PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

BERYLLIUM AND BERYLLIUM COMPOUNDS

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Public Health Goal for
Beryllium and Beryllium Compounds in Drinking Water

NOT A REGULATORY STANDARD

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PREFACE

Drinking Water Public Health Goals
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that can cause chronic disease shall be based upon currently available data and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.

10. PHGs published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR BERYLLIUM AND BERYLLIUM COMPOUNDS IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 1 µg/L (1 ppb) for beryllium in drinking water. This is based on lesions in the gastrointestinal tract of beagle dogs given beryllium in the diet. Public-health protective concentrations were estimated based on a no-observed-adverse-effect level (NOAEL) of 0.15 mg/kg per day and a benchmark dose calculation of the same data, yielding a 95% lower confidence limit on the five percent incidence level for beryllium-associated lesions of 0.20 mg/kg-day. The lowest-observed-adverse-effect level (LOAEL) for this effect was 1.5 mg/kg-day. For both calculations an uncertainty factor of 1,000 was used, which accounts for differences between species (3)[1], intraspecies variability (10), data deficiencies (3), and carcinogenic potential of ingested beryllium (10), and the same health-protective value is derived by both methods, 1 ppb (rounded). In calculating the PHG, it was assumed that dermal uptake of beryllium from water is negligible. The PHG level is also protective against potential carcinogenic effects from inhalation exposures to beryllium aerosols in showering and in other household uses of water.

Exposure to beryllium by the oral route also produced mild anemia and bone marrow hypoplasia in dogs at a dose rate of 12 mg/kg-day, and produced osteoporosis in rats at a dose of 10 mg/kg-day or higher. Exposure to airborne particles containing beryllium has been shown to cause lung cancer in both humans and experimental animals. Beryllium and certain beryllium compounds have also been shown to produce bone cancer (osteosarcoma) following intravenous injection or injection directly into bone in rabbits. After review of scientific evidence, it was determined that there is not an adequate basis for estimating a carcinogenic potency for exposure to beryllium or beryllium compounds in drinking water.

INTRODUCTION

The purpose of this document is to describe the development of a PHG for beryllium and beryllium compounds in drinking water. The federal MCL for beryllium or beryllium compounds, established in 1992, is 4 µg beryllium per liter (4 ppb), and the federal MCLG is also set at this level. In 1994, the federal standard of 4 ppb was adopted as the California MCL for beryllium and beryllium compounds. The U.S. EPA (1998a,b) has established a reference dose (RfD) of 0.002 mg/kg-day, which was derived from the same feeding study in male and female beagle dogs used for developing the proposed PHG.

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[1] "3" means one-half log unit, or half of 10 on a logarithmic scale; in this notation, 3 x 3 = 10 (or literally, 3.1623 x 3.1623 = 10).

On October 1, 1987, beryllium and beryllium compounds were placed on the list of chemicals known to the State of California to cause cancer, as required under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The International Agency for Research on Cancer (IARC) has classified beryllium and beryllium compounds in IARC group 1 (carcinogenic to humans) based on sufficient evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in experimental animals. U.S. EPA's Office of Water has classified beryllium and beryllium compounds in group B1 (probable human carcinogen) (ASTDR, 2002). However, the U.S. EPA's more recent evaluation (U.S. EPA, 1998a,b) concluded that the human carcinogenic potential of ingested beryllium could not be determined.

CHEMICAL PROFILE

Chemical Identity

Beryllium is the fourth element in the periodic table. In its oxidized state, it forms a large number of compounds. The chemical formula, synonyms, and Chemical Abstracts Service (CAS) Registry numbers of beryllium compounds formed during the refining of beryllium or used in commerce are listed in Table 1 (U.S. EPA, 1998b).

Physical and Chemical Properties

Beryllium is the lightest chemically stable metal. It melts at a higher temperature and is harder than steel but is more brittle. Copper alloys containing two percent beryllium are six times harder than copper and are resistant to oxidation. Aluminum alloys containing 4.5-6.0 percent beryllium are lightweight and are stronger than aluminum. Beryllium oxide is used to make ceramics and ceramic coatings that can withstand high temperatures and are resistant to corrosion (IARC, 1993).

Naturally-occurring beryllium is oxidized and is found in more than 40 minerals. Examples of naturally occurring beryllium compounds are beryl ($3BeO.Al_2O_3.6SiO_2$), bertandite ($4BeO.2SiO_2.H_20$), emerald, and aquamarine (IARC, 1993). The chemical formula and physical properties of beryllium and beryllium compounds are listed in Table 2.

Production and Uses

Beryllium is produced from beryl ore by melting the ore, quenching the melted ore in water, reheating to 900 ^oC, and extracting beryllium (as beryllium hydroxide) in sulfuric acid. The next step in beryllium metal production is formation of beryllium fluoride by dissolving beryllium hydroxide in a solution of ammonium hydrogen fluoride. This produces ammonium tetrafluoroberyllate as a precipitate, which upon heating decomposes to yield beryllium fluoride and ammonium fluoride. Heating beryllium fluoride with magnesium produces metallic beryllium.

Table 1. Chemical Identity of Beryllium and Its Compounds (U.S. EPA, 1998b)

Chemical name	Chemical formula	CAS Registry number	Synonyms
Beryllium metal	Be	7440-41-7	Beryllium element; beryllium metallic; glucinium; glucinum
Beryllium-aluminum alloy	Al.Be	12770-50-2	Aluminum alloy, nonbase, Al, Be; aluminum-beryllium alloy
Beryllium-copper alloy	Be.Cu	11133-98-5	Copper alloy, base, Cu,Be; copper-beryllium alloy
Beryl	$Al_2Be_3(SiO_3)_6$	1302-52-9	Beryllium aluminosilicate; beryllium aluminum silicate
Beryllium chloride	$BeCl_2$	7787-47-5	Beryllium dichloride
Beryllium fluoride	BeF_2	7787-49-7	Beryllium difluoride
Beryllium hydroxide	$Be(OH)_2$	13327-32-7	Beryllium dihydroxide
Beryllium sulfate	$BeSO_4$	13510-49-1	Sulfuric acid, beryllium salt (1:1)
Beryllium sulfate tetrahydrate	$BeSO_4.4H_2O$	7787-56-6	Sulfuric acid, beryllium salt (1:1), tetrahydrate
Beryllium oxide	BeO	1304-56-9	Beryllia; beryllium monoxide Thermalox™
Beryllium carbonate basic	$BeCO_3.Be(OH)_2$	1319-43-3	Carbonic acid, beryllium salt, mixture with $Be(OH)_2$
Beryllium nitrate	$Be(NO_3)_2$	13597-99-4	Beryllium dinitrate; nitric acid, beryllium salt
Beryllium nitrate trihydrate	$Be(NO_3)_2.3H_2O$	7787-55-5	Nitric acid, beryllium salt, trihydrate
Beryllium nitrate tetrahydrate	$Be(NO_3)_2.4H_2O$	13510-48-0	Beryllium dinitrate tetrahydrate; nitric acid, beryllium salt, tetrahydrate
Beryllium phosphate	$BeHPO_4$	13598-15-7	Phosphoric acid, beryllium salt (1:1)
Beryllium silicate	$Be_2(SiO_4)$	13598-00-0	Phenazite; phenakite
Zinc beryllium silicate	Unspecified	39413-47-3	Silicic acid, beryllium zinc salt

Table 2. Physical and Chemical Properties of Beryllium and Its Compounds (from U.S. EPA, 1998b)

Chemical name	Molecular weight	Melting point (^oC)	Physical description	Density (g/cm^3)	Solubility
Beryllium metal	9.0122	1287	Grey, close-packed, hexagonal, brittle metal	1.85 (20 ^oC)	Sol in most dilute acids and alkali; decomposes in hot water; insol in mercury and cold water
Beryllium chloride	79.92	399.2	Colorless to slightly yellow, orthorhombic, deliquescent crystal	1.8899 (25 ^oC)	Sol in water, ethanol, diethyl ether and pyridine; sl sol in benzene, carbon disulfide and chloroform; insol in acetone, ammonia and toluene
Beryllium fluoride	47.01	555	Colorless or white, amorphous, hygroscopic solid	1.986	Sol in water, sulfuric acid, mixture of ethanol and diethyl ether; sl sol in ethanol; insol in hydrofluoric acid
Beryllium hydroxide	43.03	138	White, amorphous, amphoteric powder	1.92	Sol in hot concentrated acids and alkali; sl sol in dilute alkali; insol in water
Beryllium sulfate	105.07	550	Colorless, crystal	2.443	Forms sol tetrahydrate in hot water, insol in cold water
Beryllium sulfate tetrahydrate	177.14	NR	Colorless tetragonal crystal	1.713	Sol in water, sl sol in concentrated sulfuric acid; insol in ethanol
Beryllium oxide	25.01	2530	Colorless to white, hexagonal crystal or amorphous, amphoteric powder	3.01 (20 ^oC)	Sol in concentrated acids and alkali; insol in water
Beryllium carbonate	69.02	NR	NR	NR	Sol in acids and alkali; insol in cold water; decomp in hot water
Beryllium carbonate basic	112.05	NR	White powder	NR	Sol in acids and alkali; insol in cold water; decomp in hot water
Beryllium nitrate, trihydrate	187.97	60	White to faintly yellowish, deliquescent mass	1.56	V sol in water and ethanol
Beryllium phosphate	104.99	NR	NR	NR	Sl sol in water

sol = soluble; sl sol = slightly soluble; insol = insoluble; v sol = very soluble; decomp = decomposes

Beryllium sulfate tetrahydrate is produced by dissolving beryllium hydroxide in sulfuric acid. Beryllium sulfate is produced by heating beryllium sulfate tetrahydrate or by dissolving beryl ore in sulfuric acid. Beryllium nitrate is produced by dissolving beryllium hydroxide in nitric acid. Beryllium oxide is produced by heating beryllium sulfate tetrahydrate to 1150-1450 ^{o}C. Beryllium carbonate is produced by adding a beryllium salt to a solution of ammonium carbonate.

