CHRONIC TOXICITY SUMMARY

ACRYLONITRILE

(Acrylonitrile monomer, cyanoethylene, propenenitrile, 2-propenenitrile, VCN, vinyl cyanide.)

CAS Number: 107-13-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**5 µg/m^3** (2 ppb)
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 g/mol
Density	0.81 g/cm^3 @ 25^{o}C
Boiling point	77.3^{o}C
Melting point	–82^{o}C
Vapor pressure	100 torr @ 23^{o}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). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3948 pounds of acrylonitrile (CARB, 2000). US EPA (1993) reported a mean ambient air concentration of acrylonitrile at four urban locations in the U.S.of 0.66 µg/m^3.

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, feelings of apprehension, and nervous irritability were observed in the majority of workers. Other less common symptoms observed included low-grade anemia, leukocytosis, 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. Although 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, since 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) of 2 mg/m^3 derived by the U.S. EPA from the animal study of Quast *et al.* (1980).

Czeizel *et al.* (1999) studied congenital abnormalities in 46,326 infants born between 1980 and 1996 to mothers living within a 25 km radius of an acrylonitrile factory in Nyergesujfalu, Hungary. Ascertainment of cases with congenital abnormalities was based on the Hungarian Congenital Abnormality Registry plus review of pediatric, pathology and cytogenetic records. Particular attention was paid to indicators of germinal mutations (sentinel anomalies, Down's syndrome, and unidentified multiple congenital abnormalities) and to indicators of teratogens (specific pattern of multiple congenital abnormalities). Three congenital abnormalities: pectus excavatum in Tata, 1990-1992 (OR = 78.5, 95%CI = 8.4-729.6), undescended testis in Nyergesujfalu between 1980 and 1983 (8.6, 1.4-54.3) and in Esztergom, 1981-1982 (4. 2, 1.3-13.5) and clubfoot in Tata, 1980-1981 (5.5, 1.5-20.3) showed significant time-space clusters in the study area. The risk of undescended testis decreased with increasing distance from the factory. An unusual increase for the combination of oral cleft and cardiac septal defects was seen in multimalformed babies in Tatabanya in 1990. Unfortunately there were no data on levels of acrylonitrile or any other exposure.

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 acrylonitrile 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 (see table below). Thus the LOAEL was 20 ppm. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory epithelium were observed at either concentration.

Effects of acrylonitrile reported by Quast *et al*. (1980)

Effect	Sex	0 ppm	20 ppm	80 ppm
Respiratory epithelium hyperplasia in the nasal turbinates	Male	0/11	4/12	10/10*
Hyperplasia of the mucous secreting cells	Male	0/11	7/12*	8/10*
Focal inflammation in the nasal turbinates	Female	2/11	6/10	7/10*
Flattening of the respiratory epithelium of the nasal turbinates	Female	1/11	7/10*	8/10*
Lung: pneumonia, consolidation, atelectasis, or edema	Male	14/100	27/100*	30/100*
Lung: pneumonia, consolidation, atelectasis, or edema	Female	7/100	2/100	7/100

* statistically significant difference from controls ($p<.05$)

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.

Gagnaire *et al*. (1998) studied motor and sensory conduction velocities (MCV and SCV, respectively) and amplitudes of the sensory and motor action potentials (ASAP and AMAP) of the tail nerve in male Sprague-Dawley rats during chronic treatment with acrylonitrile. (Four other unsaturated aliphatic nitriles were also given orally to other rats.) Rats were given doses of 12.5, 25, and 50 mg/kg of acrylonitrile once a day, 5 days per week for 12 weeks. Rats were also exposed by inhalation to 25, 50, and 100 ppm of acrylonitrile vapors for 6 h/day, 5 days per week, for 24 weeks and neurophysiological examinations were carried out. After oral acrylonitrile, animals developed behavioral sensitization characterized by salivation, locomotor hyperactivity, and moderately intense stereotypies. Rats dosed with 50 mg/kg developed hindlimb weakness associated with decreases in sensory conduction velocity (SCV) and in the amplitude of the sensory action potential (ASAP). Rats exposed to acrylonitrile by inhalation exhibited time- and concentration-dependent decreases in motor conduction velocity (MCV), SCV, and ASAP, which were partially reversible after 8 weeks of recovery. The authors

concluded that the nervous system of the rat appears to be a target following either oral or inhalation exposures of acrylonitrile. The NOAEL by inhalation for 24 weeks was 25 ppm.

