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Health Effects Research Laboratory
Cincinnati, Ohio 45268
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REVIEWS OF THE ENVIRONMENTAL EFFECTS OF POLLUTANTS: VI. Beryllium

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REVIEWS OF THE ENVIRONMENTAL EFFECTS OF POLLUTANTS: VI. BERYLLIUM

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CONTENTS

FIGURES

TABLES

FOREWORD

A vast amount of published material is accumulating as numerous research investigations are conducted to develop a data base on the adverse effects of environmental pollution. As this information is amassed, it becomes continually more critical to focus on pertinent, well-designed studies. Research data must be summarized and interpreted in order to adequately evaluate the potential hazards of these substances to ecosystems and ultimately to public health. The Reviews of the Environmental Effects of Pollutants (REEPs) series represents an extensive compilation of relevant research and forms an up-to-date compendium of the environmental effect data on selected pollutants.

Reviews of the Environmental Effects of Pollutants: VI. Beryllium includes information on chemical and physical properties; pertinent analytical techniques; transport processes to the environment and subsequent distribution and deposition; impact on microorganisms, plants, and wildlife; toxicologic data in experimental animals including metabolism, toxicity, mutagenicity, teratogenicity, and carcinogenicity; and an assessment of its health effects in man. The large volume of factual information presented in this document is summarized and interpreted in the final chapter, "Environmental Assessment," which presents an overall evaluation of the potential hazard resulting from present concentrations of beryllium in the environment. This final chapter represents a major contribution by Andrew L. Reeves from Wayne State University.

The REEPs are intended to serve various technical and administrative personnel within the Agency in the decision-making processes, i.e., in the development of criteria documents and environmental standards, and for other regulatory actions. The breadth of these documents makes them a useful resource for public health personnel, environmental specialists, and control officers. Upon request these documents will be made available to any interested individuals or firms, both in and out of the government. Depending on the supply, the document can be obtained directly by writing to:

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HIGHLIGHTS

This study is a comprehensive, multidisciplinary review of the health and environmental effects of beryllium and specific beryllium derivatives. Over 330 references are cited.

Commercially, beryllium is used as the metal, as beryllium-copper alloys and other alloys, and as beryllium oxide ceramic products. United States production of beryllium metal is about 45 to 68 metric tons per year. Human exposure to beryllium is an industrial problem from processing and fabrication of beryllium products. The primary nonoccupational source of beryllium exposure is coal combustion. Beryllium has also been added to the atmosphere from mining, extracting, and machining; foundry operations; ceramic plant operations; space vehicle and rocket fuel manufacture; and nuclear reactor and classified weapons manufacture.

The high toxicity of beryllium compounds is manifest only after inhalation. Acute chemical pneumonitis and chronic pulmonary granulomatosis (berylliosis) have been observed in humans following beryllium inhalation. Chronic berylliosis eventually involves the adrenals, liver, kidney, and heart. Some beryllium compounds can cause malignancies in experimental animals, but epidemiological studies have failed to demonstrate a relationship between beryllium and human cancer. No data were found concerning teratogenic or mutagenic effects of beryllium compounds. The existing occupational standard of 2 $\mu g/m^3$ is thought adequate to prevent acute and chronic beryllium disease in the industrial population. Current beryllium emissions from industries are controlled so that there is apparently no hazard to the general population.

This report was submitted in partial fulfillment of Interagency Agreement No. D5-0403 between the Department of Energy and the U.S. Environmental Protection Agency. The draft report was submitted for review on March 1977. The final report was completed in October 1977.

SECTION 1

SUMMARY

1.1 PROPERTIES AND ANALYSIS

Beryllium is a moderately rare element, existing naturally only as ^{9}Be in some forty-odd mineralized forms. Principal among these are beryl, a beryllium aluminum silicate, and bertrandite, a hydrated beryllium disilicate. These minerals are mined and beryllium hydroxide recovered. Beryl ore is usually obtained as a by-product of other mining operations. Most is imported from Brazil, South Africa, Argentina, and Uganda (1969 data), with less than 10% of the U.S. consumption coming from domestic sources (Section 2.2.9). Commercially, beryllium is used as the metal (about one-third of U.S. consumption), as beryllium-copper alloys (about 50%) and other alloys (about 10%), and as beryllium oxide ceramic products (about 5%) (Section 2.2.9).

Beryllium metal is steel gray and brittle. It is the only stable light metal with an unusually high melting point, a high modulus of elasticity, a low coefficient of thermal expansion, and a high stiffness-to-weight ratio. These are specifications required for certain aerospace and precision instrument applications. Metallic beryllium is also a good thermal and electrical conductor. Due to its low atomic weight, it is relatively transparent to x rays and is used as window material in some x-ray tubes. Its low neutron absorption cross section and high melting point recommend beryllium as structural and moderator materials for certain nuclear reactors (Section 2.2.1).

Beryllium oxide, beryllia, is a colorless crystalline solid or an amorphous white powder with an extremely high melting point, high thermal conductivity, low thermal expansion, and high electrical resistivity. Beryllia powder is compacted to form a ceramic material which has applications as nuclear reactor reflectors and moderators, high-voltage electrical components, spark plug insulators, combustion chamber liners for rockets, inertial guidance components, laser tubes, and electric furnace liners (Section 2.2.2).

Beryllium sulfate, usually $BeSO_4 \cdot 4H_2O$, is soluble in water and insoluble in ethanol. In aqueous solution, beryllium sulfate and other soluble beryllium salts are readily hydrolyzed, increasing the hydrogen ion concentration of the solution. If a buffer is present to remove the hydrogen ions, the beryllium salt can be completely converted to the insoluble hydroxide, which has an extremely long residence time in the body. Such precipitation can be reduced or prevented if the soluble beryllium salt is first chelated, for example by oxalic or citric acid (Section 2.2.3). Although there is very little demand for beryllium sulfate, it is used occasionally in the laboratory.

Beryllium hydroxide is an important intermediate in all of the currently used methods for refining beryllium from its ores. As discussed

above, its insoluble nature makes $Be(OH)_2$ important physiologically, since it is retained in various tissues under normal conditions (Section 2.2.4).

Beryllium fluoride (BeF_2) and beryllium chloride ($BeCl_2$) are conventionally used in the commercial preparation of metallic beryllium, the former in the United States and the latter in France. The fluoroberyllate ion (BeF_4^{2-}) can form from the interaction of BeF_2 with fluorides of the alkali and alkaline earth metals, yielding fluoroberyllates of the general types $M_2^{I}BF_4$ and $M^{II}BF_4$. Structurally these compounds are similar to silicates, and they have been used in the production of unique fluoroberyllate glasses having low dispersion and a wide transmission range (Section 2.2.5). The bromide and iodide of beryllium are seldom used, except for research.

Beryllium alloys are valuable because they display greatly improved strength, hardness, durability, and resistance to fatigue. Applications for these alloys are found in communications, computer, electronic, and electrical industries. The primary beryllium alloy is with copper; but others include beryllium-nickel, beryllium-aluminum, and beryllium-iron (Section 2.2.6).

Beryllides, intermetallic compounds of beryllium, are typically prepared by heating the blended metal powders and then consolidating the materials by hot-pressing techniques. The small amounts of beryllides produced are used for high-temperature components in nuclear power plants, special turbine engines, and nuclear equipment. Toxicity and carcinogenicity testing indicates little or no biologic activity for beryllides, in spite of their relatively high beryllium content (Section 2.2.7).

Beryllium nitrate [$Be(NO_3)_2 \cdot 3H_2O$] is used to stiffen mantles for gas lamps. There is a potential health hazard during the first 15 min of burning a new mantle, when most of the beryllium salt is volatilized (Section 2.2.8).

A variety of analytical techniques are available for detection and quantitation of beryllium, and in some cases, these techniques are sensitive to less than 1 ppb. A major consideration is the nature of the sample to be analyzed and the special requirements for preparation of biological, air, water, and ore samples (Section 2.3.1). Procedures in use are atomic absorption spectrophotometry, fluorometry, emission spectroscopy, and gas chromatography (Section 2.3.3). Newer developments have made atomic absorption spectrophotometry the most convenient and useful technique except where very great sensitivity is required (i.e., less than about 2 ppb). The gas chromatographic method is sensitive to as little as 0.08 pg of beryllium, with usually rapid and convenient sample preparation for environmental and biological samples (Section 2.3.4).

1.2 BIOLOGICAL ASPECTS IN MICROORGANISMS

Microorganisms absorb beryllium when exposed to soluble compounds (Section 3.3.1). Increased growth results in some magnesium-deficient species when dilute alkaline solutions of beryllium salts are added, but such compounds generally prove toxic to microorganisms at or below pH 7

(Section 3.3.2). Toxic thresholds vary widely, depending on pH, growth conditions, Mg^{2+} concentration, and the particular microorganism in question.

1.3 BIOLOGICAL ASPECTS IN PLANTS

Normally, plant beryllium levels are very low, but soluble beryllium compounds can be taken up by roots, especially in acid soils (Section 4.2.1). Although there is poor translocation of beryllium to the shoots of bean, barley, sunflower, and tomato plants, corn appears to be an exception (Section 4.2.2). There is no indication that plants can eliminate beryllium, other than by abscission of dead leaves. Further, beryllium can be concentrated several hundredfold by roots from nutrient solution (Section 4.2.1). About 2 ppm beryllium inhibits growth of a variety of plants. Although beryllium inhibits plant phosphatase in vitro, no effect on enzyme activity has been detected in vivo (see Sections 4.3 and 6.3.2.1). No specific toxic effects are noted for beryllium poisoning in plants, but beryllium does enhance the yield of ethyl methanesulfonate-induced chromosome aberrations (Section 4.3).

1.4 BIOLOGICAL ASPECTS IN WILD AND DOMESTIC ANIMALS

Beryllium effects have been noted in amphibia, molluscs, fish, birds, and cattle. Limb regeneration in salamander larvae can be inhibited by topical application of beryllium; regeneration proceeds upon removal of the beryllium-inhibited stump. Normal embryonic development is retarded by Be^{2+} treatment of frog and snail eggs (Section 5.2.2.1).

Fish exhibit a toxic beryllium response which increases with decreasing water hardness. There are some data suggesting that fish can develop a limited tolerance to beryllium (Section 5.2.2.2).

Cattle fed radioactive $^{7}BeCl_2$ accumulated most of the absorbed beryllium in the liver, kidney, and skeletal system. However, over 68% of the initial dose was rapidly eliminated in the feces and urine. Milk contained less than 0.002% of the beryllium (Sections 5.4.1.1 and 5.4.2).

1.5 BIOLOGICAL ASPECTS IN HUMANS AND EXPERIMENTAL ANIMALS

Beryllium exposure to humans is an industrial problem and can be a problem to the general population living in the vicinity of industrial sources (Section 6.3.1). Inhalation is the primary route of uptake, followed by ingestion and skin absorption. Uptake by ingestion and skin absorption contribute only insignificant amounts to the total body burden. Inhaled beryllium is retained in the lungs and slowly mobilized to the blood, whereas ingested beryllium is poorly absorbed in the intestine and quickly passes out of the body in the feces. Urinary excretion of ingested beryllium is minimal. Beryllium that reaches the bloodstream is rapidly distributed to various tissues and stored, chiefly in pulmonary lymph nodes and bone, for long periods of time. The ultimate storage site is the skeleton (Section 6.2.2).

The most likely fundamental reason for the chronic toxicity of beryllium is its immunologic behavior. The Be ion is an allergen (hapten) to which delayed (cell-mediated) hypersensitivity develops in skin and perhaps in other organs. The symptoms of beryllium disease are thought to be the manifestations of autoimmunity. Two additional theories of beryllium toxicity, applicable in certain situations, are: (1) beryllium affects phosphate metabolism by inhibiting the enzymes alkaline phosphatase, phosphoglucomutase, and to a lesser extent, other phosphate-transferring enzymes (Section 6.3.2.1); or (2) beryllium exerts its effects by complexing with the cellular DNA, inhibiting replication and cell proliferation (Section 6.3.2.2). Beryllium compounds react selectively only with certain proteins; cytoplasmic protein changes from a soluble to insoluble form, but proteins in nuclei and mitochondria are unaltered (Section 6.3.7.3).

Beryllium skin contact can result in allergic dermatitis, skin ulcers, and conjunctivitis. Acute contact dermatitis is generally associated with soluble fluoride or sulfate salts of beryllium, whereas insoluble beryllium oxide powder may cause cutaneous granulomas (Section 6.3.3). Acute beryllium pneumonitis results from inhalation of soluble compounds in relatively high concentrations. All segments of the respiratory tract may be involved, with rhinitis, pharyngitis, and tracheobronchitis. Although there were some fatalities from the acute syndrome, recovery after several weeks or months was the rule and no nonoccupational cases were observed.

Chronic beryllium disease can be latent up to 20 years. The manifestation may be related to stress situations such as infection or surgery. The main lesion is pulmonary granulomatosis; it is thought that altered adrenal function, related to stress, triggers beryllium translocation, which in turn, leads also to liver and kidney damage. Diagnosis is difficult without knowledge of beryllium exposure history (Section 6.3.4). Chronic beryllium disease becomes progressively more severe and resulted in 30% mortality in the early years. Complication of cor pulmonale with myocardial decompensation was the common cause of death. This disease occurs in industrial workers and has been found among residents in the near vicinity, usually within a 3/4-mile radius of the point source. Cases in the general population result from airborne beryllium carried from the plant or from handling workers' contaminated clothing. An effective treatment of chronic beryllium disease involves long-term therapy with steroids and the adrenocorticotropic hormone (Section 6.3.4.7).

Some beryllium compounds (beryllium oxide, beryllium sulfate, beryllium fluoride, beryllium phosphate, and the phosphor zinc manganese beryllium silicate) are capable of inducing malignant tumors in experimental animals. However, epidemiological studies have failed to demonstrate a relationship between beryllium and human cancer (Section 6.3.5). No data were found concerning human teratogenic or mutagenic effects by beryllium compounds (Section 6.3.6).

1.6 ENVIRONMENTAL OCCURRENCE

The primary source of human exposure to beryllium is through processing and fabrication of beryllium products. Current limits for such operations

are 2 μg of beryllium per cubic meter (8-hr average) for plant workers and 0.01 $\mu g/m^3$ (30-day average) or 10 g in 24 hr for plant emissions (Section 7.3). Sampling of 100 U.S. locations indicated an average daily concentration of less than 0.0005 $\mu g/m^3$ (Section 7.3.4). Pollution control devices are now used throughout the industry, and the beryllium concentration in the U.S. atmosphere does not appear to present a health hazard.

United States production of beryllium metal is about 45 to 68 metric tons (50 to 75 tons) per year. It is estimated that annual domestic consumption will increase to approximately 1500 metric tons by the year 2000 and that about half the ore will be mined within the United States (Section 7.2).

According to 1968 data (Section 7.3.1), an annual total of 148 metric tons (164 tons) of beryllium is released to the U.S. environment from a variety of sources. Coal combustion accounts for 85% of the beryllium released to the environment, while beryllium production is responsible for only 4%. However, 25% of the domestic beryllium pollution is released in Pennsylvania and Ohio, where the two American beryllium producers are located.

Prior to implementation of pollution control devices, airborne beryllium pollution was as much as 500-fold higher in the vicinity of beryllium plants than it is now. Now, with efficient emission control, there is no apparent hazard (Section 7.3.4).

Beryllium in rocks and minerals generally ranges from 1 to 10 ppm, although beryl ore can contain up to 5%. The worldwide average soil concentration (about 6 ppm) is much higher than the average U.S. soil concentration (about 1 ppm) (Section 7.3.2).

The beryllium concentration in natural waters is essentially nil (Section 7.3.3).

Since beryllium is so valuable, there is very little solid beryllium waste. Beryllium scrap is salvaged and resold to producers. Beryllium trapped by pollution control devices is also recycled by producers, and that not recycled is buried in sealed containers (Section 7.5).

The limited information available indicates low beryllium levels in foods (Section 7.6). No direct information on biomagnification of beryllium in animals was found, but since there is very little beryllium absorption from ingested sources (Section 6.2), we suggest that human consumption of beryllium in foods presents no health hazard at present levels (Section 7.7).

1.7 CONCLUSIONS

1. The primary nonoccupational source of beryllium exposure is coal combustion; however, the most significant human health hazard is to beryllium workers.

2. Ingested beryllium is only poorly absorbed through the intestine but can be efficiently retained in the lungs after inhalation. A few cases of toxic exposure by skin contact have also been reported.

3. Beryllium mobilized in the bloodstream, for example from the lungs, can be deposited in liver and bone as the insoluble hydroxide.

4. Currently, the methods of choice for beryllium analysis are atomic absorption spectroscopy and gas chromatography.

5. Beryllium production in the United States is about 45 to 68 metric tons annually.

6. There is very little beryllium waste because it is economically feasible to recycle the metal, both from commercial products and from emissions trapped by pollution control devices.

7. Beryllium does not appear to move efficiently through the environment (except in the atmosphere) or through the food chain. It is generally undetectable in natural waters. Beryllium is strongly fixed in many soils, since it can displace other divalent cations which share common sorption sites.

8. Beryllium can partially replace the magnesium requirement in microorganisms and plants, but it becomes toxic at higher levels, especially at neutral to low pH.

9. Three theories regarding the mechanism of beryllium toxicity are: (1) beryllium hypersensitivity due to allergic reactions, (2) beryllium inhibition of phosphate-transferring enzymes, and (3) beryllium complexation with DNA.

10. Certain beryllium compounds can induce malignant tumors in experimental animals, but epidemiological studies have failed to show a correlation between beryllium exposure and human cancer.

11. Acute beryllium disease, generally resulting from inhalation and skin contact, is manifested in respiratory symptoms, dermatitis, skin ulcers, and conjunctivitis.

12. Chronic beryllium disease can be latent for up to 20 years. The onset of symptoms appears to be correlated with stress situations such as infection or surgery and involves pulmonary granulomatosis with necrosis in liver and kidney. The untreated condition resulted in 30% mortality in the early years.

13. No information exists on the teratogenic properties of beryllium compounds in mammals. Beryllium does have inhibitory and teratogenic effects on amphibian embryogenesis.

14. Beryllium can enhance the yield of mutagen-induced chromosome aberrations in plants.

15. No data were found indicating that beryllium is biomagnified in the food chain. In fact, data describing the inefficient absorption of ingested beryllium suggest that biomagnification is unlikely.

16. At present levels, beryllium does not appear to present any health hazard to the general population.

SECTION 2

CHEMICAL AND PHYSICAL PROPERTIES AND ANALYSIS

2.1 SUMMARY

Beryllium is a moderately rare element, ranking 44th in abundance and constituting about 0.0006% of the earth's crust. Discovered by Vauquelin in 1798, the element was first named glucinium or glucinum because of the sweet taste of its salts; its present name was officially sanctioned by the International Union of Pure and Applied Chemistry in 1957.

Beryllium does not occur in the elementary state in nature — it is found in some forty-odd mineralized forms, which are widely distributed in the earth's crust, but only rarely in concentrations suitable for mining. The most important of these minerals are beryl, a beryllium aluminum silicate which has the composition $3BeO \cdot Al_2O_3 \cdot 6SiO_2$, and bertrandite, a hydrated disilicate which has the composition $4BeO \cdot 2SiO_2 \cdot H_2O$. The latter has been mined commercially only since 1969. Beryllium hydroxide has been recovered from beryl by means of the Copaux-Kawecki fluoride process or by the more current Sawyer-Kjellgren sulfate process. In the first method, not used since 1970, ore is roasted with sodium fluoroferrate(III), which converts the insoluble beryllium mineral to a soluble form, sodium fluoroberyllate. The latter is heated with alkali to form beryllium hydroxide. In the sulfate process, refractory ore is melted, quenched, heat treated, and leached with sulfuric acid; the resulting beryllium sulfate is converted to the hydroxide by treatment with alkali. Beryllium hydroxide can be recovered from pulverized bertrandite ore by leaching directly with sulfuric acid. The beryllium sulfate thus obtained is purified by solvent extraction and converted to hydroxide after treatment with aqueous ammonium carbonate.

The most important commercial forms of the element are the metal itself, beryllium-copper alloys, and beryllium oxide. All these forms are prepared from beryllium hydroxide. The oxide is obtained by calcining the sulfate, the metal is prepared by converting the oxide to beryllium fluoride and reducing the latter with magnesium metal, and the beryllium-copper alloys are made by reducing beryllium oxide with carbon in the presence of molten copper.

The pure metal is steel gray and brittle; it has several unique properties that make it attractive, and sometimes essential, to designers of high-performance products in the metallurgical, nuclear energy, and aerospace technologies. Beryllium is the only stable light metal with an unusually high melting point; it also has a high modulus of elasticity, low coefficient of thermal expansion, high stiffness-to-weight ratio, and extreme hardness — properties frequently required by aerospace and precision instrument applications. Beryllium is also a good electrical and thermal conductor. Because of its low atomic weight, beryllium has a high permeability to x rays, and thin sheets of the metal are frequently used as windows for x-ray tubes. Its low atomic weight, low thermal-neutron

absorption cross section, and high melting point also make beryllium useful as a structural component and moderator in certain nuclear reactors. About one-fifth of the U.S. consumption of beryllium is in the form of the metal.

When beryllium is added to copper and certain other metals, alloys are formed which can be readily worked in the soft annealed state and which have, after further heat treatment, greatly improved strength, hardness, durability, and resistance to fatigue. Approximately two-thirds of the total beryllium consumed in the United States is used to produce such alloys for the communications, computer, electronic, and electrical industries.

Beryllium oxide is a colorless crystalline solid or an amorphous white powder. It has an extremely high melting point, high thermal conductivity, high electrical resistivity, and low thermal expansion. Powdered beryllium oxide, easily compacted at temperatures well below its melting point by sintering techniques, produces a ceramic material that has great strength at elevated temperatures. About 10% of the annual U.S. production of beryllium is consumed in such forms. They are used primarily in nuclear reactor reflectors and moderators, high-voltage electrical components, inertial guidance components, laser tubes, electronic ignition systems, and resistor cores.

Beryllium is the smallest of the group II metals — the crystal radius of the divalent ion is only 0.31 Å. The small ionic radius and the resultant large surface charge density are dominant influences on the chemistry of beryllium. Thus, beryllium forms stable compounds with small anions, such as fluoride and oxide, because unusually close approaches to these ion centers are possible. The highly hydrated state of the beryllium ion in acid solution, the amphoteric nature of beryllium, and its tendency to olation in basic media are all further consequences of the small size and high surface charge density of the beryllium ion.

Beryllium and most of its compounds are among the most toxic and hazardous nonradioactive substances currently used in industry. Exposure to airborne beryllium products causes both acute and chronic inhalation effects; only intermetallic forms of beryllium, certain alloys of low beryllium content, some low-grade minerals, and high-fired beryllium oxide show little or no biologic activity. The carcinogenicity of beryllium and some of its salts is also well established for rats and certain other animals, but not man. No well-defined biochemical theory exists which explains the above physiological effects. Tentative explanations of acute and chronic beryllium poisoning are based on enzyme inhibition and on immune and nucleic acid transcription mechanisms, but further research is needed to establish the validity and the detailed biochemistry of the proposed mechanisms.

2.2 PHYSICAL AND CHEMICAL PROPERTIES

Although beryllium forms a large number of cationic and anionic compounds with oxygen, fluorine, silicon, and related elements, only a few forms of the element have commercial importance or environmental significance; these include the metal, oxide, and hydroxide, which are produced on an industrial scale (Heindl, 1970; Versar, Inc., 1975), various intermediate forms, such as beryllium fluoride, ammonium fluoroberyllate, and beryllium sulfate, and certain alloys and silicates. Pertinent physical and chemical characteristics of these materials are discussed in the following sections.

2.2.1 Beryllium

Beryllium ranks 44th in abundance among the elements, constituting about 0.0006% of the earth's crust (Weast, 1977); it is thus more abundant than uranium (0.0004%) and some 12 times as plentiful as mercury (0.00005%). Beryllium was discovered (as the oxide) by Vauquelin in 1798. The metal was not isolated until 30 years later, when Wöhler and then Bussy, in independent researches, reduced beryllium chloride with potassium metal.

In the older literature, beryllium is sometimes called glucinium or glucinum (symbol Gl) because of the sweet taste of its salts; the name beryllium was officially sanctioned by the International Union of Pure and Applied Chemistry in 1957. The *Chemical Abstracts* identification number for beryllium is 7440417.

2.2.1.1 Physical Properties — Refined beryllium is a brittle, steel gray metal. It has several unique properties that make it attractive to designers of high-performance products in the metallurgical, nuclear energy, and space technologies. Beryllium is the only stable light metal with an unusually high melting point; it also has extreme hardness, high stiffness-to-weight ratio, a modulus of elasticity one-third greater than that of steel, and minimal response to thermal fluctuations (Weast, 1977). Beryllium has a high permeability to x rays, and thin sheets of the metal are widely used as windows for x-ray tubes. Beryllium metal is a good electric and thermal conductor. Its low atomic weight, low thermal neutron absorption cross section, and high melting point make it useful as a structural component and moderator for some nuclear reactors. Beryllium occurs naturally only as the beryllium-9 nuclide; however, isotopes of mass 6 through 11 have been made and identified by various nuclear techniques (Krejci and Scheel, 1966, p. 48). Normally occurring beryllium is a convenient and important source of neutrons which form when the element is bombarded with alpha particles:

$$^{9}_{4}\mathrm{Be} + {}^{4}_{2}\mathrm{He} \longrightarrow {}^{12}_{6}\mathrm{C} + {}^{1}_{0}n \ . \qquad (1)$$

The yield is about 30 neutrons per million alpha particles (Schwenzfeier, 1964, p. 451).

Because of its highly dendritic structure and low ductility, cast beryllium cracks and chips easily and is difficult to shape and machine properly. Cast beryllium is converted to powder and hot-pressed to billet form. The billets are readily machined to finished shapes. Billet sections are rolled to sheet or extruded at 750°C to 790°C.

Numerical values for various physical properties of beryllium are given in Table 2.1.

2.2.1.2 Chemical Properties — At ambient temperatures, beryllium is very resistant to oxidation in air; polished surfaces of the pure metal remain bright for years. At elevated temperatures, however, the metal becomes very reactive, rapidly forming the oxide (BeO) at 850°C. The heat generated per gram of metal is greater than that for the oxidation of any other metal; this property is the basis for the attractiveness of beryllium and beryllium hydride propellants in high-performance rocket fuels (Back, 1970; Robinson, 1973). Above 900°C, beryllium reacts with nitrogen and carbon to form the nitride (Be_3N_2) and carbide (Be_2C), respectively (Schwenzfeier, 1964, p. 452). Finely divided beryllium metal burns in air at about 550°C.

Beryllium is readily attacked by sulfuric and hydrochloric acids; cold concentrated nitric acid has little effect, but dilute solutions react slowly. Boiling alkalies dissolve beryllium with evolution of hydrogen. The resulting beryllium hydroxide is amphoteric. Beryllium reacts with fused alkali halides — but not with fused alkaline earth halides — liberating the alkali metal; halides of aluminum and heavier elements are similarly reduced. Beryllium can be obtained from its halide salts by reduction with any of the alkaline earth metals. However, poor yields are obtained, except with magnesium, because of the formation of water-insoluble fluoroberyllates.

Beryllium is the smallest of the group II metals — the crystal radius of the divalent ion is only 0.31 Å. Beryllium's ionic charge-to-radius ratio (z/r) is thus 6.45, similar to that for aluminum (6.0) and much greater than that for the adjacent elements, magnesium (3.1), calcium (2.0), strontium (1.8), barium (1.5), lithium (1.5), and sodium (1.0). As a consequence, the chemistry of beryllium is very similar to that of aluminum, and complete separation of these elements is difficult.

The small ionic radius of beryllium and the resultant large surface charge density exert a dominating influence on the chemistry of beryllium. For example, the most stable compounds are found with smaller anions, such as fluoride (r = 1.36 Å) and oxide (r = 1.40 Å), since unusually close approaches to these ion centers by bivalent beryllium is possible. Indeed, the oxide ion, with its high ratio of charge to radius, forms the most stable bond of which beryllium is capable (Krejci and Scheel, 1966, p. 46). In view of this circumstance, it is not surprising that bivalent beryllium ion is the most heavily hydrated of all bivalent ions in aqueous solution (Fricke and Schutzdeller, 1923; Spandau and Spandau, 1943). The high charge-to-radius ratio of bivalent beryllium also accounts for the amphoteric nature of the ion (Basolo, 1956, p. 423; Cartledge, 1928) as well as its strong tendency to hydrolyze (Section 2.2.4). In general, beryllium

TABLE 2.1 PHYSICAL PROPERTIES OF BERYLLIUM

Property	Value
Atomic number	4
Atomic weight (^{12}C = 12.000)	9.01218
Atomic radius, kX	1.123
Atomic volume, cm^3/mole, 25°C	4.877
Electron configuration	$1s^2 2s^2$
First ionization potential, eV	9.320
Second ionization potential, eV	18.206
Ionic radius (Be^{2+}), Å	0.31
Electronegativity (Pauling's)	1.5
Thermal conductivity, cal/(sec)(cm^2)(°C/cm), 0-100°C	0.349
Density, g/cm^3, 25°C	1.8477 ± 0.0007
Melting point, °C	1287-1292 ± 3
Brinell hardness	60-125
Latent heat of fusion, kcal/mole	2.8 ± 0.5
Mean specific heat, cal/(°C)(mole), 300-1300°K	$3.40 + (2.90 \times 10^{-3})T$
Entropy, S_{298}, cal/(°C)(mole)	2.28 ± 0.02
Enthalpy, H_{298}-H_0, cal/mole	465
Vapor pressure, atm, 150-1550°K	$\log P = 6.186 + (1.454 \times 10^{-4})T - (16{,}734 \pm 80)T^{-1}$
Latent heat of evaporation, kcal/mole	53.55
Boiling point, °C	2970
Electrical resistivity, μohm-cm	4.31
Electrochemical equivalent, mg/coulomb	0.04674
Diamagnetic Hall coefficient	0.0024 ± 0.0001
Optical properties	Steel gray color, reflectivity 50-55%
Sound conductance, m/sec	12,600
ft/sec	41,300
Emissivity, 650 nm	Solid 0.61, liquid 0.61
550 nm	Solid 0.61, liquid 0.81
Photoelectric work function, eV	3.92
Spin and parity	3/2,-
Magnetic dipole moment, nuclear magnetons	-1.1774
Electric quadrupole moment, $cm^2 \times 10^{-24}$	0.02
Binding energy of last neutron, MeV	1.664
Thermal-neutron cross section (Be^9), mb	6 ± 1.2
Crystal structure (α-beryllium)	Hexagonal a = 2.2810 ± 0.005 kX (2.2856 A) c = 3.5760 ± 0.005 kX (3.5832 A) c/a = 1.5677

Optical spectrum

Wavelength (nm)	Intensity	
	Arc	Spark
332.1343	1000 r[a]	30
332.1086	100	
332.1013	50	
313.1072	200	150
313.0416	200	200
265.0781	25	
234.8610	2000 R[a]	50

[a] r = narrow self-reversal; R = wide self-reversal.

Source: Adapted from Krejci and Scheel, 1966, Table 4.2, pp. 49-50. Reprinted by permission of the publisher.

is cationic in aqueous solutions at pH values lower than 5, forms insoluble hydroxides or hydrated complexes at pH 5 to 8, and produces beryllate-like complexes at pH values greater than 8. The entire process, from hydration to formation of the beryllates, can be represented by the generalized reaction

$$n\mathrm{Be}^{2+} + n\mathrm{H_2O} = (\mathrm{BeOH})_n^{n+} + n\mathrm{H}^{+} \quad , \tag{2}$$

which increases in extent as the pH of the solution increases (Everest, 1964, p. 8). The distribution of the different species in this system is somewhat controversial. Early investigators concluded that $Be_3(OH)_3^{3+}$, Be_2OH^{3+}, and $Be(OH)_2$ were the principal species present in solutions of low beryllium concentration and moderate acidity (Kakihana and Sillen, 1956). Later workers concurred in the choice and importance of the first two species but suggested that the third species was probably $Be(OH)_7^{3+}$ or $Be_6(OH)_8^{4+}$, rather than $Be(OH)_2$ (Mesmer and Baes, 1967). Their calculated distribution of the various hydrolysis products is shown as a function of temperature, concentration, and solution acidity in Figure 2.1. Calculated thermodynamic quantities for the hydrolysis reactions at 25°C are given in Table 2.2.

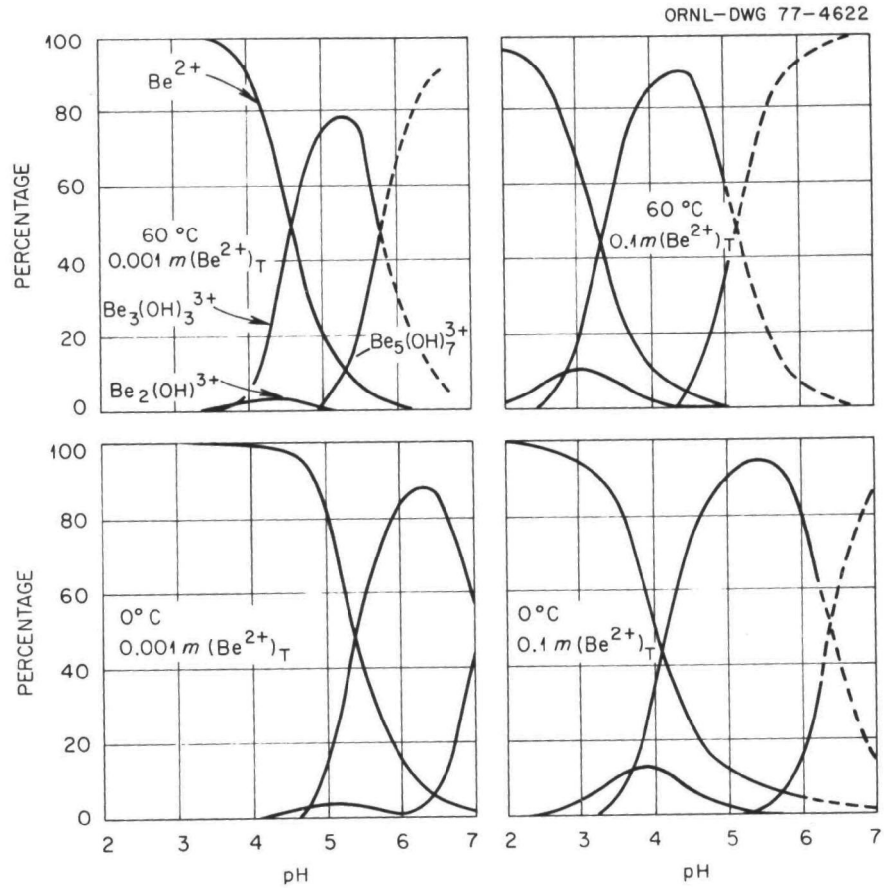

Figure 2.1. Calculated distribution of the beryllium species $Be_3(OH)_3^{3+}$, Be_2OH^{3+}, and $Be_5(OH)_7^{3+}$. Dashed lines represent regions where precipitation occurs. Source: Adapted from Mesmer and Baes, 1967, Figure 5, p. 1958. Reprinted by permission of the publisher.

TABLE 2.2. CALCULATED THERMODYNAMIC QUANTITIES FOR THE HYDROLYSIS REACTIONS AT 25 °C

$$x\mathrm{Be}^{2+} + y\mathrm{H_2O} = \mathrm{Be}_x(\mathrm{OH})_y^{(2x-y)+} + y\mathrm{H}^+$$

Species	$\Delta G°$ (kcal)	$\Delta H°$ (kcal)	$\Delta S°$ (eu)	$\Delta G_f°$ (kcal)
$Be_2(OH)^{3+}$	4.5	5.0 (4.4)[a]	1.4 (0.2)	-234.0
$Be_3(OH)_3^{3+}$	12.2	16.0 (15.2)	15.3 (11.3)	-430.6
$Be_5(OH)_7^{3+}$	34.8	45.3	35.2	-816.5

[a]Data in parentheses from B. Carell and A. Olin, Acta Chem. Scand. 16:2357(1962).

Source: Adapted from Mesmer and Baes, 1967, Table IV, p. 1958. Reprinted by permission of the publisher.

From the preceding discussion it is apparent that weak-acid salts of beryllium are largely undissociated in aqueous solutions at a pH greater than 5. This complication has discouraged research on these systems, and relatively little work has been reported; consequently, it is not possible to predict or interpret in detail the biochemical behavior of beryllium with such physiologically important anions as phosphate, carbonate, acetate, and amino acid complexes, especially at the pH of body fluids (Krejci and Scheel, 1966, p. 50). However, an apparent behavioral trend seems discernible. For example, under physiological conditions the removal of hydrogen ion through the action of buffering agents normally present in the living cell should shift the equilibrium of reaction (1) to the right, forcing complete hydrolysis of the beryllium salt unless some other complexing action is operative. Thus, a hydrolytic product or complex appears to be the most probable ultimate form of physiologically active beryllium (Krejci and Scheel, 1966, p. 56). This conclusion is supported by the work of Veerkamp and Smits (1953), who attributed the reversal of alkaline phosphatase inhibition at increasing beryllium concentrations to precipitation of beryllium hydroxide. It is also consistent with the observed fixation of beryllium in soft tissues (Schepers, 1962) and with the very slow elimination of beryllium from body tissues exposed to beryllium salts (Stokinger, 1972, p. 24); however, much additional research is required before the chemistry of beryllium in the biologic system can be definitively described.

2.2.1.3 Occurrence, Preparation, and Use — Beryllium does not occur in the elementary state in nature (Latimer and Hildebrand, 1951, p. 60); instead, it is found in some forty-odd mineralized forms (Table 2.3) which are widely distributed in the earth's crust but which rarely exist in concentrations economically suitable for mining. The most important of these minerals is beryl, a beryllium aluminum silicate which has the composition $3BeO{\cdot}Al_2O_3{\cdot}6SiO_2$, and bertrandite, a hydrated disilicate which has the composition $4BeO{\cdot}2SiO_2{\cdot}H_2O$. The latter has been mined commercially only since

TABLE 2.3. BERYLLIUM MINERALS

Mineral	Chemical composition	Crystal system	Color	Hardness	Specific gravity	Theoretical BeO content (%)	Beryllium content (%)	Type of occurrence
Barylite	$Be_2BaSi_2O_7$	Orthorhombic	Colorless	6-7	4.0	15	5.6	Contact metamorphic
Bertrandite	$4BeO \cdot SiO_2 \cdot H_2O$	Orthorhombic	Colorless, white, or yellowish	6-7	2.6	42	15.1	Granitic pegmatite
Beryl	$3BeO \cdot Al_2O_3 \cdot 6SiO_2$	Hexagonal	Green, blue, yellow, or white	7.5-8	2.6-2.8	14	3.0-5.0	Granitic pegmatite
Beryllonite	$Na_2O \cdot 2BeO \cdot P_2O_5$	Orthorhombic	Colorless, white, or yellowish	5.5-6	2.8	20	7.1	Granitic pegmatite
Brommellite	BeO	Hexagonal	White	9	3.0	100	36.0	Contact metamorphic
Chrysoberyl	$BeO \cdot Al_2O_3$	Orthorhombic	Green	8.5	3.5-3.8	20	7.1	Granitic pegmatite
Danalite	Fe, Zn, Be, Mn sulfosilicate	Isometric	Flesh red or gray	5.5-6	3.4	14	9	Various
Euclase	$2BeO \cdot Al_2O_3 \cdot 2SiO_2 \cdot H_2O$	Monoclinic	Colorless, pale green, blue, or white	7.5	3.1	17	6.1	Granitic pegmatite
Eudidymite	$Na_2O \cdot 2BeO \cdot 6SiO_2 \cdot H_2O$	Monoclinic	White	6	2.6	10	3.7	Nepheline syenite
Gadolinite	$2BeO \cdot FeO \cdot 2Y_2O_3 \cdot 2SiO_2$	Monoclinic	Black, greenish black, or brown	6.5-7	4.0-4.5	10	3.2-4.7	Granitic pegmatite
Hambergite	$4BeO \cdot B_2O_3 \cdot H_2O$	Orthorhombic	Grayish white	7.5	2.3	53	19.2	Granitic and syenitic
Helvite	Mn, Fe, Be sulfosilicate	Isometric	Yellow, brown, green, or colorless	6-6.5	3.2-3.4	14	3.8-5.4	Various
Herderite	$CaO \cdot CaFOH \cdot 2BeO \cdot 2P_2O_5$	Monoclinic	Yellowish or greenish white	5	3.0	15	5.6-5.9	Granitic pegmatite
Kolbeckite	H, Be, P silicate	Monoclinic	Blue or gray	3.5-4	2.4	Variable	Up to 3.1	Hydrothermal
Leucophanite	Ca, Na, Be fluosilicate	Orthorhombic	Whitish green or yellow	4	3.0	10	4.0	Syenitic pegmatite
Meliphanite	Ca, Na, Be fluosilicate	Tetragonal	Yellow or red	5-5.5	3.0	13	3.4-5.0	Syenitic pegmatite
Milarite	$K_2O \cdot 4CaO \cdot 4BeO \cdot Al_2O_3 \cdot 24SiO_2 \cdot H_2O$	Monoclinic	Pale green	5.5-6	2.6	2	Up to 1.8	Granitic pegmatite
Phenacite	$2BeO \cdot SiO_2$	Hexagonal	Colorless, white yellow, rose, or brown	7.5-8	3.0	46	16.4	Granitic pegmatite
Trimerite	$(Mn, Ca) \cdot Be \cdot SiO_4$	Monoclinic	Salmon pink	6-7	3.5	17	6.1	Contact metamorphic

Source: Adapted from U.S. Department of the Interior, 1953, Table I-1, p. I-10.

1969. Several processes are available for converting these minerals to beryllium hydroxide, the intermediate from which all other beryllium products are made. The method currently used to process beryl is the Sawyer-Kjellgren sulfate process. Until 1970, the Copaux-Kawecki fluoride process was also used.

