1% disease incidence within 1/4 mile (500 individuals). Atmospheric sampling in 1947 identified an average beryllium level of 0.2 µg Be/m^3 at 1/4 mile decreasing to 0 µg Be/m^3 at 10 miles, but samples varied widely (up to 100 fold) over the 10 week sampling period. Utilizing current and historic exposure estimates based on discharge, process, inventory and building design changes, this study estimated a chronic LOAEL in the range of 0.01 to 0.1 µg Be/m^3 for continuous exposure to beryllium compounds, based on the development of chronic berylliosis.

Metzner and Lieben (1961) also reported 26 cases of chronic berylliosis in a population of approximately 100,000 living within 7 miles of a refining and alloy fabrication plant (duration 6 to 19 years). Neighborhood exposure assessment conducted over 14 months during1958 and 1959 identified a mean level of 0.0155 µg Be/m^3, with 10% of the samples registering over 0.03 µg Be/m^3. Limited measurements conducted earlier at the site were higher (1.0 to 1.8 µg Be/m^3 in 1953 and 0.91 to 1.4 µg Be/m^3 in 1954).

Chronic beryllium disease appears to involve a cell-mediated immune response, especially granulomatous reactions found in the lungs of sensitive individuals. Humans exposed to beryllium compounds have demonstrated increased T-cell activity (*in vitro*) and histological abnormalities of the lymph nodes (Cullen *et al.*, 1987; Johnson, 1983). Johnson (1983) described granuloma of lymph nodes and chronic interstitial pneumonitis in a small number of beryllium metal handling machinists (LOAEL = 4.6 µg Be/m^3). A second study identified granulomatous lung lesions, scarred lung tissue, and breathing difficulties in workers from a precious metal refining facility exposed to a mixture of beryllium and other metals (Cullen *et al.*,

1987). Also, altered proliferative responses of lymphocytes obtained by bronchoalveolar lavage indicated increased T-cell activity in vitro. This study reported a LOAEL of 1.2 µg Be/m^3 for the immunological and respiratory endpoints.

V. Effects of Animal Exposure

Three chronic studies, two in rats (Vorwald and Reeves, 1959; Reeves *et al.*, 1967) and one in guinea pigs (Reeves *et al.*, 1970), observed adverse inflammatory and proliferative respiratory changes following inhalation exposure to beryllium compounds. Vorwald and Reeves (1959) observed inflamed lungs and fibrosis in rats exposed to 0.006 mg Be/m^3 (as BeO) for an unspecified duration. A later study exposed Sprague-Dawley CD rats for 72 weeks (7 hr/d, 5 d/wk) to 34.25 µg Be/m^3 from $BeSO_4$ (Reeves *et al.*, 1967). Gross and histological changes observed in exposed versus unexposed rats included increased lung weight, inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (LOAEL = 34.25 µg Be/m^3). In guinea pigs exposed to either 0, 3.7, 15.4 or 29.3 µg Be/m^3 (from the sulfate) for 6 hours/day, 5 days/week for up to 1 year, respiratory alterations observed in the beryllium-exposed groups included increased tracheobronchial lymph node and lung wet weights, interstitial pneumonitis, and granulomatous lesions. These adverse respiratory effects were observed in all the beryllium dosed groups and indicated a chronic inhalation LOAEL of 3.7 µg Be/m^3.

Wagner *et al.* (1969) exposed monkeys, rats and hamsters to 0.21 and 0.62 mg Be/m^3 as fumes from bertrandite or beryl ore, respectively. Rats, exposed 6 hours/day, 5 days/week for up to 17 months, displayed more severe effects, including (1) bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions after exposure to 0.21 mg Be/m^3 from bertrandite ore, and (2) inflamed lungs, fibrosis, and granuloma after exposure to 0.62 mg Be/m^3 from beryl ore. Lung inflammation was observed in the exposed monkeys, and a few granulomatous lung lesions were observed in the hamsters after similar exposure conditions (up to 23 months).

Immunological effects have been observed in a few subchronic studies (Schepers, 1964; Schepers *et al.*, 1957; Stiefel *et al.*, 1980). Schepers (1964) exposed monkeys (*Macacus mullata*) to three soluble forms of beryllium (BeF_2, $BeSO_4$, $BeHPO_4$) daily for 6 hours/day over 7 to 30 days. Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed after 17 days at 0.198 mg Be/m^3 (as $BeSO_4$). Histological examination found pleuritis, congestion, emphysema, consolidation and edema of the lung. Immunological effects were seen as hyperplasia of the lymph nodes typical of immune activation after 7 to 18 days exposure to either 0.198 or 0.184 mg Be/m^3 as the sulfate or fluoride. A subchronic inhalation study reported immunological effects as increased, beryllium-specific stimulation of T-lymphocytes *in vitro* from Wistar rats and guinea pigs exposed daily (6 hours/day) over 10 weeks (LOAEL = 0.5 mg/m^3) (Stiefel *et al.*, 1980). However, a subchronic inhalation study on Wistar and Sherman rats (Schepers *et al.*, 1957) observed multiple lung alterations including granulomas (LOAEL = 35 µg Be/m^3) but did not find any accompanying immunological effects after 30 days discontinuous exposure (5-6 d/wk, 4-8 hr/d) to beryllium fumes from $BeSO_4$.

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Reference Exposure Level

Study	Eisenbud *et al.* (1949)
Study population	Approximately 10,000 individuals within 2 miles of a beryllium manufacturing plant
Exposure method	Environmental exposure
Critical effects	Pulmonary berylliosis
LOAEL	0.03 µg/m^3 (geometric mean of range of measured exposures associated with berylliosis of 0.01 to 0.1 µg/m^3)
NOAEL	Not observed
Exposure continuity	Continuous
Average exposure	Estimated to be approximately 0.3 µg/m^3 (historical exposures estimated to be 10-fold higher than measured values) for LOAEL group
Human equivalent concentration	0.3 µg/m^3 for LOAEL group
Exposure duration	Up to 7 years
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.001 µg/m^3

Eisenbud *et al.* (1949) reported 11 cases of non-occupational chronic pulmonary granulomatosis (berylliosis) among approximately 10,000 residents screened (health survey and x-ray) in the vicinity of a beryllium manufacturing plant. Ten of the cases resided within 3/4 mile of the facility, but neither these individuals nor their spouses had occupational contact with the plant. Five cases occurred within 1/4 mile of the plant from an approximate population of 500 residents. Although this study gave minimal case and population descriptions, environmental exposure assessment was conducted (fixed and mobile stations over 10 weeks) at the time of study (1947). In addition historical estimates were developed from earlier measurements, downwind effluent models, inventory, process and building design changes over time (plant operated from 1935 to 1947). In 1947, air concentrations ranged from 2 µg Be/m^3 at 1/4 mile to 0 µg Be/m^3 at 2 miles distance (detection limit = 0.001 µg Be/m^3). The estimated concentration at 3/4 mile distance from the plant was 0.01 µg Be/m^3. The authors estimated the airborne beryllium concentration associated with berylliosis as 0.01 to 0.10 µg Be/m^3. This estimate included multiplication of the 0.01 µg/m^3 concentration by a factor of 10 to account for greater historical exposures.

One other report describes 26 cases of berylliosis due to environmental exposure to beryllium plant effluent (Metzner and Lieben, 1961). This study reported a similar mean air concentration of 0.0155 µg Be/m^3, while limited historic measurements ranged from 0.91 to 1.8 µg Be/m^3.

Occupational studies have reported berylliosis and/or alterations in pulmonary function after exposure to higher concentrations of beryllium (2- to 10-fold). Cotes *et al.* (1983) reported on 146 workers surveyed three times since 1963 (1963, 1973, and 1977). Exposure assessment was based on plant sampling from 1952 to 1963. The estimated overall daily average was < 2 µg Be/m^3, however, a wide range of individual integrated exposures was estimated. Seven cases of berylliosis-related disease were observed in 130 workers examined in 1973. No association was seen between lung function and estimated exposure in normal subjects. However, Kriebel *et al.* (1988a; 1988b) did find decrements in lung function significantly associated with cumulative exposure to beryllium. Lifetime beryllium exposure histories were estimated for 309 of 350 workers (mean duration = 17 years) and 297 underwent medical testing. The median cumulative exposure was 65 µg Be/m^3-years (mean cumulative exposure = 37 µg Be/m^3) and the mean lifetime exposure was 3 µg Be/m^3. After controlling for age, height, and smoking in multivariate regression models, decrements in lung function (FVC and FEV_1) were associated with cumulative exposure to beryllium, in the period up until 20 years before the survey.

The major strength of the REL is the use of human data among residentially-exposed persons. The major uncertainties are the lack of a NOAEL observation, the lack of long-term exposure data, the difficulty of estimating exposures, and the lack of chronic exposure data.

Derivation of Chronic Oral Reference Exposure Level* (U.S. EPA RfD*)

Study	Schroeder and Mitchner, 1975
Study population	Rats
Exposure method	Drinking water
Critical effects	No adverse effects at dose given
LOAEL	Not observed
NOAEL	5 ppm in water (0.54 mg/kg bw-day)
Exposure continuity	Continuous
Exposure duration	Lifetime
Average experimental exposure	0.54 mg/kg bw-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.005 mg/kg bw-day

*Conversion Factors: 5 ppm (5 mg/L) x 0.035 L/day / 0.325 kg bw = 0.54 mg/kg bw/day

The Oral Reference Exposure Level (REL) for beryllium is the U.S. EPA's Reference Dose for chronic oral exposure (RfD) (U.S.EPA, 1996). Fifty-two weanling Long-Evans rats of each sex

received 0 or 5 ppm beryllium (as $BeSO_4$, beryllium sulfate) in drinking water (Schroeder and Mitchner, 1975). Exposure was for the lifetime of the animals. At natural death the rats were dissected and gross and microscopic changes were noted in heart, kidney, liver, and spleen. There were no effects of treatment on these organs or on life span, urinalysis, serum glucose, cholesterol, and uric acid, or on numbers of tumors. Male rats showed decreased growth rates from 2 to 6 months of age. Similar studies were carried out on Swiss (CD strain) mice in groups of 54/sex at doses of approximately 0.95 mg/kg/day (Schroeder and Mitchner, 1975). Female animals showed decreased body weight compared with untreated mice at 6 of 8 intervals. Male mice exhibited slight increases in body weight. These effects were not considered adverse, therefore, 0.95 mg/kg/day is considered a NOAEL. An unpublished investigation by Cox *et al.* (1975) indicates a much higher dose level (approximately 25 mg/kg/day) in the diet may be a NOAEL.

The uncertainty factor (UF) of 100 reflects a factor of 10 each for interspecies conversion and for the protection of sensitive human subpopulations. No modifying factor (MF) was used.

This RfD is limited to soluble beryllium salts. Data on the teratogenicity or reproductive effects of beryllium are limited. It has been reported to produce embryolethality and terata in chick embryos.

U.S. EPA stated its confidence in the RfD as: Study - Low; Data Base – Low, and RfD - Low. Confidence in the study is rated as low because only one dose level was administered. Although numerous inhalation investigations and a supporting chronic oral bioassay in mice exist, along with the work by Cox *et al.* (1975) which indicates that a higher dose level might be a NOEL, these studies are considered as low to medium quality. Thus, the data base is given a low confidence rating. The overall confidence in the RfD is low, reflecting the need for more toxicity data by the oral route.

VII. References

ATSDR. 1993. Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Beryllium. TP-92/04. Atlanta, GA: ATSDR. April 1993.

Cotes JE, Gilson JC, McKerrow CB, and Oldham P. 1983. A long-term follow-up of workers exposed to beryllium. Br. J. Ind. Med. 40:13-21.

Cullen M, Kominsky J, Rossman M, Cherniack M, Rankin J, Balmes J, Kern J, Daniele R, Palmer L, Naegel G, McManus K, and Cruz R. 1987. Chronic beryllium disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume. Am. Rev. Respir. Dis. 135:201-208.

Eisenbud M, and Lisson J. 1983. Epidemiological aspects of beryllium-induced nonmalignant lung disease: A 30 year update. J. Occup. Med. 25:196-202.

Eisenbud M, Berghout CF, and Steadman L. 1948. Environmental studies in plants and laboratories using beryllium: the acute disease. J. Ind. Hyg. Toxicol. 30:282-285.

Eisenbud M, Wanta R, Dustan C, Steadman L, Harris W, and Wolf B. 1949. Nonoccupational berylliosis. J. Ind. Hyg. Toxicol. 31:282-294.

Infante PF, Wagoner JK, and Sprince NL. 1980. Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. Environ. Res. 21:35-43.

Johnson NR. 1983. Beryllium disease among workers in a spacecraft-manufacturing plant - California. MMWR. 32:419-425.

Kriebel D, Sprince NL, Eisen EA, Greaves I, Feldman H and Greene R. 1988a. Beryllium exposure and pulmonary function: A cross sectional study of beryllium workers. Br. J. Ind. Med. 45:167-173.

Kriebel D, Sprince NL, Eisen EA, and Greaves I. 1988b. Pulmonary function in beryllium workers: Assessment of exposure. Br. J. Ind. Med. 45:83-92.

Lieben J, and Metzner F. 1959. Epidemiological findings associated with beryllium extraction. Am. Ind. Hyg. Assoc. 20:494-499.

Metzner F, and Lieben J. 1961. Respiratory disease associated with beryllium disease - A case study. J. Occup. Med. 3:341-345.

Reeves AL, Deitch D, and Vorwald AJ. 1967. Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. Cancer Res. 27:439-443.

Reeves AL, Swanborg RH, Busby EK, and Krivanek ND. 1970. In: Target Organ Toxicology Series: Immunotoxicology and Immunopharmacology. Dean J, Luster M, Munson A, and Amos H, eds. New York, NY: Raven Press, Inc. pp. 441-456.

Schepers GW. 1964. The biological action of beryllium: Reaction of the monkey to inhaled aerosols. Ind. Med. Surg. 33:1-16.

Schepers GW, Durkhan TM, Delahunt AB, and Creedon FT. 1957. The biological action of inhaled beryllium sulfate. A preliminary chronic toxicity study in rats. AMA Arch. Ind. Health 15:32-58.

Schroeder HA, and Mitchner M. 1975. Life-term studies in rats: Effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105:421-427.

Stiefel T, Schulze K, Zorn H, and Toelg G. 1980. Toxicokinetic and toxicodynamic studies of beryllium. Arch. Toxicol. 45:81-92.

U.S. Environmental Protection Agency. 1996. Integrated Risk Information System (IRIS) Database.

Vorwald A, and Reeves A. 1959. Pathologic changes induced by beryllium compounds. Arch. Indust. Health 19:190-199.

Wagner W, Groth D, Holtz J, Madden G, and Stokinger H. 1969. Comparative chronic inhalation toxicity of beryllium ores bertrandite and beryl, with production of pulmonary tumors by beryl. Toxicol. Appl. Pharmacol. 15:10-29.

CHRONIC TOXICITY SUMMARY

1,3-BUTADIENE

(butadiene; buta-1,3-diene; biethylene; bivinyl; vinylethylene)

CAS Registry Number: 106-99-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**8 µg/m^3**
Critical effect(s)	Increased incidence of ovarian atrophy in mice
Hazard index target(s)	Reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Colorless gas
Molecular formula	C_4H_6
Molecular weight	54.09
Boiling point	-4.4^{o}C
Vapor pressure	910 mm Hg at 20°C
Solubility	Soluble in water (735 mg/L); soluble in ethanol, ether, acetone, benzene
Conversion factor	1 ppm = 2.21 mg/m^3 at 25°C

III. Major Uses and Sources

1,3-Butadiene is a major commodity product of the petrochemical industry, usually produced as a by-product of ethylene. The majority of 1,3-butadiene is used in the production of styrene-butadiene rubber copolymers (SBR). Other applications include as a polymer component for polybutadiene, hexamethylene diamine, styrene-butadiene latex, acrylonitrile-butadiene-styrene (ABS) resins, chloroprene and nitrile rubbers. A variety of industrial syntheses use 1,3-butadiene resins (AB as a chemical intermediate, such as in the production of adiponitrile (a nylon precursor), captan and captofol fungicides, ethylidene norbornene and sulfolane, boron alkyls, and hexachlorobutadiene. Additionally, 1,3-butadiene has been found in automobile exhaust, gasoline vapor, fossil fuel incineration products, and cigarette smoke (HSDB, 1995).

IV. Effects of Human Exposure

An early occupational study reported complaints of irritation of eyes, nasal passages, throat, and lungs in rubber manufacturing workers following acute exposure to unknown levels of 1,3-butadiene (Wilson, 1944). Additional symptoms reported included coughing, fatigue, and drowsiness, however, all symptoms ceased on removal from the exposure.