Changes in electrophysiological parameters after 24 wks of exposure (Gagnaire *et al*., 1998)

Acrylonitrile	MCV (m/sec)	SCV (m/sec)	AMAP (mvolts)	ASAP (μvolts)
0 ppm	42.9 ± 0.9[a]	53.3 ± 1.0	17.8 ± 1.2	186 ± 8
25 ppm	41.6 ± 0.8	50.5 ± 0.8*	16.1 ± 0.8	164 ± 11
50 ppm	38.1 ± 0.9**	49.1 ± 0.5***	15.7 ± 1.0	159 ± 5*
100 ppm	38.5 ± 1.2**	48.4 ± 1.0***	17.4 ± 0.9	133 ± 11***

[a] Mean ± SEM; * $p<0.05$; ** $p<0.01$; ***$p<0.001$

In a developmental study, Murray *et al.* (1978) exposed rats to acrylonitrile vapors at 0, 40 ppm (87 mg/m^3), or 80 ppm (174 mg/m^3) 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 differences 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. After adjustment to continuous exposure, this study identified a developmental NOAEL of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity).

Saillenfait *et al*. (1993) studied the developmental toxicity of eight aliphatic mononitriles in Sprague-Dawley rats after inhalation exposure for 6 hr/day during days 6 to 20 of gestation. The range of exposure levels for acrylonitrile was 12, 25, 50, and 100 ppm; group sizes were 20-23 females. Embryolethality was observed after exposure to 25 ppm (54 mg/m^3) acrylonitrile in the presence of overt signs of maternal toxicity. Fetal weights were significantly lower at 25 ppm. Thus 12 ppm (26 mg/m^3) is a NOAEL for developmental toxicity using this study design.

VI. Derivation of Chronic Reference Exposure Level

Study	Quast *et al.*, 1980
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
BMC_{05}	1.5 ppm
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	0.27 ppm for BMC_{05} (1.5 x 6/24 x 5/7)
Human equivalent concentration	0.067 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	Not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.002 ppm (2 ppb; 0.005 mg/m^3; 5 $\mu g/m^3$)

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). The U.S. EPA (1994) based its RfC of 2 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 10 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

OEHHA used a benchmark dose approach to determine the chronic REL for acrylonitrile. The cumulative gamma distribution model in the U.S. EPA's BMDS sotware was individually fit to the data on respiratory epithelium hyperplasia in the nasal turbinates in males, hyperplasia of the mucous secreting cells in males, focal inflammation in the nasal turbinates in females, and flattening of the respiratory epithelium of the nasal turbinates in females. The resulting BMC_{05} values (1.27, 1.33, 2.18, 1.35) were averaged to yield a value of 1.5 ppm. The RGDR adjustment and appropriate uncertainty factors were applied as indicated in the above table and resulted in a chronic REL of 5 $\mu g/m^3$.

For comparison, Gagnaire *et al*. (1998) found a NOAEL for nervous system effects at 24 weeks of 25 ppm, which is equivalent to a continuous exposure of 4.5 ppm. Use of the default RGDR of 1 for systemic effects, a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 45 ppb (100 $\mu g/m^3$). We were unable to derive a BMC from the neurotoxicity data due partly to the tendency of the animals in the 100 ppm group to yield values for two of the four endpoints measured closer to the controls than those in the 50 ppm group.

As another comparison, Saillenfait *et al*. (1983) found a 12 ppm (26 mg/m^3) NOAEL for fetal weight reduction (6 h/d exposure). This is equivalent to a continuous exposure of 3 ppm (on

days 6 to 20 of gestation). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 100 ppb (200 $\mu g/m^3$).

Finally, after adjustment to continuous exposure, Murray *et al*. (1978) identified a developmental NOAEL, adjusted to continuous exposure, of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity at both levels). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 30 ppb (70 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the chronic REL for acrylonitrile 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, (2) the lack of a NOAEL in the 2 year study, (3) lack of inhalation bioassay in a second species, and (4) lack of reproductive data for inhalation exposures when an oral study showed adverse reproductive effects

When assessing the health effects of acrylonitrile, its carcinogenicity must also be assessed.

VIII. Potential for Differential Impacts on Children's Health

The chronic REL is considerably lower than the comparison estimate based on developmental effects. Although neurotoxicity, an endpoint which is often associated with increased sensitivity of younger animals or humans, was evaluated as one of the alternative endpoints, the comparison reference level for this end point in adults was more than an order of magnitude higher that the REL based on histological changes in the upper respiratory tract. It is therefore considered that the REL is likely to be adequately protective of infants and children.