In 1989, U.S. mine shipments of beryllium ores were 184 metric tons of beryllium metal equivalent, and consumption of beryllium and beryllium compounds in the U.S. was estimated to be 230 metric tons of beryllium metal equivalent (ATSDR, 2002). Beryllium metal is used in nuclear reactors to reflect neutrons. It is used in windows for some X-ray tubes and is used in mirrors and other components of satellites. Beryllium-copper alloys are used to make moving parts of aircraft engines and to make electrical switches and relays. Beryllium-aluminum alloys are used in the manufacture of high-performance aircraft. Beryllium oxide is used for microelectronic substrates and transistor mountings. It is also used for the manufacture of crucibles and coatings that withstand high temperatures. Other uses are listed by Cunningham (1998).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Beryllium and beryllium compounds occur in air as aerosols, which can be produced during the mining of beryllium ore and during refining and processing beryllium ore and beryllium compounds. Solid waste or soil contaminated with beryllium can also be sources of beryllium-containing aerosols. Beryllium is a component of smoke from combustion of coal, cigarettes, and certain other sources (HSDB, 2002). Beryllium was detected in 12 percent of air samples collected from 16 cities, with concentrations ranging from 0.001 to 0.002 $\mu g/m^3$ in urban areas, versus 0.00013 $\mu g/m^3$ in more rural areas (U.S. EPA, 1980).

Soil

Beryllium (as beryllium-containing minerals) comprises 6 mg/kg of the earth's crust (Reeves, 1986). The major anthropogenic source is coal ash where the concentration is approximately 100 mg/kg. Beryllium concentrations in sediments from Lake Pontchartrain, Louisiana were 0.5-5.0 mg/kg dry sediment (Byrne and DeLeon, 1986), and concentration from Detroit River and Western Lake Erie sediment were 0.1-3.8 mg/kg dry sediment (Lum and Gammon, 1985).

Water

The beryllium concentration in one survey of drinking water throughout the U.S. was below the limit of detection (10 ng/L) in 94.6 percent of 1,588 samples analyzed. The

mean concentration in samples where beryllium was detected was 190 ng/L, and the range was 10 ng/L - 1,220 ng/L (U.S. EPA, 1980). In a survey of beryllium in New Jersey wells (1977-79), a mean concentration of 1 µg/L was detected, with a maximum concentration of 84 µg/L (HSDB, 2002). In California, beryllium was detected in 59 out of 9669 samples analyzed from 1984-2001, where the detection limit for the purpose of reporting (DLR) was 1 µg/L (DHS, 2002).

Food

Beryllium is commonly found as a trace element in foods. It was reported as 0.08 ppm in polished rice, 0.12 ppm in bread, 0.17 ppm in potatoes, 0.24 ppm in tomatoes, and 0.33 ppm in lettuce, all expressed on a dry weight basis (U.S. EPA, 1980). Its concentration in fresh corn and carrots was reported to be less than 25 ppb, the limit of detection in this study (Wolnick *et al*., 1984). The beryllium content of English sole from Commencement Bay near Tacoma, Washington was 6 ppb (Nicola *et al*., 1987). The beryllium level in cow's milk has been reported as 0.02 ppm in ash (U.S. EPA, 1980). Beryllium may be accumulated in some plants, being found at concentrations as high as 3 ppm in birch, aspen, and willow (HSDB, 2002). The average daily beryllium intake has been estimated as about 20 µg/day, mostly from foods (HSDB, 2002).

METABOLISM AND PHARMACOKINETICS

Absorption

In the study of Furchner *et al*. (1973) discussed in the section on elimination, the fraction of an orally-administered dose of beryllium that was detected in the urine excreted during the following two days by rats, monkeys and dogs was, respectively, 0.11, 3.71 and 0.38 percent. These data are consistent with the study of Reeves (1965) showing that rats given an oral dose of beryllium sulfate excreted less than 0.5 percent of the administered dose in their urine. These results suggest that only a small fraction of ingested beryllium is absorbed in the gastrointestinal (GI) tract. However, beryllium absorption in the GI tract cannot be accurately estimated from quantification of beryllium in urine because some absorbed beryllium is excreted in feces and some remains in body tissues. Finch *et al.* (1990) provide support for biliary excretion with their measurements of radiolabeled beryllium in the feces following an inhalation exposure. The authors reported that the predominant mode of excretion at early times after exposure was through the feces, with urinary excretion assuming predominance at later times.

The study of Furchner *et al*. (1973) presents additional data that can be used to estimate GI absorption. Furchner *et al*. (1973) administered carrier-free ^{7}Be as $BeCl_2$ to groups of mice, rats, dogs and monkeys by the oral route and by intravenous injection. The same substance was administered to mice and rats by intraperitoneal injection. Following intravenous injection of beryllium in monkeys, the amount recovered in urine during the six days following administration was 18.13 percent, and nearly all of this was detected

in urine excreted during the first two days. Assuming that the distribution and elimination of intravenous beryllium is identical to distribution and elimination of beryllium absorbed from the GI tract, the observed 3.71 percent urinary elimination in monkeys corresponds to an absorption of 20 percent in the GI tract. Lower estimates can be calculated for mice, rats and dogs from the data presented by Furchner *et al*. (1973).

Distribution

Finch *et al*. (1990) exposed beagle dogs to aerosols of beryllium oxide for up to 42 minutes. In dogs exposed to beryllium oxide calcined at 500 ^{o}C, approximately 16 percent of the dose initially deposited in the respiratory tract remained at this site and 16 percent was present in bone 180 days after treatment. For beryllium oxide calcined at 1,000 ^{o}C, 88 percent of the initial amount deposited remained in the lungs and 1.5 percent was in bone after 180 days. Following a single dose of beryllium oxide administered by inhalation, beryllium was detected in tracheobronchial lymph nodes in rats (Sanders *et al*., 1975) and in dogs (Finch *et al*., 1990). Following a single dose of beryllium oxide (calcined at 1,000 ^{o}C) by intratracheal instillation, small amounts of beryllium were detected in bone, liver, heart, and kidney (Clary *et al*., 1975). The two calcined forms of beryllium do have different chemical properties, which may account for the differences in absorption noted by Finch *et al* (1990).

In rats killed 24 hours after intravenous injection of carrier-free ^{7}Be as beryllium chloride at pH 2, 43 percent of the injected dose was in bone and bone marrow, four percent was in the liver, 0.1 percent was in the spleen, and 47 percent had been excreted predominantly in urine. When ^{7}Be was injected at pH 6, the fraction in liver was 25 percent and that in the spleen was one percent. Addition of unlabeled beryllium chloride to the radioactive beryllium chloride further increased the amount of beryllium in the liver, but addition of citrate reduced the amount taken up by the liver (Klemperer *et al*., 1952). At neutral pH, beryllium rapidly forms insoluble complexes with phosphate, and it is these complexes that appear to be taken up by phagocytic cells in the liver and spleen (Skilleter, 1984).

While the levels of trace elements in mother sera and umbilical cord were evaluated, Krachler *et al.* (1999) provide evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of several trace elements and toxins, including beryllium, were determined in umbilical cord (n = 29) and corresponding maternal sera (n = 29) as well as in colostrum (n = 27). The levels of beryllium in the umbilical cord serum and in colostrum were higher than in maternal serum.

Metabolism

Beryllium and beryllium compounds are not known to participate in metabolic reactions, but soluble beryllium compounds may form insoluble complexes (*e.g*., beryllium phosphate) within tissues (Reeves and Vorvald, 1967).

Excretion

Furchner *et al*. (1973) administered carrier-free ^{7}Be as $BeCl_2$ to groups of mice, rats, dogs and monkeys by the oral route and by intravenous injection. The same substance was administered to mice and rats by intraperitoneal injection. Beryllium excreted in feces and urine was measured and the dose remaining in the body was calculated. Following oral administration of carrier-free ^{7}Be as $BeCl_2$, at least 97 percent of administered beryllium was eliminated rapidly (half time of 0.1-0.4 days). In mice, rats, monkeys and dogs, urinary excretion was, respectively, 0.24, 0.11, 3.71, and 0.38 percent of the administered dose.

Following intravenous administration, there was an initial rapid phase of elimination with a half time of 0.2-0.5 days followed by a slow phase with a half time of 50-53 days. During the first day following administration (when rapid elimination occurred), the ratio of urinary elimination to fecal elimination in mice, rats, monkeys, and dogs was 3.5, 21.3, 4.0, and 48.6, respectively. However, on the second day, these decreased to 0.5, 1.0, 0.5, and 4.6, respectively. The ratio of cumulative urinary excretion to cumulative fecal excretion over the first 6-7 days in mice, rats, monkeys and dogs was, respectively, 2.7, 9.7, 1.7, and 10.2.

Following intraperitoneal administration in mice and rats, approximately 50 percent of the dose was eliminated during the initial phase with a half time of 0.3 days. This was followed by a slow phase with half time of 51-52 days. The ratio of urinary elimination to fecal excretion in mice and dogs was 3.2 and 10.2, respectively, and this ratio during the first seven days was 2.7 and 5.1, respectively. Following intratracheal injection of beryllium sulfate in rats, approximately 50 percent of the amount excreted was found in feces and approximately 50 percent was found in urine (Van Cleave and Kaylor, 1955), indicating that biliary elimination may be significant.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Oral

In rats, the acute LD_{50} for orally administered beryllium sulfate, beryllium chloride, beryllium fluoride and beryllium oxyfluoride was 120 mg beryllium/kg (Reeves, 1986), 200 mg beryllium/kg (Kimmerle, 1966), 18.8 mg beryllium/kg, and 18.3 mg beryllium/kg (Venugopal and Luckey, 1977), respectively. In mice, the acute oral LD_{50} was 140 mg beryllium/kg for beryllium sulfate (Ashby *et al*., 1990) and 18-50 mg beryllium/kg for beryllium fluoride (Kimmerle, 1966; Venugopal and Luckey, 1977; Reeves, 1986). The greater toxicity of beryllium fluorides may be largely due to the fluoride ion (ATSDR, 1993b).