Studies on the chronic effects of 1,3-butadiene have been centered in the styrene-butadiene rubber manufacturing industry, which uses large quantities of 1,3-butadiene, and the 1,3-butadiene monomer industry. One retrospective epidemiological study reported an increase in overall mortality, emphysema, and cardiovascular diseases (chronic rheumatic and arteriosclerotic heart disease) among rubber workers (McMichael *et al.*, 1976). Two other occupational studies have described the potential for adverse hematological effects due to butadiene exposure (Checkoway and Williams, 1982; McMichael *et al.*, 1975). A survey of workers at a styrene-butadiene rubber plant revealed slightly lower levels (but within normal range) of red blood cells, hemoglobin, platelets, and neutrophils in exposed (mean 20 ppm) versus unexposed workers (Checkoway and Williams, 1982). And 1,3-butadiene has been implicated in hematopoietic malignancies among styrene-butadiene rubber workers at levels lower than 20 ppm (McMichael *et al.*, 1975). Since the workers in these studies were exposed to mixtures of chemicals, the specific contribution of butadiene to the adverse respiratory and hematopoietic effects remains unclear.

V. Effects of Animal Exposure

The few available chronic animal inhalation studies have focused on the potential carcinogenicity of 1,3-butadiene. The National Toxicology Program (NTP) has sponsored two chronic inhalation studies in $B6C3F_1$ mice (NTP, 1984; Melnick *et al.*, 1990; NTP, 1993), while Hazelton Laboratories Europe (HLE) Ltd. conducted a chronic inhalation study in Sprague-Dawley rats (HLE, 1981; Owen *et al.*, 1987; Owen and Glaister, 1990).

The two $B6C3F_1$ mice inhalation studies sponsored by NTP (Huff *et al.*, 1985; Melnick *et al.*, 1990; NTP, 1984; NTP, 1993), although focused on carcinogenicity, identified other adverse chronic effects. The earlier NTP (1984) study in mice administered 0, 625 or 1250 ppm 1,3-butadiene for 6 hours/day, 5 days/week for up to 61 weeks. Nonneoplastic changes observed were elevated testicular and ovarian atrophy at both doses (625 and 1250 ppm); liver necrosis in male mice at both doses and in female mice at 1250 ppm; and nonneoplastic lesions in the nasal cavity at 1250 ppm. At the highest dose, adverse changes in the nasal cavity included chronic inflammation, fibrosis, cartilaginous metaplasia, osseous metaplasia, and atrophy of the sensory epithelium. No nasal or respiratory lesions were seen in the controls. This study identified a chronic LOAEL of 625 ppm for gonadal atrophy in both sexes.

The later NTP study (Melnick *et al.*, 1990; NTP, 1993) used lower exposure concentrations of 1,3-butadiene (0, 6.25, 20, 62.5, 200 or 625 ppm) administered 6 hours/day, 5 days/week for up to 2 years. Two-year survival was significantly decreased in mice exposed to 20 ppm and greater, primarily due to chemical-related malignant neoplasms. Increased incidences of nonneoplastic lesions in exposed mice included bone marrow atrophy, gonadal atrophy (testicular, ovarian and uterine), angiectasis, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and cardiac endothelial hyperplasia. Gonadal atrophy was observed at 200 ppm and 625 ppm for males and at 6.25 ppm and higher for females. Bone marrow toxicity (regenerative anemia) was seen at 62.5 ppm and higher. This study identified a chronic LOAEL

of 6.25 ppm for reproductive toxicity, and a NOAEL of 200 ppm and a LOAEL of 625 for nonneoplastic hematotoxic effects.

The U.S. EPA (1985) reviewed data from a 2-year chronic inhalation toxicity study sponsored by the International Institute of Synthetic Rubber Producers (IISRP) at Hazelton Laboratories Europe, Ltd (1981) on Sprague-Dawley rats exposed to 0, 1000 or 8000 ppm 1,3-butadiene. Results from the study were also reported later by Owen *et al.* (1987; 1990). Minor clinical effects, including excessive eye and nose secretions plus slight ataxia, were observed between 2 and 5 months in rats exposed to 8000 ppm 1,3-butadiene. Alterations in organ weight were also observed in this high exposure group. A dose-related increase in liver weights was observed at both the 52-week interim kill and at study termination. Absolute and relative kidney weight was also significantly increased and associated with nephrosis. No reproductive organ atrophy was reported in this rat study.

The U.S. EPA (1985) described another secondary report, that of Miller (1978), which reviewed a group of Russian studies of subchronic 1,3-butadiene exposure in rats. One study (reported by Ripp in 1967) continuously exposed rats to relatively lower concentrations of 0.45, 1.4 or 13.5 ppm. At 13.5 ppm, blood cholinesterase was elevated, blood pressure was lowered, and motor activity was decreased. Histopathological changes reported at 0.45 ppm were congestion in the spleen and hyperemia and leukocyte infiltration of cardiac tissue. Alterations in lung tissue noted at 1.4 and 13.5 ppm included atelectasis, interstitial pneumonia, and emphysema. No other studies used such low exposure levels or measured such endpoints. Unfortunately, the specific research methods and results for this study are unavailable for direct review and comparison.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP (1993)
Study population	$B6C3F_1$ mice (70/sex/group)
Exposure method	Discontinuous inhalation (0, 6.25, 20, 62.5, 200, 625 ppm) over 2 years
Critical Effects	Increased incidence of ovarian atrophy
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	103 weeks
LOAEL	6.3 ppm
NOAEL	Not observed
Average experimental exposure	1.1 ppm for LOAEL group (6.3 x 6/24 x 5/7)
Human equivalent concentration	1.1 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic factor	1
LOAEL uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	4 ppb (0.004 ppm; 0.008 mg/m^3; 8 $\mu g/m^3$)

The chronic REL for butadiene is based on an increased incidence of ovarian atrophy in mice. Significant reproductive toxicity was observed in both sexes of mice at the interim 9-month, interim 15-month, and 2-year study termination as gonadal atrophy (NTP, 1993). Testicular atrophy was induced in male B6C3F1 mice at 625 ppm or above in this principal study and in a previous study (NTP, 1984). In female mice exposed for 9-months, ovarian atrophy was observed at 200 and 625 ppm (442 or 1381 mg/m^3, respectively). After 15 months, ovarian atrophy was observed at exposure levels of 20 ppm (44.2 mg/m^3) and above. In mice exposed for up to 2 years (103 weeks), the incidence of ovarian atrophy increased at all exposure concentrations relative to controls, which establishes a chronic LOAEL of 6.25 ppm (13.81 mg/m^3) for reproductive toxicity. The incidence of ovarian atrophy was 4/49 in controls and 19/49 (39%) at 6.25 ppm. Because atrophy of a major organ is the critical effect observed at the LOAEL, and no NOAEL was recorded, the full LOAEL uncertainty factor of 10 is used.

Few chronic animal studies are available for comparison to the above; however, an acute and subchronic (10 week) study identified male-mediated F1 effects in mice exposed to 12.5 or 1250 ppm 1,3-butadiene (6 hour/day, 5 days/week) (Anderson *et al.*, 1993). At 1250 ppm (2762.4 mg/m^3), statistically significant effects observed were a reduction in the number of implantations, an induction of dominant lethal mutations, an increased incidence of early and late deaths, and an increase in abnormalities. The lower dose, 12.5 ppm (27.63 mg/m^3), resulted in an increase of early deaths and fetal abnormalities. The IISRP sponsored study (Owen *et al.* 1987; 1990) did not report any noncancer adverse reproductive effects in Sprague-Dawley rats exposed to 1000 or 8000 ppm 1,3-butadiene (2210 or 17,680 mg/m^3, respectively); however, tumors were found in reproductive tissues (Owen *et al.*, 1987).

The mouse ovary is more sensitive to butadiene's epoxide metabolites than the rat ovary. Doerr *et al*. (1996) administered butadiene monoepoxide (BMO) or butadiene diepoxide (BDE) intraperitoneally to female B6C3F1 mice and Sprague-Dawley rats for 30 days and found that BMO and BDE exhibited a greater ovotoxic potential in the mice compared to the rats. Dahl et al. (1991) reported that, for equivalent inhalation exposures, the concentrations of total butadiene metabolites in blood were 5-50 times lower in the monkeys than in the mice and 4-14 times lower than in the rats. People may be more like the monkey than the mouse or the rat in their formation of epoxides from butadiene. Several pharmacokinetic models (reviewed by Himmelstein *et al*., 1997) have been developed to adjust for species differences in pharmacokinetics. However, an interspecies pharmacodynamic adjustment for this ovarian atrophy endpoint with butadiene is still needed. Therefore OEHHA staff use an interspecies uncertainty factor of 3 to account for pharmacodynamic differences between mice and men.

The major strength of the butadiene REL is the observation of a dose-response effect in a well-conducted lifetime inhalation exposure study. The major weaknesses are the lack of adequate human health effects data and the lack of a NOAEL observation.

VII. References

Anderson D, Edwards AJ, and Brinkworth MH. 1993. Male-mediated F1 effects in mice exposed to 1,3-butadiene. In: Butadiene and Styrene: Assessments of Health Hazards. Sorsa, M, Peltonen K, Vainio H, Hemminki K, eds. IARC Scientific Publications No. 127. Lyon, France: International Agency for Research on Cancer. pp. 171-181.

Checkoway H, and Williams TM. 1982. A hematology survey of workers at a styrene-butadiene synthetic rubber manufacturing plant. Am. Ind. Hyg. Assoc. J. 43(3):164-169.

Dahl AR, Sun JD, Birnbaum LS, Bond JA, Griffith WC Jr, Mauderly JL, Muggenburg BA, Sabourin PJ, Henderson RF. 1991. Toxicokinetics of inhaled 1,3-butadiene in monkeys: comparison to toxicokinetics in rats and mice. Toxicol. Appl. Pharmacol. 110(1):9-19. (Published erratum appears in Toxicol. Appl. Pharmacol. 1992. 116(1):152.)

Doerr JK, Hollis EA, and Sipes IG. 1996. Species difference in the ovarian toxicity of 1,3-butadiene epoxides in B6C3F1 mice and Sprague-Dawley rats. Toxicology 113(1-3):128-136.

Himmelstein MW, Acquavella JF, Recio L, Medinsky MA, Bond JA. 1997. Toxicology and epidemiology of 1,3-butadiene. Crit. Rev. Toxicol. 27(1):1-108.

HLE. 1981. Hazelton Laboratories Europe, Ltd. 1,3-Butadiene: The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Prepared for the International Institute of Synthetic Rubber Producers, New York, NY. Unpublished. [as reported in U.S. EPA, 1985].

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 1995)

Huff JE, Melnick RL, Solleveld HA, Haseman JK, Powers M, and Miller RA. 1985. Multiple organ carcinogenicity of 1,3-butadiene in B6C3F1 mice after 60 weeks of inhalation exposure. Science 227(4686):548-549.

McMichael AJ, Spirtas R, and Kupper KK. 1975. Solvent exposure and leukemia among rubber workers: An epidemiologic study. J. Occup. Med. 17:234-239.

McMichael AJ, Spirtas, R, Gamble JF, and Tousey PM. 1976. Mortality among rubber workers. Relationship to specific jobs. J. Occup. Med. 18(3):178-185.

Melnick RL, Huff J, Chou BJ, and Miller R. 1990. Carcinogenicity of 1,3-butadiene in C57BL/6xC3H F1 mice at low exposure concentrations. Cancer Res. 50(20):6592-6599.

Miller LM. 1978. Investigation of selected potential environmental contaminants: Butadiene and its oligomers. Philadelphia, PA: Franklin Research Center. [as reported in U.S. EPA, 1985].

NTP. 1984. U.S. National Toxicology Program. Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No.106-99-0) in B6C3F1 Mice (Inhalation Studies) (TR No. 288) Research Triangle Park, NC: National Institute of Environmental Health Sciences.

NTP. 1993. U.S. National Toxicology Program. Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No.106-99-0) in B6C3F1 Mice (Inhalation Studies) (TR No. 434). Research Triangle Park, NC: National Institute of Environmental Health Sciences.

Owen PE, Glaister JR, Gaunt IF, and Pullinger DH. 1987. Inhalation toxicity studies with 1,3-butadiene. 3. Two-year toxicity/carcinogenicity studies in rats. Am. Ind. Hyg. Assoc. J. 48:407-413.

Owen PE, and Glaister JR. 1990. Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. Environ. Health Perspect. 86:18-25.

U.S. EPA. 1985. U.S. Environmental Protection Agency. Mutagenicity and Carcinogenicity Assessment of 1,3-Butadiene. Publication No. EPA/600/8-85/004F. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

Wilson RH. 1944. Health hazards encountered in the manufacture of synthetic rubber. JAMA 124(11):701-703.

CHRONIC TOXICITY SUMMARY

CADMIUM AND CADMIUM COMPOUNDS

CAS Registry Number: 7440-43-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.02 μg/m^3** (respirable)
Critical effect(s)	Kidney effects (proteinuria) and respiratory effects (reduction in forced vital capacity and reduction in peak expiratory flow rate) in occupationally exposed humans
Hazard index target(s)	Kidney; respiratory system

II. Physical and Chemical Properties (ATSDR, 1993)

Description	Blue-white solid
Molecular formula	Cd
Molecular weight	112.41
Density	8.642 g/cm^3 @ 20ºC
Boiling point	767ºC
Melting point	320.9ºC
Vapor pressure	1 torr @ 394ºC
Conversion factor	Not applicable

III. Major Uses or Sources

The production of nickel-cadmium batteries is currently the primary use of cadmium (ATSDR, 1993). Cadmium, a by-product of zinc- and sulfide-ore processing, is also used for metal plating and in pigments and plastics.

IV. Effects of Human Exposure

Pulmonary and renal function were examined in three worker groups: women with less than 20 years of exposure [group E1]; men with less than 20 years of exposure [group E2], and men with more than 20 years of exposure [group E3] (Lauwerys *et al.*, 1974). Although urine cadmium concentrations were significantly elevated, the subjects in E1 did not exhibit pulmonary function changes or proteinuria indicative of renal impairment. The workers in E1 had been exposed for a mean of 4.08 years to 31 μg/m^3 total cadmium (1.4 μg/m^3 respirable cadmium). The 27 workers in E2 had been exposed for a mean of 8.6 years to 134 μg/m^3 total cadmium (88 μg/m^3 respirable cadmium). The blood and urinary cadmium levels of these workers were also significantly

elevated compared to matched controls. Glomerular proteinuria was observed in 15% of the workers in E2 and in 68% of workers in E3. The 22 workers of E3 had been exposed for a mean of 27.8 years to 66 $\mu g/m^3$ total cadmium (21 $\mu g/m^3$ respirable cadmium). Significantly increased levels of cadmium were observed in the blood and urine and workers in E3 also exhibited significant decreases in some measures of pulmonary function (forced vital capacity, forced expiratory volume in one second, and peak expiratory flow rate). This study identifies the kidney as the key target organ of chronic cadmium exposure. For respirable cadmium, this study indicates a LOAEL of 21 $\mu g/m^3$ for workers exposed for 28 years and a NOAEL of 1.4 $\mu g/m^3$ for workers exposed for 4 years.

A study of 82 cadmium exposed workers reports the time-weighted cumulative exposure index (TWE) and cadmium body burden determined in vivo (Ellis *et al.*, 1985). Evidence of renal dysfunction (usually elevated urinary β_2-microglobulin) was consistently observed when the worker's liver cadmium burden exceeded 40 ppm and the time-weighted cumulative exposure index exceeded 400-500 μg years/m^3.

A detailed investigation of renal function in 75 male cadmium-exposed workers identified significant increases in urinary excretion of several low- and high molecular weight proteins, including β_2-microglobulin, and significant decreases in renal reabsorption of calcium, urate, and phosphate compared to controls (Mason *et al.*, 1988). Exposures, which ranged from 36 to 600 $\mu g/m^3$, were determined from background or personal exposure measurements made between 1964 and 1983, or were estimated. A time-weighted cumulative exposure index (TWE) was determined for each subject. A two phase linear regression model was applied to the data to identify inflection points for each biochemical parameter. The biochemical indicators most highly correlated to exposure were urinary retinol binding protein and urinary β_2-microglobulin. Of these, the most sensitive parameter, urinary β_2-microglobulin, demonstrated an inflection point at 1108 μg years/m^3 with a 95% lower confidence limit of 509 μg years/m^3. The endpoint selected is indicative of defects in tubular reabsorption of proteins.

Diminished sensitivity of smell has also been observed in cadmium exposed workers (Rose *et al.*, 1992). Cadmium body burden, β_2-microglobulin levels, and olfactory function were measured in a group of 55 male workers exposed to cadmium fumes in a brazing operation. A group of 15 control workers was also tested. Exposed workers exhibited high urinary cadmium levels, tubular proteinuria, and a significant, selective defect in odor detection threshold.

