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DRINKING WATER CRITERIA DOCUMENT FOR BERYLLIUM

Prepared for

HEALTH AND ECOLOGICAL CRITERIA DIVISION
OFFICE OF SCIENCE AND TECHNOLOGY
OFFICE OF WATER

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1986; however, more recent data have been added during the review process, and final revisions updating this document were made.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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ATPase	Adenosine triphosphatase
CNS	Central nervous system
DNA	Deoxyribonucleic acid
DWEL	Drinking water equivalent level
GI	Gastrointestinal
HA	Health advisory
Hb	Hemoglobin
i.v.	Intravenous
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
RBC	Red blood cell
RfD	Reference dose
RNA	Ribonucleic acid

I. SUMMARY

Beryllium (Be) is a hard grayish-white metal of the alkaline earth family. It occurs in nature as a mineral component of pegmatite rocks. In addition to the gemstones emerald (chromium-containing beryl) and aquarmarine (iron containing-beryl), beryl and bertrandite are the only two beryllium minerals of economic significance. Because of its low atomic number (^{9}Be), beryllium is very permeable to x-rays and is used as a window for x-ray tubes. Although pure beryllium metal has a unique combination of properties that makes it particularly useful in the manufacture of high performance products in metallurgical, aerospace and nuclear technologies, most of the beryllium ore mined is converted into metal alloys. Beryllium alloys are used in the electronics, plastics and tooling industries. Beryllium oxide is used to make high-technology ceramics as well as laser structural components.

Methods used to detect beryllium include flame and flameless absorption spectroscopy, spectrophotometry, gas chromatography/electron capture and laser ion mass analysis (LIMA). Generally, beryllium behaves as a cation with a 2^{+} valence at a pH of ≥ 5; it forms poorly soluble compounds at a pH of 5-8 and forms beryllate-like complexes at a pH of ≥ 8. It is likely to occur in natural waters only in trace amounts since beryllium compounds are relatively insoluble at the pH of natural waters. Detectable concentrations of beryllium are found in acidified waters, and in view of the increased acidification of some natural waters, there is a potential for an increased solubility of beryllium salts.

Beryllium may enter the body by ingestion, inhalation and skin absorption. Inhalation and ingestion are the main routes of beryllium intake for man. When ingested, beryllium is only minimally absorbed (<1%) by the GI tract because at neutral pH of the intestines, the major site of GI absorption, precipitation of beryllium compounds occurs. Absorption through unbroken skin, even following prolonged or repeated contact, adds insignificant amounts of beryllium to the body, although a contact dermatitis may occur.

The major route of exposure by which beryllium enters the body is inhalation. Most of the beryllium that can be inhaled is emitted into the air by the burning of coal or fuel oil in which beryllium occurs as an impurity. Beryllium also occurs naturally in various tobaccos and may be inhaled during smoking. The greatest potential for beryllium exposure occurs in the work place and in the vicinity of the industries that process beryllium ore or compounds. Atmospheric beryllium eventually reaches soils and sediments where it is retained in the relatively insoluble form of beryllium oxide.

Beryllium compounds may be mobilized from the lungs, but the rate of mobilization (clearance and deposition) depends on the solubility of the compound, particle size and dose. Blood steady state is reached within 8-12 hours of exposure. A large portion of the beryllium transported by the blood is deposited in the skeleton. Intratracheal doses have been measured in the liver, spleen, kidney and muscle. Beryllium has also been shown to accumulate in the lung following interaction with macromolecules in lung cells. Increased beryllium levels have been detected in human lungs as long as 20 years after the last exposure.

The major route of excretion following oral exposure is through the feces. Urine represents the major route of excretion if beryllium is administered intratracheally or parenterally.

Systemic toxicity associated with oral administration of beryllium to animals is limited to the development of beryllium rickets and a slight growth depression in male rats.

Inhalation exposure results in both acute and chronic lung disease, as well as anemia. Short-term exposure to high concentrations of beryllium salts can cause inflammation of the lungs (similar to pneumonia) and long-term exposure to beryllium at low air concentrations can cause berylliosis (manifested by the appearance of granulomas in the lung). Intratracheal administration of beryllium sulfate has also produced pulmonary lesions. Injection of even small amounts of beryllium oxide, silicate and phosphate are extremely toxic to animals, with reports of lung and liver effects, CNS changes and osteosclerotic changes.

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits and by inhalation or intratracheal exposure of rats and monkeys. Carcinogenic responses have been induced by a variety of forms of beryllium including beryllium sulfate, phosphate, oxide, and beryl ore. The carcinogenic evidence in mice (intravenously injected or exposed by inhalation), guinea pigs and hamsters (exposed by inhalation) is equivocal.

Osteosarcomas are the predominant types of tumors induced in rabbits. These tumors are highly invasive, metastasize readily, and are judged to be histologically similar to human osteosarcomas. In rats, pulmonary adenomas and/or carcinomas have been found, although pathologic end points have not been well documented in many cases. While inhalation, intratracheal instillation, and intravenous or intramedullary injection have produced positive results, evidence of animal carcinogenesis resulting from drinking water or dietary exposure is not definitive. In the only published oral study with rats, however, the dose levels were well below the MTD. Studies using mice and dogs were of inadequate duration.

Although, individually, many of the animal studies have methodologic and reporting limitations compared with current standards for bioassays, collectively, the studies provide evidence for carcinogenicity. Tumorgenic responses have been noted in multiple species at multiple sites and, in some cases, afford evidence of a dose-response. On this basis, the U.S. EPA has classified the weight of evidence for carcinogenicity in experimental animals as sufficient. Since positive responses were seen for a variety of beryllium compounds, all forms of beryllium are considered to be carcinogenic. While evidence for oral exposure is inconclusive, the nature of the nonoral positive data suggests that beryllium may also pose a risk by the ingestion route.

Occupational epidemiologic studies provide equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early 1970s epidemiologic studies of beryllium exposed workers do not report positive evidence for increased cancer incidence. However, recent 1980s studies do report a significantly increased risk of lung cancer in exposed workers.

The absence of beryllium exposure levels and a demonstrated concern about possible confounding factors within the workplace make the reported positive correlations between beryllium exposure and increased risk of cancer difficult to substantiate. This relegates the reported statistically significant increases in lung cancer to, at best, a somewhat elevated risk that is not statistically significant. Because of these limitations, the available epidemiologic evidence is considered to be "inadequate" to support or refute the existence of a carcinogenic hazard for humans exposed to beryllium.

Using the U.S. EPA weight-of-evidence criteria for evaluating both human and animal evidence, beryllium is classified in Group B2, indicating that, on the strength of animal studies, beryllium should be considered a probable human carcinogen. In this particular case, the animal evidence demonstrates that all beryllium species should be regarded as probably being carcinogenic for humans.

Beryllium sulfate and chloride have been shown to be nonmutagenic in all bacterial and yeast gene mutation assays. Mutagenicity studies of beryllium sulfate indicate that beryllium has the potential to cause gene mutations, chromosomal aberrations and sister chromatid exchange in cultured human lymphocytes and Syrian hamster embryo cells. Beryllium was found to block the cell cycle and inhibit cell division. It has also been reported to affect DNA polymerase and thus, increase the frequency of mutations. However, the lack of data in whole animals preclude any definitive statement on the potential heritable effects of beryllium.

Teratogenicity studies have found positive results in snails, salamanders and chick embryos. Limited information is available regarding teratogenic and reproductive effects in animals. Results of a recent Russian study in pregnant rats indicated that beryllium chloride compounds produced some teratogenic effects described only as "internal abnormalities." The available information is not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects in humans.

Numerous studies have identified possible mechanisms responsible for the effects observed following beryllium exposure. Beryllium has been noted to inhibit several enzyme systems, such as alkaline phosphatase, and has also been shown to affect nucleic acid protein production and metabolism in the cell. The involvement of an immunologic factor following beryllium exposure is now generally accepted as a cell-mediated hypersensitivity reaction. Responses observed varied with the individual; humans and guinea pigs can be sensitized, whereas present data indicate that no such mechanism exists for the rat. Sensitization in guinea pigs has been shown to be controlled and transmitted as a dominant, nonsex-linked trait. Presently, the lymphoblast transformation test is regarded as the most useful test to detect hypersensitivity to beryllium.

The following health advisories were derived from ingestion studies in which beryllium was added to the drinking water or diet of rats. For noncarcinogenic effects a 10-day HA (10 kg child) of 30 mg/ℓ was calculated based on an animal feeding study. The 10-day HA (10 kg child) of 30 mg/ℓ was adopted for the 1-day HA as a conservative estimate since no

suitable data were located in the available literature on which to base this criterion directly. Longer-term HAs of 4 mg/ℓ (10 kg child) and 20 mg/ℓ (70 kg adult) were derived from a subchronic dietary study in rats. A drinking water equivalent level (DWEL) of 0.2 mg/ℓ was derived based on a NOAEL of 0.5 mg/kg/day in rats from a drinking water study.

Although evidence exists that beryllium is a carcinogen by the inhalation route, no definitive evidence exists that correlates the ingestion of beryllium with tumor appearance since it has not been tested orally at the MTD. However, since beryllium is carcinogenic by inhalation and parenteral routes, and also induces chromosomal abnormalities, it is possible that beryllium in water could pose a carcinogenic risk to man. The quantitative estimate by ingestion is regarded as an upper limit estimate since it was derived from the upper limit of a study that showed no significant carcinogenic effects: $q_1^* = 4.3\ (mg/kg/day)^{-1}$. The concentration corresponding to lifetime risk of 10^{-6} is 8 µg/ℓ or for a risk of 10^{-5} is 80 µg/ℓ. These numbers should be used with caution because of the severe limitations in their derivation.

II. PHYSICAL AND CHEMICAL PROPERTIES

Characteristics of Beryllium (Be)

Beryllium (Be) is a lightweight, grayish-white metal of the alkaline earth family with an atomic weight of 9.01. A fairly rare element, it ranks 44th in abundance and was originally called glucinum (Gl) because beryllium salts have a sweet taste. In nature, beryllium exists in mineralized forms such as beryl and bertrandite. The most important forms commercially are the metal itself, beryllium-copper alloys and beryllium oxide. Beryllium is often used in high-performance products in metallurgical, aerospace and nuclear technologies because of its unique combination of properties, such as an unusually high melting point, high modulus of elasticity, extreme hardness, low coefficient of thermal expansion and a high stiffness-to-weight ratio (Weast, 1977). Also, because beryllium has a low atomic weight, it is highly permeable to X-rays, and thin sheets are commonly used as windows for X-ray tubes.

Beryllium has a Chemical Abstracts (CAS) Registry number of 7440-41-7 and a Registry of Toxic Effects of Chemical Substances (RTECS) number of DS 1750000. It has the following physical and chemical properties:

Molecular weight:	9.012	Windholz, 1976
Boiling point:	2500°C	U.S. EPA, 1980a
Melting point:	1287°C	U.S. EPA, 1980a
Brinell hardness:	60-125	U.S. EPA, 1980b
Vapor pressure:	10 mm Hg at 1860°C	Toxicology Data Bank, 1985
Specific gravity:	1.85 at 20°C (solid)	Weiss, 1980
Conversion factor (ppm (air) to mg/m^3):	1 ppm = 0.375 mg/m^3 gas at 2500°C	

The ionic radius of beryllium is only 0.31Å, with a large ionic charge-to-radius ratio of 6.45. Because of this, the most stable beryllium compounds are formed with smaller anions such as fluoride and oxide (Krejci and Scheel, 1966). This high charge-to-radius ratio of bivalent beryllium also accounts for the amphoteric nature of the ion (Basolo, 1956; Cartledge, 1928) and the strong tendency of beryllium to hydrolyze. Generally, it behaves as a cation with a 2^+ valence at pH values <5, forms insoluble hydroxides or hydrated complexes at pH values of 5-8, and forms beryllate-like complexes at pH values >8 (Drury et al., 1978).

Many common beryllium compounds (for example, the chloride and nitrate) are readily soluble in water. Others, such as the sulfate complex, the carbonate and hydroxide compounds, are almost insoluble in cold water (McKee and Wolf, 1963). Beryllium is not likely to be found in natural waters except in trace amounts because in the normal pH range of such water the oxides and hydroxides are relatively insoluble (oxide solubility reported at 20-70 µg/ℓ in pure water at 28°C) (NAS, 1977). Hem (1970) estimates that the average concentration of beryllium in fresh surface waters is <1 µg/ℓ.

Characteristics of Beryllium Compounds

An important beryllium compound is beryllium oxide (BeO), a chemical intermediate in the extraction of beryllium from beryl and bertrandite. It is soluble in acids and alkalis, but mostly insoluble in water (Table II-1). It is an extremely stable compound, with a negligible vapor pressure ≤2000°C (Erway and Seifert, 1951).

TABLE II-1

Physical and Chemical Properties of Beryllium Compounds*

	Beryllium Oxide	Beryllium Sulfate	Beryllium Hydroxide	Beryllium Carbonate	Beryllium Fluoride	Beryllium Chloride	Beryllium Nitrate
Molecular formula	BeO	$BeSO_4$	$Be(OH)_2$	$BeCO_3 \cdot Be(OH)_2$	BeF_2	$BeCl_2$	$Be(NO_3)_2 \cdot 3H_2O$
Molecular weight	25.01	105.07	43.03	112.05	47.01	79.93	187.07
CAS registry number	1304-56-9	13510-49-1	13327-32-7	13106-47-3	7787-49-7	7787-47-5	13597-99-4
Specific gravity (20°)	3.01	2.44	1.92	NR	1.986 (25°)	1.899 (25°)	1.557
Boiling point, °C	3900	NR	NR	NR	NR	482.3	142
Melting point, °C	2530 ± 30	decomposes 550-600	NR	NR	555	399.2	60
Vapor pressure, mm Hg	NR	NR	NR	NR	NR	1291°C	NR
Water solubility, mg/L	0.2, 30°C	Insoluble in cold water; converted to tetrahydrate in hot water.	Slightly soluble	Insoluble in cold water. Decomposes in hot water.	Extremely soluble	Very soluble	Very soluble

*Sources: Windholz, 1976; Weast, 1977

NR = Not reported

Beryllium sulfate is a pure intermediate in the production of beryllium oxide. It is most often found as the tetrahydrate form ($BeSO_4 \cdot 4H_2O$), which is insoluble in ethanol but soluble in water. Like other soluble beryllium salts, the sulfate is hydrolyzed in aqueous solution. If the excess hydrogen ions are removed from this system, such as happens in the living cell, the soluble salts convert to insoluble products, which have long residence times in the body (Krejci and Scheel, 1966).

Beryllium hydroxide [$Be(OH)_2$] is an important intermediate in all of the current methods of extracting the metal from its ores, and it is also formed and retained in some tissues of the body. The hydroxide occurs in several forms, the amorphous form being more soluble than the α or β form. The α product solubility is reported to be $<10^{-7}$ mole/ℓ (Gilbert and Garrett, 1956).

The most important beryllium halide is the fluoride (BeF_2), which is extremely soluble in water. Aqueous solutions of BeF_2 are only slightly hydrolyzed (~1%). The other important halide is beryllium chloride ($BeCl_2$); the anhydrous form of the chloride is very soluble in water and ethanol and is hydrolyzed to 4.6% in a 0.1 N solution (Drury et al., 1978).

Beryllium nitrate [$Be(NO_3)_2 \cdot 3H_2O$] was formerly used in gas and acetylene lamps (Stecher, 1968); however, its use was discontinued in 1973 because it represented a potential health hazard (Griggs, 1973; Lerza, 1974). Data on the above described beryllium compounds are listed in Table II-1.

Methods of Determination

Several methods are used to determine beryllium content in air, water, biologic tissues and urine. Two of these methods are flame and flameless absorption spectroscopy. In the flame technique, the photodetector is usually calibrated to read the concentration directly (Environmental Instrumentation Group, 1973) and has a detection limit of 2-10 ng/mℓ (Hurlbut, 1974). The flameless technique is more sensitive, with a detection limit of 0.1 ng/mℓ for urine (Hurlbut, 1974). A third method for determining beryllium is spectrophotometry, which has a detection limit of ~5 ng/mℓ, but this method is sometimes a long and tedious process. Atomic absorption spectrometry is a useful and convenient procedure, but is not as sensitive as other techniques. Determinations that require even greater sensitivity and specificity are possible through the use of gas chromatography.

Measures and Edmond (1986) describe a method for the determination of beryllium content in seawater at oceanic concentration levels (2-30 pM). The technique uses gas chromatography/electron capture detection of the 1,1,1-trifluoro-2,4-pentanedione derivative and has a detection limit of ~2 pM and a relative precision of ±5% at 23 pM. The method has been utilized in the laboratory on stored acidified seawater samples as well as at sea on three oceanographic cruises. In addition, the technique has been applied to hydrothermal fluids and other natural waters such as river and rain water.

Beryllium is measured in urine with use of the Stabilized Temperature Platform Furnace (STPF) technology recently developed for electrothermal atomic absorption (Paschal and Bailey, 1986). Urine is diluted with a matrix modifier containing magnesium nitrate, nitric acid and Triton X-100

and is quantified with simple aqueous standards. The characteristic amount, which is the amount in picograms needed for 0.0044 Absorbance seconds (A•s), was calculated to be 1.7 pg. A detection limit of 0.05 µg/ℓ was calculated (three standard deviation). Linearity is observed from 0-16 µg/ℓ beryllium in the undiluted specimen. The precision and accuracy of the method have been evaluated with lyophilized urine reference material prepared by the National Bureau of Standards, as well as with in vitro spiked, frozen urine material. This procedure is rapid, simple, and highly accurate. Within- and among-day precision values of 4.1 and 10% were observed for an in vitro spiked urine with a mean value of 4.8 µg/ℓ beryllium.

Williams and Kelland (1986) investigated the value of laser ion mass analysis (LIMA) for the detection of beryllium disease in routine histologic sections. LIMA uses a pulsed microfocused laser beam to ionize a small volume (μm^3) of material. The ions released are detected by a time of flight mass spectrometer, producing a complete mass spectrum of all elements in the periodic table with a sensitivity range from 1-10 ppm. Conventional 5 µm histologic sections mounted on plastic film or on glass slides are used. The sections are viewed through a standard optical microscope, and the micron diameter laser beam is directed as required. Spectra can thus be obtained from individual or groups of cells, such as granulomas, and values compared with those of adjacent normal tissue.

Summary

Beryllium (Be) is a lightweight, grayish-white metal of the alkaline earth family with an atomic weight of 9.01. In nature, beryllium exists in

mineralized forms such as beryl and bertrandite. The most commercially important forms are the metal itself, beryllium-copper alloys and beryllium oxide. Beryllium is often used in high-performance products of the metallurgical, aerospace and nuclear technologies because of its unique combination of properties, such as an unusually high melting point, high modulus of elasticity, extreme hardness, low coefficient of thermal expansion and a high stiffness-to-weight ratio. Also, because beryllium has a low atomic weight, it is highly permeable to X-rays, and thin sheets are commonly used as windows for X-ray tubes.

Many common beryllium compounds (for example, the chloride and nitrate) are readily soluble in water. Others, such as the sulfate complex, the carbonate and hydroxide compounds are almost insoluble in cold water. Beryllium is not likely to be found in natural waters except in trace amounts, because in the normal pH range of such water the oxides and hydroxides are relatively insoluble. The average concentration of beryllium in fresh surface waters is <1 µg/ℓ.

Several methods are used to detect beryllium content in air, water, biologic tissues and urine. Two of these methods are flame and flameless absorption spectroscopy. In the flame technique, the photodetector is usually calibrated to read the concentration directly and has a detection limit of 10 to 2 ng/mℓ. The flameless technique is more sensitive, with a detection limit of 0.1 ng/mℓ for urine. A third method for determining beryllium is spectrophotometry, which has a detection limit of ~5 ng/mℓ. Gas chromatography/electron capture techniques have been used for the determination of beryllium in seawater at a concentration of 2-30 ppm.

Laser ion mass analysis (LIMA) has been used for the detection of beryllium disease in routine histologic sections.

III. TOXICOKINETICS

The absorption, distribution, retention, metabolism and excretion of beryllium was most recently reviewed by U.S. EPA (1987).