IX. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Czeizel AE, Hegedus S and Timar L. 1999. Congenital abnormalities and indicators of germinal mutations in the vicinity of an acrylonitrile producing factory. Mutat. Res. 427(2):105-123

Gagnaire F, Marignac B, and Bonnet P. 1998. Relative neurotoxicological properties of five unsaturated aliphatic nitriles in rats. J. Appl. Toxicol. 18(1):25-31.

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.

Saillenfait AM, Bonnet P, Guenier JP and de Ceaurriz J. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fundam. Appl. Toxicol. 20(3):365-375.

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.

United States Environmental Protection Agency (U.S. EPA) (1993). Kelly TJ RMPASCCL. Ambient Concentration Summaries for Clean Air Act Title III Hazardous Air Pollutants. U.S. EPA Contract No. 68-D80082.

U.S. EPA 1994. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS) Database. Reference concentration (RfC) for acrylonitrile. Available online at http://www.epa.gov/ngispgm3/iris

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

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	**0.007 mg Be/m^3**
Critical effect(s)	Beryllium sensitization and chronic beryllium disease in occupationally exposed humans
Hazard index target(s)	Respiratory system; immune system
Oral reference exposure level	0.002 mg/kg-day
Critical efect	Small intestinal lesions in dogs
Hazard index target(s)	Gastrointestinal tract/liver

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

	Metallic beryllium	*Beryllium oxide*	*Beryllium hydroxide*	*Beryllium sulfate*
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 g/mol	25.01 g/mol	43.03 g/mol	105.07 g/mol
Solubility	Insoluble in water			Soluble
Conversion factor	Not applicable			

III. Major Uses and Sources

Beryllium is a metallic element mined as 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 aircraft 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 four species listed, there are many other beryllium-containing compounds, including other salts, ores, and alloys (see, e.g., CRC, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2279 pounds of beryllium (CARB, 2000).

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, including the 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 (0-0.0005 μg/cigarette) (Smith *et al*., 1997).

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 (CBD) 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 occupational exposure to beryllium. Exposure to soluble beryllium compounds is associated with acute beryllium pneumonitis (Eisenbud *et al.*, 1948). Exposure to either 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). 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). 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 seven 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. 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 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-year (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 one 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 x-ray and clinical examination of approximately 10,000 residents near a beryllium fabrication facility in Lorain, Ohio. 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 estimated a 1% disease incidence within 1/4 mile (500 individuals). Atmospheric sampling in 1947 identified an average 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 up to 100 fold over the 10 week sampling period. Utilizing current and historical 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 during 1958 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*. Cullen *et al.* (1987) reported a mean exposure level of 1.2 μg Be/m^3 (range = 0.22 – 43 μg/m^3). USEPA (1998) and ATSDR (2000) considered 0.52 μg Be/m^3 to be the LOAEL for CBD from this study since this was the average concentration in the furnace area where 4 of the 5 CBD cases worked.

Sensitization to beryllium, as measured by the beryllium lymphocyte proliferation test (BeLPT), can occur in the absence of chronic beryllium disease (Kreiss *et al.*, 1989). The authors hoped that the identification of sensitized individuals without disease might prevent clinical disease, presumably by removing the individuals from exposure to beryllium. Some beryllium-sensitized individuals progress to having clinical disease (Newman *et al.*, 1992). Data obtained from a four-year survey conducted at beryllium-copper alloy manufacturing factories in Japan (Yoshida *et al.*, 1997) indicated that the T cells of workers continuously exposed to more than 0.01 μg Be/m^3 were activated and that the cell-mediated immune (CMI) response was promoted. The BeLPT in workers exposed to less than 0.01 μg Be/m^3 was unaffected.

Genetic influences on development of CBD have been identified. CBD is associated with the allelic substitution of glutamic acid for lysine at position 69 in the HLA-DPB1 protein (Richieldi *et al.*, 1993). Up to 97% of CBD patients may have the Glu69 marker, but only 30-45% of beryllium-exposed, unaffected individuals carry the same marker. Because CBD occurs in only 1-6% of exposed workers, Glu69 is not likely to be the only genetic factor influencing the development of CBD. Changes in other sequences of the HLA-DPB1 gene and in the copy number of Glu69 are also involved (Wang *et al.*, 1999).