V. Effects of Animal Exposure

Interstitial infiltration of lymphocytes and leukocytes and hyaline casts were observed in the kidneys of rabbits following exposure to 6.5 mg/m^3 cadmium-iron dust for 3 hours per day, 21 days per month for 9 months (Friberg, 1950). Proteinuria was observed in the majority of exposed rabbits by the fourth month of exposure. Increased lung weights and emphysema were also observed. The trachea and nasal mucous membranes exhibited chronic inflammatory changes (not specified) and lymphocyte infiltration. The kidney contained the greatest concentration of cadmium. This study also exposed a group of rabbits to 9.1 mg/m^3

cadmium-iron dust for 3 hours per day, 23 days per month, for 7 months. Two rabbits in this group died from acute pneumonia at one month, and one rabbit was terminated at 3 months of exposure. Findings at necropsy were similar, although more severe than those observed in rabbits exposed to 6.5 mg/m^3. Chronic bronchitis and hyperplasia of the bronchiolar epithelium were observed in the higher dose group in addition to the findings previously noted.

Male and female rats were exposed to 0, 0.3, 1.0, or 2.0 mg Cd/m^3 (as $CdCl_2$) 6 hours per day, 5 days per week for a total of 62 exposures (Kutzman *et al.*, 1986). Rapid, shallow breathing and marked weight loss were observed in the highest dose group; all animals in this group died within the first 45 days of exposure. A dose-dependent increase in lung weight was observed in the remaining dose groups and a statistically significant increase in lung collagen and elastin was observed in rats exposed to 1.0 mg/m^3. Pathological changes noted in the terminal bronchioles include flattening and hyperplasia of type II cells, and infiltration of macrophages, mononuclear cells, and polymorphonuclear leukocytes. Proliferation of fibroblasts with deposition of collagen was also noted.

Male rats were exposed continuously to 0, 30, or 90 µg Cd/m^3 cadmium oxide (CdO) dust for up to 18 months (Takenaka *et al.*, 1990). Animals exposed to 30 µg/m^3 were sacrificed at 6 and 18 months of exposure. Although some rats in the high dose group were terminated after 6 months of exposure, the remaining rats were terminated after 7 months due to increased mortality and were not included in the study. Inflammation and hyperplasia of the alveolar epithelium occurred in animals of both groups after 6 months of exposure with more marked changes observed in the high dose group. Abnormal proliferation of the epithelium was observed in the low dose group following 18 months of exposure. Lung tumors observed in both dose groups were characterized as being duration dependent.

VI. Derivation of Chronic Reference Exposure Levels (REL)

Derivation of Chronic Inhalation Reference Exposure Level

Study	Lauwerys *et al.*, 1974
Study population	Humans (22 exposed men and 22 unexposed men in LOAEL group; 31 exposed women and 31 non-exposed women in NOAEL group)
Exposure method	Occupational exposures
Critical effects	Kidney effects - proteinuria in 68% of LOAEL group Respiratory effects – reduction in forced vital capacity in 1 second (FEV_1); reduction in peak expiratory flow rate
LOAEL	21 µg/m^3 respirable cadmium
NOAEL	1.4 µg/m^3 respirable cadmium
Exposure continuity	Assumed to be 5 days/week for 8 hours/day during which 10 m^3 air is breathed

Average occupational exposure	0.5 μg/m^3 for NOAEL group (1.4 x 10/20 x 5/7)
Human equivalent concentration	0.5 μg/m^3 for NOAEL group
Exposure duration	Average of 4.1 years (1 to 12 years) for NOAEL group
Subchronic uncertainty factor	3
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.02 μg/m^3

This evaluation is strengthened by being based on a human exposure study of workers exposed to cadmium for periods of 1 to over 20 years. The exposed group was matched to a control group in terms of age, body size, cigarettes smoked per day, duration of smoking, and duration of employment. The factory process was unchanged over the study period suggesting that exposures may have remained relatively constant over time.

Significant areas of uncertainty include an incomplete knowledge of the past exposures over the full study interval and the relatively small study size.

A similar evaluation of the LOAEL group led to an alternate inhalation reference exposure level estimate of 0.05 μg/m^3. The LOAEL group had an average occupational exposure of 5.0 μg/m^3 and an average exposure duration of 27.8 years (21 to 40 years). Default uncertainty factors would include a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor (UF).

Using data presented by Ellis and associates (1985) and Mason and associates (1993) correlating human cumulative exposures (in terms of μg-years/m^3) and renal tubular protein reabsorption, a LOAEL of 500 μg-years / m^3 was predicted. This correlates to 7 μg/m^3 over 70 years. A time-weighted exposure to account for continuous exposure rather than 40 hour per week occupational exposure is 1.7 μg/m^3. Applying a 10-fold LOAEL uncertainty factor and a 10-fold intraspecies uncertainty factor results in a REL value of 0.02 μg/m^3, the same value obtained using the Lauwerys *et al*. data.

Derivation of Chronic Oral Reference Exposure Level **(U.S. EPA RfD)**

Study	U.S. EPA, 1985
Study population	Humans
Exposure method	Food and drinking water
Critical effects	Significant proteinuria
LOAEL	Not observed
NOAEL	0.005 mg/kg bw-day
Exposure continuity	Chronic
Exposure duration	Up to lifetime
Average exposure	0.005 mg/kg bw-day

LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies factor	10
Cumulative uncertainty factor	10
Oral reference exposure level	0.0005 mg/kg bw-day

The oral REL is the U.S. EPA's Reference Dose (RfD) (U.S. EPA, 1996). A concentration of 200 μg cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 μg Cd/gm wet weight human renal cortex. The model assumes that 0.01% of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 μg Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day.

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect. Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

The uncertainty factor of 10 is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the RfD as: Study - Not applicable; Data Base - High; and RfD – High. The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium including absorption, distribution, metabolism, and elimination. All this information considered together gives high confidence in the data base. High confidence in the RfD follows as well.

VII. References

ATSDR. 1993. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Cadmium. Prepared under contract No. 205-88-0606 for: US Department of Health and Human Services, Public Health Service. Atlanta, GA: ATSDR.

Ellis KJ, Cohn SH, and Smith TJ. 1985. Cadmium inhalation exposure estimates: Their significance with respect to kidney and liver cadmium burden. J. Toxicol. Environ. Health 15:173-187.

Friberg L. 1950. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. Acta Med. Scand. (Suppl. 240) 138:1-124.

Lauwerys RR, Buchet JP, Roels HA, Brouwers J, and Stanescu D. 1974. Epidemiological survey of workers exposed to cadmium. Arch. Environ. Health 28:145-148.

Kutzman RS, Drew RT, Shiotsuka RN, and Cockrell BY. 1986. Pulmonary changes resulting from subchronic exposure to cadmium chloride aerosol. J. Toxicol. Environ. Health 17:175-189.

Mason HJ, Davison AG, Wright AL, Guthrie CJG, Fayers PM, Venables KM, *et al.* 1988. Relations between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. Br. J. Ind. Med. 45:793-802.

Rose CS, Heywood PG, and Costanzo RM. 1992. Olfactory impairment after chronic occupational cadmium exposure. J. Occup. Med. 34(6):600-605.

Takenaka S, Glaser U, Oldiges H, and Mohr U. 1990. Morphological effects of Cd-aerosols on the rat lung. Toxicol. Environ. Chem. 27:163-172.

U.S.EPA. 1985. United States Environmental Protection Agency. Drinking Water Criteria Document on Cadmium. Final draft. Office of Drinking Water. Washington, DC: U.S. EPA.

U.S. Environmental Protection Agency. 1996. Integrated Risk Information System (IRIS) Database. Cadmium.

CHRONIC TOXICITY SUMMARY

CARBON DISULFIDE

(carbon bisulfide; carbon sulfide; dithiocarbonic anhydride)

CAS Registry Number: 75-15-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**700 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	CNS/PNS (reduction in motor nerve conduction velocities in occupationally-exposed humans)
Hazard index target(s)	Nervous system; reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Clear, colorless or faintly yellow liquid
Molecular formula	CS_2
Molecular weight	76.14
Boiling point	46.5^{o}C
Vapor pressure	297 mm Hg @ 20°C
Solubility	Slightly soluble in water (2.94 g/L); miscible in anhydrous methanol, ethanol, ether, benzene, chloroform, and carbon tetrachloride
Conversion factor	3.1 mg/m^3 per ppm at 25°C

III. Major Uses and Sources

The most prominent industrial use of carbon disulfide is in the production of viscose rayon fibers. Other uses are in the production of carbon tetrachloride and cellophane, and, as a solvent for rubber, sulfur, oils, resins and waxes. In the past, carbon disulfide was used in 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 (HSDB, 1995).

IV. Effects of Human Exposure

A primary target of carbon disulfide (CS_2) toxicity is the nervous system. The major neurotoxic action of carbon disulfide is the development of mental disturbances. These include change of personality, irritability, and forgetfulness, often with accompanying neurophysiological and

neuropathological changes after prolonged exposure. Such changes include decreased peripheral nerve impulse conduction, motor and/or sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes (Aaserud *et al.* 1988, 1990, 1992; Foa *et al.*, 1976; Hirata *et al.* 1992; Ruijten *et al.* 1990, 1993). Alterations in behavioral indices have historically been associated with high levels of CS_2, often in the excess of 20 ppm (Foa *et al.* 1976; Hanninen *et al.*, 1978).

Studies have identified alterations in the nerve conduction of workers chronically exposed to lower CS_2 levels (Hirata *et al.*, 1992a; Johnson *et al.*, 1983; Ruijten *et al.*, 1990; Ruijten *et al.*, 1993). A cross-sectional study of Japanese spinning workers identified alterations in the central nervous system as measured by brain stem auditory evoked potential (BAEP) (Hirata *et al.*, 1992). The latencies of the three main BAEP components increased significantly in the CS_2 exposed workers (more than 20 years duration) when compared to controls. CS_2 exposures ranged from 3.3 to 8.2 ppm (mean 4.76 ppm). Ruijten *et al.* (1993) identified mild presymptomatic nerve impairment (decreased conduction velocities and response amplitudes) in 44 CS_2-exposed workers with an average cumulative exposure range from 192 to 213 ppm-year (mean duration 26.1 years).

Another occupational study evaluated the effects of CS_2 on the peripheral nervous system. Johnson *et al.* (1983) identified a significant dose related reduction in the motor nerve conduction velocities in the calves and ankles of workers exposed to high (median = 7.6 ppm) CS_2 levels versus a comparison group (median = 0.2 ppm). Since this motor nerve reduction was still within normal values, the authors considered the measured difference an indication of minimal neurotoxicity. The mean exposure concentration for all exposed workers (n = 145) ranged from 0.6 to 16 ppm (mean 7.3 ppm) with a mean duration of 12.1 years. This study established a chronic LOAEL of 7.6 ppm for minor neurological effects (decreased peroneal nerve MCV and sural nerve SVC).

Vascular atherosclerotic changes are also considered a major effect of chronic carbon disulfide exposure. Several occupational studies have demonstrated an increase in the mortality due to ischemic heart disease in CS_2 exposed workers (Hernberg *et al.*, 1970; MacMahon and Monson, 1988; Tiller *et al.*, 1968; Tolonen *et al.*, 1979). A 2.5-fold excess in mortality from coronary heart disease in workers exposed to CS_2 was first reported by Tiller *et al.* (1968). A subsequent prospective study by Hernberg *et al.* (1970) found a 5.6-fold increased risk in coronary heart disease mortality and a 3-fold increased risk of a first nonfatal myocardial infarction in CS_2 exposed workers.

Egeland *et al.* (1992) and Vanhoorne *et al.* (1992) have reported that human exposure to CS_2 for more than one year causes increases in biochemical changes often associated with cardiovascular disease - diastolic blood pressure, low density lipoprotein cholesterol, and apolipoproteins A1 and B. Egeland *et al.* (1992) used cross sectional data on 165 CS_2-exposed workers (245 controls) collected in 1979 by Fajen *et al.* (1981). The affected workers were exposed for at least 1 year in a viscose rayon factory to an estimated median TWA (8-hour) of 7.6 ppm. The Egeland *et al.* (1992) study indicated that modest CS_2 exposure (range 3.4 to 5.1 ppm, median 4.1 ppm) was associated with increased low density lipoprotein cholesterol (LDLc), the type of increase associated with atherosclerotic heart disease. No significant differences were seen

between controls and the low CS_2 exposed group (range 0.04 to 1.02 ppm, median 1.00 ppm). This study indicates a chronic NOAEL of 1.00 ppm and a LOAEL of 4.1 ppm for increased LDLc and diastolic blood pressure. Vanhoorne *et al.* (1992) identified increased LDL-cholesterol, apolipoprotein B, systolic and diastolic blood pressure indicative of a increased coronary risk in workers from a Belgium viscose rayon factory (115 exposed and 76 controls). CS_2 concentrations ranged from 1 to 36 ppm. Duration of exposure was not indicated. Even though these biochemical changes were observed, no significant increases in mild cardiovascular disease, such as angina, myocardial infarction, or ischemia, were determined by ECG changes.

CS_2 causes reproductive toxicity in both males and females. Lancranjan *et al.* (1969), Lancranjan (1972), Cirla *et al.* (1978), and Wagar *et al.* (1983) studied male reproductive effects of occupational exposure to CS_2 and showed significant adverse effects on spermatogenesis, levels of serum FSH and LH, and libido; these effects persisted in 66% of the workers subject to follow-up. Zhou *et al.* (1988) investigated pregnancy outcomes and menstrual disturbances in 265 women occupationally exposed to CS_2 and 291 controls. The CS_2-exposed women had significantly higher incidence of menstrual disturbances versus the control group (overall 34.9% vs. 18.2%). CS_2 levels varied between the five facilities (exposure category means of low = 3.1 mg/m^3, intermediate = 6.5 mg/m^3, and high = 14.8 mg/m^3), but all workers from these CS_2 facilities had significantly higher incidences of menstrual disturbance. Irregularity of menstruation was the most common disturbance, followed by abnormal bleeding. No evidence was observed to indicate an adverse effect on the term and outcome of pregnancy.

Price and colleagues (1996) conducted a statistical analysis of the National Institute for Occupational Safety and Health (NIOSH) carbon disulfide (CS_2) exposure database. They analyzed the effects of CS_2 on the peripheral nervous system and on ischemic heart disease risk factors. Changes in the responses associated with increases in work place CS_2 exposure were relatively small after adjustment for confounding. Only peroneal nerve motor conduction velocity and peroneal nerve amplitude ratio had statistically significant relationships with CS_2. In order to investigate the association between CS_2 exposure and ischemic heart disease (IHD) mortality, Price *et al*. (1997) reviewed historical CS_2 exposure data in the viscose rayon industry to identify trends and to use the data to suggest a standard mortality ratio (SMR)-exposure relationship and a threshold level for occupational exposure. Exposure data were extracted from published studies and used with the SMR versus exposure score relationship developed previously by Sweetnam and associates to relate SMRs directly to exposure. Upper and lower bound exposure profiles were derived and used to identify exposure thresholds. For an IHD SMR equal to 100, the upper and lower bound exposures were 60 and 20 ppm, respectively. The analysis indicated that the risk of IHD mortality and its relationship to CS_2 exposure is meaningful only for workers exposed to high level (20-60 ppm and above) for many years. These high levels, which existed in the past, are no longer found in the workplace. The results of their analysis suggested to them a safe workplace exposure level for CS_2 between 15 and 20 ppm.

The possibility of determining LOAEL and/or NOAEL values for the major CS_2-related adverse effects from epidemiology studies, which predominately use workers from the viscose rayon industry, is limited. The limitations include incomplete historical exposure measurements, concurrent exposure to other chemicals (including hydrogen sulfide or methylene chloride), lack

of personal exposure determinations, and a high variability of individual exposures due to decreases of plant CS_2 concentrations over time.

V. Effects of Animal Exposure

Studies investigating the potential for CS_2 toxicity in animals have usually been limited by intermediate or subchronic duration (less than 1 year) and a lack of multiple dose or exposure groups. The neuropathologic changes consistently observed in rodents following CS_2 exposure include axonal swelling, demyelination, swelling at neuromuscular junctions, muscle atrophy and degeneration, damage to terminal axons, and nerve fiber breakdown (Clerici and Fechter, 1991; Colombi *et al.* 1981; Eskin *et al.*, 1988; Jirmanova and Lukas, 1984; Maroni *et al.*, 1979; Szendzikowski *et al.*, 1973). These adverse effects have been observed over a range of exposures (250 to 800 ppm), but few studies have attempted to establish a dose response for this CS_2-induced neurotoxicity.

In a 90 day subchronic inhalation study, Sprague-Dawley and Fischer 344 rats exposed discontinuously (6 hours/day, 5 days/week) to CS_2 developed morphological alterations in nerves including axonal swelling and myelin degradation (Gottfried *et al.*, 1985). This study established a subchronic NOAEL of 50 ppm and a LOAEL of 300 ppm for morphological changes in nerves. A longer inhalation study in Wistar rats observed impairment in the conduction velocity of the sciatic and tibial nerves after 6 and 12 months of intermittent exposure to 289 ppm CS_2 (LOAEL of 289 ppm) (Knobloch *et al.*, 1979).