In the Copaux-Kawecki fluoride process, the pulverized ore is mixed with sodium fluoroferrate(III), briquetted, roasted at 750°C, crushed, and leached with water. The resulting solution consists principally of sodium fluoroberyllate:

$$2Na_3FeF_6 + 3BeO{\bullet}Al_2O_3{\bullet}6SiO_2 \longrightarrow 3Na_2BeF_4 + Fe_2O_3 + Al_2O_3 + 6SiO_2 \ . \quad (3)$$

The latter is heated with caustic soda to precipitate beryllium hydroxide, which is filtered, washed, and calcined to the oxide:

$$Na_2BeF_4 + 2NaOH \longrightarrow Be(OH)_2 + 4NaF \ , \qquad Be(OH)_2 \xrightarrow{heat} BeO + H_2O \ . \quad (4)$$

The beryllium oxide is recovered in good yield (about 90%) with sufficient purity to serve as an intermediate in the production of beryllium copper and other alloys, but not elemental beryllium.

In the Sawyer-Kjellgren sulfate process the beryl ore is melted, quenched with water, and reheated to 950°C. The resulting glass is pulverized, digested at 250°C with 85% sulfuric acid, and leached with water:

$$3BeO{\bullet}Al_2O_3{\bullet}6SiO_2 + 6H_2SO_4 \longrightarrow 3BeSO_4 + Al_2(SO_4)_3 + 6SiO_2 + 6H_2O. \quad (5)$$

The silica that is formed is removed by filtration, leaving a solution of beryllium and aluminum sulfates. The latter is precipitated and removed as alum after addition of ammonium hydroxide:

$$H_2SO_4 + Al_2(SO_4)_3 + 2NH_4OH + 22H_2O \longrightarrow Al_2(SO_4)_3{\bullet}(NH_4)_2SO_4{\bullet}24H_2O \ . \quad (6)$$

A chelating agent is supplied to hold iron impurities in solution, and caustic soda is added; the resulting sodium beryllate solution yields granular beryllium hydroxide on heating:

$$BeSO_4 + 4NaOH \longrightarrow Na_2SO_4 + Na_2BeO_2 + 2H_2O \ , \qquad Na_2BeO_2 + 2H_2O \longrightarrow 2NaOH + Be(OH)_2 \ . \quad (7)$$

As in the Copaux-Kawecki process, beryllium oxide is obtained from the hydroxide by calcination. The yield from the sulfate process (about 85%) is slightly lower than that from the fluoride method, but product purity is substantially better (Schwenzfeier, 1964, p. 458).

Although imported beryl ore continues to be an important source of U.S.-produced beryllium hydroxide, an increasing fraction of the annual total since 1969 is derived from native bertrandite ore. The technology

used in this extraction is outlined in a Bureau of Mines information circular (U.S. Department of Interior, 1971). Pertinent details are also available for an efficient solvent extraction technique for recovering beryllium hydroxide from bertrandite ore, which has been extensively studied by the U.S. Bureau of Mines (U.S. Environmental Protection Agency, 1973*a*, p. 3-3). In the latter procedure, a liquor obtained by leaching pulverized bertrandite ore with sulfuric acid is adjusted to pH 2, treated with sodium hydrosulfide to convert trivalent iron to the nonextractable divalent form, and extracted with a kerosene solution of di-2-ethylhexylphosphoric acid (EHPA):

$$BeSO_4(aq) + 2HOP(OR)_2(org) \rightarrow Be[OP(OR)_2]_2(org) + H_2SO_4(aq) \ , \qquad (8)$$

where aq and org represent the aqueous solution and organic solvent, respectively.

In the United States, metallic beryllium is produced on a commercial scale by reducing high-purity beryllium fluoride with magnesium metal:

$$BeF_2 + Mg \longrightarrow Be + MgF_2 \ . \qquad (9)$$

The operation is usually performed in an induction-type electric furnace equipped with a graphite crucible. A stoichiometric excess of beryllium fluoride is usually used because the reaction is strongly exothermic and difficult to control (Heindl, 1970, p. 492). The beryllium fluoride required in the reduction step is obtained by treating purified beryllium oxide from the Copaux-Kawecki fluoride process or the Sawyer-Kjellgren sulfate extraction process with ammonium bifluoride and thermally decomposing the resulting ammonium fluoroberyllate:

$$\begin{aligned} BeO + 2NH_4F{\cdot}HF &\longrightarrow (NH_4)_2BeF_4 + H_2O \ , \\ (NH_4)_2BeF_4 &\xrightarrow{\text{heat}} 2NH_4F + BeF_2 \ . \end{aligned} \qquad (10)$$

Alternatively, impure beryllium oxide can be used initially if the resulting ammonium fluoroberyllate is purified prior to the thermal dissociation step.

Purification of scrap beryllium by electrorefining — to prepare flake — is practiced in the United States and elsewhere. In this process, beryllium oxide is first heated with carbon and chlorine gas at 1000°C. The reaction produces beryllium chloride and carbon dioxide:

$$2BeO + 2Cl_2 + C \xrightarrow{1000°C} 2BeCl_2 + CO_2 \ . \qquad (11)$$

The vaporized beryllium chloride is collected by passing the effluent gases through a condenser maintained at a temperature below 400°C. The beryllium chloride is then mixed with 99 parts of anhydrous sodium chloride or a lithium chloride-potassium chloride eutectic and electrolyzed at 400°C or 500°C in a stainless steel cell equipped with an iron or nickel cathode

and an annular anode basket containing the beryllium to be refined. An electrical potential of 5 to 9 V is normally used. Good quality beryllium metal flakes, which have a very low oxygen content, are produced.

Over 300,000 kg of beryllium was consumed industrially in the United States in 1968 — about one-half in beryllium-copper alloys, nearly one-third as beryllium metal, and the balance in other alloys and ceramics (Heindl, 1970, p. 494). Almost all the metal is used in nuclear and aerospace applications, where beryllium's low density, high modulus of elasticity, high stiffness-to-weight ratio, high heat capacity, and low neutron and x-ray absorption cross sections make it uniquely suitable as a structural component of orbiting satellites, missiles, aircraft brakes and rudders, jet engine parts, special-purpose nuclear reactors, and x-ray tube windows. The same properties also make beryllium metal attractive for use in inertial guidance applications, space optics, ballistic missiles, and other classified military uses (National Research Council, 1971, p. 10).

2.2.1.4 Biochemistry — Beryllium and most of its compounds are among the most toxic and hazardous nonradioactive substances currently used in industry (Berry, Osgood, and St. John, 1974, p. 87). Exposure to airborne beryllium products causes both acute and chronic inhalation effects as well as skin and conjunctival effects (U.S. Environmental Protection Agency, 1973*b*); only intermetallic forms of beryllium, certain alloys of low beryllium content, some low-grade minerals, and high-fired beryllium oxide show little or no biologic activity. The carcinogenicity of beryllium compounds is also well established for rats and certain other animals, but there is no evidence to incriminate beryllium as a human carcinogen (Stokinger, 1972, pp. 18-19).

No unified theory exists to explain the various physiological effects described above — indeed, they may be due to various biochemical properties. The biochemistry of beryllium is complex; because of its amphoteric nature (Section 2.2.1.3), beryllium can exist as a cation, Be^{2+}, or as an anion, BeO_2^{2-}, each having a different toxicologic potential. Furthermore, at physiologic pH, beryllium forms colloidal hydrates (Section 2.2.1.3). It has a variable, and thus far only partially explored, capability to form compounds with body proteins; some of the formed complexes are autoantigenic. Beryllium also alters phosphate metabolism by inhibition of several enzymes and garbles nucleic acid transcription during cell division. The relevance of these effects in the clinical toxicology of beryllium is not fully understood at this time.

Beryllium enters the body chiefly by inhalation; little accumulation or toxicity results from oral exposures because ingested forms of beryllium are poorly absorbed through the intestinal wall (Aldridge, Barnes, and Denz, 1949; Stokinger, 1972, pp. 22-23). Inhaled aerosols of soluble beryllium salts hydrolyze to a colloidal form immediately on impingement on the mucous surfaces of the bronchopulmonary tract. At low concentrations this colloid appears to be mostly beryllium orthophosphate with small amounts of the hydroxide admixed (Vorwald, Reeves, and Urban, 1966, p. 222). Body proteins do not seem to be complexed under these conditions, although adsorption and subsequent denaturation of proteins on the surface of colloidal beryllium phosphate appears probable.

Some beryllium is retained in the lung for long periods; portions are transported to and stored in all the major tissues of the body. The manner in which this distribution occurs has been the subject of many investigations (Klemperer, Martin, and Liddy, 1952; Reeves and Vorwald, 1961; Vacher and Stoner, 1968*a*, 1968*b*); it seems to depend more on the extent of exposure and the physiochemical state of the beryllium than on metabolic differences of animal species (Browning, 1969, p. 69; Stokinger, 1972, p. 24; Vacher, Deraedt, and Benzoni, 1973). When small doses of soluble beryllium salts are administered to rats by inhalation, beryllium appears in the blood plasma as a soluble diffusible complex of an organic acid, chiefly citrate, which tends to be deposited in the kidney and bone or excreted in the urine; in larger concentrations, beryllium combines with plasma phosphates to form nondiffusible, insoluble particulate aggregates, which are bound to plasma globulin, such as gamma globulin (Tepper, 1972*a*, p. 245; Vacher, Deraedt, and Benzoni, 1973). These insoluble beryllium aggregates are cleared from the bloodstream by the Kupffer cells of the liver, which concentrate the aggregates in the liver cell nuclei and lysosomes (Cheng, 1956; Witschi and Aldridge, 1968). Some researchers associate the observed toxic effects of beryllium with these soluble and insoluble fractions (Vacher, Deraedt, and Benzoni, 1973; Vacher, Deraedt, and Flahaut, 1975).

Beryllium has an electronic configuration (Table 2.1) closely related to that of magnesium and calcium; it also forms extremely strong bonds with oxygen-containing molecules, such as phosphates (Section 2.2.1.2). Because of these properties, early workers sought to explain the toxicity of beryllium by demonstrating the inhibitory action of soluble beryllium salts on essential magnesium- or calcium-activated enzymes. Soluble beryllium salts were soon shown to be significant in vitro inhibitors of serum alkaline phosphatase (Grier, Hood, and Hoagland, 1949; Klemperer, Miller, and Hill, 1949), phosphoglucomutase (Cochran, Zerwic, and DuBois, 1951), RNase and DNase (Jacobson and Webb, 1952), and ATPase (DuBois, Cochran, and Mazur, 1949); despite these results, however, Aldridge, Barnes, and Denz (1949) and Vorwald, Reeves, and Urban (1966, p. 222) found no evidence of significant enzymatic interference in rats injected intravenously or exposed by inhalation to soluble beryllium salts. Unlike other hepatotoxins, soluble beryllium salts neither inhibit protein synthesis nor cause early biochemical changes in the liver (Tepper, 1972*a*, p. 245). However, Witschi and Aldridge (1967) did observe a diminished loss of hepatic glycogen and an increased conversion of glucose into glycogen in fasting rats that were treated intravenously with toxic doses of soluble beryllium salts.

Chronic berylliosis is a systemic disease characterized by a latency that sometimes extends to 20 years (Fishbein, 1973, p. 3). Some investigators suggest that the onset of chronic berylliosis is associated with the release and general dispersal of destructive enzymes from hepatic lysosomes rendered unstable by a sudden transfer to them of beryllium previously stored in other body tissues (Clary and Stokinger, 1973). According to this hypothesis the relocation of beryllium to the hepatic lysosomes is triggered by some physiological stress, such as pregnancy, surgery, or general aging, which results in an altered adrenal function. However, later studies by these workers show that pregnancy does not increase the

severity of response to beryllium in the rat (Clary, Bland, and Stokinger, 1975). The salient features of the lysosomal theory are outlined in the right portion of Figure 2.2. Other researchers attribute chronic berylliosis to a delayed hypersensitivity reaction to which auto immunity develops (Deodhar, Barna, and Van Ordstrand, 1973; Hanifin, Epstein, and Cline, 1970; Naeye, 1973; Sterner and Eisenbud, 1951; Vacher, 1972). A generalized mechanism for this approach is diagrammed in the left portion of Figure 2.2. There appears to be little reason to doubt involvement of the adrenal function in chronic berylliosis, but details of its participation and the relative importance of the proposed lysosomal and immunological mechanisms are matters that must be resolved by additional research (Stokinger, 1972, p. 30; Tepper, 1972*b*, p. 133; Vorwald, Reeves, and Urban, 1966).

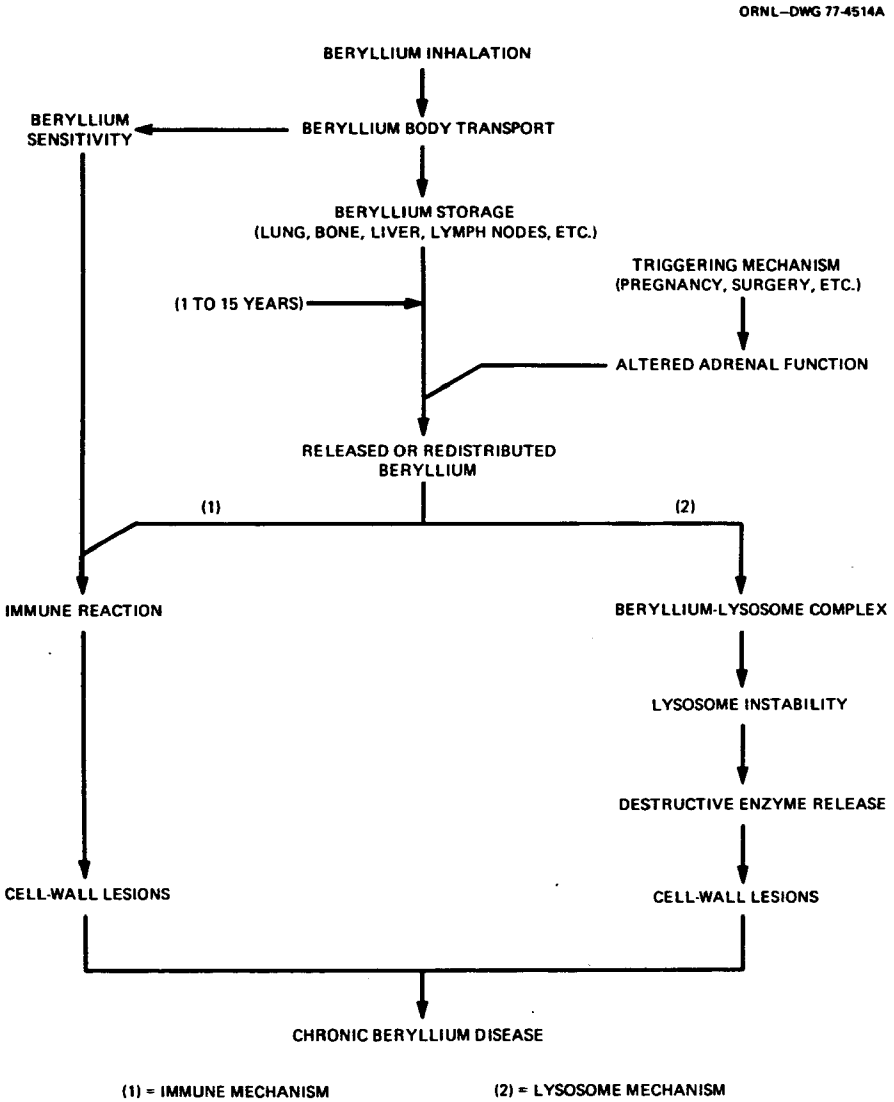

Figure 2.2. Two possible chronic beryllium disease mechanisms. Source: Adapted from Hurlbut, 1974*a*, Figure 1, p. 13.

2.2.2 Beryllium Oxide (Beryllia)

Beryllium oxide (BeO) is an important chemical intermediate resulting from the extraction of beryllium from beryl or bertrandite (Section 2.2.1.3). Beryllium oxide is also known as beryllia; its *Chemical Abstracts* identification number is 1304569.

2.2.2.1 Physical Properties — Beryllium oxide is a colorless crystalline solid or an amorphous white powder. It has a molecular weight of 25.01, a hardness of 9 (Mohs scale), and a density of 2.86 to 3.02, depending on the method of preparation (International Agency for Research on Cancer, 1972, pp. 17-18). Beryllium oxide is soluble in acids and alkalis but is essentially insoluble in water (0.7 µg per 100 ml) (Dutra and Largent, 1950). Beryllium oxide melts near 2530°C (Weast, 1977), but it can be compacted to a coherent mass at much lower temperatures by sintering techniques. Beryllium oxide has the highest thermal conductivity of any metal oxide — higher than that of some metals, including beryllium itself (Krejci and Scheel, 1966, p. 77). Beryllium oxide also has low compressibility, low thermal expansion, and exceptionally high electrical resistivity. Other physical properties are shown in Table 2.4.

2.2.2.2 Chemical Properties — Because of the strong binding forces and short bond distances between beryllium and oxygen ions in the crystal lattice, beryllium oxide is inherently an extremely stable compound. Its vapor pressure is negligibly low up to 2000°C (Erway and Seifert, 1951). Above 1200°C, however, it is readily attacked by water vapor to form gaseous beryllium hydroxide:

$$BeO + H_2O \xrightarrow{>1200°C} Be(OH)_2 \quad . \qquad (12)$$

Sintered beryllium oxide is also seriously corroded by gaseous hydrogen fluoride; the other gaseous halogens and volatile chlorides react with beryllium oxide only when it is finely divided. Liquid reagents, such as fused carbonates, fluorides, and pyrosulfates, and aqueous solutions, such as the alkali hydroxides and mineral acids, attack finely divided beryllium oxide, but not the sintered form. Among liquid reagents, the sintered form is susceptible only to fused alkalis. Sintered beryllium oxide is also essentially stable to all molten metals, except calcium (Krejci and Scheel, 1966, p. 78).

2.2.2.3 Preparation and Use — Beryllium oxide is usually prepared by calcining the hydroxide (Section 2.2.1.3), but it can also be obtained by heating the sulfate, nitrate, basic carbonate, or other compounds in which beryllium is the only element forming a nonvolatile oxide. Direct formation of the oxide from the metal is difficult because of the high ignition temperature required and the cohesive nature of the resulting oxide film, which protects the bulk of the metal from further oxidation. The chemical and physiological reactivity of the resulting oxide depends on the ignition temperature — the lower the temperature, the greater the surface area and chemical or biological reactivity of the resulting oxide. For example, beryllium oxide ignited at 400°C to 500°C is readily soluble in acids and alkalis, but if heated to 1000°C it dissolves only in hydrofluoric acid or hot concentrated sulfuric acid (Novoselova and Batsanova,

TABLE 2.4. PHYSICAL PROPERTIES OF BERYLLIUM OXIDE (BERYLLIA)

Property	Value
Formula	BeO
Molecular weight	25.01
Crystal structure, 26°C	Hexagonal a = 2.698 A, c = 4.380 A
Density, g/cm^3, 26°C	3.008 (x ray)
Melting point, °C	2550 ± 30
Boiling point, °C	3960 ± 200 (estimated)
Heat of formation, ΔH_{f298}, kcal/mole	-143.1
Entropy of formation, ΔS_{f298}, cal/(°C)(mole)	-23.43
Free energy of formation, ΔF_{f298}, kcal/mole	-136.12
Equilibrium constant	$10^{101.88}$
Dissociation energy, kcal/mole	106 ± 3
Reaction of metallic Be with O_2, 750-950°C	
Energy of activation, E, kcal/mole	50.3
Entropy of activation, ΔS^*, cal/(°C)(mole)	-10
Specific heat, cal/(°C)(mole)	
0°K	0
73°K	0.3
173°K	2.6
273°K	5.5
300°K	6.146
500°K	9.308
700°K	10.700
900°K	11.499
1200°K	12.296
Enthalpy	
$H_T - H_{273}$, cal/mole, 373-1173°K	$11.1084T + (7.1245 \times 10^{-4})T^2 + (8.40705 \times 10^5)T^{-1} - (5.31245 \times 10^7)T^{-2} - 5453.21$
$H_T - H_{298}$, joules/mole 363-1128°K	$36.36T + (7.56 \times 10^{-3})T^2 + (1.36 \times 10^6)T^{-1} - 1600$
$H_T - H_{298}$, cal/mole 1200-2820°K	$9.71T + (1.045 \times 10^{-3})T^2 - 3540$
Entropy	
S_{298}, cal/(°C)(mole) 298°K	3.37 ± 0.05
$S_T - S_{298}$, cal/(°C)(mole)	
400°K	2.089
600°K	5.807
800°K	8.872
1000°K	11.433
1200°K	12.630
Thermal conductivity, cal/(sec)(cm^2)(°C/cm)	
-253°C	0.04
-160°C	1.75 (maximum)
0°C	0.8
725°C	0.111
1825°C	0.035 (minimum)
Coefficient of expansion, cm/(cm)(°C)	
20-300°C	6.6×10^{-6}
20-600°C	7.2×10^{-6}
20-1200°C	9.5×10^{-6}
20-1800°C	9.8×10^{-6}
Magnetic susceptibility, cgs units, 24.8°C	-11.93×10^{-6}

Source: Adapted from Krejci and Scheel, 1966, Table 4.2, pp. 49-50. Reprinted by permission of the publisher.

1968, p. 7). Similarly, after intratracheal instillation, oxide prepared at 500°C is quickly distributed to the liver, kidneys, and bones of rats, while oxide calcined at 1600°C remains largely in the lungs (Spencer et al., 1965).

Although most beryllium oxide produced in the United States is consumed in manufacturing beryllium-copper alloys or beryllium metal, a small fraction of the total — 10% in 1974 — is used to produce sintered beryllium oxide ceramic products (U.S. Environmental Protection Agency, 1973*a*, p. 3-22). In a typical ceramic manufacturing process, the raw beryllium oxide is ground in a ball mill, screened to size, spray dried, mixed with binding agents, extruded through an appropriately shaped die, and sintered (U.S. Environmental Protection Agency, 1973*a*). A block diagram of this manufacturing sequence is shown in Figure 2.3. Emissions from such an operation are almost entirely in the form of dusts, fumes, and mists, which contain low-fired beryllium oxide. The source and nature of these emissions are shown in Table 2.5.

Almost all the present uses of beryllium oxide are related to its low neutron absorption cross section, high melting point, low thermal expansion, high heat conductance, high electrical resistivity, and general compatibility with corrosive environments at elevated temperatures; these properties make it valuable for use in nuclear reactor fuels and moderators, high-voltage electrical components, inertial guidance components, laser tubes, electronic ignition systems, and resistor cores (U.S. Environmental Protection Agency, 1973*a*). In addition, the superior microwave transmission characteristics of beryllium oxide make it essential for certain applications, such as radomes and microwave windows (Heindl, 1970, p. 495). Beryllium oxide is also used in limited quantities as a catalyst for certain organic chemical reactions (Durocher, 1969, p. 65).

2.2.3 Beryllium Sulfate

Beryllium sulfate most frequently occurs as the tetrahydrate, $BeSO_4 \cdot 4H_2O$, which is obtained by evaporating beryllium oxide, hydroxide, or carbonate in dilute sulfuric acid. It is a colorless crystalline compound. Its molecular weight is 177.14, and the *Chemical Abstracts* identification number is 7787566. The tetrahydrate is soluble in water (Table 2.6) but insoluble in ethanol; its solubility in water is strongly depressed by the presence of sulfuric acid. Like other soluble beryllium salts, the sulfate is extensively hydrolyzed in aqueous solution (Table 2.7), and the resulting liquid is strongly acidic (Table 2.8):

$$BeSO_4 + 2H_2O \rightleftharpoons Be(OH)_2 + 2H^+ + SO_4^{2-} \qquad (13)$$

The hydrolysis constant for the reaction is 1.4×10^{-7} (Novoselova and Batsanova, 1968, p. 12). In this equilibrium, the degree of hydrolysis is governed by the hydrogen ion concentration — if the hydrogen ion is removed by any mechanism, complete hydrolysis of the beryllium sulfate occurs. This characteristic behavior of the beryllium ion has serious physiological consequences. In the living cell, excess free hydrogen ions

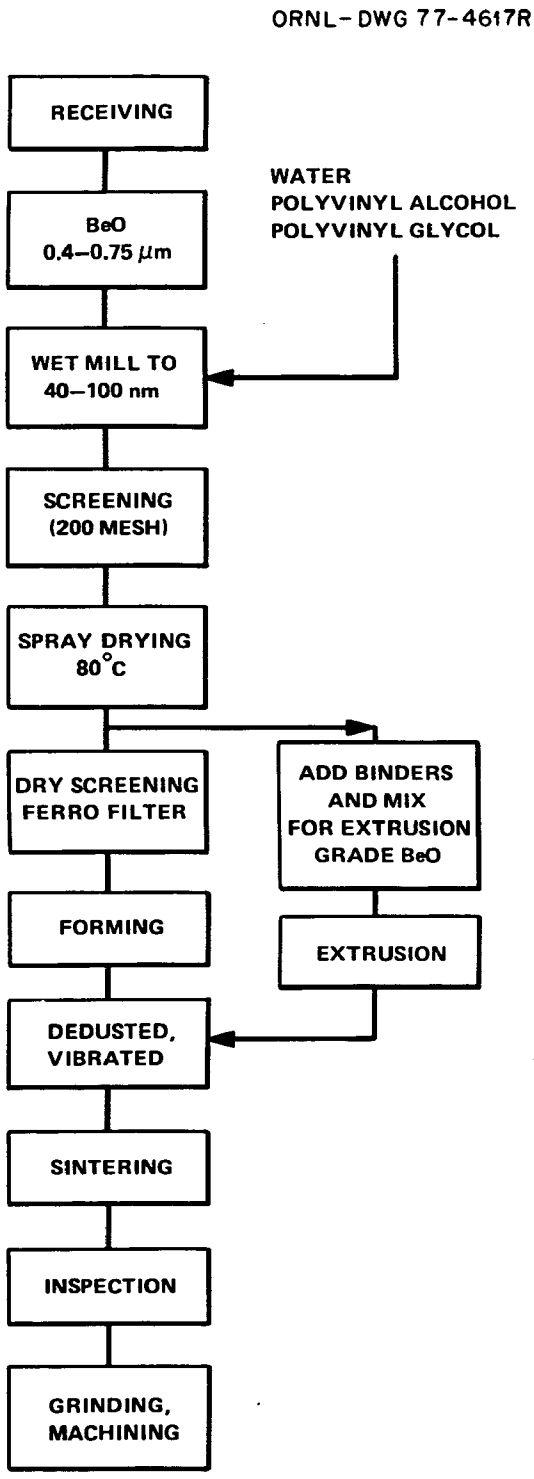

Figure 2.3. Manufacture of beryllium oxide ceramic products. Source: Adapted from U.S. Environmental Protection Agency, 1973*a*, Figure 3-14, p. 3-23.

TABLE 2.5. SOURCES OF BERYLLIUM CERAMIC PLANT EMISSIONS

Source	Emissions
Spray dryer	Water Beryllium oxide
Dry boxes	Beryllium oxide
Kilns	Beryllium oxide Binders Water
Machining	Beryllium oxide Binders Water Cutting fluids
Development laboratory	Traces of acids Beryllium oxide Binders

Source: U.S. Environmental Protection Agency, 1973*a*, Table 3-5, p. 3-24.

TABLE 2.6. SOLUBILITY OF BERYLLIUM SULFATE TETRAHYDRATE IN WATER

Temperature (°C)	Solubility (g per 100 g of solution)
25	29.32
50	32.93
75	37.98
85	41.33
95	43.45

Source: Novoselova and Batsanova, 1968, page 12.

TABLE 2.7. DEGREE OF HYDROLYSIS OF BERYLLIUM SULFATE SOLUTIONS AT 25°C

Concentration of $BeSO_4$ (*M*)	Degree of hydrolysis, α
0.8636	0.736
0.5757	0.639
0.2879	0.619
0.1079	0.712

Source: Adapted from Novoselova and Batsanova, 1968, p. 13.

TABLE 2.8. ACIDITY OF BERYLLIUM SULFATE SOLUTIONS AT 20°C

Concentration of $BeSO_4$ (*M*)	pH	Concentration of $BeSO_4$ (*M*)	pH
1	1.88	0.05	3.08
0.5	2.24	0.02	3.78
0.2	2.62	0.01	3.61
0.1	2.80		

Source: Novoselova and Batsanova, 1968, p. 13.

are systematically removed by the buffering action of proteins, bicarbonate ion, phosphate salts, or organic acids. Consequently, soluble beryllium salts in this environment tend to be converted completely to insoluble hydrolytic products, which have extremely long residence times (Krejci and Scheel, 1966, p. 56). Under favorable circumstances, however, precipitation of the hydroxide may be reduced or prevented if the soluble beryllium salt reacts first with a chelating agent, such as citric or oxalic acid.

Addition of alkali to a solution of beryllium sulfate causes the precipitation, beginning at pH 5.7, of a basic salt in which the mole ratio of alkali to beryllium sulfate is 1.8; initially, sulfate ions are retained in the precipitate, but they are gradually displaced by hydroxyl ions as more alkali is added. Precipitation is complete at pH 6.5, and addition of more alkali causes the precipitate to redissolve. Solutions of beryllium sulfate and other soluble salts readily dissolve beryllium oxide or hydroxide. This behavior reflects the formation of hydroxo complexes with Be–OH–Be bridges (Cotton and Wilkinson, 1962, p. 174).

When heated, beryllium sulfate tetrahydrate loses 2 moles of water at 92°C and 4 moles of water at 250°C (International Agency for Research of Cancer, 1972, p. 18). The resulting anhydrous beryllium sulfate dissolves only slowly in cold water; it is also less stable to heat than other alkaline earth sulfates, because of the strong polarizing effect of the small bivalent beryllium ion, which deforms the sulfate ion and weakens its sulfur-oxygen bonds. As a result, about 4% of the contained sulfur is evolved as sulfur trioxide when beryllium sulfate is heated to 600°C for 1 hr (Everest, 1964, p. 25).

Beryllium sulfate is the pure intermediate in the production of beryllium oxide, representing 10% of total beryllium usage. It is also occasionally used in the laboratory when a soluble beryllium salt is required.

2.2.4 Beryllium Hydroxide

Beryllium hydroxide is an important intermediate in all the currently used methods of recovering beryllium from its ores (Section 2.2.1.2); it is also important physiologically because of its formation and retention in various tissues under biologic conditions. The nominal formula and molecular weight of the compound are $Be(OH)_2$ and 43.03. The *Chemical Abstracts* identification number is 13327327.

Beryllium hydroxide occurs in several forms. When prepared from stoichiometric quantities of ammonium hydroxide and dilute aqueous beryllium salts at pH 5.7, beryllium hydroxide is an amorphous hydrate, $Be(OH)_2 \cdot xH_2O$. On standing, this material is transformed into a metastable crystalline form, α-$Be(OH)_2$. The latter, in turn, changes slowly into a stable crystalline β modification. The last conversion is accelerated by contacting the α form with an alkali solution (Everest, 1964, p. 12; Novoselova and Batsanova, 1968, p. 4). The stable β-beryllium hydroxide is obtained directly by treating beryllium sulfate with sodium hydroxide.

The solubility of the hydroxide decreases progressively on passing from the amorphous product to the β form. The solubility of crystalline α-beryllium hydroxide in water is less than 10^{-7} mole per liter (Gilbert and Garrett, 1956). The solubility product constant for beryllium hydroxide in water has been determined by several different investigators, but divergent results differing by several orders of magnitude were obtained, and no consensus exists (Gilbert and Garrett, 1956; Korenman, Frum, and Tsygankova, 1956; Kovalenko and Geiderovich, 1959).

The behavior of beryllium hydroxide in alkaline media is not well established. Early workers produced stable polynuclear beryllium oxide hydrosols in low concentrations of strongly coordinating anions and believed that similar olated complexes were formed when beryllium hydroxide is dissolved in alkali (Everest, 1964, p. 14). However, the data of Baes and Mesmer (1974, p. 96) only support the presence of mononuclear species in such solutions. The latter workers suggest that $Be(OH)_3^-$ and $Be(OH)_4^{2-}$ are the dominant species in aqueous solutions saturated with α-$Be(OH)_2$ in the pH range 9 to 13. These species appear to result from the following reactions:

$$\begin{aligned} \alpha\text{-}Be(OH)_2 + H_2O &= Be(OH)_3^- + H^+ \ , \\ \alpha\text{-}Be(OH)_2 + 2H_2O &= Be(OH)_4^{2-} + 2H^+ \ . \end{aligned} \qquad (14)$$

When heated, hydrated beryllium hydroxide loses water and is converted first to the anhydrous form, then to the oxide. The temperatures at which these changes occur depend on the manner in which the material was prepared. Typically, dehydration occurs at 150°C to 180°C, dissociation begins at 240°C to 300°C, and all but the last traces of water are removed at 500°C (Novoselova and Batsanova, 1968, p. 7).

Unlike the alkali hydroxides, beryllium hydroxide does not absorb carbon dioxide. Neither is it soluble in cold solutions of ammonium salts or of most amines, except ethylenediamine (Sidgwick, 1950, p. 202).

2.2.5 Beryllium Halides and the Fluoroberyllates

The fluoride BeF_2 is the most important beryllium halide; it has important applications in the preparation of metallic beryllium (Section 2.2.1.3), in the molten salt nuclear reactor, and in analytical chemistry (Novoselova and Batsanova, 1968, p. 18). The *Chemical Abstracts* identification number of this compound is 7787497. In the anhydrous state, beryllium fluoride is normally a glassy, hygroscopic substance. It has a molecular weight of 47.01 and a density of 1.986 (25°C). The glassy material has no definite melting point but softens near 800°C with sublimation (Stecher, 1968). Crystalline BeF_2, which can be prepared from the glassy form by careful thermal treatment, melts near 550°C. The molten salt is a poor conductor of electricity. Beryllium fluoride is freely soluble in water, 18 g-moles per liter dissolving at 25°C; however, it is only sparingly soluble in ethanol and is insoluble in anhydrous hydrogen fluoride. Other properties of beryllium fluoride are given in Table 2.9. Beryllium ion bonds almost as strongly with fluoride as with oxide ions — accordingly, aqueous solutions of beryllium fluoride are only about 1% hydrolyzed and are less acidic than corresponding concentrations of other beryllium salts (Table 2.10). Beryllium fluoride is prepared commercially by thermally decomposing the ammonium fluoroberyllate salt, $(NH_4)_2BeF_4$, at 240°C or higher (Section 2.2.1.2). It cannot be formed by treating the hydroxide with aqueous hydrofluoric acid, as the resulting salt, $BeF_2 \cdot 4H_2O$, hydrolyzes when heated.

Beryllium fluoride readily coordinates with the fluorides of alkali or alkaline earth metals to form compounds of the types $M^I_2BeF_4$ and $M^{II}BeF_4$:

$$\begin{aligned} BeF_2 + 2MF &\longrightarrow M_2BeF_4 \ , \\ BeF_2 + MF_2 &\longrightarrow MBeF_4 \ . \end{aligned} \qquad (15)$$

These compounds contain the fluoroberyllate ion, BeF_4^{2-}, in which the fluorine atoms are tetrahedrally arranged around the beryllium atom in the crystal lattice. The alkali metal complexes are quite stable and dissolve in water without decomposition (Table 2.11). The alkaline earth fluoroberyllates are only sparingly soluble in water; 100 g of calcium fluoroberyllate solution contains 0.0125 g of salt at 25°C, and solutions of the barium compound contain even less (Novoselova and Batsanova, 1968, p. 21). The $M^I_2BeF_4$ and $M^{II}BeF_4$ fluoroberyllates are isomorphous with the sulfates of the corresponding metals — except for the lithium and sodium salts — and have similar physical and chemical properties. The fluoroberyllates also bear a strong structural resemblance to silicates, a factor that led to the production of unique fluoroberyllate glasses having low dispersion and a wide transmission range (Krejci and Scheel, 1966, p. 71).

Beryllium chloride, $BeCl_2$, is a colorless crystalline compound. It has a molecular weight of 79.92 and a density of 1.899 (25°C). The *Chemical Abstracts* identification number is 7787475 (Weast, 1977). The melting points reported for anhydrous beryllium chloride vary widely because of the strong tendency of the salt to supercool; they fall into two groups, one near 404°C, the other near 425°C. A similar uncertainty exists with boiling point determinations of the salt, which vary from 482.5°C to 510°C

TABLE 2.9. PROPERTIES OF THE BERYLLIUM HALIDES

Property	Beryllium fluoride	Beryllium chloride	Beryllium bromide	Beryllium iodide
Formula	BeF_2	$BeCl_2$	$BeBr_2$	BeI_2
Molecular weight	47.01	79.93	168.85	262.85
Melting point	(See text)	(See text)	490°C 488 ± 2°C	510°C 480 ± 4°C
Boiling point	Sublimes	(See text)	Sublimes	Sublimes
Heat of formation, ΔH_{f298}, kcal/mole Gas Crystalline	-191.3 ± 2.0 (2nd law) -191.2 ± 0.4 (3rd law) -241.2 ± 0.8 (cristobalite)	 -118.03 ± 0.56 -118.25	 -86.7	 -54.3
Entropy, S_{298}, cal/(°C)(mole), gas	54.4 ± 0.3			
Heat of vaporization, ΔH_{vap}, kcal/mole	53.25 ± 0.25 (550 - 950°C)	26.24 (573 - 733°C)	22	19
Entropy of vaporization, ΔS_{vap}, cal/(°C)(mole)	38.7 ± 0.6 (550 - 950°C)	573 - 753°K 30.84		
Heat of sublimation, ΔH_{sub}, kcal/mole		440 - 600°K 32.9 ± 0.4 (2nd law) 298°K 33.1 ± 0.5 440 - 600°K 32.1 (3rd law) 440 - 600°K 42.7 ± 1.4 (2nd law)		
Entropy of sublimation, ΔS_{sub}, cal/(°C)(mole)		298°K 43.2 ± 1.5		

Source: Adapted from Krejci and Scheel, 1966, Table 4.2, pp. 49-50. Reprinted by permission of the publisher.

TABLE 2.10. ACIDITY OF AQUEOUS BERYLLIUM FLUORIDE SOLUTIONS AS A FUNCTION OF CONCENTRATION

Concentration of BeF_2 (*M*)	pH	Concentration of BeF_2 (*M*)	pH
0.10	4.55	0.60	3.71
0.25	4.25	0.70	3.59
0.45	3.96	1.00	3.55

Source: Novoselova and Batsanova, 1968, p. 18.

TABLE 2.11. SOLUBILITY OF ALKALI FLUOROBERYLLATES AT 25 °C

Fluoroberyllate	Formula	Solubility (%)
Ammonium	$(NH_4)_2BeF_4$	32.3
Monoammonium	NH_4BeF_3	54.2
Sodium, 20 °C	Na_2BeF_4	1.45
Potassium	K_2BeF_4	1.52
Rubidium	Rb_2BeF_4	10.22
Cesium	Cs_2BeF_4	56.76

Source: Adapted from Novoselova and Batsanova, 1968, p. 21.

(Krejci and Scheel, 1966, p. 70). Anhydrous beryllium chloride is very soluble in water (Table 2.12), ethanol, and ether but is insoluble in non-donor solvents such as benzene, carbon tetrachloride, and chloroform. Beryllium chloride is more strongly hydrolyzed in aqueous solution than the fluoride — 4.6% for a 0.1 *N* solution — since the larger chloride ion competes less effectively for the beryllium ion than its smaller congener; the hydrolysis constant for the reaction

$$2BeCl_2 + 2H_2O \rightleftharpoons Be_2(OH)_2^{2+} + 2HCl + 2Cl^- \qquad (16)$$

is 1.6×10^{-7} (Gilbert and Garrett, 1956). The resulting solution is accordingly more acidic than a similar fluoride solution (Table 2.13). Unlike beryllium fluoride, the chloride does not readily form anionic chloro complexes in aqueous solution (Everest, 1964, p. 52). Anhydrous

TABLE 2.12. SOLUBILITY OF BERYLLIUM CHLORIDE IN WATER

Temperature (°C)	Solubility (g $BeCl_2$ per 100 g of solution)
0	40.35
20	42.24
30	43.52
40	44.12

Source: Novoselova and Batsanova, 1968, p. 16.

TABLE 2.13. ACIDITY OF AQUEOUS BERYLLIUM CHLORIDE SOLUTIONS AS A FUNCTION OF CONCENTRATION

Concentration of $BeCl_2$ (*M*)	pH	Concentration of $BeCl_2$ (*M*)	pH
1	1.27	0.005	3.07
0.5	1.85	0.002	3.40
0.2	2.41	0.001	3.65
0.1	2.76		

Source: Novoselova and Batsanova, 1968, p. 16.

beryllium chloride strongly resembles aluminum chloride in its ability to catalyze organic syntheses. It is nearly but not quite as efficient (Sidgwick, 1950, p. 204). Anhydrous fused beryllium chloride is a poor electrical conductor, but small amounts of alkali metal fluorides considerably improve this property, evidently by the formation of chloroberyllates (Schmidt, 1926). Anhydrous beryllium chloride forms numerous complexes of the type $BeCl_2X_2$, where X represents a wide variety of neutral organic ligands. Examples of such complexes, which can be prepared either by direct interaction or by addition of the ligand to an ether solution of beryllium chloride, include diethyl ether, pyridine, acetone, nitriles, aldehydes, quinoline, aliphatic amines, piperidine, thiourea, and tetrahydrofuran. Usually the stoichiometry of the complexes involves two ligands per atom of beryllium, though some departures from this ratio occur (Everest, 1964, p. 55). Beryllium chloride is prepared on a commercial scale by passing chlorine over a mixture of beryllium oxide and carbon heated to about 1000°C (Section 2.2.1.3). The product is hygroscopic and must be kept dry to prevent deterioration by hydrolysis. Small

quantities of the chloride are consumed in the United States for electrorefining beryllium metal scrap.