Inhalation

Rats and mice exposed for one hour to a beryllium sulfate aerosol (1.1 mg Be/m^3) were killed and examined on days 1 to 21 after exposure (Sendelbach *et al*., 1986). DNA synthesis increased to a maximum eight days after exposure in rats and five days after exposure in mice. Cell proliferation in rats involved type II alveolar cells, interstitial cells and capillary endothelial cells, and there was an increase in the number of macrophages and neutrophils. In mice, there was proliferation of interstitial and capillary endothelial cells and an increase in the number of macrophages.

Sendelbach *et al*. (1989) exposed male rats to an aerosol of beryllium sulfate (4.05 mg beryllium/m^3) for one hour and observed the course of lung injury by assaying bronchoalveolar lavage fluid. The concentration of alkaline phosphatase and lactate dehydrogenase peaked three months after exposure. Histopathologic examination revealed a progressive focal pneumonitis characterized by infiltration of macrophages and neutrophils.

Haley *et al*. (1989) administered a single inhalation dose of BeO to groups of dogs and examined the lungs of dogs killed 8, 32, 64, 180 and 365 days after exposure. Perivascular and peribronchiolar lymphocytes and macrophages were seen in lung tissue eight days after exposure. In animals killed 32 days or more after exposure, microscopic granulomas were seen in lung tissue. Following administration to dogs of a single dose of BeO by inhalation, Haley *et al*. (1997) incubated lymphocytes from blood or bronchoalveolar lavage fluid in the presence of irradiated monocytes and $BeSO_4$ and derived cell lines from lymphocytes that proliferated during this incubation. These lymphocyte cell lines proliferated in the presence of $BeSO_4$ but not in the presence of $ZnSO_4$ or $NiSO_4$.

Haley *et al*. (1990) exposed rats for 50 minutes to an aerosol of 0.8 mg/m^3 beryllium metal and examined animals 3, 7, 10, 14, 31, 59, 115 and 171 days after exposure. The initial reaction was a necrotizing hemorrhagic pneumonitis that peaked at 14 days. At 31 days, necrotizing inflammatory lesions were minimal. At 59 days, necrotizing inflammatory lesions were again noted, and these became progressively more severe.

Nikula *et al*. (1997) administered a single dose of beryllium metal by inhalation to strain A/J mice and to strain C3H/HeJ mice. Histopathological examination of the lungs of mice killed six months after exposure found granulomatous pneumonia in both strains. Microscopic granulomas were present in interstitial regions as were infiltrates of lymphocytes and plasma cells. Lymphocytes in granulomas displayed the T-helper phenotype. Neutrophils, macrophages, and giant cells were seen in alveoli.

Dermal

Marx and Burrell (1973) administered 0.5 µg beryllium sulfate to guinea pigs by intradermal injection on two days per week for 12 weeks and then applied beryllium fluoride, beryllium sulfate and beryllium oxide at doses of 0.48, 0.25 and 1.8 µg, respectively, to the surface of the skin. Each beryllium compound initiated an inflammatory reaction at the site of application characterized by the accumulation of giant cells, histiocytes, eosinophils, and lymphocytes. Similar results were reported by

Belman (1969) following sensitization of guinea pigs by dermal or intradermal administration of beryllium fluoride followed by topical application of beryllium chloride or beryllium fluoride.

Intravenous

Intravenous administration of 0.5 mg/kg beryllium (as beryllium sulfate) was lethal in rats, and administration of 0.75 mg/kg beryllium was lethal in rabbits (Aldridge *et al.*, 1950). The cause of death was liver failure.

Subchronic Toxicity

Administration of beryllium carbonate in feed to groups of rats at dose rates calculated to be 10, 20, 40, 80, 160 or 240 mg beryllium per kg per day for 24-28 days resulted in fragility of bones that increased in severity with increasing dose. The bone pathology appeared to be similar to human osteoporosis (Guyatt *et al*., 1933). Administration of beryllium carbonate in feed to rats at dose rates of 141 or 242 mg beryllium per kg per day for 42 days also produced osteoporosis (Jacobson, 1933). These authors noted that beryllium in the diet may form an insoluble complex with dietary phosphate and that this may result in inadequate phosphate for normal bone formation.

Immunotoxicology

As noted in the section on acute toxicity, intradermal administration of beryllium compounds to guinea pigs results in a delayed hypersensitivity reaction when beryllium compounds are applied to the skin of previously treated animals. Inhalation studies reviewed in the section on acute toxicity demonstrate granuloma formation in the lungs of dogs and mice given beryllium by the respiratory route. As reviewed by Finch *et al*. (1996), there are similarities between beryllium-induced lung disease in these species and chronic beryllium disease. The human lung effects are discussed in the section on toxicological effects in humans.

Developmental and Reproductive Toxicity

Mathur *et al*. (1987) administered 0.021 mg/kg beryllium nitrate by intravenous injection to groups of female Sprague-Dawley rats on day 1, 11, 12, 13, 15 and 17 of gestation. Beryllium injection on day 11 resulted in fetal death. Following injection on day 1, 12, 13, 15, and 17, fetuses survived but all pups died within three days of delivery. The dose in this experiment is equivalent to 0.045 mg beryllium per kilogram, which is approximately one-tenth the intravenous LD_{50} for rats. Other parenteral studies (as reviewed by U.S. EPA, 1991) have found developmental effects (increased fetal mortality, decreased fetal body weight, internal abnormalities, and delayed neurodevelopment) in the offspring of rodents following intratracheal or intraperitoneal administration of beryllium chloride, beryllium oxide, or beryllium sulfate during gestation.

Chronic Toxicity and Carcinogenicity

Oral

Schroeder and Mitchener (1975a) administered beryllium sulfate at a beryllium concentration of five ppm in drinking water to 52 male and 52 female Long-Evans rats, starting at the time of weaning and continuing until natural death occurred. Groups of 52 males and females were observed as controls. The dose rate for groups given 5 ppm beryllium was calculated to be 0.63 and 0.71 mg beryllium/kg per day for males and females, respectively. At death, animal weight was recorded, and gross necropsy was performed. Heart, lung, kidney, liver, spleen, and tumor tissues were examined histopathologically. No signs of systemic toxicity were reported in treated animals. Average body weight and life span were not reduced in treated animals as compared to control animals. The incidence of tumors at all sites in the control group and treated group of males was 4/26 and 9/33, respectively, and was 17/24 and 14/17 in control and treated females, respectively. The authors classified animals with multiple tumors as malignant-tumor-bearing animals. With this definition, the incidence of malignant tumors in males was 2/26 and 4/33 in control and treated rats, respectively, and in these groups of females was 8/24 and 8/17. None of the increased incidences is statistically significant. The NOAEL for this study would be 0.63 mg/kg-day for the males and 0.71 mg/kg-day for the females. No explanation is given for the large differences between the number of animals in treatment groups and the number of animals examined for tumors.

Morgareidge *et al*. (1975, 1977) administered beryllium sulfate in feed to groups of 50 male and 50 female Wistar rats for 104 weeks at beryllium concentrations of 0, 5, 50, or 500 ppm. The doses corresponded to 0.36, 3.6, and 37 mg/kg-day for males in the 5, 50, and 500 ppm groups, and 0.42, 4.2, and 43 mg/kg-day for females in the 5, 50, and 500 ppm groups, respectively. No statistically significant increases in tumors were found in groups of treated rats. There was a small decrease in body weight (within 10 percent of control body weights) of high-dose males compared to controls and decreases in mean weight of the liver and kidneys in this group. No other treatment-related effects were found. The NOAELs for this study were 37 and 42 mg/kg-day for the males and females, respectively.

Schroeder and Mitchener (1975b) administered beryllium sulfate in drinking water at beryllium concentrations of 0 or five ppm to groups of 54 male and 54 female Swiss mice, starting at weaning (18-20 days of age) and continuing until natural death occurred. The dose rate for groups given 5 ppm beryllium was calculated to be 1.2 mg beryllium/kg-day for both sexes. At death, animal weight was recorded, and gross necropsy was performed. Heart, lung, kidney, liver, and spleen were examined histopathologically. No statistically significant increases in tumor incidence were noted in males (11/38 in control and 17/48 in treated mice) or in females (14/47 in control and 20/52 in treated mice), and no signs of systemic toxicity were reported in treated animals. Average body weight and life span were not reduced in treated animals as compared to control animals. The NOAEL for this study was 1.2 mg/kg-day.

Morgareidge *et al*. (1976) administered beryllium sulfate in feed to groups of five male and five female beagle dogs (aged 8 to 12 mo) at concentrations of 0, 5, 50, or 500 ppm beryllium. Animals in the high-dose groups were killed and examined after 33 weeks because signs of severe toxicity were noted. At this time, a replacement group of 5 male and 5 female dogs was added. This group was fed a diet containing 1 ppm beryllium for a period of 143 weeks. In the other groups, the study was terminated at 172 weeks. From measured body weights and food consumption, the dose rate in dogs administered 1, 5, 50 or 500 ppm beryllium was calculated to be 0.023, 0.12, 1.1 or 12 mg/kg-day, respectively, in males and 0.029, 0.15, 1.3 or 17 mg/kg-day in females. Individual animal examinations included hematology, clinical chemistry and urine analysis, organ weight measurement, and histopathology. In animals receiving the high dose, lesions of the small intestine were found in four of five males and in all five females (Table 3). Pathological changes included edema and desquamation, necrosis and ulceration of the epithelium, acute and chronic inflammation, and fibrin thrombi. Bone marrow hypoplasia, accompanied by mild anemia, and vasculitis of the liver were also found. One female dog given 50 ppm beryllium died during week 71 and was found to have gastrointestinal lesions that were qualitatively similar to those seen in high-dose animals but were less severe. The study authors believed these lesions to be treatment-related. No treatment-related lesions were found in other animals given 50 ppm beryllium, and no treatment-related adverse effects were found in animals given 5 ppm beryllium. This concentration was established as the NOAEL (0.15 mg/kg-day) and will be used in the calculation of the proposed PHG.