The Rocky Flats Environmental Technology Site in Colorado is part of the U.S. Department of Energy nuclear weapons complex. Operations using Be began in 1953, Be production operations began in 1957, and the first case of CBD was diagnosed in a machinist in 1984. Exposures could have occurred during foundry operations, casting, shearing, rolling, cutting, welding, machining, sanding, polishing, assembly, and chemical analysis operations. Since 1991, 29 cases of CBD and 76-78 cases of beryllium sensitization have been identified (Stange *et al.*, 1996). Several cases appear to have had only minimal Be exposure, since the employees were in administrative functions, not primary beryllium operations. Personal air monitoring devices used over a period of 4 years showed a breathing zone level of 1.04 μg Be/m^3. ATSDR (2000) considered 1.04 μg Be/m^3 to be the LOAEL for this study. A recent case-control study of workers at Rocky Flats (Viet *et al.*, 2000) suggested that exposures of workers to lower Be levels might lower the future incidence of CBD, but not necessarily the incidence of sensitivity to Be.

Kreiss *et al.* (1996) investigated the prevalence of beryllium sensitization in relation to work process and beryllium exposure measurements in a beryllia ceramics plant that had operated since 1980. In 1992 they interviewed 136 employees (97.8% of the workforce), ascertained beryllium sensitization with the beryllium lymphocyte proliferation blood test (BeLPT), and reviewed industrial hygiene measurements. Eight employees were beryllium-sensitized (5.9%); six of the eight had granulomatous disease based on transbronchial lung biopsy. Machinists had a Be sensitization rate of 14.3% compared to 1.2% among other employees. Machining operations (drilling, dicing, centerless grinding, and/or surface grinding) had significantly higher general area and breathing zone measurements than other work processes during the time in which most beryllium-sensitized cases had started machining. Daily weighted average estimates of exposure for matching processes also exceeded estimates for other work processes in that time period (median daily weighted average = 0.9 $\mu g/m^3$). Daily weighted averages for the machining process accounted for the majority of exceedances of the 2.0 $\mu g/m^3$ OSHA Permissible Exposure Limit (PEL); 8.1% of machining daily weighted averages were above the PEL. The LOAEL from this study was 0.55 $\mu g/m^3$, the median exposure of the sensitized workers.

The facility was again surveyed in 1998 after some attempts were made to lower exposure to beryllium (Henneberger *et al*., 2001). The investigators separated the workers into 77 long-term workers hired before the 1992 screening and 74 short-term workers hired after 1992. Among 20 short-term workers exposed to the lowest mean Be level (0.05 to 0.19 $\mu g/m^3$), two showed Be sensitivity by the BeLPT test. Thus a fraction of workers appears to be exquisitely sensitive to beryllium.

Based on a review of this and other occupational studies Wambach and Tuggle (2000) have suggested that the workplace standard of 2 $\mu g/m^3$ be lowered to 0.1 $\mu g/m^3$. Some workers might still be sensitized to beryllium at this level (Yoshida *et al*., 1997).

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). Guinea pigs were exposed to 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 (Reeves *et al.*, 1970). 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, for 6 hours/day, 5 days/week for up to 17 months. Exposed animals displayed 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 in 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

Key study	Kreiss *et al*., 1996
Study population	8 beryllium-sensitized workers among 136 employees in a beryllia ceramics plant
Exposure method	Workplace
Critical effects	Beryllium sensitization (chronic beryllium disease)
LOAEL	0.55 µg/m^3 (median exposure of sensitized workers)
NOAEL	Not observed
Exposure continuity	Workplace
Average experimental exposure	0.2 µg/m^3 for LOAEL group (0.55 x 10/20 x 5/7)
Human equivalent concentration	0.2 µg/m^3
Exposure duration	6.1 years (5 mo – 10 yr)
LOAEL uncertainty factor	10 (low incidence but serious, irreversible chronic disease)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3 (sensitized may not be only sensitive subpopulation) (see below)
Cumulative uncertainty factor	30
Inhalation chronic REL	0.007 µg/m^3

Supportive 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 in 11 residents
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	3
Cumulative uncertainty factor	100
Inhalation chronic REL	0.003 µg/m^3