Wronska-Nofer (1973) showed a positive relationship between the level of triglycerides, the rate of cholesterol synthesis, and CS_2 exposure in Wistar rats exposed to 0, 73.8, 160, 321 or 546 ppm CS_2 for 5 hours/day, 6 days/week over 8 months. This study found a subchronic LOAEL of 73.8 ppm for disturbances in lipid metabolism (increase in serum cholesterol and serum triglycerides). Hepatic toxicity has also been induced in rats exposed to relatively high doses of CS_2, usually following pretreatment with liver inducers such as phenobarbital. Bond *et al.* (1969) showed that high doses of CS_2 to rats produced an increase in periportal liver fat, and decreases in hepatic cytochrome P450 content and in microsomal mixed function oxidase (MFO) activity. After phenobarbital induction, exposed rats exhibited more severe hepatoxicity characterized by hydropic degeneration and necrosis. Other hepatotoxic effects seen after CS_2 exposures greater than 400 ppm include increases in relative liver weight (Sokal, 1973), stimulation of liver microsomal lipid peroxidation (Wronska-Nofer *et al.*, 1986), and decreases in hepatic cholesterol synthesis (Simmons *et al.*, 1988).

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Johnson *et al.* (1983); U.S. EPA (1995)
Study population	145 occupationally exposed workers and 212 nonexposed workers
Exposure method	Discontinuous occupational inhalation exposures (mean of 7.3 ppm and range of 0.6 to 16 ppm)

Critical effects	Reduction in motor nerve conduction velocities (decreased peroneal nerve MCV and sural nerve SVC)
LOAEL	7.3 ppm
NOAEL	Not observed
Average occupational exposure	2.6 ppm for LOAEL group (7.3 x 10/20 x 5/7)
Benchmark concentration (BMC_{10})	17.7 ppm (continuity-weighted exposure of 6.3 ppm)
Exposure continuity	8 hr/day, 5 days/week
Human equivalent concentration	6.3 ppm for BMC
Exposure duration	Mean of 12.1 years (SD 6.9 years)
Subchronic factor	3
LOAEL factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Modifying factor	3 (database deficiencies)
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.7 mg/m^3; 700 µg/m^3)

The major strengths of the REL are the use of human data, the observation of a dose-response effect, and the duration of exposures. The major uncertainties are the poor quantitation of actual exposure magnitude over time and the limited nature of health effects studies conducted.

VII. References

Aaserud O, Gjerstad L, Nakstad P, Nyberg-Hansen R, Hommeren OJ, Tvelt B, Russell D, and Rootwelt K. 1988. Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulfide. Toxicology 49(2-3):277-282.

Aaserud O, Hommeren OJ, Tvedt B, Nakstad P, Mowe G, Efskind J, Russell D, Jorgensen EB, Nyberg-Hansen R, and Rootwelt K. 1990. Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers. Am. J. Ind. Med. 18(1):25-37.

Aaserud O, Russell D, Nyberg-Hansen R, Rootwelt K, Jorgensen EB, Nakstad P, Hommeren OJ, Tvedt B, and Gjerstad L. 1992. Regional cerebral blood flow after long-term exposure to carbon disulfide. Acta Neurol. Scand. 85(4):266-271.

Bond EJ, Butler WH, De Matteis F, and Barnes JM. 1969. Effects of carbon disulphide on the liver of rats. Br. J. Ind. Med. 26(4):335-337.

Cirla AM, Bertazzi PA, Tomasini M, Villa A, Graziano C, Invernizzi R, Gilioli R. 1978. Study of endocrinological functions and sexual behaviour in carbon disulphide workers. Med. Lav. 69(2):118-129.

Clerici WJ, and Fechter LD. 1991. Effects of chronic carbon disulfide inhalation on sensory and motor function in the rat. Neurotoxicol. Teratol. 13(3):249-255.

Colombi A, Maroni M, Picchi O, Rota E, Castano P, and Foa V. 1981. Carbon disulfide neuropathy in rats. A morphological and ultrastructural study of degeneration and regeneration. Clin. Toxicol. 18(12):1463-1474.

Egeland GM, Burkhart GA, Schnorr TM, Hornung RW, Fajen JM, and Lee ST. 1992. Effects of exposure to carbon disulphide on low density lipoprotein cholesterol concentration and diastolic blood pressure. Br. J. Ind. Med. 49(4):287-293.

Eskin TA, Merigan WH, and Wood RW. 1988. Carbon disulfide effects on the visual system. II. Retinogeniculate degeneration. Invest. Ophthalmol. Vis. Sci. 29(4):519-527.

Fajen J, Albright B, and Leffingwell SS. 1981. A cross-sectional medical and industrial hygiene survey of workers exposed to carbon disulfide. Scand. J. Work Environ. Health. 7(Suppl 4):20-27.

Foa V, Cassitto MG, and Forzi M. 1976. Mental performance and personality disorders among workers exposed to carbondisulphide: Comparison between two different rayon plants. In: Adverse Effects of Environmental Chemicals and Psychotrophic Drugs, Neurophysiological and Behavioural Tests. Vol. 2. pp. 173-182.

Gottfried MR, Graham DG, Morgan M, Casey HW, and Bus JS. 1985. The morphology of carbon disulfide neurotoxicity. Neurotoxicology. 6(4):89-96.

Hanninen H, Nurminen M, and Tolonen M. 1978. Psychological tests as indicators of excessive exposure to carbon disulfide. Scand. J. Psychol. 19:163-174.

Hernberg S, Partanen T, Nordman CH, and Sumari P. 1970. Coronary heart disease among workers exposed to carbon disulphide. Br. J. Ind. Med. 27:313-325.

Hirata M, Ogawa Y, Okayama A, and Goto S. 1992. A cross-sectional study on the brainstem auditory evoked potential among workers exposed to carbon disulfide. Int. Arch. Occup. Environ. Health 64(5)321-324.

HSDB. 1995. Hazardous Substances Data Bank. (Edition of January 1995). National Library of Medicine, Bethesda, MD (TOMES® CD-Rom Version). Denver, CO: Micromedex, Inc.

Jirmanova I, and Lukas E. 1984. Ultrastructure of carbon disulphide neuropathy. Acta Neuropathologica 63(3):255-263.

Johnson BL, Boyd J, Burg JR, Lee ST, Xintaras C, and Albright BE. 1983. Effects on the peripheral nervous system of workers' exposure to carbon disulfide. Neurotoxicology 4(1)53-65.

Knobloch K, Stetkiewicz J, and Wronska-Nofer T. 1979. Conduction velocity in the peripheral nerves of rats with chronic carbon disulphide neuropathy. Br. J. Ind. Med. 36(2):148-152.

Lancranjan I, Popescu HI, Klepsch I. 1969. Changes of the gonadic function in chronic carbon disulphide poisoning. Med. Lav. 60(10):566-571.

Lancranjan I. 1972. Alterations of spermatic liquid in patients chronically poisoned by carbon disulphide. Med. Lav. 63(1):29-33.

MacMahon B, and Monson RR. 1988. Mortality in the US rayon industry. J. Occup. Med. 30(9):698-705.

Maroni M, Colombi A, Rota E, Antonini C, Picchi O, Foa V, Caimi L, Tettamanti G, and Castano P. 1979. Biochemical and morphological investigations on nervous tissue of rats inhaling carbon disulphide. Med. Lav. 70(6):443-451.

Price B, Berner T, Henrich RT, Stewart JM, and Moran EJ. 1996. A Benchmark Concentration for carbon disulfide: Analysis of the NIOSH carbon disulfide exposure database. Regul. Toxicol. Pharmacol. 24:171-176.

Price B, Bergman TS, Rodriguez M, Henrich RT, and Moran EJ. 1997. A review of carbon disulfide exposure data and the association between carbon disulfide exposure and ischemic heart disease mortality. Regul. Toxicol. Pharmacol. 26:119-128.

Ruijten MW, Salle JH, Verberk MM, and Muijser H. 1990. Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. Br. J. Ind. Med. 47(9):589-595.

Ruijten MW, Salle HJ, and Verberk MM. 1993. Verification of effects on the nervous system of low level occupational exposure to CS_2. B. J. Ind. Med. 50(4):301-307.

Simmons JE, Sloane RA, and Van Stee EW. 1988. Hepatic cholesterol metabolism as a function of carbon disulfide concentration and treatment with phenobarbital. Am. Ind. Hyg. Assoc. J. 49(9):427-433.

Sokal JA. 1973. Effect of chronic exposure to carbon disulphide upon some components of the electron transport system in rat liver microsomes. Biochem. Pharmacol. 22(1):129-132.

Szendzikowski S, Karasek M, Stetkiewicz J, and Wronska-Nofer T. 1973. Ultrastructure of the peripheral nerve in rats chronically exposed to carbon disulphide, preliminary report. Folia Histochemica et Cytochemica 11(3):353-354.

Tiller JR, Schilling RS, and Morris JM. 1968. Occupational toxic factors in mortality from coronary heart disease. Br. Med. J. 4:407-411.

Tolonen M, Nurminen M, and Hernberg S. 1979. Ten-year coronary mortality of workers exposed to carbon disulfide. Scand. J. Work Environ. Health 5(2):109-114.

USDHHS. 1994. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Carbon Disulfide. Draft.

U.S. Environmental Protection Agency. 1995. Integrated Risk Information System (IRIS) Database.

Vanhoorne M, De Bacquer D, and De Backer G. 1992. Epidemiological study of the cardiovascular effects of carbon disulphide. Int. J. Epidemiol. 21(4):745-752.

Wagar G, Tolonen M, Tanner P, and Helpio E. 1983. Serum gonadotropins and testosterone in men occupationally exposed to carbon disulfide. J. Toxicol. Environ. Health 11(4-6):691-701.

Wronska-Nofer T. 1973. Disturbances of lipids metabolism in rats in dependence upon carbon disulphide concentrations in the air. Med. Lav. 64(1):8-12.

Wronska-Nofer T, Klimczak J, Wisniewska-Knypl JM, Jajte J, and Opalska B. 1986. Combined effect of ethanol and carbon disulphide on cytochrome P-450 mono-oxygenase, lipid peroxidation and ultrastructure of the liver in chronically exposed rats. J. Appl. Toxicol. 6(4):297-302.

Zhou SY, Liang YX, Chen ZQ, and Wang YL. 1988. Effects of occupational exposure to low-level carbon disulfide (CS2) on menstruation and pregnancy. Ind. Health 26(4):203-214.

CHRONIC 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. Chronic Toxicity Summary

Inhalation reference exposure level	**40 µg/m^3**
Critical effect(s)	Increased liver weight and hepatic fatty infiltration in guinea pigs
Hazard index target(s)	Alimentary system; development (teratogenicity); nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless liquid
Molecular formula	CCl_4
Molecular weight	153.8
Density	1.59 g/cm^3 @ 20°C
Boiling point	76.7° C
Vapor pressure	91.3 mm Hg @ 20°C
Vapor density	5.3 at the boiling point (air = 1.0)
Solubility	Soluble in acetone, ethanol, benzene, carbon disulfide, slightly soluble in water
Conversion factor	1 ppm = 6.3 mg/m^3 @ 25°C

III. Major Uses or Sources

Carbon tetrachloride was formerly used for metal degreasing and as a dry-cleaning fluid, fabric-spotting fluid, fire-extinguisher fluid, grain fumigant and reaction medium (DeShon, 1979). Carbon tetrachloride is used as a solvent for the recovery of tin in tin-plating waste and in the manufacture of semiconductors. It is 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 some pesticides (HSDB, 1995).

IV. Effects of Human Exposure

Kazantzis *et al.* (1960) evaluated 17 employees of a quartz processing factory who were occupationally exposed to 45-100 ppm (284-630 mg/m^3) carbon tetrachloride (CCl_4) vapor. Fifteen of the 17 workers complained of symptoms including nausea, anorexia, vomiting, flatulence, epigastric discomfort or distention, depressive symptoms, headache or giddiness for up to 4 months prior to the evaluation. A week after CCl_4 concentrations were reduced to 0-9 ppm with control measures, workers were symptom-free.

V. Effects of Animal Exposure

Adams *et al.* (1952) chronically exposed albino Wistar rats, guinea pigs, albino rabbits and rhesus monkeys to 0, 5, 10, 25, 50, 100, 200 and 400 ppm CCl_4 for varying duration. For each exposure group, two control groups were devised (unexposed and air-exposed controls) consisting of animals similar in age, sex, weight and number. The 2 control groups responded similarly to the experimental protocol.

In the 100, 200 and 400 ppm exposure groups, mortality was excessive with moderate to severe liver cirrhosis and other various pathological changes in all the species tested. Fifteen male and 15 female rats were exposed to 50 ppm CCl_4 134 times for 187 days. They experienced decreased body weight gain and liver weight increase as well as moderate fatty degeneration and slight to moderate liver cirrhosis. Females showed kidney weight increase and four rats showed slight to moderate swelling of the kidney tubular epithelium. Guinea pigs (8 males and 8 females; 143 exposures in 200 days) showed depressed growth in the first two weeks, enlarged livers, moderate fatty degeneration and liver cirrhosis, and increased levels of liver total lipids, neutral fat, esterified cholesterol and plasma prothrombin clotting time.

The rabbit group of 2 males and 2 females, which underwent 155 exposures to 50 ppm in 216 days, showed slightly depressed growth and increased kidney weights, prolonged plasma prothrombin clotting time, and moderate fatty degeneration and cirrhosis of the liver.

No change was seen in the group of 2 male monkeys exposed 198 times to 50 ppm in 277 days. One monkey experienced depressed weight gain compared to the other monkey and the controls, but no other adverse effects were seen with respect to organ weights, tissue examination, total liver lipid, blood urea nitrogen, blood non-protein nitrogen, serum phosphatase, plasma prothrombin clotting time, phospholipid, neutral fat, and free esterified cholesterol.

At 25 ppm CCl_4, 15 male and 15 female rats were exposed 137 times for 191 days. Early growth depression in males was observed, although final body weights did not significantly differ from the controls. Significant liver weight increase and slight to moderate fatty degeneration occurred. Liver lipid content was nearly twice the level of the controls and esterified cholesterol was five times that of the controls. For this exposure, phospholipid and neutral fat were not measured. Five male guinea pigs were exposed 133 times over 185 days and 5 female guinea pigs were exposed 93 times over 126 days. Symptoms included growth depression, liver weight

increase, increased plasma prothrombin clotting time, slight to moderate fatty degeneration, twice the level of the control total liver lipid, and five times the control level of esterified cholesterol. After 178 exposures to 25 ppm over 248 days, rabbits (2 per sex) showed increased liver weights and slight to moderate liver cirrhosis and fatty degeneration.

Twenty male and 20 female rats were exposed 136 times over a period of 192 days to 10 ppm CCl_4. These rats exhibited increase in liver weight, slight to moderate fatty degeneration and total lipid, neutral fat and esterified cholesterol levels that were twice the control levels. Guinea pigs (8 male and 8 female), who were exposed 139 times over 197 days, experienced liver weight increase, slight to moderate fatty degeneration without cirrhosis, and increased levels of total lipid, neutral fat, and esterified cholesterol. In an additional group of 18 male rats exposed 13 times to 10 ppm, slight fatty degeneration was seen as early as 17 days. Two male and two female rabbits tolerated the same regimen as the guinea pigs and showed no symptoms as a result of the exposure. Sixteen additional guinea pigs developed hepatic changes after 12 exposures in 16 days.

Twenty-five male and 23 female rats, exposed 145 times over 205 days to 5 ppm CCl_4, had no adverse effects. Nine male and nine female guinea pigs exposed 143 times over 203 days showed a statistically significant increase in the liver weights (females only), but only slightly higher liver lipid content. No additional histopathological effects were seen at this level of exposure.

Prendergast *et al.* (1967) exposed 15 Long-Evans or Sprague-Dawley rats, 15 guinea pigs, 3 rabbits, 2 dogs and 3 monkeys 30 times to a concentration of 515 $\pm$39 mg/m^3 (81.7 ppm) carbon tetrachloride (CCl_4) 8 hours a day, 5 days a week, for 6 weeks. Additionally, two 90 day continuous exposure studies were conducted. One study exposed 15 rats, 15 guinea pigs, 2 rabbits, 2 dogs and 3 monkeys to 61$\pm$5.2 mg/m^3 CCl_4 and the other exposed 15 rats, 3 rabbits, 2 dogs and 3 monkeys continuously to 6.1$\pm$0.3 mg/m^3 CCl_4 in inhalation chambers. Control groups consisted of 304 rats, 314 guinea pigs, 34 dogs, 48 rabbits and 57 monkeys. All the animals' weights were recorded prior to the study, at monthly intervals throughout the study, and at the conclusion of the study.