The preparation and chemical reactions of beryllium bromide and iodide are similar to those described for the chloride, except that hydrolysis becomes more pronounced with increasing anion radius — the anhydrous iodide reacts violently with water, releasing hydrogen iodide (Stecher, 1968). These compounds are seldom used, except for research. Some of their published physical properties are tabulated in Table 2.9.

2.2.6 Beryllium Alloys

When beryllium is added to copper and certain other metals, alloys are formed which can be readily worked in the soft annealed state and which have, after heat treatment, greatly improved strength, hardness, durability, and resistance to fatigue. Approximately half the total beryllium consumed in the United States in 1970 was used for beryllium-copper alloys needed primarily in communications, computer, electronic, and electrical equipment (Heindl, 1970, pp. 489, 494). The most important alloy of this group contains cobalt as well as beryllium and copper; the cobalt helps to control the grain size during casting and the subsequent heat treatment response. The composition commonly used for this alloy is 1.9% to 2.05% beryllium, about 0.25% cobalt, and the balance copper (Schwenzfeier, 1964, p. 465). The extraordinary contrast in the physical properties of this alloy before and after heat treatment is shown in Table 2.14.

Although alloys can be formed by melting together appropriate quantities of the separate metals, this procedure is not followed in the commercial production of beryllium-copper alloys because of the high cost of producing pure beryllium metal; instead, these alloys are made by directly reducing beryllium oxide with carbon in the presence of molten copper (Schwenzfeier, 1964, p. 466). The reduction is usually performed in a

TABLE 2.14. PHYSICAL PROPERTIES OF BERYLLIUM COPPER No. 25 STRIP BEFORE AND AFTER HEAT TREATMENT

Temper	Heat treatment	Tensile strength (psi)	Proportional limit (psi)	Yield strength, 0.2% offset (psi)	δ^a	Rockwell hardness	Fatigue strength (psi) (10^8 load cycles)	σ^b
A		60-78,000	15-20,000	28-36,000	35-60	30T46-67	30-35,000	17-19
1/4 H		75-88,000	40-60,000	60-80,000	10-35	30T62-75	31-36,000	16-18
1/2 H		85-100,000	55-70,000	75-90,000	5-25	30T74-79	32-38,000	15-17
H		100-120,000	70-85,000	90-112,000	2-8	30T79-83	35-39,000	15-17
AT	3 hr, 600°F	165-190,000	100-125,000	140-175,000	4-10	30N56-61	34-38,000	22-25
1/4 HT	2 hr, 600°F	175-200,000	110-135,000	150-185,000	3-6	30N58-63	35-39,000	22-25
1/2 HT	2 hr, 600°F	185-210,000	120-145,000	160-195,000	2-5	30N59-65	39-43,000	22-25
HT	2 hr, 600°F	190-215,000	125-155,000	165-205,000	1-4	30N60-66	41-46,000	22-25

[a] Elongation in 2 in., %.
[b] Electrical conductivity, percent of International Annealed Copper Standard.

Source: Adapted from Schwenzfeier, 1964, Table 7, p. 466. Reprinted by permission of the publisher.

carbon-lined electric arc furnace equipped with graphite electrodes, such as that shown in Figure 2.4. The reaction temperature is maintained between 1800°C and 2000°C; part of the beryllium oxide is reduced to beryllium. The following reaction probably occurs:

$$BeO(s) + C(s) \longrightarrow Be(d) + CO(g) \ , \qquad (17)$$

where s indicates the solid phase; d, dissolution in molten copper; and g, the gas phase. A flowsheet of the production process is shown in Figure 2.5. The finished beryllium-copper ingots, which usually contain about 4% beryllium, are subsequently remelted with copper chips to produce the finished 2% beryllium alloy stock forms (U.S. Environmental Protection Agency, 1973*c*, p. 3-9).

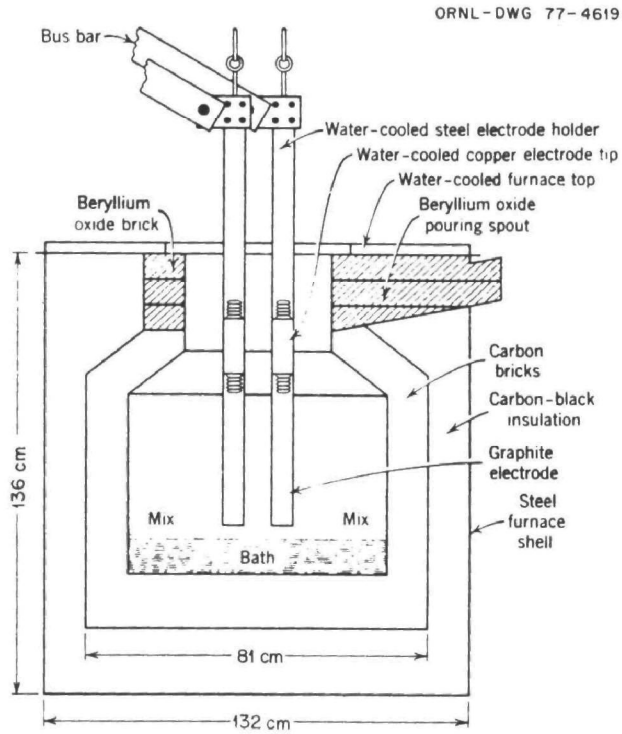

Figure 2.4. An arc furnace used in preparing beryllium copper. Source: Adapted from Schwenzfeier, 1964, Figure 1, p. 467. Reprinted by permission of the publisher.

Other alloys of beryllium are also used, although on a greatly reduced scale compared with copper. Nickel containing up to 2.6% beryllium is heat treatable and has strengths similar to those of the stronger stainless steels. Castings of this alloy are used in the glass industry as plungers, molds, and neck rings. Wrought forms of beryllium-nickel are about 20% stronger than cast forms and are attractive for use as instrument springs, diaphragms, and mechanical fasteners. The addition of 0.1% to 0.5% beryllium to aluminum results in an alloy with improved fluidity

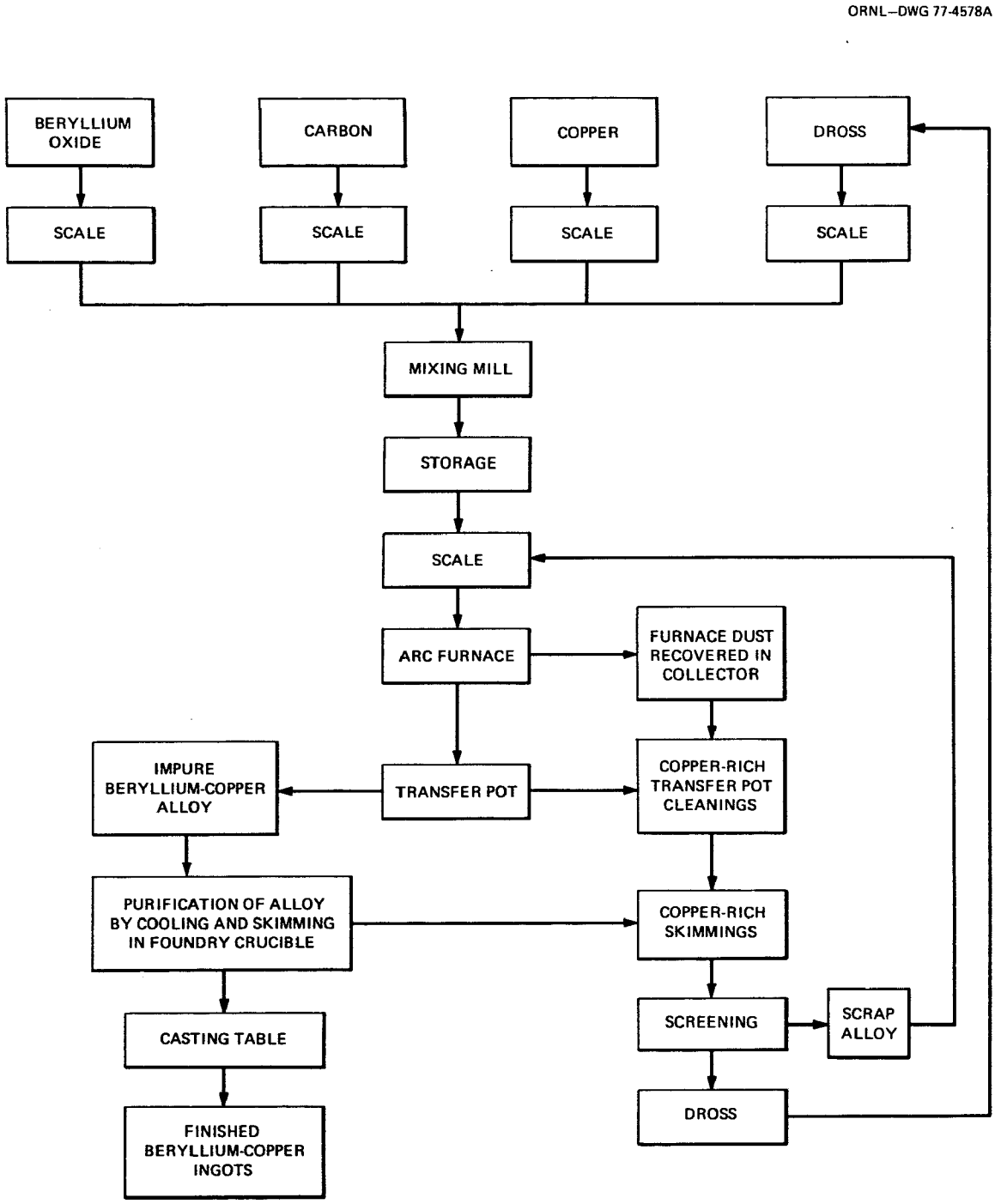

Figure 2.5. Flowsheet for the production of beryllium copper from beryllium oxide. Source: Adapted from Schwenzfeier, 1964, Figure 2, p. 468. Reprinted by permission of the publisher.

and grain structure which is useful for polished castings such as cookware. Beryllium-iron alloys have coarse grain structures generally unsuitable for commercial applications, but beryllium steels containing nickel and chromium have exceptionally high strengths and hardness at high temperatures. The latter may be used when special properties not producible with carbon are desired (Schwenzfeier, 1964, p. 469). Beryllium alloys are discussed further in surveys by the U.S. Department of the Interior (1953), Schwenzfeier (1964), and Ricksecker (1965).

2.2.7 Beryllides

Beryllium forms intermetallic compounds — beryllides — with a variety of metals (Table 2.15), some of which have unusual combinations of physical, mechanical, thermal, and electrical properties. Several beryllides that have excellent resistance to oxidation, high strength at elevated temperatures, good thermal conductivity, low density, and good hardness, compared with refractory metals and many ceramics, are listed in Tables 2.16-2.18.

Beryllides are prepared by powder-metallurgy techniques. Typically, the blended powders are heated to about 1260°C in inert magnesium oxide or beryllium oxide containers, and the reacted powder is consolidated in

TABLE 2.15. BERYLLIDE TYPES

Formula	Structure	Metals
MBe	Cubic	Ti(?), Co, Ni, Cu, Pd, Au
MBe_2	Face-centered cubic	Ti, Cu, Nb, Ag, Ta
	Hexagonal	V, Cr, Mn, Fe, Zr, Mo, Hf, W, Re
MBe_5	Face-centered cubic	Fe, Co(?), Pd
	Cubic	Au
	Hexagonal	Zr, Hf
M_2Be_{17}	Rhombohedral	Ti, Zr, Nb, Hf, Ta
MBe_{12}	Body-centered tetragonal	Ti, V, Cr, Mn, Fe, Co, Nb, Mo, Pd, Ag, Ta, W, Pt
MBe_{13}	Face-centered cubic	Mg, Ca, Sc, Sr, Y, Zr, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Th, U, Np, Pu, Am
MBe_{22}	Face-centered cubic	Mo, Te, W, Re

Source: Stonehouse, 1971, Table 1, p. 73. Reprinted by permission of the publisher.

TABLE 2.16. HIGH-TEMPERATURE OXIDATION-RESISTANT BERYLLIDES

Beryllide system	Compound	Weight percent beryllium	Melting point (°C)	X-ray density (g/cm^3)	Structure
Nb-Be	$NbBe_{12}$	53.8	1690	2.92	Body-centered tetragonal
	Nb_2Be_{17}	45.2	1700	3.28	Rhombohedral
Ta-Be	$TaBe_{12}$	37.4	1850	4.18	Body-centered tetragonal
	$TaBe_{17}$	29.8	1990	5.05	Rhombohedral
Mo-Be	$MoBe_{12}$	53.2	~1700	3.03	Body-centered tetragonal
Ti-Be	$TiBe_{12}$	69.3	1600	2.26	Hexagonal
	Ti_2Be_{17}	61.5	1630	2.46	Rhombohedral
Zr-Be	$ZrBe_{13}$	56.2	1900	2.72	Face-centered cubic
	Zr_2Be_{17}	45.7	1980	3.08	Rhombohedral
Hf-Be	$HfBe_{13}$	39.7	1600	3.93	Face-centered cubic
	Hf_2Be_{17}	30.0	<1750	4.78	Rhombohedral

Source: Adapted from Stonehouse, 1971, Table 2, p. 74. Reprinted by permission of the publisher.

TABLE 2.17. THERMAL CONDUCTIVITY OF SEVERAL BERYLLIDES

Compound	Thermal conductivity [$cal/sec(cm^2)(°C/cm)$]				
	650°C	870°C	1090°C	1320°C	1430°C
Nb_2Be_{17}	0.0748	0.0764	0.0781	0.0797	0.0805
$NbBe_{12}$	0.0731	0.0739	0.0752	0.0764	0.0768
Ta_2Be_{17}	0.0698	0.0723	0.0752	0.0781	0.0752
$TaBe_{12}$	0.0690	0.0756	0.0805	0.0867	0.0921
$ZrBe_{13}$	0.0954	0.0909	0.0867	0.0826	0.0805

Source: Adapted from Stonehouse, 1971, Table 8, p. 78. Reprinted by permission of the publisher.

graphite molds by the vacuum hot-pressing technique (Stonehouse, 1971, p. 79). Cold-pressing procedures and sintering techniques are also used.

Only minor amounts of beryllium are consumed as beryllides. The principal applications are for high-temperature components for nuclear power plants, high-performance turbine engines, and nuclear equipment components requiring high strength and low density in the 1200°C to 1400°C temperature range.

TABLE 2.18. ROOM-TEMPERATURE HARDNESS OF SELECTED BERYLLIDES

Compound	Vickers hardness, 2.5-kg load
Nb_2Be_{17}	1000
$NbBe_{12}$	500
Ta_2Be_{17}	1120
$TaBe_{12}$	720
Zr_2Be_{17}	1130
$ZrBe_{13}$	1000
$MoBe_{12}$	950

Source: Stonehouse, 1971, Table 3, p. 74. Reprinted by permission of the publisher.

Several beryllium-rich beryllides — niobium beryllide ($NbBe_{12}$), tantalum beryllide ($TaBe_{12}$), titanium beryllide ($TiBe_{12}$), and vanadium beryllide (VBe_{12}) — have been examined for potential toxicity by intratracheal injections in rats. Despite the relatively high beryllium content of these compounds, none of them showed pulmonary tumor induction and, in general, had little or no biologic activity (Stokinger, 1972, p. 20).

2.2.8 Beryllium Nitrate

Beryllium nitrate, $Be(NO_3)_2 \cdot 3H_2O$, is a white to slightly yellow deliquescent crystalline compound. It has a molecular weight of 187.07, density of 1.557, melting point of 60°C, and boiling point of 142°C; it is very soluble in water and ethanol. The *Chemical Abstracts* identification number of beryllium nitrate trihydrate is 7787555.

Beryllium nitrate trihydrate is prepared by crystallizing a solution of beryllium hydroxide or carbonate that has been treated with a slight excess of concentrated nitric acid. The dihydrates and monohydrates are also formed, depending on the concentration of the acid used. The anhydrous form may be obtained by treating an ethyl acetate solution of beryllium chloride with dinitrogen tetroxide but not by dehydration of one of the hydrated species; the latter operation results in the thermal decomposition of the nitrate, with evolution of nitrous fumes (Everest, 1964, p. 28).

Beryllium nitrate exhibits the usual hydrolytic reactions of the divalent beryllium ion (Section 2.2.1.2). The salt is noteworthy only because it has been used to stiffen and harden mantles in gas and acetylene lamps (Stecher, 1968), but it constituted a potential health hazard, and its use was discontinued in 1973 (Griggs, 1973; Lerza, 1974).

2.2.9 Beryllium Minerals

There are some forty-odd recognized mineral forms of beryllium. The most important of these are listed in Table 2.3 with pertinent physical properties. These minerals usually occur in pegmatites, in granites, in syenites, and occasionally in gneisses and mica schists. At present, only beryl and bertrandite are mined commercially.

Beryl is by far the most abundant and economically significant mineral form; it occurs in pegmatites as crystals, which sometimes weigh as much as 50 to 60 tons. The commercial mineral is nontransparent and has a vitreous luster resembling that of quartz. The beryllium oxide content varies from 10% to 14%. Commercial ores usually contain 17% to 19% alumina, 64% to 70% silica, 1% to 2% alkali metal oxides, and 1% to 2% iron and other oxides (U.S. Department of the Interior, 1953, p. I-8). Beryl ore is rarely found in quantities sufficient to permit mining as a primary ore; it is usually produced as a by-product of other mining operations. Most of the beryl consumed in the United States in 1969 was imported from Brazil, South Africa, Argentina, and Uganda. Numerous small-scale beryl mining operations exist in the United States, but firm data on production rates are not available. In 1973, the total output from these operations was estimated to be less than 10% of the total beryl ore process in the United States (U.S. Environmental Protection Agency, 1973*a*, p. 2-4).

During the late 1950s and early 1960s, several new nonberyl deposits of beryllium minerals were discovered in North America, the most important being a large body of beryllium-bearing volcanic ash located in the Topaz district of Utah. Typical ores from this region contain 0.5% to 1.0% beryllium oxide (National Research Council, 1971, p. 18). Commercial mining of this deposit began in 1969 (Heindl, 1970, p. 490); in 1973, it was the only large operating beryllium mine in the United States. The ore is mainly hydrated bertrandite, which can be readily extracted in high yield by simple leaching with mineral acids (Section 2.2.1.3).

2.2.10 Other Beryllium Compounds

Beryllium combines with many acidic, neutral, and metallic reactants to form other salts, coordination compounds, and alloys. Most of these substances are rarely used, and only a few need to be noted here; they are listed and characterized in Table 2.19. Other properties of these compounds are reviewed in Everest (1964), Krejci and Scheel (1966), and Novoselova and Batsanova (1968).

2.3 ANALYSIS FOR BERYLLIUM

A variety of methods are available for the determination of beryllium in environmental and biologic samples. Several of these methods are sufficiently sensitive to detect beryllium in the low parts per billion concentration range (Tables 2.20-2.24). The method of choice for a particular application depends on several factors. Sample load, equipment availability, and cost are key considerations. Detection limits, sample matrix, specificity, speed of analysis, and accuracy are also relevant. These and other factors pertinent to the selection of an analytical method and to the evaluation of reported analytical data are summarized in this section.

TABLE 2.19. PROPERTIES OF SELECTED BERYLLIUM COMPOUNDS

Beryllium compound	Formula	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility in	
					Water	Ethanol
Acetate	$Be(C_2H_3O_2)_2$	127.10	300 d[a]		Insoluble	Insoluble
Acetate, basic	$BeO(C_2H_3O_2)_6$	406.32	284	331	d	Soluble
Carbide	Be_2C	30.04	>2100 d		d	
Carbonate, basic	$BeCO_3 + Be(OH)_2$	112.05			Insoluble	
Di-*n*-butylberyllium	$Be(C_4H_9)_2$	123.24		170 (25 torr)	d	
Diethylberyllium	$Be(C_2H_5)_2$	67.14	12	110 (15 torr)	d	
Dimethylberyllium	$Be(CH_3)_2$	39.09		Subl. 200	d	
Dipropylberyllium	$Be(C_3H_7)_2$	95.19	<-17	245		
Hydride	BeH_2	11.03	125 d		d	Insoluble
Hydroxide	$Be(OH)_2$ (see text)	43.03 (see text)			Insoluble	
Nitrate	$Be(NO_3)_2 \cdot 3H_2O$	187.07	60	142	Very soluble	Very soluble
Nitride	Be_3N_2	55.05	2200 d	350 d	d	
Oxalate	$BeC_2O_4 \cdot 3H_2O$	151.08	$-3H_2O$, 220	∿3900	Soluble	
Oxide	BeO	25.01	2530		Insoluble	
Phosphate	$Be_3(PO_4)_2 \cdot 3H_2O$	271.03	$-H_2O$, 100		Soluble	
Sulfate	$BeSO_4$	105.07	550-600 d		Insoluble	
Sulfide	BeS	41.08			d	

[a]Decomposes.

Source: Adapted from Weast, 1977, pp. B94, C688. Reprinted by permission of the publisher.

TABLE 2.20. METHODS FOR DETERMINING BERYLLIUM: ATOMIC ABSORPTION SPECTROSCOPY

Important application	Air, natural and treated waters, biologic tissues, urine, ores
Sample preparation	Some liquid and solid samples require no preparation if the flameless technique is used. In the flame method, liquid samples are acidified, and, if necessary, beryllium is separated from interfering contaminants by chelation and extraction into an organic solvent. Organic samples are wet-ashed with nitric, hydrofluoric, and hydrochloric acids or muffled at 400°C. The ash is dissolved in acid, purified by solvent extraction, dried, and taken up in dilute hydrochloric acid. Ores and refractory solids are solubilized by fusion, purified by extraction, and dissolved in dilute hydrochloric acid.
Methodology or technique	In the flame variation of this method the prepared sample is continuously aspirated into a nitrous oxide–acetylene flame through which 234.9-nm radiation from a hollow-cathode lamp is passed. The flame atomizes the sample, and radiation from the lamp is selectively absorbed by beryllium atoms in proportion to their concentration in the vapor. A photodetector measures the degree of absorption and registers the concentration of beryllium in the sample.
Limit of detection	
Flame method	0.01 to 0.002 μg/ml[a] 0.01 μg/g[b] (animal tissues)
Flameless method	0.1 ng/ml[c] (urine) 1 to 10 ng/ml[d] (petroleum) 0.4 to 0.06 ng/g[e] (air filter sample)
Precision (relative standard deviation)	
Flame method	34%[f] (5 ng Be/g, water)
Flameless method	8%[c] (5 ng Be/g, urine) 10%[d] (30 ng Be/g, petroleum) 7%[g] (1.5 μg Be/g, coal)
Accuracy (relative error)	
Flame method	20%[f] (5 ng Be/g, water) 2%[f] (50 ng Be/g, water)
Flameless method	3%[h] (1 μg/ml, bovine liver) 2%[c] (5 ng Be/g, urine) 5%[e] (4 ng Be/filter, air sample)
Interfering substances	Aluminum and silicon interfere at concentrations of 500 μg/ml or greater. Numerous ions enhance or depress the beryllium 4000 μg/ml or more.[i]
Selectivity	Total beryllium is measured.
Comments	Atomic absorption spectrometry is the method of choice for many samples; however, the flame technique may lack sufficient sensitivity for some environmental samples.

[a] Hurlbut, 1974*b*.

[b] Sanders et al., 1974.

[c] Hurlbut, 1974*b*.

[d] Robbins, Runnels, and Merryfield, 1975.

[e] Hurlbut and Bokowski, 1974.

[f] Lishka and McFarren, 1970.

[g] Owens and Gladney, 1975.

[h] Lockwood and Limtiaco, 1975.

[i] Fleet, Liberty, and West, 1970.

TABLE 2.21. METHODS FOR DETERMINING BERYLLIUM: SPECTROPHOTOMETRY

Important application	Air, natural and treated waters, ores, dusts, biologic samples
Sample preparation	Solids are dissolved. Interfering contaminants in liquid samples are chemically separated or masked by complexing agents such as ethylenediaminetetraacetic acid or sodium cyanide.
Methodology or technique	The sample is treated with aluminon, zenia, or other complexing agents to form a colored beryllium lake or compound. The optical absorbance of the latter is measured with a spectrophotometer at a specified wavelength and related to the beryllium concentration in the sample by a previously determined calibration chart.
Limit of detection	5 ng/ml[a] (aluminon method; water sample) 500 ng Be/filter[b] (aluminon method; air filter sample)
Precision (relative standard deviation)	7%[a] (250 ng Be/ml; aluminon method, water sample) 8%[c] (5 g Be/filter; zenia method, air filter sample)
Accuracy (relative error)	12%[a] (250 ng Be/ml; aluminon method, water sample) 5-10%[b] (500 ng Be/filter; aluminon method, air filter sample) 1-3%[c] (3 µg Be/filter; zenia method, air filter sample)
Interfering substances	Many metals interfere. In the aluminon method, moderate amounts of aluminum, cobalt, copper, iron, manganese, nickel, titanium, zinc, and zirconium can be effectively masked with ethylenediaminetetraacetic acid.
Selectivity	The method is not specific for beryllium; many other metals also form colored complexes that absorb radiation in varying degrees.
Comments	This method was used extensively earlier but is now being replaced by more rapid, sensitive, and convenient techniques.

[a] American Public Health Association, 1971.

[b] Crawley, 1960.

[c] Hiser, Donaldson, and Schwenzfeier, 1961.

2.3.1 Sampling and Sample Handling

Although some ores, alloys, and beryllides contain beryllium in relatively high concentrations, most environmental samples contain only trace levels of the element. In biological samples, such as lung or liver tissue, the concentration of beryllium is frequently in the parts per billion range (Spencer et al., 1972). Under such circumstances, sample handling techniques become very important. Containers and other equipment should be scrupulously cleaned in hot detergent solutions, soaked in 8 *N* nitric acid for 2 hr, and rinsed in distilled water following each use to prevent the formation of adsorptive surfaces that might lead to cross contamination of subsequent samples (Coulson et al., 1973, p. B7.1). It is also important to control the acidity of beryllium solutions that are to be stored or processed to prevent the hydrolysis and subsequent adsorption of the hydrated species on the container wall. At pH 6, up to 20% of the ^{7}Be in a carrier-free solution of 0.1 *M* sodium chloride buffered with 0.001 *M* sodium acetate is adsorbed on the surface of a glass container; under similar conditions, somewhat less than 5% is adsorbed by polyethylene containers (Figure 2.6). The adsorption of trace-level ^{7}Be by both glass and polyethylene is essentially eliminated by reducing the solution pH to 4.5 and 5, respectively (Fairhall, 1960, p. 8). Other authorities recommend acidifying beryllium solutions to below pH 2 to minimize transfer losses between containers (Keenan, 1966, p. 134).

TABLE 2.22. METHODS FOR DETERMINING BERYLLIUM: FLUOROMETRY

Important application	Air, natural and treated waters, blood, biologic tissues, bone, urine
Sample preparation	Solids are fused or ashed and are dissolved in acid. Liquids are purified by extraction or by precipitation of beryllium hydroxide, or interfering contaminants are masked by a suitable complexing agent. The final solution is carefully alkalized and treated with a fluorescing agent, such as morin, immediately prior to analysis.
Methodology or technique	The prepared sample is excited with ultraviolet radiation, and a selected wavelength of the emitted fluorescence is measured with a fluorometer. The beryllium concentration in the sample is related to the intensity of the emitted fluorescence by use of calibrated standards. When morin is used, the exciting and emitted wavelengths are usually 436 and 550 nm, respectively.
Limit of detection	400 pg/11 ml[a] (synthetic sample) 4 ng/11 ml[b] (air filter samples, routine analysis)
Precision (relative standard deviation)	0.4%[a] (0.2 g Be/11 ml, synthetic sample) 2%[c] (100 ng Be/5 ml, air filter sample)
Accuracy (relative error)	8%[c] (60 ng/5 ml, air filter samples) 10%[d] (500 ng/10 ml, air filter samples)
Interfering substances	Yttrium, scandium, lanthanum, lithium, thorium, and zirconium produce fluorescence with morin and must be removed or masked by appropriate complexing agent.
Selectivity	Current fluorometric methods are not specific for beryllium.
Comments	Sensitive, but sample preparation can be long and tedious. Good technique required

[a] Sill and Willis, 1959.

[b] Kupel et al., 1971.

[c] Welford and Harley, 1952.

[d] Walkley, 1959.

Organic matter in beryllium samples must usually be destroyed before any of the separating or estimating procedures are applied. This ashing process is sometimes troublesome and is frequently a significant source of error. Ashing can be done wet or dry; wet ashing is convenient for processing large numbers of samples and probably reduces the risk of exchanging beryllium between the sample and the glaze of the ashing container, but it is limited to relatively small samples. Dry ashing is usually required for large bone samples. Early investigators reported losses of beryllium up to 90% when dry ashing samples in platinum at 500°C to 900°C, presumably because of volatilization of beryllium chloride (Cholak and Hubbard, 1948; Peterson, Welford, and Harley, 1950). However, subsequent work established that the beryllium was converted to the insoluble oxide (Toribara and Chen, 1952; Toribara and Sherman, 1953) or pyrophosphate complex (Keenan and Holtz, 1964; Sill and Willis, 1959), which could be quantitatively recovered by hydrolyzing the insoluble salt in strong mineral acids. An acid hydrolysis step should thus be an essential part of recovery procedures in which dry ashing has been used.

Recently, the presence of a volatile beryllium compound was reported in orchard leaves. Black and Sievers (1973) observed a beryllium loss greater than 85% during wet and dry ashing of such samples in an open beaker at temperatures below 200°C. The addition of a cover glass to the

TABLE 2.23. METHODS FOR DETERMINING BERYLLIUM: SPECTROMETRY

Important application	Air, biological samples
Sample preparation	Solids are dissolved. Refractory and highly insoluble compounds must be fused. Organic solids are digested with acids. Liquids are treated with hydrochloric acid, extracted with acetylacetone, and subsequently concentrated to about 0.5 ml of aqueous solution, which is adjusted to pH 1 to 2 with ammonium hydroxide.
Metholodogy or technique	The prepared sample is placed on or in graphite electrodes, which are excited by an ac, dc, or plasma arc or a spark. The resulting radiation passes through a monochromator, and emission lines characteristic of each excited element are recorded on film or photographic plates. The concentration of each element is determined by comparing the density of its emitted lines with that of an internal standard.
Limit of detection	1 ng Be/0.05 ml[a] 3 ng Be/ml[b] 20 ng Be/liter[c]
Precision (relative standard deviation)	5-20%[a] (1 to 100 ng Be/2 mg rabbit liver ash) 2-30%[d] (0.1 to 200 µg Be/ml, synthetic sample) 20%[c] (20 ng Be/liter urine)
Accuracy (relative error)	5-16%[a] (0.5-3.1% Be ore) 10-20%[e] (50-500 ng Be per air filter) 20%[d] (1-25 µg Be per air filter)
Interfering substances	High concentrations of iron interfere if the 234.83-nm beryllium line is used.
Selectivity	Spectroscopic determinations are highly specific for beryllium.
Comments	Chemical preparation and determination of typical samples and standards are very time-consuming.

[a] Keenan and Holtz, 1964.

[b] Cholak, 1959.

[c] Barnes et al., 1949.

[d] Peterson, Welford, and Harley, 1950.

[e] Watts et al., 1959.

beaker did not appreciably reduce the amount of beryllium lost; however, the use of a cold trap or condenser greatly improved the retention of beryllium (Table 2.25). The existence of volatile beryllium compounds in NBS orchard leaves has been challenged, however, by Florence et al. (1974), who carefully repeated the work of Black and Sievers without observing volatile beryllium compounds. Florence et al. (1974) obtained essentially complete recoveries of spiked samples processed by dry ashing, open beaker digestion with acids, and wet ashing in closed systems (Table 2.26). The results obtained by Black and Sievers were attributed by Florence et al. (1974) to interference with the gas chromatographic measuring technique by undestroyed organic matter.

2.3.1.1 Beryllium in Air — Airborne beryllium can occur as particulates, dust, fumes, and volatile organic compounds. Beryllium in air is most commonly sampled by means of a high-volume pump that draws air to be analyzed through a filter for a specified sampling period. Low-ash cellulose fiber, cellulose ester, or fiberglass papers are usually used as filters for nonvolatile contaminants, but they must be supplemented with liquid- or solid-filled scrubbers or cold traps if volatile forms of beryllium are

TABLE 2.24. METHODS FOR DETERMINING BERYLLIUM: GAS CHROMATOGRAPHY

Important application	Air, water, and biologic samples
Sample preparation	Refractory solids are fused with sodium carbonate. Air samples are wet-ashed and extracted into benzene as the trifluoroacetylacetonate complex. Biologic fluids and tissues are wet-ashed or ground, if necessary, and extracted directly with trifluoroacetone in benzene. Excess complexing agent in the extract is removed by washing with aqueous sodium hydroxide.
Methodology or technique	In a typical procedure, the benzene extract of beryllium trifluoroacetylacetonate is injected into a borosilicate or polytetrafluoroethylene chromatographic column packed with gas-chrom Z and 5% SE 52, a methyl phenyl silicone gum. The sample is eluted at 100°C with nitrogen gas into a calibrated electron-capture detector. The concentration of beryllium in the sample is determined from the area of the appropriate peak in the sample chromatogram.
Limit of detection	0.04 pg[a] <40 pg/m^3 air[b] 0.4 pg[c] 1 ng/ml[d] 0.08 pg[e]
Precision (relative standard deviation)	7-10%[e] (20-1000 ng Be/ml, blood) 13%[a] (30 ng/g, meteorite) 7%[f] (3-15 µg/ml, dog blood, rat liver) 3%[b] (24 ng Be/ml, synthetic air filter sample)
Accuracy (relative error)	5%[e] (20-1000 ng Be/ml, blood) 3-6%[d] (1 ng-2.7 µg Be/ml, urine) 10-30%[e] (1-100 ng Be, urine, blood) 5%[f] (3-15 µg/ml, dog blood, rat liver) 4%[b] (9 ng Be/ml, synthetic air filter sample)
Interfering substances	Iron(III), aluminum(III), ammonium, and phosphate can interfere at levels normally occurring in blood, urine, and tissues. Organic materials can interfere in direct extractions.
Selectivity	Gas chromatography is highly specific for beryllium.
Comments	A rapid, ultrasensitive, reliable technique.

[a] Eisentraut, Griest, and Sievers, 1971.

[b] Ross and Sievers, 1972.

[c] Noweir and Cholak, 1969.

[d] Foreman, Gough, and Walker, 1970.

[e] Taylor and Arnold, 1971.

[f] Frame et al., 1974.

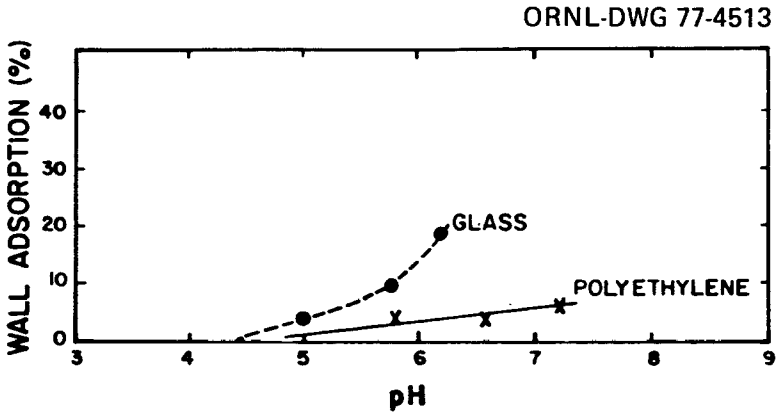

Figure 2.6. Adsorption of beryllium on the walls of polyethylene and glass vessels as a function of the pH of the solution. Source: Fairhall, 1960, Figure 1, p. 8.

TABLE 2.25. BERYLLIUM CONCENTRATION IN ORCHARD LEAVES AS A FUNCTION OF ORGANIC DIGESTION PROCEDURE

Type of digestion	Beryllium (ppm) (with relative standard deviation)
Wet digestion, HNO_3 and H_2SO_4	
Open beaker	0.017 ± 0.003
Covered beaker	0.017 ± 0.002
Low-temperature asher (ash), oxygen plasma	0.0075 ± 0.0036
Low-temperature asher (cold trap)[a]	0.085
Wet digestion, HNO_3 and H_2SO_4, with condenser	0.11 ± 0.01

[a]Average of two measurements.

Source: Black and Sievers, 1973, Table 1, p. 1774. Reprinted by permission of the publisher.

TABLE 2.26. BERYLLIUM IN NBS ORCHARD LEAVES

Ashing procedure	Beryllium in orchard leaves (ppm)[a,b]	Recovery of spike (%)
Dry ashing[a]		
450°C	0.019, 0.019[c]	101
600°C	0.017[d]	
800°C	0.023, 0.027	
Siliceous residue	0.008	
Open beaker,[b] HNO_3 + H_2SO_4	0.027, 0.024, 0.018, 0.020	94, 95
Siliceous residue	0.009, 0.009	
Method blank	<0.002[e]	
Refluxed with HNO_3 + H_2SO_4 for 1 hr; then fumed in open beaker[f]	0.019	
Gorsuch apparatus,[c] HNO_3 + H_2SO_4		
HNO_3	<0.002	
H_2SO_4	0.020	
Gorsuch apparatus[d] with dry ice trap		
HNO_3	<0.002, <0.002[g]	
H_2SO_4	0.021, 0.022[g]	95
Trap	<0.002, <0.002[g]	

[a]Results are for separate 5-g weighings and have been corrected for moisture content of 5.9% (24 hr at 90°C).

[b]Results do not include beryllium in siliceous residue.

[c]Ash, 3.6%.

[d]Ash, 7.2%.

[e]Limit of detection.

[f]0.5 µg Be spike added at start of analysis.

[g]These three results were obtained on a second sample of orchard leaves received from NBS six months after the first sample.

Source: Florence et al., 1974, Table 1, p. 1876. Reprinted by permission of the publisher.

also present. The filter is then processed by wet or dry oxidation, and the residue is treated as required by the particular analytical technique used. Extensive processing of the filter may be required if the sample contains many metals that interfere with the identification and measurement of beryllium. A basic sampling train suitable for all forms of airborne beryllium is shown in Figure 2.7; it is described in detail by Martin (1971). Current methods of monitoring airborne trace-metal particulates are discussed further by Hendrickson (1968), Johnson (1974), and Skogerboe (1974).

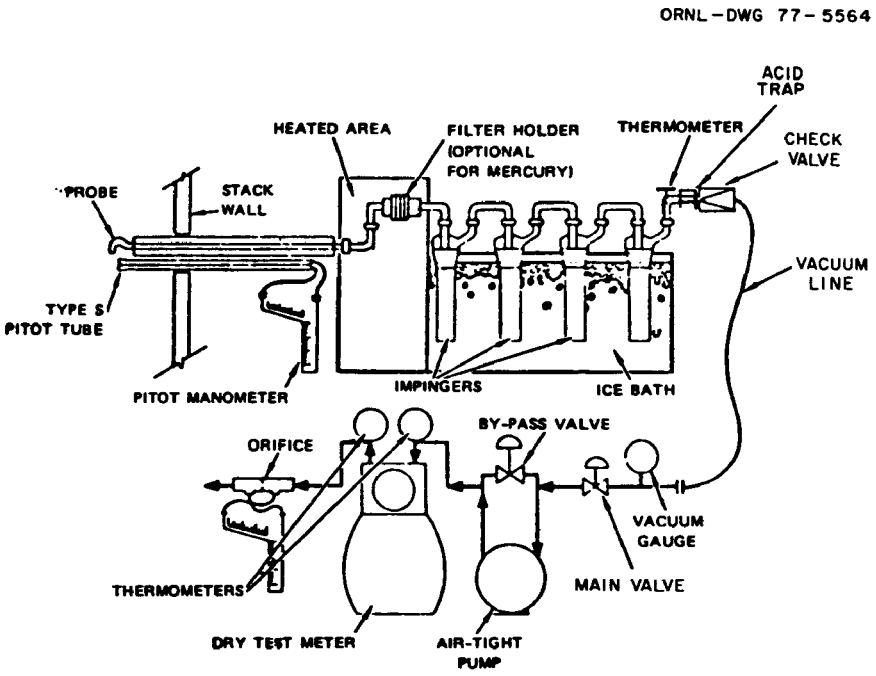

Figure 2.7. Sampling train. Source: Coulson et al., 1978, Figure 2-1, p. 2-2.

2.3.1.2 Beryllium in Water — Because of the strong tendency of beryllium salts to form insoluble hydrolytic species in aqueous solutions at pH 7 (Section 2.2.1.2), neutral environmental waters rarely contain beryllium in concentrations as great as 1 µg/liter (Kopp and Kroner, 1970). This level of concentration is two to three orders of magnitude below the limits set to avoid deleterious effects to marine organisms (1.5 mg/liter) or agricultural soils (0.1 mg/liter) (National Academy of Sciences-National Academy of Engineering, 1973, pp. 244, 341) and is well below the detection limit of all but the most sensitive analytical techniques. Consequently, analyses of beryllium in neutral environmental waters are made only infrequently, and this sample category is relatively unimportant. However, the highly acidic or basic waste streams from facilities manufacturing or using beryllium products are capable of dissolving toxic quantities of the element and may require monitoring to avoid loss of an expensive raw material and to protect the public welfare. Such samples should be collected in borosilicate glass or plastic containers and acidified, if necessary to below

pH 2 to avoid losses by adsorption on the container wall. Sediments or particulate matter in aqueous samples should be removed by filtration and analyzed separately. Care should be taken to ensure that samples are representative of the source material. This requirement is frequently difficult to achieve; it involves the number of locations sampled, the size of the individual samples, and the manner in which the samples are collected. Brown, Skougstad, and Fishman (1970) discuss this subject extensively. When the purpose of testing is to establish average concentrations in a stream, 24-hr composite samples should be taken. If the aim is to show peak concentrations, batch samples should be taken at appropriate intervals. Descriptions of appropriate sampling systems are given in American Public Health Association, American Water Works Association, and Water Pollution Control Federation (1971).