Absorption

The three major routes by which beryllium may enter the body are by ingestion, inhalation and dermal absorption. Several investigators have found that following oral administration of beryllium compounds, a majority of the beryllium passes through the GI tract unabsorbed; <1% is absorbed through the gut (Reeves, 1965; Hyslop et al., 1943; Shima et al., 1983; Furchner et al., 1973; Watanabe et al., 1985). Studies on guinea pigs fed 10 or 30 mg/day beryllium sulfate (~0.08 or 0.24 mg/kg/day) showed that the amount of beryllium absorbed was 0.006% of that ingested (Hyslop et al., 1943).

Reeves (1965) gave two groups of rats (4/group) either 6.6 or 66.6 µg Be in their drinking water. One rat/group was killed at 6, 12, 18 and 24 weeks after exposure. The results of these studies indicated that 60-90% of the ingested beryllium was eliminated. Reeves (1965) concluded that the low solubility of beryllium in intestinal fluid was due mainly to its precipitation as a phosphate.

Watanabe et al. (1985) investigated the absorption of different beryllium compounds following oral administration in hamsters. Measurable amounts of beryllium were found in the liver, kidneys, lungs and intestines

following dietary administration of beryllium sulfate (5 mg Be/day); however, beryllium was found only in the intestine when given as the oxide or metal.

The primary route by which beryllium is absorbed into the body is through the lungs (inhalation). Animal studies have shown that following the inhalation of beryllium nitrate (aerosol), beryllium concentrations in the blood reached a steady state within 8-12 hours of exposure in rats and hamsters (Stiefel et al., 1980). Reeves and Vorwald (1967) studied the rate of accumulation of beryllium sulfate in the lungs of rats exposed to 34 $\mu g/m^3$ beryllium. After 36 weeks of exposure, beryllium concentration in the whole lung reached steady state; however, tracheobronchial lymph node concentration peaked at about week 36 for females and week 52 for males and then declined. Rats exposed to 447 $\mu g/m^3$ beryllium oxide for 1 hour absorbed ~200 ng beryllium in 2.5 hours (Hart et al., 1984). Dermal absorption of beryllium or beryllium compounds is very poor even following prolonged or repeated contact, although contact dermatitis can occur (Berry et al., 1974). Petzow and Zorn (1974) showed that small quantities of beryllium can be absorbed through the tails of rats.

Distribution

Once beryllium enters through the lungs, its compounds may be transported to other tissues. The rate of mobilization, however, may depend on the solubility of the specific compound. A study by Van Cleave and Kaylor (1955) reported that soluble, nonionizing beryllium-citrate was completely mobilized from the lung after 4 days following intratracheal injection, while $BeSO_4$ was either retained in the lung for longer periods or mobilized after 16 days. Insoluble compounds, such as beryllium ores, tend to

remain in the lung for indefinite periods of time (Wagner et al., 1969). Increased beryllium levels have been detected in human lungs as long as ≥20 years after the last exposure occurred (Sprince et al., 1976).

Beryllium is transported from the lungs by the blood and lymph. *In vitro* studies with artificial serum indicated that orthophosphate and hydroxide are the forms of beryllium compounds transported by the body fluids (Reeves and Vorwald, 1961). According to Reeves (1977), the available evidence indicates that colloidal phosphate, probably adsorbed on plasma α-globulin, represents the major form of circulating beryllium, with minor portions carried as hydroxide or citrate.

Transport of beryllium in the body is a function of the physicochemical state of the metal (Stokinger, 1972). However, regardless of the beryllium form or the route of administration, a large portion of the beryllium transported in the blood goes to the skeleton. Studies have indicated that both ionic and citrated beryllium are bone seekers when injected intravenously or intramuscularly into rats (Crowley et al., 1949; Klemperer et al., 1952). Deposits of beryllium in the osteoid tissue adjacent to the epiphyseal plate have been noted on radiographs (Van Cleave and Kaylor, 1955). Other studies have indicated that BeO administered intratracheally is deposited in greatest concentrations in the bone and in lesser concentrations in the spleen, liver, kidney and muscle (Spencer et al., 1972). Van Cleave and Kaylor (1955) reported that in rats during the first several weeks after injection, doses of 50 µg Be/kg accumulated in the bone while doses of 500 µg Be/kg were deposited in the liver. Klemperer et al. (1952) noted that the soluble beryllium settles rapidly in the

skeleton, while the colloidal beryllium is taken up by the reticuloendothelial organs first, mainly the liver. Beryllium deposited in the liver is gradually mobilized and then either transferred to bone or excreted.

The organs that retain beryllium in significant amounts are the skeleton, liver and kidney. Crowley et al. (1949) reported that in rats, 40% of 20 μCi of ^{7}Be as $BeCl_2$ was absorbed from an intramuscular injection site after 24 hours, with 29% of that amount absorbed and maintained in the bone up to the 64th day. Levels in the liver and kidney were comparable with those in the bone at first, but decreased by a factor of 10 by the 64th day. Cikrt and Bencko (1975) reported that after intravenous administration of beryllium as $BeCl_2$ or $BeSO_4$, rat liver and kidneys contained 23.6% and 1.6%, respectively, of a dose of 25 μg/kg bw and 32.3% and 1.3%, respectively, of a dose of 0.250 μg/kg bw. A study by Furchner et al. (1973) reported that, in rats and mice, bone and muscle tissue retained >1% of an i.p. dose of $BeCl_2$ 71 days after administration. Beryllium was retained to a greater degree following i.v. administration than following i.p. administration; almost no beryllium was retained following ingestion. Furchner et al. (1973) reported retention half-lives of 1210, 890, 1770 and 1270 days for mice, rats, monkeys and dogs, respectively, after i.v. administration of $BeCl_2$.

Reeves (1965) also studied the tissue distribution of beryllium. Beryllium sulfate (6.6 or 66.6 μg Be/day) was added to the drinking water of male Sprague-Dawley rats for 24 weeks. The levels of beryllium were highest in the GI tract and the skeleton, with somewhat lower levels in the blood and liver. Watanabe et al. (1985) gave powdered foods containing 5 mg beryllium as $BeSO_4$, BeO or Be-metal to hamsters every day for 3-12

months. Body weight and beryllium distribution in various organs was studied. The results of the study demonstrated that when $BeSO_4$ was administered, beryllium was mainly retained in the liver, large intestine, small intestine, kidneys, lungs, stomach, and spleen. Be-metal and BeO were absorbed poorly and beryllium was mainly found in the intestine.

Rhoads and Sanders (1985) reanalyzed the data of an earlier study (Sanders and Cannon, 1975) in which young adult Wistar rats (35/sex) were administered beryllium oxide by nose inhalation only for 30-180 minutes. Serial necropsies were performed on 5 rats/sex at 1, 7, 14, 21, 35, 49 and 63 days after exposure. Feces, urine, lungs, thoracic lymph nodes, liver, kidneys and skeleton were analyzed for beryllium content. Beryllium was cleared slowly from the lung. After 63 days, only 12-21% of the beryllium had cleared the lungs (Sanders and Cannon, 1975). The time to clear 50% of the initial lung burden (138-156 μg total deposition) was 405 days. The data for beryllium demonstrated a two-phase lung clearance curve; during the rapid initial phase, 30% of initial lung burden was cleared with a half-time of 2.5 days and during the second phase, 70% of the initial lung burden was cleared with a half-time of 833 days. Beryllium had a whole-body clearance time very similar to that of the lung. However, whole-body clearance was best fit by a one-stage model. Beryllium did not concentrate in any tissue outside of pulmonary tissue and was not detected in the liver or skeleton at any time. Nearly all the material cleared from the lungs was recovered in the feces.

Metabolism

A few data are available on the metabolism of beryllium in the body. Early work on metabolism centered on the capacity of beryllium to produce

rickets in animals, which was thought to be partially due to an inactivation of alkaline phosphatase. More recent work is generally discussed in terms of the toxic effect mechanisms of beryllium. Therefore, these studies will be presented in Chapter VII, "Mechanism of Toxicity."

Excretion

The route of administration influences the route of excretion, at least in rats. Fecal excretion is the major route of excretion if administration is oral or inhalation. Approximately 60-90% of an oral dose of 6.6 and 66.6 μg/day was recovered in the feces of rats (Reeves, 1965). Rhoads and Sanders (1985) showed that nearly all the beryllium cleared from the lungs was excreted in the feces. Urinary excretion is the major route following parenteral administration of beryllium (Furchner et al., 1973). Small doses of intravenously administered beryllium in rats were excreted primarily through the urine; however, increasing the dose lowered the urinary excretion rate (Scott et al., 1950). Rats given an intravenous dose of beryllium at 9.3×10^{-11} g/kg bw excreted 38.8% of the dose within 24 hours; however, only 24.2% of a 1.5×10^{-4} g/kg bw dose of $BeSO_4$ was excreted. Citrated beryllium sulfate, when administered intratracheally, was mobilized from the lungs after 4 days and 79% was excreted, primarily in the urine. Non-citrated $BeSO_4$ stayed in the lungs for a longer period ($\leq$16 days), but the fate of both forms of $BeSO_4$ were ultimately the same (Van Cleave and Kaylor, 1955).

Over a 10-month period, Zorn et al. (1986) studied the changes in analytical and clinical parameters of 25 people accidentally exposed to beryllium dust for 10-20 hours. Although no exposed person showed any

symptoms of an acute beryllium intoxication, increased beryllium concentrations ≤5-fold could be detected in serum samples ~10 hours after exposure. The beryllium clearance showed a biologic half-time in the range of 2-8 weeks.

Summary

The three routes by which beryllium may enter the body are by ingestion, skin absorption and inhalation. From an exposure standpoint, the oral route is less significant since beryllium is only minimally absorbed from the GI tract. This poor rate of absorption of beryllium can be explained by its chemical properties. Because it is amphoteric, in aqueous solutions it can form positive or negative ions in acidic or basic media, but at pH 5-8, it forms only the hydroxide and poorly soluble particulates. Consequently, in the neutral environment of human tissues, beryllium salts are readily precipitated. Absorption of beryllium through unbroken skin adds only insignificant quantities to the body, even after prolonged or repeated contact. However, a contact dermatitis can occur.

The major route by which beryllium enters the body is by the lungs, where absorption and distribution to other tissues may occur. Following an initial clearance of 2.5 days, the time required to remove 50% of the deposited beryllium from the lungs is 405 days.

Once the beryllium enters through the lungs, its compounds may be transported from the lungs by the blood and lymph to other tissues. Insoluble compounds, however, such as beryllium ores, tend to remain in the lung for indefinite periods of time. Increased beryllium levels have been detected in human lungs as long as ≥20 years after the last exposure occurred.

The route of administration influences the route of excretion, at least in rats. Fecal excretion is the major route of excretion if administration is oral, since little beryllium is absorbed in the GI tract. Urinary excretion is the major route following parenteral administration of beryllium. Small doses of intravenously administered beryllium in rats were excreted primarily through the urine or deposited in the kidneys. Following inhalation exposure, urinary and fecal excretion appear to be the major routes of elimination.

IV. EXPOSURE

(Text to be provided by the Office of Drinking Water)

V. HEALTH EFFECTS IN ANIMALS

General Toxicity

Acute Toxicity.

Oral -- Beryllium compounds are less acutely toxic in animals when oral exposures are compared with other modes of administration. Lower acute oral toxicity has been attributed to the low rate of beryllium absorption from the GI tract. U.S. EPA (1977) reported the oral LD_{50} of beryllium to be 9.7 mg Be/kg (as $BeCl_2$). Oral LD_{50}s in rats for beryllium fluoride, beryllium chloride and beryllium sulfate were reported as 20, 200 and 120 mg Be/kg, respectively (Reeves, 1986). Rats fed diets of $\leq$2% beryllium carbonate survived for several weeks (Guyatt et al., 1933).

Parenteral Exposure -- Intravenous injections of small doses of beryllium are highly toxic to animals. Witschi and Aldridge (1967) reported an LD_{50} for soluble beryllium salts of 0.44 mg Be/kg for 200 g male rats, while Vacher and Stoner (1968) found an LD_{50} of 0.51 mg Be/kg for female rats injected with $BeSO_4$. Cheng (1956) showed that a single intravenous dose of 1.1 mg Be/kg bw as $BeSO_4$ could produce liver necrosis in rats. The intraperitoneal LD_{50} in mice was 18 mg/kg bw when administered as a sulfate (Basinger et al., 1982). Injection of beryllium into the spinal subarachnoid space or cerebello-medullary cistern resulted in changes in the CNS of rabbits (Zelman et al., 1967), and one study of rabbits noted osteosclerotic changes by this route (Gardner and Heslington, 1946).

Inhalation Exposure -- Inhalation represents the most common route of exposure to beryllium and its compounds. The most common effect of acute inhalation exposure is chemical pneumonitis. Susceptibility to the toxic effects of inhaled beryllium varies between species. Stokinger et al.

(1950) exposed several species to $BeSO_4$ for 6 hours/day, 5 days/week for 51 days at 2 mg Be/m³ and for 14 days at 4.3 mg Be/m³. Mortality rates for exposure to 2 mg Be/m³ varied greatly: 13/15 rats, 4/5 dogs, 4/5 cats, 1/10 rabbits, 7/12 guinea pigs, 1/1 monkeys, 5/10 hamsters and 3/48 mice. Exposure to 4.3 mg Be/m³ was lethal to 10/10 rats and 3/10 guinea pigs. Drury et al. (1978) noted that a variety of species exposed to $BeSO_4$ at 2 mg Be/m³ displayed two separate types of responses: 1) an acute phase in which the most susceptible species die and 2) a delayed phase in which there is little effect initially, but increasingly severe changes occur at $\leq$7-10 weeks of exposure. Pulmonary lesions were similar to those found in humans with acute beryllium disease.

Schepers (1964) exposed female monkeys to various beryllium compounds (fluoride, sulfate, phosphate) and found BeF_2 to be the most toxic while $BeHPO_4$ was least toxic. Monkeys (4/group) exposed to aerosols of either beryllium sulfate (202 µg Be/m³), beryllium fluoride (185 µg Be/m³) or beryllium phosphate (1141 or 8380 µg Be/m³) died of pneumonitis. The highest concentrations of $BeHPO_4$ studied (8380 µg Be/m³) killed all the monkeys within 20 days and concentrations of 1141 µg Be/m³ killed all the monkeys in 92 days. Reported effects included severe pulmonary reactions as well as changes in the liver, pancreas, spleen, adrenals, kidneys and thyroid. Many of these effects cannot be attributed to the high phosphate or fluoride concentrations of these compounds (Schepers, 1964).

The acute, cellular kinetic and histopathologic response of rat and mouse lung to $BeSO_4$ was investigated by Sendelbach (1986) and Sendelbach et al. (1986). Animals were exposed to 13 µg/ℓ (13 mg/m³) $BeSO_4$

in a nose-only chamber for 1 hour and killed over a period of 21 days; H_2SO_4 aerosol was used as a positive control. Cellular kinetics were measured as the labeling index (LI), defined as the percentage of cells labeled with tritiated thymidine and differentiated as to type. A peak LI response was seen in rats 8 days after exposure was terminated, while for mice a maximum response occurred on day 5. In rats, a proliferative response involving type II alveolar epithelial cells, interstitial and capillary endothelial cells was observed. Hyperplasia and vacuolization of the type II alveolar cell cytoplasm and a thickened interstitium with infiltrates of interstitial macrophages and segmental leukocytes was noted upon histopathologic examination. Alveolar macrophages with ragged membranes were also observed. Three weeks after exposure, the interstitial response was largely resolved. In mice, the proliferative response was mainly found in the alveolar macrophage population and the interstitial and endothelial cells. Histopathologic changes were similar to those found in rats, although less severe.

Intratracheal instillation is another route by which beryllium is administered. When used in a study in rabbits, Spencer et al. (1968) showed that at dose levels of 2 mg/kg bw, low-fired BeO (calcined at 500°C) caused pulmonary damage while high-fired BeO (calcined at 1600°C) produced a reaction roughly equivalent to that expected of an inert dust. These findings may again be related to solubility; calcining at 500°C produces a relatively soluble product with a large surface area, whereas beryllium calcined at 1600°C produces an insoluble compound.

Subchronic and Chronic Toxicity.

Oral Exposure -- There is only limited evidence of toxic effects following oral beryllium exposure. One of the earliest effects observed was the development of rickets in young rats fed diets containing soluble beryllium salts (Branion et al., 1931; Guyatt et al., 1933; Kay and Skill, 1934). Guyatt et al. (1933) reported that 21- to 24-day-old rats fed diets containing 0.125-3.0% beryllium carbonate developed rickets after 3 weeks. The effects were dose dependent with the lowest dose (1.25 g $BeCO_3$/kg diet or 163 mg Be/kg diet) resulting in a mild case of rickets while at higher doses there appeared to be an almost complete lack of calcification of the long bones (femur and tibia). Businco (1940) conducted a series of experiments in which young rats (30-40 g) were fed beryllium carbonate produced by different manufacturers. In one study, rats received daily doses of 0.06 g $BeCO_3$/animal on days 0-14, 0.16 g $BeCO_3$/animal on days 15-34 and 0.24 g $BeCO_3$/animal on days 35-83. A time-weighted average (TWA) dose of 0.19 g $BeCO_3$/rat (0.025 g Be) was estimated from the data provided by the author. No effects on body weight or general appearance were observed in animals fed 0.06 g $BeCO_3$. After 40 days of exposure, a 25% weight loss was observed in treated rats compared with controls. A reduction in weight gain of >50% was seen in treated animals at the end of the study (day 83). In addition, histologic and radiographic examination of the long bones (femur, tibia and fibula) and vertebrae revealed typical rackitic lesions.

Goel et al. (1980) gave 20 mg beryllium nitrate (1.35 mg Be) to eight male albino rats in their diet every third day for 2.5 months. Histopathologic examination of the lungs of treated animals revealed a number of pathogenic changes in the bronchioles, alveoli and arterioles including a

general hardening of the lungs. Since the compound was administered as a powder mixed with food pellets, lung effects may have resulted from aspiration of beryllium.

Schroeder and Mitchener (1975a) administered 5 mg/ℓ beryllium (as $BeSO_4$) in the drinking water of Long-Evans rats (52/group/sex) for life. Based on data provided in the study, this level corresponds to 0.538 mg Be/kg/day. At the time of natural death, the rats were weighed and dissected; gross and microscopic pathologic changes were evaluated. Specific organs examined included the heart, lung, liver, kidney and spleen, as well as any tumors. Blood and urine samples were also taken and clinical chemistry and urine analysis were performed. No treatment-related effects were observed in any parameter tested. There was a slight depression in growth of male rats from 2-6 months of age. A similar study was also conducted in Swiss (CD) mice, 54/sex, at doses of 0.98 mg Be/kg/day (Schroeder and Mitchener, 1975b). A slight decrease in body weight at 2 and 8 months of age was seen in females and a slight increase in male body weight was noted. No other treatment-related effects were found. Morgareidge et al. (1977) fed beryllium sulfate at 0, 5, 50 or 500 ppm diet to rats for 2 years. The only effect reported was a slight decrease in body weight in the high-dose group.

The biotoxicity of beryllium by the oral route was studied in hamsters (Watanabe et al., 1985). Powdered foods containing 5 mg Be as $BeSO_4$, BeO or Be-metal were fed to hamsters daily for 3-12 months. Body and organ weights and beryllium retention and distribution were monitored. The only toxic effects reported were a slight reduction in body weight in the $BeSO_4$ group when compared with controls, BeO or Be-metal fed groups.

Inhalation Exposure -- There are a number of chronic inhalation studies of beryllium in animals that report effects similar to humans. Several investigators have studied the effects of beryllium exposure in monkeys (Vorwald et al., 1966; Schepers, 1964), dogs (Robinson et al., 1968b; Conradi et al., 1971), guinea pigs (Reeves et al., 1971, 1972) and hamsters (Wagner et al., 1969). The most common effect seen in all species was chronic beryllium disease and pneumonitis.

Robinson et al. (1968a) reported that beagles exposed to rocket fuel exhaust containing beryllium fluoride, chloride and oxide at an average concentration of 115 mg .Be/m^3 developed lung tissue lesions representing early stages of chronic beryllium disease. Sanders and Cannon (1975) exposed rats and hamsters to BeO (calcined at 1000°C) at concentrations of 1-100 µg Be/ℓ (1-100 mg/m^3) of air, and reported rapid damage to alveolar macrophages that developed into a mild granulomatous reaction within 8 months of the exposure.

In a review of their earlier work, Vorwald et al. (1966) reported that in rats exposed to beryllium sulfate aerosol at concentrations of 2.8-194 µg/m^3, 7 hours/day for 1-560 days, there was a dose-related increase in lung toxicity. While exposures of 2.8 µg/m^3 did not result in any significant changes, exposure to 21 µg/m^3 caused significant inflammatory changes. At 42 µg/m^3 chronic pneumonitis was produced and exposure to 194 µg/m^3 resulted in acute beryllium disease.