Table 3. Incidence of Lesions of the Small Intestines in Dogs (N = 5/group/sex) Fed Beryllium (Morgareidge et al., 1976)

Treatment Group	Dose	Sex	Incidence
0 ppm	0	Male	0
	0	Female	0
1 ppm	0.023	Male	0
	0.029	Female	0
5 ppm	0.12	Male	0
	0.15	Female	0
50 ppm	1.1	Male	0
	1.3	Female	1
500 ppm	12.2	Male	4
	17.4	Female	5

Inhalation and intratracheal instillation

The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence for the carcinogenicity of beryllium in experimental animals (IARC,

1993). The summary of evidence stated "Beryl ore and bertandite ore were tested for carcinogenicity in rats, hamsters and monkeys by inhalation exposure in three experiments in one study. Beryl ore was shown to produce malignant and benign lung tumors in rats. The experiments in hamsters and monkeys were inadequate for evaluation, as were all experiments with bertandite ore."

"In one study in rats by single intratracheal instillation, beryllium metal, passivated beryllium metal (99% beryllium, 0.26% chromium as chromate) and beryllium-aluminum alloy (62% beryllium) produced dose-related increases in lung tumors, which were mostly adenocarcinomas and adenomas."

"Various beryllium compounds were tested by inhalation in five studies in rats, rabbits and monkeys. In two studies in rats, beryllium sulfate tetrahydrate produced lung tumors, which were mostly adenocarcinomas. In one study, both beryllium oxide and beryllium chloride produced dose-related increases in the incidence of malignant epithelial lung tumors in rats. The studies in rabbits and monkeys were considered to be inadequate for evaluation. Beryllium hydroxide and low- and high-temperature-fired beryllium oxide were tested in rats by intratracheal instillation; beryllium hydroxide produced lung adenocarcinomas and adenomas in one study, and low-temperature-fired (below 900°C) beryllium oxide produced malignant lung tumors in two studies."

Intravenous injection

The IARC (1993) review of evidence for carcinogenicity stated "Rabbits given intravenous injections of beryllium metal and various compounds of beryllium (zinc beryllium silicate, beryllium silicate, beryllium oxide and beryllium phosphate) developed osteosarcomas." This refers to the study by Araki *et al*. (1954). Basically, the authors gave a single *i.v*. injection of one g beryllium phosphate and found that osteosarcomas developed in two of four rabbits within 18 months. No bone tumors occurred in three untreated rabbits. Similar findings were obtained in rabbits treated by implantation or injection into the bone of beryllium oxide, zinc beryllium silicate, and beryllium carbonate.

Genetic Toxicity

In the *Salmonella typhimurium* mutagenesis test, beryllium chloride produced conflicting results in strains TA1537 and TA2637 in the absence of metabolic activation. It did not produce mutations in strains TA98, TA100, TA102 and TA1535 in the absence of metabolic activation (Ogawa *et al.*, 1987). It did not produce mutations in TA98 in the presence of metabolic activation (Kuroda *et al*., 1991). In the *Bacillus subtilis rec* assay, it inhibited growth when spores were used but not when vegetative calls were used (Nishioka, 1975; Kuroda *et al*., 1991). In *Escherichia coli,* it did not induce prophage (Rossman *et al*., 1984), and it produced mutations in one strain but not in another (Zakour and Glickman, 1984; Rossman and Molina, 1986). It produced mutations and sister chromatid exchanges in Chinese hamster V79 cells *in vitro* (Miyaki *et al*., 1979; Kuroda *et al*., 1991), and it produced chromosomal aberrations in swine lymphocytes *in vitro* (Vegni-Talluri and Guigiani, 1967).

In the *Salmonella typhimurium* mutagenesis test, beryllium nitrate did not produce mutations in strain TA100 in the absence of metabolic activation (Tso and Fung, 1981), and it did not produce mutations in TA98 and TA100 in the presence or absence of metabolic activation (Kuroda *et al*., 1991). It produced growth inhibition in the *Bacillus subtilis* spores *rec* assay and caused sister chromatid exchanges in Chinese hamster V79 cells *in vitro* (Kuroda *et al*., 1991).

In the *Salmonella typhimurium* mutagenesis test, beryllium sulfate produced conflicting results in strain TA100 (Simmon, 1979; Dunkel *et al*., 1984; Arlauskas *et al*., 1985; Ashby *et al.,* 1990). It did not produce mutations in other *Salmonella* strains (Simmon, 1979; Rosenkranz and Poirier, 1979; Dunkel *et al*., 1984; Arlauskas *et al*., 1985; Ashby *et al.,* 1990) and did not produce mutations in *Escherichia coli* WP2 (Dunkel *et al*., 1984). It transformed mammalian cells *in vitro* (Pienta *et al*., 1977; DiPaola and Casto,1979; Dunkel *et al*., 1981) and produced sister chromatid exchanges (Larramendy *et al*., 1981). It produced conflicting results in tests for chromosomal aberrations (Paton and Allison, 1972; Larramendy *et al*., 1981; Brooks *et al*., 1989; Ashby *et al*., 1990) and did not produce mutations in mammalian host-mediated *Salmonella typhimurium* mutagenesis tests (Simmon *et al*., 1979).

Beryllium oxide did not produce mutations in the *Salmonella typhimurium* mutagenesis test and did not inhibit growth in the *Bacillus subtilis* spore *rec* assay (Kuroda *et al*., 1991). Beryllium oxide did produce DNA strand breaks in rat tracheal epithelial cells and transformed mammalian cells *in vitro* (Steele *et al*., 1989). It did not produce sister chromatid exchanges in Chinese hamster V79 cells (Kuroda *et al*., 1991).

Interpretation of *in vitro* tests for genotoxicity of beryllium salts is complicated by the low solubility of beryllium phosphate. Because phosphate is the source of the essential element phosphorus in these tests, addition of a beryllium salt may result in inadequate concentrations of bioavailable phosphate (Rosenkranz and Poirier, 1979).

Toxicological Effects in Humans

Noncarcinogenic Effects

Oral

No reports documenting human beryllium poisoning following exposure to beryllium or beryllium compounds by the oral route have been identified.

Inhalation

Acute exposure to the soluble beryllium compounds beryllium sulfate and beryllium fluoride at concentrations greater than 0.1 mg beryllium/m^3 has been associated with pneumonitis (Eisenbud *et al*., 1948). In general, exposure to beryllium can result in two types of non-neoplastic respiratory disease: acute beryllium disease (berylliosis) and chronic beryllium disease (chronic berylliosis; CBD). Acute berylliosis is usually associated with exposure to high concentrations of soluble beryllium compounds like those described by Eisenbud *et al*. (1948). This type of disease is a fulminating

inflammatory reaction of the entire respiratory tract with symptoms ranging from mild nasopharyngitis to a severe chemical pneumonitis (ASTDR, 2002). With the initiation of strict exposure limits in 1950, the syndrome of acute beryllium disease has been practically eliminated in the workplace (ASTDR, 2002).

Chronic beryllium disease (CBD) is a progressive lung disease characterized by formation of non-caseating granulomas that contain beryllium (Rossman, 2001; Newman *et al*., 1996; IARC, 1993). CBD is only observed in individuals who are sensitized to beryllium (usually <15% of an exposed population (ASTDR, 2002). The disease results from a hypersensitivity response to some antigenic form of beryllium (termed beryllium antigen) and the presence of beryllium antigen in the lung. The immune response is mediated by subsets of T-helper cells (CD4+ T cells) that recognize and respond to beryllium antigen by initiating a type IV (delayed hypersensitivity) allergic response (Fontenot *et al*., 2001; Fontenot *et al*., 2000; Fontenot *et al*., 1999; Fontenot *et al*., 1998; Tinkle, Schwitters and Newman, 1996).

Susceptibility to CBD is associated with specific alleles of a class II histocompatibility gene that are expressed on the surface of cells presenting antigens to lymphocytes (Fontenot *et al*., 2000; Wang *et al*., 1999). These alleles have been identified as HLA DP alleles (Fontenot *et al*., 1998) that are part of the major histocompatibility complex (MHC). Furthermore, sensitivity to beryllium is highly associated with the presence of a glutamic acid codon at position 69 of the DPB1 gene: In one study of 25 beryllium-sensitive individuals, 22 possessed a HLA DPB1 allele with a glutamic acid codon at position 69 (Wang *et al*., 1998, 2001). In another study of 25 beryllium-sensitive individuals, all possessed a HLA DPB1 allele with a glutamic acid codon at position 69 (Lombardi *et al*., 2001).

As reviewed by Rossman (2001), a glutamic acid codon at position 69 of the HLA DPB1 gene is present in 30-40 per cent of individuals in control populations. This suggests that 30-40 percent of the U.S. population may be susceptible to beryllium sensitization. Populations of beryllium-exposed individuals with frequencies of beryllium sensitization in this range have not been identified. Frequencies as high as 11.4 and 11.9 per cent were found in beryllium machinists and health physics technicians, respectively, who were formerly employed at a nuclear weapons manufacturing facility (Kreiss *et al*., 1993; Stange *et al*., 2001). The frequency of beryllium-sensitization was 9.4 per cent in workers at a beryllium machining plant (Newman *et al*., 2001) and was 9.9 per cent in workers at a beryllium ceramics plant (Henneberger *et al*., 2001).

More recently, Rossman *et al.* (2002) have suggested that the susceptibility to beryllium hypersensitivity and its progression to CBD may be due to presence of certain alleles (e.g., HLA-DPB1, HLA-DQB1, and/or HLA-DRB1). In their study, Rossman *et al*. (2002) performed DNA-based typing of HLA-DPB1, HLA-DQB1, and HLA-DRB1 loci on 55 subjects with beryllium hypersensitivity and compared this with the results for 82 beryllium-exposed workers with no evidence of beryllium hypersensitivity. Their results suggest that not all individuals with beryllium hypersensitivity will develop CBD.