2.3.1.3 Beryllium in Inorganic Solids — This sample category consists chiefly of collected atmospheric dusts and fumes and of ores. All samples should be ground, if necessary, to pass a 200-mesh sieve and should be mixed thoroughly before sampling for analysis. Atmospheric particulates and electrostatic precipitator dusts can frequently be dissolved in hot nitric acid. Refractory residues and beryllium-containing silicate minerals, such as beryl, the bertrandites, phenacite, and chrysoberyl, can be solubilized by fusing with a sodium carbonate-sodium tetraborate mixture at 900°C or by treatment with potassium fluoride, followed by fusion with sodium pyrosulfate (Keenan, 1966, pp. 140-141). The latter method not only dissolves the beryllium but eliminates the silica and fluorides as well. High-fired beryllium oxide is best dissolved by fusing with potassium hydroxide (Everest, 1964, p. 118). Minerals in which beryllium occurs as the phosphate or borate can be decomposed by heating with acids (Novoselova and Batsanova, 1968, p. 154).

2.3.1.4 Beryllium in Organic Media — This sample category includes soft animal tissues, bone, urine, and vegetable matter. Body tissue samples should be collected in chemically clean glass containers and preserved in formalin, or the container should be packed in dry ice to prevent decomposition of the sample before analysis. Soft tissues, up to 20 g, and bone samples, up to 4 g, can usually be satisfactorily prepared for analysis by the nitric acid wet-ashing procedure, in which the sample is repeatedly heated just to dryness after being covered initially with 5 ml of concentrated nitric acid and subsequently with just enough acid to moisten the residue. The resulting white or light-colored soluble residue is dried briefly at 400°C and cooled prior to weighing and quantitative analysis. Some samples of lung tissue may contain refractory forms of beryllium oxide or silicate, which require a potassium fluoride-sodium pyrosulfate fusion (Section 2.3.1.3) before becoming soluble. After small bone samples have been wet ashed, calcium is removed from solution by adding 5 ml of concentrated sulfuric acid and filtering the resulting calcium sulfate. Larger samples of soft tissue and the few samples not amenable to the previously described nitric acid wet-ashing procedure can be satisfactorily digested with mixtures of nitric, sulfuric, and perchloric acid (Sill and Willis, 1964). Although very effective, this perchloric acid ashing procedure is potentially hazardous because of the possibility of sublimed perchloric acid accumulating on, and subsequently reacting violently with, organic materials from the fume hood in which the ashing procedure is performed.

Accordingly, the perchloric acid ashing procedure should be used only in specially fabricated organic-free Transite fume hoods (Keenan, 1966, p. 138).

Large bone samples are not suitable for wet-ashing procedures. After drying to constant weight at 105°C, such samples can be dry ashed by placing them in a cold muffle furnace, raising the temperature gradually to 500°C, and heating for several hours. The resulting ash is extracted with hydrochloric acid to recover the beryllium.

Urine should be collected in glass-stoppered borosilicate bottles and acidified by the addition of 5 ml of concentrated nitric acid for each 250 ml of urine to prevent the adsorption of beryllium on the container wall. Some analysts also add 2 ml of a 37% formalin solution to the sample container to preserve the specimen until processed (Keenan and Holtz, 1964). Small samples of urine (about 100 ml) are prepared for analysis by adding 5 ml of concentrated nitric acid and repeating the nitric acid wet-ashing procedure described above for soft tissues. After the ashing procedure is completed, the walls of the beaker should be washed with three separate 5-ml portions of 6 *N* hydrochloric acid, evaporating just to dryness after each addition. This treatment hydrolyzes any condensed phosphates to orthophosphate and converts the residue to the chloride form. The resulting salt is suitable for use in the usual quantitative analytical procedures. Large samples of urine (1 liter or more) cannot be treated as described above because the resulting high concentration of calcium interferes with subsequent analytical procedures. In such samples the bulk of the calcium is removed by a sulfate precipitation in strongly acid solution, and the remaining calcium and other heavy metals are complexed by addition of 20 ml of 10% disodium ethylenediaminetetraacetic acid solution. The beryllium in the resulting solution is then amenable to extraction by acetylacetone or other appropriate chelating agents (Keenan, 1966, p. 146).

Thorough precautions must be taken to avoid contamination of the urine sample during contribution. This is best accomplished by obtaining samples after workers have showered and changed clothes at the end of the work shift or prior to changing into working clothes at the beginning of the work shift.

2.3.2 Separation and Concentration Methods

Because many of the current analytical techniques lack specificity, beryllium must often be separated from interfering elements prior to analysis. Furthermore, in many tissue and urine samples, the concentration of beryllium is well below the detection limit of particular analytical techniques, and preanalysis concentration is required. Solvent extraction is probably the most useful method for separating and concentrating beryllium; other techniques include ion exchange, electrolytic methods, and precipitation. The chief characteristics of these methods are discussed in the following sections.

2.3.2.1 Solvent Extraction — Solvent extraction is a rapid and relatively simple technique for separating and concentrating beryllium from other elements. The technique has considerable selectivity and, unlike

precipitation, can be used for very small quantities of material (Andelman, 1971, p. 38). In this method, a beryllium complexing agent in an immiscible organic solvent is equilibrated with an aqueous solution containing beryllium and cationic impurities which have been complexed with ethylenediaminetetraacetic acid. The solvents are then separated, and the organic phase, in which the complexed beryllium species preferentially concentrates, is used as required, either for further separation and concentration or directly in analysis. The smaller the volume of extracting solvent, the greater will be the concentration factor. The distribution coefficient for a solute that is nonionic and in the same molecular form in the two solvents is essentially equal to the ratio of its solubilities in the solvents. By judiciously choosing the complexing agent and the organic solvent, essentially all of the beryllium and little of the undesirable elements are extracted from the aqueous phase. Acetylacetone is commonly used to complex beryllium, but many other complexing agents, such as trifluoroacetylacetone, diethyldithiocarbamate, 8-hydroxyquinaldine, and cyclopentanone-2-carboxyaniline, are also useful (Butler, 1969; Hurlbut, 1974*a*, p. 4). Benzene, chloroform, and carbon tetrachloride are often used as organic solvents. The extractability of acetylacetonates of beryllium and selected group IB, IIB, and IIA metals in benzene as a function of the pH of the aqueous solution is shown in Figure 2.8. It can be seen that beryllium is quantitatively extracted between pH 4 and 7, while magnesium, calcium, strontium, barium, and zinc are not extracted at all. By using chloroform and other organic solvents instead of benzene, beryllium can also be separated from other metals (Novoselova and Batsanova, 1968, p. 118). Ethylenediaminetetraacetic acid is an effective masking agent for these extractions because it strongly complexes the impurities but not beryllium (Keenan, 1966, p. 146).

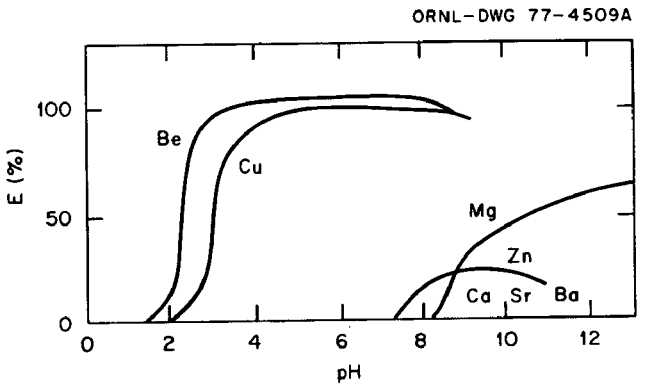

Figure 2.8. Extraction curves of beryllium, copper, magnesium, zinc, calcium, strontium, and barium with a 0.1 *M* solution of acetylacetone in benzene as a function of the pH of the aqueous solution. Source: Novoselova and Batsanova, 1968, Figure 27, p. 118.

2.3.2.2 Ion Exchange — Beryllium can be effectively separated from substances that interfere with its fluorometric or chemical determination by an ion exchange technique. For example, under acid conditions, positively charged ions may be absorbed on cation exchangers, which characteristically retain the polyvalent alkaline earth elements when the absorbed beryllium is displaced with an appropriate eluting agent. Conversely, if a suitable chelating agent, such as ethylenediaminetetraacetic acid, is used, aluminum, trivalent iron, and other heavy metals may be eluted from the ion exchange resin while beryllium is retained. Similar separations can be made with anion exchange resins under alkaline conditions. Typical resin forms, eluting agents, and operating conditions for a variety of ion exchange systems are tabulated in Table 2.27. Other ion exchange separations of beryllium are discussed by Korkisch and Feik (1965), Merrill, Honda, and Arnold (1960), Strelow and Weinert (1970), and Toribara and Sherman (1953).

2.3.2.3 Electrolytic Methods — Many interfering elements can be simply and conveniently removed from beryllium solutions by electrolysis with a mercury cathode; the contaminants dissolve in the mercury to form amalgams, which can be analyzed for their constituent metals if required. The technique is useful for the removal of 26 elements, including iron, chromium, nickel, cadmium, copper, zinc, molybdenum, and tin. Beryllium, aluminum, manganese, phosphorus, vanadium, the alkaline earths, and the rare earths remain in solution (Keenan, 1966, p. 145). The latter impurities can be removed, if necessary, by means of an acetylacetone extraction (Section 2.3.2.1). Conditions for the electrolysis vary with sample type; 0.5 g of iron can be separated in 30 to 40 min using 3 to 4 A of current at 4 to 6 V. Even faster deposition rates can be achieved with cathodic current densities of 1 to 6 A/dm^2. The deposition rate is also a function of the acidity of the solution; higher current yields occur at higher pH values (Novoselova and Batsanova, 1968, p. 151). Needless to say, beryllium-free mercury must be used to avoid contamination of samples when trace-level determinations of beryllium are made. Other applications of this technique are cited by Noweir and Cholak (1969), Toribara and Sherman (1953), and Vinci (1953).

2.3.2.4 Precipitation — Macro quantities of beryllium can be separated from small amounts of impurities by precipitation as the phosphate, hydroxide, or organic complex. Good selectivities are achieved if the impurities are first complexed with sodium ethylenediaminetetraacetate; otherwise, the precipitates are likely to be contaminated by adsorbed impurities (Novoselova and Batsanova, 1968, pp. 143, 145). It is not feasible, however, to separate micro amounts of beryllium from large quantities of other elements by precipitation of sparingly soluble compounds; instead, beryllium is coprecipitated with calcium, manganese, titanium, and iron phosphates and with aluminum and iron hydroxides. Recovery of coprecipitated beryllium can be quantitative in the microgram range, but losses become appreciable at lower concentrations. For example, Toribara and Chen (1952) recovered only 70% of the beryllium coprecipitated with calcium phosphate when the initial beryllium content was 0.1 µg or less. Although precipitation is probably the oldest and one of the easiest means of separating and concentrating beryllium, it is not the procedure of choice and must be used cautiously. Any procedure for separating trace quantities of one element from large

TABLE 2.27. ION EXCHANGE METHODS FOR SEPARATING BERYLLIUM

Resin form	Eluting agent	Ions eluted	Ions retained
		Cation exchange	
HR	Ca. 1 *M* HCl	Be	Al, Ba, Ca, Mg, Sr
HR	0.05 *M* Ca or Mg	Be	Al
HR	0.4 *M* oxalic acid	Al, Fe(III), UO_2^{2+} Th, others	
HR	Oxalic acid, pH 4.4-5	Al, Fe	Be
HR	5 *M* HCl	Be	PO_4^{3-}
NH_4R	0.55 *M* ammonium lactate, pH 5	Be	Other alkaline earths
NH_4R	10% $(NH_4)_2CO_3$, pH 8.5-9.0	Be	Cu, Ni
NaR	EDTA, pH 3.5-4.0	Al, Fe(III), Mn(II), heavy metals, others	Be, alkaline earths
NH_4R	0.35 *M* acetate	Be	Al, alkaline earths, U, others
NaR	Acetylacetone, pH 5	Be	Al, alkaline earths, U, others
NH_4R	0.02 *M* sulfosalicylic acid, pH 3.5-4.5	Be	Ca, Cu, U
		Anion exchange	
RC_2O_4	0.1 *M* oxalic acid, 0.15 *M* HCl	Be	Al
R citrate	1 *M* ammonium citrate, pH 8	Be	Other alkaline earths
RCl	Various concentrations of HCl	Be	Many transition elements
RCl	13 *M* LiCl	Alkali metals, Mg	Be

Source: Adapted from Keenan, 1966, Table 5.3, p. 149. Reprinted by permission of the publisher.

amounts of other substances is subject to losses or contamination by occlusion, adsorption, and coprecipitation. It is therefore necessary for the user to demonstrate the validity of the precipitation procedure under experimental conditions applicable to the samples before it is used for analysis of unknown samples (Keenan, 1966, p. 143). Additional aspects of the separation and concentration of beryllium by precipitation techniques are discussed by Barnes et al. (1949), Klemperer and Martin (1950), and Toribara and Chen (1952).

2.3.3 Methods of Analysis

Beryllium in environmental samples can be determined by a variety of analytical procedures; those currently important or showing promise of future usefulness are described in this section. The performance and limitations of each method are emphasized rather than minute details of operation. Summaries of the methods are given in Tables 2.20-2.24. It is worth noting that variations in sensitivity, precision, and accuracy occur not only among different methods but also among various models of equipment and among different operators (Karasek, 1975); the tabulated data should therefore be considered representative rather than definitive. Performance data cited by workers responsible for developing an analytical technique usually are obtained under optimized conditions and may not accurately reflect all of the sources of error associated with the collecting, processing, and analysis of environmental samples; interlaboratory comparisons — when they exist — offer more realistic appraisals of particular analytical techniques.

2.3.3.1 Atomic Absorption Spectroscopy — Beryllium in air, natural and treated waters, biologic tissues, and urine can be rapidly determined by flame and flameless atomic absorption spectroscopy. In the flame technique, a previously prepared sample is continuously injected into a nitrous oxide–acetylene flame through which 234.9-nm radiation from a hollow-cathode lamp is passed. The flame atomizes the sample, and radiation from the lamp is selectively absorbed by beryllium atoms in proportion to their concentration in the vapor. A photodetector measures the intensity of the 234.9-nm radiation after its passage through the flame and compares it with the intensity of the original line spectrum emitted by the lamp (Figure 2.9). The output of the photodetector is usually calibrated to read directly in concentration values (Environmental Instrumentation Group, 1973*a*). The sensitivity (1% absorption) and detection limits (twice background) under

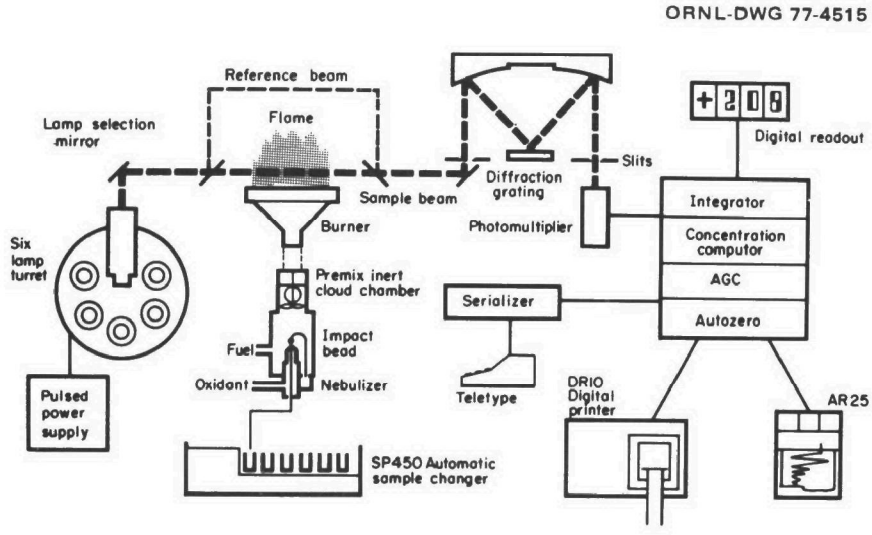

Figure 2.9. Schematic diagram for the Unicam SP 1900, a double-beam spectrophotometer. Source: Environmental Instrumentation Group, 1973*a*, Figure 2, p. 4.

normal operating conditions are only about 0.03 and 0.01 to 0.002 µg/ml, respectively, but these levels can be improved through solvent extraction and concentration prior to assay (Bokowski, 1968; Hurlbut, 1974*b*). Silicon and aluminum in concentrations of about 500 µg/ml and numerous other metals at 4000 µg/ml or more interfere with the beryllium absorption signal. Interference by aluminum is reduced by adding 8-hydroxyquinoline (Fleet, Liberty, and West, 1970). In interlaboratory comparisons of the flame version of the atomic absorption method, unknown samples containing aluminum, barium, and beryllium were analyzed in ten different laboratories with good accuracy and moderately good precision, depending on the concentration of beryllium in the sample (Table 2.28).

TABLE 2.28. SUMMARY OF INTERLABORATORY COMPARISONS OF BERYLLIUM BY FLAME ATOMIC ABSORPTION SPECTROSCOPY

Sample	Beryllium concentration (mg/liter)	No. of results	No. of outliers	Mean	Mean error	S.D.[a]	R.E.	R.S.D.
1	0.005	10	1	0.006	+0.001	0.0017	20.0	34.0
2	0.050	11	2	0.051	+0.001	0.020	2.0	39.2
3	0.100	11	2	0.103	+0.003	0.036	3.0	35.0

[a]S.D. = standard deviation; R.E. = relative error; R.S.D. = relative standard deviation.

Source: Adapted from Lishka and McFarren, 1970, Tables C-4, C-5, and C-6, pp. 40-42. Reprinted by permission of the publisher.

The flameless atomic absorption procedure for determining beryllium is generally much more sensitive than the flame method. In this technique a discrete volume of sample is atomized with an electrically heated carbon rod, cup, or furnace (Figure 2.10) rather than a flame. An absorbance peak of relatively short duration results, but the efficiency of atomization approaches 100%, as compared with 2% to 8% by the flame technique (Environmental Instrumentation Group, 1973*a*). As a consequence, the detection limit of beryllium by the flameless atomic absorption procedure is reduced tenfold or more compared with that for the flame technique. In addition, in many instances, samples can be analyzed in the flameless procedure without prior preparation. For example, in urine samples containing beryllium at a concentration of 5 ng/g, Hurlbut (1974*b*) determined the element directly with a sensitivity (1% absorption) of 0.2 ng/g, a detection limit (twice background) of about 0.1 ng/g, a relative standard deviation of 8%, and a relative error of 2%. The precision and accuracy at other sample concentrations are shown in Table 2.29. The rapidity and convenience of the flameless atomic absorption technique is indicated by the author's reporting the possibility of analyzing up to 200 urine samples per day by the method. Robbins, Runnels, and Merryfield (1975) determined beryllium in petroleum and petroleum products at the 30 to 40 ng of beryllium per gram level with a precision of 10% and good recoveries from spiked samples; the detection limit varied from 1 to 10 ng of beryllium per gram,

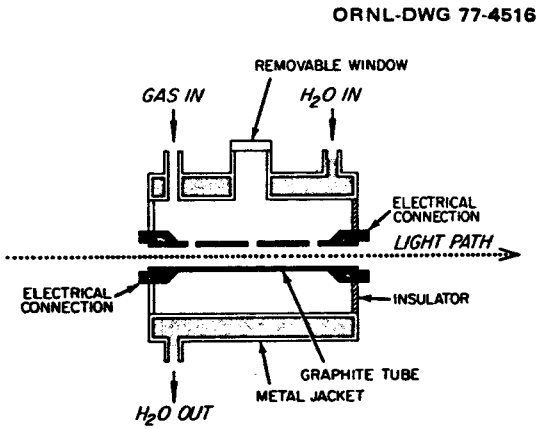

Figure 2.10. Cross section of the HGA-2000 (Perkin-Elmer) graphite oven. Source: Environmental Instrumentation Group, 1973*a*, Figure 4, p. 5.

TABLE 2.29. RECOVERY OF BERYLLIUM FROM SPIKED URINE AND SPIKED ASHED URINE BASED ON AQUEOUS STANDARDS

Sample[a]	Beryllium concentration (µg/liter)	
	Actual	Recovered
Blank urine	0.0	0.1
Blank water	0.0	0.0
Urine	10.0	10.9[b,c]
	5.0	5.1[b,c]
	2.0	2.0[b,c]
Ashed urine	5.0	5.1[b,c]

[a]All solutions were 4% (V/V) in sulfuric acid and about 3% (V/V) in nitric acid.

[b]The standard deviation is about ±0.4 µg/liter based on six determinations.

[c]Aqueous 5.0-µg/liter standards have a standard deviation of about ±1.0 on the basis of eight separate determinations.

Source: Hurlbut, 1974*b*, Table 1, p. 3.

depending on the type of furnace used. The accuracy of the results depended somewhat on the experience of the analyst. Owens and Gladney (1975) applied the flameless technique to four standard reference materials from the National Bureau of Standards. Excellent agreement was obtained for samples of coal (1.5 ppm Be) and fly ash (12 ppm Be), which were processed by wet ash digestion, but disparate results occurred when orchard leaves were analyzed directly and by wet ash digestion (Table 2.30). Whether the orchard leaves data reflect loss of volatile organoberyllium compounds (Section 2.3.1), formation of nonvolatile beryllium carbide in the graphite atomizer (Runnels, Merryfield, and Fisher, 1975), anomalies associated with the use of a tantalum sample boat, or some unspecified perturbation was not determined. The data again emphasize the necessity of verifying the validity of an analytical technique before introducing it for routine use. Finally, Hurlbut and Bokowski (1974) demonstrated the effectiveness of flameless atomic absorption spectrometry by determining nanogram amounts of beryllium in air filter samples. They analyzed as little as 4 ng of beryllium per paper filter with a relative standard deviation of 8% and a relative error of 5%. The detection of beryllium collected on glass filters was limited to about 0.1 μg of beryllium per filter because of an interfering nonatomic peak attributed to aluminum. However, aluminum interference is not a major factor when a double-beam spectrometer equipped with a deuterium background corrector is used.

2.3.3.2 Spectrophotometry — This analytical technique involves the formation of a colored beryllium complex that absorbs radiation in the visible portion of the electromagnetic spectrum. The amount of radiation absorbed by the sample is measured with a spectrophotometer and related to the metal concentration by means of a previously prepared calibration chart. Numerous complexes have been used for determining beryllium; most are formed by

TABLE 2.30. BERYLLIUM CONTENT OF NBS STANDARD REFERENCE MATERIALS

(All values in ppm plus or minus standard deviation)

Standard reference material	This work	Other work
Fly ash (1633)	12.0 ± 0.8[a]	12
Coal (1632)	1.5 ± 0.1[a]	1.5
Orchard leaves (1571)	0.036 ± 0.004[a] 0.067 ± 0.007[b]	0.030 ± 0.004
Bovine liver (1577)	0.005 ± 0.003[b]	

[a]Wet ash digestion.

[b]Direct insertion of solid (Ta boat).

Source: Owens and Gladney, 1975, Table 1, p. 77. Reprinted by permission of the publisher.

treating the beryllium cation with an organic chelating agent. A few of these complexing agents and the absorption maxima of their beryllium complexes are shown in Table 2.31. Unfortunately, none of these reagents are specific for beryllium, and many cationic and anionic interferences exist, which must be removed chemically or masked by the addition of sodium ethylenediaminetetraacetate or a similar reagent. Accordingly, spectrophotometric procedures for beryllium are sometimes lengthy and tedious.

TABLE 2.31. COMPLEXING AGENTS COMMONLY USED FOR THE SPECTROPHOTOMETRIC DETERMINATION OF BERYLLIUM

Reagent	Maximal absorption (nm)
Acetylacetone	295
Aurintricarboxylic acid (aluminon)	515
Chrome Azurol S	575
Eriochrome Cyanine R	512
Fast Sulfon Black F	630
8-Hydroxyquinaldine	380
p-Nitrophenylazoorcinol (Zenia)	525
2-Phenoxyquinizarin-3,4'-disulfonic acid	550
Quinizarin-2-sulfonic acid	575

Source: Adapted from Keenan, 1966, Table 5.6, pp. 156-157. Reprinted by permission of the publisher.

In a typical determination of beryllium in natural or treated water using the aluminon method, the sample solution is first treated with ethylenediaminetetraacetic acid to prevent interference from moderate amounts of aluminum, cobalt, copper, iron, manganese, nickel, titanium, zinc, and zirconium; then the beryllium complex is formed by adding a buffered solution of aluminon. The colored complex is developed in darkness for 20 min, after which its absorbancy at 515 nm is measured with a spectrophotometer using 5-cm cells. The detection limit of the method is about 5 ng of beryllium per milliliter. The precision and accuracy depend on the type and concentration of the sample. In a study involving 32 laboratories, the beryllium in a synthetic unknown sample of distilled water containing 250 µg/liter beryllium, 40 µg/liter of arsenic, 240 µg/liter of boron, 20 µg/liter of selenium, and 6 µg/liter of vanadium was determined by the aluminon method with a relative standard deviation of 7% and a relative error of 12% (American Public Health Association, American Water Works Association, and Water

Pollution Control Federation, 1971, p. 68). This level of precision and accuracy is adequate for many environmental samples such as dusts, ores, surface waters, and air filters, but the spectrophotometric technique is being used less frequently today than formerly; it is being replaced by more convenient or sensitive methods such as atomic absorption spectrometry or gas chromatography.

2.3.3.3 Fluorometry — The fluorometric method is based on the measurement of fluorescence radiation emitted by a beryllium compound previously excited by ultraviolet or visible light. The emitted radiation results from the transition of the excited molecule from the first excited singlet state to the ground state — the frequency of the emitted light is therefore characteristic of the analyte. The intensity of the emission is proportional to the concentration of the analyte as well as the intensity of the exciting radiation; accordingly, fluorometry is inherently very sensitive. Under favorable conditions it can be four orders of magnitude more sensitive than molecular absorption spectrophotometry (Mancy, 1971, p. 70). A simplified schematic diagram of a filter-type fluorometer is shown in Figure 2.11. In a typical application of fluorometry to the determination of beryllium in environmental or biologic media, samples are prepared as described in Section 2.3.1, treated with morin (2',4',3,5,7-pentahydroxyflavone), and irradiated with either 365- or 436-nm radiation from a mercury or xenon lamp. The intensity of the emitted 550-nm fluorescence is measured with a photodetector tube and related to the concentration of the beryllium in the sample by a predetermined calibration chart (Kupel et al., 1971). The intensity of the fluorescence varies with temperature, morin concentration, pH, and time. Lithium, scandium, zinc, and calcium also produce fluorescence with morin in alkaline solution, and they must be removed or chelated with ethylenediaminetetraacetic acid or a similar complexing agent to avoid interference (Sill and Willis, 1959). Fluorescing agents other than morin, such as 1-amino-4-hydroxyanthraquinone, 2,3-hydroxynaphthoic acid, and 8-hydroxyquinaldine can also be used but are not as sensitive as morin (Mancy,

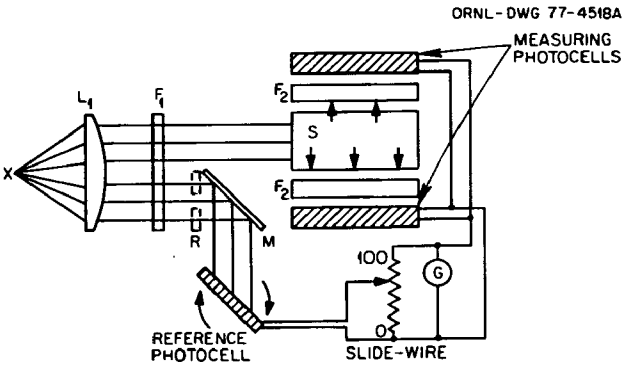

Figure 2.11. A schematic diagram of a filter-type fluorometer. X, ultraviolet light source; L_1, collimating lens; F_1, primary filter passing only ultraviolet light of a selected wavelength; F_2, secondary filter passing only fluorescent light; R, reduction plate; M, front-surface mirror; and G, galvanometer. Source: Adapted from Mancy, 1971, Figure 6, p. 71. Reprinted by permission of the publisher.

1971, p. 74). With the latter, under idealized conditions, as little as 400 pg of beryllium in 11 ml of solution can be detected, and 200 ng of beryllium in 11 ml of solution can be determined with a relative standard deviation of 0.4% (Sill and Willis, 1959). For routine analyses, a ten-fold higher detection limit and less precision appear more realistic (Kupel et al., 1971), but even with relaxed standards the fluorometric method is exceeded in sensitivity only by the gas chromatographic method of determining beryllium. Only limited data are available for the precision and accuracy of the method under routine conditions. Welford and Harley (1952) reported an average recovery of 92% in analyses of 200 spiked air filter samples. Walkley (1959) recovered 110% of the beryllium in ten spiked samples on filter paper. This level of accuracy is adequate for most air, water, bone, blood, and organic tissue samples (American Industrial Hygiene Association, 1969).

Despite the attractive sensitivity and accuracy of fluorometric determinations of beryllium and the relatively low cost of equipment, sample preparation is sometimes lengthy, with many variables and potential interferences. As a consequence, more convenient techniques, such as atomic absorption spectrometry and gas chromatography, are preferred in some analytical laboratories.

2.3.3.4 Emission Spectroscopy — In emission spectroscopy, prepared samples are thermally or electrically excited, the resulting radiation is resolved with a monochromator, and emission lines characteristic of each excited element in the sample are recorded on film or photographic plates. The concentration of each element is determined by comparing the density of its emitted line with that of an internal or external standard. Use of an internal standard — an element added to the sample in known amount — is preferable to use of a separate external standard, since the former tends to minimize the influence of procedural variables. The sample can be excited by various techniques. When an ac or dc arc is used, the sample is usually placed on an electrode, and light from the electric discharge between the electrodes is focused on the monochromator. In the cathode layer technique, the graphite cathode is coated with the sample and only light from the vicinity of the cathode is monitored. This technique increases the sensitivity of the analysis, but critical focusing is required. In the porous cup technique, the liquid sample is fed into a spark discharge by percolation through the thin base of a hollow graphite electrode. The various modes of sample excitation, emission lines, interferences, internal standards, and sensitivities characteristic of several commonly used spectroscopic procedures for determining beryllium are summarized in Table 2.32. In general, the spectroscopic determination of beryllium is very specific, and elaborate sample purification procedures are not needed; only when a strong emission line from an impurity falls very near the chosen beryllium line — for example, iron at 234.83 nm and beryllium at 234.86 nm — is it necessary to separate an impurity before satisfactory measurement of the density of the beryllium line can be made (Tepper, 1972*a*, p. 254).

On the other hand, attainment of maximum sensitivity by the spectroscopic technique requires the concentration of beryllium into a very small

TABLE 2.32. SPECTROGRAPHIC METHODS OF DETERMINING BERYLLIUM

Current	Internal standard	Interferences	Wavelengths (nm)	Sensitivity
dc	Molybdenum		Be:265.1, 313.1; Mo:313.3	0.5 µg/ml
dc	Thallium	Iron	Be:234.9; Tl:238.0	0.25 µg/ml
dc	Aluminum	Organics and phosphates	Be:234.9, 265.1; Al:236.7	0.05 µg/sample
ac	Aluminum		Be:313.1; Al:257-5 Be:313.1; Al:308.2 Be:234.9; Al:308.2	0.05 µg/sample
dc	Aluminum		Be:234.5; Al:232.2	0.004 µg/sample
ac	Aluminum		Be:313.1; Al:305.9	
dc	Barium, thallium	Alkali metals	Be:234.9; Tl:276.8 Be:234.9; Ba:251.9	0.002 µg/sample

Source: Adapted from American Industrial Hygiene Association, 1969, Table 1. Reprinted by permission of the publisher.

volume; therefore, preanalysis processing to remove large quantities of extraneous matter is commonly practiced. The relationship between spectroscopic sensitivity for beryllium and sample size varies with sample type and is illustrated in Table 2.33. These data are based on a spectroscopic sensitivity of 3 ng of beryllium per milliliter and the use of 1/5 ml of solution on the electrode (Cholak, 1959). Sensitivities of this order are typical of many spectroscopic determinations of beryllium. Keenan and Holtz (1964) observed sensitivities of 2 to 5 ng of beryllium per aliquot (0.05 ml) using a sustaining ac arc excitation technique. The precision of spectroscopic analyses of beryllium at this level varies appreciably and is frequently poor (Hurlbut, 1974*a*, p. 6), but Keenan and Holtz (1964) analyzed four replicate sets of rabbit liver ash samples containing 1 to 100 ng of beryllium with a relative standard deviation of 20% or less over a six-month period (Table 2.34). The accuracy of the spectroscopic method is generally inferior to that of other methods (Table 2.35), but this characteristic is not as decisive for many environmental samples as specificity and sensitivity (Cholak, 1959).

Until the 1960s, emission spectroscopy was the most satisfactory procedure for detecting and determining beryllium in trace-level samples. Recently, cheaper, more accurate and convenient methods, such as atomic absorption spectrometry and gas chromatography, have been developed and are gradually replacing the older technique. However, the spectroscopic determination of beryllium may continue to be economically attractive in instances where multielement analyses are required.

2.3.3.5 Gas Chromatography — Gas chromatography is an analytical process in which components of a volatile sample are physically partitioned between a stationary bed of large surface area and a gas that percolates through

TABLE 2.33. RELATIONSHIP BETWEEN SPECTROSCOPIC SENSITIVITY FOR BERYLLIUM AND SIZE OF SAMPLE

Material	Sensitivity desired	Size of sample
Urine	0.01 μg/liter	333 ml
Tissue (lung)	0.01 μg/100 g	33.3 g
Air (in plant)	0.01 $\mu g/m^3$	333 liters (11.77 ft^3)
Air (outside)	0.001 $\mu g/m^3$	3333 liters (117.7 ft^3)
Urine	0.06-0.03 μg/liter	50 ml
Tissue (lung)	0.30-1.50 μg/100 g	1 g

Source: Cholak, 1959, Table 2, p. 125. Reprinted by permission of the publisher.

TABLE 2.34. RECOVERY OF BERYLLIUM ADDED TO 2-mg QUANTITIES OF RABBIT LIVER ASH

Beryllium added (μg)	Beryllium recovered[a] (μg)	Standard deviation from beryllium added (μg)	Coefficient of variation (%)
0.001	0.0012	0.00020	20.0
0.002	0.0019	0.00026	13.0
0.005	0.0051	0.00029	5.8
0.010	0.0108	0.00112	11.2
0.050	0.0478	0.00577	11.5
0.100	0.1055	0.02181	21.8

[a]Mean of four determinations.

Source: Keenan and Holtz, 1964, Table III, p. 261. Reprinted by permission of the publisher.

and along the stationary bed. Typically, the stationary bed is a finely divided column packing that is covered with a suitable liquid or solid sorbent. An inert gas such as helium, argon, or nitrogen is usually used as the carrier of the volatile phase. When the sample is introduced into the chromatographic column, the unadsorbed carrier gas moves the various

TABLE 2.35. RECOVERY OF BERYLLIUM FROM SPIKED SAMPLES

Beryllium added (µg)	Collecting filter	Compound	Beryllium recovered by morin method (µg)	Beryllium found by spectrographic method (µg)
0.05	Millipore	Beryllium oxide	0.08	0.034
0.63	Millipore	Beryllium oxide	0.61	0.65
0.05	Millipore	Beryllium sulfate	*a*	0.032
0.15	Millipore	Beryllium sulfate	0.23	0.31
0.50	Millipore	Beryllium sulfate	0.45	0.60
1.5	Millipore	Beryllium sulfate	*a*	1.64
0.063	Glass	Beryllium oxide	*a*	0.11
0.63	Glass	Beryllium oxide	0.48	0.62
6.3	Glass	Beryllium oxide	6.8	7.1
0.10	Glass	Beryllium sulfate	0.12	*a*
1.0	Glass	Beryllium sulfate	0.88	*a*
0.1	Whatman 41	Beryllium sulfate	*a*	0.15
0.63	Whatman 41	Beryllium sulfate	0.64	*a*
1.0	Whatman 41	Beryllium sulfate	*a*	1.2
10.0	Whatman 41	Beryllium sulfate	*a*	9.8
12.6	Whatman 41	Beryllium sulfate	12.6	*a*
30.0	Whatman 41	Beryllium sulfate	*a*	28.2
0.63	Whatman 41	Beryllium oxide	*a*	0.85
12.5	Whatman 41	Beryllium oxide	*a*	16.0

[a]Identical samples not available for analysis.

Source: Tepper, Hardy, and Chamberlin, 1961, Table XI, p. 165. Reprinted by permission of the publisher.

constituents of the sample through the column at a rate determined by the interaction of each constituent with the sorbent. Since each constituent has a slightly different affinity for the sorbent, each fraction of the sample usually emerges from a well-designed column completely resolved from other components after the passage of a characteristic volume of carrier gas. Under standardized operating conditions, each component can be identified by its characteristic elution time. The composition of the original sample is determined by identifying and measuring each component. Various kinds of detectors are available for quantifying the fractions; electron capture, flame ionization, and thermal conductivity types are commonly used. A schematic diagram of a typical system is shown in Figure 2.12.

Use of gas chromatography for the determination of beryllium requires that the metal be converted to a volatile form, such as a halide, β-diketone, or fluorinated β-diketone; the trifluoroacetylacetonate appears to be the most popular derivative (Frame et al., 1974; Schwarberg, Moshier, and Walsh, 1964). In a typical gas chromatographic analysis of environmental air samples, Ross and Sievers (1972) prepared and injected this beryllium complex into a 2-m-long, 3-mm-ID borosilicate glass column packed with 2.8%

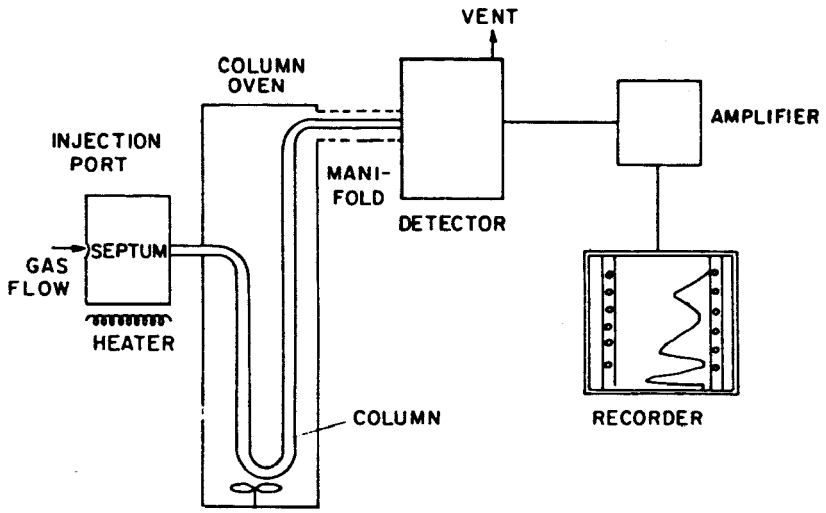

Figure 2.12. Schematic diagram of a gas chromatograph. Source: Environmental Instrumentation Group, 1973*b*.

W-98 silicone on Diataport S. The detector was an electron-capture type equipped with a tritium ionizing source.

A mixture of methane (10%) and argon (90%) was used as the carrier gas; the column and detector were maintained at 110°C and 200°C, respectively. Excellent sensitivity, precision, and accuracy were obtained. Beryllium was determined at the 400 pg of beryllium per cubic meter level with a relative standard deviation of 3% and a relative error of 4%. The limit of detection under the observed conditions was less than 40 pg of beryllium per cubic meter. Preparation and analysis of the air filter samples required about 40 min. Other investigators applied the gas chromatographic technique to the determination of beryllium in biologic media. Taylor and Arnold (1971) determined beryllium in human blood spiked with 20 to 1000 ng of beryllium per milliliter with a relative standard deviation of 7% to 10% and an average relative error of 5%. The limit of detection was 0.08 pg of beryllium in 0.5 to 1.0 µl of injected sample. Less precise results were obtained with liver and spleen tissues of rats, but the homogeneity of these samples was not established. The time required for sample preparation and analysis averaged 15 min. Foreman, Gough, and Walker (1970) determined beryllium in human and rat urine by gas chromatography. Spiked samples containing from 1 to 2.7 µg of beryllium per milliliter were extracted directly or after wet combustion with average recoveries of 97% and 94%, respectively. A variety of chromatographic substrates were studied; the best separation was achieved with Gas-Chrom Z coated with a methyl phenyl silicone gum. The detection limit for beryllium under these conditions was 1 µg/ml.

The superior sensitivity, selectivity, speed, and convenience of the gas chromatographic method make it very attractive for the determination of beryllium in environmental and biologic media, especially at ultratrace

levels. These factors and the relatively modest cost of the required equipment suggest that this technique may soon become the method of choice for such samples in most analytical laboratories.

Other aspects and applications of the gas chromatographic technique are discussed by Eisentraut, Griest, and Sievers (1971), Kawaguchi, Sakamoto, and Mizuike (1973), Krugers (1968), Noweir and Cholak (1969), Pauschmann and Bayer (1974, pp. 143-165), Ross and Sievers (1968), and Wolf et al. (1972).

2.3.3.6 Other Methods — Other techniques for determining beryllium have been demonstrated by various researchers. Most of these methods appear attractive under special circumstances but seem unlikely to find widespread acceptance in environmental or biologic applications. Included in this category are polarography (Bacon and Ferguson, 1972; Blasius, Janzen, and Fallot-Burghardt, 1971; Fogg, Kumar, and Burns, 1971; Gálová and Pantony, 1971), alpha activation (Engelmann, 1971*a*, 1971*b*), proton activation (Golicheff, Loeuillet, and Englemann, 1972), neutron activation (Golánski, 1969), gamma activation (Lutz, 1971), microemission spectrography (Brokeshoulder et al., 1966; Robinson et al., 1968), enzyme inhibition (Guilbault, Sadar, and Zimmer, 1969; Townshend and Vaughan, 1969), atomic fluorescence (Chakrabarti, 1975), and ion-specific electrodes (Fleet and Rechnitz, 1970).