Reeves et al. (1967) exposed Sprague-Dawley (CD strain) rats (150/sex/group) to 0 or 34 µg Be/m^3 (as $BeSO_4$) for 7 hours/day, 5 days/week for

72 weeks. Three rats/sex were killed every 3 months and histopathology of the lung tissue was performed. The most common findings were increased lung weight, inflammation and proliferation of lung tissue and increased macrophage infiltration of alveolar spaces.

Monkeys exposed intermittently to average daily concentrations of 35 $\mu g/m^3$ beryllium sulfate for several months developed typical chronic beryllium disease with pneumonitis and granulomatosis (Vorwald et al., 1966). Monkeys exposed to beryllium salts (sulfate, fluoride or phosphate) at levels of 200 μg Be/m^3 (6 hours/day up to 30 days) developed signs of toxicity typical of human chronic beryllium disease within 1-2 weeks following exposure to the sulfate or fluoride compounds and 30 days for the phosphate (Schepers, 1964). Exposure to 3.3 or 4.4 mg Be/m^3 for 30 minutes at 3-month intervals resulted in no pathologic changes in monkeys or dogs (Conradi et al., 1971).

One systemic effect shown in animals exposed by inhalation to beryllium is a mild, macrocytic-like anemia. Dogs, rats and rabbits exposed to beryllium fluoride at 2.2 ± 0.25 mg/m^3 for 6 hours/day, 5 days/week for 23 weeks all developed anemia, but the exact parameters were somewhat different for each species. In the dog, a decrease in hemoglobin level, red blood cell count and mean corpuscular volume that conformed to a normochromic macrocytic anemia was observed. Rabbits had less of a tendency toward lowered hemoglobin levels and tended to return to normal values. The rat maintained normal hemoglobin levels but the other two parameters resembled those seen in macrocytic anemia (Stokinger and Stroud, 1951).

Dermal Exposure -- Although inhalation of beryllium has been considered the classic route of exposure producing beryllium lung disease, Moritz et al. (1982) suggested that intradermal exposure should also be considered. Guinea pigs were injected with BeF_2 intradermally 2 times/week for 6 weeks at 10 µg/treatment. Since earlier studies in animals had shown dermal exposure to produce mononuclear cell alveolitis consisting of sensitized lymphocytes and activated alveolar macrophages, mononuclear cells were analyzed from the lung, spleen and blood. While there was no beryllium detected from the blood or spleen of the exposed animals, significantly large amounts of beryllium were detected in the mononuclear cells of the lung. This finding suggested that intradermal exposure may result in selective accumulation of beryllium in the lung.

Target Organ Toxicity

While several organs may be affected by beryllium exposure, the significant target organ is the lung. Insoluble forms of beryllium remain in the lungs for indefinite periods of time (Wagner et al., 1969), and increased levels have been detected in humans $\geq$20 years after the last exposure (Sprince et al., 1976). Beryllium may also accumulate in the lung following intradermal exposure (Moritz et al., 1982). The noncarcinogenic effects of beryllium in the lung (acute and chronic disease) have been discussed in previous sections and the carcinogenic effects (lung cancer) are described in following sections.

A large portion of the beryllium entering the body by any route is deposited in the skeleton, which is a second major target organ. Ionic and citrated beryllium are bone seekers (Crowley et al., 1949; Klemperer et al.,

1952), and intratracheally administered BeO was also reported to be deposited in greatest concentrations in the bone (Spencer et al., 1972). The latter study also showed that lesser concentrations were deposited in the liver, spleen, kidney and muscle. The effects on the bone include beryllium rickets (Branion et al., 1931; Guyatt et al., 1933; Kay and Skill, 1934) and osteosarcoma (Dutra et al., 1951; Gardner and Heslington, 1946).

Liver necrosis was reported to occur following a single intravenous dose of $BeSO_4$ in rats (Cheng, 1956) on injection of beryllium into the subarachnoid space or cerebello-medullary cistern has caused CNS changes in rabbits (Zelman et al., 1967). Beryllium also exerts an effect on the blood system, as demonstrated by the development of a macrocytic-like anemia in dogs, rats and rabbits exposed to inhaled BeF_2 (Stokinger and Stroud, 1951).

Carcinogenicity

Beryllium compounds can induce malignant tumors in laboratory animals either by injection or inhalation (Vorwald et al., 1966). The two types of cancers observed to date are lung cancer and osteosarcoma. Gardner and Heslington (1946) reported induction of osteosarcoma following injections of zinc beryllium oxide into rabbits. Since then, numerous other studies of beryllium compounds have produced similar results. Most of the studies utilized intravenous exposure and demonstrated that many different beryllium compounds, including beryllium metal, are tumorigenic by this route. Tapp (1969) surgically implanted 10 mg of zinc beryllium silicate, beryllium silicate, or beryllium oxide into rabbits and reported the development of osteogenic sarcomas within a period of 10-25 months for all three. The initial finding was a granulomatous reaction, which was more severe with the

silicate than the oxide. Subsequent tumors were shown to have metastasized to the lung. The only study reporting the development of osteosarcoma following inhalation exposure was that of Dutra et al. (1951) in which 1/6 rabbits exposed to 6 mg Be/m³ as BeO for 25 hours/week for 11 months developed malignancies. A summary of the studies resulting in osteosarcoma is presented in Table V-1. Studies of oral exposures conducted in the 1930s, described earlier, produced a type of osteosclerosis but not osteosarcoma. However, these experiments were conducted in a shorter time frame than that expected to allow for the development of tumors.

A study using two dogs fed 1.3 g beryllium carbonate for 104 days or 0.5-1.5 g beryllium carbonate for 109 days revealed no tumors upon examination of the teeth and parathyroid glands (Casarotto, 1952). Likewise, no tumors were found in mice given 1% beryllium sulfate in drinking water over a period of 1 year (Barnes et al., 1950). Schroeder and Mitchener (1975a,b) reported a slight but nonsignificant increase in leukemias in female mice and a slightly higher but nonsignificant incidence of grossly observed tumors in male rats fed beryllium sulfate at a concentration of 5 ppm in drinking water over a lifetime.

In an unpublished 2-year study, Morgareidge et al. (1975) administered dietary levels of 0, 5, 50 and 500 ppm Be as beryllium sulfate to Wistar albino rats (50/sex/group). Reticulum cell sarcoma in the lung was seen in all dose groups and in controls, and the same lesions were seen in lymph nodes, bone marrow and abdominal organs. The incidence of lung reticulum cell sarcoma was higher in males than females and was statistically significant in males at the lowest two doses but not the highest dose. This study

TABLE V-1

Induction of Osteosarcomas in Experimental Animals by Beryllium[a]

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors[b]	Time of Measurement (months)	Reference
Beryllium oxide	6 mg/m³	inhalation	5 hours/day, 5 days/week, 11 months	rabbit	16	11	Dutra et al., 1951
	NR	multiple i.v.		rabbit	25	NR	Nash, 1950
	90-660 mg as Be, 13-116 mg/kg bw as Be	17-21 i.v.		rabbit	89	9+	Dutra and Largent, 1950
	100-200 mg total	1-45 i.v.		rabbit	0	NR	Kawada, 1963
	1250 mg total	i.v.	25 weekly injections	rabbit	72	NR	Fodor, 1971
	large animals: 1 g total small animals: <1 g	i.v.		rabbit	6	15	Komilowski, 1969
	100 mg total	injection into femur	10 weekly injections	rabbit	60	19	Kawada, 1963
	450 mg total	injection into femur	45 weekly injections	rabbit	88	11	Kawada, 1963
	300 mg total	one injection into femur		rabbit	70	12	Kawada, 1963
	300 mg total	injection, femur periosteum		rabbit	78	14.5	Kawada, 1963
	10 mg	implanted under right tibia periosteum		rabbit male and female	33	10-25	Tapp, 1969
	220-400 mg	injected into femur	twice weekly for 1-43 weeks	rabbit	89	85 days-average latency from last injection	Yamaguchi and Katsura, 1963

TABLE V-1 (cont.)

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors[b]	Time of Measurement (months)	Reference
Beryllium oxide (cont.)	420-600 mg	injected into femur	twice weekly for 1-43 weeks	rabbit	100	85 days-average latency from last injection	Yamaguchi and Katsura, 1963
	620-800 mg	injected into femur	twice weekly for 1-43 weeks	rabbit	50	85 days-average latency from last injection	Yamaguchi and Katsura, 1963
	820-860 mg	injected into femur	twice weekly for 1-43 weeks	rabbit	75	85 days-average latency from last injection	Yamaguchi and Katsura, 1963
Zinc beryllium oxide[c]	1 g total	i.v.	20 injections over 6 weeks	rabbit	100	7+	Gardner and Heslington, 1946
	1 g	multiple i.v. injections		rabbit	25	30+	Barnes et al., 1950; Sissons, 1950
	1 g	i.v.	22 semi-weekly injections	rabbit	80	12+	Cloudman et al., 1949
Zinc beryllium silicate	0.264 mg	multiple i.v. injections		mice	Some positive, percent not reported	NR	Cloudman et al., 1949
	1 g total	i.v.	10 weekly injections	rabbit	60	11-24	Hoagland et al., 1950
	1 g total	i.v.	20 twice-weekly injections	rabbit	50	9-11	Janes et al., 1954
	NR	i.v.	10 weekly injections	rabbit	71	9-14	Kelly et al., 1961
	1 g total	injection	20 weekly injections	rabbit	30	NR	Higgins et al., 1964
	10 mg	implanted under right tibia periosteum		rabbit	16	10-25	Tapp, 1969

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors[b]	Time of Measurement (months)	Reference
Zinc beryllium silicate (cont.)	33 mg as Be	Injection intra-osseous		rabbit	70	4	Mazabraud, 1975
Beryllium silicate	10 mg	Implanted under right tibia periosteum		rabbit	16	10-25	Tapp, 1969
Metallic beryllium	40 mg	i.v.		rabbit	40	NR	Barnes et al., 1950
Beryllium phosphate	16 mg total	i.v.	10 weekly injections	rabbit	Some positive, percent unknown	11-24	Hoagland et al., 1950
Beryllium phosphor[d]	90 mg	i.v.		rabbit	1/1	12-14	Dutra and Largent, 1950
	80 mg	i.v.		rabbit	1/1	12-14	Dutra and Largent, 1950
	64 mg	i.v.		rabbit	0/1	12-14	Dutra and Largent, 1950

[a]Source: U.S. EPA, 1980a

[b]Percent exhibiting tumors or cancer

[c]1 g of zinc beryllium silicate contains 33.6 mg of Be expressed as the oxide

[d]Be oxide, Zn oxide and silica in a molar ratio of 1:1:1

NR = Not reported

is considered to be suggestive of a carcinogenic response to ingested beryllium, but the lack of a response at the highest dose level severely limits interpretation as a positive study.

Numerous studies have demonstrated the development of pulmonary cancer in animals exposed to beryllium. The majority of these studies used an inhalation or intratracheal route of exposure; a summary of these data are presented in Table V-2. A more detailed discussion of these studies can be found in U.S. EPA (1987). Development of lung cancer generally required 7-18 months in rats and 5-6 years in monkeys (Vorwald et al., 1966). Pulmonary tumors were produced in 18/19 rats that survived exposure to 15 mg beryl ore/m^3 over 17 months (Wagner et al., 1969). Reeves et al. (1967) exposed 150 rats to 34 µg Be/m^3 in an aerosol for 35 hours/week for a 72-week period. The initial response appeared 4 weeks after the first exposure and consisted of hyperplasia of the pulmonary epithelium, which progressed to metaplasia and lung cancer. The first tumors were discovered after 9 months of exposure, and the incidence rate was 100% at 13 months. The tumor type was alveolar adenocarcinoma.

Studies by Groth et al. (1976) found that the size, number and characteristics of lesions produced by single intratracheal injections of beryl, BeO, $Be(OH)_2$, beryllium metal, Be-aluminum alloy and chromium-passivated beryllium were determined by the age of the rat and the dose of the compound. Metaplastic foci were found in greater numbers in the older rats at the higher doses; no foci were found in the low-dose group. Groth et al. (1972) showed that the lowest dose producing interstitial fibrosis, mast cell and lymphocytic infiltrates and proteinaceous material in the alveoli

TABLE V-2

Induction of Pulmonary Cancer in Experimental Animals by Beryllium Compounds[a]

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors	Time of Measurement (months)	Reference
Beryllium sulfate	0.11 mg as Be	Intratracheal	NA	rat	Some positive, percent not reported	9 or longer	Vorwald and Reeves, 1959
	6 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	rat	Some positive, percent not reported	9 or longer	Vorwald and Reeves, 1959
	55 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	rat	Some positive, percent not reported	9 or longer	Vorwald and Reeves, 1959
	35 µg/m³ as Be	Inhalation	6 months	rat	Some positive percent not reported	18	Schepers, 1961
	2.8 µg/m³ as Be	Inhalation	7 hours/day, 5 days/week, 18 months	rat	62	18	Vorwald et al., 1966
	21 µg/m³ as Be	Inhalation	7 hours/day, 5 days/week, 18 months	rat	almost 100	18	Vorwald et al., 1966
	42 µg/m³ as Be	Inhalation	7 hours/day, 5 days/week, 18 months	rat	almost 100	18	Vorwald et al., 1966
	34 µg/m³ as Be	Inhalation	7 hours/day, 5 days/week, until sacrifice	rat, male and female	100	13	Reeves et al., 1967
	35 µg/m³ as Be	Inhalation	7 hours/day, 5 days/week, 18 months	monkey, rhesus	20, 2 of 10 exposed 3241 3871 hours	5-6 years	Vorwald et al., 1966
	2.32 mg/m³ 0.20 mg/m³ as Be	Inhalation	6 hours/day, 7 days	monkey, Macacus mullata	0, only 1 of 4 survived 180 days	8	Schepers, 1964

TABLE V-2 (cont.)

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors	Time of Measurement (months)	Reference
Beryllium oxide	4.5 mg as Be	Intratracheal	NA	rat	Some positive, percent unknown	9 or longer	Vorwald and Reeves, 1959
	25 mg calcined at 500°C	Intratracheal	NA	rat, male and female	100	15-20	Spencer et al., 1968
	25 mg/kg calcined at 1100°C	Intratracheal	NA	rat, male and female	25	15-17	Spencer et al., 1968
	25 mg calcined at 1600°C	Intratracheal	NA	rat, male and female	30	18 24	Spencer et al., 1968
	50 mg/kg calcined at 500°C	Intratracheal	NA	rat, female	0	11	Spencer et al., 1972
	50 mg/kg calcined at 500°C	Intratracheal	NA	rat, female	40	17	Spencer et al., 1972
	50 mg/kg calcined at 500°C	Intratracheal	NA	rat, female	100	23	Spencer et al., 1972
	250-500 mg	Intratracheal	NA	monkey, rhesus	15	54+	Vorwald et al., 1966
Beryllium fluoride	48 µg/m³	Inhalation	6 months	rat	10-12 in 200	15	Schepers, 1961
	950 µg/m³ 180 µg/m³ as Be	Inhalation	6 hours/day, 7-16 days	monkey, Macacus mullata	0, all died within 28 days of exposure	<1	Schepers, 1964
Beryllium fluoride and chloride	0.2 or 0.4 mg/m³	Inhalation	1 hour/day, 5 days/week, 4 months	rat	Some positive, percent unknown	22	Litvinov et al., 1975

TABLE V-2 (cont.)

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors	Time of Measurement (months)	Reference
Beryllium phosphate	3.5 mg/m³	Inhalation	6 months	rat	Some positive, percent unknown	12	Schepers, 1961
	2.32 mg/m³ 0.20 mg/m³ as Be	Inhalation	6 hours/day, 30 days	monkey, Macacus mullata	0	up to 9 post-exposure	Schepers, 1964
	13.1 mg/m³ 1.11 mg/m³ as Be	Inhalation	6 hours/day, 10 days	monkey, Macacus mullata	1 of 4 (25%) exposed survived 82 days post exposure and developed cancer	up to 82 days	Schepers, 1964
Zinc beryllium silicate	24 mg/m³	Inhalation	6 months	rat	Some positive, percent unknown	9	Schepers, 1961
Beryl ore	15 mg/m³ 210 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	rat	95	17	Wagner et al., 1969
	15 mg/m³ 210 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	hamster	0	17	Wagner et al., 1969
	15 mg/m³ 210 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	squirrel monkey, Saimiri sciurea	0	23	Wagner et al., 1969
Bertrandite ore	15 mg/m³ 620 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	squirrel monkey, Saimiri sciurea	0	23	Wagner et al., 1969
Bertrandite ore	15 mg/m³ 620 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	rat	0	17	Wagner et al., 1969
	15 mg/m³ 620 µg/m³ as Be	Inhalation	6 hours/day, 5 days/week until sacrifice	hamster	0	17	Wagner et al., 1969

TABLE V-2 (cont.)

Compound	Dose	Exposure Route	Exposure Duration	Species	Percent Exhibiting Tumors	Time of Measurement (months)	Reference
Beryllium hydroxide	0.4 µg Be	Intratracheal	NA	rat, 3 months old	0	6	Groth et al., 1976
	0.4 µg Be	Intratracheal	NA	rat, 12 months old	0	6	Groth et al., 1976
	4 µg Be	Intratracheal	NA	rat, 6 months old	0	6	Groth et al., 1972
	4 µg Be	Intratracheal	NA	rat, 12 months old	0	6	Groth et al., 1972
Beryllium hydroxide	40 µg Be	Intratracheal	NA	rat, 3 months old	0	6	Groth and MacKay, 1971
	40 µg Be	Intratracheal	NA	rat, 12 months old	10	6	Groth and MacKay, 1971

*Source: U.S. EPA, 1980a

NA = Not applicable

was 4 µg. Metaplasia was produced at the 4 µg dose and was considered by the authors to represent a probable precancer condition (Groth and MacKay, 1971).

Developmental Toxicity

Limited information is available concerning the teratogenic potential of beryllium and its salts. Raven and Spronk (1953) reported that beryllium exposure resulted in morphogenic abnormalities in the embryo of the snail (Lymnea stagnalis). Limb regeneration of the salamander (Amblystoma punctatum) was inhibited when immersed in a 0.05 molar solution of beryllium nitrate (Thornton, 1950).

Pertinent data regarding the developmental toxicity of beryllium after inhalation, oral or dermal exposure in animals were not located in the available literature. Selivanova and Savinova (1986) treated pregnant rats intratracheally with beryllium chloride or beryllium oxide at 0 or 50 mg/kg on day 3, 5, 8, or 20 of gestation. Statistically significant ($p<0.05$) differences compared with controls included increased fetal mortality in rats treated with beryllium chloride on day 5 and with beryllium oxide on days 3 and 5, decreased average fetal weight in rats treated with either compound on day 3, and increased percentage of pups with internal abnormalities in rats treated with beryllium chloride on days 3 and 5 and with beryllium oxide on days 3, 5 and 8. There were no differences in the number of live births/dam or in fetal length.

Hoshishima et al. (1978) presented a brief abstract and later a more extensive report (Tsujii and Hoshishima, 1979) on the effects of trace

quantities of beryllium injected into pregnant CFW strain mice. Six females per group were exposed to $BeSO_4$ (140 ng/mouse/day). The mice received intraperitoneal injections (0.1 mℓ) 11 times during pregnancy. The injections were given once for 3 consecutive days and then every other day for eight treatments. The offspring (24/group) were tested for changes in reflexes and behavioral characteristics from days 1-16 of birth. Beryllium (140 ng/day) produced the following differences in the pups exposed in utero as compared with the control group: delayed response in head turning in the geotaxis test, acceleration in the straight walking test, delayed bar holding (for a moment) response, and acceleration of bar holding (for 60 seconds).

In a study by Bencko et al. (1979) the soluble salt of beryllium, $BeCl_2$, was evaluated for its ability to penetrate the placenta and reach the fetus. Radiolabeled $^7BeCl_2$ (0.1 mg/kg) was injected into the caudal vein of 7-9 ICR SPF mice and was administered in three different time periods: 1) before copulation (group A), 2) the 7th day of gestation (group B), and 3) the 14th day of gestation (group C). The animals were sacrificed on the 18th to 19th day of pregnancy and the radioactivity associated with the fetal and maternal compartment were evaluated.