Carcinogenicity

Oral

Studies regarding the association between cancer incidence and exposure to beryllium in drinking water or food in human populations were not found.

Inhalation

Evidence for carcinogenicity of beryllium in humans was judged by IARC (1993) to be sufficient. The data supporting this conclusion are published in epidemiological studies of workers exposed to beryllium compounds by inhalation (Wagoner *et al*., 1980; Ward *et al*., 1992). The IARC (1993) summary of evidence from the studies states "In an early series of cohort mortality studies of workers at two beryllium extraction, production and fabrication facilities in the USA (Wagoner *et al.*, 1980), a consistent, marginally significant excess of deaths from lung cancer was observed. The excess increased with time since first exposure. In a more recent mortality analysis of some 9000 workers at seven beryllium plants in the USA, including the two plants studied previously (Ward *et al*. 1992), a small but significant excess in mortality from lung cancer was found in the total cohort. The risks for lung cancer were consistently higher in those plants in which there was also excess mortality for nonmalignant respiratory disease. Also the risk for lung cancer increased with time since first exposure, and was greater in workers first hired in the period when exposures to beryllium in the work place were relatively uncontrolled. Mortality from cancers at other sites was not increased. The association between lung cancer risk and exposure to beryllium was judged not to be confounded by smoking."

"Follow-up of deaths among workers entered into the US Beryllium Case Registry (which registered cases of acute beryllium-related pneumonitis and chronic beryllium-related nonmalignant lung disease, including cases from the plants mentioned above) revealed excess mortality from cases of lung cancer; the excess was greater in those who were entered into the Registry with acute beryllium pneumonitis. Potential confounding by smoking was addressed in several ways and did not appear to explain the increased risk for lung cancer. The results of the follow-up of the Case Registry subjects yielded a higher risk for lung cancer than had been found in the previous cohort mortality study of the seven production facilities."

"In a nested case-control study of cancers of the central nervous system among workers at two nuclear facilities in the USA, an increasing risk of cancer of the central nervous system was suggested with longer duration of employment in jobs with more highly ranked exposure to beryllium." However, none of the increased risks associated with potential beryllium exposure is statistically significant. More-detailed information on these studies can be found in the original articles and the IARC review.

U.S. EPA (1998a) concluded that the evidence for carcinogenicity of beryllium in humans is "limited," based on evaluation of the same cohort mortality studies reviewed by IARC (1993). The difference in evaluating the weight of evidence is based on the potential effects of confounding exposures in epidemiological studies of workers exposed

to beryllium: the U.S. EPA concluded that there was insufficient discussion or control of potential confounding exposures including exposure to tobacco smoke.

In a study published after the IARC and U.S. EPA evaluations, Sanderson *et al*. (2001) compared incidence of lung cancer with estimated beryllium exposure in workers at a beryllium alloy production plant. When exposure was calculated as total exposure 10 years or more before occurrence of lung cancer (10-year lag) or 20 years or more before cancer occurrence (20-year lag), the study authors found a statistically significant association between lung cancer incidence and beryllium exposure. The authors examined data on cigarette smoking habits of the workers and concluded that there was a lack of evidence for confounding by cigarette smoking.

Developmental and Reproductive Toxicity

Savitz *et al*. (1989) identified pregnancies in the 1980 U.S. National Survey of Natality and Infant Mortality where there was a maternal or paternal employment with possible exposure to beryllium or beryllium compounds. For the pregnancies with possible paternal exposure or for those with possible maternal exposure, the incidences of stillbirths, preterm births, and low birth weight were not increased above national incidences.

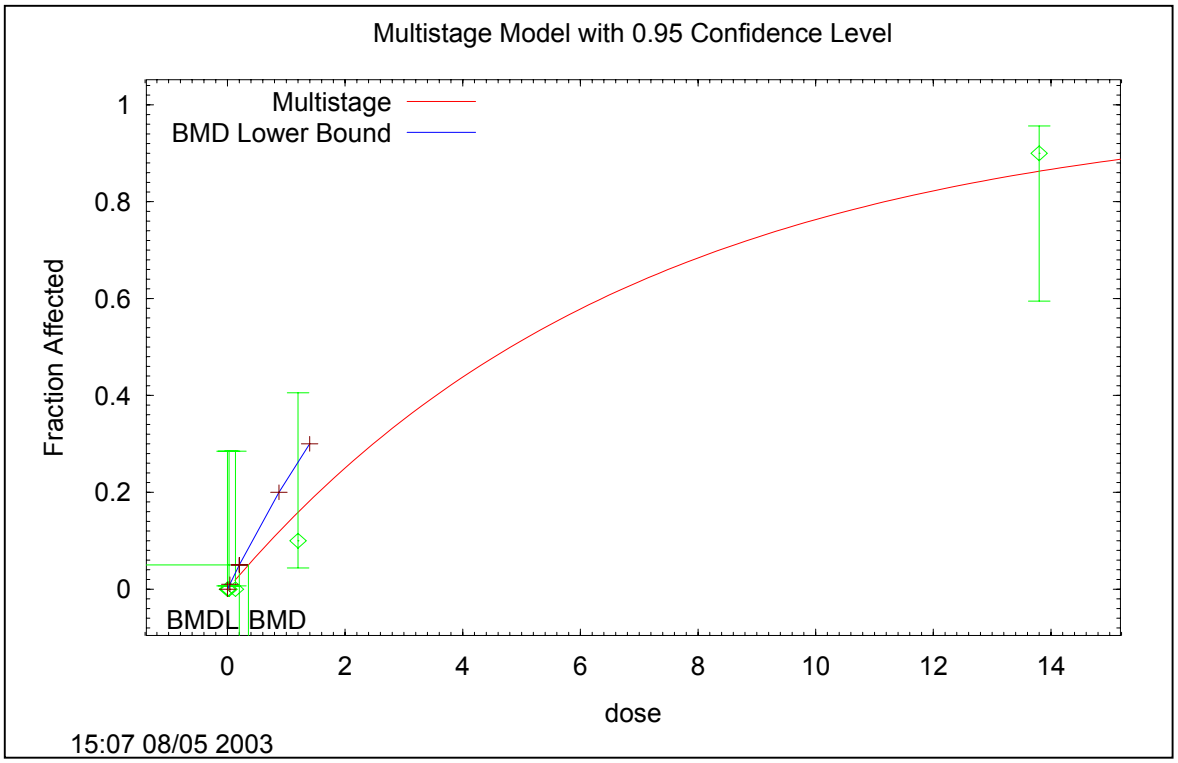
DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Toxic effects in laboratory animals exposed to beryllium or beryllium compounds in water or food are liver toxicity, osteoporosis, anemia, and ulceration and inflammation of the intestinal mucosa. The most sensitive target identified is the intestinal mucosa where the LOAEL in the chronic feeding study in female dogs was 1.3 mg/kg-day. The NOAEL observed in this study was 0.15 mg/kg-day (Morgareidge *et al.*, 1976). The dataset is described in Table 3.

A benchmark dose was also calculated for comparative purposes using U.S. EPA's Benchmark Dose Software 1.3.2 (U.S. EPA, 2003). The benchmark dose software was developed as a tool to facilitate the application of benchmark dose (BMD) methods. A goal of the BMD approach is to define a starting point for extrapolation to low doses, or point of departure (POD), for the estimation of a public-health protective exposure level. In this case, the calculated BMD reflects a 5 percent increase in the incidence of small intestinal lesions (BMD05), which we consider to be equivalent to a NOAEL. The most appropriate dose-response model (a multistage model) was used for the dataset in Table 3. Figure 1 (below) provides a graphical representation of the dose-response function and its lower 95 percent confidence limit (BMDL). A good fit of the first-degree multi-stage model to the data ($p = 0.9621$) was obtained. The BMDL05 calculated under these conditions was 0.20 mg/kg-day. The U.S. EPA (1998a,b) used the BMDL10 in their risk assessment, which was reported as 0.46 mg/kg-day.

Figure 1. Best fitting dose-response model for Morgareidge *et al*. (1986) data using U.S. EPA's Benchmark Dose software.



In lifetime studies of beryllium administered to laboratory rodents by the oral route, the NOAEL was 37 mg/kg-day for male rats given beryllium sulfate in feed (Morgareidge *et al.*, 1975, 1977), 0.63 mg/kg-day for male Long-Evans rats given beryllium sulfate in drinking water (Schroeder and Mitchener, 1975a), and 1.2 mg/kg-day for male and female Swiss mice given beryllium sulfate in drinking water (Schroeder and Mitchener, 1975b). However, these studies are severely limited for the purpose of defining a NOAEL because no toxic effects were noted.

Carcinogenic Effects

The U.S. EPA (1998b) estimated the carcinogenic potency of inhaled beryllium to be 2.4×10^{-3} $(\mu g/m^3)^{-1}$. The basis for this estimate was the incidence of lung cancer in workers exposed to beryllium aerosol (Wagoner *et al*., 1980). OEHHA has recalculated this as 8.4 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 1999). This inhalation potency factor can be applied to the estimation of beryllium cancer risk from inhalation of aerosol droplets in showering.

The U.S. EPA (1995) estimated an upper bound of 4.3 $(mg/kg\text{-}d)^{-1}$ for the potency of ingested beryllium. This estimate was made using the linearized multistage model and

was based on the incidence of tumors at all sites in male rats of the Schroeder and Mitchener (1975a) study. While it has not been a common practice for U.S. EPA to use a "negative" study as the basis for a potency estimate, there is some support for this procedure. In its proposed guidelines for carcinogen risk assessment, U.S. EPA states that it may be possible to obtain potency estimates from "negative" epidemiologic studies "to provide a check on the plausibility of available estimates based on animal tumor or other responses" (U.S. EPA, 1996). A "negative" animal bioassay can similarly be used to calculate the highest value of carcinogenic potency that is consistent with the data. While the U.S. EPA has not recommended that this be done, using a "negative" laboratory animal study to calculate an upper-bound potency estimate is consistent with the proposed guidelines and can help ensure that all relevant cancer data are considered.