During the 6 week study, one monkey died following the 7th exposure, and 3 guinea pigs died following the 20th, 22nd and 30th exposures, respectively. Monkeys, guinea pigs, dogs and rabbits all exhibited weight loss. A high percentage of mottled livers was seen in all species except dogs. Histopathologic examination of the lungs and livers showed morphological changes in all the animals exposed to CCl_4 (most prominently the guinea pigs). The guinea pigs were the most sensitive species displaying discolored lungs, fatty livers, bile duct proliferation, fibrosis, focal inflammatory cell infiltration, hepatic cell degeneration and regeneration, early portal cirrhosis, and alteration of lobular structure. Hepatic lipid content in the guinea pigs was 35.4$\pm$10.7% compared to the control value of 11.0$\pm$3.6%. Alterations of liver lipid content were also observed, to a lesser extent, in the other four species; the most severe alteration occurred in the rats, less severe alteration in rabbits and dogs, and the least severe in the monkeys.

During the 61 mg/m^3 (9.7 ppm) CCl_4 continuous exposure study, 3 guinea pigs died (one each after 47, 63 and 71 days). All the monkeys were emaciated and experienced hair loss.

Depressed body weight increases were seen in all exposed animals compared to the controls. Autopsies showed enlarged and/or discolored livers in a high percentage (not given) of monkeys, guinea pigs, rabbits and rats. Rats and guinea pigs showed hepatic fatty acid changes, and a moderate reduction in succinic dehydrogenase activity was also evident in guinea pigs. Varying but lesser degrees of these changes were also seen in the other species tested.

The low concentration of 6.1 mg/m^3 (1 ppm) CCl_4 was attained by diluting the CCl_4 to 10% of the above concentration with *n*-octane, resulting in a solution of 6.1 mg/m^3 CCl_4 in 61 mg/m^3 of *n*-octane. The level of *n*-octane used was shown to be negligible by an *n*-octane control which yielded no effects. (The current TLV is 1400 mg/m^3 (ACGIH, 1992).) No animals died during this study, and no signs of toxicity were noted. All exposed animals except the rats showed reduced weight gain when compared to the controls, and all species exhibited nonspecific inflammatory lung changes. Guinea pig liver lipid contents and serum urea nitrogen concentrations were similar to the control values. In several animals there were some nonspecific inflammatory changes in the liver, kidney and heart, but the authors did not attribute these to the chemical exposure. There was no other observed hematologic or histopathologic toxicity at this level.

Shimizu *et al.* (1973) exposed groups of 4 female Sprague-Dawley rats to 10, 50 and 100 ppm of CCl_4 vapor for 3 hours a day, 6 days a week for up to 6-8 weeks. The rats were terminated two days after the last inhalation. Accumulation of CCl_4 occurred in the adipose tissue and was measured after 1 and 3 weeks of exposure. For the 10 ppm group, accumulation was gradual, reaching a level of 1/3 the amount found in the 50 ppm group after 6 weeks. A slight increase of triglycerides in the liver (6.2-6.4 mg/g) was observed in the 10 ppm group, but no control group was used for comparison.

The intermittent exposure caused a more pronounced and higher number of change indices to occur (34 as opposed to the 17 change indices of the monotonous regimen), indicating a greater intensity of liver damage. Changes included a significant decrease in hippuric acid synthesis, presence of mitochondrial enzymes (glutamate dehydrogenase and ornithine carbonyl transferase) in the blood (indicating severe damage to hepatocytes), significant increase in cytoplasmic enzyme activity, and a decrease in the level of cytochrome P-450 in liver tissue. The effects seen in the monotonous group were the same variety as those in the intermittent group, but were less intense. The content of CCl_4 in the blood was similar for both the intermittent and monotonous exposure groups. Another test was performed over a period of 27 days varying the regimen, and therefore the concentration, of intermittent exposure while keeping the TWA level of CCl_4 stable. Increasing the concentration threefold or fivefold with five 10 minute peaks did not potentiate the toxic effects. Varying the regimen tenfold to five 5-minute peaks (peak exposure 402 mg/m^3 (63.8 ppm)) with a time weighted average exposure of 6.5 ppm (41$\pm$1 mg/m^3) did, however, result in more severe liver damage.

Sakata *et al.* (1987) exposed 10-15 male Sprague-Dawley rats to <10 ppm CCl_4 vapor for 15 minutes a day, twice a week for 8 weeks. All the rats had chronic liver damage involving nodular liver surfaces and extensive fibrosis. Researchers also found similar results in rats after 8 weeks of subcutaneous injections of 0.1 mL of 50% CCl_4 solution in olive oil twice a week.

Ideura *et al.* (1993) exposed male Wistar rats to CCl_4 vapor for 7 minutes, 3 times a week for 6-10 weeks (concentration unspecified). Six experimental groups of 4-5 rats were used, two of which were exposed for 10 weeks, another two for 6 weeks, and two unexposed control groups. Following the last exposures, rats were injected with varying amounts of endotoxin (1.0 mL lipopolysaccharide (LPS)). The rats were sacrificed 24 hours after the injection and processed for histological examination. Examination of the rats' left kidneys and livers revealed liver cirrhosis with destruction of normal structure and massive ascites retention after 10 weeks of exposure as compared to the controls. Those exposed for 6 weeks exhibited an increase in fibrous tissue. The control groups displayed normal liver structure. Researchers found that rats previously resistant to endotoxin became susceptible following CCl_4 exposure, which were manifested as induced acute renal tubular necrosis in cirrhotic rats.

Yoshimura *et al.* (1993) performed a similar experiment to that of Ideura *et al.* (1992) by exposing male Wistar rats for 6 (5 rats) and 10 weeks (5 rats) to 99% CCl_4 vapor for 3 minutes a day. A control group of 5 rats was given phenobarbitone for 10 weeks. After 24 hours following the final exposure, rats were injected with endotoxin. Six weeks of CCl_4 exposure caused liver fibrosis with bridging fibrosis, while 10 weeks of exposure to CCl_4 caused liver cirrhosis and destruction of the normal liver architecture.

Pregnant rats were exposed to 0, 300, or 1000 ppm (0, 1938, or 6460 mg/m^3) carbon tetrachloride for 7 hours/day on days 6-15 of gestation (Schwetz *et al*., 1974). Significant fetal growth retardation, measured by decreased crown-rump length and body weight, was observed in the offspring of the exposed groups (n = 22 litters) compared with controls (n = 43 litters). Subcutaneous edema was observed in the 300 ppm group but not in the 1000 ppm group. Sternebral anomalies were observed in the 1000 ppm group.

Table 1. Effects of Chronic CCl_4 Exposure (Adams *et al.*, 1952)

Species	**Concentration (ppm)**	**Group size**	**Endpoint**	**Exposure scenario** (days exposed/ experiment length)
rats (male)	50 ppm	15	liver damage: fatty degeneration and cirrhosis; growth depression	134/187
rats (female)	50 ppm	15	same effects as males with the addition of increased kidney weight	134/187
guinea pigs	50 ppm	16	liver damage: fatty degeneration and cirrhosis; growth depression	143/200
rabbits	50 ppm	4	enlarged kidney; liver damage: fatty degeneration and cirrhosis; growth depression	155/216
monkeys	50 ppm	2	one experienced growth depression	198/277
rats	25 ppm	30	liver damage; early growth depression	137/191
guinea pigs (male)	25 ppm	5	liver damage: fatty degeneration; growth depression	133/185
guinea pigs (female)	25 ppm	5	liver damage: fatty degeneration; growth depression	93/126
rabbits	25 ppm	4	liver damage: fatty degeneration; and cirrhosis	178/248
rats	10 ppm	40	liver damage: fatty degeneration	136/192
guinea pigs	10 ppm	16	liver damage: fatty degeneration	139/197
rats	5 ppm	48	no adverse effects	145/205
guinea pigs (male)	5 ppm	9	no adverse effects	143/203
guinea pigs (female)	5 ppm	9	liver damage	143/203

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Adams *et al.* (1952)
Study population	9 male and 9 female guinea pigs
Exposure method	Discontinuous whole-body inhalation
Critical effects	Increase in liver weight and liver lipid content in females
LOAEL	5 ppm
NOAEL	Not observed
Exposure continuity	7 hours/day, 5 days/week
Average experimental exposure	1.0 ppm
Human equivalent concentration	1.7 ppm (gas with systemic effects, based on RGDR = 1.7 for lambda (a) : lambda (h) (Gargas *et al.* 1989))
Exposure duration	143 exposures over 203 days (7.3 months)
LOAEL uncertainty factor	10
Subchronic factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm; 6 ppb (40 $\mu g/m^3$; 0.04 mg/m^3)

Of the 2 adequate chronic inhalation studies available on CCl_4, the Adams *et al.* (1952) study was chosen over the Prendergast *et al.* (1967) study as the key reference for the carbon tetrachloride chronic REL. The Adams *et al.* (1952) experiment was conducted over a longer duration. In comparison, the Prendergast study was only conducted for a subchronic period of 6 weeks. In addition, the Adams study contained more specific endpoints of liver damage that were consistent with the mechanism of carbon tetrachloride toxicity. Both studies resulted in hepatic effects with exposed rats appearing less sensitive than the affected monkeys or guinea pigs.

The major strength of the REL is the use of a chronic exposure study. The major uncertainties are the lack of human data, the lack of a NOAEL observation, the small sample sizes used, and the lack of comprehensive multiple dose studies. For comparison, conversion of the oral U.S. EPA RfC value of 0.7 μg/kg/day to an equivalent inhalation value results in a concentration of 2.5 $\mu g/m^3$.

VII. References

Adams E, Spencer H, Rowe V, McCollister D, and Irish D. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Indust. Hyg. Occup. Med. 6(1):50-66.

ACGIH. 1992. American Conference of Governmental and Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Vol. I.

DeShon ND. 1979. Carbon Tetrachloride. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. Grayson M, and Eckroth D, eds. New York: John Wiley and Sons, Inc. 5:704-714. [as cited by Santodonato J. 1985. Monograph on human exposure to chemicals in the workplace: Carbon tetrachloride; PB86-143377; SRC-TR-84-1123.]

Gargas ML, Burgess RJ, Voisard DE, Cason GH, and Andersen ME. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (CD-ROM version). Denver, CO: Micromedex, Inc. (edition expires 7/31/95).

Ideura T, Yoshimura A, Shirai M, Taira T, and Koshikawa S. 1993. Endotoxin induced acute tubular necrosis in cirrhotic rats. Scand. J. Urol. Nephrol. 27:433-439.

Kazantzis G, Bomford RR, and Oxon DM. 1960. Dyspepsia due to inhalation of carbon tetrachloride vapour. Lancet 360-362.

Prendergrast J, Jones R, Jenkins L, and Siegel J. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl Pharmacol 10:270-289.

Sakata T, Watanabe N, Hobara N, and Nagashima H. 1987. Chronic liver injury in rats by carbon tetrachloride inhalation. Bull. Environ. Contam. Toxicol. 38:959-961.

Santodonato J. 1985. Monograph on human exposure to chemicals in the workplace: Carbon tetrachloride; PB86-143377; SRC-TR-84-1123. NTIS.

Schwetz BA, Leong BK, and Gehring PJ. 1974. Embryo - and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28:452-464.

Shimizu Y, Nagase C, and Kawai K. 1973. Accumulation and toxicity of carbon tetrachloride after repeated inhalation in rats. Ind. Health 11:48-54.

Yoshimura A, Ideura T, Shirai M, Tiara T, Iwasaki S, Kitaoka T, and Koshikawa S. 1993. The distribution of ^{3}H-labeled endotoxin in the kidney of liver cirrhotic rats. Scand. J. Urol. Nephrol. 27:295-299.

CHRONIC TOXICITY SUMMARY

CHLORINE DIOXIDE

(anthium dioxcide; alcide; chlorine oxide; chlorine peroxide; chloryl radical; doxcide 50)

CAS Registry Number: 10049-04-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 μg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Vascular congestion and peribronchiolar edema; hemorrhagic alveoli and congested capillaries in the lung in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Yellow to red liquid or gas
Molecular formula	ClO_2
Molecular weight	67.64
Density	1.642 g/cm^3 @ 0°C (liquid)
Boiling point	11° C
Vapor pressure	Unknown
Solubility	Soluble in water, alkaline and sulfuric acid solutions
Conversion factor	1 ppm = 2.76 mg/m^3

III. Major Uses or Sources

Chlorine dioxide is used as a bleaching agent for cellulose, textiles, flour, leather, oils, and beeswax. It is also used in the purification of water and as a bactericide and antiseptic (HSDB, 1994).

IV. Effects of Human Exposures

Case reports of human occupational exposure to chlorine dioxide have shown that 19 ppm was fatal to one worker and 5 ppm was definitely irritating (Elkins, 1959). Seven out of 12 workers exposed regularly to chlorine dioxide at levels generally below 0.1 ppm (0.28 mg/m^3) reported symptoms of ocular and respiratory irritation leading to slight bronchitis (Gloemme and Lundgren, 1957). Concurrent exposure to chlorine and chlorine dioxide in pulp mill workers

resulted in an increase in the reporting of subjective symptoms of irritation (Ferris *et al.*, 1967). In this study, the chlorine dioxide concentrations ranged from trace levels to 0.25 ppm (0.69 mg/m^3). No differences were found between these workers and controls for pulmonary function tests.

V. Effects of Animal Exposures

Eight rats (sex unspecified) were exposed for 5 hours/day, 5 days/week, for 2 months to 0 or 1 ppm (2.8 mg/m^3) chlorine dioxide (Paulet and Debrousses, 1972). The number of control animals was not specified. Microscopic evaluation of the lungs revealed vascular congestion and peribronchiolar edema in all animals exposed to chlorine dioxide. The LOAEL for respiratory effects was therefore 1 ppm (2.8 mg/m^3). An earlier study by these researchers (Paulet and Debrousses, 1970) examined the effects of exposure to 2.5, 5, or 10 ppm chlorine dioxide for several hours/day for 30 days in rats and rabbits (n = 4-10 animals per group). Body weights, blood cell counts, and histopathological examination of the liver, lungs, and other tissues were measured in each group. At 10 ppm, nasal discharge, localized bronchopneumonia, and desquamated alveolar epithelium were observed. White and red blood cell counts were also increased with this exposure. Rats and rabbits exposed to 2.5 ppm for 7 hours/day for 30 days or for 4 hours/day for 45 days, respectively, showed significant respiratory effects, including hemorrhagic alveoli and inflammatory infiltration of the alveolar spaces.

Rats exposed to 5, 10, or 15 ppm (13.8, 27.6, or 41.4 mg/m^3) chlorine dioxide for 15 minutes, 2 or 4 times/day, for 1 month showed an increase in congested lungs, nasal discharge, and catarrhous lesions of the alveoli beginning at 10 ppm (Paulet and Debrousses, 1974). No significant changes in these parameters were seen at 5 ppm.

Dalhamn (1957) found that acute exposure to 260 ppm chlorine dioxide for 2 hours resulted in the death of 1 out of 4 rats. Five out of 5 rats died during exposures of 4 hours/day for 14 days. All exposed animals exhibited signs of respiratory distress and ocular discharge. No effects were seen in 5 rats exposed to 0.1 ppm for 5 hours/day, 7 days/week, for 10 weeks.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Paulet and Debrousses (1970, 1972); U.S. EPA (1995)
Study population	Wistar rats (8 per exposure concentration)
Exposure method	Discontinuous whole-body inhalation (0 or 1 ppm)
Critical effects	Vascular congestion; peribronchial edema; lung alveolar damage
LOAEL	1 ppm
NOAEL	Not observed
Exposure continuity	5 hours/day, 5 days/week
Exposure duration	2 months
Average experimental exposure	0.15 ppm for LOAEL group (1 x 5/24 x 5/7)
Human equivalent concentration	0.23 ppm for LOAEL group (gas with thoracic respiratory effects, RGDR = 1.57 based on MV = 0.17 m^3, SA(Th) = 3,460 cm^2)
LOAEL uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Subchronic factor	10
Modifying factor	3 (database deficiencies)
Cumulative uncertainty factor	3,000
Inhalation reference exposure level	0.00008 ppm (0.08 ppb, 0.0002 mg/m^3, 0.2 $\mu g/m^3$)

There were uncertainties in all areas of concern. Thus the best available study still was limited by lack of multiple exposure concentrations, the relatively short duration of exposures, the small number of animals examined, and the lack of adequate human health effects information. Other limitations were the lack of dose-response information and the lack of comprehensive multi-organ effects data.

VII. References

Dalhamn T. 1957. Chlorine dioxide: Toxicity in experimental animals and industrial risks. AMA Arch. Ind. Hyg. 15:101-107.

Elkins HB. 1959. The Chemistry of Industrial Toxicology, 2nd ed. New York: Wiley and Sons, Inc. pp.89-90.

Ferris BG Jr, Burgess WA, and Worcester J. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br. J. Ind. Med. 24(1):26-37.

Gloemme J, and Lundgren KD. 1957. Health hazards from chlorine dioxide. Arch. Ind. Health. 16: 169-176.