In fetuses exposed on the 14th day of gestation, higher levels of radioactivity were associated with the fetal compartment as compared with other exposure periods, (group A, 0.0002 μg ^7Be/g fetus, group B, 0.0002 μg ^7Be/g fetus, and group C, 0.0013 μg ^7Be/g fetus). The amount of radioactivity in selected organs of the mothers was generally not influenced by beryllium exposure, except the spleen and liver. The amount of ^7Be

penetrating the spleen was decreased, while in the liver it was increased when $^{7}BeCl$ was given on the 14th day of pregnancy.

Puzanova et al. (1978) conducted a two-phase study on the effects of beryllium on the development of chick embryos. In the first phase, $BeCl_2$ (0.00003-300 µg dissolved in 3 µl twice-distilled water) was injected subgerminally into chick embryos (10 embryos per dose) on the second day of embryogenesis. After a 24-hour incubation, the eggs were opened and stained with 0.1% neutral red, and the distance between the origin of the vitelline arteries and the caudal tip of the body measured. In the second phase, the doses of $BeCl_2$ that were toxic but not lethal (0.03-0.3 µg) were administered subgerminally to 2-day embryos, and intra-amniotically to 3- and 4-day embryos. The surviving embryos were examined after the sixth day of incubation.

A dose of 300 µg $BeCl_2$ caused complete embryolethality while 0.3 µg was not lethal to any embryos. Doses of $\leq$0.003 µg had no observable effect on the development of the embryos. When the eggs were treated on day 2, the most common malformation was caudal regression, open abdominal cavity and ectopia cordis. When administered on the fourth day, malformations described as strait jacket syndrome, exencephalia and mandibular malformation were described. It is not known, however, if these types of teratogenic effects in chick embryos are reflective of effects that might occur in humans. Additional studies would have to be conducted using mammals to determine whether beryllium has teratogenic potential.

Reproductive Toxicity

Pertinent data regarding the reproductive toxicity of beryllium after inhalation, oral or dermal exposure in animals were not located in the available literature.

Clary et al. (1975) treated male and female Sprague-Dawley rats intratracheally with ^{7}BeO (0.2 mg Be/rat) calcined at 960°C or 500°C or with saline. The rats were allowed to mate repeatedly over a 15-month period. There were no consistent effects on reproductive performance as determined by the average number of pregnancies per female, live pups/litter, dead pups/litter, live pups/female, lactation index or average fetal weight.

Mutagenicity

Beryllium has been tested for its ability to cause genetic damage in both prokaryotic and eukaryotic systems. The prokaryotic systems include gene mutations and DNA damage in bacteria. The eukaryotic systems include DNA damage and gene mutations in yeast and cultured mammalian cells and studies for chromosomal aberrations and sister chromatid exchanges in mammalian cells *in vitro*. The available literature indicates that beryllium does not induce mutations in bacteria and yeast but does cause gene mutations, chromosomal aberrations, and sister chromatid exchange in mammalian somatic cells in culture (Tables V-3, V-4 and V-5).

Gene Mutations in Bacteria.

Simmon (1979a) found beryllium sulfate to be negative in mutagenic response in *Salmonella typhimurium* strains TA1535, TA1536, TA1537, TA98 and TA100. Liquid incubation assay with and without S-9 metabolic activation as

TABLE V-3

Mutagenicity Testing of Beryllium: Gene Mutations in Bacteria*

Test System	Strain	Concentration of Test Compounds	S-9 Activation System	Results	Comments	Reference
Salmonella typhimurium	TA1535 TA1536 TA1537 TA100 TA98	250 µg/plate $BeSO_4$	±	Reported negative in all strains	Highest concentration tested	Simmon, 1979a
S. typhimurium	TA1530 TA1535 TA1538	mice treated with $BeSO_4$, 25 mg/kg bw i.m. or 1200 mg/kg bw gavage	Host-mediated assay	Reported negative in all strains by both routes of exposure	Mice served as host for 4 hours	Simmon et al., 1979
S. typhimurium	TA1535 TA1538	25 µg/plate 250 µg/plate $BeSO_4$	±	Reported negative		Rosenkranz and Poirier, 1979
Escherichia coli	WP2	0.1-10 µmol/plate (10.5-105 µg Be/plate)		Reported negative		Ishizawa, 1979
E. coli (pol assay)	Pol A^+ Pol A^-	250 µg/plate $BeSO_4$	±	Reported negative		Rosenkranz and Poirier, 1979

*Source: U.S. EPA, 1987

TABLE V-4

Mutagenicity Testing of Beryllium: Gene Mutations in Yeast and Mammalian Cells in vitro*

Test System	Strain	Concentration of Test Compounds	S-9 Activation System	Results	Comments	Reference
Chinese hamster	V79 cells; resistance to 8-azaguanine	2 mM (10 µg/mℓ) 3 mM (15 µg/mℓ) beryllium chloride	None	Reported positive	99% pure, no dose response	Miyaki et al., 1979
Chinese hamster	CHO cells; resistance to 8-azaguanine	Not stated	±	Reported positive, weakly mutagenic	No details	Hsie et al., 1979a,b
Saccharomyces cerevisiae	D_3	mice treated with $BeSO_4$, 25 mg/kg bw i.m., or 1200 mg/kg bw gavage	Host-mediated assay	Reported negative	Mice served as host for 4 hours	Simmon et al., 1979

*Source: U.S. EPA, 1987

TABLE V-5

Mutagenicity Testing of Beryllium: Mammalian *in vitro* Cytogenetics Tests*

Test System	Species	Concentration $BeSO_4 \cdot 4H_2O$	S-9 Activation System	Results
Chromosomal aberrations	Human lymphocytes	2.82×10^{-5} M (5 µg/mℓ)	--	Reported positive
Chromosomal aberrations	Syrian hamster embryo cells	2.82×10^{-5} M (5 µg/mℓ)	--	Reported positive
Sister chromatid exchanges	Human lymphocytes	5.6×10^{-6} M (1 µg/mℓ) 1.41×10^{-5} M (2.5 µg/mℓ) 2.82×10^{-5} M (5 µg/mℓ)	--	Reported positive
Sister chromatid exchanges	Syrian hamster embryo cells	5.6×10^{-6} M (1 µg/mℓ) 1.41×10^{-5} M (2.5 µg/mℓ) 2.82×10^{-5} M (5 µg/mℓ)	--	Reported positive

*Source: Larramendy et al., 1981

described by Ames was employed. The highest concentration of beryllium sulfate tested was 250 µg/plate (1.41 µmole).

No significant differences in the mutation frequencies between the experimental and the control plates were noted in S. typhimurium strains TA1535 and TA1538 with and without S-9 activation system (Rosenkranz and Poirier, 1979). The concentrations of the $BeSO_4$ used were 25 and 250 µg/plate.

Beryllium sulfate ($BeSO_4$) was assayed in the Ames S. typhimurium mutagenesis assay using the usual five tester strains with and without metabolic activation (Tong et al., 1985). $BeSO_4$ was not mutagenic in this assay.

The mutagenic activity of beryllium sulfate was tested in the intraperitoneal host-mediated assay, with the tester strains of S. typhimurium TA1530, TA1535 and TA1538 (Simmon et al., 1979). Mice were injected intramuscularly with 25 mg $BeSO_4$/kg bw or were administered 1200 mg $BeSO_4$/kg bw orally. Four hours after the treatment, microorganisms were recovered from the peritoneal cavity and plated for mutant colonies. Mutation frequencies significantly different from control frequencies were not observed.

A negative mutagenic response in the Escherichia coli WP2 system was obtained with beryllium sulfate at concentrations ranging from 0.1-10 µmole/plate (Ishizawa, 1979).

These results should not be taken as proof that beryllium is nonmutagenic because as discussed by McCann et al. (1976), bacterial and yeast systems are generally insensitive for the detection of metal mutagens, and because of the large amounts of magnesium salts, citrate and phosphate in the minimal medium, which prevents the entry of metal mutagens into bacterial cells.

Gene Mutations in Yeast and Cultured Mammalian Cells. Beryllium has been tested for mutagenic activity in yeast assay systems. Simmon (1979b) tested $BeSO_4$ (0.5%) in the tester strain D_3 of Saccharomyces cerevisiae with and without S-9 activation. $BeSO_4$ did not increase mitotic recombination. The mutagenic activity of $BeSO_4$ was also tested in the intraperitoneal host-mediated assay with strain D_3 of S. cerevisiae (Simmon et al., 1979). Mice were injected intramuscularly with 25 mg $BeSO_4$/kg bw or were administered 1200 mg $BeSO_4$/kg bw orally. Four hours after the treatment, microorganisms were recovered from the peritoneal cavity and plated for mutant colonies. Mutation frequencies significantly different from control frequencies were not observed.

The induction of 8-azaguanine-resistant mutants by beryllium chloride was demonstrated in the Chinese hamster V79 cells (Miyaki et al., 1979). Beryllium chloride at concentrations of 0, 2 and 3 mM induced mutations (35.0$\pm$1.4 and 36.5$\pm$1.7 mutant colonies per 10^6 survivors) at ~6 times the control. The cell survival rates were 56.9% at 2 mM concentration and 39.4% at 3 mM. Analysis of mutant colonies revealed that they were deficient in the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) indicating that the mutation had occurred at the HGPRT locus.

Tong et al. (1985) tested $BeSO_4$ in the adult rat liver epithelial cell hypoxanthine guanine phosphoribosyl transferase (ARL/HGPRT) mutagenesis assay. $BeSO_4$ did not induce a significant increase in mutant incidence.

Hsie et al. (1979a,b) also reported that beryllium sulfate induced 8-azaguanine-resistant mutants in the Chinese hamster ovary (CHO) cells. However, the authors did not provide details about the concentrations of the test compound and the number of mutants induced per 10^6 survivors.

These studies indicate that beryllium has the ability to cause gene mutations in cultured mammalian cells.

Cytogenetic Effects. Beryllium causes chromosomal abnormalities and mitotic changes in cell cultures (Vegni-Talluri and Guiggiani, 1967). It also induces molecular aggregation and flocculation, suggesting an irreversible nucleic acid effect (Needham, 1974). Beryllium sulfate (2.82×10^{-5} M; 5 µg $BeSO_4$/mℓ) was tested for its clastogenic potential in cultured human lymphocytes and Syrian hamster embryo cells (Larramendy et al., 1981). A minimum of 200 metaphases were scored for chromosomal aberrations. In the treated human lymphocytes, there were 19/200 cells (9.5%) with chromosomal aberrations or 0.10 ± 0.02 aberrations per metaphase. In the control cells, only three cells (1.5%) had chromosomal aberrations. This 6-fold increase in the aberration frequency was primarily due to an increase in DNA breaks.

A concentration of 2.82×10^{-5} M beryllium sulfate induced aberrations in 38/200 Syrian hamster embryo cells (19%) 24 hours after the treatment.

Aberrations per metaphase were 0.21±0.03 and 0.01±0.01 aberrations per cell in treated and control cells, respectively. In these studies, chromosomal gaps were also considered as aberrations; however, this does not significantly enhance the aberration frequency. These results indicate that beryllium sulfate has clastogenic potential in cultured mammalian cells (Larramendy et al., 1981).

Larramendy et al. (1981) also studied the potential of beryllium to induce sister chromatid exchanges. Both cultured human lymphocytes and Syrian hamster embryo cells were employed in these studies. Exposure of lymphocytes to 5.6×10^{-6} M (1.0 µg/mℓ), 1.41×10^{-5} M (2.5 µg/mℓ) and 2.82×10^{-5} M (5 µg/mℓ) of beryllium sulfate resulted in dose-dependent increases in sister chromatid exchanges of 17.75±1.10, 18.15±1.79 and 20.70±1.01, respectively. At least 30 metaphases were scored for each concentration of the test compound. The background sister chromatid exchange level was 11.30±0.60.

In the Syrian hamster embryo cells the same concentrations of beryllium sulfate induced sister chromatid exchanges of 16.75±1.52, 18.40±1.49 and 20.50±0.98, respectively. The background sister chromatid level was 11.55±0.84. Although the authors state that a dose-response relationship was shown, it should be noted that increases were <2-fold.

Other Tests of Genotoxic Potential. Kanematsu et al. (1980) found beryllium sulfate (0.01 M) to be weakly positive in the Rec assay. Inhibitions of growth were measured in both Bacillus subtilis strains H17 (rec^+) and M75 (rec^-). The difference in growth between wild-type and

sensitive strain was 4 mm, which was considered to indicate a weak positive response. Similar results were also obtained by Kada et al. (1980). However, Rosenkranz and Poirier (1979) and Rosenkranz and Leifer (1980) reported beryllium sulfate (250 µg) did not result in differential killing in the E. coli Pol A assay.

William et al. (1982) reported that beryllium sulfate at concentrations ≤10 mg/ml did not induce unscheduled DNA Synthesis in primary rat hepatocytes.

Kubinsky et al. (1981) reported that beryllium induces DNA-protein complexes (adducts) when E. coli cells and Ehrlich ascitis cells were treated with radioactive DNA in the presence of 30 mM of beryllium.

Skilleter et al. (1983), using cytofluorometric analysis in cultured synchronized rat liver-derived epithelial cells, demonstrated that beryllium blocked the cell cycle at the G_1-S phase and caused inhibition of cell division. The remaining parts of the cell cycle, namely the final portion of S, G_2 and M, showed no significant variation in DNA content.

Beryllium sulfate did not induce mitotic recombination in the yeast Saccharomyces cerevisiae D_3 (Simmon, 1979b). A single concentration (0.5%) of beryllium induced 10 mutant colonies/10^5 survivors; in the control the frequency was 6 colonies/10^5 survivors, a 3-fold increase. The negative response of beryllium may be due to the fact that it is not able to penetrate into the cell as in other microbial tests.

Other Effects in Cell Cultures. Newman and Campbell (1986) cultured $B6D2F_1$ mouse spleen cells, bone marrow cells, thymus cells, nylon non-adherent spleen T-cell, and nude mouse spleen cells in the presence of varying concentrations of $BeSO_4$. Mitogenesis was measured as the increase in iodouracildeoxyriboside (^{125}IUdR) incorporation into lymphocyte DNA. $BeSO_4$ was weakly mitogenic for mouse $B6D2F_1$ spleen cells. However a more marked response occurred with bone marrow cells and nude mouse spleen cells suggesting an effect on B-cells. Thymocytes and B-cell depleted nylon nonadherent T-cells showed no response to beryllium.

The toxicity of beryllium was evaluated using a mammalian cell culture system (Mochida and Gomyoda, 1986). Since the ID_{50} (a 50% inhibitory dose to growth of cells after 72 hours of incubation) values for HEL-R66, KB, Vero and MDCK cells to beryllium were $0.8x10^{-3}$, $1x10^{-3}$, $0.9x10^{-3}$ and $1.2x10^{-3}$ mM, respectively, there was no remarkable difference in the sensitivity for these cells to beryllium.

Summary

Beryllium is toxic by several routes of exposure. Oral exposure represents the least toxic route, presumably because of poor absorption. Beryllium rickets and slight growth depression have been reported in male rats following chronic oral exposures. The available cancer bioassay data base for oral exposure is limited to two studies, both of which have major deficiencies. From these studies, no substantial evidence exists that the ingestion of beryllium in any form causes tumors. For these reasons, the oral carcinogenic potential of beryllium can be neither demonstrated nor refuted. However, evidence of inhalation, injection and i.v. exposures with

notable carcinogenic responses raises suspicion that beryllium may be a carcinogenic risk by oral exposure. The tumorigenic potential of beryllium by ingestion exposure may be modulated by minimal intestinal absorption (<1%). Inhalation exposure results in both acute and chronic lung disease, anemia and cancers of the lung and bone. Pulmonary lesions observed in various species resembled those of humans with acute beryllium disease, and the toxic effect varied both with the species exposed and the beryllium compound used. One study has reported changes in the liver, pancreas, kidneys, thyroid, adrenals and spleen. A mild, macrocytic-like anemia has also been produced by inhalation exposure in rats, rabbits and dogs, with specific reactions varying between species. One study provided suggestive evidence of the induction of osteosarcomas by inhalation, and numerous studies confirm the development of pulmonary cancer in animals exposed to inhaled beryllium. Pulmonary lesions are also produced by intratracheal administration.

Administration by injection of even small amounts of beryllium is extremely toxic to animals, with toxic effects produced in the liver and lung. One study has also reported CNS changes, while others have noted osteosarcoma.

Dermal absorption was recently reported as a route deserving more attention because of a possible selective accumulation of beryllium in the lung when administered intradermally.

Very few studies have investigated the teratogenic or reproductive effects produced by beryllium exposure. An evaluation of reflexes and

behavioral responses of offspring exposed to beryllium sulfate during pregnancy showed delayed responses in the glotaxis test and bar holding response. Soluble beryllium salts have been shown to penetrate the placenta and accumulate in the fetal compartment. However, results of a recent Russian study in pregnant rats indicate that beryllium compounds may have the potential to produce adverse teratogenic effects. A study designed to investigate the reproductive toxicity in rats showed no consistent effect on reproductive performance. The current reproductive and teratogenic data are not sufficient to determine whether beryllium or its compounds have the potential to produce adverse effects.

Beryllium has been tested for its ability to cause genetic damage in both prokaryotic and eukaryotic systems. The prokaryotic systems include gene mutations and DNA damage in bacteria. The eukaryotic systems include DNA damage and gene mutations in yeast and cultured mammalian cells and studies for chromosomal aberrations and sister chromatid exchanges in mammalian cells in vitro. The available literature indicates that beryllium has the potential to cause gene mutations, chromosomal aberrations, and sister chromatid exchange in mammalian somatic cells. In addition beryllium salts are mitogenic for mouse B-cells in vitro and not for T-cells.

VI. HEALTH EFFECTS IN HUMANS

Introduction

Exposure to beryllium causes a variety of toxic effects in both animals and humans. In humans, dose-response relationships are much less certain than in animals. For example, one study reported that a concentration of 30 mg/m³ BeO in the air produced no acute effects from short-term exposure, while another study showed a high incidence of both acute disease and fatalities associated with an exposure of 4 mg/m³ (NAS/NRC, 1958). This apparent discrepancy, however, may be explained by differences in the method of beryllium production, duration of exposure, solubility, particle size, susceptibility or the resulting product chemistry. When beryllium is calcined at 500°C (the low-fired beryllium), the product is a relatively soluble substance with increased surface area; however, calcining at 1600°C (high-fired beryllium) results in a highly insoluble form (Spencer et al., 1968).

In humans, acute disease has been reported following inhalation exposure of soluble beryllium salts at concentrations of <100 µg/m³ for an unspecified time period (Hall et al., 1959). Ambient air concentrations of ≤25 µg/m³ appear not to cause acute beryllium disease in humans (NAS/NRC, 1958). The acute disease seems related to the intensity of exposure, with symptoms disappearing following termination of exposure (Hardy, 1955).

General Toxicity

Acute. Acute beryllium disease was defined by Tepper et al. (1961) as beryllium-induced disease patterns that persist for <1 year. These disease processes include an acute inflammatory reaction at the site of deposition

following inhalation of beryllium compounds either as a mist, vapor or dust (Vorwald, 1966). The amount of exposure, the degree of toxicity, concentration of the compound and host susceptibility may all play a role in the severity of symptoms (Van Ordstrand et al., 1945). Respiratory disorders ranging from upper respiratory tract irritation and inflammation to damage of the lung parenchyma occur following inhalation of beryllium (Tepper, 1972a).

The respiratory response to inhalation of beryllium compounds includes inflammation of the nasal mucosa, pharynx and tracheobronchial tree and acute pneumonitis (Tepper et al., 1961). The involvement of the upper respiratory tract is a direct result of contact secondary to inhalation of beryllium particles. The resultant rhinitis and pharyngitis are frequently associated with nosebleeds, and ulceration may occur in the mucous membranes because of blood and fluid accumulation. Diagnosis may be difficult because of similarity between beryllium-related symptoms and those associated with the common cold. Depending on the extent of exposure, beryllium-induced acute tracheobronchitis may be rapid or insidious in its onset. Symptoms include a nonproductive spasmodic cough, chest tightness and burning, as well as moderate dyspnea with exertion. Inflammation of the tracheobronchial tree will usually resolve within 1-4 weeks (DeNardi et al., 1953).