The U.S. EPA has withdrawn its 1995 oral potency factor. In the April 3, 1998 IRIS update for beryllium and beryllium compounds, the U.S. EPA stated "The basis for not using the Schroeder and Mitchener rat study (1975a) is that the incidences of gross or malignant tumors in the control and beryllium-exposed groups were not significantly different." Around the same time, OEHHA prepared a draft document for the Air Toxics program, which included the 1995 U.S. EPA oral potency factor for ingested beryllium. However, the final document (OEHHA, 1999) does not list a cancer potency factor for ingested beryllium. Our review for the PHG development concurs with the 1999 conclusion. There are no available studies that are judged adequate for calculating an oral carcinogenic potency that may be used for regulatory purposes.

CALCULATION OF THE PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water and for preparing foods and beverages. It is also used for bathing, showering and washing, resulting in potential dermal and inhalation exposures. Use of tap water in toilets and other household devices may also contribute to inhalation exposure.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for beryllium and beryllium compounds in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{\text{NOAEL (or LOAEL)} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{W}}$$

where,

NOAEL	=	no-observed-adverse-effect-level, or lowest-observed-adverse-effect-level (LOAEL) if a NOAEL is not available;
BW	=	adult body weight (default value is 70 kg);
RSC	=	relative source contribution (default values are 20, 40 and 80 percent);
UF	=	uncertainty factors (customarily 3-10 to account for interspecies extrapolation, 10 for potentially sensitive human subpopulations, 3-10 for the use of a LOAEL in place of a NOAEL, 10 for subchronic to chronic study extrapolation, and 1-10 for inadequate but suggestive evidence of carcinogenic potential);
W	=	daily drinking water consumption rate (default value of 2 L/day) plus a volume of water accounting for inhalation exposure due to volatilization and dermal uptake.

The NOAEL for beryllium toxicity in the principal study (Morgareidge *et al*., 1975, 1977) is 0.15 mg/kg-day based on ulcerative and inflammatory lesions of the intestine in male and female beagle dogs (Table 3). A benchmark dose calculation on the same data provides a BMDL05 of 0.2 mg/kg-day, which OEHHA considers conceptually equivalent to a NOAEL. The adult human body weight is assumed to be 70 kg, the standard default value. A value of 20 percent for the RSC is used for beryllium to account for the multi-route exposures to beryllium, most of which is derived from food (HSDB, 2002).

It is highly probable that the ulcerative and inflammatory lesions of the intestine produced by beryllium in the diet are the result of direct contact with beryllium in the intestinal lumen. Therefore, a factor of 3 is used for interspecies differences. This factor is based on possible differences in tissue sensitivity and not on possible differences in pharmacokinetics, because the toxicity is a direct effect at the point of contact. A factor of 10 is assumed for differences in sensitivity within the human population. As in the calculation of the federal MCL (U.S. EPA, 1992b, 1998a), additional uncertainty factors are used to account for the database deficiencies (3) and possible carcinogenic potential of ingested beryllium (10).

Because the vapor pressure of beryllium and beryllium compounds is very low, the water volume accounting for inhalation of vapor phase beryllium is assumed to be negligible. The equivalent water volume from inhalation of aerosol droplets is also very small, and has been estimated at 0.027 mL/day in a 10-minute daily shower (Keating and McKone, 1993). This exposure produces a negligible additional exposure for non-cancer effects.

The potential for dermal absorption of beryllium compounds in solution can be assessed using values for the skin permeability coefficient, k_p. While values of k_p for beryllium compounds are not available, a range of plausible values can be estimated from the range of k_p values, $1\times10^{-3} – 9\times10^{-6}$ cm/hr, for other inorganic compounds (U.S. EPA, 1992a). For a 10-minute bathing or showering event, the maximum value in this range corresponds to dermal uptake of the amount of chemical contained in 3 mL of water. This is considered to be negligible. Therefore, the default value of 2 L/day was used as the daily water consumption rate associated with beryllium exposure.

A health-protective water concentration (C) for beryllium and beryllium compounds based on non-cancer effects, using both the NOAEL and the benchmark dose approach, is therefore calculated as follows:

$$C = \frac{0.15 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.20}{1000 \times 2 \text{ L}eq\text{/day}}$$

$$= 0.001 \text{ mg/L} = 1 \ \mu\text{g/L (1 ppb)}$$

$$C = \frac{0.20 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.20}{1000 \times 2 \text{ L}eq\text{/day}}$$

$$= 0.0014 \text{ mg/L} = 1 \ \mu\text{g/L (1 ppb) (rounded)}$$

Carcinogenic Effects

As stated previously, U.S. EPA and OEHHA have concluded that there is not an adequate scientific basis for estimation and application of a carcinogenic potency for ingested beryllium. However, the small exposure to beryllium aerosols by the inhalation route in showering should be considered. A 70-kg adult breathing 20 m^3 of air per day, taking a 10-minute shower (U.S. EPA, 1997) is estimated to inhale 0.027 mL of liquid per shower per day (Keating and McKone, 1993). The concentration of beryllium in water associated with 10^{-6} risk of cancer due to inhalation of water droplets in the shower can be calculated by the following equation:

$$C = \frac{R \times BW}{CPF \times L/day}$$

where

R = a target risk level of one in a million, or $10^{-6;}$

BW = adult body weight, a default of 70 kg;

CPF = cancer potency factor, or 8.4 $(mg/kg\text{-}day)^{-1}$ for beryllium by inhalation

L/day = daily exposure to the contaminated medium, or 0.027 mL/day for inhalation of aerosol droplets in a daily 10 minute shower.

The calculation of cancer risk from inhalation of aerosols results in an estimated health-protective level, C (mg/L), of:

$$C = \frac{10^{-6} \text{ risk} \times 70 \text{ kg}}{8.4 \text{ (mg/kg-day)}^{-1} \times 27\text{x}10^{-6} \text{ L/day}} = 0.31 \text{ mg/L} = 310 \text{ ppb}$$

Conclusions:

Two health-protective concentrations were developed, one based primarily on non-carcinogenic effects from ingestion of water containing beryllium, and one for carcinogenic effects from inhalation of aerosol droplets in showering. Although it is not possible to calculate a carcinogenic potency for oral exposure to beryllium, an extra 10-fold uncertainty factor has been included in the oral estimate to account for the potential carcinogenicity by this route. The estimated health-protective level based on beryllium ingestion is much lower than that for inhalation. This is due to the much greater exposure by the ingestion route as well as the relatively high potency for non-cancer effects, with a consideration of possible carcinogenicity by the oral route. The PHG for beryllium is therefore set at 1 ppb, the more health-protective of the two estimates.

RISK CHARACTERIZATION

The PHG of 1 ppb was calculated based on toxicity to the gastrointestinal tract in feeding studies in male and female beagle dogs. Sources of uncertainty in the development of the PHG for beryllium and beryllium compounds in drinking water are also the general issues of uncertainty in any risk assessment, particularly mode of action, inter- and intra-species extrapolation, and extrapolation of higher-concentration effects to lower environmental levels.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA's drinking water risk assessment methodology. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day), and the RSC, respectively. The RSC defaults are 20, 40, and 80 percent (0.2, 0.4 and 0.8); other values may be used depending on the scientific evidence. In this case, the default value of 20 percent (0.2) is used because the major exposure to beryllium appears to be beryllium in food. Some exposure also occurs via ambient air, particularly in urban areas. Data on relative exposures of California populations to beryllium in food, water, and air are inadequate to accurately estimate the contributions from these different sources.

U.S. EPA follows a general procedure promulgating MCLGs for Group C chemicals (*i.e.*, limited evidence of carcinogenicity). In this procedure, either an RfD approach is used (as with a noncarcinogen), but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range. In this case the chemical is a known human carcinogen, based on exposures by the inhalation route, but oral cancer potency cannot be determined. OEHHA has chosen to use the former type of approach, i.e., including an extra uncertainty factor). The same

approach was used by U.S. EPA in the derivation of its MCL for beryllium (U.S. EPA, 1992b).

The PHG of 1 ppb is judged to be adequately protective of infants, children, and the elderly from the critical effect, gastrointestinal lesions, and is also protective against potential carcinogenicity by inhalation of aerosolized beryllium in showering. The adequacy of protection of individuals previously sensitized to beryllium is uncertain, although it should be noted that the major exposure to beryllium for this population (and the population at large) is from food. Minimizing drinking water concentrations will also help protect this pre-sensitized population.

OTHER GUIDANCE VALUES AND REGULATORY STANDARDS

The federal MCL for beryllium and beryllium compounds, established in 1992, is 4 ppb. This is also the federal MCLG (U.S. EPA, 1992b). In 1994, California adopted the federal MCL of 4 ppb for beryllium and beryllium compounds. The MCL was based on the Schroeder *et al*. (1975a) study in which no adverse effects were seen in rats given beryllium (as beryllium sulfate) at the rate of 0.5 mg/kg-day. In calculating the MCL, U.S. EPA used an uncertainty factor of 100 and a drinking water contribution to total intake of 20 percent. U.S. EPA also applied an additional factor of 10 "to account for possible carcinogenic potential of this contaminant via ingestion."

More recently, U.S. EPA established a reference dose (RfD) of 2×10^{-3} mg/kg-day for oral exposure to beryllium and beryllium compounds (U.S. EPA, 1998a,b) based on the study of Morgareidge *et al*. (1976), which was also the basis for the PHG. Both the RfD and the PHG are based on lesions of the GI tract in this study. U.S. EPA used the benchmark dose (BMD) methodology as an alternative to the NOAEL for this effect, but used as their critical value the BMD_{10} (the 95 percent lower confidence limit of the dose that produces a 10 percent incidence of small intestinal lesions), which they estimated as 0.46 mg/kg-day. An uncertainty factor of 300 was used, which is the product of a factor of 100 for intraspecies differences and intraspecies variation, and a factor of 3 for database deficiencies. U.S. EPA noted that "human toxicity data by the oral route are lacking, and reproductive/developmental and immunotoxicological endpoints have not been adequately addressed in animals." The U.S. EPA RfD is based on a benchmark dose that is approximately three times higher than the NOAEL identified in the Morgareidge *et al*. study and the five percent response level, which were used for the PHG calculation. The RfD and the PHG are based on the same study and the same data.