HSDB. 1994. Hazardous Substances Data Bank. TOMES®. Vol. 20. Denver, CO: Micromedex, Inc.

Paulet G, and Debrousses S. 1970. On the action of ClO_2 at low concentrations on laboratory animals. Arch. Mal. Prof. Med. Trav. Secur. Soc. 35(9):97-106.

Paulet G, and Debrousses S. 1972. On the toxicology of chlorine dioxide. Arch. Mal. Prof. Med. Trav. Secur. Soc. 33(1-2):59-61.

Paulet G, and Debrousses S. 1974. Action of a discontinuous exposure to chlorine dioxide on the rat. Arch. Mal. Prof. Med. Trav. Secur. Soc. 35(9):797-803.

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

CHRONIC TOXICITY SUMMARY

CHLOROBENZENE

(monochlorobenzene; benzene chloride; benzene monochloride; chlorbenzene; chlorbenzol; phenyl chloride)

CAS Registry Number: 108-90-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1000 μg/m^3**
Critical effect(s)	Increased liver weights, hepatocellular hypertrophy, renal degeneration and inflammation, and testicular degeneration in rats
Hazard index target(s)	Alimentary system; kidney; reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Description	Colorless, neutral liquid
Molecular formula	C_6H_5Cl
Molecular weight	112.56
Boiling point	132°C
Vapor pressure	11.8 mm Hg at 25°C
Solubility	Practically insoluble in water (0.049 g/100 ml); soluble in alcohol, benzene, chloroform, diethyl ether
Conversion factor	1 ppm = 4.60 mg/m^3 at 25 ^{o}C

III. Major Uses and Sources

As one of the most widely used chlorinated benzenes, mono-chlorobenzene has been a major chemical for at least 50 years. It was historically important in the manufacture of chlorinated pesticides, especially DDT, and in the production of phenol and aniline. Monochlorobenzene's principal current use is as a chemical intermediate in the production of chemicals such as nitrochlorobenzenes and diphenyl oxide. These chemicals are subsequently used in the production of herbicides, dyestuffs and rubber chemicals. Additionally, monochlorobenzene is used as a solvent in degreasing processes (e.g., in metal cleaning operations), paints, adhesives, waxes and polishes (HSDB, 1995; NIOSH, 1993).

IV. Effects of Human Exposure

Even though monochlorobenzene has been used industrially for many years, few epidemiologic and/or occupational studies have addressed the potential health status of workers chronically exposed to monochlorobenzene (NIOSH, 1993). A Russian occupational study (Rozenbaum *et al.*, 1947, as reported by the U.S. EPA, 1988) describes multiple central nervous system effects, including headache, numbness, dizziness, cyanosis, hyperesthesia, and muscle spasms, after intermittent exposure over 2 years to monochlorobenzene in a mixed chemical environment. No specific exposure levels or histopathologic data were reported.

Two small studies utilizing volunteers exposed to single doses of monochlorobenzene have reported central nervous system effects (Ogata *et al.*, 1991; Tarkhova, 1965). An exposure chamber study of five volunteers exposed up to 60 ppm monochlorobenzene (276 mg/m^3) for a single 7 hour exposure described acute subjective symptoms such as drowsiness, headache, eye irritation, and sore throat (Ogata *et al.*, 1991). One other human volunteer study described altered electrical activity of the cerebral cortex in four individuals exposed to 43.4 ppm monochlorobenzene vapors for 2.5 minutes (Tarkhova, 1965).

V. Effects of Animal Exposure

No chronic inhalation studies have evaluated the toxicity of monochlorobenzene. Only a single, oral chronic carcinogenicity study (NTP, 1985) has evaluated the long-term adverse affects of monochlorobenzene administration. However, a few subchronic inhalation studies have demonstrated adverse effects on the liver, the kidney, and, to a lesser extent, blood parameters following monochlorobenzene exposure over a period of weeks or months (Dilley, 1977; John *et al.*, 1984; Nair *et al.*, 1987).

One subchronic study evaluated Sprague-Dawley male rats and rabbits exposed to 0, 75, or 200 ppm of monochlorobenzene for 7 hr/day, 5 days/week, for up to 24 weeks (Dilley, 1977). In rats, monochlorobenzene-related toxicity included increased absolute and relative (to brain- or body-weight) organ weights (especially the liver) after 11 and 24 weeks of exposure (LOAEL 75 ppm). Male rabbits also demonstrated increases in liver weight after 24 weeks of exposure (LOAEL 75 ppm). Some hematological changes were reported in rats including differences in platelet and reticulocyte counts between control and exposed animals; however, some changes observed at 11 weeks were variable and comparable to controls at 24 weeks (red blood cell count, hemoglobin, hematocrit, and white blood cell count). Pathological changes were observed in rats, with occasional focal lesions in the adrenal cortex, tubular lesions in the kidneys, and congestion in the liver and kidneys.

Two other subchronic inhalation studies reported adverse organ effects following monochlorobenzene exposure in rats and rabbits (John *et al.*, 1984; Nair *et al.*, 1987). In the first study, John *et al.* (1984) reported increased liver weights in rats and rabbits following short-term (10 or 13 day, 6 hours/day) monochlorobenzene exposure (LOAEL = 590 ppm in rats and 210 ppm in rabbits). Nair *et al.* (1987) exposed male and female Sprague-Dawley rats to 0, 50, 150 or 450 ppm monochlorobenzene vapors daily for 6 hours over 10-11 weeks prior to mating, and

up to day 20 of gestation for 2 generations. Nair *et al*. found dose-related changes in the livers, kidneys, and testes in both generations of males (F_0 and F_1). Hepatotoxicity occurred as hepatocellular hypertrophy and increased liver weights (mean and absolute) at concentrations greater than 50 ppm (LOAEL = 150 ppm). At this concentration, renal changes included tubular dilation, interstitial nephritis, and foci of regenerative epithelium. Testicular degeneration of the germinal epithelium occurred in both generations of exposed males, but no chlorobenzene-induced adverse effects on reproductive performance or fertility were seen.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Nair *et al.* (1987)
Study population	Sprague-Dawley rats (30/sex/group)
Exposure method	Discontinuous inhalation exposures (0, 50, 150, and 450 ppm)
Critical Effects	Increases in absolute and relative liver weights (F_0 and F_1 both sexes), hepatocellular hypertrophy (F_0 and F_1 males), renal degeneration and inflammation (F_0 and F_1 both sexes), testicular degeneration (F_0 and F_1 males).
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hours/day, 7 days/week
Exposure duration	11 weeks
Average experimental exposure	13 ppm for NOAEL group (50 x 6/24)
Human equivalent concentration	26 ppm (gas with systemic effects, based on RGDR = 2.0 for lambda (a) : lambda (h)) (Gargas *et al*., 1989)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.3 ppm (300 ppb; 1.0 mg/m^3, 1000 µg/m^3)

Of the three inhalation studies available (Dilley, 1977; John *et al.*, 1984; Nair *et al.*, 1987), the Nair *et al.* (1987) two generational developmental study was selected for identifying a NOAEL and LOAEL. It best presented the histopathology of the adverse effects, and demonstrated a dose response relationship for these effects (statistically significant increases in mean liver weights, incidence of renal changes, and testicular degeneration).

Another subchronic inhalation study (Dilley, 1977) also observed increases in organ weights, including the liver, in rats after 11 and 24 weeks exposure to 75 and 250 ppm monochlorobenzene (LOAEL = 75 ppm), and, in rabbits at 24 weeks. Similar adverse liver and kidney effects were found in subchronic oral bioassays (Kluwe *et al.*, 1985; NTP, 1985). These

include increases in liver weight and hepatocellular degeneration in rats (LOAEL = 125 mg/kg/day) and mice (LOAEL = 250 mg/kg/day), and renal necrosis and degeneration in rats (LOAEL = 500 mg/kg/day) and mice (LOAEL = 250 mg/kg/day) after 13 weeks oral exposure to chlorobenzene.

Uncertainty factors are appropriate due to the lack of chronic studies, both animal bioassay and human, and the limited number of subchronic inhalation studies, thereby requiring estimation of the chronic REL from this shorter term, single species study. The magnitude of interspecies variation remains unknown, as few species have been tested and human data for comparison are lacking. However, metabolic studies have demonstrated species variation in the urinary elimination of chlorobenzene metabolites (Ogata and Shimada 1983; Ogata *et al.*, 1991; Yoshida *et al.*, 1986). Humans metabolize and excrete chlorobenzene predominately as free and conjugated forms of 4-chlorocatechol and chlorophenols, while the main rodent urinary metabolite, p-chlorophenylmercapturic acid, is found in minor amounts (<0.5%). No information exists which identifies human subpopulations possibly susceptible to monochlorobenzene exposure.

The strengths of the inhalation REL include the observation of a NOAEL, the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis, and the demonstration of a dose-response relationship. Major areas of uncertainty are the lack of adequate human exposure data and limited reproductive toxicity data.

VII. References

Dilley JV. 1977. Final Report: Toxic evaluation of inhaled chlorobenzene (monochlorobenzene). Stanford Research Institute. Contract No. 210-76-0126. Prepared for: National Institute of Occupational Safety and Health, Division of Biomedical and Behavioral Sciences. Cincinnati, OH: NIOSH. NTIS No. PB-276623.

Gargas ML, Burgess RJ, Voisard DE, Cason GH, and Andersen ME. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

HSDB. 1995. Hazardous Substances Data Bank. TOMES® Denver, CO: Micromedex, Inc.

John JA, Hayes WC, Hanley TR, Johnson KA, Gushow TS, and Rao KS. 1984. Inhalation teratology study on monochlorobenzene in rats and rabbits. Toxicol. Appl. Pharmacol. 76:365-373.

Kluwe WM, Dill G, Persing R, and Peters A. 1985. Toxic responses to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. J. Toxicol. Environ. Health 15(6):745-767.

Nair RS, Barter JA, Schroeder RE, Knezevich A, and Stack CR. 1987. A two-generation reproduction study with monochlorobenzene vapor in rats. Fundam. Appl. Toxicol. 9:678-686.

NTP. 1985. National Toxicology Program. Toxicology and carcinogenesis studies of chlorobenzenes (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, NTP TR 261. NIH Pub. No. 86-2517, NTIS PB86-144714.

NIOSH. 1993. National Institute for Occupational Safety and Health. NIOH and NIOSH basis for an occupational health standard: Chlorobenzene. U.S. Department of Health and Human Services, Public Health Service, DHHS(NIOSH) Publication No. 93-102.

Ogata M, and Shimada Y. 1983. Differences in urinary monochlorobenzene metabolites between rats and humans. Int. Arch Occup. Environ. Health 53:51-57.

Ogata M, Taguchi T, Hirota N, Shimada Y, and Nakae S. 1991. Quantitation of urinary chlorobenzene metabolites by HPLC: Concentrations of 4-chlorocatechol and chlorophenols in urine and of chlorobenzene in biological specimens of subjects exposed to chlorobenzene. Int. Arch. Occup. Environ. Health 63:121-128.

Rozenbaum ND, Blekh RS, and Kremneva SN. 1947. [Use of chlorobenzene as a solvent from the standpoint of industrial hygiene.] Gig. I Sanit. 12:21-24. (Russian) [as cited in U.S. EPA, 1988.]

Tarkhova LP. 1965. Materials for determining the maximum permissible concentration of chlorobenzol in atmospheric air. Hygiene and Sanitation 30:327-333. (Jerusalem, Israel Program for Scientific Translation available for NTIS.)

U.S. EPA. 1988. United States Environmental Protection Agency. Health effects criteria document for chlorobenzene. Final draft. EPA 600/88-90/99. Washington DC: U.S. EPA. National Technical Information Service, PB89-192116.

Yoshida M, Sunaga M, and Hara I. 1986. Urinary metabolites levels in workers exposed to chlorobenzene. Ind Health 24:255-258.

CHRONIC TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 µg/m^3**
Critical effect(s)	Increased mortality, increased lung weight, nasal rhinitis in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (from HSDB (1996) except as noted)

Description	Colorless to faint yellow liquid
Molecular formula	CCl_3NO_2
Molecular weight	164.4
Boiling point	112°C
Vapor pressure	5.7 mm Hg @ 0°C; 24 mm Hg @ 25°C (Fries and West, 1921)
Solubility	1.6 g/L water @ 25°C; 2.272 g/L water @ 0°C 1.9 g/L water @ 20°C; miscible with benzene, ethanol, carbon disulfide, ether, carbon tetrachloride, acetone, methanol, acetic acid
Conversion factor	6.72 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Chloropicrin is primarily used as a fumigant against insects and fungi in grain elevators and storage bins (HSDB, 1996). It has also been used in the fumigation of non-deciduous fruit trees and produce. Chloropicrin is used as an indicator chemical in other fumigants such as methyl bromide because of its potent irritational properties. Chloropicrin kills weed and grass seeds when applied to soil. Chloropicrin was used in World War I as a chemical warfare agent because of its potent activity as a lachrymator. Chloropicrin has a minor use in the chemical synthesis of methyl violet. Chloropicrin can also form in drinking water as a result of chlorination processes (Duguet *et al.*, 1985; Merlet *et al.*, 1985).

IV. Effects of Human Exposure

No studies are available which describe toxic effects to humans from chronic exposure to chloropicrin. Human exposures to concentrations less than 1 ppm for very short periods of time are extremely irritating (ACGIH, 1992; Fries and West, 1921). The threshold of odor detection in humans is approximately 1 ppm (ACGIH, 1992).

V. Effects of Animal Exposure

Burleigh-Flayer and Benson (1995) conducted a chronic inhalation bioassay with CD rats (60 per sex per dose) exposed discontinuously to 0, 0.1, 0.5 or 1.0 ppm 99.6% pure chloropicrin vapor 6 hours/day for 5 days/week over 107 weeks. Increased mortality was noted in males at 0.5 and 1 ppm and in females at 1 ppm. Absolute and relative increased lung and liver weights and increased nasal rhinitis were reported in both sexes at the 1 ppm level. However, no effects were seen at 0.1 ppm. Thus this study yielded a NOAEL of 0.1 ppm for chronic non-cancer effects in rats. A similar study carried out in mice for 78 weeks (Burleigh-Flayer et al., 1995) resulted in the same NOAEL.

Male Swiss-Webster mice (group numbers ranging from 16-24) were exposed by inhalation to a single level of different sensory irritants including chloropicrin for 6 hours/day for 5 days, with unexposed control groups of 8-10 mice (Buckley *et al.*, 1984). The exposure level for chloropicrin was 7.9 ppm, which approximated the level sufficient to cause a 50% decrease in respiratory rate in mice (RD50) (Kane *et al.*, 1979). Half the exposed mice and half the control animals were terminated immediately after the exposures and the other half 72 hours after the last exposure. All were examined for respiratory tract lesions. Body weights of chloropicrin exposed animals were reduced 10-25% below controls, but increased to normal levels during the recovery period. Nasal exudate and distention of the abdomen were observed. "Moderate" lesions characterized by exfoliation, erosion, ulceration, or necrosis were observed in the respiratory and olfactory epithelium and minimal inflammation and squamous metaplasia were observed in the respiratory epithelium alone. Moderate to severe damage to the lower respiratory tract was described as "fibrosing peribronchitis and peribronchiolitis". Exfoliation, hyperplasia, and squamous metaplasia were also noted.

Condie *et al.* (1994) conducted a study of the toxicity of chloropicrin by oral exposure in Sprague-Dawley rats. Ten and ninety-day studies were conducted by dosing animals daily with chloropicrin in vehicle (corn oil) at a volume of 1 ml/kg. Groups of 10 rats/sex/group were dosed with 0, 10, 20, 40, and 80 mg/kg for the 10-day study and with 0, 2, 8, and 32 mg/kg for the 90-day study. Parameters examined included mortality, body weight, food and water consumption, hematology, serum clinical chemistry, and gross pathology and histology of organs. Only the high-dose group and the control group animals from the 90-day study were examined histopathologically. In the 90-day study, 6 males and 2 females in the 32 mg/kg dose group and 1 male and 3 females in the 8 mg/kg dose group died before the scheduled termination time. The authors noted signs of pulmonary complications (inflammation and congestion) in the dead animals. Previously, the animals had shown signs of respiratory distress, including wheezing and dyspnea. The deaths were considered to be exposure related and most likely due

to aspiration of chloropicrin. Among the survivors, mean body weight, hemoglobin levels, and hematocrit were significantly reduced in males in the 32 mg/kg dose group. Absolute thymus weights were reduced in female rats at 32 mg/kg, and female rats in the 8 mg/kg dose group showed decreased white blood cell count. Most animals in the 32 mg/kg dose group (>60%) showed histopathological changes in the forestomach including chronic inflammation, acantholysis, and hyperkeratosis.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer and Benson (1995)
Study population	CD rats (60 per sex per dose)
Exposure method	Discontinuous inhalation (0, 0.1, 0.5 or 1.0 ppm)
Critical effects	Increased mortality, increased lung weight, nasal rhinitis
LOAEL	0.5 ppm
NOAEL	0.1 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	107 weeks
Average experimental exposure	0.018 ppm for NOAEL group (0.1 x 6/24 x 5/7)
Human equivalent concentration	0.004 ppm for NOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.25 based on MV = 0.33 m^3/day and SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.0002 ppm (0.2 ppb; 1 $\mu g/m^3$; 0.001 mg/m^3)

Significant strengths in the REL include the duration of exposure (lifetime) in the key study, the multiple dose study design with adequate sample sizes, and the demonstration of a NOAEL.