U.S. EPA (1998) developed an RfC of 0.02 μg/m^3 based on beryllium sensitization and progression to chronic beryllium disease (CBD) identified by Kreiss *et al*. (1996). The Kreiss *et al*. (1996) occupational exposure study identified a LOAEL for beryllium sensitization in workers of 0.55 μg/m^3 (median of average exposure concentrations of the 8 Be sensitized workers). The Eisenbud *et al*. (1949) study, which U.S. EPA used as a co-principal study and which in U.S. EPA's opinion used relatively insensitive screening methods, suggested a NOAEL of 0.01-0.1 μg/m^3 in community residents living near a beryllium plant. U.S. EPA used the LOAEL from the Kreiss *et al*. (1996) study for the operational derivation of the RfC, because the screening method used in the Eisenbud *et al*. (1949) study was considered to be less sensitive than the method used in the Kreiss *et al*. (1996) study. The LOAEL was time adjusted to 0.2 μg/m^3, then a total UF of 10 was used to obtain the RfC of 0.02 μg/m^3. The UF of 10 was comprised of a UF of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization) and a database UF of 3 to account for the poor quality of exposure monitoring in the Kreiss *et al*. and Eisenbud *et al*. studies. Poor exposure monitoring was also a problem in other epidemiology studies that assessed the incidence of beryllium sensitization. The U.S. EPA did not explicitly apply a LOAEL to NOAEL uncertainty factor. Thus implicitly the factor is 1.

OEHHA prefers to use the methodology for assignment of UFs, which is described in OEHHA (2000) and used in our derivation of the REL for beryllium, including use of a LOAEL to NOAEL Uncertainty Factor of 10. Since chronic beryllium disease (CBD) is serious, chronic, disabling, usually irreversible, and often fatal (Newman *et al*., 1997), it is difficult to justify use of a LOAEL to NOAEL factor of only 3. OEHHA has not used database deficiency UFs since the criteria for use of such factors are not well specified by U.S. EPA. The people who get CBD are likely that part of the population who are by nature more sensitive to beryllium, for example those with the human leukocyte antigen (HLA) class II marker HLA-DP Glu69 (Richeldi *et al*., 1993; Saltini *et al*., 1998). Although it is likely that the effects are seen in a "sensitive subpopulation," OEHHA applied an intraspecies uncertainty factor (UF_H). OEHHA used an intermediate UF_H of 3, since 1) there may be other population factors involved in being sensitive, such as immature lungs, and 2) all the diseased were initially healthy adult workers.

For comparison the LOAEL from guinea pigs of 3.7 μg Be/m^3 (Reeves *et al.*, 1970) is equivalent to a continuous exposure of 0.66 μg/m^3. Division by UFs of 10 for intraspecies, 10 for interspecies (since HEC adjustments are not available yet for guinea pigs), and 10 for use of a LOAEL results in a REL of 0.0007 μg/m^3

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation chronic REL for beryllium is the use of human data from persons occupationally exposed. The major uncertainties are the lack of a NOAEL observation in the key study, the lack of long-term exposure data, the difficulty of estimating exposures, and the lack of chronic exposure data.

VIII. Potential for Differential Impacts on Children's Health

No evidence to support a differential effect of beryllium on infants or children was found in the literature. However, children have developed beryllium disease from metal brought home on the parents' work clothes and by living near a facility using beryllium. Unfortunately the number of children and their ages were not published (Eisenbud *et al*., 1948).

Derivation of Chronic Oral Reference Exposure Level

In addition to being inhaled, airborne beryllium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for beryllium is also required for conducting Air Toxics Hot Spots risk assessments.

Study	Morgareidge *et al*., 1976
Study population	Male and female dogs (5/sex/group)
Exposure method	Diet containing 0, 1, 5, 50 or 500 ppm Be as beryllium sulfate tetrahydrate
Critical effects	Small intestinal lesions
LOAEL	500 ppm
NOAEL	50 ppm (1.2 mg/kg bw-day)
Exposure continuity	Continuous
Exposure duration	Up to 3 years, 4 months
Average experimental exposure	1.2 mg/kg bw-day (males, 1.1; females, 1.3)
BMD_{05}	0.244 mg/kg-day
LOAEL uncertainty factor	Not needed in BMD approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.002 mg/kg-day

Morgareidge *et al*. (1976) conducted a long-term feeding study in which beagle dogs (aged 8 to 12 mo) were fed diets (for 1 h per day) containing 0, 5, 50, or 500 ppm Be for 172 weeks. The 500 ppm group was terminated at 33 weeks because of overt signs of toxicity, and an additional group was added to the study and fed a diet containing 1 ppm Be (for 143 weeks). The 1, 5, 50, and 500 ppm concentrations corresponded to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for males and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine and to a lesser extent in the stomach and large intestine, and were considered treatment related. All animals with stomach or large intestinal lesions also had lesions in the small intestine, except for one animal (whose stomach lesions were very localized and not very severe). Lesions in the small intestine (4/5 males and 5/5 females) were considered to be treatment-related and included desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium, and ulceration. High-dose animals also showed

moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment related. (Bile stasis and vasculitis in the liver, acute inflammation in the lymph nodes, and kidney occurring in these animals was attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa.) In the 50 ppm group, one female dog, which died after 70 weeks of treatment, showed gastrointestinal lesions, which were less severe, but occurred in the same locations and appeared to be the same types of lesions as those in dogs administered 500 ppm. The observation that beryllium is poorly absorbed by the gastrointestinal tract (Owen, 1990; ATSDR, 2000) probably explains why lesions were not seen outside the gastrointestinal tract. In addition the predominance of lesions in the small intestine may have been partly due to precipitation of beryllium phosphate there due to the slightly alkaline pH (Reeves, 1965). Thus 500 ppm was a LOAEL and 50 ppm was a NOAEL (statistically) for gastrointestinal lesions.