The most recent U.S. EPA summary of the status of regulated chemicals (U.S. EPA, 2002) indicates that the beryllium MCLG is to be re-examined based on the revised RfD and other factors. The document states that "EPA believes that any likely revision to the MCLG for beryllium could range from 0.01 mg/L to 0.001 mg/L, based on the change in the RfD in the 1998 assessment, the inclusion or non-inclusion of the risk management factor [for cancer], and using a 20 percent relative source contribution (RSC)" (U.S. EPA, 2002). The U.S. EPA MCLG is comparable in purpose with the OEHHA PHG, i.e., a health-protective goal.

U.S. EPA (1998a,b) has established a reference concentration (RfC) of 2×10^{-2} µg/m^3 for inhalation exposure to beryllium and beryllium compounds. This was based on an occupational morbidity study demonstrating sensitization to beryllium at a mean concentration of 0.55 µg/m^3 (Kreiss *et al*., 1996). U.S. EPA cited the study of Eisenbud *et al*. (1949) that supports a NOAEL for sensitization in the range 0.01-0.1 µg/m^3. To calculate a point estimate of a NOAEL, the LOAEL was divided by a safety factor of 10. The NOAEL for occupational exposure was adjusted by a factor of (10 m^3)/(20 m^3) for respiratory intake volume and by a factor of (5 days)/(7 days) for duration, to calculate the RfC.

The U.S. EPA (1980) proposed a water quality standard of 11 µg/l for the protection of aquatic life in soft fresh water; 1,100 µg/l for the protection of aquatic life in hard fresh water; and 100 µg/l for continuous irrigation on all soils except 500 mg/l for irrigation on neutral to alkaline lime-textured soils.

Other state drinking water guidelines include 0.007 µg/L for Arizona and 0.08 µg/L for Minnesota (U.S. EPA, 1993).

REFERENCES

Aldridge WN, Barnes JM, Denz FA (1950). Biochemical changes in acute beryllium poisoning. Br. J. Exp. Pathol. 31:473-484.

Araki M, Okada S, Fujita M (1954). Beryllium. Experimental studies on beryllium-induced malignant tumors of rabbits. Gann 45:499-501.

Arlauskas A, Baker RSU, Bonin AM, *et al*. (1985). Mutagenicity of metal ions in bacteria. Environ. Res. 36:379-388.

Ashby J, Ishidate J Jr., Stoner GD, *et al*. (1990). Studies on the genotoxicity of beryllium sulphate *in vitro* and *in vivo*. Mutat. Res. 240:217-225.

ATSDR (2002). *Toxicological Profile for Beryllium (Update)*. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1993a). *Toxicological Profile for Beryllium*. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

ATSDR (1993b). *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine*. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Barna BP, Chiang T, Pillarisetti SG, *et al*. (1981). Immunological studies of experimental beryllium lung disease in the guinea pig. Clin. Immunol. Immunopathol. 20: 402-411.

Belman S (1969). Beryllium binding of epidermal constituents. J. Occup. Med. 11:175-183.

Brooks AL, Griffith WC, Johnson NF, *et al*. (1989). The induction of chromosome damage in CHO cells by beryllium and radiation given alone and in combination. Radiat. Res. 120:494-507.

Byrne CJ, DeLeon IR (1986). Trace metal residues in biota and sediments from Lake Pontchartrain, Louisiana USA. Bull. Environ. Contam. Toxicol. 37:151-158.

Clary JJ, Bland LS, Stokinger HF (1975). The effect of reproduction and lactation on the onset of latent chronic beryllium disease. Toxicol. Appl. Pharmacol. 33:214-221.

Cloudman AM, Vining D, Barkulis S, Nickson JJ (1949). Bone changes observed following intravenous injections of beryllium (Abstract). Am. J. Pathol. 25:810-811.

Cunningham LD (1998). *Beryllium, Mineral Yearbook*. US Geological Survey, K1-K4.

DHS (2002). Chemical contaminants in drinking water. Division of Drinking Water and Environmental Management, California Department of Health Services, Sacramento, CA. http://www.dhs.ca.gov/ps/ddwem/chemicals/chemindex.htm

DiPaolo JA, Casto BC (1979). Quantitative studies of *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res. 39:1008-1013.

Dunkel VC, Pienta RJ, Sivak A, Traul KA (1981). Comparative neoplastic transformation responses of Balb/3T3 cells, Syrian hamster embryo cells, and Rauscher murine leukemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. J. Natl. Cancer Inst. 67:1303-1307.

Dunkel VC, Zeiger E, Brusick D, *et al*. (1984). Reproducibility of microbial mutagenicity assays: I. Tests with *Salmonella typhimurium* and *Escherichia coli* using a standardized protocol. Environ. Mutagen. 6(Suppl 2):1-254.

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

Eisenbud M, Wanta RC, Dustan C, *et al*. (1949). Non-occupational berylliosis. J. Ind. Hyg. Toxicol. 31:282-294.

Finch GL, Hoover MD, Hahn FF, Nikula KJ, Belinsky SA, Haley PJ, Griffith WC (1996). Animal models of beryllium-induced lung disease. Environ. Health Perspect. 104S(5):973-979.

Finch GL, Mewhinney JA, Hoover MD, *et al*. (1990). Clearance, translocation and excretion of beryllium following acute inhalation of beryllium oxide by beagle dogs. Fundam. Appl. Toxicol. 15:231-241.

Fontenot AP, Kotzin BL, Comment CE, Newman LS (1998). Expansions of T-cell subsets expressing particular T-cell receptor variable regions in chronic beryllium disease. Am. J. Respir. Cell. Mol. Biol. 18:581-589.

Fontenot AP, Falta MT, Freed BM, Freed BM, Newman LS, Kotzin BL (1999). Identification of pathogenic T cells in patients with beryllium-induced lung disease. J. Immunol. 163(2):1019-1026.

Fontenot AP, Newman LS, Kotzin BL (2001). Chronic beryllium disease: T cell recognition of a metal presented by HLA-DP. Clin. Immunol. 100(1):4-14.

Fontenot AP, Torres M, Marshall WH, Newman LS, Kotzin BL (2000). Beryllium presentation to CD4+ T cells underlies disease-susceptibility HLA-DP alleles in chronic beryllium disease. Proc. Natl. Acad. Sci. U S A. 97(23):12717-12722.

Furchner JE, Richmond CR, London JE (1973). Comparative metabolism of radionuclides in mammals. VIII. Retention of beryllium in the mouse, rat, monkey and dog. Health Physics 24: 293-300.

Guyatt BL, Kay HD, Branion HD (1933). Beryllium "rickets." J. Nutr. 6:313-324.

Haley PJ, Finch GL, Hoover, MD, *et al*. (1990). The acute toxicity of inhaled beryllium metal in rats. Fundam. Appl. Toxicol. 15:767-778.

Haley PJ, Finch GL, Mewhinney JA, Harmsen AG, Hahn FF, Hoover MD, Muggenburg BA, Bice DP (1989). A canine model of beryllium-induced granulomatous lung disease. Lab. Invest. 61(2):219-227.

Haley PJ, Swafford DS, Finch GL, Hoover MD, Muggenburg BA, Johnson NF (1997). Immunologic specificity of lymphocyte cell lines from dogs exposed to beryllium oxide. Immunopharmacol. Immunotoxicol. 19(4):459-471.

Henneberger PK, Cumro D, Deubner DD, Kent MS, McCawley M, 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.

HSDB (2002). Beryllium and beryllium compounds. Hazardous Substance Data Bank, an online database maintained by the National Library of Medicine at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IARC (1993). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 58: Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry*. International Agency for Research on Cancer, World Health Organization, Lyon, France.

Jacobson SA (1933). Bone lesions in rats produced by the substitution of beryllium for calcium in the diet. Arch. Pathol. 15:18-26.

Keating GA, McKone TE (1993). Measurements and evaluation of water-to-air transfer and air concentration for trichloroethylene in a shower chamber, modeling of indoor air quality and exposure, ASTM STP 1205. Niren L. Nagada, Ed., American Society for Testing and Materials, Philadephia, PA. pp. 14-24.

Kimmerle G (1966). *Beryllium. Vol 21. Handbook of Experimental Pharmacology.* Springer-Verlag, Berlin.

Klemperer FW, Martin AP, Liddy RE (1952). The fate of beryllium compounds in the rat. Arch. Biochem. Biophys. 41:148-152.

Krachler M, Rossipal E, Micetic-Turk D (1999). Trace element transfer from the mother to the newborn--investigations on triplets of colostrum, maternal and umbilical cord sera. Eur J Clin Nutr. 53(6):486-94.

Kreiss K, Mroz MM, Zhen B, *et al*. (1993). Epidemiology of beryllium sensitization and disease in nuclear workers. Am. Rev. Respir. Dis. 148:985-991.

Kreiss K, Mroz MM, Newman LS, *et al*. (1996). Machining risk of beryllium disease and sensitization with median exposures below 2 $\mu g/m^3$. Am. J. Ind. Med. 30:16-25.

Kuroda K, Endo G, Okamoto A, *et al*. (1991). Genotoxicity of beryllium, gallium, and antimony in short-term assays. Mutat. Res. 264:163-170.

Larramendy ML, Popescu NC, DiPaolo JA (1981). Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ. Mutagen. 3:597-606.

Lombardi G, Germain C, Uren J, Fiorillo MT, du Bois RM, Jones-Williams W, Saltini C, Sorrentino R, Lechler R (2001). HLA-DP allele-specific T cell responses to beryllium account for DP-associated susceptibility to chronic beryllium disease. J. Immunol. 166(5):3549-3555

Lum KR, Gammon KL (1985). Geochemical availability of some trace and major elements in surficial sediments of the Detroit River and western Lake Erie. J. Great Lakes Res. 11:328-338.