Major areas of uncertainty are the lack of adequate human exposure data and limited reproductive toxicity data.

VII. References

ACGIH. 1992. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the threshold limit values and biological exposure indices. Sixth edition. Cincinnati, OH: ACGIH.

Buckley LA, Jiang XZ, James RA, Morgan KT, and Barrow CS. 1984. Respiratory tract lesions induced by sensory irritants at the RD50 concentration. Toxicol. Appl. Pharmacol. 74:417-429.

Burleigh-Flayer HD, and Benson CL. 1995. Chloropicrin: Vapor inhalation oncogenicity study in CD rats. Bushy Run Research Center, July 29, 1995.

Burleigh-Flayer HD, Kintigh WJ, and Benson CL. 1995. Chloropicrin: Vapor inhalation oncogenicity study in CD-1 mice. Bushy Run Research Center, April 20, 1995.

Condie LW, Daniel FB, Olson GR, and Robinson M. 1994. Ten and ninety-day toxicity studies of chloropicrin in Sprague-Dawley rats. Drug Chem. Toxicol. 17:125-137.

Duguet JP, Tsutsumi Y, Bruchet A, and Mallevialle J. 1985. Chloropicrin in potable water: conditions of formation and production during treatment processes. In: Water Chlorination: Chemistry, Environmental Impact and Health Effects. Jolley RL, Bull RJ, Davis WP, Katz S, Roberts MH, and Jacobs VA. (eds.) Chelsea, MI: Lewis Publishers, pp. 1201-1213.

Fries AA, and West CJ. 1921. Chapter VIII. Chloropicrin. In: Chemical Warfare. First edition. New York, NY: McGraw-Hill Book Company, Inc.

HSDB. 1996. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

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

Merlet N, Thibaud H, and Dore M. 1985. Chloropicrin formation during oxidative treatments in the preparation of drinking water. Sci. Total Environ. 47:223-228.

CHRONIC TOXICITY SUMMARY

HEXAVALENT CHROMIUM (SOLUBLE COMPOUNDS)

Molecular Formula	***Molecular Weight***	***Synonyms***	***CAS #***
CrO_3	99.99	Chromic trioxide, chromium oxide, chromium trioxide, chromium (VI) oxide	1333-82-0
K_2CrO_4	194.20	Potassium chromate, dipotassium chromate, potassium (VI) chromate, dipotassium monochromate, chromate of potash	7789-00-6
Li_2CrO_4	129.87	Lithium chromate, dilithium salt, chromium lithium oxide, chromic acid, lithium chromate (VI)	14307-35-8
Na_2CrO_4	161.97	Sodium chromate, chromic acid disodium salt, chromium disodium oxide, sodium chromate (VI), chromate of soda	7775-11-3
$K_2Cr_2O_7$	294.20 g/mol	Potassium dichromate, dichromic acid dipotassium salt, bichromate of potash	7778-50-9
$Na_2Cr_2O_7$	261.96	Sodium dichromate, bichromate of sodium, chromic acid disodium salt, chromium sodium oxide	10588-01-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.0008 µg/m^3 Cr(VI)**
Critical effect(s)	Respiratory effects (nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes) in human occupational study
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties of Chromic Acid (HSDB, 1994)

Description	Dark red or brown solid
Molecular formula	See above
Molecular weight	See above
Density	2.70 g/cm^3 @ 25°C
Boiling point	Not found
Melting point	197 °C
Vapor pressure	Not found
Solubility	Soluble in water, ethyl alcohol, ethyl ether, sulfuric and nitric acid
Conversion factor	Not applicable

III. Major Uses or Sources

Hexavalent chromium is more toxic than Cr (III), the form most commonly found naturally (ATSDR, 1993). While more information is available on the toxicity of soluble Cr (VI) compounds, information on insoluble Cr (VI) compounds has been included where applicable.

Chromates are used in paints and locomotives to inhibit metal corrosion due to recirculating water. Sources of chromium emissions include sewage sludge, municipal incineration, and chemical manufacture. Chromic acid, used to electroplate metal parts, is the most common hexavalent chromium compound produced (ATSDR, 1998).

IV. Effects of Human Exposure

Workers exposed to 2 µg/m^3 Cr(VI) as chromic acid for a mean of 2.5 years exhibited an increased incidence of nasal atrophy, nasal mucosal ulcerations, and nasal septal perforations as compared to controls (Lindberg and Hedenstierna, 1983). The same study reported statistically significant decreases in FEV_1, FVC, and FEF_{25-75} measurements taken on a Thursday afternoon as compared to those taken on a Monday morning in nonsmoking workers exposed to 2 µg/m^3 Cr(VI) or more. Similar changes were observed in the smokers although only the difference in the FVC measured on a Thursday was statistically significant. No significant differences were observed between pulmonary function measurements of exposed and unexposed workers taken on a Monday morning (prior to a work week of exposure). Thus the authors infer that the observed pulmonary function changes are transient.

Gastritis and duodenal ulcers, in addition to ulceration and perforation of the nasal septum, were observed in chrome platers exposed to a mean breathing zone concentration of 4 µg/m^3 chromic acid for an average of 7.5 years (Lucas and Kramkowski, 1975).

Male workers in the chromate and dichromate production industry, whose occupational exposures were 0.05-1.0 mg Cr(VI)/m^3 as chromium trioxide for a mean of 7 years, were reported to have elevated levels of low molecular weight proteins (retinol binding protein and

tubular antigens) in the urine (Franchini and Mutti, 1988). The authors suggest that the presence of such proteins in the urine is an early indicator of kidney damage.

V. Effects of Animal Exposure

Rats exposed to 200 µg/m^3 Cr(VI) as sodium dichromate by inhalation for 22 hours per day, for 42 days exhibited decreased alveolar macrophage phagocytic activity; the lung clearance of inert iron oxide was significantly reduced in exposed rats compared to controls (Glaser *et al.*, 1985). Increased alveolar macrophage activity and a significantly elevated antibody response to injected sheep red blood cells were observed in rats exposed to 25 or 50 µg/m^3 Cr(VI) for 22 hours per day for 28 days.

A later experiment exposed male rats to 0, 50, 100, 200, or 400 µg Cr/m^3 22 hours per day, 7 days per week for 90 days (Glaser *et al*., 1990). Bronchoalveolar lavage fluid contained elevated levels of albumin, LDH, and total protein in all exposed groups. Statistically significant elevations in these parameters were observed mainly in the 200 and 400 µg/m^3 exposure groups. At necropsy, a statistically significant increase in lung weight was observed in rats exposed to 100, 200, and 400 µg/m^3 as compared to controls. An analysis of the data (Malsch *et al.*, 1994) determined a benchmark dose (95% confidence interval with dose associated with a 10% elevation in the parameter) for each of these endpoints. The analysis also examined changes in lung and spleen weight reported in Glaser *et al.* (1985). The most sensitive endpoint was LDH in BALF.

Nasal septal perforation, hyperplastic and metaplastic changes in the larynx, trachea and bronchus, and emphysema were observed in mice exposed two days per week for 12 months to CrO_3 mist in concentrations of either 3.63 mg/m^3 for 30 minutes per day or 1.81 mg/m^3 for 120 minutes per day (Adachi, 1987; Adachi *et al.*, 1986).

VI. Derivation of Chronic Reference Exposure Level (REL)

Derivation of Chronic Inhalation Reference Exposure Level

Study	Lindberg and Hedenstierna, 1983
Study population	Human workers (100 exposed workers, 119 unexposed controls)
Exposure method	Occupational exposure
Critical effects	Nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes
LOAEL	Average occupational exposure of 1 µg/m^3 Cr(VI) as chromic acid, with a range between non-detectable concentrations (< 0.2 µg/m^3) and 2 µg/m^3
NOAEL	Not observed

Exposure continuity	8 hours per day, 5 days per week
Exposure duration	Mean of 2.5 years (range = 0.2 - 23.6 years)
Average exposure	0.24 µg/m^3 Cr(VI)
Human equivalent concentration	0.24 µg/m^3 Cr(VI)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0008 µg/m^3 Cr(VI)

The human exposure study of Lindberg and Hedenstierna (1983) was selected as the best available human study. The available animal studies had shortcomings that limited their usefulness. A 10-fold uncertainty factor was applied due to the lack of a NOAEL observation. The mean exposure duration (3% of lifetime) was less than the 8 to 12% of lifetime that has been used to differentiate chronic from subchronic studies. However, since exposure ranged up to 26 years, a factor of 3 was considered adequate.

The major strength of the REL is the use of adequate human data. The major uncertainties are the lack of controlled and quantified exposure data, the lack of an observation of a NOAEL, the lack of dose-response information, and the lack of comprehensive data on multi-organ effects.

***Derivation of Chronic Oral Reference Exposure Level* (U.S. EPA RfD)**

Study	Mackenzie *et al.*, 1958
Study population	8 male and 8 female Sprague-Dawley rats
Exposure method	Drinking water
Critical effects	No adverse effects seen
LOAEL	None
NOAEL	2.4 mg/kg-day (converted from 25 mg/L of chromium as K_2CrO_4)
Exposure continuity	Continuous
Exposure duration	1 year
Average experimental exposure	0.11 ppm chromium VI
LOAEL uncertainty factor	1
Subchronic uncertainty factor	5 (see below)
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	500
Oral reference exposure level	0.005 mg/kg bw-day

*Conversion Factors: Drinking water consumption = 0.097 L/kg/day (reported)

The oral REL is the U.S. EPA's oral Reference Dose (RfD) (U.S. EPA, 1996). Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0-11 ppm (0-11 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group (10/sex)

received distilled water. A second experiment involved three groups of 12 males and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (as K_2CrO_4); a second received 25 ppm chromium in the form of chromic chloride; and the controls received distilled water. No significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K_2CrO_4) showed an approximate 20% reduction in water consumption. This dose corresponds to 2.4 mg chromium (VI)/kg/day based on actual body weight and water consumption data.

For rats treated with 0-11 ppm (in the diet), blood was examined monthly, and tissues (livers, kidneys and femurs) were examined at 6 months and 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except that no animals were killed at 6 months. An abrupt rise in tissue chromium concentrations was noted in rats treated with greater than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group.

Similar no-effect levels have been observed in dogs and humans. Anwar *et al.* (1961) observed no significant effects in female dogs (2/dose group) given up to 11.2 ppm chromium(VI) (as K_2CrO_4) in drinking water for 4 years. The calculated doses were 0.012-0.30 mg/kg of chromium(VI). In humans, no adverse health effects were detected (by physical examination) in a family of four persons who drank for 3 years from a private well containing chromium(VI) at approximately 1 mg/L (0.03 mg/kg/day for a 70-kg human).

This RfD is limited to soluble salts of metallic chromium(VI). Examples of soluble salts include potassium dichromate ($K_2Cr_2O_7$), sodium dichromate ($Na_2Cr_2O_7$), potassium chromate (K_2CrO_4) and sodium chromate (Na_2CrO_4). Trivalent chromium is an essential nutrient. There is some evidence to indicate that hexavalent chromium is reduced in part to trivalent chromium in vivo (Petrilli and DeFlora, 1978; Gruber and Jennette, 1978). The literature available on possible fetal damage caused by chromium compounds is limited. No studies were located on teratogenic effects resulting from ingestion of chromium.

The uncertainty factor of 500 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 5 to compensate for the less-than-lifetime exposure duration of the principal study.

U.S. EPA stated its confidence in the RfD as: Study - Low; Data Base - Low; and RfD - Low. Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured, and the lack of toxic effect at the highest dose tested. Confidence in the database is low because the supporting studies are of equally low quality, and teratogenic and reproductive endpoints are not well studied. Low confidence in the RfD follows.

VII. References

Adachi S, Yoshimura H, Katayama H, Takemoto K. 1986. [Effects of chromium compounds on the respiratory system. IV. Long term inhalation of chromic acid mist in electroplating to ICR female mice.] Sangyo Igaku (Jpn. J. Ind. Health) 28:283-287. [cited in ATSDR, 1993].

Adachi S. 1987. [Effect of chromium compounds on the respiratory system. V. Long term inhalation of chromic acid mist in electroplating by C57BL female mice and recapitulation on our experimental studies.] Sangyo Igaku (Jpn. J. Ind. Health) 29:17-33. [cited in ATSDR, 1993].

ATSDR. 1993. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium. Prepared by Syracuse Research Corporation under subcontract to Clement International Corporation under Contract No. 205-88-0608. Prepared for U.S. Department of Health and Human Services, Public Health Service, ATSDR.

ATSDR. 1998. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chromium. Prepared by Sciences International under subcontract to Research Triangle Institute under Contract No. 205-93-0606. Prepared for U.S. Department of Health and Human Services, Public Health Service, ATSDR.

Anwar RA, Langham, FF, Hoppert CA, *et al*. 1961. Chronic toxicity studies. III. Chronic toxicity of cadmium and chromium in dogs. Arch. Environ. 3:456-460.

Franchini I, and Mutti A. 1988. Selected toxicological aspects of chromium (VI) compounds. Sci. Total Env. 71:379-387. [cited in ATSDR, 1993].

Glaser U, and Hochrainer H. 1988. Report on the subchronic inhalation toxicity of sodium dichromate in rats with attachment and cover letter dated 112089. Industrial Health Foundation Inc. Available from: EPA\OTS Doc#FYI-OTS-1289-0729; Fiche No. OD-NTIS/OTS 0000729.

Glaser U, Hochrainer D, Kloppel H, and Kuhnen H. 1985. Low level chromium (VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. Arch. Toxicol. 57:250-256.

Glaser U, Hochrainer D, Steinhoff, D. 1990. Investigation of irritating properties of inhaled Cr(VI) with possible influence on its carcinogenic action. In: Environmental Hygiene II. Seemayer NO, Hadnagy W. (eds.) Berlin/New York: Springer-Verlag.

Gruber JE, Jennette KW. 1978. Metabolism of the carcinogen chromate by rat liver microsomes. Biochem. Biophys. Res. Commun. 82(2):700-706.

HSDB. 1994. Hazardous Substances Data Bank. TOMES® Vol. 20. Denver, CO: Micromedex, Inc.

Lindberg E, and Hedenstierna G. 1983. Chrome plating: symptoms, findings in the upper airways, and effects on lung function. Arch. Environ. Health 38(6):367-374.

Lucas JB, and Kramkowski RS. 1975. Health hazard evaluation/ toxicity determination report H.H. 74-87-221 Industrial Platers Inc. Columbus, OH. Cincinnati, OH: National Institute for Occupational Safety and Health. NTIS #PB 249 401.

MacKenzie RD, Byerrum RU, Decker CF, Hoppert CA, and Langham RF. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. AMA Arch. Ind. Health. 18:232-234.

Malsch PA, Proctor DM, and Finley BL. 1994. Estimation of a chromium inhalation reference concentration using the benchmark dose method: A case study. Regul. Toxicol. Pharmacol. 20:58-82.

Petrilli FL, De Flora S. 1978. Metabolic deactivation of hexavalent chromium mutagenicity. Mutat. Res. 54(2):139-147.

U.S. EPA. 1984. United States Environmental Protection Agency. Health Assessment Document for Chromium. Environmental Criteria and Assessment Office, Office of Research and Development. Research Triangle Park, NC: U.S. EPA.

U.S. EPA. 1996. Integrated Risk Information System (IRIS). Chromium (VI).

CHRONIC TOXICITY SUMMARY

CRESOL MIXTURES

Compounds	*Synonyms*	*CAS Reg. No.*
cresols	cresylic acid; tricresol; hydroxytoluene; methylphenol	1319-77-3
o-cresol	1-hydroxy-2-methylbenzene; 2-hydroxytoluene; 2-methylphenol	95-48-7
m-cresol	1-hydroxy-3-methylbenzene; 3-hydroxytoluene; 3-methylphenol	108-39-4
p-cresol	1-hydroxy-4-methylbenzene; 4-hydroxytoluene; 4-methylphenol	106-44-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**180 µg/m^3**
Critical effect(s)	Neurotoxicity
Hazard index target(s)	Nervous system

II. Chemical Property Summary (HSDB, 1995, unless otherwise noted)

Description	Colorless in pure form; yellowish, brownish-yellow, or pinkish liquid
Molecular formula	C_7H_8O
Molecular weight	108.13
Boiling point	195.95°C (o-cresol) 202°C (m-cresol) 201.9°C (p-cresol)
Vapor pressure	0.299 mm Hg @ 25°C (o-cresol) 0.138 mm Hg @ 25°C (m-cresol) 0.11 mm Hg @ 25°C (p-cresol) (Chao *et al.*, 1983; Daubert and Danner, 1985) 1 mm Hg @ 38-53°C
Solubility	Soluble in 50 parts water; miscible with alcohol, benzene, ether, glycerol, petroleum ether; soluble in vegetable oils, glycol
Conversion factor	4.42 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Cresol compounds (mixtures of the ortho-, meta- and para-isomers) can be obtained from coal tar and petroleum or synthesized by sulfonation or oxidation of toluene (HSDB, 1995). Crude cresol (commercial grade) contains approximately 20% o-cresol, 40% m-cresol, and 30% p-cresol. Phenol and xylenols are present in small amounts as contaminants. Cresylic acid compounds are called cresol when the boiling point is below 204°C.