Acute pneumonitis is associated with the inhalation of almost all beryllium compounds, including the metal, oxide, sulfate, hydroxide, chloride and fluoride (Durocher, 1969). The observed effects have followed pulmonary deposition of beryllium in the form of a mist of the soluble salt or as a fume of the insoluble compounds. The reaction with the relatively soluble,

low-fired beryllium oxide has been a widely dispersed focal pneumonitis of a granulomatous nature as noted by Tepper (1972b). These investigators found that BeO particles were surrounded by a dense central core of proliferating histiocytes and often invaded by epithelioid cells and one or two layers of fibroblasts. Some lymphocytes, plasma cells, and an occasional multinucleated giant cell were noted. The area of involvement eventually became less cellular, more collagenous and then hyalinized. Recovery times from this acute pneumonitis varied from 1-6 weeks in mild cases and $\leq$6 months in more severe forms. Tepper et al. (1961) noted 18 deaths involving the development of pulmonary edema and subsequent progression to acute beryllium pneumonitis.

Symptoms resulting from dermal exposure to beryllium have been reported by numerous authors (U.S. EPA, 1980a). The characteristic symptoms of acute toxicity are dermatitis, skin ulceration or conjunctivitis (Vorwald, 1966; Higgins, 1968). The solubility of the beryllium compound is a factor in dermatitis, since the lesions have only been reported following contact with soluble beryllium salts (McCord, 1951). An allergic dermatitis is occasionally observed and is expressed as itching with reddened, elevated or fluid-accumulated lesions in exposed areas of the face, neck and sometimes the arms and hands. The chest and back may also be involved if in contact with contaminated hands or clothing (Tepper et al., 1961).

A beryllium ulcer occasionally occurs following deposition of crystalline beryllium compounds in skin abrasions or cuts (U.S. EPA, 1980a). The dermatoses begins as a localized, indurated, raised, reddened lesion that progresses to an ulcer (Vorwald, 1966). The lesion persists until removal

of the crystal and curettage of the ulcer base (Tepper et al., 1961). Healing usually occurs within 2 weeks. The incidence rate of skin ulceration in a beryllium refining plant has been reported at 5.7% (Nishimura, 1966).

Eye involvement may also occur and has been manifested as a conjunctivitis secondary to splash burns or contact dermatitis. The symptoms can range from inflammatory congestion and hyperemia to cellular infiltration. This ocular damage cannot be differentiated from that caused by other chemical irritants (Vorwald, 1966). The incidence of conjunctivitis has been reported at 20.9%, usually among workers exposed to high concentrations of BeO (Nishimura, 1966).

Chronic. Chronic beryllium disease is the result of inhalation of beryllium compounds over a considerable period of time. According to Tepper et al. (1961), the chronic disease differs from the acute form by a latent period of up to 20 years or more, a long duration, a progressive severity despite the termination of exposure and systemic manifestation of the disease. The acute disease may progress to the chronic form with an asymptomatic period between the resolution of the acute form and the emergence of the chronic disease (Hardy and Chamberlin, 1972). The dose of beryllium that will result in chronic disease is not known. In 1949 before air standards were set to control beryllium exposure, both acute and chronic forms of toxicity were common; however, consistent monitoring was not performed before 1949, so it is difficult to relate the disease to specific conditions of exposure. It is known that the concentrations were high; a 1946 survey by Laskin et al. (1946) reported concentrations of beryllium dust of 0.1-0.5 mg/m^3 during beryllium furnace coke removal operations, and Zielinski

(1961), studying a beryllium alloy plant, reported concentrations of 11.3-43.3 mg/m³. No cases related to ambient air dispersion or contact with dust brought home on work clothes have been reported since the 1949 air standard was established and exposure control procedures were put into effect.

One recent study also identified another possible high-risk group for the respiratory effects of beryllium. Rom et al. (1984) reported an epidemiologic study of 178 dental laboratory technicians that included a chest radiograph and pulmonary function test. They concluded that dental laboratory technicians are at risk for beryllium-related lung disorders and simple pneumoconiosis from grinding nonprecious metal alloys. This study is of very limited value in assessing risks since the individuals studied were exposed simultaneously to a variety of potentially toxic metals, such as nickel and chromium, in the manufacture of dental fillings and prostheses.

The symptoms associated with chronic disease include granulomatous inflammation of the lungs with accompanying cough, chest pain and general weakness (Hardy and Stoeckle, 1959). Right-sided cardiomegaly secondary to congestive heart failure, as well as liver and spleen enlargement, cyanosis, digital clubbing and kidney stones are other potential effects. The symptoms of weight loss, fatigue and anorexia usually imply a poor prognosis with a high case fatality rate and some degree of permanent disability in survivors (Greenburg, 1972).

Lymphocyte transformation (LT) was studied as an endpoint related to beryllium exposure. Lymphocytes have been shown to undergo blast transformation in vitro when exposed to beryllium salts (Epstein et al., 1982). Rom

et al. (1983) conducted a 3-year study investigating the relationship between beryllium exposure and pulmonary changes, including blastogenic transformation of lymphocytes obtained by bronchoalveolar lavage. The subjects exposed to beryllium were male employees of a surface mine and process mill in Utah. Mean exposures were estimated to be 7.18, 0.25, 0.40 and 0.99 μg Be/m^3 (an 8-hour TWA) for the years 1979, 1980, 1981 and 1982, respectively. Positive LTs were reported for 15.9% (13/82 exposed workers) in 1979 and 8.2% (5/61 exposed workers) in 1982. Eleven of the positive LTs in 1979 were retested in 1982 and eight of these were found to be negative. This reduction correlates with the significant reduction in exposure during these years. A positive LT was not associated with reduced pulmonary function. Also, chest radiographs of the exposed workers revealed no changes associated with beryllium disease. The authors conclude that lymphocyte transformation is related to beryllium exposure and that it is reversible upon reduction of exposure levels.

Lung inflammation, which characterizes chronic beryllium disease, is a diffuse interstitial lesion that lacks the edematous and exudative changes of acute disease. Scattered densities seen on X-rays are mostly large irregularly shaped monocytes caused by extension of thickened alveolar walls (Vorwald, 1966). Granulomatous lesions are also noted within other organ systems, such as the skin, lymph nodes, kidney, liver and skeletal muscles (Dudley, 1959).

Rossman et al. (1986) have demonstrated <u>in vitro</u> proliferation of lung cells in response to the presence of beryllium salts. The proliferation test may be used to identify workers with chronic hypersensitivity to beryllium.

Cullen et al. (1987) undertook a clinical-epidemiologic investigation of employees in a precious metal refinery. Five workers developed granulomatous lung disease between 1972 and 1985. The original diagnosis was sarcoidosis, but four of the workers were subsequently proven to have a hypersensitivity to beryllium when tested for in vitro proliferative responses of lymphocytes obtained by bronchoalveolar lavage. A review of medical records of coworkers and extensive industrial hygiene surveillance of the plant demonstrated that four cases resulted from exposure in the furnace area where air concentrations of beryllium fume were consistently below the permissible exposure limit of 2 $\mu g/m^3$. A single case was attributed to exposure in parts of the refinery where levels of cold beryllium dust often exceeded the standard by as much as 20-fold. These data demonstrate that chronic beryllium disease still occurs and confirm the importance of specific immunologic testing in patients suspected of having sarcoidosis but with potential exposure to beryllium. The data raise concern about the adequacy of modern industrial controls, especially in the setting of exposure to highly respirable beryllium fume.

Other Effects

Carcinogenicity. The carcinogenic potential of beryllium and its compounds in man, unlike that shown in animals, has not been clearly demonstrated or refuted. Epidemiologic cohort studies have focused on beryllium exposure in occupational settings. Since the effects of beryllium exposure were not recognized until about 1950, the data base was not established until 1951, and therefore, little monitoring data are available before that time. Consequently, attempts to relate beryllium exposure to the development of respiratory cancer did not begin until much later (U.S. EPA, 1980a).

Niemoller (1963) reported two cases of delayed lung carcinoma thought to be caused by occupational exposure to beryllium, along with one case from a smoker. The two industrial cases were both detected 16 years after the exposure, and the investigator's conclusions were based on knowledge of past exposure, tumor location and presence of beryllium in the tissue.

Gold (1967) described a woman who had a history of traumatic vaginal lesions after repeated douching with water containing 0.035 µg/ℓ of soluble beryllium, and who had developed a peritoneal mesothelioma of the recto-vaginal septum. Tissue analysis showed beryllium to be present at a level of 0.04 µg/g and also revealed asbestos, to which the patient was also exposed environmentally. The author concluded that the etiologic factor was beryllium, although as in Niemoller (1963), some conjecture is apparent (U.S. EPA, 1980a).

Hardy et al. (1967) studied a group of 535 members of the Beryllium Case Registry, and found 14 cases of cancer, including three with lung cancer and three with bone sarcoma. However, the same author reported in 1976 that the bone sarcomas were not listed correctly and confirmed only one case.

The first in a series of government-sponsored studies of cancer in workers exposed to beryllium was accomplished by Bayliss et al. (1971). This cohort mortality study consisted originally of some 10,365 former and current employees of the beryllium-processing industry (two companies in Ohio and Pennsylvania). Selection criteria ultimately reduced the cohort to 6818 males. Only a slightly elevated risk of lung cancer was evident overall (36 observed deaths vs. 34.06 expected). No significant risk of

lung cancer was found to exist in relation to length of employment, beginning date of employment, or kind of employment (office vs. production), nor were significant risks of other forms of cancer evident from these data.

This study had several deficiencies, including the fact that over 2000 individuals had to be eliminated from the original cohort because data regarding birth date, race and sex could not be obtained. The authors indicated that this reduction in the size of the study necessitated the elimination of some 251 deaths, and represented a loss of >20% of the cohort and 25% of the known deaths, a factor that has the potential for introducing considerable bias into the results. A second major problem with the study is that it did not analyze the data according to length of time since initial employment in the industry. The lack of such an analysis meant that questions dealing with latency could not be addressed in the study. A third deficiency is that the populations of several different plants were combined into one cohort for the study. As a result, the study failed to consider the many potential differences of exposure levels in different plants. Individuals were studied in groups according to their beginning dates and durations of employment, despite the fact that their exposure histories may have been totally dissimilar. For these reasons, this study (Bayliss et al., 1971) was deemed not adequate for the evaluation of cancer mortality in beryllium-exposed workers.

In an attempt to remedy the deficiencies of their earlier study, Bayliss and Lainhart (1972) narrowed the scope of the study to only one beryllium-processing company, which had seemingly complete employment records for two locations in Pennsylvania. This change effectively reduced the size of the cohort to 3795 white males, while retaining the same starting date and

cut-off date as was used in the earlier study. Bayliss and Lainhart (1972) found that 601 members of the cohort had died, as compared with 599.9 expected deaths based on period- and age-specific U.S. white male death rates. Again, no significant excess of unusual mortality from any cause was evident. For lung cancer overall, 25 deaths were observed vs. 23.69 expected. Even when latency was considered, no significant excess risk of lung cancer was apparent after a lapse of 15 years from initial exposure, at which time 14 deaths were observed vs. 13.28 expected. In addition, no significant risks were apparent in relation to intensity and duration of exposure or beginning date of employment. The Bayliss and Lainhart (1972) study was criticized by Bayliss and Wagoner (1977) in a third version of the study. Among the criticisms were the following: 1) the study included clerical and administrative workers who presumably had not been exposed to beryllium; 2) the data were obtained from industrial representatives, which precluded an independent assessment of plant employment files to ensure that all potentially exposed workers were included; and 3) the study did not assess latency $\geq$20 years after initial employment, although it did examine mortality after a 15-year lapse.

The Bayliss and Wagoner (1977) cohort mortality study consisted of workers employed at only one of the original company's plants. The cohort studied was composed of 3070 white males, who were followed until January 1, 1976. Vital status was unknown for only 80 members of the cohort (3%), and these individuals were considered to be alive until the end of the study's cut-off period. Altogether, 884 deaths were observed, as compared with 829.41 expected deaths based on period- and age-specific U.S. white male death rates. A significant excess of lung cancer was noted, with 46 cases

observed vs. 33.33 expected ($p<0.05$). A significant excess of heart disease was also noted (399 observed vs. 335.15 expected, $p<0.05$), as was a significant excess of nonmalignant respiratory disease (32 observed vs. 19.02 expected, $p<0.01$). Irrespective of duration of employment, a significant excess was noted in bronchogenic cancer following a lapse of $\geq$25 years since initial employment.

In the Bayliss and Wagoner (1977) study, the authors discussed for the first time the impact of cigarette smoking as a possible confounding agent contributing to the excess risk of lung cancer. A study by the U.S. Public Health Service (PHS) in 1968 revealed some difference in the cigarette smoking patterns of the surveyed employees, as compared with smoking patterns in the United States as a whole. An increase in the percentage of heavier smokers was indicated in the 1968 survey, as compared with national data (21.4 vs. 15.3%). Cigarette smoking however, was dismissed by the authors as the cause of the increased risk of bronchogenic cancer and other diseases in the cohort under study; this may have been unwarranted for several reasons. First, the smoking patterns of the 379 employees surveyed in 1968 were probably not the same as those of the entire cohort of 3795, which included employees from as early as 1942. Second, the first national reports of smoking as a cause of lung cancer were produced in 1964 and were accompanied by a great deal of media attention. By 1968, intense media coverage dealing with the health consequences of smoking probably produced a diminution of cigarette smoking among various subgroups of the population in the 4-year interim period between surveys. Furthermore, while the 1968 survey done at the plant did speak of current cigarette smoking patterns, the issue of prior cigarette smoking was not addressed, nor was the issue of

pipe smoking and cigar smoking. Additional criticisms of the Bayliss and Wagoner (1977) study, as well as subsequent iterations of the same study, including the final version (Wagoner et al., 1980), are discussed in the following review.

Wagoner et al. (1980) slightly reduced the cohort of Bayliss and Wagoner (1977) to a study of 3055 white males employed at some time between January 1, 1942 and December 31, 1967, in the same beryllium-processing facility. The results showed a significantly high incidence of lung cancer (47 observed vs. 34.29 expected, $p<0.05$) for those individuals followed until December 31, 1975. This excess extended to members of the cohort followed for more than 24 years since initial employment (20 observed vs. 10.79 expected, $p<0.01$). When the analysis was confined to those whose initial employment occurred before 1950, but who were followed for 15 years or more from date of initial employment, a significantly high risk of lung cancer was apparent (34 observed vs. 22.46 expected, $p<0.05$). Deaths from lung cancer for those whose initial employment occurred after 1950 was 4 observed vs. 2.4 expected. The authors concluded that this excessive risk of lung cancer "could not be related to an effect of age, chance, self-selection, study group selection, exposure to other agents in the study facility, or place of residence."

This study has received severe criticism from several sources; an internal Center for Disease Control (CDC) Review Committee was appointed to investigate defects in the study, plus several professional epidemiologists (MacMahon, 1977, 1978; Roth, 1983), including one of the study's co-authors (Bayliss, 1980). An extensive review of these reports including a detailed

discussion of the association between lung cancer and cigarette smoking can be found in U.S. EPA (1987) and therefore will only be summarized in this document.

The cohort studied in Wagoner et al. (1980) was composed of workers at the facility who had been employed before December 31, 1967. The cohort excluded employees who were not directly engaged in the extraction, processing or fabrication of beryllium, or in on-site administrative, maintenance or support activities. The numbers of expected deaths used in the study were based on U.S. white male death rates that had been generated by an analytic life table program designed by the National Institute for Occupational Safety and Health (NIOSH). Unfortunately, at the time of this study and subsequent studies on beryllium, cause of death information was not available on a year-to-year basis after 1967. In order to estimate expected deaths during the period from 1968 through 1975, death rates were assumed by the authors to be unchanged from those generated by the NIOSH life table program for the period from 1965 through 1967. The result was that for causes of death with declining death rates, expected deaths were overestimated, with a resultant underestimate of risk. Similarly, for those causes with increasing death rates during the interval studied, expected deaths were underestimated, with a resultant upward risk bias, as was the case with respect to all of the lung cancer risk calculations made by the authors. After this problem had been corrected by the inclusion of actual lung cancer mortality data for the period in question, expected lung cancer deaths were recomputed before the publication of the Wagoner et al. (1980) study by Bayliss (1980). The result was an increase from 34.29 to 38.2 expected lung cancer deaths, or an excess of 11%. This correction in itself was enough to

eliminate the statistical significance calculated by Wagoner et al. (1980) in their overall lung cancer tabulation. With respect to latency, the risk of lung cancer was reduced to one of only borderline significance in the cohort subgroup that was observed for 25 years or more after initial employment. These corrections have been confirmed as correct by Richard Monson (MacMahon, 1977, 1978).

An extensive discussion of the influence of cigarette smoking on the increase in cancer reported by Wagoner et al. (1980) is presented in U.S. EPA (1987). Contrary to the findings by Wagoner et al. (1980) that smoking influence was negligible, U.S. EPA (1987) estimated a 4.1% increase in expected lung cancer cases.

The authors (Wagoner et al., 1980) have stated that the expected deaths were overestimated by 19% because of the use of death rates for white males in the United States as a whole, rather than those for Berks County, Pennsylvania, where the plant was located. This statement was based on a comparison in Mason and McKay (1973) of the 1950-1969 age-adjusted lung cancer death rate for white males in Berks County, Pennsylvania, United States. Bayliss (1980) has criticized this statement by the fact that the periods of observation were different, i.e., that the Mason data covered the period from 1950 through 1969, while that of Wagoner et al. (1980) covered the period from 1942 through 1975. Roth (1983) criticized the use of Berks County rates as not being reflective of greatly elevated lung cancer death rates for the City of Reading, which they maintained were 12% higher than the national rates. U.S. EPA (1987) concluded that death rates calculated for Berks County should be weighted toward the higher City of Reading rates, which increases the number of estimated expected deaths.

Wagoner et al. (1980) have also noted an unusual histopathologic distribution of cell types in the cases of 27 of the 47 lung cancer deaths for which pathologic specimens could be obtained. Adenocarcinomas were noted in 8/25 individuals histologically confirmed to have died from bronchogenic carcinoma (Smith and Suzuki, 1980). Smith and Suzuki (1980) concluded, however, that "the prevalence of histopathologic cell types of bronchogenic carcinomas among beryllium-exposed workers could not be presently defined." Wagoner et al. (1980), however, citing data from earlier studies (Haenszel et al., 1962; Axtell et al., 1976) to the effect that the frequency of adenocarcinomas in U.S. white males was 15 or 16%, concluded that a significant "shift" of histologic cell types was apparent in lung cancer deaths in beryllium workers. Smith (1978) discussed more recent data by Vincent et al. (1977) that indicated a shift in the prevalences of histopathologic cell types of lung cancer in the general population over time has led to an increase in the prevalence of adenocarcinoma to 24%, and therefore the prevalence of adenocarcinomas in the lung cancer deaths of beryllium workers is not significantly different from that expected.

To summarize, it appears that the authors of the Wagoner et al. (1980) study tended to exaggerate the risk of lung cancer in a population of workers potentially exposed to beryllium, and underemphasized or did not discuss sufficiently the shortcomings of the study. The net effect was to turn a "suggested association" of lung cancer with beryllium exposure into a questionable "significant association." However, despite the study's problems, there still remains a possibility that the elevated risk of lung cancer reported therein was due in part to beryllium exposure, and although the Human Health Assessment Group (HHAG) of the U.S. EPA considers the study

inadequate to assess the risk of lung cancer from exposure to beryllium, further refinement and follow-up of this cohort was recommended to determine if the reported increase would become statistically significant.

In a companion paper by Infante et al. (1980), lung cancer mortality was studied in white males for whom data had been entered into the Beryllium Case Registry (BCR) with diagnoses of beryllium disease. A person was adjudged to have beryllium disease if three or more (two were mandatory) of the following five criteria were met (Hasan and Kazemi, 1974):

Mandatory -- 1. Establishment of significant beryllium exposure based on sound epidemiologic history.

2. Objective evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease.

Mandatory -- 3. Chest X-ray films with radiologic evidence of interstitial fibronodular disease.

4. Evidence of restrictive or obstructive defect with diminished carbon monoxide diffusing capacity by physiologic studies of lung function.

5. a. Pathologic changes consistent with beryllium disease on examination of lung tissue.

b. Presence of beryllium in lung tissue or thoracic lymph nodes.

Close to 900 individuals had been entered into the BCR as of August 1983, based on evidence of nonmalignant respiratory disease objectively determined by appropriate and established medical procedures.

Infante et al. (1980) eliminated from their cohort all nonwhite and female subjects because of their lack of "statistical sensitivity," and also eliminated all subjects who were deceased at the time of the BCR entry.