2.3.4 Comparison of Analytical Procedures

Prior to the 1960s, beryllium in environmental and biologic samples was determined primarily by spectroscopic, fluorometric, and spectrophotometric methods. Among these, emission spectroscopy was probably the most satisfactory method for detecting and determining traces of beryllium because of its specificity and freedom from interferences; nevertheless, it was still time-consuming, imprecise, and required expensive equipment (Hurlbut, 1974*a*, p. 6). Fluorometry, especially the morin method, was the most sensitive technique, easily detecting submicrogram concentrations of beryllium; however, it was subject to many variables and interferences, and samples frequently required lengthy preanalysis processing as well as a high level of operator competence for satisfactory results. The spectrophotometric methods — of which the aluminon technique was probably the most popular — lacked specificity and sensitivity, suffered from many interferences, and were frequently very time-consuming. As a result of these deficiencies, the older methods have been replaced in many laboratories by newer, more rapid and convenient techniques, such as atomic absorption spectrometry and gas chromatography.

With the development by Willis (1965) of the high-temperature nitrous oxide—acetylene flame, atomic absorption spectrometry became a useful and convenient, though not ultrasensitive, beryllium procedure, which is rapid and reasonably free of interferences. When needed, greater sensitivity can often be obtained by substituting an electrically heated graphite atomizer for the nitrous oxide—acetylene flame. In some instances, use of the flameless atomic absorption technique also eliminates the need for sample preparation. Atomic absorption spectrometry is thus attractive for environmental samples requiring only moderate sensitivity.

Even greater sensitivity and specificity are available in the gas chromatographic method. When beryllium is chelated with trifluoroacetylacetone and an electron-capture detector is used, as little as 0.08 pg of beryllium can be detected by this technique (Taylor and Arnold, 1971). In addition, sample preparation and analysis are usually rapid, interferences are few, and equipment costs are moderate; the technique is thus very attractive for determining beryllium in environmental and biologic media.

Other analytical methods such as polarography, enzyme inhibition, and various types of activation techniques also appear attractive for specific limited applications but seem unlikely to be used extensively in the analysis of a variety of environmental and biologic samples.

SECTION 2

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SECTION 3

BIOLOGICAL ASPECTS IN MICROORGANISMS

3.1 SUMMARY

Microorganisms absorb beryllium when exposed to soluble compounds; however, the form of the absorbed element is not known. The addition of beryllium at an initial pH of 11.4 promotes growth of magnesium-deficient algae due to partial substitution of beryllium for magnesium in the organism's metabolism. The substitution appears to be pH-dependent, as beryllium is toxic to microorganisms below pH 7 regardless of the magnesium level.

Normally, beryllium inhibits the growth of microorganisms. Growth may be inhibited by more than 50% in the presence of 2×10^{-6} *M* beryllium solutions. The degree of beryllium toxicity depends on environmental conditions, with toxicity increasing in a suboptimal environment.

3.2 METABOLISM

In microorganisms, beryllium is absorbed into the cell as well as adsorbed to the outer cell surface (Hoagland, 1952; Karlander and Krauss, 1972). Green algae absorb 1 to 44 ng of beryllium per milligram of dry weight when grown in constant levels of soluble beryllium compounds (Karlander and Krauss, 1972). The form of beryllium that is most likely to be absorbed by algae has not been determined.

3.3 EFFECTS

3.3.1 Physiological Effects

Under high initial pH conditions, beryllium can serve as a growth promoter in magnesium-deficient microorganisms (Figure 3.1). Beryllium concentrations of 2×10^{-4} to 3×10^{-4} *M* increased growth nearly 60% in magnesium-deficient *Chlorella pyrenoidosa* at an initial pH of 11.3 to 11.5 (Hoagland, 1952). Steinberg (1946) increased the yield of magnesium-deficient *Aspergillus niger* by the addition of 5 mg of beryllium per liter but found that as magnesium levels were increased to optimum, the beryllium-induced response decreased. A decrease in pH or an excess of micronutrients in the solution prevented the increased growth.

Although beryllium stimulates growth by substituting for magnesium in the microorganisms' metabolism (Hoagland, 1952), the substitution is not perfect because magnesium is an essential element and must be present at a minimum concentration for the organism to thrive. The substitution appears to increase growth only at high pH. At pH 7 or below, beryllium is toxic to algae regardless of the magnesium levels of the organism. It is not clear whether pH affects the site of action for beryllium or magnesium, the state of the beryllium itself, the lability of bound magnesium, or a combination of these possibilities. Hoagland (1952) has suggested

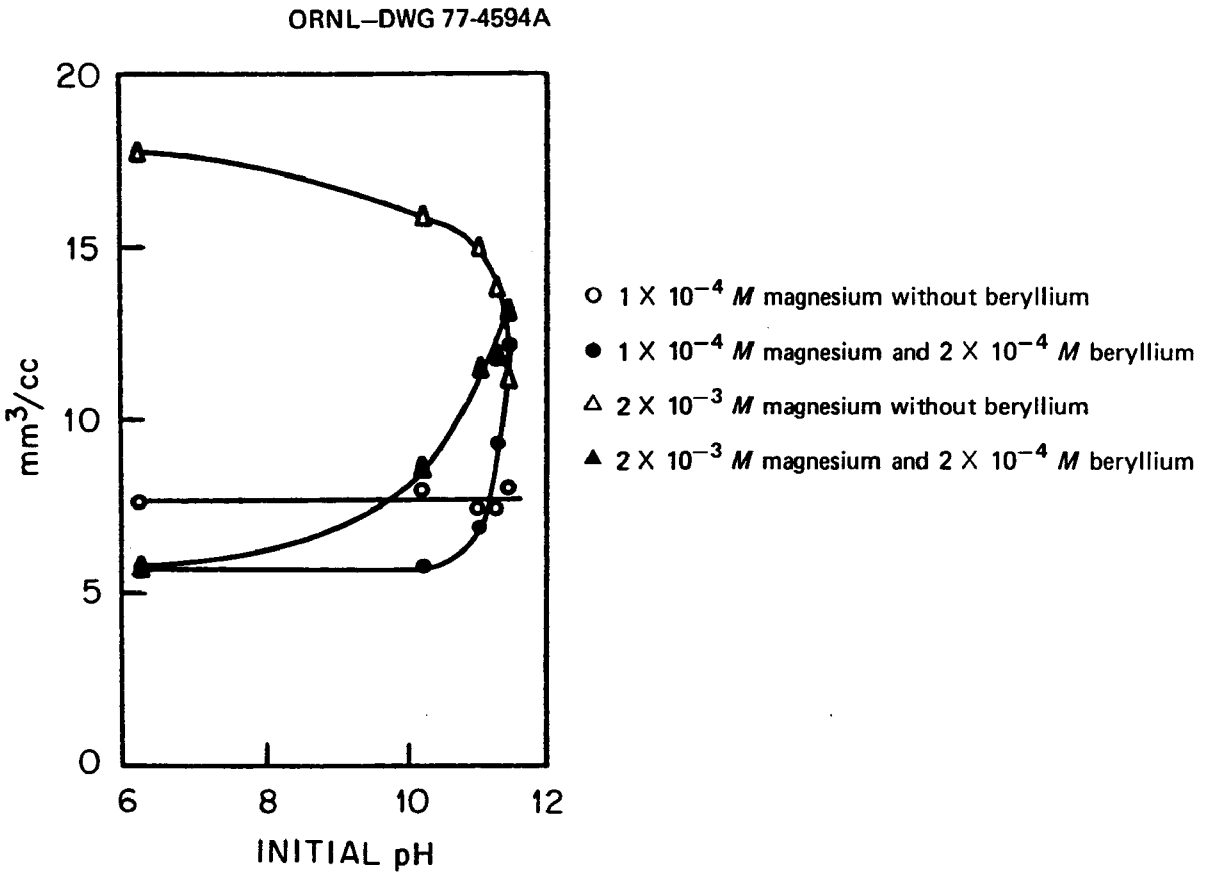

Figure 3.1. The growth of algae (70 hr) as a function of the initial pH of the nutrient solution (one of four similar experiments).

that at high pH the beryllate ion $(BeO_2)^{2-}$ forms and is responsible for growth promotion of magnesium-deficient algae, while at low pH a different species of beryllium causes toxicity.

3.3.2 Toxic Effects

Under normal pH and magnesium conditions, beryllium inhibits the growth of microorganisms. Beryllium chloride, fluoride, and sulfate inhibit the growth of the yeast *Saccharomyces cerevisiae* and of *Escherichia coli* (Loveless, Spoerl, and Weisman, 1954). Yeast cells were found to undergo abnormal multiple budding after incubation (Manil and Straszewska, 1953). Beryllium concentrations of 2000 µg/ml reduced growth by over 50%. MacCordick, Hornsperger, and Wurtz (1975) and MacCordick, Wurtz, and Hornsperger (1975) found the beryllium concentrations of 2×10^{-6} *M* or more reduced growth of *Pseudomonas fluorescens*.

The toxicity of beryllium depends on the environmental conditions as well as the concentration of the metal in solution (Karlander and Krauss, 1972). Under optimal conditions, the growth of *Chlorella vanniellii* was not affected by a concentration of 100 mg of beryllium per liter. Under suboptimal conditions (limited CO_2, limited light, variable temperature), however, the same beryllium concentration completely halted growth.

SECTION 3

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SECTION 4

BIOLOGICAL ASPECTS IN PLANTS

4.1 SUMMARY

Few data exist on the metabolism or effects of beryllium in higher plants. Soluble beryllium is absorbed by roots from solution cultures and soils. The amount absorbed increases with increasing acidity of the source solution. Only a small amount of beryllium is translocated from roots to shoots. Beryllium concentrations in crop plants and noncrop plants are usually small (about 0.1 ppm dry weight in plants containing beryllium; however, many do not contain measurable amounts). There are no data on the bioelimination of beryllium from living plant tissues.

Although low beryllium concentrations may enhance growth, most results show beryllium to be toxic. The symptoms of beryllium toxicity are not specific. Root damage is a common observation. Leaves may become a darker green or become mottled (citrus). In the culture solution, the concentration of beryllium which induces this toxicity is about 1 ppm; typically, the corresponding concentration of beryllium in the root is a few hundred parts per million.

At pH values greater than 9, beryllium can increase growth when magnesium levels are low; however, at lower pH values, increased growth may not occur. Plant phosphatases are inhibited in vitro by beryllium, but data on the significance of this experiment in vivo are lacking.

4.2 METABOLISM

4.2.1 Uptake

Few data exist addressing the problem of beryllium uptake in higher plants. It is apparent, however, that uptake of beryllium from both soil and nutrient solutions does occur (Romney and Childress, 1965; Williams and Le Riche, 1968). Nikonova (1971) considers pine, birch, aspen, and willow the best accumulator plants for soil beryllium. In these plants, beryllium content may rise as high as 3 ppm; they are recommended as indicators of exploitable ore deposits underneath. Increasing the beryllium concentration in nutrient solution culture experiments increases the beryllium content of plant material (Table 4.1). Similar increases are found in bush beans growing in nutrient culture with beryllium (Table 4.2) (Romney, Childress, and Alexander, 1962) and in *Zea mays* grown in soil with beryllium nitrate (Oustrim et al., 1967). Holst, Schmid, and Yopp (1975) suggest that uptake by excised barley roots was passive because the Q_{10} for uptake was only 1.2.

The form of beryllium in soil affects the extent of uptake in plants. High concentrations of insoluble $BeCO_3$ and BeO did not influence bean growth, whereas $Be(NO_3)_2$ and $BeSO_4$ at 10 ppm did inhibit growth (Romney and Childress, 1965). Presumably, inhibition reflects increased uptake

TABLE 4.1 BERYLLIUM CONCENTRATION IN PLANT MATERIAL EXPOSED TO BERYLLIUM IN NUTRIENT SOLUTIONS

Plant tissue	Beryllium concentration in nutrient solution (ppm)	Beryllium concentration in dry plant tissue (ppm)
Alfalfa (leaf and stem)	0	0.0
	4	5.3
	8	21.8
	16	27.6
Barley (foliage)	0	0.0
	2	8.6
	4	11.3
	8	22.8
	16	68.0
Barley (roots)	0	0.0
	2	110.0
	4	775.0
	8	1130.0
	16	2030.0
Lettuce (foliage)	0	0.0
	2	23.7
	4	33.0
	8	37.0
	16	55.0
Pea (leaf and stem)	0	0.0
	2	15.1
	4	23.0
	8	31.4
	16	75.3

Source: Adapted from Romney and Childress, 1965, Table 4, p. 213. Reprinted by permission of the publisher.

TABLE 4.2. BERYLLIUM CONCENTRATION IN BUSH BEANS EXPOSED TO BERYLLIUM IN NUTRIENT SOLUTIONS

Beryllium content in nutrient solution (ppm)	Beryllium content in dry plant tissue (ppm)			
	Roots	Stems	Leaves	Fruit
0.0	0	0	0	0
0.5	271	4	8	1
1.0	431	6	16	2
2.0	668	15	34	4
3.0	978	18	42	5
5.0	1076	24	70	6

Source: Adapted from Romney, Childress, and Alexander, 1962, Table 1, p. 786. Reprinted by permission of the publisher.

when beryllium is in the soluble state. Soils can bind beryllium, affecting uptake. The ^{7}Be isotope was strongly adsorbed by Hanford and Vina soil and by bentonite, but not kaolinite. Magnesium, barium, or calcium did not replace beryllium from Hanford and Vina soils or bentonite; these ions, however, did compete effectively with beryllium for sorption sites in soil, but not in bentonite. Additions of 40 ppm beryllium to soil slightly stimulated grass and kale growth, whereas additions of 40 ppm beryllium to quartz produced severe inhibition (Williams and Le Riche, 1968). Again, most of the beryllium may have been rendered unavailable for plant uptake because of soil binding. Beryllium (40 ppm added in soluble form) is more available in acid soils (pH 5.8) than in slightly alkaline soils (7.5 to 8.0) (Williams and Le Riche, 1968). Although no uptake data were presented to support this, beryllium significantly reduced yield only in the acid soil (Table 4.3).

TABLE 4.3 YIELD OF KALE WITH BERYLLIUM APPLIED AT DIFFERENT STAGES OF GROWTH

Soil	Soil pH	Soluble beryllium added (ppm)	Mean yield per pot of fresh matter (g)	
			Application to large plants	Application to seedlings
Bedfordshire	5.8	0.0	84.5	110.0
		40.0	72.8	61.9
Hertfordshire	7.5	0.0	167.9	264.4
		40.0	164.4	300.3[a]
Lincolnshire	7.5	0.0	173.1	288.7
		40.0	172.9	285.8
Rothamsted	8.0	0.0	172.1	253.5
		40.0	175.7	258.4

[a] $P \leq 0.05$.

Source: Adapted from Williams and Le Riche, 1968, Table 2, p. 321. Reprinted by permission of the publisher.

4.2.2 Translocation

Beryllium is not readily translocated from roots to shoots. Table 4.2 illustrates that most beryllium absorbed from the nutrient solution is retained within the root, a small amount is translocated to the foliage, and still smaller amounts are found in the stems and fruit. A similar result was obtained when ^{7}Be was supplied for 30 days to bean, barley, sunflower, and tomato plants (Romney and Childress, 1965). Over 95% of the activity was found in the roots of each species. Williams and Le Riche (1968) report low values (7.3 ppm) for the beryllium content in laminae from leaves of kale grown in nutrient solutions with 10 ppm beryllium.

Apparently, though, beryllium may be transported in large amounts to some plants. Oustrin et al. (1967) found that in maize supplemented with beryllium sulfate, the highest beryllium concentration (8.1 to 15.7 ppm) was in the reproductive apparatus. Shoots (2.4 to 2.8 ppm) and roots (2.7 to 2.8 ppm) contained less. Bingham and Steucek (1972) reported that 46% of the ^{7}Be applied to leaves was absorbed and of that amount, 4% was transported out of the leaves, presumably through the phloem. They state that the mobility of beryllium in phloem is similar to that of magnesium and greater than that of the other alkaline earth elements.

4.2.3 Distribution

There are few data on the beryllium concentration in crop and non-crop plants. Table 4.4 lists the concentrations reported by several researchers. Values are in parts per million ash weight; therefore, for comparison with uptake data and data on toxic levels presented later, usually given as parts per million dry weight, the ash values should be divided by ten to give approximate parts per million dry weight estimates. Where examined, plant concentrations of beryllium are apparently quite low. Shacklette (1965) states that beryllium is found in only.3.1% of vascular plant samples (Table 4.3). By examining the concentration of many elements in bryophytes and vascular plants, he further concluded that beryllium is present in higher concentrations in vascular plants than in bryophytes, although the percent of occurrence was greater in bryophytes (26.3%). This last observation, he suggests, may be due to higher surface contamination of the bryophytes.

4.2.4 Bioelimination

No data were found suggesting that beryllium is actively eliminated from living plant material. As with all elements that produce toxic symptoms — signifying buildup of that element in the tissue — the death and abscission of the affected organ eliminates a certain portion of beryllium from the plant.

4.3 EFFECTS

Beryllium typically inhibits plant growth; however, in some cases it has been reported to stimulate growth. Pea roots increased in fresh weight when exposed to 10^{-3} *M* ($\sim$9 ppm) for 20 hr (Gerola and Gilardi, 1955). The data of Mazé and Mazé Fils (1939) also suggest that beryllium may give a slight growth increase in corn. The results of Hoagland (1952*a*) with tomatoes in nutrient culture showed that, at pH greater than 9, beryllium at 2×10^{-4} *M* slightly decreased growth when magnesium was at adequate levels. When magnesium was low, 2×10^{-4} *M* beryllium increased growth above normal-level magnesium controls. But, beryllium at concentrations of 4×10^{-4} *M* led to death (dark green leaves and deep purple stems), regardless of the magnesium concentration; also, at pH values lower than 9, beryllium was always inhibitory.

Growth inhibition is the more frequent observation in experiments with beryllium. Romney and Childress (1965) observed that 2 ppm beryllium

TABLE 4.4. BERYLLIUM CONTENT IN PLANTS

Plant	Beryllium content (ppm)		Reference
	Ash weight	Average	
Algae rockweeds	0.02-0.54	0.28	Meehan and Smythe, 1967[a]
Algae rockweeds		0.01	Meehan and Smythe, 1967
Lichens			
Parmelia saxatilis *Xanthoria parietina*	0-"trace"		Fearon, 1935
Bryophytes		6[b]	Shacklette, 1965
"Vegetation"		<2	Cannon, 1960
Vascular plants		9[b]	
"Angiosperms"	0.15-2.00	0.69	Meehan and Smythe, 1967
Acacia	0.10-1.06	0.46	Meehan and Smythe, 1967
Field lupine seeds		0.02	Meehan and Smythe, 1967
Artemisia and other plants	0.01-0.50		Mursaliev, 1969
Zostera	0.28-1.12	0.60	Meehan and Smythe, 1967
Beans		0.01	Meehan and Smythe, 1967
Cabbage		0.03	Meehan and Smythe, 1967
Nuts			
Peanut kernels	0.01-0.03	0.02	Meehan and Smythe, 1967
Peanut shells	0.41-0.52	0.47	Meehan and Smythe, 1967
Almond kernels		0.01	Meehan and Smythe, 1967
Almond shells		0.01	Meehan and Smythe, 1967
Tomatoes		0.02	Meehan and Smythe, 1967

[a]Sampling sites were in New South Wales, Australia.

[b]Average value for the samples containing beryllium.

or more in nutrient solution reduced fresh weight in peas, soybeans, lettuce, and alfalfa. Amounts of beryllium greater than 4% of the cation exchange capacity of soil reduced yield of beans, wheat, and ladino clover. Root damage (browning, cessation of elongation, and stubby rootlets) was observed within one week after addition of 4 ppm beryllium to nutrient cultures. No chlorosis occurred, but foliage did turn a darker blue green.

The symptoms of beryllium toxicity are not distinct. Table 4.5 summarizes the beryllium toxicity data and symptoms observed (Yopp, Schmid, and Holst, 1974). In nutrient solution, toxicity is observed at concentrations of about 1 ppm. This leads to extensive beryllium concentration in roots (Section 4.2.1) and subsequent root damage. Leaves may turn a darker green and stunted growth may occur. Obviously there is a lack of data on toxic concentrations and symptoms in a wide variety of species.

TABLE 4.5. PHYTOTOXIC EFFECT EXERTED BY BERYLLIUM ON PLANTS OF ECONOMIC IMPORTANCE IN ILLINOIS

Plant type	Growing medium	Minimum phytotoxic concentration	Plant part affected	Developmental status	Symptomatology
Alfalfa	Defined nutrient	2.0 ppm	Roots, shoots	Entire	Foliage turns dark green
Barley	Defined nutrient	2.0 ppm	Roots, shoots	Entire	Stunted roots and leaves; roots turn brown and form profuse secondary growth; foliage turns dark green as dwarfing intensifies
Bean, bush	Defined soil type	4% of total cation exchange capacity	Shoots	Early seedling	Stunted growth; early flowering and senescence
Bean, bush	Defined nutrient	0.5 ppm	Shoots, roots	Entire	Stunting and browning of roots; secondary root production
Clover, ladino	Defined soil type	4% of total cation exchange capacity	Shoots	Early seedling	Stunted growth; early flowering and senescence
Corn	Defined soil type	1.0 ppm	Roots, shoots	Entire	General growth retardation
Lettuce	Defined nutrient	2.0 ppm	Shoots, roots	Entire	Stunting and browning of roots; general growth depression
Pea, green	Defined nutrient	2.0 ppm	Shoots, roots	Entire	Stunting and browning of roots; general growth depression
Soybean	Defined nutrient	2.0 ppm	Roots, shoots	Entire	Stunted roots and leaves; roots turn brown and form profuse secondary growth; foliage turns dark green as dwarfing intensifies
Tomato	Defined nutrient	0.5 ppm	Shoots, roots	Entire	General growth depression
Tomato	Defined nutrient	2.0 ppm	Shoots, roots	Entire	Stunting and browning of roots; general growth depression
Wheat	Defined nutrient	2.0 ppm	Roots, shoots	Entire	Stunted roots and leaves; roots turn brown and form profuse secondary growth; foliage turns dark green as dwarfing intensifies

Source: Adapted from Yopp, Schmid, and Holst, 1974, Table 1, pp. 44-45. Data collected from several sources. Reprinted by permission of the publisher.

Yellow mottling occurred in rough lemon seedlings exposed to 2 ppm beryllium in nutrient culture (Haas, 1932). Other citrus showed injury at concentrations above 2.73 ppm; root injury, leaf mottle, and burn were prevalent. Beryllium increased plant uptake of phosphorus, decreased uptake of calcium into roots and shoots, and decreased uptake of magnesium into roots (Romney and Childress, 1965).

The effects of beryllium on specific enzymes have not been well studied. Hoagland (1952*b*) observed in vitro that beryllium inhibited plant phosphatase but not hexokinase. Magnesium, calcium, zinc, and manganese did not reverse the inhibition. Wallace and Romney (1966) found that beryllium slightly inhibited phosphoenolpyruvate carboxylase and the ribose-5-phosphate carboxylation sequence (hexose-monophosphate shunt). Beryllium did not substitute for either the magnesium or manganese requirements of these enzymes. Slight stimulation of activity with 1 micromole of $Be(NO_3)_2$ per milliliter ($\sim$9 ppm beryllium) occurred in the presence of manganese. Inhibition of ribose-5-phosphate carboxylation sequence was about 70% for 90 ppm beryllium.

There are several miscellaneous observations on the effects of beryllium. There are two reports on the effects of beryllium on respiration. Holst, Schmid, and Yopp (1975) observed that the respiration of excised barley roots was unaffected by 1000 ppm beryllium even after 18 hr. The toxic level of beryllium to barley is about 1 ppm. Oxygen consumption decreased 7.85% in apical roots of pea seedlings treated with 10^{-3} *M* beryllium (about 9 ppm) (Gerola and Gilardi, 1955). However, fresh weight and free and organically bound phosphorus increased in the roots.

Tobacco grown in 1 ppm beryllium nutrient solution contained a significantly higher nicotine content than controls; fresh weight increased slightly (1.8% above control) and tissue beryllium concentration ranged from 15 ppb to 75 ppm (Tso, Sorokin, and Engelhaupt, 1973). Beryllium significantly increased the percentage of chromosomal aberrations induced in barley by ethyl methanesulfonate (Degraeve, 1971).

SECTION 4

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SECTION 5

BIOLOGICAL ASPECTS IN WILD AND DOMESTIC ANIMALS

5.1 SUMMARY

Beryllium uptake by fish varies directly with the beryllium content of the surrounding medium and, to a lesser extent, with exposure time. Most of the beryllium may be found in the gastrointestinal tract. Beryllium is more toxic to freshwater fish than lead chloride but less toxic than pentachlorophenol, cyanide, selenium, or arsenic compounds. Toxicity to fish increases as water hardness decreases, and it appears to be a result of the effects of beryllium on vital organs, rather than a function of total beryllium uptake. Preexposure to low levels of beryllium can increase tolerance to very high concentrations at a later time.

Beryllium inhibits regeneration of amputated limbs in some amphibians. The mechanism of inhibition is unknown, but it is thought to be related to the influence of beryllium on enzyme activity. Histological changes in limb stumps treated with beryllium include skin constriction, absence of blastemata formation, and atypical tissue differentiation.

Embryonic development can also be inhibited by beryllium. Embryos treated with beryllium have exhibited exogastrulation, spina bifida, axial defects, hemicephaly, and abnormal development of the central nervous system.

Beryllium is eliminated rapidly by dairy cattle, with 68% of an oral dose being excreted within 83 hr. More than 90% of the oral dose is excreted in feces; milk contains less than 0.002%. The small amount of absorbed beryllium is deposited in the liver, kidney, and skeletal system.

5.2 AQUATIC ORGANISMS

5.2.1 Metabolism: Uptake and Distribution

Radioberyllium studies (Slonim and Damm, 1972; Slonim and Slonim, 1973) have shown that beryllium uptake by guppies (*Lebistes reticulatus*) varies directly with the beryllium concentration of the surrounding medium and, to a lesser extent, with the length of exposure. Total uptake is not influenced by fish age, $NaHCO_3$-buffered solutions, or water hardness. Slonim and Damm (1972) found that beryllium levels in guppies are highest in the gastrointestinal tract, followed by kidneys and ovaries. The lowest amounts were found about equally in gills, liver, brain, heart, eye, and spleen.

5.2.2 Effects

5.2.2.1 Physiological Effects — Beryllium solutions inhibit regeneration of amputated limbs in some amphibians. The mechanism of inhibition is not known, but it may be related to the influence of beryllium on the activity

of enzymes, particularly those which are magnesium dependent (Tepper, 1972). In salamander (*Ambystoma opacum* and *A. maculatum*) larvae, the extent of inhibition is related to larval size and to the amount of limb amputated (Thornton, 1949). A solution of *N*/7 beryllium nitrate applied to the limb stump of small larvae completely inhibited regeneration regardless of the amputation site. In larger larvae, the treatment inhibited regeneration following amputation through the upper arm, but not the forearm. Regeneration of the forearm was suppressed by tripling the beryllium dose.

Inhibition of regenerating *Ambystoma* limbs occurs only if beryllium is present in the limb tissues at the time of amputation (Thornton, 1950). The beryllium reaction was localized within 0.5 mm of the wound surface, and removing the beryllium-inhibited stump stimulated normal regeneration. Histological changes in limb stumps following beryllium treatment included skin constrictions, absence of blastemata formation, and atypical tissue differentiation (Thornton, 1951).

Scheuing and Singer (1957) amputated the upper arm of adult newts (*Triturus* sp.) and infused the regenerating blastemata with 0.001 to 0.1 *M* beryllium nitrate (Table 5.1). Concentrations of 0.1 *M* or more suppressed regeneration and caused tissue destruction, while concentrations of 0.001 *M* had no effect. Bone, muscle, and fibrous connective tissue were the most sensitive to beryllium; nerves and epidermis were the most resistant. Suppressed regeneration in newt limbs treated with beryllium has also been reported by Carlson (1970).

The development of eggs and tadpoles of the common frog (*Rana temporaria*) was retarded by beryllium nitrate treatment (Needham, 1941) (Table 5.2). The early gastrula period was especially susceptible. Overall detrimental effects included exogastrulation, spina bifida, axial defects, hemicephaly, and microcephaly. The same treatment retarded regeneration of newt limbs and tails and halves of planaria (*Polycelius nigra*).

Beryllium sulfate acts as a mitotic suppressor in snail (*Lymnaea* sp.) embryos (Bose, 1973). After treatment with 50 µg/ml beryllium sulfate, uncleared egg masses developed to the trochophore stage but did not develop normally after this stage. When a solution containing 100 µg/ml beryllium sulfate was used, normal development was scarce, and at 500 µg/ml mortality was quite high.

An injection of 0.02 cc of a 5% suspension of beryllium hydroxide into unamputated newt forelimbs resulted in the formation of accessory limbs (Breedis, 1952). Carlson (1970), however, was unable to produce accessory limbs after injecting the same species with *N*/7 beryllium nitrate.

5.2.2.2 Toxic Effects — Tarzwell and Henderson (1960) determined the 96-hr median tolerance limit (TL_{50}) of fathead minnows and bluegill to several metals (Table 5.3). Beryllium was the most toxic of the less common metals tested; for fathead minnows the TL_{50} in soft water was 0.2 mg/liter. Beryllium sulfate toxicity to freshwater fish was tested by Cardwell et al. (1976) (Tables 5.4, 5.5, and 5.6). Beryllium was more toxic than lead chloride but less toxic than pentachlorophenol, cyanide, selenium, or arsenic compounds. Susceptibility to beryllium decreased in the following

TABLE 5.1. EFFECTS OF $Be(NO_3)_2 \cdot 3H_2O$ ON REGENERATION OF LIMBS IN ADULT *TRITURUS*

Molar concentration of beryllium ion	Infusion time (hr)[a]	Age of regenerate (days after amputation)	Stage of regeneration	Number of animals	Resorption after infusion			Regeneration after infusion	
					Extensive[b]	Slight[c]	Absent	Absent[d]	Present[e]
0.1	5	12	Early bud	20	20	0	0	20	0
	3	12	Early bud	5	5	0	0	5	0
	1-2	12	Early bud	20	16	2	1	18	2
0.015	4	3	Wound healing	5	0	4	1	4	1
		6	Wound healing	8	3	2	5	5	3
		9	Wound healing	6	0	6	0	6	0
		10	Very early bud	8	0	3	5	3	5
		12	Early bud	15	3	8	4	11	4
		13-15	Medium bud	8	0	8	0	8	0
		16-18	Late bud	8	0	8	0	8	0
0.01	2-6	12	Early bud	76	5	21	50	26	50
0.0075	4	12	Early bud	5	0	0	5	0	5
0.001	4	12	Early bud	7	0	0	7	0	7

[a] Infusion at the rate of 0.0013 ml/hr.

[b] Both regenerate and stump involved. In most instances, resorption set in after an initial delay of seven to ten days; in other cases it was earlier.

[c] Confined to regenerate.

[d] Includes those showing resorption.

[e] Most regenerates were heteromorphic, and some appeared only after a delay of one to two months.

Source: Scheuing and Singer, 1957, Table 1, p. 303. Reprinted by permission of the publisher.

TABLE 5.2. RESULTS OF TREATMENT OF FROG EMBRYOS WITH BERYLLIUM
(3-hr treatment except as stated)

Stage	*N*/3 beryllium	*N*/7 beryllium	*N*/14 beryllium
2-4 cells		30% mortality, abnormalities slight	
20 cells		80% mortality, survivors abnormal	
64 cells	High mortality	High mortality	High mortality
128 cells	No mortality, few abnormals among survivors	No mortality, normal survivors	No mortality, normal survivors
Mid blastula	80% mortality, axial abnormals among survivors	Low mortality, 80% axial abnormals among survivors	No effect
Late blastula	100% mortality in 2 hr, survivors abnormal[a]	50% mortality, all survivors abnormal	Low mortality, few abnormalities
Late blastula (jelly removed)		1 hr, 95% mortality; 1/2 hr, 30% mortality	
Early gastrula	All dead neurula, great abnormalities	All dead tail bud stages, great abnormalities	All dead late tail bud stage, abnormalities
Mid gastrula	2 hr, low mortality, great abnormality	2 hr, no mortality, all abnormal; 3 hr, 90% mortality	2 hr, no mortality, few abnormalities
Late gastrula	Dead before hatching, axial abnormalities	Low mortality, 20% axial abnormalities	48 hr, no effect
Neurula	No mortality, abnormalities slight	No mortality, abnormalities slight	No mortality, all normal
Tail bud hatching	No effect	No effect	No effect
External gills	4 hr, fatal	4 hr, not fatal	14 hr, fatal
Internal gills	2 1/2 hr, fatal	5-6 hr, fatal	6-8 hr, fatal

[a]See Needham, 1941.

Source: Needham, 1941, Table 1, p. 61. Reprinted by permission of the publisher.

order: fathead minnow, flagfish fry, goldfish, brook trout, and channel catfish. The median lethal concentrations determined by Cardwell et al. (1976) were 1.5 to 7 times higher than those of Slonim (1973) and Slonim and Slonim (1973). The difference is probably due to the intermittent flow system with toxicant renewal used by Cardwell et al. (1976) as opposed to the static bioassays of the latter authors.

Beryllium toxicity to fish increases as water hardness decreases. This is partially due to the increased buffering capacity of hard water and the antagonism of calcium to beryllium (Slonim, 1973). Also, beryllium may penetrate to vital organs more readily in soft water. Beryllium toxicity is not a function of total beryllium absorbed as much as it is

TABLE 5.3. THE 96-HR MEDIAN TOLERANCE LIMITS (TL_{50}) OF SEVERAL LESS COMMON METALS TO FISH (mg/liter of metal ion)

Compound	TL_{50}			
	Fathead minnow		Bluegill	
	Soft water	Hard water	Soft water	Hard water
Antimony potassium tartrate ($2KSbOC_4H_4O_6 \cdot H_2O$)	20	12		
Antimony trichloride ($SBCl_3$)	9	17		
Antimony trioxide (Sb_2O_3)	>80	>80		
Beryllium chloride ($BeCl_2$)	0.15	15		
Beryllium nitrate [$Be(NO_3)_2 \cdot 3H_2O$]	0.15	20		
Beryllium sulfate ($BeSO_4 \cdot 4H_2O$)	0.2	11	1.3	12
Cadmium chloride ($CdCl_2 \cdot 2.5H_2O$)	0.9	5		
Copper sulfate ($CuSO_4 \cdot 5H_2O$)	0.05	1.4	0.2	10
Lead chloride ($PbCl_2$)	2.4	>75		
Molybdic anhydride (MoO_3)	70	370		
Nickelous chloride ($NiCl_2 \cdot 6H_2O$)	4	24		
Titanium sulfate [$Ti_2(SO_4)_3$]	8.2	120		
Uranyl acetate [$UO_2(C_2H_3O_2)_2 \cdot 2H_2O$]	3.7			
Uranyl nitrate [$UO_2(NO_3)_2 \cdot 6H_2O$]	3.1			
Uranyl sulfate ($UO_2SO_4 \cdot 3H_2O$)	2.8	135		
Vanadium pentoxide (V_2O_5)	13	55		
Vanadyl sulfate ($VOSO_4$)	4.8	30	6	55
Zirconium oxychloride ($ZrOCl_2 \cdot 6H_2O$)	18	240	15	270
Zirconium sulfate [$Zr(SO_4)_2 \cdot 4H_2O$]	14	145		

Source: Adapted from Tarzwell and Henderson, 1960, Table 1, p. 12. Reprinted by permission of the publisher.

TABLE 5.4. MEDIAN LETHAL CONCENTRATIONS (LC_{50}) AND MEDIAN LETHAL TIMES (LT_{50}) FOR FLAGFISH FRY EXPOSED TO BERYLLIUM SULFATE

Group	Median response estimate	95% confidence limits
	96-hr LC_{50} (mg/liter $BeSO_4$)	
I	46.3	43.9-48.8
II	41.1	37.2-45.3
III	41.1	38.4-44.0
	LT_{50} (hr) for 47.8 ± 2.2 mg/liter $BeSO_4$	
I	41.3	10.5-162.1
II	74.8	61.1-91.4
III	55.4	48.3-63.5

Source: Adapted from Cardwell et al., 1976, Appendix Table 41, p. 115.

TABLE 5.5. MEDIAN LETHAL CONCENTRATIONS (LC_{50}) FOR JUVENILE GOLDFISH EXPOSED TO BERYLLIUM SULFATE

Exposure time (hr)	LC_{50}[a] (mg/liter)	95% confidence limits for LC_{50} (mg/liter)
96	55.9	49.0-63.7
120	49.3	44.0-55.3
168	48.3	42.7-54.6
186	46.5	40.8-53.1
216	41.6	37.2-46.6
240	38.4	34.4-43.0

[a] As $BeSO_4$.

Source: Adapted from Cardwell et al., 1976, Appendix Table 42, p. 116.

TABLE 5.6. MEDIAN LETHAL CONCENTRATIONS (LC_{50}) FOR JUVENILE FATHEAD MINNOWS EXPOSED TO BERYLLIUM SULFATE[a]

Exposure time (hr)	LC_{50}[b] (mg/liter)	95% confidence limits for LC_{50} (mg/liter)
92	40.2	27.6-58.5
96	37.9	27.5-52.3
121	30.8	29.4-32.3
164	27.7	26.1-29.3
192	27.4	25.9-29.0
283	26.1	24.4-27.9
336	25.4	23.9-27.0

[a] At a concentration of 47.8 mg/liter, the median lethal time was 75 hr.

[b] As $BeSO_4$.

Source: Adapted from Cardwell et al., 1976, Appendix Table 40, p. 114.

the result of the effect of beryllium on a particular organ. Slonim (1973) and Slonim and Slonim (1973) found that beryllium sulfate was 100 times as toxic to the common guppy (*Lebistes reticulatus*) in soft water as in hard water (Table 5.7). A 55-fold difference in toxicity between soft and hard water was reported for fathead minnows by Tarzwell and Henderson (1960). Acute toxicity of beryllium sulfate to salamander larvae was investigated by Slonim and Ray (1975) in a static bioassay (Table 5.8). The 96-hr TL_{50} was 20.3 mg/liter in hard water and 0.19 mg/liter in soft water.

TABLE 5.7. MEDIAN TOLERANCE LIMITS OF GUPPIES TO BERYLLIUM SULFATE IN WATER OF VARYING HARDNESS

Water hardness (mg/liter)	Median tolerance limit (mg/liter Be^{2+})		
	24 hr	48 hr	96 hr
400	22.0	22.0	20.0
275	14.0	13.7	13.7
150	6.8	6.8	6.1
22	>2	0.32	0.16

Source: Slonim and Slonim, 1973, Table 2, p. 297. Reprinted by permission of the publisher.

TABLE 5.8. MEDIAN TOLERANCE LIMITS OF SALAMANDERS TO BERYLLIUM SULFATE BY GRAPHIC INTERPOLATION (in mg beryllium per liter)

Bioassay	Hard water			Soft water		
	24 hr	48 hr	96 hr	24 hr	48 hr	96 hr
A	31.5	31.5	31.5	23.7	4.21	3.15
B	31.5	31.5	31.5	8.83	4.21	3.15
C	18.2	18.2	18.2	>10	>10	8.02
D	21.2	18.2	18.2	>10	>10	8.32
Mean	25.60	24.85	24.85	>12	>7	5.65

Source: Slonim and Ray, 1975, Table 2, p. 309. Reprinted by permission of the publisher.

Slonim (1973) showed that preexposure conditioning of guppies to low levels of beryllium sulfate significantly increased their tolerance to very toxic concentrations (Table 5.9). Each concentration in the first column of Table 5.9 represents a 20-fold increase in the beryllium level at which the fish were preexposed. These data indicate that fish may be able to develop a limited tolerance to beryllium.

TABLE 5.9. ACUTE TOXICITY OF $BeSO_4$ SOLUTIONS TO UNEXPOSED AND PREVIOUSLY EXPOSED GUPPIES

		Unexposed fish		Preexposed fish		
Be^{2+} concentration (mg/liter)	Water hardness (mg/liter)	Number of fish	Mean survival time (hr)	Preexposure period (days)	Number of fish	Mean survival time (hr)
2[a]	24	10	28.9	14	8	41.2
5	24	10	27.3	14	8	41.8
100	400	10	8.38	14	10	9.37
200	400	10	3.13	14	10	3.98
4	80	10	11.8	159	7	18.7
14	80	10	17.6	159	4	10.3
40	80	10	8.90	159	3	8.92
20	200	10	19.2	159	7	20.6
80	200	10	7.43	159	6	6.55

[a]Concentrations are a 20-fold increase over preexposure concentration.

Source: Slonim, 1973, Table V, p. 2117. Reprinted by permission of the publisher.

5.3 BIRDS

5.3.1 Metabolism: Uptake and Distribution

Data concerning uptake and distribution of beryllium in birds are very limited. This is not unusual, considering that beryllium is not commonly found in significant concentrations in the natural environment (Section 7.3). In the only study located, Baker et al. (1976) found no beryllium in liver, muscle, or brain tissue of seven species of waterfowl sampled in New York. The limit of detection was 1.0 μg/g.

5.3.2 Effects

5.3.2.1 Physiological Effects — Palmer (1972) found that beryllium sulfate inhibits embryonic development of chicks (*Gallus gallus*). In this study, eggs were injected with beryllium sulfate 24 to 48 hr after incubation and sacrificed between 60 and 216 hr after incubation. Injections early in embryonic development affected heart formation; injections at later stages produced deformities in the intestinal tract and calcification of bone structures. Limb bud formation was affected, and the central nervous system developed abnormally. Compression of the brain and eyes as a result

of defective skull growth probably caused the central nervous system abnormalities. Inhibition of the alkaline phosphatase system was suggested as a possible explanation for most of the abnormalities resulting from beryllium injections.