USEPA used the same study to derive its RfD of 0.002 mg/kg-day. The U.S. EPA stated its confidence in the RfD as: study - medium; database – low to medium, and RfD - low to medium. USEPA used a BD_{10} approach and included a database UF of 3. OEHHA used a BD_{05} approach (specifically a Weibull model in the USEPA's BMDS software) and did not include a database UF since the criteria for use of modifying factors such as this are not well specified by U.S. EPA. However, the final value for the oral chronic REL was the same as the USEPA's RfD.

This RfD and the oral REL are limited to soluble beryllium salts. Data on the teratogenicity or reproductive effects of beryllium are limited. Beryllium has been reported to produce terata and increased mortality in chick embryos.

When assessing the health effects of beryllium, its carcinogenicity must also be assessed.

IX. 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.

ATSDR. 2000. 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 (update). Dreaft for Public Comment. Atlanta, GA: ATSDR. September 2000.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

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.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

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.

Henneberger PK, Cumro D, Deubner DD, Kent MS, McCawley M and Kreiss K. 2001. Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. Int. Arch. Occup. Environ. Health. 74(3):167-176.

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.

Kreiss K, Newman LS, Mroz MM, and Campbell PA. 1989. Screening blood test identifies subclinical beryllium disease. J. Occup. Med. 31(7):603-608.

Kreiss K, Mroz MM, Newman LS, Martyny J, and Zhen B. 1996. Machining risk of beryllium disease and sensitization with median exposures below 2 micrograms/m^3. Am. J. Ind. Med. 30(1):16-25.

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.

Morgareidge K, Cox GE and Gallo MA. (1976) Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America, Alcan Research & Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc.

Newman LS, Mroz MM, Schumacher B, Daniloff E, and Kreiss K. 1992. Beryllium sensitization precedes chronic beryllium disease. Am. Rev. Resp. Dis. (Suppl) 145:A324.

Newman LS, Lloyd J, and Daniloff E. 1996. The natural history of beryllium sensitization and chronic beryllium disease. Environ. Health Perspect. 104S(5):937-943.

OEHHA. 2000. Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Available on-line at http://www.oehha.ca.gov

Owen BA. 1990. Literature-derived absorption coefficients for 39 chemicals via oral and inhalation routes of exposure. Regul. Toxicol. Pharmacol. 11(3):237-252.

Reeves AL. 1965. The absorption of beryllium from the gastrointestinal tract. Arch. Environ. Health. 11(2):209-214.

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.

Richeldi L, Sorrentino R, and Saltini C. 1993. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science 262(5131):242-244.

Saltini C, Amicosante M, Franchi A, Lombardi G and Richeldi L. 1998. Immunogenetic basis of environmental lung disease: lessons from the berylliosis model. Eur Respir J. 12(6):1463-75.

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.

Smith CJ, Livingston SD and Doolittle DJ. 1997. An international literature survey of "IARC Group I carcinogens" reported in mainstream cigarette smoke. Food Chem. Toxicol. 35(10-11):1107-1130.

Stange AW, Hilmas DE, and Furman FJ. 1996. Possible health risks from low level exposure to beryllium. Toxicology 111(1-3):213-224.

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. 1998. Integrated Risk Information System (IRIS) Database. Available online at http://www.epa.gov/iris

Viet SM, Torma-Krajewski J, and Rogers J. 2000. Chronic beryllium disease and beryllium sensitization at Rocky Flats: a case-control study. AIHAJ. 61(2):244-254.

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.

Wambach PF, and Tuggle RM. 2000. Development of an eight-hour occupational exposure limit for beryllium. Appl. Occup. Environ. Hyg. 15(7):581-587

Wang Z, White PS, Petrovic M, Tatum OL, Newman LS, Maier LA, and Marrone BL. 1999. Differential susceptibilities to chronic beryllium disease contributed by different Glu69 HLA-DPB1 and -DPA1 alleles. J. Immunol. 163(3):1647-1653.