Altogether, Infante et al. (1980) included in their study cohort only 421 members of the BCR, <50% of the total. Of these, vital status could not be determined on 64 (15%), while 139 (33%) were found to have died by December 31, 1975. In this latter group, the causes of death could not be ascertained for 15 individuals.

Since the same NIOSH life table program that was used to calculate lung cancer deaths in the Wagoner et al. (1980) study was the method used to derive expected lung cancer deaths in the Infante et al. (1980) study, it was subject to the same problems mentioned previously, i.e., a -11% error in the calculated expected lung cancer deaths.

As expected, Infante et al. (1980) found a significantly high excess risk of "nonneoplastic" respiratory disease (52 observed deaths vs. 3.17 expected). In terms of total cancer, 19 deaths were observed vs. 12.41 expected. With respect to lung cancer, 6 deaths occurred >15 years after the onset of beryllium exposure vs. 2.81 expected ($p<0.05$). If the expected deaths are adjusted upwards by 11% to compensate for the underestimate produced by the NIOSH life table program, the authors' p value is reduced to one of borderline significance (6 observed vs. 3.12 expected deaths; $p<0.05$).

Infante et al. (1980) divided their cohort on the basis of "acute" vs. "chronic" beryllium disease. However, the authors definition of acute vs. chronic differed from that commonly accepted for describing acute and chronic beryllium diease. Subjects were considered acute if the BCR records indicated a diagnosis of chemical bronchitis or pneumonitis or other acute respiratory illness at time of entry into the registry. Subjects were

called chronic if BCR records indicated a diagnosis of pulmonary fibrosis or some recognized chronic lung condition at time of entry into the registry. The authors found no excess of lung cancer in their chronic respiratory disease group of 198 persons (1 observed death vs. 1.38 expected). However, in their acute respiratory disease group, they found 6 observed lung cancer deaths vs. 1.91 expected ($p<0.05$), and in the interval of >15 years since initial onset of beryllium exposure, 5 observed lung cancer deaths were found vs. 1.56 expected ($p<0.05$). These findings must be regarded as questionable with respect to their implications because of the previously discussed weaknesses.

The possibility cannot be discounted that cigarette smoking may have also contributed to an excess risk in the Infante et al. (1980) study, despite the authors' claim that it is unlikely to have played a role. Although the criteria for inclusion in the BCR have been evolving and undergoing revision to improve their sensitivity and specificity since the Registry's inception in 1952, it is possible that in the early years of the Registry, the criteria could have allowed the inclusion of individuals with respiratory disease either brought on or exacerbated by cigarette smoking. Of the 7 lung cancer cases discussed by Infante et al. (1980), 6 were admitted to the hospitals for treatment before 1955, and one was admitted in 1964. The ability to detect subtle radiographic changes consistent with a diagnosis of beryllium disease was relatively undeveloped in the early 1950s. Given current practices in the interpretation of X-rays and pulmonary function data, such a misdiagnosis would be unlikely today.

Any one of the factors referred to above could have been of sufficient magnitude to produce a significant excess lung cancer risk in the group

under study. The findings of Infante et al. (1980) are thus seen to be, at best, only suggestive of an increased risk of lung cancer from exposure to beryllium.

The first in a series of four epidemiologic studies of mortality in workers exposed to beryllium was conducted by Mancuso and El-Attar (1969) on the same study population as was used in the Bayliss and Wagoner (1977) and Wagoner et al. (1980) studies. The cohort in the Mancuso and El-Attar (1969) study, however, was derived from quarterly earnings reports provided by the Social Security Administration. With respect to beryllium, Mancuso and El-Attar (1969) obtained reports for both companies studied by Bayliss and Wagoner (1977) and Wagoner et al. (1980), but limited their study to the period of employment from 1937-1948. Altogether, they identified 3685 white males from two beryllium plants. Only 729 white males were found to have died through the year 1966. Included in this group were 31 lung cancers. The authors contrasted internally generated age-, plant- and period-specific death rates by cause with internally generated age-specific death rates by cause from an unidentified "industrial control." Unfortunately, because of the small numbers involved, the authors did not include any employees of age 55 or over. The 729 deaths were distributed into 160 narrow subcategories, based on four broad age groups, two companies, four periods of time, and five broad death categories. Internal death rates were computed in each subcategory. Because the numbers from which these internal rates were derived are so small (in some instances nonexistent) from one subcategory to another, the comparisons with 20 rates generated from the industrial control are shaky at best and appear to vary considerably. No trends are evident; no significance tests were done; thus, the data are open to interpretation.

The authors themselves conclude, based on their analysis, that their data are "severely limited" with respect to answering the question of carcinogenic risk.

In the second study of the same cohort, Mancuso (1970) added duration of employment as a variable and divided his cohort into a 1937-1944 component and a 1945-1948 component, by dates of initial employment. A higher rate of lung cancer was noted by the author among workers whose first employment occurred during the period 1937-1944 in age category 25-64, and who were employed for 5 or fewer quarters (99.9 per 100,000) compared with those employed 6 quarters or longer (33.2 per 100,000) based on 16 and 4 lung cancers, respectively. In one company, a higher rate of lung cancer was found among workers with histories of chemical respiratory illness versus those who did not have this condition. During the period 1940-1948, 142 white males with respiratory illness were identified in this plant. Of a total of 35 deaths occurring in this group, 6 were due to lung cancer. Based on these six lung cancers, an age-adjusted lung cancer death rate of 284.3 per 100,000 was calculated, compared with an age-adjusted rate of 77.7 per 100,000 (based upon nine lung cancer deaths) in the total cohort of this company's workers employed from 1937-1948. These calculations were confined to individuals who were in the age group 25-64 in the year 1940. No significance tests were done, and the observations were based upon small numbers, as was pointed out by the author.

Although Mancuso (1970) found elevated risks in these groups, the results are subject to considerable variability. Mancuso criticized his own study for several alleged deficiencies. The deficiencies, according to Mancuso, consisted of the following:

"The marked influence of labor turnover on duration of employment, perhaps induced by the presence of respiratory disease; the inability to define the specific populations by department, process, or by type or form of beryllium exposure; the presence of competing causes of death; and the shortness of the period of observation."

Other potential problems with these data, which were not mentioned by the author, are a lack of consideration of the effects of smoking and the effects of exposure to potential carcinogens in other jobs the workers may have had before and after their exposure to beryllium, since the suggested increase appeared only in "short-term employees." This is discussed further in a later description of the study (Mancuso, 1979). The author's conclusion that prior chemical respiratory illness influenced the subsequent development of lung cancer among beryllium workers may be somewhat overstated, in view of the many limitations of the study.

In the third update of this study, Mancuso (1979) divided his cohort into two subgroups, each consisting of former and current employees of the two beryllium-manufacturing companies. Employees were included in the study if they had worked at any time during the period from 1942-1948. The Ohio cohort consisted of 1222 white males, of which 334 were deceased. The Pennsylvania cohort consisted of 2044 white males, of which 787 were deceased. A life table analysis was performed by NIOSH, utilizing U.S. white male age- and period-specific rates (5-year age groupings) to generate expected lung cancer deaths, through 1974 for the Ohio cohort, and through 1975 for the Pennsylvania cohort. An excess risk of lung cancer appeared in the Ohio employees after a lapse of 15 years from the onset of employment (22 observed vs. 9.9 expected; $p<0.01$). The same was true for the Pennsylvania

employees (36 observed vs. 22.0 expected; $p<0.01$) following a similar latent period. The author noted that this risk occurred in workers who had been employed for <1 year in the industry.

Several questions must be considered before any conclusions can be accepted as valid. These data, although derived from social security quarterly earnings reports and not from personnel records, are not independent of the data set utilized in the Wagoner et al. (1980) study. Both sets of data were analyzed through the use of the NIOSH life table program. The expected deaths generated in both studies are subject to the same influences introduced by the use of the same life table program, and by the use of the same comparison rates (U.S. white male lung cancer rates). In addition, the extensive cooperation between Mancuso (at the University of Pittsburgh) and Wagoner (at NIOSH) in the search for causes of death in the respective cohorts for study, contributed to the inclusion of lung cancer deaths known to one but not the other in both studies. As discussed previously, because of the use of the NIOSH life tables in the Mancuso study, the calculation of expected lung cancer deaths was on the low side (~11%). Hence, these results should not be considered independent of the results of the Wagoner study.

Another problem with this cohort is the use of social security quarterly earnings reports to constitute a cohort of potentially exposed employees. These files, for the most part, are limited with respect to the data available. It was not possible to determine from the reports what jobs these individuals performed for the companies, where their job stations were located, whether their jobs were on or off the premises, whether they had

actually been exposed to beryllium, or even precisely when during the 3-month period they actually started work. And, of course, these records give no information on workers who were not covered by the Act. Furthermore, in the period before 1942, the social security system was in the process of being established, and tremendous logistic problems in setting up the system were encountered during this time. Thus, questions remain concerning this cohort.

Another difficulty with the Mancuso (1979) study, as with his earlier studies, is a lack of discussion of other exposures these workers may have received. The author observed that the main effect (lung cancer) occurred in short-term employees >15 years after initial employment. These workers had an opportunity to be exposed to other potential carcinogens at jobs they may have held before or immediately following their short employment in the beryllium industry. This is a distinct possibility because the beryllium-manufacturing companies are located in or near heavily industrialized areas of Ohio (Cleveland, Toledo) and Pennsylvania (Reading). Roth (1983) reported the presence of several industries in the Lorain, Ohio area in the period from 1942-1948 that conceivably could have provided an opportunity for short-term employees to receive exposure to potential carcinogens.

Another serious omission of the Mancuso (1979) study is the lack of a discussion of the effect of cigarette smoking on the target organ of interest, the lung. With respect to the question of smoking, it would appear likely that since there was considerable overlapping of this study with the Wagoner et al. (1980) study, it is probable that most of the lung cancer victims in the Pennsylvania cohort of the Mancuso (1979) study were

smokers. Hence, it is possible that cigarette smoking contributed to the increased risk of lung cancer in the Pennsylvania cohort. No information was provided in the Ohio portion of the Mancuso (1979) study regarding the smoking influence, an exposure of considerable import in lung cancer. The findings of significant excesses of lung cancer in both plants must be seen as limited because of the inadequate consideration of the confounding effects of these two likely exposures, the problem with the NIOSH life table programs, and the inadequate nature of social security quarterly earnings reports in defining an occupationally-exposed cohort for study.

In the fourth update to his study of workers potentially exposed to beryllium in two beryllium-manufacturing facilities, Mancuso (1980) found statistically significant elevated risks of lung cancer in 3685 white males employed in the period from 1937-1948 and followed until the end of 1976, when contrasted with viscose rayon workers. The beryllium cohort, as mentioned earlier, was derived from quarterly earnings reports filed with the Social Security Administration by the two companies. The only new addition to this latest update was the introduction of a new comparison population, that of viscose rayon workers. The origin and description of this group of workers is inadequately discussed, although the Wagoner et al. (1980) study states that the viscose rayon workers cohort utilized in the Mancuso (1980) study was located somewhere in the vicinity of the Mancuso cohort.

Lung cancer mortality experience in the beryllium cohort was contrasted with that expected based on rates specific to age and duration of employment generated from the mortality experience of the viscose rayon workers cohort.

Rates were generated in two ways, the first based on the total group of employees in the viscose rayon industry, and the second based on employees with permanent assignments to only one department. Presumably, those who exhibited mobility in their employment by moving from one department to another were excluded from the lung cancer death rate calculations in the second method. No rationale is presented by the author to explain why mortality in beryllium workers should be contrasted with expected deaths derived in these two separate ways. However, the net results was to produce two separate sets of expected lung cancer rates that differed considerably from each other. Mancuso (1980) observed 80 lung cancer deaths in his beryllium cohort of employees from the two companies combined, as compared with 57.06 expected deaths based on the former set of derived rates and 50.63 expected deaths based on the latter subset of employees working their entire time in only one department. The author did not compare his beryllium workers on the basis of time since onset of employment, but did contrast them by duration of employment. He found a statistically significant excess risk of lung cancer in employees who had been employed for $\leq$1 year, and also in employees who had been employed for $\geq$4 years by the beryllium companies.

In this study there is no consideration of the effects of latency according to duration of employment. The major output of the NIOSH life table program, which was utilized by Mancuso, is a set of tabulations by time since onset of employment. Lung cancers diagnosed within 10 years of initial exposure probably were not a consequence of that exposure. Furthermore, the designation "duration of employment" is not necessarily uninterrupted continuous employment. In reality, what is meant is "total employment" (i.e., periods of time when the employee was not exposed or not

actually working). These periods of time are not counted by the NIOSH life table program in the category duration of employment. Therefore, it is possible that included in the observed deaths are the deaths of individuals who had worked only a few days for the companies, and who died from lung cancer 20 years later, as well as individuals who worked for the companies for many years continuously but who died within 5 years of initial employment.

Additionally, the viscose rayon cohort appears to have been a somewhat younger population by age at hiring than was the beryllium cohort (47.2% in the viscose rayon cohort were hired at under age 25, as compared with 38.4% hired at under age 25 in the beryllium cohort). Whether or not the author adjusted for age differences is questionable. In U.S. EPA (1983) it was reported that NIOSH had reanalyzed the data and found serious problems with Mancuso's analysis and efforts to resolve this issue have been unsuccessful. Since the viscose rayon cohort was younger than the beryllium cohort, the net impact of an adjustment would be to decrease the gap between observed lung cancer deaths based upon the beryllium cohort and expected deaths based upon the viscose rayon cohort.

Another problem concerns the acquisition of cause-of-death data. Some 4.3% of the reported deceased members of the viscose rayon cohort remained without a cause of death, versus only 1.5% of the beryllium cohort. This could potentially lead to a greater underestimate of lung cancer in the viscose rayon cohort compared with the beryllium cohort if the causes of death in these two groups were fairly evenly distributed.

As in the earlier studies by the same author, the lack of discussion of the confounding effects of smoking and the disregard of potential exposures received while not working for the beryllium companies are a weakness in this study. This is a particular problem since a large majority of this cohort worked for <1 year. Nothing is revealed in the study of the origin or make-up of the viscose rayon cohort. What is known about its location comes from the Wagoner et al. (1980) study in which the authors stated that Mancuso's viscose rayon cohort was located in the vicinity of the beryllium companies.

Furthermore, since both cohorts were run utilizing the NIOSH life table program, both cohorts suffer from the previously discussed 11% underestimation of expected lung cancer deaths.

In conclusion, despite the author's certainty regarding the existence of a causal relationship between beryllium exposure and lung cancer, the evidence presented in this study is not convincing because of the many limitations of the study, as described previously. Hence, it would appear that the study is at best only suggestive of an increased risk of lung cancer from exposure to beryllium.

Although several studies show a statistically significant excess risk of lung cancer in individuals exposed to beryllium, all of the studies cited have deficiencies that limit any definitive conclusion that a true association exists. Support for a finding of an excess risk of lung cancer in beryllium-exposed persons consists of evidence from cohort mortality studies of two companies (Table VI-1) and one cohort mortality study of cases

TABLE VI-1

Comparison of Study Cohorts and Subcohorts of Two Beryllium Companies[a]

Company Where Employed[b]	Source	Period of Employment	Comparison Population	Termination Date of Follow-up	Chief Lung Cancer Results[b]	Reference
KBI, BRUSH 6818 males	personnel records	1942-1967	U.S. males	1967	Total: 36 (O), 34.1 (E)	Bayliss et al., 1971
KBI only 3795 white males	same as above	1942-1967	U.S. white males	1967	Total: 25 (O), 23 (E) Latency 15 years+: 14 (O), 13.3 (E)	Bayliss and Lainhart, 1972
KBI-Reading facility only 3070 white males	same as above	1942-1967	U.S. white males	1975	Total: 46 (O), 33 (E) ($p<0.05$) Latency 15 years+: 37 (O), 24 (E) ($p<0.05$)	Bayliss and Wagoner, 1977
KBI-Reading facility only 3055 white males	same as above	1942-1967	U.S. white males	1975	Total: 47 (O), 34.3 (E) ($p<0.05$) Latency 15 years+: 34 (O), 24.86 (E) ($p<0.05$)	Wagoner et al., 1980
KBI, BRUSH 3685 white males	social security quarterly earnings reports	1937-1948	industrial control (unidentified)	1966	equivocal	Mancuso and El-Attar, 1969
KBI, BRUSH 3685 white males	social security quarterly earnings reports	1937-1944 and 1945-1948	internal control	1966	Duration of employment (rate): $\geq$1.25 years, $33.2/10^5$ <1.25 years, $99.9/10^5$ Prior respiratory disease only: with $284.3/10^5$ without $77.7/10^5$	Mancuso, 1975
KBI-2044 BRUSH-1222 white males	same as above	1942-1948	U.S. white males	BRUSH 1974 KBI	Latency 15 years+ only: Ohio - 22 (O), 9.9 (E) ($p<0.01$) Pennsylvania - 36 (O), 22 (E) ($p<0.01$)	Mancuso, 1979
KBI 3685 white males	same as above	1937-1948	viscose rayon workers	1976	Mobility (deaths): Among departments, 80 (O), 57.1 (E) ($p<0.01$) Remained in same department: 80 (O), 50.6 (E) ($p<0.01$)	Mancuso, 1980

[a]Source: U.S. EPA, 1987

KBI = Kaweckl-Berylco Industries (Pennsylvania); BRUSH = Brush Beryllium Company (Ohio)

(O) = observed; (E) = expected

admitted to the BCR. None of these studies can be said to be independent since all are studies of basically the same groups of workers. Extensive cooperation existed between the authors of all of these studies. Furthermore, the authors could not adequately address the confounding effects of smoking or of exposures received during prior and subsequent employment in other nonberyllium industries in the area known to produce potential carcinogens (especially in beryllium workers with short-term employment). Problems in the design and conduct of the studies further weaken the strength of the findings. There appeared to be a tendency on the part of the authors to overemphasize the positive nature of their results and minimize the contribution of qualifying factors. A list of these problems is presented in Table VI-2. If the errors detailed in the preceding paragraphs were corrected and proper consideration given to addressing the problems described, the finding of a significant excess risk would probably no longer be apparent, although the possibility nevertheless remains that a portion of the reported excess lung cancer risk may in fact be due to beryllium exposure. Thus, the Human Health Assessment Group of the U.S. EPA feels that the findings of these studies and the more recent tabulations should be considered inadequate evidence to demonstrate or refute carcinogenicity in humans.

The International Agency for Research on Cancer (IARC) has concluded that beryllium and its compounds should be classified as "limited" with respect to the human epidemiologic evidence of carcinogenicity. IARC's classification can be explained by the fact that IARC uses only data contained in published literature. In the case of beryllium more recent tabulations of the published data were available to the U.S. EPA Human

TABLE VI-2

Problems with Beryllium Cohort Studies*

A.	Loss of 2000 individuals because of insufficient data.	Bayliss et al., 1971
B.	No latency considerations.	
C.	Combined study populations of several plants from two companies.	
A.	Includes clerical and administrative personnel with no exposure.	Bayliss and Lainhart, 1972
B.	No independent assessment of plant employment files.	
C.	Latency after 20 years not assessed.	
A.	Cigarette smoking a possible confounder.	Bayliss and Wagoner, 1977; Wagoner et al., 1980
B.	Underestimate of lung cancer deaths in comparison population by 11%.	
C.	Inclusion of one lung cancer victim who did not fit definition for inclusion.	
D.	Loss of 295 individuals from study cohort.	
E.	Exposure to potential carcinogens before and following beryllium employment.	
A.	Unidentified comparison population.	Mancuso and El-Attar, 1969
B.	Internal rates based upon small numbers.	
C.	Tremendous variability and impossible to test significance.	
D.	No smoking consideration as possible confounder.	
A.	Internal rates based upon small numbers.	Mancuso, 1970
B.	Inappropriate comparison (age group 15-24 left out of comparison).	
C.	No consideration of smoking as possible confounder.	
D.	No consideration of latency.	
E.	Exposure to potential carcinogens before and following beryllium employment.	
A.	Underestimate of expected lung cancer deaths in comparison population by 11%.	Mancuso, 1979
B.	No consideration of smoking as possible confounder.	
C.	Incomplete delineation of cohort from use of Social Security Quarterly Earnings reports.	
D.	Exposure to potential carcinogens before and following beryllium employment.	