5.3.2.2 Toxic Effects — Chanh and Maciotta-Lapoujade (1966) studied the effects of beryllium sulfate on pigeons and chickens. The beryllium was administered as a profusion timed at flow rates to produce death of the subject in about 60 min. Chickens were about three times as sensitive as pigeons, with the lethal doses averaging 0.56 ± 0.15 g/kg and 1.49 ± 0.16 g/kg, respectively.

5.4 MAMMALS

5.4.1 Metabolism

5.4.1.1 Uptake and Distribution — Radioberyllium distribution in cows was studied by Mullen et al. (1972). A lactating dairy cow received an intravenous injection of 2.7 mCi of $^{7}BeCl_2$ and was sacrificed after 119 hr (Table 5.10). In addition, three calves were given oral doses of 0.76, 0.70, and 1.3 mCi $^{7}BeCl_2$ and were sacrificed at 71, 140, and 454 hr, respectively (Table 5.11). The results indicate that the liver, kidney, and skeletal system of cows accumulate most of the absorbed beryllium.

5.4.1.2 Elimination — Mullen et al. (1972) found that radioberyllium administered orally to cows was rapidly eliminated. Sixty-eight percent of the administered dose was excreted in the feces, urine, and milk pathways in the first 83 hr. Feces contained over 90% of the excreted beryllium, while milk contained less than 0.002%. The biological half-time as measured in milk was 19 hr. A cow injected intravenously with a single dose of beryllium excreted 18% of the total dose within 91 hr; 96% was in urine, 2% in feces, and the remainder in milk. The half-time of beryllium in this case as measured in milk was 40 hr. Thus, any health hazard to man resulting from ingestion of dairy products under normal circumstances appears to be slight.

5.4.2 Physiological and Toxic Effects

No data regarding the physiological or toxic effects of beryllium on mammals other than those used as human models were located in the literature. For a discussion of beryllium effects on mammals used as models, see Section 6.

TABLE 5.10. RECOVERY OF ^{7}Be IN TISSUES OF A COW 119 HOURS AFTER INTRAVENOUS ADMINISTRATION
(The values listed are percentages of dose, decay-corrected to time of administration.)

Tissue	Concentration (%/kg)	Recovery[a] (% in organ or compartment)
Abomasal contents	0.023	0.080
Abomasal tissue	0.067	0.161
Adrenal	0.098	0.004
Blood	0.020	9.44
Bone (compact)	0.304	21.6
Brain	0.002	<0.001
Eye	0.031	<0.001
Fat	0.005	0.682
Gall bladder	0.058	0.006
Hair, no skin	<0.001	<0.001
Heart	0.041	0.143
Kidney	1.03	1.41
Large intestine contents	0.016	0.131
Large intestine tissue	0.020	0.054
Liver	1.15	14.0
Lung	0.054	0.483
Muscle	0.007	1.43
Omasal contents	<0.001	<0.001
Omasal tissue	0.083	0.083
Ovaries	0.141	0.005
Pancreas	0.160	0.054
Parotid	0.072	0.001
Reticulum tissue	0.017	0.033
Rib	0.354	
Rumen reticulum contents	<0.001	0.007
Rumen tissue	0.023	0.261
Skin with hair	0.013	0.470
Skin, no hair	0.019	
Small intestine contents	0.005	0.023
Small intestine tissue	0.028	0.213
Spleen	0.100	0.133
Thyroid	0.045	<0.001
Total		50.9

[a]An estimated 49% of the administered dose had been excreted by the time of sacrifice.

Source: Mullen et al., 1972, Table 1, p. 20. Reprinted by permission of the publisher.

TABLE 5.11. RECOVERY OF ^{7}Be IN TISSUES OF THREE CALVES AFTER A SINGLE ORAL DOSE
(The values listed are percentages of dose, decay-corrected to time of administration.)

Tissue	Concentration (%/kg)			Recovery (% in organ or compartment)		
	71 hr[a]	190 hr[a]	454 hr[a]	71 hr[a]	190 hr[a]	454 hr[a]
Abomasal contents	0.275	0.002	<0.001	0.145	0.002	<0.001
Abomasal tissue	0.045	<0.001	0.001	0.013	0.003	<0.001
Adrenal	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Blood	<0.001	0.002	<0.001	<0.001	0.012	0.001
Bone (compact)	<0.001	<0.001	0.020	<0.001	0.142	0.264
Brain	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Eye	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fat	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
Gall bladder with bile	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Hair	0.299	0.022	0.012			
Heart	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Kidney	0.004	0.006	0.002	0.002	0.002	<0.001
Large intestine contents	0.083	0.034	0.003	0.381	0.015	<0.001
Large intestine tissue	0.010	0.001	<0.001	0.012	<0.001	<0.001
Liver	0.002	0.003	0.001	0.006	0.005	0.006
Lung	<0.001	<0.001	<0.001	<0.001	0.001	<0.001
Muscle	<0.001	<0.001	<0.001	0.026	<0.001	<0.001
Omasal contents	1.85	0.052	0.005	0.099	0.010	0.001
Omasal tissue	0.101	0.001	<0.001	0.038	<0.001	<0.001
Pancreas	0.001	0.001	0.002	0.001	<0.001	<0.001
Parotid	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Reticulum tissue	0.048	0.016	<0.001	0.012	0.004	<0.001
Rib	0.011	0.025	0.004			
Rumen reticulum contents	0.110	0.036	<0.001	4.72	0.141	<0.001
Rumen tissue	0.100	0.019	<0.001	0.124	0.020	<0.001
Skin with hair	0.029	0.011	0.001	0.285	0.061	0.007
Skin, no hair	0.002	<0.001	<0.001			
Small intestine contents	0.150	0.016	0.002	0.167	0.028	0.003
Small intestine tissue	0.022	0.034	0.004	0.074	0.062	0.011
Spleen	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Thyroid	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Thymus			<0.001			<0.001
Total				6.10	0.508	0.295

[a]Time after administration when calf was sacrificed.

Source: Mullen et al., 1972, Table 2, p. 21. Reprinted by permission of the publisher.

SECTION 5

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SECTION 6

BIOLOGICAL ASPECTS IN HUMANS

6.1 SUMMARY

Beryllium exposure is primarily an industrial problem, but it is to some extent an environmental problem in the vicinity of industrial sources. The metal enters the body by inhalation, ingestion, and skin absorption, with inhalation the primary route. Once inhaled, beryllium is retained in the lungs and slowly mobilized from the lungs into the blood. Beryllium is minimally absorbed from the gastrointestinal tract; consequently, ingested beryllium presents little health hazard.

The metal is transported through the body by the blood and lymph and then deposited in various tissues. Beryllium storage is of long duration, especially in pulmonary lymph nodes and bone. The skeleton is the ultimate storage site. Since little beryllium is absorbed from the digestive tract, that which accumulates in body tissue is from inhalation.

Urinary excretion is an indication of past exposure, and the excretion rate is related to the solubility of the inhaled compound. Ingested soluble beryllium is only slightly absorbed through the intestines; hence, urinary excretion of ingested beryllium is minimal. Ingested beryllium is excreted primarily in the feces.

Persons exposed to beryllium by inhalation can develop a respiratory disease, which may be either acute or chronic in form. Dermatitis and/or skin ulcers may develop as a result of direct skin contact. These effects have been caused by the metal and its compounds; no detectable illness has been caused by beryl ore. The standard for exposure of industrial workers to beryllium is 2 μg of total airborne particulate beryllium per cubic meter of air over an 8-hr work day. In neighborhoods near beryllium sources, 0.01 μg of beryllium per cubic meter as an average monthly concentration is permissible.

Acute beryllium disease is defined as that lasting less than one year. Disease severity appears dependent on amount of exposure, toxicity and concentration of the compound, and individual susceptibility. When exposed to large amounts of soluble salts, the disease can be rapidly fatal. The acute disease may be expressed as contact or allergic dermatitis, skin ulcers, conjunctivitis, and respiratory effects. Respiratory effects appear as nasopharyngitis, tracheobronchitis, and acute chemical pneumonitis. Experimentally, liver necrosis, central nervous system changes, and anemia have been produced by beryllium exposure in laboratory animals.

Chronic beryllium disease usually arises from inhalation exposure, although in a few cases, direct skin contact was stated as the cause. The chronic form can have a latent period of more than 20 years, is progressive in severity. and is a systemic disease. In some instances, the acute

form may progress to the chronic form. The dose level necessary to induce the chronic form is not known. It has been proposed that disease onset involves some form of stress, such as surgery, infection, or pregnancy, which leads to altered adrenal function resulting in beryllium translocation to organs critical in systemic disease initiation. This form of the disease is not always easily diagnosed because of lack of specific clinical criteria. A history of beryllium exposure must be established before diagnosis can be confirmed. A common cause of death is from the complication of cor pulmonale with myocardial decomposition. Besides occurring among industrial workers, chronic beryllium disease has been found among residents in the near vicinity of a plant, usually within 3/4 mile of the point source. These cases arise from inhalation of airborne beryllium carried from the plant or from direct contact from handling workers' contaminated clothing. Treatment consists of steroid and adrenocorticotropic hormone administration.

Experimental findings show that some beryllium compounds are carcinogenic in experimental animals. Pulmonary cancer has been produced in rats and monkeys by inhalation exposure. Sarcomas have also been induced in rabbits by injection. Cancer has been reported among beryllium workers; however, a direct relationship has not been proven. Epidemiological studies have failed to show a correlation between exposure and cancer incidence.

6.2 METABOLISM

6.2.1 Uptake and Absorption

Beryllium enters the body by inhalation, ingestion, and skin absorption. Inhalation is the primary route of uptake, with beryllium gaining access to the body through the lungs (Berry, Osgood, and St. John, 1974). Following inhalation exposure, the metal is retained in the lungs and slowly mobilized (Beliles, 1975) by absorption from the lungs into the blood.

Following intratracheal injection, $^{7}BeSO_4$ in trace amounts was either retained in the lungs of rats for long periods or mobilized after 16 days; ^{7}Be citrate (a soluble, nonionizing complex) was completely mobilized after four days (Van Cleave and Kaylor, 1955). In the amount of 10 Ci, $^{7}BeCl_2$ showed a pulmonary halftime of 20 days; 18% of the dose accumulated in the bones in 147 days (Kuznetsov, Matveev, and Suntsov, 1974).

Uptake by ingestion and skin absorption contributes negligible amounts of beryllium to the total body burden. Skin absorption of beryllium, even through repeated or prolonged contact, adds only insignificant quantities to the body (Berry, Osgood, and St. John, 1974). Resorption of trace levels of $^{7}BeCl_2$ through rat tail, with subsequent systemic distribution was reported by Petzow and Zorn (1974). Absorption of beryllium from the gastrointestinal tract is minimal (Schroeder and Mitchener, 1975*b*). The amount of beryllium absorbed from the stomachs of guinea pigs given beryllium sulfate orally was small and varied from animal to animal (Hyslop et al., 1943). Most of a daily dose of 0.6 to 6.6 μg of beryllium ingested by rats passed through the gastrointestinal tract unabsorbed because it was precipitated

in the intestines as the phosphate (Reeves, 1965). Furchner, Richmond, and London (1973) showed that less than 1% of an oral dose of ^{7}Be was absorbed from the gut of mice, rats, monkeys, and dogs.

6.2.2 Transport, Distribution, and Accumulation

6.2.2.1 Transport — Beryllium is transported by the blood and lymph from the site of deposition; in humans this site is usually the lungs and occasionally the skin. In vitro studies using artificial serum indicated the beryllium forms transported by the body fluids were the orthophosphate and hydroxide (Reeves and Vorwald, 1961). The principal form is thought to be the orthophosphate colloid, with 2% to 3% as the colloidal oxide (Stokinger, 1972). Following intravenous injection of beryllium sulfate in rats, the circulating beryllium was almost completely in the plasma (Vacher and Stoner, 1968*b*). The beryllium existed in two forms: a small fraction of small molecular size representing a diffusible form associated with the plasma organic acids and the bigger fraction in aggregates of beryllium phosphate. These aggregates were weakly bound to plasma protein, probably α-globulin.

Beryllium transport is governed by the physiochemical state of the metal rather than by differences in species metabolism (Stokinger, 1972). A significant portion of beryllium transported in blood is carried to the skeleton, irrespective of route of administration or beryllium form. The ionic form of the remaining beryllium goes directly to the kidney, whereas the colloidal form is carried first to the liver.

6.2.2.2 Distribution and Accumulation — Beryllium in the body is ultimately stored in bone. The distribution of beryllium in patients with beryllium disease has not been well defined and does not necessarily duplicate that in animals, since humans appear to retain a body burden of beryllium longer than the life of experimental animals (Tepper, Hardy, and Chamberlin, 1961). It must also be realized that the presence of beryllium in tissue indicates exposure but does not indicate the presence of beryllium disease (Tepper, 1972*a*).

6.2.2.2.1 Tissue concentration — Beryllium storage in tissues is of long duration, especially in pulmonary lymph nodes and bone (Stokinger, 1972), with the ultimate site of beryllium storage in the skeleton (Van Cleave and Kaylor, 1955). In human pulmonary tissue, amounts less than 2 μg/100 g (dry weight basis) are not regarded as indicative of occupational exposure; in exposed workers, the levels may be as high as several mg/100 g. Small quantities of beryllium which pass the kidney are diffusible and are associated with organic acids such as citrate (Tepper, 1972*a*).

Analysis of lung tissue for beryllium has shown that there is no correlation between beryllium concentration and intensity of disease (Preuss, 1975). Therefore, great variability exists in beryllium distribution in different stages of beryllium disease. This variability is demonstrated in Table 6.1; within an individual there is little correlation between beryllium concentration levels in various tissues. From these data it appears that beryllium is distributed throughout the lung. Sumino et al. (1975) reported low beryllium values of 0.01 to 0.03 μg per gram of wet tissue in the lungs of Japanese.

TABLE 6.1. TISSUE DISTRIBUTION OF BERYLLIUM
(in micrograms per 100 g of tissue)

Organ	Case 7	Case 77	Case 176	Case 178	Case 286	Case 314	Case 439	Case 467	Case 610	Case 617
Lung		12.0	3.8				18.4			
							15.2			
Right upper lobe										
Apical segment				0.1	0.2					
Posterior segment								440		
Anterior segment					16.0					
Right middle lobe										
Lateral segment					9.5					
Medial segment										
Right lower lobe										
Apical segment					0.1					
Medial basal segment					7.9					
Anterior basal segment					0.6					
Lateral basal segment										
Left upper lobe										
Anterior segment	3.2									0.6
Apical-posterior segment	1.6				0.7	8.8				0.1
					28.2					
Superior lingular segment	2.1				0.1	18.0				0.7
Inferior lingular segment	1.2					4.6				1.2
Left lower lobe				0.3						
Apical segment	1.8				15.4	11.6				0.3
						7.0				
Anterior basal segment	2.4				9.8	4.5				0.1
Lateral basal segment	2.5				4.0	4.8				0.3
Posterior basal segment	2.5					12.0				0.9
Lymph node										
Hilar	10.2		4.2					600	18.0	8.4
	1.1									
Tracheobronchial				0.5						
Liver		8.4	0.1	0.1		0.1	2.0	1.2		
Kidney		27.2	0.0	0.2		0.1	0.2	1.3	0.01	
Spleen		4.3	0.3	0.1		0.1	0.4		0.02	
Myocardium				0.1		<0.02			0.0	
Brain								0.3		
Bone		13.5					0.4		2.5	

Source: Tepper, Hardy, and Chamberlin, 1961, Table IX, p. 137. Reprinted by permission of the publisher.

The distribution of beryllium in rats, as in humans, is a function of the physicochemical state of the metal. Soluble beryllium reaches the skeleton rapidly, whereas colloidal beryllium is first transported to the reticuloendothelial organs (Klemperer, Martin, and Liddy, 1952). Table 6.2 shows the distribution of both acidic and neutral beryllium salts following intravenous injection into albino rats. Colloidal beryllium that was deposited in the liver was mobilized gradually and redistributed to bone tissue or excreted (Table 6.3).

The skeleton, liver, and kidney are the organs in rats which accumulate and retain beryllium to a significant degree. Twenty-four hours following intramuscular injection into rats of 20 μCi of ^{7}Be as $BeCl_2$, 40% of the dose was absorbed from the injection site (Crowley, Hamilton, and Scott, 1949). The bone accumulated 29% of this absorbed amount and maintained this level to the 64th day. The liver and kidney initially contained a comparable level, which decreased tenfold by the 64th day. These organs which had the highest levels of beryllium are the target organs of the toxicological action of stable beryllium when administered parenterally in a soluble form. Cikrt and Bencko (1975) and Scott, Neuman, and

TABLE 6.2. DISTRIBUTION OF INTRAVENOUSLY INJECTED BERYLLIUM COMPOUNDS 24 HOURS FOLLOWING INJECTION IN RATS[a]

Material injected	Bone plus marrow[b] (%)	Liver (%)	Spleen (%)	Number of rats
$^{7}BeCl_2$, carrier-free, pH 2	43 (±6)	4 (±0.4)	0.1 (±0.1)	10
$^{7}BeCl_2$ plus 0.15 micromole of $^{9}BeCl_2$, pH 2	53 (±8)	3 (±0.5)	0.05 (±0.05)	2
$^{7}BeCl_2$ plus 1 micromole of $^{9}BeCl_2$, pH 2	37 (±2)	25 (±3)	1 (±0)	2
$^{7}BeCl_2$, carrier-free, pH 6	17 (±4)	59 (±5)	1.7 (±0.7)	9
$^{7}BeCl_2$ plus 1 micromole of $^{9}BeCl_2$, pH 6[c]	13 (±0)	44 (±1)	6 (±2)	2
$^{7}BeCl_2$ plus 0.15 micromole of $^{9}BeCl_2$, plus 3 micromoles of citrate, pH 6	50 (±6)	2 (±1)	0.15 (±0.05)	2
$^{7}Be(OH)_2$ plus 0.3 micromole of $^{9}Be(OH)_2$[d]	15[b] (±3)	61 (±8)	8 (±3)	5

[a]The values represent the average percent of the total recovered radioactivity per organ. Figures in parentheses refer to the average deviation.

[b]Femoral marrow, counted separately, had minimal activity except following the injection of $Be(OH)_2$. In this case the activity corresponded to 7% per gram of tissue.

[c]The acid solution was neutralized and injected immediately before any visible precipitation occurred.

[d]Precipitated with NH_3, coagulated by heating, washed by high-speed centrifugation, and suspended in saline.

Source: Adapted from Klemperer, Martin, and Liddy, 1952, Table I, p. 150. Reprinted by permission of the publisher.

Allen (1950) also found that the skeleton, liver, kidneys, and spleen of both rats and rabbits contained the highest amounts of beryllium (^{7}Be as $^{7}BeCl_2$ or $^{7}BeSO_4$) administered intravenously. Rat liver and kidneys contained 23.6% and 1.6%, respectively, of a given dose at 0.025 mg of beryllium per kilogram of body weight; and 32.3% and 1.3%, respectively, of a dose at 0.25 mg of beryllium per kilogram of body weight (Cikrt and Bencko, 1975). The distribution of ^{7}Be differs when it is administered intravenously as the isotope alone or with a carrier (Scott, Neuman, and Allen, 1950). The beryllium administered as the isotope alone is taken up rapidly in the bone, because the small amount of beryllium present is soluble in the body fluids. However, when administration is with the isotope plus carrier, some of the beryllium is insoluble and is excreted to a greater extent than the soluble beryllium.

TABLE 6.3. REDISTRIBUTION AND EXCRETION OF BERYLLIUM IN RATS

State of ^{7}Be injected	Bone plus marrow (%)			Liver (%)			Excretion (%)			Number of rats[a]	
	1 day	21 days	Difference	1 day	21 days	Difference	1 day	21 days	Difference	1 day	21 days
Carrier-free, pH 2	46	48	+2	4	0.4	-3.6	39	49	+11	4	4
$^{7}Be(OH)_2$ + 3 micromoles $^{9}Be(OH)_2$	15	28	+13	61	23	-38	8	31	+23	5	5
Carrier-free, pH 6	12	22[b]	+12	66	36[b]	-30	17	35[b]	+18	4	3[b]

[a]Animals sacrificed after seven days.

[b]Femoral marrow, counted separately, had minimal activity except following the injection of $Be(OH)_2$. In this case the activity corresponded to 7% per gram of tissue.

Source: Adapted from Klemperer, Martin, and Liddy, 1952, Table II, p. 151. Reprinted by permission of the publisher.

Furchner, Richmond, and London (1973) reported that only the bone and muscle of rats contained significant levels of beryllium 71 days after intraperitoneal injection. These tissues retained more than 1% of the dose ($^{7}BeCl_2$) (Table 6.4). Rats and mice were also given $^{7}BeCl_2$ by intravenous injection and oral administration. More ^{7}Be was retained from intravenous than from intraperitoneal injection, and almost no ^{7}Be was retained from oral administration.

Reeves (1965) fed beryllium sulfate in drinking water to Sprague-Dawley male rats for up to 24 weeks. Most of the beryllium was unabsorbed in the gastrointestinal tract. Distribution levels were, therefore, highest in the gastrointestinal tract and contents; levels in the skeleton were also high, followed by levels in the blood and liver (Table 6.5). On the average, 80% of the ingested beryllium was recovered, primarily in the feces.

Rats exposed by inhalation to $BeSO_4$ aerosol (34.25 μg of beryllium per cubic meter, a concentration that produces lung cancer in 100% of the animals) showed decreasing accumulation rates in the lungs and tracheobronchial lymph nodes during continuous exposure (Reeves and Vorwald, 1967). Pulmonary beryllium levels increased until 36 weeks of exposure, when the concentration plateaued, possibly because equilibrium was established between deposition and clearance (Figure 6.1). Males accumulated higher beryllium levels than females because of their larger size. Lymph node levels of beryllium peaked concurrently with the plateau of pulmonary beryllium levels and then decreased after the 52nd week (Figure 6.2). Females had lower beryllium levels in lymph nodes because of less efficient utilization of this clearance route. The metal was systemically distributed from the nodes and possibly incorporated into the nuclei of certain pulmonary cells. Beryllium incorporation into the cell nuclei may be involved in the development of pulmonary carcinogenesis in rats.

Intravenously injected $^{7}BeSO_4$ also has an affinity for cell nuclei in rats (Witschi and Aldridge, 1968). For in vivo studies, 63% of the dose (83 micromoles of ^{7}Be as $^{7}BeSO_4$ per kilogram of body weight) was found in the nuclear fraction of the liver which, however, also contained cell debris. Beryllium was also taken up by lysosomes. Table 6.6 shows that as the beryllium dose injected into rats increased to toxic levels, the amount of beryllium in the nuclear fraction of the liver homogenate increased. This increase in concentration does not appear in the other homogenate fractions. Kharlamova and Potapova (1968) also showed that beryllium was distributed in all cellular fractions but was mainly concentrated in the nuclei.

6.2.2.2.2 Blood levels — Data concerning blood beryllium concentrations are available only for experimental animals. Beryllium levels in rat blood decrease with time following administration. At 0.25 day after intraperitoneal injection, the blood contained 0.47% of the dose and 0.82% of the body burden; at 71 days, 0.044% of the dose and 0.26% of the body burden was retained in the blood (Furchner, Richmond, and London, 1973). Following intravenous administration of $^{7}BeCl_2$, rat blood levels of the metal also decreased rapidly with time (Cikrt and Bencko, 1975). A disproportionately high beryllium level of 4.47% (2.2 μg of Be^{2+} per milliliter of

TABLE 6.4. DISTRIBUTION OF ^{7}Be IN RATS AFTER INTRAPERITONEAL INJECTION

Tissue	Effective retention						
	0.25 day	1 day	3 days	6 days	10 days	30 days	71 days
Whole body	57.04-100.0[a] (386)[b]	55.86-100.0 (362)	52.47-100.0 (327)	46.83-100.0 (366)	44.83-100.0 (390)	30.17-100.0 (380)	16.86-100.0 (394)
Carcass	40.26-70.58 (225)	42.11-75.38 (211)	41.45-79.00 (210)	39.32-80.85 (213)	38.89-87.79 (229)	28.65-94.96 (225)	16.49-97.80 (236)
Pelt	2.09-3.66 (74.8)	1.70-3.04 (73.4)	1.40-2.67 (67.2)	0.98-2.02 (70.5)	0.73-1.65 (70.5)	0.31-1.03 (68.6)	0.16-0.95 (71.4)
Liver	4.38-7.68 (13.9)	4.40-7.88 (13.2)	4.16-7.93 (12.3)	2.49-5.12 (13.4)	1.30-2.93 (15.0)	0.31-1.03 (13.9)	0.12-0.71 (13.9)
Gut	3.84-6.73 (32.1)	3.10-5.55 (24.5)	2.44-4.65 (26.2)	1.57-3.32 (28.6)	1.13-2.55 (31.5)	0.39-1.29 (29.4)	0.13-0.77 (30.5)
Remains	1.17-2.05 (19.4)	1.13-2.02 (21.3)	0.96-1.83 (17.5)	0.75-1.54 (20.3)	0.64-1.44 (24.4)	0.24-0.80 (22.7)	0.17-1.01 (20.5)
Kidney	3.54-6.21 (2.94)	3.18-5.69 (2.63)	1.62-3.09 (2.58)	0.85-1.75 (2.88)	0.51-1.15 (2.89)	0.12-0.40 (3.00)	0.10-0.59 (3.19)
Spleen	0.16-0.28 (0.85)	0.17-0.30 (0.89)	0.18-0.34 (0.82)	0.17-0.35 (0.90)	0.13-0.29 (0.79)	0.18-0.60 (0.85)	0.12-0.71 (0.93)
Lung	0.26-0.46 (2.53)	0.17-0.30 (2.28)	0.28-0.53 (3.47)	0.14-0.29 (2.72)	0.10-0.23 (2.22)	0.082-0.27 (2.70)	0.092-0.54 (3.06)
Testis	0.07-0.12 (3.72)	0.08-0.14 (3.68)	0.08-0.15 (3.71)	0.05-0.10 (3.60)	0.05-0.11 (3.79)	0.041-0.14 (4.01)	0.12-0.71 (4.06)
Bone	34.72-60.87 (26.26)	36.0-164.46 (25.66)	36.62-69.79 (26.61)	34.63-71.21 (24.29)	36.00-81.26 (26.45)	25.93-85.95 (27.57)	15.65-92.82 (27.64)
Muscle	5.03-8.82 (189)	3.31-5.92 (186)	3.38-6.44 (184)	3.77-7.75 (188)	2.32-5.24 (203)	2.01-6.66 (198)	6.64-9.73 (208)

[a]The first value is percent of injected dose, and the second is percent of body burden.

[b]Wet tissue weight (in grams).

Source: Adapted from Furchner, Richmond, and London, 1973, Table 3, p. 297. Reprinted by permission of the publisher.

TABLE 6.5. TISSUE DISTRIBUTION AND BALANCE OF BERYLLIUM IN RATS FED $BeSO_4$ IN DRINKING WATER

Beryllium source and tissues analyzed	0.16 µg of Be^{2+} per liter of drinking water				1.66 µg of Be^{2+} per liter of drinking water			
	No. 1 (6 weeks)	No. 2 (12 weeks)	No. 3 (18 weeks)	No. 4 (24 weeks)	No. 1 (6 weeks)	No. 2 (12 weeks)	No. 3 (18 weeks)	No.4 (24 weeks)
Consumption	157.90[a]	446.00	639.50	862.90	2069.60	3891.10	5830.80	10,344.60
Spillage	4.10	20.00	13.00	9.70	125.00	26.00	18.00	180.00
Total intake	153.80	426.00	626.00	853.20	1944.60	3865.10	5812.80	10.164.60
Heart	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.00
Lungs	0.01	0.00	0.00	0.00	0.04	0.01	0.02	0.01
Kidneys	0.01	0.01	0.00	0.01	0.10	0.00	0.01	0.01
Spleen	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00
Gastrointestinal tract	2.00	3.00	3.60	3.10		14.00	12.00	21.00
Skeleton[b]	1.08	1.24	2.86	0.77	0.73	1.94	0.95	1.12
Blood[b]	0.00	0.16	0.15	0.16	0.15	0.27	0.14	0.14
Liver[b]	0.20		0.00	0.07	0.01	0.02	0.16	0.04
Total body[c]	3.32	4.42	6.61	4.12	1.05	16.26	13.28	22.32
Body + output		324.02	536.81	744.92	1163.85	3199.86	5297.48	7407.12
Percent recovery[d]	78	76	86	87	60	83	91	73

[a] Micrograms.

[b] From aliquot.

[c] Sum of organs analyzed.

[d] Body + output x 100 per intake.

Source: Adapted from Reeves, 1965, Table 2, p. 212. Reprinted by permission of the publisher.

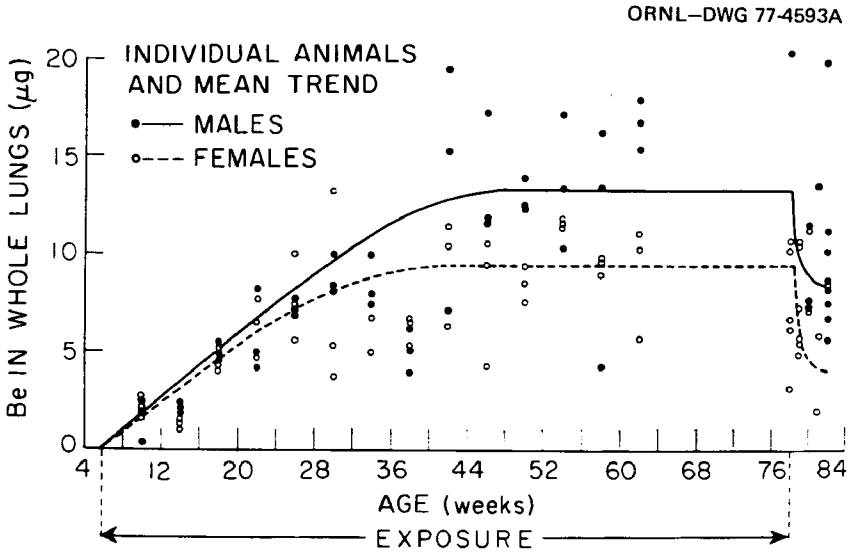

Figure 6.1. Pulmonary beryllium levels during and after $BeSO_4$ exposure in rats. Source: Adapted from Reeves and Vorwald, 1967, Chart 1, p. 447. Reprinted by permission of the publisher.

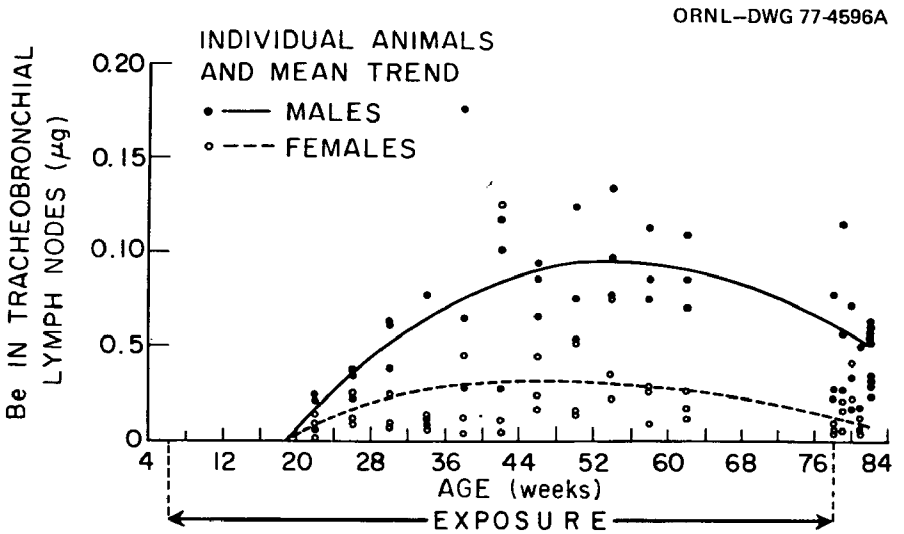

Figure 6.2. Tracheobronchial lymph node beryllium levels during and after $BeSO_4$ exposure in rats. Source: Adapted from Reeves and Vorwald, 1967, Chart 2, p. 448. Reprinted by permission of the publisher.

blood) of a dose of 0.25 mg of Be^{2+} per kilogram of body weight was found 5 hr after injection, compared with 0.02% (0.0013 μg of Be^{2+} per milliliter of blood) of a 0.025-mg/kg dose. The differences, however, became balanced with respect to dose 24 hr following injection and at 48 hr. The rapid and great decrease between 5 and 24 hr corresponded to an increase in beryllium content in the liver. One day after intramuscular injection of carrier-free ^{7}Be into rats, blood beryllium concentrations reached 1.99% of the dose (Crowley, Hamilton, and Scott, 1949). Again, beryllium levels decreased with time until at 64 days following administration the concentration was 0.24% of the dose.

TABLE 6.6. BERYLLIUM ($^{7}BeSO_4$) IN SUBCELLULAR FRACTIONS FROM RAT LIVER AFTER VARIOUS DOSES INJECTED INTRAVENOUSLY

Dose of $BeSO_4$ (micromoles/kg)	Specific activity[a] of beryllium (% of that of homogenate)				
	Nuclear	Heavy mitochondrial	Light mitochondrial	Microsomal	Supernatant
0.083	44	110	260	70	160
0.83	141	98	295	93	125
1.8	98				
8.3	98		315		
28	280	200	310	57	35
83	340	175	204	63	
110	410				20

[a]Specific activity expressed as nanomoles of beryllium per milligram of protein.

Source: Adapted from Witschi and Aldridge, 1968, Table 5, p. 814. Reprinted by permission of the publisher.

Disappearance of beryllium from rat blood is influenced by the size of the dose. Beryllium in the 10^{-9} g range, injected intravenously, disappeared more slowly from circulation than carrier-free ^{7}Be (in 10^{-18} g range) (Vacher and Stoner, 1968*a*). Beryllium removal from blood was biphasic, with the second phase having an inverse relationship between dose and removal rate.

The difference between the clearance rate from blood of carrier-free beryllium and beryllium plus carrier is demonstrated in Figure 6.3 (Scott, Neuman, and Allen, 1950). Eighty percent of the carrier-free beryllium dose injected intravenously into rabbits was removed within 7 min; after 2 hr the concentration in the blood remained constant. The disapperance of beryllium plus carrier was constant over the time period.

6.2.2.2.3 Placental transfer — No data were found concerning placental transfer of beryllium.

6.2.3 Elimination

6.2.3.1 Biological Half-life — Data on the biological half-life of beryllium are limited to experimental animals exposed by injection, inhalation, intravenous injection, and intraperitoneal injection. Furchner, Richmond, and London (1973) administered carrier-free ^{7}Be as the chloride intravenously, intraperitoneally, and orally to mice, rats, monkeys, and dogs. The half times in days are shown in Table 6.7; the whole-body activity following parenteral injection for all species consisted of three components. By calculation the biological half-lives after intravenous injection were 1210, 890, 1770, and 1270 days in mice, rats, monkeys, and dogs, respectively. In an inhalation study using high-fired beryllium oxide, Sanders and Cannon (1975) estimated a biological half-life for beryllium oxide in rats of about six months.

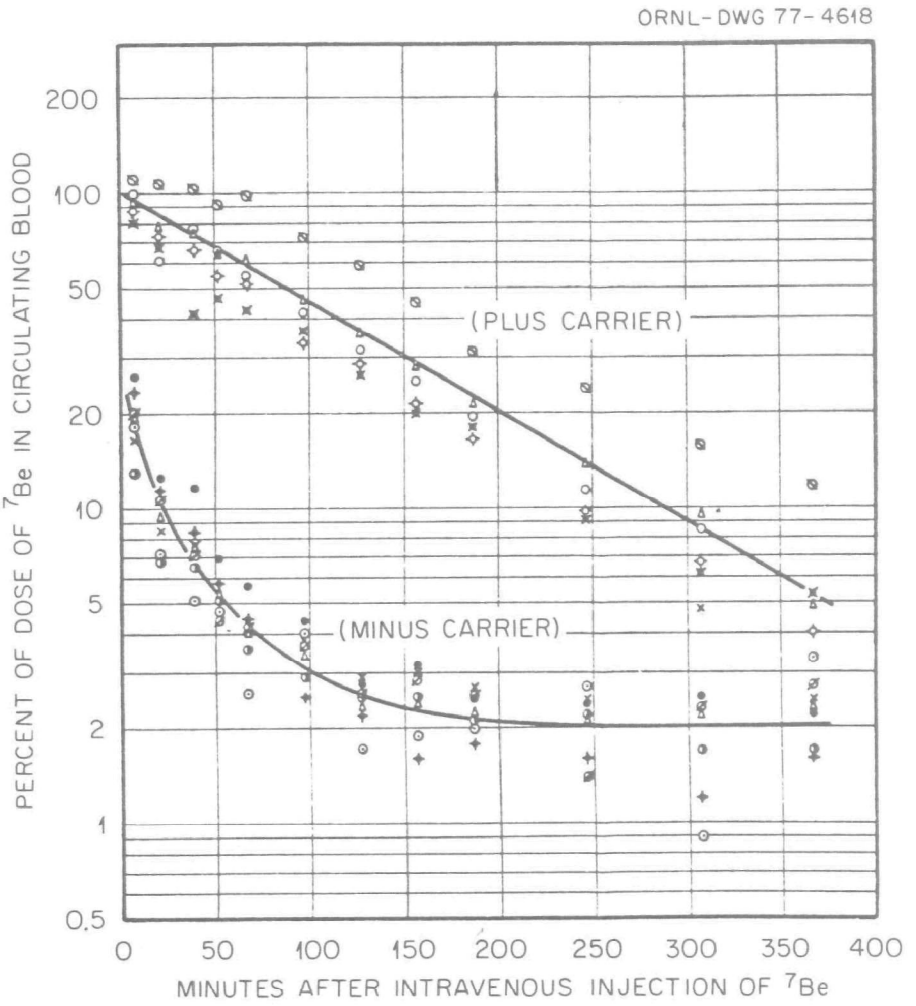

Figure 6.3. The blood clearance of ^{7}Be injected with and without a carrier in rabbits. Symbols indicate data from individual animals. Source: Adapted from Scott, Neuman, and Allen, 1950, Figure 2, p. 295. Reprinted by permission of the publisher.

6.2.3.2 Urinary Excretion — Urinary analysis for beryllium in humans has been studied as a means of diagnosing beryllium disease. Urinary excretion of beryllium indicates past exposure but is not necessarily associated with the disease (Tepper, Hardy, and Chamberlin, 1961); conversely, the disease may exist even though beryllium excretion is not detectable. The excretion rate appears related to the solubility of the inhaled compound (Browning, 1969).

Negative assays do not represent the absence of beryllium disease; 20 to 38 diseased patients had negative beryllium urinary assays (Stoeckle, Hardy, and Weber, 1969). The beryllium levels in those patients with positive tests ranged from 0.01 to 1.0 μg of beryllium per liter of urine. There was no correlation between urinary beryllium levels and time after exposure (Figure 6.4). Lieben, Dattoli, and Vought (1966) analyzed the

TABLE 6.7. EFFECTIVE RETENTION OF ^{7}Be IN MICE, RATS, MONKEYS, AND DOGS

Species	Half time (days)		
	Component 1	Component 2	Component 3
		Oral	
Mice	0.1	0.5	
Rats	0.3		
Monkeys	0.3	3.7	
Dogs	0.4	2.7	
		Intraperitoneal	
Mice	0.3	6.3	51.6
Rats	0.3	8.5	51.1
		Intravenous	
Mice	0.2	8.2	51.7
Rats	0.2	6.9	50.9
Monkeys	0.3	21.7	52.4
Dogs	0.5	9.7	51.8

Source: Adapted from Furchner, Richmond, and London, 1973, Table 2, p. 294. Reprinted by permission of the publisher.

urinary beryllium content from beryllium refinery workers, beryllium manufacturing workers, and residents in the immediate neighborhood of a beryllium refinery. As shown in Table 6.8, there was no correlation between presence or concentration of urinary beryllium and length of exposure to the metal. However, it should be noted that except for cases 40 and 41, none of the residents of the immediate area had positive tests. The two positive cases were persons drinking water from a well contaminated with beryllium. Of the ten beryllium disease cases and suspected cases, only one had a positive urine beryllium test.

Ingested soluble beryllium is only slightly absorbed through the intestines; hence, urinary excretion is minimal. Rats given 6.6 or 66 μg of beryllium per day (as $BeSO_4$) in drinking water excreted in the urine less than 1% of the fecal excretion level (Reeves, 1965). Urinary excretion peaked sharply at one or two days following administration, peaked again during the third week, and finally declined to trace levels (Figure 6.5).

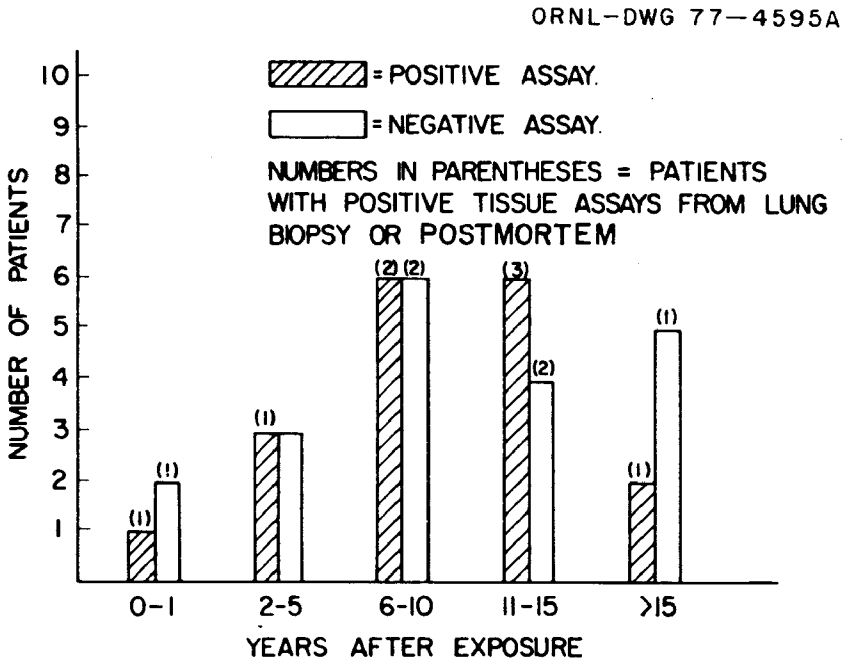

Figure 6.4. Occurrence of urinary beryllium excretion by years from last exposure in 38 patients. Source: Stoeckle, Hardy, and Weber, 1969, Figure 8, p. 554.