Yoshida T, Shima S, Nagaoka K, Taniwaki H, Wada A, Kurita H, and Morita K. 1997. A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. Ind. Health 35(3):374-379.

CHRONIC TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.4 µg/m^3** (0.05 ppb)
Critical effect(s)	Nasal rhinitis and bronchiectasis in mice
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 g/mol
Boiling point	112°C
Melting point	–64°C (CRC, 1994)
Vapor pressure	5.7 torr @ 0°C (Fries and West, 1921); 3.2 kPa (24 torr) @ 25°C (Tomlin, 1994)
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 used primarily as a preplant soil fumigant against insects and fungi; it also kills weed and grass seeds when applied to soil. Chloropicrin is occasionally used as a fumigant in grain elevators and storage bins (HSDB, 1996). Chloropicrin is used as an indicator chemical in other fumigants such as methyl bromide because of its potent irritant properties. 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). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1507 pounds of chloropicrin (CARB, 2000). This does not include emissions from its major use as a preplant soil fumigant, either alone or in combination with other fumigants, because agricultural field applications are not covered under the Air Toxics Hot Spots

program. Approximately 3,630,000 lbs. of chloropicrin were used in agriculture in California in 1999 (DPR, 2000).

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 (50-60 per sex per dose) exposed discontinuously to 0 (air), 0.1, 0.5, or 1.0 ppm 99.6% pure chloropicrin vapor 6 hours/day for 5 consecutive days/week over 107 weeks. Clinical signs (such as hypoactivity and decreased startle response) were increased in both sexes, primarily at 1.0 ppm. 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 (0.67 mg/m^3) for chronic non-cancer effects in rats.

Results from chronic inhalation of chloropicrin in rats (Burleigh-Flayer and Benson, 1995)

Chloropicrin	Lung wt., m	Lung wt., f	Rhinitis, m	Rhinitis, f	Mean survival, m
0	2.086 g	1.574 g	20/50	18/50	696 d
0.1 ppm	2.089 g	1.464 g	24/50	17/50	669 d
0.5 ppm	2.202 g	1.460 g	21/50	26/50	672 d*
1.0 ppm	2.448 g	1.633 g	35/50**	23/50	647 d**

*$p<0.05$; **$p<0.01$

A similar study in mice (Burleigh-Flayer *et al*., 1995) resulted in the same NOAEL. CD-1 mice (50/sex/dose) were exposed to chloropicrin (99.6% pure) vapor at 0 (air), 0.1, 0.5, or 1.0 ppm for 6 hours/day, 5 days/week for at least 78 weeks. Body weights and body weight gains were significantly decreased in both sexes at ≥ 0.5 ppm. Food consumption was decreased in males at 1.0 ppm and in females at ≥ 0.5 ppm. Absolute and relative lung weights were increased in a dose-related manner in both sexes at ≥ 0.5 ppm. Changes in pathology observed macroscopically in the 1.0 ppm males included increased numbers of lung nodules and increased numbers of kidney cysts. In females lung masses and kidney cysts were seen at 0.5 ppm. Microscopic pathology changes included increased nasal cavity lesions (including serous exudate, hyaline epithelial inclusions, rhinitis, olfactory and epithelial atrophy) and lung lesions (including alveolar protein deposits, alveolar histiocytosis, hemorrhage, peribronchiolar lymphocytic infiltrate, bronchiectasis, bronchial submucosal fibrosis, peribronchiolar smooth muscle hyperplasia), in addition to kidney cysts at ≥ 0.5 ppm (CDPR, 2000).

Results from chronic inhalation of chloropicrin in mice (Burleigh-Flayer *et al*., 1995)

Chloropicrin	Rhinitis, m	Rhinitis, f	Bronchiectasis, m	Bronchiectasis, f	
0	6/50	3/50	0/50	0/50	
0.1 ppm	7/50	6/50	3/50	5/50	
0.5 ppm	17/50**	18/50**	28/50**	28/50**	
1.0 ppm	35/50**	32/50**	41/50**	44/50**	

**p<0.01

Yoshida *et al*. (1987) exposed groups of 12 male Fischer 344 rats intermittently to 0, 0.37, 0.67, 1.58, or 2.93 ppm chloropicrin vapor 6 h/day, 5 days/week for 13 weeks. Mean body weights were reduced in the highest 2 exposure groups, and red blood cell count, hematocrit, and hemoglobin concentration were significantly increased in the 2.93 ppm group. The treatment-related histological lesions reported were degeneration and necrosis of the bronchial and bronchiolar epithelia at 2.93 ppm and hypertrophy of these epithelia at 1.58 ppm. Thus the primary target organ was the respiratory tract and the subchronic NOAEL was 0.67 ppm (4.5 mg/m^3). (Eyelid closure and decrease in motor activity were seen in all exposure groups only during exposure. No morphological changes were seen at 0.67 ppm, so the authors deemed the behavior changes minor and not toxicologically important.)