Cresols have a wide variety of uses including the manufacture of synthetic resins, tricresyl phosphate, salicylaldehyde, coumarin, and herbicides. Cresols also serve as components of degreasing compounds in textile scouring and paintbrush cleaners as well as fumigants in photographic developers and explosives. Cresols also function as antiseptics, disinfectants, and parasiticides in veterinary medicine. An approximate breakdown of cresol and cresylic acid use is 20% phenolic resins, 20% wire enamel solvents, 10% agricultural chemicals, 5% phosphate esters, 5% disinfectants and cleaning compounds, 5% ore flotation, and 25% miscellaneous and exports.

Any combustion process, which results in the generation of phenolic compounds (such as automobile exhaust or coal, wood or trash smoke), may be a potential source of exposure to cresols. However, under normal conditions low vapor pressure limits the inhalation hazard presented by cresols (HSDB, 1995).

IV. Effects of Exposures to Humans

Brief exposure to 6 mg cresol/m^3 resulted in irritation of the throat and nose, nasal constriction, and dryness in 8 of 10 subjects (Uzhdavini *et al.*, 1972).

Chemical burns may result from exposure to cresols (Pegg and Campbell, 1985). The lungs of humans exposed to cresols have shown signs of emphysema, edema, bronchopneumonia, and small hemorrhages (Clayton and Clayton, 1982). Skin contact has resulted in the development of white patches and blistering, eventually turning brown or black (Lefaux, 1968). Other reported effects include turbidity, inflammation, and fatty degeneration of the liver, nephritis, and hemorrhage of the epicardium and endocardium. An infant fatally exposed to ~20 ml of a 90% cresol solution dermally showed widespread edema of the internal organs, especially the brain and kidney (Green, 1975). The liver showed signs of centrilobular and midzonal necrosis.

Chronic systemic poisoning by any route of exposure may produce symptoms of vomiting, dysphagia, salivation, diarrhea, loss of appetite, headache, fainting, dizziness, and mental disturbances (Sittig, 1981). Skin rash and discoloration may also result from prolonged or repeated exposure of the skin. Death may result from severe damage to the liver and kidneys. Oral poisoning has resulted in kidney problems (likely from the direct action of cresol) and pancreatitis (from constriction of the pancreatic ducts) (Klimkiewicz *et al.*, 1974, as reported in HSDB, 1995).

V. Effects of Exposures to Animals

The effects of inhaled o-cresol were examined in several species (Uzhdavini *et al.*, 1972, as reported in ATSDR, 1992 and U.S. EPA, 1982). Cats exposed for 30 minutes to 5-9 mg o-cresol/m^3 showed signs of respiratory irritation as indicated by increased parotid gland secretions. Exposure of mice for 2 hrs/day for 1 month to 50 mg o-cresol/m^3 did not have an effect on mortality, however, heart muscle degeneration and degeneration of nerve cells and glial elements were observed.

Uzhdavini *et al.* (1972) exposed rats (both sexes, numbers not stated) by inhalation to 9.0 ± 0.9 mg o-cresol/m^3, first for 2 months (6 hours/day, 5 days/week), then for 2 more months (4 hours/day, 5 days/week). Endpoints examined in rats included elementary conditioned defensive reflex, white blood cell levels, bone marrow elements, and liver function (as indicated by increased susceptibility to hexobarbital narcosis). Both cresol-exposed and control animals showed some loss of the defensive reflex; the effect occurred in all exposed animals before the end of the second month and in control animals at later times. White blood cell counts were elevated in male animals, peaked at the end of the exposure period, and returned to normal one month after cessation of exposure. Exposed animals also showed a statistically significant change in the leukoid-to-erythroid ratio in the bone marrow. Liver toxicity was suggested by an extension in the duration of hexobarbital narcosis in treated animals. Although guinea pigs were similarly evaluated for changes in blood cell counts and ECG, scant reporting of experimental detail limits the usefulness of this portion of the study.

NR rats were exposed by inhalation to 0.0052 or 0.05 mg tricresol/m^3 for 3 months (Kurliandskii *et al.*, 1975; as described by U.S. EPA, 1982). The proportional composition of the compound was not specified. Effects observed in the high-dose group included decreased weight gain, increased central nervous system excitability, increased oxygen consumption, and histological changes in the lung and liver. Serum gamma-globulin levels were also reduced. No effects were observed in the low-dose group. Rats (6/group, sex unspecified) were also exposed for 24 hours to 0.01, 0.1, and 2.4 mg tricresol/m^3 with a control group of 6 rats for each exposure group. The absorption of neutral red dye by lung tissue was used as an indicator of protein denaturation in the tissue. Significantly increased dye absorption over control animals was observed at both 2.4 and 0.1 mg tricresol/m^3. The degree of dye absorption in the low-dose group was not significantly increased over controls.

In a 90-day subchronic toxicity study (U.S. EPA, 1986), 30 Sprague-Dawley rats/sex/dose were gavaged daily with 0, 50, 175, or 600 mg/kg/day p-cresol. Body and organ weights, food consumption, mortality, clinical signs of toxicity, and clinical pathology were evaluated. At 600 mg/kg/day, o-cresol showed 47% combined mortality (9/30 males, 19/30 females), and a 30% reduction in body weight at week 1 and 10% at final sacrifice. Kidney-to-body weight ratio was 13% higher than that of the control value at the end of the study. CNS effects such as lethargy, ataxia, coma, dyspnea, tremor, and convulsions were seen within 15 to 30 minutes after dosing; but recovery occurred within 1 hour post-gavage. At 450 mg/kg/day, combined mortality was 20% (1/10 male, 1/10 female). In the 175 mg/kg/day group, two animals exhibited tremors on day 1 of the study during the hour following gavage administration, and one of the two became comatose. At 50 mg/kg/day, no significant adverse effects were observed (USEPA, 1999a,b).

In a 90-day neurotoxicity study (U.S. EPA, 1987), 10 Sprague-Dawley rats/sex/dose were gavaged daily with o-cresol at 0, 50, 175, 450, or 600 mg/kg/day. In addition to the parameters evaluated above various signs of neurotoxicity were monitored. The lowest dose of o-cresol caused clinical signs of CNS-stimulation post-dosing, such as salivation, rapid respiration, and hypoactivity; however, these symptoms were low in incidence and sporadic in nature. Higher doses of o-cresol (greater than 450 mg/kg/day) produced significant neurological events, such as increased salivation, urination, tremors, lacrimation, palpebral closure, and rapid respiration. High dosed animals also showed abnormal patterns in the neurobehavioral tests. The NOAEL based on systemic toxicity was 50 mg/kg/day (USEPA, 1999a,b).

Dermal exposure of rats to 1.0-1.7 ml cresol/kg body weight for 1-2 hours resulted in skin discoloration and death of the animals (Campbell, 1941).

Exposure to high concentrations of toluene vapors, or to intravenous o-cresol, a toluene metabolite, at about 0.9 mg/min, caused excitation of the somatosensory evoked potential (SEP) and electroencephalograph (EEG) of Fischer 344 rats (Mattsson et al., 1989). Both substances induced an increase in EEG beta activity and caused a large increase in activity at 5 Hz. Toluene exposed rats were lightly anesthetized, while o-cresol rats were conscious but hyperreactive. When exposure was continued, both sets of rats had involuntary muscle movements and tremors. Neither benzoic acid and hippuric acid, also metabolites of toluene, caused neuroexcitation. The authors concluded that metabolically derived cresols are plausible candidates for the neuroexcitatory properties of toluene.

In rat liver slices at equimolar concentrations, p-cresol was 5- to 10-times as toxic as the o- or m-isomers for cell killing (Thompson *et al*., 1994). p-Cresol rapidly depleted intracellular glutathione levels, while the o- and m-isomers depleted it to a lesser extent. p-Cresol was metabolized to a reactive intermediate which bound covalently to protein. The reaction was inhibited by N-acetylcysteine.

The National Toxicology Program (NTP) sponsored reproductive toxicity tests of cresol isomers in Swiss CD-1 mice using the risk assessment by continuous breeding (RACB) protocol (Heindel *et al*., 1997a, 1997b). For o-cresol the exposure concentrations in the continuous cohabitation task were 0.05%, 0.2%, and 0.5% in feed (approximately 60, 220, and 550 mg/kg/day (Heindel *et al*., 1997a). At these doses o-cresol was not a reproductive toxicant. When a m-/p-cresol was used at concentrations of 0.25, 1.0 and 1.5% in feed (approximately 370, 1500, and 2100 mg/kg/day), the m/p mixture was a reproductive toxicant, since (1) fewer F_1 pups per litter were produced, (2) both generations showed reduced pup weights, and (3) reproductive organs showed weight reductions. Unfortunately the responses were not dose-dependent and the mixture was judged not to be a selective reproductive toxicant.

VI. Derivation of Inhalation Chronic Reference Exposure Level

Study	U.S. EPA, 1986, 1987, 1999a, 1999b
Study population	Sprague-Dawley rats
Exposure method	Gavage

Critical effects	Decreased body weights and neurotoxicity (tremors, salivation, lacrimation, etc.)
LOAEL	150 mg/kg-day
NOAEL	50 mg/kg-day
Exposure continuity	Daily gavage
Exposure duration	90 days
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
U.S. EPA Reference Dose (RfD)	0.05 mg/kg/day
Route-to-route extrapolation factor	3500 $\mu g/m^3$ per mg/kg/day
Inhalation REL	180 $\mu g/m^3$

The same RfD was derived by the USEPA for both o-cresol and m-cresol (USEPA 1998a, 1998b). The RfD for p-cresol was withdrawn by the USEPA.

The available literature on the observed toxicity of cresol compounds and cresol mixtures to humans by inhalation indicates that at high concentrations these compounds are initially toxic due to their ability to cause chemical burns and are therefore of concern at the site of contact. In humans occupationally exposed, inhalation exposure is reported to cause respiratory effects including the development of pneumonia, pulmonary edema, and hemorrhage (Clayton and Clayton, 1982). Other case reports of cresol toxicity to humans are confounded by the presence of other compounds, such as phenol, formaldehyde, and ammonia (Corcos, 1939; NIOSH, 1974). The only quantitative information from inhalation exposures to humans, however, comes from acute exposure studies showing irritation at 6 mg cresol/m^3 (Uzhdavini *et al.*, 1972, as reported in ATSDR, 1992). Toxic effects reported in animals include bone marrow and liver toxicity in rats from 4 month exposure to 9 mg cresol/m^3 (Uzhdavini *et al.*, 1972, as reported in U.S. EPA, 1982). Other animal studies have shown more systemic effects from inhalation exposure to cresols. Uzhdavini *et al.*, 1972 reported cardiac and nerve cell degeneration in mice exposed for 2 hour/day for 1 month to 50 mg o-cresol/m^3, Kurliandskii *et al.*, 1975, (as reported in HSDB, 1995) observed decreased weight gain with histological changes in the liver and lungs of rats exposed for 3 months to 0.05 mg tricresol/m^3. Although this study reports adverse effects at levels below those observed in the Uzhdavini *et al.* (1972) study, limited experimental detail precludes the use of these data in the development of the chronic REL.

The only useful inhalation data for the development of a chronic REL are those showing hematological toxicity to the bone marrow of rats exposed for 4 months to o-cresol (Uzhdavini *et al.*, 1972, as reported in U.S. EPA, 1982). These authors report a LOAEL of 9 mg tricresol/m^3. OEHHA staff decided not to use this study because: (1) a complete translation from the original Russian was not available so that only the interpretations of others were available; (2) some endpoints tested are not commonly used in toxicology; and (3) some of the results reported were unusual (e.g., elevation of white blood cells in male but not female rats).

As noted above, the inhalation study conducted by Kurliandskii *et al.* (1975) suggests that adverse health effects occur in experimental animals at exposure levels considerably below those reported by Uzhdavini *et al.* (1972) (9 mg/m^3 vs. 0.05 mg/m^3). The report from which the lower level is drawn has limitations. Human subjects exposed briefly to levels below the LOAEL have reported respiratory irritation.

The strengths of the REL include the use of measured exposure data of animals exposed over a significant fraction of their lifetime. Major areas of uncertainty are route-to-route extrapolation, the lack of chronic human data, and the paucity of reproductive and developmental toxicity studies. Additional inhalation studies of cresols will be useful.

VII. References

ATSDR. 1992. Agency for Toxic Substances and Disease Registry. Toxicological profile for cresols: o-cresol, p-cresol, and m-cresol. Atlanta, GA: ATSDR. NTIS No. PB93-110732.

Campbell I. 1941. Petroleum cresylic acids. A study of their toxicity and the toxicity of cresylic disinfectants. Soap and Sanitation Chemistry 17:103.

Chao J, Lin CT, and Chung TH. 1983. Vapor pressure of coal chemicals. J. Chemistry Reference Data 12:1033-1063.

Clayton GD, and Clayton FE (eds). 1982. Patty's Industrial Hygiene and Toxicology. Third, revised ed. New York: John Wiley Sons, p. 2133.

Corcos A. 1939. [Contribution to the study of occupational poisoning by cresols]. Dissertation. Paris (Vigot Freres Editeurs).

Daubert TE, and Danner RD. 1985. Data compilation tables of properties of pure compounds. In: Design Institute for Physical Property Data. New York: American Institute for Chemical Engineers.

Green MA. 1975. A household remedy misused - fatal cresol poisoning following cutaneous absorption (a case report). Med. Sci. Law 15:65-66.

Heindel J, George J, Fail P, Izard MK, Grizzle T. 1997a. o-Cresol. Environ. Health Perspect. 105(Suppl 1):293-294.

Heindel J, Izard MK, George J, Fail P, Grizzle T. 1997b. m-/p-Cresol. Environ. Health Perspect. 105(Suppl 1):295-296.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Klimkiewicz E, Klinger M, Kurbiel A, and Soltys W. 1974. [Case of liquid lysol poisoning complicated by acute pancreatitis and acute renal failure]. Wiad. Lek. 27:1211-1214.

Kurliandskii BA, Partsef DI, and Chernomorskii AR. 1975. [A method of determining the daily average maximum permissible concentration of tricresol in the atmosphere]. Gig. Sanit. 5:85-87.

Lefaux R. (ed.) 1968. Practical Toxicology of Plastics. Cleveland: CRC Press, Inc.

Mattsson JL, Albee RR, and Gorzinski SJ. 1989. Similarities of toluene and o-cresol neurotoxication in rats. Neurotoxicol Teratol 11:71-75.

NIOSH. 1974. National Institute for Occupational Safety and Health. Health hazard evaluation / Toxicity determination report no. 73-5-110. Prepared by Cummins Northeastern Incorporated. Dedham, MA.

Pegg SP, and Campbell DC. 1985. Children's burns due to cresol. Burns Incl. Therm. Inj. 11(4):294-296.

Sittig M. (ed) 1981. Handbook of Toxic and Hazardous Chemicals. Park Ridge, NJ: Noyes Data Corporation.

Thompson DC, Perera K, Fisher R, Brendel K. 1994. Cresol isomers: comparison of toxic potency in rat liver slices. Toxicol. Appl. Pharmacol. 125(1):51-58

U.S. EPA 1982. United States Environmental Protection Agency. Health effects assessment for cresols. Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA/540/1-86/050. Cincinnati, OH: US EPA. NTIS. PB86-134616.

U.S. EPA. 1986. o, m, p-Cresol. 90-Day oral subchronic toxicity studies in rats. Office of Solid Waste. Washington, DC: U.S. EPA.

U.S. EPA. 1987. o, m, p-Cresol. 90-Day oral subchronic neurotoxicity study in rats. Office of Solid Waste. Washington, DC: U.S. EPA.

U.S. EPA. 1999a. 2-Methyphenol. Integrated Risk Information System (IRIS).

U.S. EPA. 1999b. 3-Methylphenol. Integrated Risk Information System (IRIS).

Uzhdavini ER, Astaf'yeva K, Mamayeva AA, and Bakhtizina GZ. 1972. [Inhalation toxicity of o-cresol]. Trudy Ufimskogo Nauchno-Isseldovatel'skogo Instituto Gigiyeny Profzabolevaniya, 7:115-119.