In rats the route of beryllium administration determines the route of excretion. Fecal excretion is the major route following oral dosing, while urinary excretion is the major route after intramuscular and intravenous injection. Rats injected intramuscularly with carrier-free ^{7}Be (1 cc of isotonic solution with 1400 counts per second of ^{7}Be per rat) excreted 15.0%, 14.6%, 24.4%, and 44.0% of the dose in the urine at 1, 4, 16, and 64 days, respectively, after administration (Crowley, Hamilton, and Scott, 1949). Scott, Neuman, and Allen (1950) reported that urinary excretion of beryllium following intravenous injection in rats and rabbits was the major excretory route. Rats given carrier-free ^{7}Be (9.3×10^{-11} g per kilogram of body weight) excreted 38.8% of the dose during the first 24 hr, whereas those animals receiving ^{7}Be plus a carrier, such as $BeSO_4$ (1.5×10^{-4} g of ^{7}Be per kilogram of rat), excreted only 24.2% of the dose. Rabbits likewise excreted more beryllium, 27.3% of the dose, during the first 6 hr when given carrier-free Be than when given beryllium with the carrier, for which they excreted only 12.2% of the dose. The difference may result from a more rapid mobilization of beryllium from the liver, spleen, and bone marrow and a slower mobilization from the bone, since the bone was the only tissue with large amounts of beryllium when only the isotope was injected.

Differences in excretory route following various means of administration are further demonstrated in Table 6.9. In all species — mice, rats, monkeys, and dogs — urinary beryllium excretion was the major route following parenterally or intravenously administered beryllium (Furchner, Richmond, and London, 1973). Later, the amount lost in the feces was about equal to that lost in the urine. That which was excreted in the urine following oral dosage is almost negligible.

TABLE 6.8. BERYLLIUM WORKERS AND NEIGHBORHOOD RESIDENTS

Case number	Type of work	Length of exposure	Berylliosis	Micrograms of beryllium per liter of urine	Residence distance from plant (miles)
1	Billet worker	7 years (1941-48)	Yes	0.26 0.23 (6 months later)	
2	Furnace workers	9 years (1941-50)	No	0.07	
3	Rolling department	7 years (1948-55)	No	Negative	
4	Oxide department, rolling mill	3 months (1942)	Yes	Negative	
5	Oxide department	5 months (1942)	Yes	Negative	
6	Alloy worker	6 months (1942)	?	Negative	
7	Laboratory worker	4 months (1944)	Yes	Negative	
8	Machine repair	1 year (1962)	No	Negative	
9	Ventilating contractor	Intermittently, 2 months total (1955-56)	Dermatitis	Negative	
10	Sheet metal worker	Intermittently, 2 months total (1963)	Dermatitis	Negative	
11	Mold manufacture	For 9 years prior to 1962	No	0.155 0.052 Negative	
12	Mold manufacture	For 4 years prior to 1962	No	0.0017 Negative Negative	
13	Machine repair	For 1 year prior to 1962	No	Negative Negative	
14	Mold manufacture	For 10 years prior to 1962	No	Negative	
15	Mold manufacture	For 12 years prior to 1962	No	Negative	
16	Grinding of alloy parts	3 years intermittently prior to 1963	No	Negative	
17	Grinding of alloy parts	3 years intermittently prior to 1963	No	Negative	
20	Neighborhood resident		Yes	Negative	1 1/2
21	Neighborhood resident		Yes	Negative	1/2
22	Neighborhood resident		Yes	Negative	5
23	Neighborhood resident		?	Negative	3
24	Neighborhood resident		?	Negative	1/4
25	Neighborhood resident		?	Negative	4
26	Neighborhood resident		?	Negative	1
27	Neighborhood resident		No	Negative	1/4
28	Neighborhood resident		?	Negative	5
29	Neighborhood resident		Dermatitis	Negative	1/2
30	Neighborhood resident			Negative	1/4
31	Neighborhood resident			Negative	1/4
32	Neighborhood resident			Negative	1/4
33	Neighborhood resident			Negative	1/4
34	Neighborhood resident			Negative	1/4
35	Neighborhood resident			Negative	1/4
36	Neighborhood resident			Negative	1/4
37	Neighborhood resident			Negative	1/4
38	Neighborhood resident			Negative	1/4
39	Neighborhood resident			Negative	1/4
40	Neighborhood resident			0.019	1/4
41	Neighborhood resident			0.057	1/4

Source: Adapted from Lieben, Dattoli, and Vought, 1966, Tables 1-5, pp.332-333. Reprinted by permission of the publisher.

Dose levels appear to influence the amount of beryllium excreted in urine following intravenous injections into rats. These urinary beryllium levels seem to correspond to beryllium blood plasma levels (Cikrt and Bencko, 1975). A dose of 0.025 mg of Be^{2+} per kilogram of body weight produced a higher urine beryllium level (21.1% of dose) than did a dose of 0.25 mg of Be^{2+} per kilogram of body weight (4.2% of dose). However, the higher dose gave the maximum excretion level after 5 to 24 hr. During this rise in renal excretion there was a corresponding decrease in beryllium blood plasma levels.

6.2.3.3 Fecal Excretion — As previously mentioned, oral administration of beryllium leads to greater excretion in feces than in urine. Sixty to ninety percent of the total oral dose of 6.6 μg of beryllium per day and of 66.6 μg of beryllium per day was found in the feces of rats (Reeves, 1965). The daily fecal beryllium excretion peaked during the first week of exposure, decreased, and finally plateaued below the intake level during the ninth week of exposure. Greater fecal beryllium excretion following oral dosing also occurs in mice, monkeys, and dogs. Furchner, Richmond,

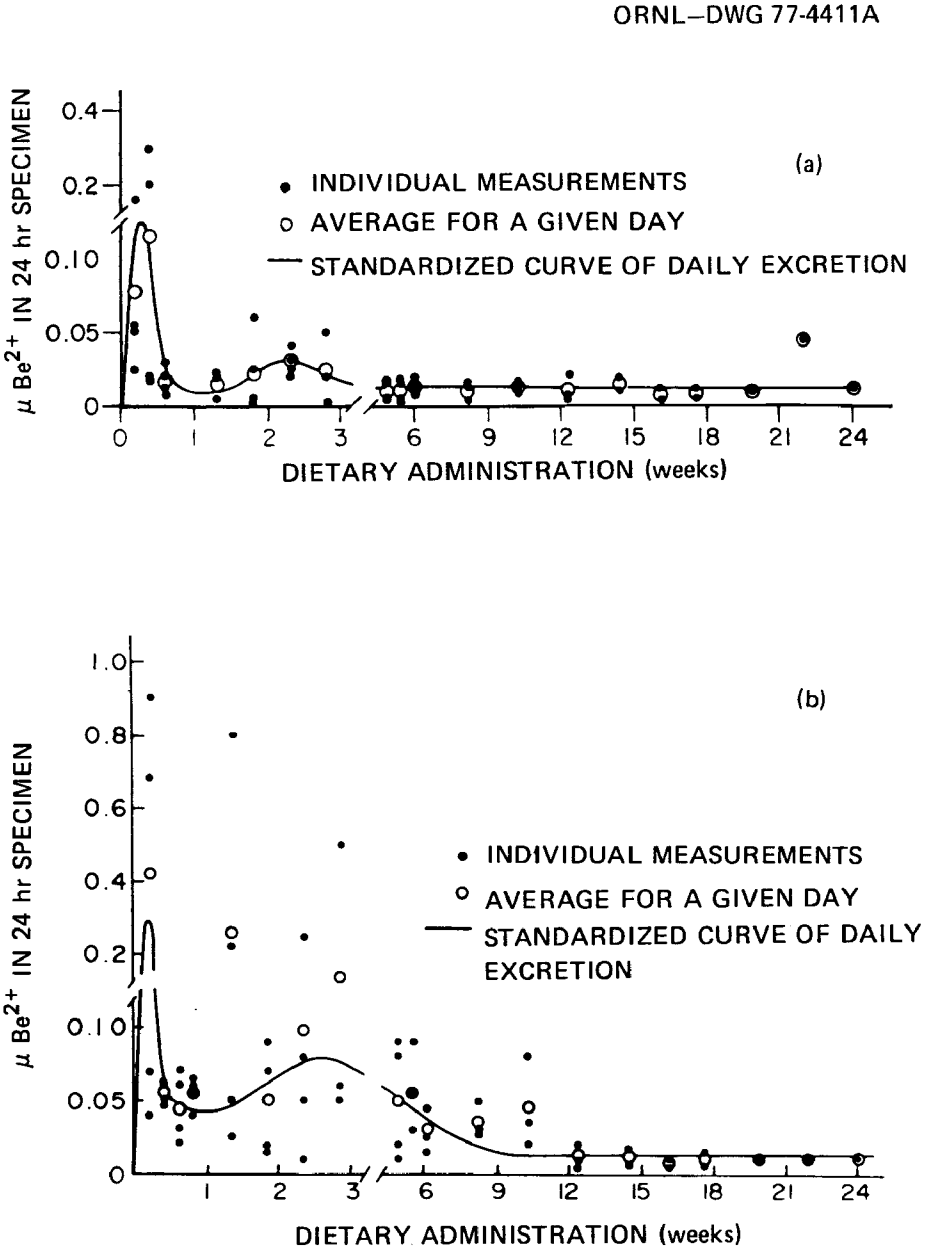

Figure 6.5. Urinary excretion of beryllium in male rats fed Be^{2+} in drinking water. (*a*) 0.16 mg of beryllium per liter of drinking water, (*b*) 1.66 mg of beryllium per liter of drinking water. Source: Adapted from Reeves, Arch. Environ. Health, August, Vol. 11, Figures 5 and 6, p. 211, Copyright 1965, American Medical Association. Reprinted by permission of the publisher.

TABLE 6.9. EXCRETION OF ^{7}BE

Species	Urinary/fecal ratio			
	1 day	2 days	7 days	14 days
		Oral		
Mice	0.0024			
Rats	0.0008	0.0021		
Monkeys	0.0029	0.0460		
Dogs		0.0035		
		Intravenous		
Mice	3.50	0.51	0.96	1.17
Rats	21.35	1.00	1.51	1.44
Monkeys	4.03	0.52		
Dogs	48.61	4.62		
		Intraperitoneal		
Mice	3.21	0.80	0.91	0.62
Rats	10.20	0.75	1.13	1.17
		Chronic oral (56 days)[a]		
	0.0044			

[a]Average urinary/fecal ratio during 56 days.

Source: Adapted from Furchner, Richmond, and London, 1973, Table 4, p. 298. Reprinted by permission of the publisher.

and London (1973) reported that mice excreted 98% of the administered dose during the first day, whereas urinary excretion, by comparison, was only 0.24% of the dose. During the second day, rats, monkeys, and dogs all excreted 100% of the dose.

By contrast, rats and rabbits excreted only 9.8% and 2.3%, respectively, of intravenous injection of ^{7}Be over a seven-day period (Scott, Neuman, and Allen, 1950). Beryllium fecal excretion in rabbits increased gradually, peaked on the fourth day, and then decreased. The addition of a carrier, $BeSO_4$, to the isotope did not influence the amount excreted. In rats, ^{7}Be was excreted in greater quantities by those animals receiving the isotope plus carrier than by animals receiving only the isotope (Table 6.10). Excretion in all rats was approximately equal on the first day, with the differences in excretion taking place during the next six days. Rats intravenously injected with two levels of $^{7}BeCl_2$ excreted approximately the same amounts of ^{7}Be in the feces (Cikrt and Bencko, 1975).

TABLE 6.10. DAILY FECAL EXCRETION OF ^{7}Be IN RABBITS AND RATS

(percent of administered dose)

	1 day	2 days	3 days	4 days	5 days	6 days	7 days	Total
Rabbits	0.1	0.3	0.3	0.5	0.3	0.3	0.2	2.0
Rats, isotope plus carrier	4.2	1.6	2.0	1.2	1.1	1.0	0.7	11.8
Rats, isotope only	3.5	0.8	0.4	0.3	0.2	0.2	0.2	5.6

Source: Adapted from Scott, Neuman, and Allen, 1950, Table III, p. 294. Reprinted by permission of the publisher.

Those animals dosed with 0.025 mg of Be^{2+} per kilogram of body weight excreted 1.7%, 2.2%, and 1.6% of the dose at 5, 24, and 48 hr, respectively. Rats given 0.25 mg of Be^{2+} per kilogram of body weight excreted 1.7%, 1.6%, and 2.1% at 5, 24, and 48 hr, respectively. Intramuscular injection of carrier-free ^{7}Be produces slightly higher beryllium excretion levels in rats: 4.25%, 4.17%, 9.25%, and 12.1% of the dose at 1, 4, 16, and 64 days, respectively (Crowley, Hamilton, and Scott, 1949).

6.2.3.4 Biliary Excretion — Biliary excretion of intravenously injected ^{7}Be and $^{7}BeCl_2$ in rats represents only a small portion of total excreted ^{7}Be. Rats given 0.025 mg of Be^{2+} per kilogram of body weight excreted 0.56% of the dose 5 hr after dosing and 0.27% of a dose of 0.25 mg of Be^{2+} per kilogram of body weight (Cikrt and Bencko, 1975). Both of these amounts are far below the levels excreted in the urine and contributed only about 1/6 of the beryllium content of feces. The dose levels influenced not only the total amount excreted but also the excretion rate (Figure 6.6). The highest bile excretion rate of ^{7}Be from the lower dose occurred between 1 and 4 hr after administration, whereas the peak excretion rate from the higher dose occurred after the first 5 hr. The biliary excretion rate of ^{7}Be was related to the ability of beryllium to bind itself on certain bile components. In respect to total body beryllium excretion, bile plays only a minor role.

6.3 EFFECTS

Persons exposed to beryllium by inhalation can develop a respiratory disease, which may be either acute or chronic. Dermatitis or ulcers can result from direct skin contact. These exposure effects will be referred to as acute or chronic beryllium disease. The term berylliosis will not be used.

6.3.1 Potential Exposure Sources

Beryllium metal and its industrially used compounds are known to cause disease (Roschin, 1971). Prior to 1950, many cases of beryllium disease were associated with the manufacture and use of fluorescent lamps containing beryllium phosphors. Use of these compounds was discontinued in 1949. Since 1950 the increased use of beryllium in aerospace industries, gyroscopes, and nuclear reactors has resulted in increased exposures (Hasan and Kazemi, 1973, pp. 1052-1053). The use of beryllium in U.S. industry

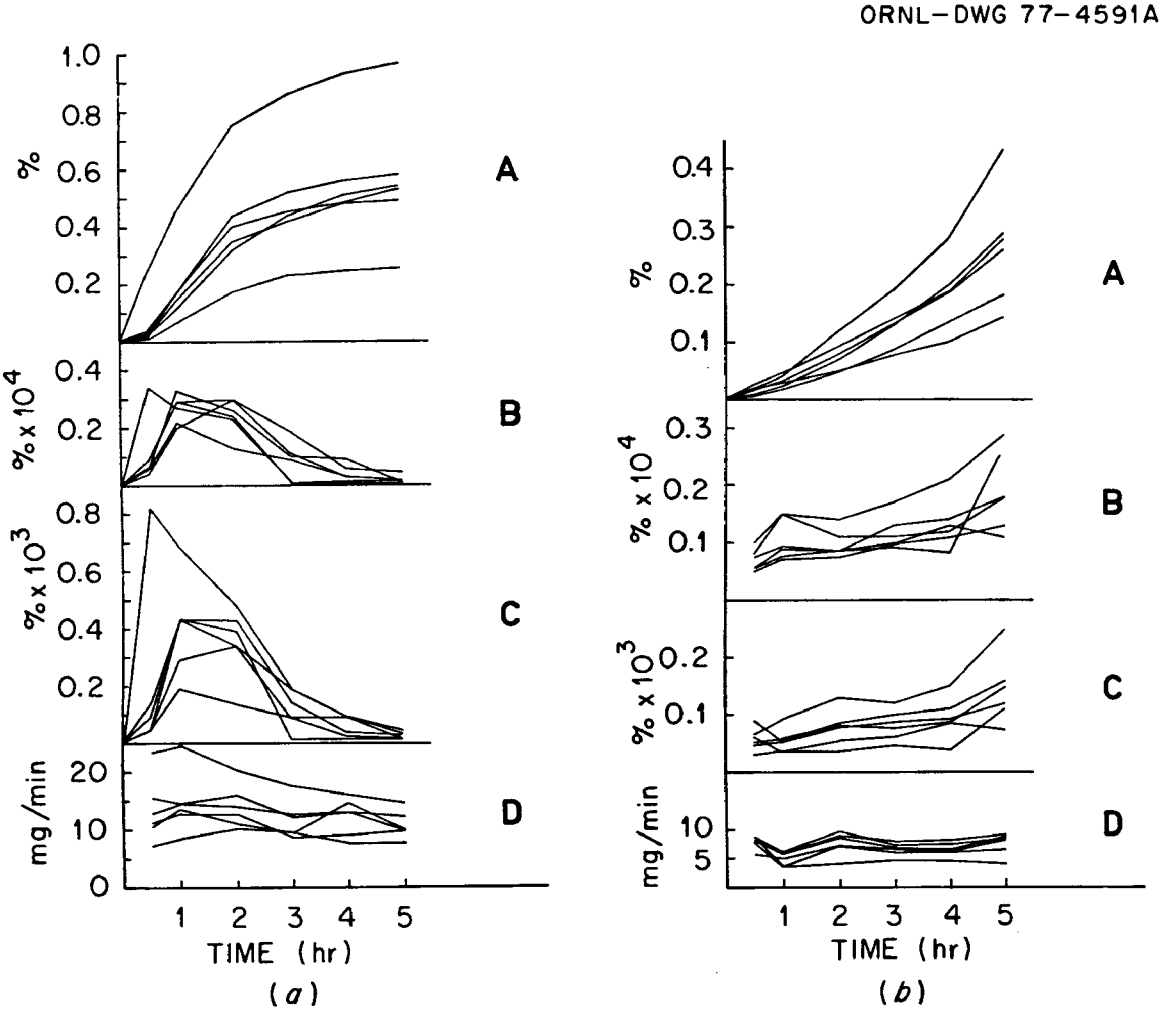

Figure 6.6. ^{7}Be bile excretion in rats after intravenous administration of $^{7}BeCl_2$. Dose: (*a*) 0.025 mg of Be^{2+} per kilogram of body weight; (*b*) 0.25 mg of Be^{2+} per kilogram of body weight. A, cumulative ^{7}Be excretion; B, percentage of ^{7}Be excreted per milligram of bile per minute; C, percentage of ^{7}Be excreted per minute; D, bile flow rate. Source: Adapted from Cikrt and Bencko, 1975, Figures 1 and 2, pp. 54-55. Reprinted by permission of the publisher.

continues to be widespread (Cralley, 1972) and is expected to increase four- to sixfold by the year 2000 (Heindl, 1970, p. 498). Processes that release beryllium into the air include melting, casting, sawing, grinding, buffing, welding, cutting, electroplating, molding, ball milling, drilling, machining, and packaging. Thus worker exposure in beryllium industries can be widespread. Industries where beryllium is processed and its compounds manufactured and handled include mining and beneficiation of beryllium minerals, extraction of beryllium, alloy manufacturing, metallurgical operations, phosphor manufacturing, beryllium ceramic products, electronic equipment manufacturing, nonferrous foundry products, aerospace equipment specialty products, tool and die manufacturing, chemicals, and beryllium alloy machining and fabrication. Beryl ore has not caused detectable illness in humans (Hamilton and Hardy, 1974).

The chemical and metallurgical procedures used in beryllium processing plants present exposure problems through inhalation and skin contact (Donaldson, 1959). Proper equipment and ventilation must be used to reduce air beryllium concentrations to permissible levels. To help alleviate exposure problems at a refining plant where beryl ore is taken down to nuclear-grade beryllium metal, clean clothing is supplied daily to employees, exhaust ventilation systems keep air streams at optimum velocities for accumulating dust particles, and air samples are routinely taken (Epstein, 1959). In beryllium machining operations a high-vacuum-type control system, high air velocity but low air capacity, reduces beryllium concentrations in the air near the machines (Chamberlin, R. I., 1959). Beryllium contamination of the work atmosphere in research operations can result from using pure metal blocks in critical assemblies for nuclear rocket engines and in preparation of beryllium targets for cyclotrons (Hyatt et al., 1959).

Besides industrial exposure, persons may be exposed in other surroundings. Beryllium may be found in alloys in the fabrication of prosthodontic appliances (Hinman et al., 1975). Because of this, employees of dental laboratories may be exposed to high concentrations of beryllium, 23 $\mu g/m^3$, when using a lathe without local lathe ventilation in operation.

Persons may be exposed to beryllium unknowingly from mantle-type camp lanterns (Griggs, 1973). The mantle contains approximately 600 µg of beryllium metal, which is volatilized and becomes airborne during the first 15 min of use of a new mantle. Such exposures may present an inhalation hazard to users.

People living near beryllium-using plants are also exposed to the metal. The chief neighborhood problems of beryllium pollution are associated with extractive processing, metal production, and alloy production (Silverman, 1959). Through site selection of the plant, emission controls, and proper stack height, the neighborhood beryllium air levels can be maintained below hazardous concentrations. Use of large beryllium-powered rocket motors had been considered at one time; however, policy is against the firing of these missiles within the continental United States, and thus this is not a current source of exposure (Robinson, 1973).

Beryllium-level standards have been set forth for work areas and neighborhoods surrounding beryllium-using plants. Workers may not be exposed to a concentration of beryllium greater than 2 µg of total airborne particulate beryllium per cubic meter of air determined as a time-weighted average exposure for an 8-hr work day, and no peak concentration exceeding 25 µg of beryllium per cubic meter as determined by a minimum sampling time of 30 min (U.S. Department of Health, Education, and Welfare, 1972). In neighborhoods near plants, the average monthly concentration of beryllium should not exceed 0.01 µg of beryllium per cubic meter (Cholak et al., 1962). At present, operators of plants have the option of determining compliance either by measurement of ambient levels in the vicinity of the plant or by emission testing. If the second option is exercised, total emission into the atmosphere should not exceed 10 µg Be/24 hr.

Separate standards apply for rocket firing. Emissions to the atmosphere from that source shall not cause atmospheric concentrations of beryllium to exceed 75 $\mu g/m^3$ within 10 to 60 min, accumulated during any two consecutive weeks, measured anywhere beyond the property line of such source or at the nearest place of human habitation. If combustion products containing beryllium propellant are fired into a closed tank, emissions from such tanks shall not exceed 2 g/hr at a maximum of 10 hr/day. However, for beryllium oxide calcined in excess of 1600°C, a standard of 1.5 $mg/min/m^3$ within 10 to 60 min is allowable.

6.3.2 Physiological Effects

6.3.2.1 Enzymes — Beryllium is a very potent enzyme inhibitor and is active at concentrations as low as 10^{-6} *M* (Vorwald and Reeves, 1959). Some affected enzymes are those which are altered in hosts having cancer induced by nonberyllium agents. For example, nucleotidases, hyaluronidase, and alkaline phosphatase activity, which are inhibited by beryllium, are altered in cancer-bearing hosts. Along with enzyme inhibition, beryllium also has an activating influence on ATPase and succinoxidase.

Thomas and Aldridge (1966) studied the action of beryllium on several enzymes; the results are summarized in Table 6.11. Of the phosphatases tested, only alkaline phosphatase was inhibited at concentrations of 1 μM or less, and only phosphoglucomutase of the phosphotransferases tested was inhibited. With phosphoglucomutase the inhibitory process was competitive but progressive with respect to magnesium; when the inhibition was established it was no longer reversed by adding magnesium sulfate.

The inhibition of phosphoglucomutase occurs only in the presence of a complex-forming agent such as cysteine or imidazole (Aldridge, 1966; Aldridge and Thomas, 1966). The rate of the inhibition follows first-order kinetics. Magnesium and beryllium compete with each other in directing the enzyme activity. In the presence of chelators, together with Mg^{2+}, 1 g-atom of beryllium is bound per mole of rabbit muscle phosphoglucomutase (Hashimoto et al., 1967). Beryllium binding prevents phosphorylation of dephosphoenzyme and dephosphorylation of phosphoenzyme. Beryllium also inhibits phosphoglucomutases from shark and flounder muscle and rabbit liver. Beryllium blocks the tricarboxylic cycle by inhibiting the activity of the dehydrogenases of ketoglutaric, malic, and succinic acid (Mukhina, 1967).

In beryllium-induced midzonal liver necrosis, elevation of liver-free acid phosphatase occurred 8 hr after injection of 0.8 mg of beryllium per kilogram of body weight (as $^7BeSO_4$) into rats (Clary and Groth, 1973). Elevation of serum enzymes isocitric dehydrogenase, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase took place 48 hr after injection; the level of lactic dehydrogenase was not elevated.

The induction of certain drug-metabolizing enzymes in rat liver, including tryptophan pyrrolase, acetanilide hydroxylase, and aminopyrine demethylase are inhibited by beryllium (Witschi and Marchand, 1971). Activity of deoxythymidine kinase (Mainigi and Bresnick, 1969) and DNA polymerase, thymidine kinase, and thymidylate kinase was also inhibited (Witschi, 1970, 1971).

TABLE 6.11. EFFECT OF BERYLLIUM ON VARIOUS ENZYMES

(Beryllium sulfate was used, and in each case the enzyme was preincubated with beryllium for at least 10 min in the absence of substrate. At pH above 7, precipitates were obtained with concentrations of $BeSO_4$ of 1 m*M* and above. Inhibition at these concentrations may be nonspecific.)

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

[a] 134 m*M* 3-phosphoglyceric acid as substrate.

[b] 20 m*M* 2-phosphoglyceric acid as substrate.

Source: Adapted from Thomas and Aldridge, 1966, Table 1, p. 96. Reprinted by permission of the publisher.

Sodium- and potassium-activated adenosinetriphosphatase is inhibited by beryllium in the presence of Mg^{2+} or Mn^{2+} (Toda, 1968; Toda, Koide, and Yoshitoshi, 1971). Fifty percent inhibition was reached at a beryllium level of 1.8×10^{-6} *M*, as shown in Figure 6.7. In the presence of Mg^{2+}, K^+ stimulated the rate of inhibition; NH_4^+ and Rb^+ also stimulated enzyme inhibition. Rat lung aryl hydrocarbon hydroxylase was inhibited by 150 micromoles/kg of $BeSO_4$ within the first two days following intratracheal injection in rats (Jacques and Witschi, 1973). The pulmonary induction of this enzyme by methylcholanthrene was not prevented by beryllium exposure.

Beryllium has a marked inhibitory action on alkaline phosphatase, but serum alkaline phosphatase activity in rats remained unaffected by inhalation exposure to beryllium sulfate (Reeves, 1974). In rabbits given 1% beryllium solutions intravenously or 25 mg of beryllium orally, alkaline phosphatase activity (measured histochemically) was decreased in all parenchymatous organs (Komitowski, 1972). Both $BeSO_4$ and $BeCl_2$ inhibited

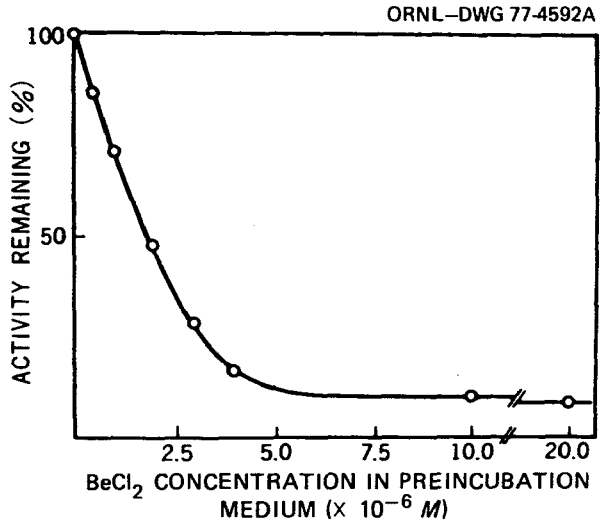

Figure 6.7. The inhibition of Na-K ATPase and $BeCl_2$ concentration. Source: Toda, 1968, Figure 2, p. 459. Reprinted by permission of the publisher.

kidney and blood serum alkaline phosphatase from mice; in rats the renal alkaline phosphatase activity decreased, whereas the enzyme's activity in blood serum increased (Arkhipova and Demokidova, 1967). A relation exists between total beryllium concentration and the amount of enzyme inhibition (Bamberger, Botbol, and Cabrini, 1968). Below 10^{-7} *M*, beryllium produced no inhibition when added to media containing the enzyme. Maximum inhibition occurred at 10^{-5} *M*.

In addition to enzyme inhibition, beryllium also increases the activity of certain enzymes. Following intravenous injection of 12.5 to 1000 μg of beryllium per kilogram of body weight into mice, there was an increase in plasma β-glucuronidase activity (Vacher, Deraedt, and Flahaut, 1975). Beryllium levels above 200 μg produced a biphasic variation of β-glucuronidase activity which peaked 7 and 96 hr following administration. Doses below 100 to 200 μg produced a peak of activity only at 7 hr. The peak at 96 hr was accompanied by an increase in transaminase activities. The first activity phase was attributed to selective exocytosis of lysosomal enzymes, while the second phase was attributed to toxic cell damage.

6.3.2.2 Nucleic Acids — Beryllium intratracheally injected into rats as beryllium oxide (10.8 mg of beryllium total) altered cell RNA distribution (Vorwald and Reeves, 1959). Microsomal RNA dropped from 40% to 22% of the total value, while there was a comparable rise in the RNA content of the soluble supernatant cell fraction. Chèvremont and Firket (1951) showed that beryllium sulfate at a concentration of 10^{-3} *M* inhibited cell division in the metaphase, with marked decrease in the intensity of the Feulgen reaction for DNA. This was interpreted as blockade of DNA biosynthesis (Bassleer, 1965). The effect was specific to DNA, with RNA biosynthesis remaining unaffected (Witschi, 1968). Modes of interaction of the beryllium ion with DNA of various species were studied by Truhaut,

Festy, and LeTalaer (1968) who noted preferential accumulation of radioberyllium in the nuclei of regenerating rat liver and an increase of the sedimentation constant of DNA after contact with beryllium sulfate. Needham (1974) found depression of the typical absorbance bands of DNA in the presence of Be^{2+}. Truhaut, Festy, and LeTalaer (1968) found inhibition of DNase (50% at a concentration of 10^{-4} *M*) by beryllium and postulated the formation of a DNA-beryllium complex. Vegni-Talluri and Guiggiani (1967) expressed the opinion that beryllium exerted its effect on nuclear activity by competing with magnesium in the activation of DNA polymerase; however, Witschi (1970) showed that while beryllium did inhibit the replication of DNA in regenerating rat livers, it did not become attached to DNA, and DNA cell content was not changed. Beryllium did not affect RNA synthesis in early regenerating rat livers (Marcotte and Witschi, 1972). The incorporation of ^{14}C-orotic acid into total cellular RNA, a procedure to measure RNA synthesis, was not affected by beryllium. Beryllium in various physical forms can suppress DNA synthesis (Jones and Amos, 1975). The response of normal lymphocytes from beryllium-allergized guinea pigs to phytohemagglutinin was inhibited by beryllium sulfosalicylate. Witschi (1968) also reported inhibition of DNA synthesis; this inhibition was caused by depression of the incorporation of thymidine into DNA. There is increasing evidence that beryllium can present interference with nucleic acid function at the transcriptional level. Misincorporation of polydeoxyadenosylthymidine by micrococcal DNA polymerase in the presence of beryllium, with strong inhibition of 3'-5' exonuclease ("editing") activity of the enzyme, was recently noted by Luke, Hamilton, and Hollocher (1975), and beryllium alone, among several divalent cations, substantially affected the fidelity of in vitro DNA transcription by single base substitutions (Sirover and Loeb, 1976).

Needham (1974) has agreed that the target for beryllium toxicity is the cellular DNA and that inhibition of cell proliferation, regeneration and development, teratogenesis, and anemia are effects resulting from beryllium inhibition of DNA replication and transcription. He presents data showing a strong affinity of Be^{2+} for DNA in vitro and cites other work that supports this point of view.

6.3.2.3 Proteins — Beryllium compounds react selectively only with certain proteins (Reiner, 1971). Beryllium affects the cellular distribution of protein in rats given 33 mg of beryllium (in three equal doses) by intratracheal injection (Vorwald and Reeves, 1959). The protein in microsomes of cells from lung tissue almost doubled when compared with that of control animals. No change occurred in the protein content of the nuclei or mitochondria, however. Cytoplasmic protein appeared to change from a soluble to an insoluble form. Changes in the protein-carbohydrate components of pulmonary connective tissue from beryllium-exposed rats were expressed as a rise in the oxyproline levels of pulmonary tissue (Ivanova, 1970). Total hexosamine content also increased; the greatest increase of these components occurred during the first month following exposure to beryllium. Pavlova, Kharlamova, and Kurysheva (1970) studied protein metabolism during experimental berylliosis in rats and found an increase in reactive sulfhydryl groups and in the rate of incorporation of lysine-1-C^{14} into the soluble hepatic proteins. This was viewed as an increase in the rate of protein biosynthesis (Kurysheva, 1969).

Intravenous injection of beryllium into rats produces the appearance in the serum of an immunologically specific protein referred to as α-macrofeto protein (Vacher, Deraedt, and Benzoni, 1974). Production of this protein was initiated by phagocytosis of the insoluble phosphate fraction formed following beryllium introduction into rats. At 24 hr after intravenous injection of 0.75 mg of beryllium per kilogram of body weight, a decrease in capacity to incorporate amino acids into liver protein occurred (Witschi and Aldridge, 1967).

6.3.2.4 Immunologic Reactions — Sterner and Eisenbud (1951) suggested that the epidemiology of berylliosis cases could involve an immunological factor. Curtis (1951) concurrently developed a patch test. The patch test itself appeared to be sensitizing and was believed to be responsible for both dermal and pulmonary exacerbations of beryllium disease. It was concurrently not used much as a diagnostic tool (Curtis, 1951; Niemöller, 1962; Zschunke and Folesky, 1969). However, the phenomenon did indicate that beryllium was antigenic. A search for humoral antibodies was made (Voisin et al., 1964; Pugliese et al., 1968; Resnick, Roche, and Morgan, 1970; Resnick and Morgan, 1971) but it now seems well established that beryllium hypersensitivity is essentially cell-mediated (Alekseeva, 1965; Cirla, Barbiano di Belgiojoso, and Chiappino, 1968). Passive transfer of hypersensitivity was accomplished in guinea pigs with lymphoid cells while the transfer of serum was ineffective. Chiappino, Barbiano di Belgiojoso, and Cirla (1968) and Chiappino, Cirla, and Vigliani (1969) were also able to inhibit all cutaneous reactions to beryllium in guinea pigs by injection of an antilymphocyte serum from rabbits; Turk and Polak (1969) could suppress reactivity by intravenous injection of beryllium lactate. Inhalation exposure to beryllium sulfate could also suppress cutaneous reactivity (Reeves, Krivanek, and Palazzolo, 1975). Among guinea pigs, not all individuals responded identically to the beryllium challenge; ability to become sensitized was genetically controlled and transmitted as a nonsex-linked, dominant trait (Polak, Barnes, and Turk, 1968).

Mode of administration and choice of beryllium compound also influenced the nature of the immunological reaction. Vacher (1972) found only those forms and routes which were capable of producing a complex with skin constituents as immunogenic; freely diffusible forms were "tolerogenic," including a very low dose of beryllium (4.78 μg/kg) intraperitoneally, or a high toxic dose (400 μg/kg) intravenously. Krivanek and Reeves (1972) showed that the beryllium ion acts as a hapten in provoking the immunological reaction. Complexes where the beryllium ion was unavailable (aurintricarboxylate, citrate) could not elicit sensitivity, whereas beryllium-serum-albuminate could elicit stronger sensitivity than the beryllium ion alone (Table 6.12). Vasil'eva (1969, 1972) detected beryllium-nucleoprotein complexes that were antigenic. However, evidence was also presented that beryllium can interact with cells without prior complexing to macromolecules and can inhibit the response of allergized lymphocytes to antigen (Jones and Amos, 1974, 1975).

Measures of hypersensitivity, other than skin response, were recently developed. Among these, lymphocyte blast transformation (Hanifin, Epstein,

TABLE 6.12. SKIN RESPONSE TO ORAL ADMINISTRATION AND INTRADERMAL INJECTION OF $BeSO_4$, Be-ATA, Be-H CITRATE, AND Be-ALBUMINATE IN GUINEA PIGS

Compound	Beryllium concentration	Group	Average reaction diameter in millimeters at 24 hr (±1 standard deviation)
$BeSO_4$	1.0 μg	Untreated	2.5 ± 1.7
		Beryllium orally	1.4 ± 1.7
		Beryllium injected	4.1 ± 1.6
Be-ATA	0.45 μg	Untreated	1.8 ± 1.1
		Beryllium orally	2.0 ± 1.2
		Beryllium injected	2.5 ± 1.0
Be-H citrate	0.45 μg	Untreated	2.3 ± 1.4
		Beryllium orally	2.0 ± 1.2
		Beryllium injected	1.3 ± 1.0
Be-albuminate	1.0 μg	Untreated	3.6 ± 2.1
		Beryllium orally	3.8 ± 2.3
		Beryllium injected	5.7 ± 2.1

Source: Adapted from Krivanek and Reeves, 1972, Tables III, IV, V, and VI, pp. 49-50. Reprinted by permission of the publisher.

and Cline, 1970) and macrophage migration inhibition (Henderson et al., 1972) appear promising. They were applied both to human clinical material (Jones-Williams, Grey, and Pioli, 1972; Deodhar, Barna, and Van Ordstrand, 1973) and to experimental guinea pigs (Marx and Burrell, 1973; Palazzolo and Reeves, 1975).

The relation of cutaneous hypersensitivity to pulmonary berylliosis is incompletely understood at present. There are reports on occasional exacerbation or flareup of pulmonary berylliosis cases after patch testing. There is also evidence that in guinea pigs dermal sensitivity and pulmonary response to beryllium are in inverse relation (Reeves et al., 1971, 1972). Maintenance of hypersensitivity through intracutaneous injection modified and alleviated the pulmonary response after beryllium inhalation (Reeves and Krivanek, 1974). The situation showed some similarity to the relation between tuberculin sensitivity and tuberculosis, where a controlled induction of sensitivity (e.g., with BCG vaccine) was associated with increased resistance to tuberculosis. Perhaps the lymphocytic and histiocytic response that followed the induction of cutaneous hypersensitivity stimulated the phagocytosis of inhaled beryllium particles, or otherwise helped to destory the autoantigen formed in the lungs.

6.3.2.5 Other Physiological Effects — Mitochondrial changes were produced in rats with experimental beryllium disease (Potapova and Seleznev, 1967). Both disintegration and swelling of the mitochondrial apparatus occurred, with a loss of cristae. In pulmonary structures the basal membranes of the alveolar septa became edematous and swollen, later becoming

dense and thick. These changes corresponded to desquamation of cells lining the alveoli and sclerosing of alveolar septa. Beryllium increases plasma volume (Mosser and Clark, 1970). A single intravenous injection of 6.67 micromoles of $BeSO_4$ per kilogram of body weight in rabbits caused a significant increase in the mean plasma volume. Increased globulin levels and plasma volume occurred between 7 and 14 days following injection, whereas there was no effect on albumin levels or red cell mass. Mean hematocrits decreased for 12 days and then rose toward normal.

Concentrations of beryllium as the sulfate from 0.0025 to 10^{-6} *M* inhibited growth of chick embryo tissue cultures (Chèvremont and Firket, 1951). Mitotic abnormalities occurred by prolonged contact with beryllium ions. In some cells, metaphase was lengthened up to several hours. These cells usually degenerated and became pycnotic or changed back into elongated cells, with a resting nucleus reappearing. Thus anaphase and telophase do not take place. Goldblatt, Lieberman, and Witschi (1973) reported inhibition of mitosis in rat liver cells from partially hepatectomized animals intravenously administered 15, 30, or 60 micromoles of $BeSO_4$ per kilogram of body weight treated 20 to 16 hr before death. Changes also occurred in lysosomes 24 hr following beryllium injection: they included vacuolization, loss of fibrils, and distortion of bile canaliculi.

6.3.3 Acute Beryllium Disease

Acute beryllium disease is defined as including those beryllium-induced disease patterns which last less than one year (Tepper, Hardy, and Chamberlin, 1961). Patients develop acute inflammatory reactions at the deposition site when challenged by toxic beryllium compounds in the form of a mist, vapor, or dust (Vorwald, 1966). Severity of symptoms seems dependent on the amount of exposure, toxicity and concentration of the compound, and individual susceptibility (VanOrdstrand et al., 1945). Acute chemical pneumonitis can be caused by inhalation of practically all beryllium compounds (Love, 1972). Exposure to large concentrations of soluble salts in beryllium processing plants has led to rapidly fatal cases. Peyton and Worcester (1959) found that of those workers exposed to beryllium, 6.4% to 10.8% developed acute beryllium disease. The U.S. Beryllium Case Registry, up to 1972, reports 211 acute cases and 44 with both acute and chronic beryllium disease (Hasan and Kazemi, 1973).

Acute beryllium disease is primarily a manifestation of direct upper and/or lower respiratory tract irritation (Tepper, 1972*a*). Dermatitis, skin ulcers, and conjunctivitis result from contact with soluble beryllium salts (Vorwald, 1966; Higgins, 1968).