Marx JJ, Burrell R (1973). Delayed hypersensitivity to beryllium compounds. J. Immunol. 111:590-598.

Mathur R, Sharmi S, Mathur S, *et al*. (1987). Effects of beryllium nitrate on early and late pregnancy in rats. Bull. Environ. Contam. Toxicol. 38:73-77.

Miyaki M, Akamatsu N, Ono T, *et al*. (1979). Mutagenicity of metal cations in cultured cells from Chinese hamster. Mutat. Res. 68:259-263.

Morgareidge K, Cox GE, Bailey DE (1975). *Chronic Feeding Studies with Beryllium Sulfate in Rats. Evaluation of Carcinogenic Potential.* Submitted to Alcan Research and Development, Ltd. By Food and Drug Research Laboratories, Inc.

Morgareidge K, Cox GE, Bailey DE (1976). *Chronic Feeding Studies with Beryllium in Dogs.* Submitted by Food and Drug Research Laboratories, Inc. to Alcan Research and Development, Ltd., to the Aluminum Company of America and to Kawecki-Berylco Industries, Inc. and to Brush-Wellman, Inc.

Morgareidge K, Cox GE, Bailey DE, Gallo MA (1977). Chronic oral toxicity of beryllium in the rat (Abstract no. 175). Toxicol. Appl. Pharmacol. 41:204-205.

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

Newman LS, Mroz MM, Maier LA, Daniloff EM, Balkissoon R (2001). Efficacy of serial medical surveillance for chronic beryllium disease in a beryllium machining plant. J. Occup. Environ. Med. 43(3):231-237.

Nicola RM, Branchflower R, Pierce D (1987). Chemical contaminants in bottomfish. J. Environ. Health 49:342-347.

Nikula KJ, Swafford DS, Hoover MD, Tohulka MD, Finch GL (1997). Chronic granulomatous pneumonia and lymphocytic responses induced by inhaled beryllium metal in A/J and C3H/HeJ mice. Toxicol. Pathol. 25(1):2-12.

Nishioka H (1975). Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31:185-189.

OEHHA (1998). *Air Toxics Hot Spots Program Risk Assessment Guidelines. Part II. Technical Support Document for Describing Available Cancer Potency Factors. Public and Scientific Review Panel Review Draft*. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

OEHHA (1999). *Air Toxics Hot Spots Program Risk Assessment Guidelines. Part II. Technical Support Document for Describing Available Cancer Potency Factors*. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

Ogawa HI, Tsuruta S, Niyitani Y, *et al*. (1987). Mutagenicity of metal salts in combination with 9-aminoacridine in *Salmonella typhimurium*. Jpn. J. Genet. 62:159-162.

Paton GR, Allison AC (1972). Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16:332-336.

Pienta RJ, Poiley JA, Lebhertz WB (1977). Morphological transformation of early passage golden Syrian hamster embryo cells derived from cryopreserved primary cultures as a reliable *in vitro* bioassay for identifying diverse carcinogens. Int. J. Cancer 19:642-655.

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

Reeves AL (1986). Beryllium. In: *Handbook on the Toxicology of Metals. Second edition, Volume II: Specific metals.* Friberg L, Norberg GF, Vouk VB, eds. Elsevier Science Publisher, New York, NY.

Reeves AL, Vorvald AJ (1967). Beryllium carcinogenesis. II. Pulmonary deposition and clearance of inhaled beryllium sulfate in the rat. Cancer Res. 27:446-451.

Rosenkranz HS, Poirier LA (1979). Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 62:873-892.

Rossman MD (1991). Chronic beryllium disease: a hypersensitivity disorder. Appl. Occup. Environ. Hyg. 16(5):615-618.

Rossman MD, Stubbs J, Lee CW, Argyris E, Magira E, Monos D (2002). Human leukocyte antigen Class II amino acid epitopes: susceptibility and progression markers for beryllium hypersensitivity. Am. J. Respir. Crit. Care Med. 165(6):788-94.

Rossman TG, Molina M (1986). The genetic toxicology of metal compounds: II. Enhancement by ultraviolet light-induced mutagenesis in *Escherichia coli* WP2. Environ. Mutagen. 8:263-271.

Rossman TG, Molina M, Meyer LW (1984). The genetic toxicology of metal compounds: I. Induction of λ prophage in *Escherichia coli* $WP2_s(\lambda)$. Environ. Mutagen. 6:59-69.

Sanders CL, Cannon WC, Powers GI, *et al*. (1975). Toxicology of high-fired beryllium oxide inhaled by rodents. I. Metabolism and early effects. Arch. Environ. Health 30:545-551.

Sanderson WT, Ward EM, Steenland K, and Petersen MR (2001). Lung cancer case-control study of beryllium workers. Am. J. Indust. Med. 39(2):133-144.

Savitz DQA, Whelan EA, Kleckner RC (1989). Effects of parents' occupational exposure on risk of stillbirth, preterm delivery and small-for-gestational-age infants. Am. J. Epidemiol. 29:1201-1218.

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

Schroeder HA, Mitchener M (1975b). Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J. Nutr. 105:452-458.

Sendelbach LE, Witschi HP, Tryka AF (1986). Acute pulmonary toxicity of beryllium sulfate inhalation in rats and mice: Cell kinetics and histopathology. Toxicol. Appl. Pharmacol. 85:248-256.

Sendelbach LE, Tryka AF, Witschi HP (1989). Progressive lung injury over a one-year period after a single inhalation exposure to beryllium sulfate. Am. Rev. Respir. Dis. 139:1003-1009.

Simmon VF (1979). *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. J. Natl. Cancer Inst. 63:893-899.

Simmon VE, Rosenkrantz HS, Zeiger E, Poirier LA (1979). Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62:911-918.

Skilleter DN (1984). Biochemical properties of beryllium potentially related to its carcinogenicity. Toxicol. Environ. Chem. 7:213-228.

Steele VE, Wilkinson BP, Arnold JT, Kutzman RS (1989). Study of beryllium oxide genotoxicity in cultured respiratory epithelial cells. Inhal. Toxicol. 1:95-110.

Stange AW, Hilmas DE, Furman FJ, Gatliffe TR (2001). Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. Appl. Occup. Environ. Hyg. 16(3):405-417.

Tinkle SS, Schwitters PW, Newman LS (1996). Cytokine production by bronchoalveolar lavage cells in chronic beryllium disease. Environ. Health Perspect. 104S(5):969-971.

Tso W-W, Fung W-P (1981). Mutagenicity of metallic cation. Toxicol. Lett. 8:195-200.

U.S. EPA (1980). *Ambient Water Quality Criteria for Beryllium.* Office of Water Regulations and Standards, Criteria and Standards Division, U.S. Environmental Protection Agency. Publication no. EPA-440/5-80-024, Washington, DC.

U.S. EPA (1987). *Health Assessment Document for Beryllium.* Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (1991). *Drinking Water Criteria Document for Beryllium*. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Drinking Water, Washington, DC. NTIS PB92-173301.

U.S. EPA (1992a). *Dermal Exposure Assessment: Principles and Applications.* Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (1992b). *National Primary Drinking Water Regulations for Synthetic Organic Chemicals and Inorganic Chemicals; Final Rule.* Federal Register 57(138):31776-31849.

U.S. EPA (1993). Summary of State and Federal Drinking Water Standards and Guidelines. Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Office of Water, U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (1995). *Integrated Risk Information System; Beryllium. CASRN 7440-41-7*. Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA (1996). *Proposed Guidelines for Carcinogen Risk Assessment*. Federal Register 61(79):17960-18001.

U.S. EPA (1997). *Exposure Factors Handbook*, Volume III, Activity Factors. EPA/600/P-95/002Fc Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (1998a). *Integrated Risk Information System; Beryllium. CASRN 7440-41-7*. Criteria and Assessment Office, Cincinnati, OH. http://www.epa.gov/iris/.

U.S. EPA (1998b). *Toxicological Review of Beryllium and Compounds (CAS No. 7440-41-7)*. U. S. Environmental Protection Agency, Washington, DC.

U.S. EPA (2002). Announcement of the Results of EPA's Review of Existing Drinking Water Standards and Request for Public Comment. National Primary Drinking Water Regulations, Fed. Reg. April 17, 2002, 67(74):19029-19090.

U.S. EPA (2003). Benchmark Dose Software. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167

Van Cleave CD, Kaylor CT (1955). Distribution, retention and elimination of Be^7 in the rat after intratracheal injection. Arch. Ind. Health 11:375-392.

Vegni-Talluri M, Guigiani V (1967). Action of beryllium ions on primary cultures of swine cells. Caryologia 20:355-367.

Venugopal B, Luckey TD (1977). *Metal Toxicity in Mammals 2: Chemical Toxicity of Metals and Metalloids*. Plenum Press, New York, NY.

Wagoner JK, Infante PF, Bayliss DL (1980). Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. Environ. Res. 21:15-34.

Wang Z, Farris GM, Newman LS, Shou Y, Maier LA, Smith HN, Marrone BL (2001). Beryllium sensitivity is linked to HLA-DP genotype. Toxicology 165(1):27-38.

Wang Z, White PS, Petrovic M, *et al*. (1999). Differential susceptibilities to chronic beryllium disease contributed by different Glu69 HLA-DPB1 and –DPA1 alleles. J. Immunol. 163:1647-1653.

Ward E, Okun A, Ruder A, Fingerhut M, Steenland K (1992). A mortality study of workers at seven beryllium processing plants. Am. J. Ind. Med. 22(6):885-904.

Wolnik KA, Fricks FL, Gaston CM (1984). Quality assurance in the elemental analysis of foods by inductively coupled plasma spectroscopy. Spectrochimica Acta, Part B, 398:649-655.

Zakour R, Glickman BW (1984). Metal-induced mutagenesis in the *lacI* gene *of Escherichia coli*. Mutat. Res. 126:9-18.