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; unexposed control groups had 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 (RD_{50}) (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 hematocrits 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. The authors considered the NOAEL to be 8 mg/kg/day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer and Benson (1995)
Study population	CD-1 mice (60 per sex per dose)
Exposure method	Discontinuous inhalation (0, 0.1, 0.5 or 1.0 ppm)
Critical effects	Nasal rhinitis; bronchiectasis
LOAEL	0.5 ppm
NOAEL	0.1 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	107 weeks
BMC_{05}	0.042 ppm
Average experimental exposure	0.0075 ppm at the BMC_{05} (0.042 x 6/24 x 5/7)
Human equivalent concentration	0.0016 ppm at the BMC_{05} (gas with extrathoracic respiratory effects, RGDR = 0.21 based on MV = 0.044 L/min and SA(ET) = 3 cm^2)
LOAEL uncertainty factor	not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3 (since RGDR adjustment was made)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 ppb (0.4 $\mu g/m^3$)

The data on bronchiecstasis incidence in male and female mice were combined and the chronic REL for chloropicrin was developed using the BMC approach. Of the several models tested, the Gamma MultiHit Model gave the best fit to the combined bronchiecstasis data (p = 0.9750). The MLE_{05} was 0.070 ppm and the BMC_{05} was 0.042 ppm. Use of time extrapolation to equivalent continuous exposure, an RGDR adjustment for the area of the respiratory tract affected, and a total uncertainty factor of 30 resulted in a chronic REL of 0.05 ppb (0.4 $\mu g/m^3$).

The chronic study in mice (Burleigh-Flayer *et al*., 1995) yielded the same NOAEL of 0.1 ppm as the chronic study in rats (Burleigh-Flayer and Benson, 1995). Use of the mouse data with the NOAEL/UF approach led to a cREL estimate of 0.1 ppb. Use of the rat data yielded a chronic REL estimate of 0.2 ppb by the NOAEL/UF approach.

As another comparison, the study of Yoshida *et al*. (1987) found a NOAEL in rats of 0.67 ppm for intermittent exposure for 13 weeks. This is equivalent to a continuous exposure of 120 ppb.

Use of an RGDR of 0.25 for rats and a total uncertainty factor of 100 (3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL estimate of 0.03 ppb (0.2 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the REL for chloropicrin 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 in rats and mice. Major areas of uncertainty are the lack of adequate human exposure data, limited reproductive toxicity data, and the appropriateness of time extrapolation of concentrations that cause irritative effects such as rhinitis.

VIII. Potential for Differential Impacts on Children's Health

Chloropicrin is a respiratory irritant. Respiratory irritants often have steep dose-response curves. Thus use of the human intraspecies factor of 10 should result in a REL that adequately protects children. Exacerbation of asthma, which has a more severe impact on children than on adults, is a known response to some respiratory irritants. However, there is no direct evidence in the literature to quantify such a response to chloropicrin, or to quantify a differential effect of chloropicrin on infants or children. We are currently evaluating our risk assessment methodologies, in particular the intraspecies uncertainty factor (UF_H), for adequacy in protecting infants and children. While we have not so far identified any indications that the currently used UF_H of 10 might be less than adequate to protect infants and children, this possibility should be considered in evaluating any exposure situation involving chronic exposures of infants or children to chloropicrin.

IX. 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 RD_{50} 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.

CDPR. 2000. California Department of Pesticide Regulation. Review of Burleigh-Flayer et al. (1995) Chloropicrin: Vapor inhalation oncogenicity study in CD-1 mice.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

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.

DPR. 2000. California Department of Pesticide Regulation. Summary of Pesticide Use Report Data – 1999. Sacramento: DPR.

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.

Tomlin, C.D.S. (ed.). 1994. The Pesticide Manual - World Compendium. 10th ed. Surrey, UK: The British Crop Protection Council. p. 192.

Yoshida M, Ikeda T, Iwasaki M, Ikeda M, Harada T, Ebino K, Tsuda S and Shirasu. 1987. Subchronic inhalation toxicity of chloropicrin vapor in rats. J. Pesticide Sci. 12:673-681.