A. No consideration of latent effects. B. Probable lack of age adjustment. C. No consideration of effects of smoking. D. No description of origin or makeup of comparison cohort except for age. E. Underestimate of lung cancer deaths by 11% in both beryllium cohort and comparison population.	Mancuso, 1980

*Source: U.S. EPA, 1987

Health Assessment Group. These data have not been published, however, based on the reports of lung tumors in animals by inhalation exposure and previously mentioned recalculation of the epidemiologic data, beryllium is classified by the U.S. EPA as B2 (a probable human carcinogen) (U.S. EPA, 1987).

The relationship between trace metals concentration in drinking water and cancer deaths in 15 regions of the United States was studied by Berg and Burbank (1972). Ten of these regions include entire states, which were relatively well sampled. For each of these 10 basins a summary statistic, the product of the frequency of detection and the average detected concentration of the metal, was calculated. This summary statistic was used to determine the rank order of the region. This rank was then compared with the rank of the region for mortality from each of 34 types of cancer. The 18-year incidence rates were calculated separately for four groups: white men, white women, nonwhite men and nonwhite women. Spearman rank correlations between metal concentrations and cancer death rate were calculated for each of four population groups. The results were translated into probabilities and the probabilities combined to produce a summary probability of the likelihood of this degree of positive association being observed. A significant positive correlation was observed for beryllium, with cancers of the breast, bone and uterus appearing to have a probability of positive association ranging from 0.006-0.040. The association within subgroups was weak. Mortality rates for regions with beryllium in the water are really excessive only for non-white males. The mean positive level of beryllium was 0.3 µg/ℓ found for the states of Delaware, Maryland, West Virginia and Kentucky. However, since the results are based on imperfect analytical

results and sampling, and are contradicted in part by other studies of correlation and metal distribution, the positive associations for beryllium in drinking water and cancer are not proof of cause and effect relationships.

Mutagenicity and Teratogenicity. No evidence on the mutagenicity or teratogenicity of beryllium in humans was found (Drury et al., 1978).

Summary

Beryllium causes a number of toxic effects in humans. However, exact parameters for toxic concentrations and exposure times have not been determined. The acute effects are usually the result of inhalation or direct contact with beryllium salts. Symptoms of a dermatitis, conjunctivitis and a range of respiratory involvement can occur. Respiratory sequelae include rhinitis, pharyngitis, tracheobronchitis and acute pneumonitis. Pneumonitis has accounted for 18 deaths after development of pulmonary edema.

The chronic disease is usually the result of occupationally related inhalation of beryllium. The acute disease may progress to the chronic form with an asymptomatic period in between. The reaction to beryllium is a granulomatous inflamation of the lung, which is a diffuse interstitial process. Other potential effects include right heart enlargement, cyanosis, digital clubbing and kidney stones. Granulomatous lesions have been noted within the skin, lymph nodes, kidney, liver and skeletal muscles, as well as the lungs.

The carcinogenic potential of beryllium in humans remains controversial. Epidemiologic studies demonstrating increased incidences of lung cancer in beryllium workers have been criticized. However, enough evidence has been

produced to suggest that beryllium may be carcinogenic in humans when inhaled. Based on several reports of lung tumors in animals by inhalation exposure and the above-mentioned epidemiologic data, beryllium is classified by the U.S. EPA as B2 (a probable human carcinogen). More studies are needed to confirm these results and to exclude other alternative explanations for the epidemiologic findings.

VII. MECHANISM OF TOXICITY

Because the toxic effects of beryllium and its compounds are well known, numerous investigators have attempted to identify the specific mechanisms by which these effects are exerted.

Effects on Enzymes

Studies with beryllium indicated that it is capable of inhibiting several enzyme systems. Micromolar concentrations of beryllium inhibit alkaline phosphatase (Klemperer et al., 1949; Grier et al., 1949), phosphoglucomutase (Hashimoto et al., 1967) and sodium-activated ATPase (Toda, 1968) systems. Alkaline phosphatase inhibition was thought in turn to inhibit the endochondrial calcification of cartilage and produce the rickets-like effects observed in animals (Vorwald et al., 1966). Enzyme inhibition has been reported at concentrations as low as 10^{-6} M by Vorwald and Reeves (1959). Some enzymes inhibited by beryllium, such as the nucleotidases, hyaluronidases, and alkaline phosphatases, are also altered in hosts having cancer induced by nonberyllium agents.

Although beryllium inhibits alkaline phosphatase, studies of rats exposed to beryllium sulfate by inhalation showed that serum alkaline phosphatase activity was not affected (Reeves, 1974). However, histochemically measured alkaline phosphatase activity was decreased in all parenchymatous organs of rabbits given 25 mg beryllium orally or a 1% beryllium solution intravenously (Komitowski, 1972). A study by Arkhipova and Demokidova (1967) showed that rats given $BeSO_4$ orally had a decreased alkaline phosphatase activity in the kidney and an increased activity in the blood

serum, while both parameters were inhibited in mice when given as $BeCl_2$ or $BeSO_4$. Bamberger et al. (1968) showed that below a 10^{-7} M concentration, no inhibition occurred when added to media containing the enzyme, while maximum inhibition occurred at 10^{-5} M.

The effects of beryllium on several enzymes are shown in Table VII-1. Alkaline phosphatase was the only one of the phosphatases to be inhibited at beryllium concentrations of ≤ 1 µM, and phosphoglucomutase was the only phosphotransferase showing inhibition (Thomas and Aldridge, 1966). Beryllium also appears to block the tricarboxylic acid cycle by inhibiting the activity of the ketoglutaric, malic and succinic acid dehydrogenases (Mukhina, 1967). Other enzymes inhibited by beryllium are deoxythymidine kinase (Mainigi and Bresnick, 1969), DNA polymerase, thymidine kinase and thymidylate kinase (Witschi, 1970; Witschi and Marchand, 1971). The induction of enzymes such as tryptophan pyrrolase, aminopyrine demethylase and acetanilide hydroxylase by beryllium has been documented in rat liver (Witschi and Marchand, 1971), and sodium and potassium-activated ATPase are inhibited in the presence of Mg^{2+} or Mn^{2+} (Toda, 1968; Toda et al., 1971). Williams and Skilleter (1983) also noted that beryllium inhibited the enzymes involved in the phosphorylation of nuclear proteins.

Beryllium also has the ability to increase the activity of some enzymes such as ATPase and succinoxidase. For example, intravenous injection of 12.5-1000 µg Be/kg bw produced an increased activity of plasma ß-glucuronidase in mice (Vacher et al., 1975). Beryllium also irreversibly inhibits the (Na+K) dependent ATPase (Robinson et al., 1986) and this inactivation requires divalent cations, is augmented by K^+, but is diminished by Na^+ and by ATP. Similarly, prior incubation of the enzyme

TABLE VII-1

Effect of Beryllium on Various Enzymes[a,b]

Enzyme	Activated by Mg^{2+}	pH of Assay	Effect of $BeSO_4$ at the Concentration Indicated
Alkaline phosphatase (kidney)	+	9.4	50% inhibition, 1 μM
Acid phosphatase	-	5.0	No inhibition, 0.6 mM
Phosphoprotein phosphatase	-	6.0	No inhibition, 0.1 mM
Adenosine triphosphatase (liver nuclei)	+	6.8	No inhibition, 0.5 mM; 97% inhibition, 5 mM
Adenosine triphosphatase (liver mitochondria)	+	6.8	No inhibition, 0.2 mM; 40% inhibition, 2 mM
Adenosine triphosphatase (brain microsomes)	+	7.4	20% inhibition, 0.64 mM
Glucose 6-phosphatase	-	6.5	No inhibition, 0.8 mM
Polysaccharide phosphorylase[c]	-	6.0	No inhibition, 0.64 mM 91% inhibition, 6.4 mM
Phosphoglucomutase	+	7.5	50% inhibition, 5 μM
Hexokinase	+	7.4	45% inhibition, 1.5 mM; no inhibition, 0.15 mM
Phosphoglyceromutase	-	7.0	No inhibition, 2.0 mM;[c] 15% inhibition, 1.0 mM[d]
Ribonuclease	-	7.5	No inhibition, 1.0 mM
A-esterase (rabbit serum)	-	7.6	No inhibition, 1.0 mM
Cholinesterase (horse serum)	-	7.6	No inhibition, 1.0 mM
Chymotrypsin	-	7.0	10% inhibition, 1.0 mM

[a]Source: Drury et al., 1978

[b]Beryllium sulfate was used, and preincubated with enzyme for 10 minutes in the absence of substrate. At pH >7, precipitates were obtained with concentrations of $BeSO_4$ of $\geq$1 mM. Inhibition at these concentrations may be nonspecific.)

[c]134 mM 3-phosphoglyceric acid as substrate.

[d]20 mM 2-phosphoglyceric acid as substrate.

with vanadate blocks inactivation by beryllium added subsequently. Inactivation by beryllium, however, does not require a halide, and, unlike inactivation by fluoride, increases at basic pHs. These observations suggest that beryllium, as beryllium hydroxide complexes, acts as a phosphate analog, similar to AlF_4^- and vanadate.

Effect on Nucleic Acids

Numerous studies examining the mechanism of beryllium toxicity demonstrated its effect on nucleic acids in the cell. Vorwald and Reeves (1959) found that beryllium oxide altered the cell RNA distribution when injected intratracheally at 10.8 mg of total beryllium. A concentration of 1 mM $BeSO_4$ inhibited cell division in metaphase (Chevremont and Firket, 1951), and the presence of beryllium was found to block the cell cycle at the G_1-S phase (Skilleter et al., 1983). The effects were only shown in DNA; the synthesis of RNA did not change (Witschi, 1968).

Kharlamova and Potapova (1968) showed that beryllium accumulates in the nuclei, and other authors showed it to interfere with the metabolism of DNA in the liver (Marcotte and Witschi, 1972; Witschi, 1968, 1970). Skilleter (1984) noted that this localization of beryllium in the nucleus could account for the direct effects on the fidelity of DNA synthesis, but reported that the inhibition of the G_1-S phase would account for the major mutagenic effects since phosphorylation of nonhistone proteins occurs during this phase. The Be^{2+} ion also increased the misincorporation of nucleotides during polymerization by DNA polymerase (Luke et al., 1975). Results of Sirover and Loeb (1976) showed that Be^{2+} altered the accuracy of DNA synthesis. The ability of beryllium to influence this accuracy *in vitro* also suggests the possibility of the same effect *in vivo* (U.S. EPA, 1980a).

Effect on Proteins

Beryllium also reacts with proteins (Reiner, 1971). Rats given an intratracheal injection of 33 mg beryllium in three equal doses had altered cellular distribution of proteins (Vorwald and Reeves, 1959). The injected rats showed almost double the amount of protein in microsomes of lung tissue cells as untreated rats; however, no protein change was seen in the mitochondria or nuclei. Protein metabolism was studied in rats under conditions of experimental berylliosis (Pavlova et al., 1970). The authors found an increase in both reactive sulfhydryl groups and in the rate at which lysine-1-^{14}C was incorporated into soluble hepatic proteins. Kurysheva (1969) considered this indicative of an increase in the rate of protein biosynthesis. Vacher et al. (1974) reported that an immunologically specific α-macro-feto protein appeared in the serum of rats injected with beryllium. Witschi and Aldridge (1967) also found that rats injected with 0.75 mg Be/kg bw showed a decreased ability to incorporate amino acids into liver protein 24 hours after administration.

Immunologic Effects

The involvement of an immunologic factor in the development of chronic beryllium disease was suggested by Sterner and Eisenbud (1951). Hypersensitivity reactions were produced in guinea pigs by intradermal injections (Alekseeva, 1965) or by application of BeF_2 to the skin (Belman, 1969). $BeCl_2$ also induced skin hypersensitivity in rats (Vasil'eva, 1969). Curtis (1951) developed a patch test that involved application of nonirritating concentrations of soluble beryllium. Curtis showed that this test had a sensitizing effect and could elicit a positive reaction in subsequent testing.

Most patients who previously had acute beryllium reactions or a history of dermatitis showed an increased IgG fraction of immunoglobulin (Resnick et al., 1970). The phenomenon indicated that beryllium was antigenic, and the hypersensitivity is now generally agreed to be essentially a cell-mediated response (Alekseeva, 1965; Cirla et al., 1968). The basic immune reaction is an accumulation and proliferation of reticuloendothelial cells in response to contact with a poorly soluble particle (Reeves, 1983).

According to a review by Reeves and Preuss (1985), berylliosis is essentially an immune reaction expressed as granulomatous hypersensitivity in which reticuloendothelial cells accumulate and proliferate. Most or all cases appear to involve small-crystallite beryllium oxide. The proximate antigen is probably an adsorptive protein complex. The cellular response is initiated by phagocytosis of beryllium by macrophages. This results in swelling and rupture of lysosomes. Ultimately vacuolization and eventual necrosis of the cells occur. This process is accompanied by the development of delayed cutaneous hypersensitivity. The ability to respond immunologically to beryllium was genetically controlled in guinea pigs as a dominant nonsex-linked trait. It was also found that the immune response could be suppressed with lymphocyte antiserum, with large doses of beryllium lactate, or by inhalation exposure to beryllium sulfate.

The interdependence between the antigenic challenge and immune response is complex. The measurable parameters show the state of beryllium hypersensitivity rather than the state of berylliosis. In guinea pigs, maintenance of cutaneous hypersensitivity through booster shots decreased the vulnerability of the lungs to concurrent beryllium inhalation. Beryllium

neoplasia was observed in those experimental animals not immunologically responding to beryllium. Therefore, immunocompetence may be a factor in determining whether or not the response to beryllium will be neoplastic (Reeves and Preuss, 1985).

The transfer of lymphoid cells to guinea pigs could result in a passive transfer of hypersensitivity, while serum transfer did not produce the same results. Chiappino et al. (1968, 1969) showed that injection of rabbit antilymphocyte serum could inhibit the skin reaction of guinea pigs to beryllium. Intravenous injection of beryllium lactate could suppress the response as well (Turk and Polak, 1969) and inhalation exposure also reduced skin reactivity (Reeves et al., 1975). Additionally, studies have demonstrated individual variations in response. Sensitization is controlled and transmitted as a dominant, nonsex-linked trait (Polak et al. 1968). The hypersensitivity was measured by lymphocyte blast transformation (Hanifin et al., 1970; Rom et al., 1983), macrophage migration inhibition (Henderson et al., 1972) and by skin response. These methods were used both on guinea pigs (Marx and Burrell, 1973; Palazzolo and Reeves, 1975) and on humans (Jones-Williams et al., 1972; Deodhar et al., 1973).

Shima et al. (1986) conducted a study to clarify the relationship between the humoral immune response and the concentration of beryllium in the blood and in the spleen of mice. Mice were intraperitioneally injected with 0.075, 0.15, 0.3 or 0.6 mg $BeCl_2$/kg bw every day for 2 weeks. Changes in the antibody production of the spleen in response to SRBC

and the beryllium concentration in the blood and spleen of mice were studied for a 10-day period after injections were stopped. The following conclusions from the study were obtained:

1. The IgM or IgG-PFC in the spleen of mice injected with $BeCl_2$ increased when the beryllium concentration in the blood was kept between 5 and 35 ng/mℓ, and decreased when the level was >35 ng/mℓ.

2. A relationship between the change of the IgM or IgG-PFC to SRBC and the beryllium concentration in the spleen was not recognized.

It was suggested that the adjuvant activity of beryllium on the humoral immune response was related to the concentration of beryllium in the blood (Shima et al., 1986).

The relationship between the lung reactions seen in beryllium disease and the skin hypersensitivity is not understood. It has been suggested that the responses of the skin and lung may have an inverse relationship to each other (Reeves et al., 1971, 1972). For example, Reeves and Krivanek (1974) found that the pulmonary response could be modified by maintaining a hypersensitivity through intracutaneous injection. This inverse relationship may be similar to that shown by tuberculin sensitivity and resistance to tuberculosis (Drury et al., 1978).

The bioavailability of the beryllium compound used and the route of administration also seems to determine the degree of reaction. The immunogenic forms and routes were those that formed complexes with skin constituents, and even a very low intraperitoneal dose (4.78 μg/kg) or a high intravenous dose (400 μg/kg) were "tolerogenic" if the form used was

freely diffusible. Unavailable forms (citrate and aurintricarboxylate) did not produce sensitivity, while an enhanced reaction resulted from the use of beryllium-serum-albuminate (Krivanek and Reeves, 1972). Vasil'eva (1969, 1972) discovered antigenic beryllium nucleoprotein complexes, but Jones and Amos (1974, 1975) also presented evidence that beryllium can act without complexing and can inhibit the response of allergized lymphocytes to an antigen.

Synergism and Antagonism

Several studies have attempted to find an agent that might be effectively used to inhibit the acute toxicity of beryllium. These studies were summarized by Vorwald et al. (1966). Aurintricarboxylic acid (ATA) formed a chelate that accumulated in the spleen and kidneys but not in the bones, and the use of ATA in conjunction with salicylates was also considered beneficial. ATA had a mild toxicity level with intravenous LD_{50}s of 440 mg/kg for mice and 450 mg/kg for rats. However, Reeves (1977) reported chelating agents to be ineffective in clinical trials involving chronic beryllium toxicity. Joshi et al. (1984) reported that ferritin had a protective effect on the inhibition of phosphoglucomutase (PGM) through chelation. They also observed that the binding of beryllium to ferritin and PGM is reversible. Lindenschmidt et al. (1986) also studied the binding of beryllium to ferritin. Male F344 rats were injected daily with 1 mg Be/kg bw as $BeSO_4$ for 7 days and sacrificed 16 hours following the last injection. Induction of metallothionein synthesis and ferritin binding was measured in the livers of treated rats. Beryllium, unlike other divalent ions tested, did not induce the synthesis of metallothionein. However, ferritin binding of beryllium was measured in substantial quantities and was considered to be

a protective mechanism by the authors. In rats pretreated for 3 days with 4 mg/kg bw ferric ammonium citrate (i.p.), liver ferritin was elevated ~5 times and the lethality of intravenously injected beryllium was significantly reduced in the pretreated animals. This protective effect of iron was suggested to be due, at least in part, to an increased production of ferritin, which binds beryllium and transports it out of the liver.

Sendelbach and Witschi (1987) also showed that iron provides protection against beryllium toxicity. Rats were exposed for 2 hours in a nose-only inhalation chamber for 14 days to an aerosol of $BeSO_4$ containing 2.59 µg Be/ℓ. One group of rats was concurrently treated with iron salt. Mortality was significantly reduced ($p<0.05$) compared with animals that had not received iron treatment. The authors concluded that iron plays a protective role in beryllium toxicity by increasing levels of liver ferritin. Subsequent binding of beryllium to ferritin may render the beryllium inaccessible to exert cell damage.

The feeding of powdered leaves of Gymnema sylvestre (a vine that grows in central India) in the diet of rats for 10 days before and 15 days after intravenous injections of beryllium nitrate (0.316 mg/kg bw) significantly protected the animals from the full fall of blood glucose seen in rats receiving beryllium nitrate alone (Prakash et al., 1986). However, feeding of the leaves for 25 days to normal rats did not alter blood glucose significantly. The leaves may contain a substance that could be useful as a prophylactic against beryllium toxicity.

A few synergistic effects have also been noted. Uzawa (1963) reported that beryllium oxide potentiated the carcinogenic effect of 20-methyl cholanthrene (20-MC) to a greater degree than did carbon black. Stokinger et al. (1950) also reported a synergistic effect of the fluoride ion since BeF_2 nearly produced a doubling of the toxic effect of $BeSO_4$ when inhaled at any given concentration.

Summary

Beryllium is capable of inhibiting several enzyme systems, including alkaline phosphatase, sodium activated ATPase and phosphoglucomutase. It also can increase the activity of some enzymes, such as B-glucoronidase. Subcellular distribution studies show that beryllium enters the cell nucleus where it interferes with cell division by interacting with DNA, thymidine kinase and DNA polymerase. Beryllium is also antigenic and causes hypersensitivity, which is cell-mediated. Syngergistic effects were noted with 20-methyl cholanthrene on carcinogenicity. Ferritin has a protective effect on beryllium toxicity due to its ability to bind beryllium and transport it out of the liver or make it inaccessible to cause cell damage.

VIII. QUANTIFICATION OF TOXICOLOGIC EFFECTS

Introduction

The quantification of toxicologic effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = \_\_\_\_ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicologic effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1991) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$DWEL = \frac{(RfD) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell/\text{day}} = \_\_\_\_ \text{ mg/}\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (bw)}{(UF) \times (\_\_\_ \ell/\text{day})} = \_\_\_\_ \text{ mg/}\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicologic evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biologic mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

The effects of beryllium have been demonstrated by several routes of administration. Studies of intravenous injections of beryllium have shown it to be highly toxic, with an LD_{50} of 0.44 mg Be/kg reported for 200 g male rats (Witschi and Aldridge, 1967). A single intravenous dose of 1.1 mg Be/kg bw as $BeSO_4$ has been found to cause liver necrosis in rats (Cheng, 1956). The LD_{50} intraperitoneal injection for mice is 18 mg/kg when administered as a sulfate (Basinger et al., 1982). Inhalation of beryllium continues to be the major route of toxicity, with acute toxicity reported in rats at a concentration of 194 $\mu g/m^3$ as an aerosol, and pathologic changes reported within a 3-month period at a concentration of 42 $\mu g/m^3$ (Vorwald et al., 1966). A mild, macrocytic-like anemia has also been produced in dogs, rats and rabbits from inhalation, but this effect has not been shown in man (Stokinger and Stroud, 1951).

There is only limited evidence of toxic effects following oral exposure to beryllium. Beryllium rickets, one of the earliest effects observed, has been demonstrated in young animals exposed to soluble beryllium salts (Branion et al., 1931; Guyatt et al., 1933; Kay and Skill, 1934). Guyatt et al. (1933) reported that 21- to 24-day-old rats fed diets containing 0.125-3.0% beryllium carbonate developed rickets after 3 weeks. No adverse effects on body weight or general appearance were observed in young rats fed diets containing 0.06 g $BeCO_3$/day for 14 days (Businco, 1940). Increasing the dose to 0.16 g $BeCO_3$/rat/day resulted in decreased body weight after 10 days of exposure. A further increase in the dose to 0.24 g $BeCO_3$/rat resulted in a >50% reduction in body weight, decreased calcification and development of the long bones, characteristics typical of rickets. The low oral toxicity of beryllium is attributable to its minimal absorption from the GI tract (Schroeder and Mitchener, 1975b).

Dietary administration of 5 mg Be as $BeSO_4$, BeO or Be-metal daily for 3-12 months resulted in a slight reduction in body weight of hamsters fed the $BeSO_4$ compound (Watanabe et al., 1985). Morgareidge et al. (1975), in an unpublished study, reported a slight decrease in body weight in rats fed diets containing 500 ppm beryllium sulfate for 2 years. Schroeder and Mitchener (1975a) reported a slight decrease in growth of male rats given 5 ppm (5 mg/ℓ) beryllium sulfate in their drinking water over a lifetime. No effects were seen in females given the same dose.

Quantification of Noncarcinogenic Effects

The calculation of a drinking water criterion for beryllium may be made based on the available toxicity data.

Derivation of 1-Day HA. Studies with the exposure duration data appropriate for the derivation of a 1-day HA could not be located in the available literature. It is recommended therefore that the 10-day HA of 30 mg/ℓ be used as an estimate of exposure for a 1-day HA.

Derivation of 10-Day HA. Beryllium carbonate fed to young rats (30-40 g) at a daily dose of 0.06 g $BeCO_3$ (0.26 g Be/kg bw) for 14 days resulted in no adverse effects on body weight or general appearance (Businco, 1940). No other endpoints of toxicity were measured for this time period or dose; however, animals fed higher doses showed a dose-related increase in body weight reduction and a decrease in calcification and development of long bones. A NOAEL of 260 mg Be/kg bw/day can be derived based on the absence of adverse body weight and gross toxicologic effects in this study.

The 10-day HA for the 10 kg child is calculated as follows:

$$\text{10-day HA} = \frac{260 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ ℓ/day} \times 100} = 26 \text{ mg/ℓ}$$

(rounded to 30 mg/ℓ or 30,000 µg/ℓ)

where:

260 mg/kg/day	= NOAEL based on the absence of adverse effects on body weight and general appearance in rats fed beryllium carbonate for 2 weeks (Businco, 1940)
10 kg	= assumed weight of a child
1 ℓ/day	= assumed water consumption by a child
100	= uncertainty factor chosen in accordance with NAS/ODW and Agency guidelines in using a NOAEL from an animal study

Derivation of a Longer-term HA. A longer-term HA can also be derived from the subchronic oral studies by Businco (1940) in which young rats (30-40 g) were fed increasing doses of $BeCO_3$ for 83 days. Rats received daily doses of 0.06 g $BeCO_3$ (7.8 mg Be) on days 0-14, 0.16 g $BeCO_3$ (20.8 mg Be) on days 15-34 and 0.24 g $BeCO_3$ (31.2 mg Be) on days 35-83. Estimated average body weight of treated animals was 55.5 g. A TWA dose of 0.191 g $BeCO_3$/rat/day (3.4 g $BeCO_3$/kg bw) can be estimated from the information provided by the authors. The dose of 3.4 g $BeCO_3$/kg bw (443 mg Be) resulted in a >50% reduction in body weight gain and decreased development and calcification of the long bones (rickets-like characteristics). Therefore, the dose of 443 mg Be/kg bw is considered a LOAEL. However, this LOAEL should be viewed with caution because of the degree of body weight loss.

The only other oral study that may be appropriate for the derivation of a longer-term HA is the study by Watanabe et al. (1985) in which hamsters given daily doses of 5 mg Be for ≥12 months showed only a slight reduction in body weight gain. It appears that the only endpoints of toxicity measured were body weight and organ weight; however, at this time only a brief abstract of this study is available. Until more details of this study become available, the LOAEL of 443 mg Be/kg bw for the Businco (1940) study is recommended for the derivation of the longer-term HA.

The longer-term HA for the 10 kg child is calculated as follows:

$$\text{longer-term HA} = \frac{443 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ ℓ/day}} = 4.43 \text{ mg/ℓ}$$

(rounded to 4.0 mg/ℓ or 4000 µg/ℓ)

where: 443 mg/kg/day = NOAEL based on suppressed body weight and development of rickets in rats fed $BeCO_3$ for 83 days (Businco, 1940)

10 kg = assumed weight of a child

1 ℓ/day = assumed water consumption by a child

1000 = uncertainty factor chosen in accordance with NAS/ODW and Agency guidelines in using a LOAEL from an animal study

The longer-term HA for the 70 kg adult is calculated as follows:

$$\text{longer-term HA} = \frac{443 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ ℓ/day} \times 1000} = 15.5 \text{ mg/ℓ}$$

(rounded to 20 mg/ℓ or 20,000 µg/ℓ)

where: 443 mg/kg/day = NOAEL based on suppressed body weight and development of rickets in rats fed $BeCO_3$ for 83 days (Businco, 1940)

70 kg = assumed weight of an adult

2 ℓ/day = assumed water consumption by an adult

1000 = uncertainty factor chosen in accordance with NAS/ODW and Agency guidelines in using a LOAEL from an animal study

Assessment of Lifetime Exposure and Derivation of DWEL. The only oral study of the effects of beryllium in drinking water that may be considered for the derivation of a DWEL is that by Schroeder and Mitchener (1975a). In this study male and female rats were administered 5 ppm Be in their drinking water for a lifetime. The only significant effect was a slight reduction in body weight in males from 2-6 months of age. A NOAEL of 0.538 mg Be/kg bw can be calculated by multiplying the dose of 5 ppm (5 mg/ℓ) by the average water consumption (0.035 ℓ/day) of rats in this study and dividing by the average rat body weight (0.325 kg) given in this study. An RfD of 0.005 mg/kg/day has been derived for this NOAEL by the application of an

uncertainty factor of 100, according to U.S. EPA (1991) guidelines. It should be noted, however, that several weaknesses have been cited in this study such as the presence of other trace elements and minerals including chromium in the drinking water, the use of nonrandomized animals, and the administration of only one dose.

The unpublished study of Morgareidge et al. (1975) is the only other study that can be considered for the derivation of an RfD for beryllium. In this study rats were exposed to 0, 5, 50 or 500 ppm Be in the diet for 2 years. The only toxic effect observed was a slight decrease in body weight in the highest dose group. A NOAEL of 25 mg/kg bw can be calculated assuming an average food consumption of 0.05 mg/kg bw in a rat. Since this study is unpublished and presumably not peer-reviewed, it cannot at this time be used in the derivation of a DWEL for beryllium. The current verified RfD (verification date 12/02/85) (U.S. EPA, 1991) for beryllium is recommended for use in deriving the DWEL until this issue has been resolved.

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.538 \text{ mg/kg/day})}{100} = 0.005 \text{ mg/kg/day}$$

where: 0.538 mg/kg/day = adjusted NOAEL based on the absence of effects in rats fed $BeSO_4$ in drinking water over a lifetime (Schroeder and Mitchener, 1975a)

100 = uncertainty factor chosen in accordance with NAS/ODW and Agency guidelines in using a NOAEL from an animal study

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.005\ mg/kg/day) \times 70\ kg}{2\ \ell/day} = 0.175\ mg/\ell = 0.2\ mg/\ell$$

where: 0.005 mg/kg/day = RfD

70 kg = assumed weight of an adult

2 ℓ/day = assumed water consumption by an adult

The HAs are summarized in Table VIII-1.

Carcinogenic Effects

Beryllium is carcinogenic in laboratory animals when administered by inhalation, intratracheal instillation or intravenous injection (see Tables V-1 and V-2). An in vitro assay by Sirover and Loeb (1976) designed to detect potential metal mutagens and carcinogens also showed that $BeCl_2$ increased the error frequency of the incorporation of nucleotide bases into DNA.

Epidemiologic studies of the relationship between beryllium occupational exposure and the development of human cancer, while presenting evidence that a relationship may exist, have not been sufficient to exclude other possible explanations. The human evidence is therefore considered to be inadequate for determining a relationship between beryllium exposure and cancer in humans.

TABLE VIII-1

HAs and DWEL for Noncarcinogenic Effects

	Drinking Water Concentration (mg/ℓ)	Reference
1-Day HA (10 kg child)	30*	Businco, 1940
10-Day HA (10 kg child)	30	Businco, 1940
Longer-term HA (10 kg child)	4	Businco, 1940
Longer-term HA (70 kg adult)	20	Businco, 1940
DWEL	0.2	Schroeder and Mitchener, 1975a

*Adopted from 10-day HA

Very limited work has been performed with long-term oral exposures. Schroeder and Mitchener (1975a) administered 5 ppm beryllium in the drinking water over the lifetime of rats. Although no statistically significant differences were found in the incidence of tumors between the control and experimental groups, the authors did report a slight excess of grossly observed tumors in exposed male rats. These authors also conducted a similar study with mice (Schroeder and Mitchener, 1975b). In this study the authors reported an excess of lymphoma leukemias in the exposed females, but again the excess was not statistically significant. In an unpublished study, Morgareidge et al. (1975) exposed rats to beryllium at concentrations of 5, 50 or 500 ppm in the diet for 2 years. These data were also analyzed by the U.S. EPA's Human Health Assessment Group. This analysis revealed that a significantly higher number of lung reticulum cell sarcomas occurred in two of the three dose groups in males. The relationship between the dose and response was inverse; the most significant response occurred at a dose of 5 ppm and no significant response occurred at 500 ppm. The Fischer Exact p values for the lowest and intermediate dose groups were 0.0065 and 0.036, respectively. Because of this uncertain dose-response finding, limitations in design and execution of study, and because these results have never been published, the Morgareidge et al. (1975) study should not be considered a key or pivotal study for the derivation of a criterion. It can, however, be used to support a concern that such a calculation be pursued using other data.

Using the U.S. EPA weight-of-evidence criteria for evaluating both human and animal evidence, beryllium is classified in Group B2 indicating that on the strength of positive animal data and inadequate human data beryllium is

regarded as a probable human carcinogen. In the case of beryllium, the animal evidence indicates that all beryllium species should be regarded as probable carcinogens.

Because of the positive carcinogenic findings in animals exposed to beryllium by inhalation and injection, and the suggestive evidence by drinking water supported by positive mutagenicity results, it is concluded that beryllium in drinking water presents a carcinogenic risk to humans. It is therefore considered appropriate to derive a cancer potency factor for oral exposure to beryllium.

Quantification of Carcinogenic Effects

A potency estimate can be derived using data from the Schroeder and Mitchener (1975a) study, in which rats were exposed continuously to beryllium in the drinking water at 5 ppm for a lifetime, resulting in a nonsignificant increase in tumors at all sites in exposed males. The parameters used to calculate the criterion are as follows:

Dose (mg/kg/day)	Incidence (No. responding/No. Tested)
0.0	4/26
0.538	9/33

le = 1126 days
Le = 1126 days
L = 1126

W = 0.325 kg
WC = 0.035 ℓ/day

where
le = duration of exposure
Le = duration of experiment
L = lifespan of test animal

W = average weight of the experimental animal
WC = average water consumption

The carcinogenic potency factor, q_1^*, for humans obtained from these parameters is 4.3 $(mg/kg/day)^{-1}$ using Global '86 (linearized multistage model). An oral quantitative estimate for beryllium of 4.86 $(mg/kg/day)^{-1}$ was originally verified by the U.S. EPA CRAVE Workgroup in February 1989. The Shroeder and Mitchener (1975a) study was used as the basis for both the oral RfD and the slope factor for beryllium. Although identical NOAELs and animal body weights were used by both workgroups, different transformed animal doses were derived (0.538 vs. 0.455 mg/kg/day, respectively). This discrepancy appears to be due to the use of different water consumption rates (0.035 ℓ/day vs 0.029 ℓ/day). The Crave Workgroup has re-evaluated these data and has recalculated the oral slope factor for beryllium based on the parameters previously described. The resulting slope factor of 4.3 $(mg/kg/day)^{-1}$ was verified by the workgroup (December 1989) and input onto IRIS is pending. The same data set was also used to derive a potency factor in the 1980 Ambient Water Quality Criteria document (U.S. EPA, 1980a). The greater q_1^* (8.8) was also due to the use of different estimates of water intake and slightly different mean body weights.

A potency estimate for oral exposure can also be derived by extrapolation from the recommended value of 2 $(mg/m^3)^{-1}$ for inhalation exposure (U.S. EPA, 1987). For a 70 kg man breathing 20 m^3/day, making no adjustment for differences in absorption efficiency, the potency would equal 2 $(mg/m^3)^{-1}$ x 70 kg/20 m^3/day, or 7 $(mg/kg/day)^{-1}$. Exposure of 160-180 g Fischer rats to beryllium oxide at a concentration of 447 $\mu g/m^3$ for 1 hour resulted in the incorporation of 0.2 µg of beryllium into the lung tissue (Hart et al., 1984). Assuming respiration equals

0.0057 m^3/hour, the percent uptake equals 0.2/(0.0057 m^3 x 447 $\mu g/m^3$), or 7.79%. Absorption from the GI tract has been reported to equal 0.6% (Furchner et al., 1973). Oral uptake can then be estimated to be 0.6/7.79 x 100, or 7.7% as efficient as the inhalation route. Adjusting for this difference the extrapolation based oral potency estimate would equal 7 $(mg/kg/day)^{-1}$ x 0.077, or 0.54 $(mg/kg/day)^{-1}$.

A carcinogenic potency factor can also be derived from intravenous infusion studies, in which osteosarcomas were induced. Barnes et al. (1950) injected rabbits, via the ear vein, twice weekly for 5 weeks with an aqueous suspension of zinc beryllium silicate containing a total of 7.2 mg beryllium. This amount averaged over the 120-week period of the experiment is equal to a daily dose of 0.0086 mg/day. Body weights were estimated to equal 4 kg and lifespan 6 years. No adjustment was made for a less-than-lifetime observation period since it was shown in other studies that the osteosarcomas almost always developed within 2 years of exposure. Four of nine animals surviving 32 weeks or longer developed bone tumors. Based upon these data, a human carcinogenic potency of 1843 $(mg/kg/day)^{-1}$ for intravenous infusion can be derived. After adjustment for an absorption efficiency of 0.6% an oral potency of 11 $(mg/kg/day)^{-1}$ is obtained.

A considerable degree of uncertainty is associated with both of the estimates requiring route extrapolation. Because of the quality of the inhalation studies available, the inhalation q_1^* has a low degree of confidence. Extrapolation to the oral route decreases confidence further since it requires the use of two absorption estimates and since the critical target organs are likely to be different with possibly differing degrees of sensitivity. Extrapolation from the intravenous infusion route also results

in considerable uncertainty since the dose was given over a short period of time, the maximum tolerated dose may have been exceeded, the beryllium was in a different form than commonly found in drinking water, small numbers of animals were used and controls were lacking.

The carcinogenic potency estimate of 4.3 $(mg/kg/day)^{-1}$, based upon the Schroeder and Mitchener (1975a) drinking water study, is therefore recommended, despite the lack of a significant tumorigenic response. Since no significant response was detected, this estimate is an upper-bound value, that is, the risk is not expected to be greater, but may be less than the derived value. Despite uncertainties in the potency estimates derived from extrapolation of the intravenous and inhalation studies, the relatively good agreement with the upper bound carcinogenicity potency estimate increases the likelihood that it is not overly conservative. Limited evidence for carcinogenicity in the Morgareidge et al. (1975) study, at the same dose level used by Schroeder and Mitchener (1975a), provides further support for this conclusion.

When the upper bound potency estimate of 4.3 $(mg/kg/day)^{-1}$ is applied to the logarithm for deriving drinking water criteria, the resulting criteria are:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)			
	0	10^{-7}	10^{-6}	10^{-5}
2 ℓ of drinking water	0	0.8	8	80

The linearized multistage model is discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice, which announced the availability of the 1980 Ambient Water Quality Criteria Documents (U.S. EPA, 1980c). The model is linear at low doses, so the lifetime risk is proportional to the water concentration. Therefore, other risk levels and corresponding water concentrations may be obtained by multiplying or dividing the given criteria by factors of 10, 100, 1000 and so forth. Levels were obtained by assuming a lifetime exposure to drinking water containing the corresponding concentrations of beryllium. The criteria levels pertain to the incremental risks associated with this route only since data regarding other sources of beryllium exposure and their contribution to the total body burden are not adequate for quantitative use.

Existing Guidelines, Regulations and Standards

The World Health Organization has not set a guideline for drinking water quality for beryllium (IRPTC, 1987). National regulation by OSHA (1985) established a PEL - 8-hour TWA of 2 $\mu g/m^3$, an acceptable ceiling limit of 5 $\mu g/m^3$, and an acceptable maximum peak above ceiling of 25 $\mu g/m^3$ for 30 minutes. The reportable quantity for beryllium and compounds is 1 pound (U.S. EPA, 1985). Advisories issued by various agencies for air are as follows: NIOSH (1972) set an occupational exposure limit of 0.5 $\mu g/m^3$; ACGIH (1987) advised a TWA-TLV of 0.002 mg/m^3 Group A2. The U.S. EPA (1980a) established an ambient water quality criterion of 68 ng/ℓ for the consumption of 2 ℓ of ambient water and fish and 1170 ng/ℓ for the consumption of aquatic organisms only for a risk level of 10^{-5}.

The U.S. EPA (1991) has an oral RfD (verified December 1985) of 0.005 mg/kg/day based on the lifetime study by Schroeder and Mitchener (1975a) in which rats were exposed to beryllium sulfate in the drinking water at a concentration of 5 mg/ℓ beryllium.

The U.S. EPA (1987) has derived a carcinogenic potency factor of 2.4×10^{-3} ($\mu g/m^3$) based on the epidemiologic study by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been combined to estimate a plausible upper bound for incremental cancer risk associated with exposure to air. The upper bound incremental lifetime risk associated with 1 $\mu g/m^3$ of beryllium is 2.0×10^{-3}. These values are thought to be most representative for beryllium oxide compounds. Potency factors derived from animal studies using beryllium salts other than oxides provide higher potency estimates, while potency factors derived from animal studies using beryllium oxide agree quite well with the risk estimate derived from the human data.

Special Groups at Risk

It has been suggested that a small portion of the population is sensitive to very low concentrations of beryllium in the air, most likely as a result of the development of an immune reaction (Sterner and Eisenbud, 1951). However, this sensitivity has not been demonstrated to occur as a result of beryllium in food or water, and there is no evidence that the air sensitivity is aggravated by oral exposure. In terms of exposure, persons engaged in handling beryllium in occupational environments are at risk. With regard to the population at large, there may be a risk for persons living near beryllium-emitting industries.

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13. ABSTRACT (Maximum 200 words)

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1986; however, more recent data have been added during the review process, and final revisions updating this document were made.

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