6.3.3.1 Dermatitis — Contact dermatitis from beryllium exposure is the allergic type (Zielinski, 1959). Allergic dermatitis, expressed as intense dermal erythema, occurs on exposed areas of the face, neck, sometimes arms and hands, and develops within 6 to 15 days after initial exposure to soluble compounds of beryllium, especially the fluoride. Lesions that form on the trunk are usually a result of penetration of clothing or distribution to covered areas by contaminated hands (Tepper, Hardy, and Chamberlin,

1961). Acute contact dermatitis is generally associated with fluoride or sulfate salts of beryllium, and not with beryllium oxide powder (Browning, 1969). Dermatitis is generally regarded as a hypersensitizing reaction instead of being due to a primary irritant. It is characterized by itching and reddened and elevated or fluid-accumulated lesions. In a study of employees in a beryllium refining factory, 57.8% of those workers with acute beryllium disease had contact dermatitis (Nishimura, 1966). Within three months after employment, contact dermatitis occurred in 55% of those who eventually got dermatitis. The cases were seen mostly in the extracting and alloying process and in BeO manufacturing; they occurred most frequently during the summer.

Several studies have examined beryllium-induced dermatitis using guinea pigs as a model. Delayed hypersensitivity was expressed as a dermal reaction following intradermal injection of $BeSO_4$ (Palazzolo and Reeves, 1975). No reaction was produced by $BeSO_4$ inhalation. The binding of beryllium to guinea pig epidermal constituents, such as alkaline phosphatase and nucleic acids, was suggested by Belman (1969) as a possible mechanism for beryllium toxicity.

6.3.3.2 Beryllium Ulcer — The beryllium ulcer is caused by implantation of a crystalline beryllium compound in skin abrasions. It starts as a localized indurated papuloerythematous lesion which progresses to the ulcer (Vorwald, 1966). The ulcer lasts until extrusion of the crystal by surgical curettage of the ulcer base (Tepper, Hardy, and Chamberlin, 1961). Healing usually follows within two weeks. In a study of acute beryllium disease in a beryllium refining plant, Nishimura (1966) found an incidence rate of 5.7% for skin ulceration.

6.3.3.3 Conjunctivitis — Inflammation of the conjunctiva is usually associated with contact dermatitis. The pathology ranges from a simple congestion and hyperemia to cellular infiltration, and the condition cannot be differentiated from inflammatory reactions due to other types of irritants (Vorwald, 1966). Nishimura (1966) found a conjunctivitis frequency of 20.9% among workers with the acute disease in the previously discussed study. This was usually found in workers exposed to high concentrations of BeO.

6.3.3.4 Respiratory Tract Effects — Inhalation of toxic beryllium compounds can induce inflammatory reactions of the respiratory tract tissues between the nares and alveoli; upon intense exposure the inflammation may extend into the lower tract (Tepper, Hardy, and Chamberlin, 1961). Soluble acid salts have been responsible for the cases involving the upper respiratory tract, whereas beryllium metal, oxide, and phosphor mixtures, as well as acid salts, have produced pneumonitis. Acute pulmonary beryllium disease may appear within a few weeks of initial exposure (VanOrdstrand, 1959). Acute beryllium disease is not necessarily easy to diagnose, since some of the symptoms resemble those induced by other irritating chemicals.

Effects on the respiratory tract may take the form of nasopharyngitis, tracheobronchitis, or acute chemical pneumonitis (Tepper, Hardy, and Chamberlin, 1961). Nasopharyngitis has no specific clinical pattern

and can be confused with the common cold. Symptoms are irritation of the nose and pharynx with mild epistaxis, edematous and hyperemic mucous membranes, and bleeding areas in the nose. Tracheobronchitis may be either rapid or insidious in onset according to degree of exposure. A nonproductive spasmodic cough develops, with moderate exertional dyspnea and substernal discomfort, burning, or tightness. The upper respiratory tract mucosa is usually hyperemic. Acute chemical pneumonitis may take either of two forms: a fulminating illness after a brief massive exposure or an insidious illness following prolonged exposure. Symptoms of pneumonitis are development of a dry cough with substernal burning or aching, progressive dyspnea, fatigue, anorexia, weight loss, cyanosis, moist pulmonary rales, and slight temperature elevation.

Norris and Peard (1963) reported a case of acute chemical pneumonitis in a worker in contact with beryllium-copper alloys. The onset of the disease was rapid, with progression of dyspnea and evidence of systemic disturbance. The percussion note was impaired over both upper zones anteriorly. Hazard (1959) reported on six cases that ended in death from pneumonitis of employees in a beryllium extraction plant. Usual symptoms such as shortness of breath, chest pain, cough, and dyspnea were found; terminal fever and cyanosis also occurred. Death, in each case, was attributed to pulmonary embarrassment with or without acute cor pulmonale. The time between exposure and disease onset was accurately determined for only one case; this patient was exposed six days and four days prior to onset when he removed his mask while cleaning a calcining furnace. No exposure concentrations were determined.

A study by Nishimura (1966) described in detail 192 cases of acute beryllium disease that occurred between 1957 and 1964 in persons working in a refining factory. Of these cases, 19 displayed acute upper respiratory tract disease, and 11 had acute pneumonitis. Of the upper respiratory tract diseases 53% occurred during the first three months of employment. This disease was found most often among those working in the extracting and alloying processes. Symptoms were coughing, sore throat, and slight general fatigue. Sixty-nine percent of these cases were cured within one month, and none exceeded two months. Cases of acute beryllium pneumonitis occurred between 32 and 90 days of employment and were associated with extracting and alloying processes or manufacturing of BeO. The beryllium concentrations to which the workers were subjected were 20 to 60 $\mu g/m^3$. These levels did not necessarily correlate with disease severity, clinical findings, or length of illness. Table 6.13 summarizes the exposure levels and the clinical progress of the pneumonitis in the 11 workers with the disease. Table 6.14 summarizes the laboratory findings in these 11 patients.

Various studies have examined the effect of beryllium on the lungs of experimental animals. Table 6.15 presents a summary of results from exposing various animal species to beryllium by inhalation.

Various animal species show differing levels of susceptibility to beryllium inhalation. Animals exposed to $BeSO_4$ at 47 mg/m^3 displayed two separate responses: (1) a highly acute phase in which the most susceptible species die and (2) a delayed phase in which little effect is shown

TABLE 6.13. CLINICAL PROGRESS OF ACUTE BERYLLIUM PNEUMONITIS

Case number	Sex and age (years)	Employed process[a]	Air concentration peaks in decreasing frequency	Interval between employment and onset (days)	Interval between onset and peak (days)	Main symptoms	Rale of chest	Fever	Beryllium patch test: At start of employment	Beryllium patch test: At onset	Total days of illness	Prognosis
1	m 28	A	20∿40	60	20	Dry cough,[b] dyspnea, general malaise, fever	+	+	-	+	37	Complete cure
2	m 21	A	12∿20∿ (25)	32	25	Dry cough,[b] dyspnea, fever, substernal pain	-	+	-	+	45	Complete cure
3	m 34	A	42∿55.3	45	20	Dry cough,[b] dyspnea, chest pain, cyanosis (needed oxygen inhalating)	+	-	-	+	40	Complete cure
4	m 34	B	40∿60	60	20	Dry cough,[b] dyspnea, general malaise, sleeplessness	+	-	-	+	45	Complete cure
5	m 22	A	42∿60	45	20	Dry cough,[b] dyspnea, general malaise, sleeplessness	-	-	-	+	40	Complete cure
6	m 34	A	15∿30	36	15	Dry cough,[b] dyspnea, fever, cyanosis (needed oxygen inhalating)	+	-	-	+	50	Complete cure
7	m 23	B	40∿60	45	18	Dry cough,[b] dyspnea[b]	-	-	-	+	30	Complete cure
8	m 26	A	8∿15∿ (22.5)	32	27	Dry cough,[b] dyspnea, general malaise, chest pain	-	-	-	+	50	Complete cure
9	m 23	A	12∿25∿ (40)	56	19	Throat pain,[b] dry cough,[b] dyspnea,[b] headache	-	-	-	+	29	Complete cure
10	m 23	A	12∿20∿ (60.5)	90	19	Dry cough,[b] dyspnea, substernal tightness	-	-	-	+	40	Complete cure
11	m 27	B	10∿19∿ (30)	51	21	Dry cough,[b] dyspnea, subfebris	+	±	-	+	53	Complete cure

[a] A — extraction and alloying process, B — manufacturing of BeO.

[b] Initial symptoms.

Source: Adapted from Nishimura, 1966, Table 6-a, p. 23.

at first but increasingly severe changes occur up to seven to ten weeks of exposure (Stokinger et al., 1950). Figure 6.8 shows the variation in species mortality as a result of beryllium sulfate exposure. Pulmonary lesions produced in these species resemble those found in humans with acute beryllium disease. Little change in the pulmonary responses occurred with respect to changes in $BeSO_4$ concentrations ranging from 1 mg to 100 mg/m^3. A single intratracheal injection of a 1% zinc beryllium silicate solution produced pulmonary lesions in guinea pigs which were comparable with those produced by beryllium sulfate or oxide (Levy and Higgins, 1965).

TABLE 6.14. LABORATORY FINDINGS OF ACUTE BERYLLIUM PNEUMONITIS

Number	Body weight (kg)				Pulmonary function		Serum chemistry								Examination for beryllium		
	Before onset	At peak	ESR[a] (mm/h)	WBC[b]	VC(cc)[c]	Percent VC	Total protein (mg/dl)	A/G	Alk. phos.	Takada reaction	CCLF (24 hr)	BSP (30 min)	Culture for B. Tbc	Cold hemaggult.	Blood	Sputum	Urine
1	58	55	76	15.200	1.800	46	7.4	1.0	2.2	-	+	5	-	x32 ↓ x32	-	-	-
2	51	51	29	12.400	1.700	42	7.6	0.9	3.1	+	++	10	-		-	-	+
3	56	54	54	8.500	1.000	25	7.4	0.9	6.0	++	++	<5	-	x16 ↓ x16	-		-
4	50	49	40	8.600	1.400	39	7.8	1.1	5.0	-	+	<5	-	0 ↓ 0	-	+	+
5	53	53	14	6.200	2.000	49	8.0	1.4	3.0	-	+	<5	-	x16 ↓ x16	-	-	-
6	55	43	31	6.800	1.100	28	5.0	0.94	2.9	+	++	8	-	x32 ↓ x16	+	-	+
7	46	46	15	7.200	1.300	48	7.2	1.3	4.2	+	+	<5	-	0 ↓ 0	-		+
8	49	52	32	4.900	1.900	47	7.8	1.08	2.6	+	++	<5	-		-	-	-
9	51	51	31	6.100	2.000	51	7.0	1.1	3.0	+	+	<5	-		-		+
10	58	53	13	7.200	2.500	61	7.6	1.18	2.0	++	++	7	-	x16 ↓ 0	-	-	-
11	56	52	38	9.700	2.900	72	7.2	1.0	3.0	+	+	<5		0 ↓ 0	-	-	-

[a]Erythrocytic sedimentation rate.

[b]White blood cell count.

[c]Vital capacity.

Source: Adapted from Nishimura, 1966, Table 6-b, p. 24.

TABLE 6.15. EFFECTS ON VARIOUS ANIMAL SPECIES CAUSED BY EXPOSURE TO BERYLLIUM BY INHALATION

Substance	Animal	Concentration or dose	Exposure (duration)	Particle size (μm)	Effects
			Beryllium compounds		
Beryllium fluoride	5 cats, young adult	0.97 mg/m^3 in H_2O	6 hr/day (207 day)	0.61(0.33-0.94)	No deaths; lung damage
	6 cats, young adult	10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.63(0.52-0.74)	No deaths
	14 dogs, young adult	0.97 mg/m^3 in H_2O	6 hr/day (207 day)	0.61(0.33-0.94)	3 deaths; suspected macrocytic anemia
	6 dogs, young adult	10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.63(0.52-0.74)	1 death; 3 sacrificed moribund Consolidation, emphysema, & slight edema in lungs; Be tended to accumulate in lungs, pulmonary lumph nodes, liver, skeleton, & bone marrow
	6 dogs, young adult; 3 rabbits	2.2(2.0-2.4) mg/m^3 in H_2O	6 hr/day (23 wk)		↓ in RBC count & Hb levels; ↑ in mean corpuscular volume consistent with macrocytic anemia
	20 guinea pigs, young adult	10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.63(0.52-0.74)	7 deaths
	20 mice, young adult	10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.63(0.52-0.74)	6 deaths
	4 monkeys, rhesus	27 μg (5.2 μg Be)/ft^3 in H_2O	6 hr/day (7-16 day)		2/4 deaths after 13-16 exposures from pneumonitis; pulmonary emphysema, edema, granulomas (2/4), & fibrosis; marked alveolar hyperplasia (4/4) & slight to moderate metaplasia (4/4) of alveoli, & bronchial & bronchiolar epithelium; marked lymph node hyperplasis (4/4); multiple extraplumonary lesions
	10 rabbits, young adult	0.97 mg/m^3 in H_2O	6 hr/day (207 day)	0.61(0.33-0.94)	No deaths; suspected macrocytic anemia, lung damage
		10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.61(0.52-0.74)	1 death; suspected macrocytic anemia; lung damage
	120 rats, young adult	0.97 mg/m^3 in H_2O	6 hr/day (207 day)	0.61(0.33-0.94)	73 deaths; minimal lung lesions
	40 rats, young & old adult	10 mg/m^3 in H_2O	6 hr/day (3 wk)	0.63(0.52-0.74)	7 deaths; minimal lung lesions
Beryllium oxide	6 dogs, beagle, 7.3-10.8 kg	120(40-300) mg/m^3	20 min		4/6 Be-containing granulomas in lungs at 30 mo with no excess collagen formation
	65 rats	39.57 μg/liter	1-5 hr/day (1-35 hr)	0.285(0.11-1.25)	Large amounts of dust (>24 mg Be/100 g) in lungs at >1 yr; little tendency for Be to be redistributed from lungs to other tissues; fibrous tissue proliferation from 35 day to >1 yr but no granulomatous inflammation in lungs

(continued)

TABLE 6.15 (continued)

Substance	Animal	Concentration or dose	Exposure (duration)	Particle size (μm)	Effects	
Beryllium oxide	2 cats; 10 dogs; 20 guinea pigs, mixed English; 2 monkeys, rhesus; 9 rabbits, New Zealand; 90 rats, Wistar; (all young adults)	10 & 82 mg/m^3 in H_2O (special grade of BeO)	6 hr/day 5 day/wk (15-40 day)	0.47-0.59	68% mortality in rats exposed to 82 mg/m^3 for 15 day; all other treated animals survived	Damage in lungs only; dust particles in peribronchial & perivascular tissues, as well as in alveoli & phagocytes; inflammation, edema, & thickening of alveolar walls; bronchial epithelial desquamation & hyperplasia
		83 mg/m^3 in H_2O (refractory grade GC of BeO)	6 hr/day 5 day/wk (60 day)	1.13	All animals survived	
		84-86 mg/m^3 in H_2O (fluorescent grade of BeO)	6 hr/day 5 day/wk (10-17.5 day)	<1.0	5% mortality in rats exposed to 87 mg/m^3 for 10 day; all other treated animals survived	
		88 mg/m^3 in H_2O (refractory grade SP of BeO)	6 hr/day 5 day/wk (10 day)	0.71	All animals survived	
Calcined beryllium oxide	6 dogs, beagle; 5 monkeys, cynamolgus (all adults)	3.3-4.4 mg Be/m^3	3 x 30 min/mo (2 yr)		Significant Be levels in lungs with higher conc. present in monkeys; no histological or ultrastructural pulmonary changes; no changes in air-blood barrier thickness or capillary-alveolar surface area ratio	
	30 guinea pigs, 360-400 g	2 mg in saline	Single i.t. injection	1-5	Pulmonary edema in all treated animals at 15 day; peribronchial lymphoid hyperplasia at 15-60 day in animals receiving BeO calcined at 500 or 1100°C only; no specific pulmonary reaction at 30-60 day with BeO calcined at 1600°C	
Beryllium phosphate	4 monkeys, rhesus	66 μg (5.6 μg Be)/ft^3	6 hr/day (30 day)		1/4 deaths at 75 day from pneumonitis; pulmonary emphysema & fibrosis; minimal extrapulmonary lesions	
Beryllium sulfate	4 cats, young adult	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 20% body wt loss. μg Be/g fresh tissue from 4 sacrificed animals; lung, 0.08; liver, 0.02; kidney, 0.01; spleen, 0.01	
	5 cats, young adult	10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	1 death; no change in body wt	
		47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	4 deaths; 43% body wt loss	
	12 dogs	3.6-4.0 mg/m^3 in H_2O	6 hr/day (2 mo)		↓ in RBC count & Hb levels; ↑ in mean corpuscular volume consistent with macrocytic anemia; spontaneous recovery from anemia after 3.5-4 mo	

(continued)

TABLE 6.15 (continued)

Substance	Animal	Concentration or dose	Exposure (duration)	Particle size (μm)	Effects
Beryllium sulfate	5 dogs, young adult	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 10% body wt loss. μg Be/g fresh tissue from 5 sacrificed animals; lung, 0.06; pulmonary lymph nodes, 0.7; liver, 0.01; kidney, 0.003; spleen, 0.01
		10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	No deaths; 11% body wt loss; leukocytosis, μg Be/g fresh tissue from 4 sacrificed animals: lung, 4; pulmonary lymph nodes, 2; liver, 1.8; kidney, 0.8; spleen, 0.004; femur, 0.8
					Reversible macrocytic anemia after 3-8 wk; significant changes in phospholipid & free cholesterol of whole RBC; tendency to hypoalbuminemia & hyperglobulinemia; acute inflammatory response in lung, with erosion & proliferation of bronchial epithelium
		47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	4 deaths; 4% body wt loss; leukocytosis
	20 guinea pigs, 400-600 g	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 18% body wt gain
	34 guinea pigs, 400-600 g	10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	2 deaths; 100% body wt gain
	12 guinea pigs, 400-600 g	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	7 deaths; 37% body wt gain
	10 guinea pigs, 400-600 g	100 mg (4.3 mg Be)/m^3 in H_2O	6 hr/day (14 day)	1.1	3 deaths; 2% body wt loss
	83 hamsters	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; no change in body wt
	10 hamsters	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	5 deaths; 18% body wt loss
		100 mg (4.3 mg Be)/m^3 in H_2O	6 hr/day (14 day)	1.1	2 deaths; 8% body wt loss
	38 mice	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	4 deaths; 6% body wt loss
		100 mg (4.3 mg Be)/m^3 in H_2O	6 hr/day (14 day)	1.1	No deaths; 13% body wt loss
	2 monkeys	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 10% body wt gain. μg Be/g fresh tissue from 2 sacrificed animals: lung, 1.2; pulmonary lymph nodes, 1.3; liver, 0.5; kidney, 0.01; spleen, 0.1

(continued)

TABLE 6.15 (continued)

Substance	Animal	Concentration or dose	Exposure (duration)	Particle size (μm)	Effects
	5 monkeys	10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	No deaths; 31% body wt loss
	1 monkey	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	1 death; 25% body wt loss
Beryllium sulfate	4 monkeys rhesus	66 μg (5.6 μg Be)/ft^3 in H_2O	6 hr/day (7 day)		1/4 deaths at 52 day from pneumonitis; pulmonary emphysema, granulomas (1/4 at 6 mo), fibrosis; desquamation of bronchial & bronchiolar epithelium; marked lymph node hyperplasia (2/4); minimal extrapulmonary lesions
	23 rabbits, 2.6-4.0 kg	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 15% body wt gain. μg Be/g fresh tissue from 5 sacrificed animals: lung, 1.6; pulmonary lymph nodes, 0; liver, 0.004; kidney, 0.003; spleen, 0.01
	24 rabbits, 2.6-4.0 kg	10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	2 deaths; no change in body wt; leukocytosis
	10 rabbits, 2.6-4.0 kg	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	1 death; 7% body wt gain; leukocytosis
	3 rabbits, 2.6-4.0 kg	100 mg (4.3 mg Be)/m^3 in H_2O	6 hr/day (14 day)	1.1	No deaths; no change in body wt; leukocytosis
	20 rats, 250-280 g	0.95 mg (0.04 mg Be)/m^3 in H_2O	6 hr/day (100 day)	0.25	No deaths; 20% body wt gain
	40 rats	4 mg/m^3 in H_2O	6 hr/day (23 wk)		↓ in RBC count; ↑ in mean corpuscular volume consistent with macrocytic anemia
	47 rats, 250-280 g	10 mg (0.43 mg Be)/m^3 in H_2O	6 hr/day (95 day)	1.5	23 deaths; 28% body wt gain; leukocytosis; inhalation of HF vapor (8 mg/m^3) doubles toxicity of $BeSO_4$ poisoning
	15 rats, 250-280 g	47 mg (2 mg Be)/m^3 in H_2O	6 hr/day (51 day)	0.96	13 deaths; no change in body wt; leukocytosis
	10 rats, 250-280 g	100 mg (4.3 mg Be)/m^3 in H_2O	6 hr/day (14 day)	1.1	10 deaths; 2% body wt loss; leukocytosis
	150 rats, Sprague-Dawley, 6 wk	34.2 μg Be/m^3	7 hr/day 5 da/wk	0.12	↑ in mortality in ♀ only; 100% alveolar adenocarcinomas at 13 mo; ↑ in Be content in lungs with conc plateau at 36 wk; significant ↓ in Be content of excised tumors compared to nonmalignant tissue; maximum Be levels in tracheobronchial lymph nodes at 36-52 wk with greater Be deposition in ♂

(continued)

TABLE 6.15 (continued)

Substance	Animal	Concentration or dose	Exposure (duration)	Particle size (μm)	Effects
	136 rats, Wistar & Sherman, 140-210 g	12 μg (1 μg Be)/ft^3 in H_2O	8 hr/day 5.5 day/wk (6 mo)		46 deaths. Apparent effect on lung tissue; stimulation of epithelial cell proliferation without connective tissue reaction; foam-cell clustering; focal mural infiltration; lobular septal cell proliferation; peribronchial alveolar wall epithelization; granulomatosis & neoplasia
Beryllium chloride (10%), beryllium fluoride (40%), & beryllium oxide (50%) in rocket exhaust	2 dogs, beagle, 8.1-10.8 kg	115 mg Be/m^3	20 min	<1 to >5	3.9-5.5 μg Be/g wet lung at 3 yr; Be (<0.05-1 μ) deposited in histiocytic lysosomes in septal interstitium in association with collagen bundles & ↑ in numbers of septal capillaries

Source: Altman and Dittmer, 1973, pp. 954-958. Reprinted by permission of the publisher.

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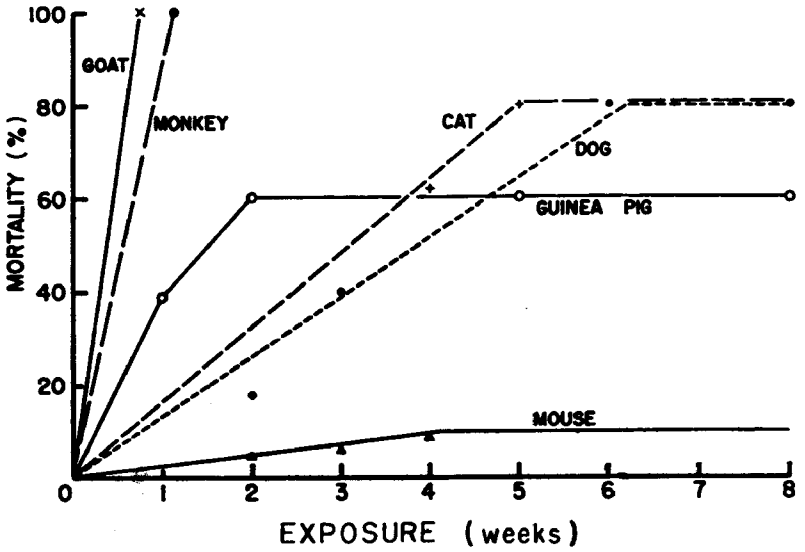

Figure 6.8. Animal mortality rate following exposure to 47 mg of $BeSO_4$ per cubic meter by inhalation. Source: Stokinger et al., Arch. Ind. Hyg. Occup. Med., April, Vol. 1, Figure 3, p. 385, Copyright 1950, American Medical Association. Reprinted by permission of the publisher.

Monkeys (*Macaca mulatta*) exposed to beryllium fluoride, beryllium sulfate, and beryllium phosphate developed symptoms related to the beryllium content of the compound to which they were exposed (Schepers, 1964). Beryllium fluoride (953 $\mu g/m^3$) was the most toxic and beryllium phosphate (2331 $\mu g/m^3$) the least toxic. However, at high levels of phosphate (97 mg/m^3), all the monkeys were killed within 20 days, and at a concentration of 13 mg/m^3 all animals died within 92 days. Beryllium fluoride and the high concentrations of beryllium phosphate caused severe and universal pulmonary reactions along with changes in the liver, kidneys, adrenals, pancreas, thyroid, and spleen. Animals exposed to beryllium sulfate (2330 $\mu g/m^3$) had little sign of any illness. Spencer et al. (1972) demonstrated that the beryllium oxide exhaust product from a beryllium-fueled NASA-JPL high-energy upper-stage motor induced a less severe pulmonary response in rats than did BeO calcined at 500°C. However, the pulmonary lesions were histologically similar. Beryllium oxide calcined at 500, 1000, or 1600°C endotracheally injected into guinea pigs produced a lung reaction morphologically similar to that characteristic of delayed hypersensitivity reactions (Chiappino, Cirla, and Vigliani, 1969). The most active oxide was calcined at the lowest temperature and was the least crystalline and most soluble. This graduation of toxicity of beryllium oxides according to their firing temperatures appears to be related to the crystallite size of the particles, with resultant variability of reactive surface. Optical birefrigence is governed by the same parameters (Crossmon and Vandemark, 1954).

6.3.3.5 Acute Effects in Experimental Animals — Beryllium produces toxic effects at sites other than the skin and respiratory tract, as demonstrated in research animals. Liver necrosis in rats was produced by a single intravenous dose of 1.1 mg of beryllium (as the sulfate) per kilogram of body weight (Cheng, 1956). Gradual obliteration of liver sinusoids and terminal development of hemorrhagic foci round terminal afferent vessels occurred, with progressive damage to Kupffer cells and sinusoidal infiltration of inflammatory cells. Degeneration and necrosis of parenchymal cells occurred mainly in the periportal and middle zone of liver lobules. Circulatory disturbances were the result and not the cause of liver cellular damage. Injection of $BeSO_4$ also inhibits reticuloendothelial system activity, due to the phosphate fraction formed by the conversion of the sulfate (Vacher, Deraedt, and Benzoni, 1973).

Changes occurred in the central nervous system of rabbits following injection of beryllium (as the chloride or sulfate) into the cerebellomedullary cistern or spinal subarachnoid space (Zelman et al., 1967). Focal injury of the neurons connected with the injection site and inflammatory changes resembling granulomatosis were induced.

Stokinger and Stroud (1951) induced anemia in dogs, rats, and rabbits by inhalation exposure to beryllium fluoride for 6 hr daily five days per week for 23 weeks at a concentration of 2.2 ± 0.25 mg per cubic meter of air. The anemia resembled the macrocytic type, was of a mild degree, and differed between species. In the dog the red blood cell count (RBC), mean corpuscular volume (MCV), and hemoglobin all changed in a manner typical of normochromic macrocytic anemia. In the rabbit there was less tendency for decreasing hemoglobin levels and a greater tendency to return to normal values, whereas in the rat, hemoglobin values were normal, while the MCV and RBC count changed in consistency with macrocytic anemia.

6.3.4 Chronic Beryllium Disease

Chronic beryllium disease arises from inhalation of beryllium compounds (Casarett and Doull, 1975). The chronic disease has a latent period of up to more than 20 years, is of long duration, is progressive in severity, and is a systemic disease (Tepper, Hardy, and Chamberlin, 1961). In some instances, the acute form of the disease may progress to the chronic form (Hardy and Chamberlin, 1972) with an asymptomatic period between recovery from the acute disease and onset of the chronic disease.

Although data exist for probable harmful and safe beryllium levels, the dose necessary to produce chronic beryllium disease is not known (Hardy and Chamberlin, 1972). Delay in disease onset and lack of data from earlier cases has contributed to the lack of knowledge concerning a dose-response relationship to the disease. However, since 1949, when efforts began to control exposure, the number and severity of cases decreased as concentrations decreased (Williams, 1959).

6.3.4.1 Incidence — The progress report of the U.S. Beryllium Case Registry, 1972, lists a total of 577 chronic cases occurring in the United States; 44 cases are listed as both chronic and acute (Hasan and Kazemi, 1973). Standards for exposure were set in 1949 not to exceed 2 $\mu g/m^3$ over

an 8-hr period to eliminate the development of chronic beryllium disease. However, since 1966, 76 new cases have been added to the Registry (Hasan and Kazemi, 1974). Of these new cases, about half had significant exposure since 1949; 17 were exposed after 1966, and 7 were exposed as late as 1972, indicating that beryllium is still an industrial hazard despite existing exposure standards, possibly because of occasional noncompliance. Most exposures since 1950 have occurred in handling and processing beryllium compounds in the aerospace and nuclear industries.

A detailed study of cases in the basic beryllium industry in northern Ohio between 1940 and 1953 revealed a total incidence of 1.1% of all personnel exposed prior to introduction of industrial hygiene controls of an engineering type (DeNardi, 1959). The incidence rate for females was 3.2% and for males 0.68%, indicating a predilection for incidence in females. The overall mortality rate was 22%, with a 17% rate in men and 4.5% in women.

6.3.4.2 Induction and Mechanism of Delayed Response — Clary and Stokinger (1973) proposed that the mechanism for disease onset involved some form of stress such as respiratory infection, surgery, or pregnancy. The stress leads to altered adrenal function, which is related to onset of the latent chronic disease. Altered adrenal function results in beryllium translocation to organs critical to systemic disease initiation. Liver enzyme activity increases, body weight decreases, renal damage occurs, lysosomal stability is reduced, and a linear correlation between beryllium and steroid levels occurs in the liver. Figure 6.9 diagrammatically shows the proposed steps leading to chronic beryllium disease. Mice and guinea pigs with altered adrenal function have a more severe reaction to beryllium, introduced as $BeSO_4$ or BeO by transthoracic or intratracheal injection, than control animals, as demonstrated by weight loss, metal-ion shift, and serum enzyme elevation (Clary, Hopper, and Stokinger, 1972).

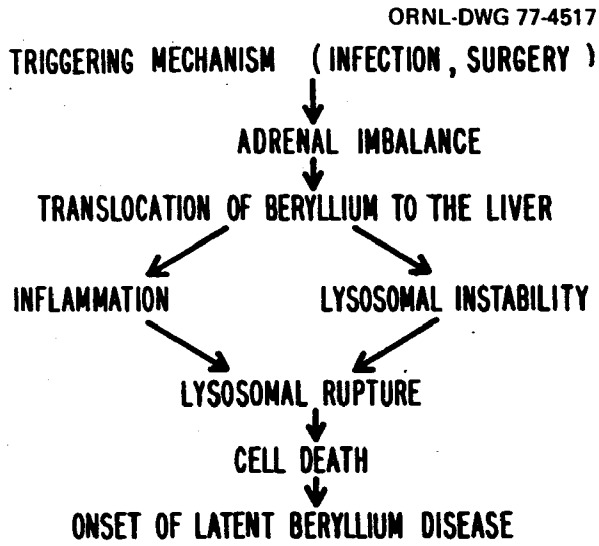

Figure 6.9. Proposed mechanism for the latency of chronic beryllium disease. Source: Clary and Stokinger, 1973, Figure 2, p. 255. Reprinted by permission of the publisher.

Hall et al. (1959) reported pregnancy as a stress that precipitated the disease. In 40% of the women with the chronic disease who became pregnant following beryllium exposure, pregnancy or the immediate postpartum period initiated or increased symptoms of the disease. Kidney damage observed in pregnant rats receiving beryllium treatment (form and dose level not given) indicated that pregnancy stress had a detrimental effect on the animal's response to beryllium (Clary and Stokinger, 1973). However, Clary, Bland, and Stokinger (1975) later reported that there was no difference in time of onset of beryllium disease, as indicated by lung granuloma, between bred and unbred beryllium-treated rats. This suggested, in opposition to their earlier findings, that pregnancy was a type of adrenal stress that did not induce latent chronic beryllium disease.

6.3.4.3 Diagnosis — Chronic beryllium disease is not always easy to diagnose (Hardy and Chamberlin, 1972), since abnormalities that occur are not specific for this disease (Tepper, Hardy, and Chamberlin, 1961). Proper diagnosis includes evidence from x rays, immunological tests, pulmonary function tests, and establishment of beryllium exposure (U.S. Department of Health, Education, and Welfare, 1972). Tissue analysis for beryllium establishes exposure but does not prove disease presence (Tepper, 1972*b*). However, all chronic cases of the disease have yielded positive lung tissue assays.

Along with establishment of exposure, clinical criteria that indicate disease presence include scattered densities on chest x rays, impaired lung function, interstitial pneumonitis, and systemic toxicity (Stoeckle, Hardy, and Chang-Wai-Ling, 1975). Radiological diagnosis is important in determining disease existence. Patterns associated with chronic beryllium disease are nodular, granular, and mixed pattern fibrosis (Hasan and Kazemi, 1974). Lesions of fine granular densities which diffusely involve the lung parenchyma are the first roentgen evidence and appear within a few weeks of symptom development (Chamberlin, G. W., 1959). A relationship seems to exist between pulmonary pathology and prognosis (Freiman and Hardy, 1970). In studying 124 chronic cases, those with minimal interstitial cellular infiltration lived longer than those with moderate to marked cellular infiltration (over 11 years as compared with 8 years). A problem in differentiating between chronic beryllium disease and sarcoidosis exists, however, these two can be correctly diagnosed by roentgenographic and clinical criteria (Israel and Sones, 1959). Weight loss may be a distinguishing symptom, since it is found in beryllium disease but not in sarcoidosis.

The beryllium patch test has been used as a diagnostic tool for chronic beryllium disease determination. However, a positive test indicates only skin sensitivity to beryllium and not necessarily disease presence (Curtis, 1959; Sarkar, Jones, and Lutwyche, 1971). The use of the patch test has been discouraged, since it may induce a skin sensitivity reaction (Sarkar, Jones, and Lutwyche, 1971).

6.3.4.4 Symptoms — The most common symptoms of the chronic disease are dyspnea on exertion (Hardy, 1948) and a usually nonproductive cough (Hardy and Stoeckle, 1959). Weight loss, fatigue, and anorexia also occur; the mortality rate in this type of case is high, and some degree of permanent

disability usually remains in all survivors (Greenburg, 1972). Table 6.16 lists the symptoms and their frequencies in 76 cases reported to the Beryllium Case Registry since 1966. Along with these symptoms, renal calculi and pneumothoraces were found (Hasan and Kazemi, 1974). The delay of symptom onset from time of last exposure for patients exposed prior to and after 1949 is shown in Figure 6.10. Most patients exposed prior to 1949 had a delay period of more than ten years, whereas those exposed after 1949 had a delay period of less than a year. This is attributed to better diagnostic techniques, with earlier recognition of the disease. Other symptoms that usually occur during the progress of the disease are clubbing of fingers, lymphadenopathy, liver enlargement, skin lesions, spleen enlargement, and thyroid gland enlargement (Hardy, 1950).

TABLE 6.16. SYMPTOMS OF 76 CASES OF CHRONIC BERYLLIUM DISEASE REPORTED TO THE BERYLLIUM CASE REGISTRY SINCE 1966

Symptom	Number of cases	Percent
Exertional dyspnea	51	67.1
Cough	40	52.6
Fatigue	28	36.8
Weight loss	21	26.6
Chest pain	20	26.3
Arthralgia	7	9.2
Fever	6	7.8
Orthopnea	5	6.5
Anorexia	4	5.3
Hemoptysis	2	2.6
Palpitations	2	2.6
Convulsions	2	2.6
Wheezing	1	1.3
Nausea, vomiting	1	1.3
Hoarseness	1	1.3

Source: Adapted from Hasan and Kazemi, 1974, Table 2, p. 290. Reprinted by permission of the publisher.

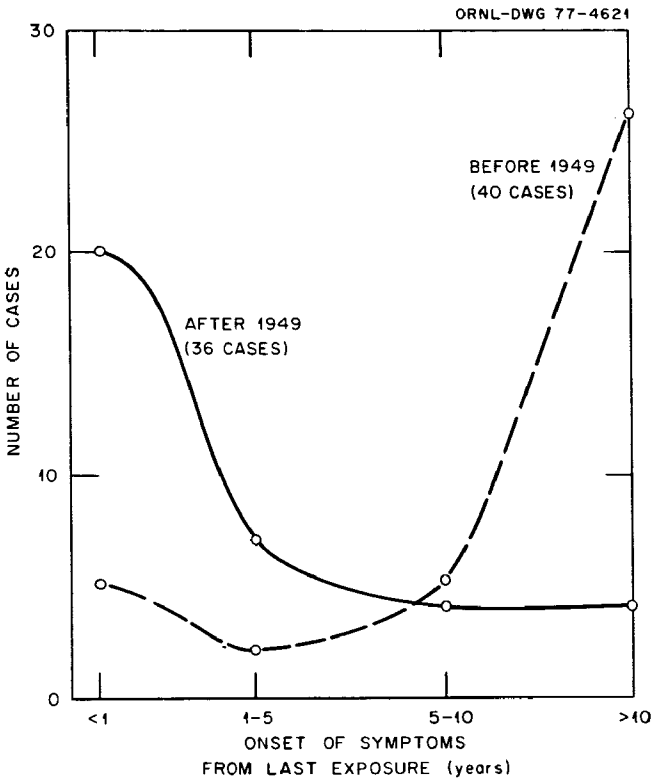

Figure 6.10. Delay in symptom onset of 76 cases of chronic beryllium disease reported to the Beryllium Case Registry since 1966. Source: Adapted from Hasan and Kazemi, 1974, Figure 1, p. 290. Reprinted by permission of the publisher.

Pulmonary changes from inhalation of beryllium compounds have occurred in experimental animals. The changes are similar to those found in humans. After inhalation of rocket exhaust products containing beryllium oxide, beryllium fluoride, and beryllium chloride at an average concentration of 115 mg of beryllium per cubic meter, beagles had lung tissue lesions representative of an early form of the chronic disease (Robinson, Schaffner, and Trachtenberg, 1968). Sanders et al. (1974) and Sanders et al. (1975) exposed rats and hamsters by inhalation to BeO calcined at 1000°C at concentrations ranging from 1 μg to 100 μg of beryllium per liter of air. Rapid damage occurred to the alveolar macrophage, which eventually produced a mild granulomatosis reaction eight months after exposure.

Moderate skin reactions of delayed-type hypersensitivity may also occur in the course of the disease (Alekseeva, Vasil'eva, and Orlova, 1974). This reaction is found also in experimental animals. Beryllium-sensitized guinea pigs developed delayed hypersensitive skin reactions when challenged with $BeSO_4$ and BeF_2 (Marx and Burrell, 1973). Reactions typical of beryllium granulomata occurred when the animals were challenged with BeO. In guinea pigs the delayed reaction results only from skin contact with beryllium (Vacher, 1972), as is the case in humans (Reeves and Krivanek, 1974). A relationship between cutaneous sensitivity and pulmonary beryllium disease appears to exist. The induction of

cutaneous beryllium sensitivity in guinea pigs produces a protective effect against pulmonary disease development (Reeves et al., 1971; Reeves et al., 1972). Hypersensitivity induction appears to provide resistance to the fibrotic and metaplastic effects of beryllium inhalation (Reeves and Krivanek, 1974). This may be significant in the prophylaxis of beryllium-exposed humans. Dudley (1959) attributed responsibility for many of the symptoms to a variable infiltration of lymphocytes and plasma cells in the tissues where the chronic reaction takes place.

6.3.4.5 Complications — The prominent complication in chronic beryllium disease is the development of cor pulmonale. Death can frequently be attributed to cor pulmonale with myocardial decomposition (Tepper, Hardy, and Chamberlin, 1961). Of 45 cases of the chronic disease, cor pulmonale was observed in 33% of the patients (Konchalovskaya and Glotova, 1969; Orlova and Glotova, 1969). The frequency and intensity increased with increased severity of pulmonary insufficiency. Kelley, Goldfinger, and Hardy (1969) reported hyperuricemia in 40% (6 of 15) of the patients examined. The elevated serum urate resulted from diminished renal clearance of uric acid rather than increased production of the compound.

6.3.4.6 Industrial and Neighborhood Cases — Chronic beryllium disease has been associated with most industries in which beryllium is used. Table 6.17 gives the mortality of the chronic disease by industry. From 1960 to 1968, 41 patients with the disease were examined at Massachusetts General Hospital (Andrews, Kazemi, and Hardy, 1969). Three different pulmonary dysfunction patterns were observed: obstructive, interstitial, and restrictive defects. These appeared to correlate with the anatomic lung alterations. As seen in Table 6.18, most of the exposures, 27 of 41, occurred in fluorescent lamp manufacturing. Smoking habits were taken into account and seemed to play a part in the appearance of the obstructive pattern in some of the patients. A case of the chronic disease, which had been ongoing for ten years, was observed in Spain (Matilla et al., 1973). The case was not diagnosed until hospital admittance, at which time the patient showed labial cyanosis, cough, dyspnea, a tender epigastrum, and rales. The patient had been exposed for 14 years while working in a French electrical appliance factory.

A study of a beryllium extraction and processing plant in operation for 14 years revealed 31 cases of the chronic disease out of 214 workers studied; 2 cases appeared between 1971 and 1973 (Kanarek et al., 1973). These 31 had radiographic abnormalities compatible with interstitial disease, and 11 of the 31 had hypoxemia. The beryllium air levels usually exceeded the standard of 2 $\mu g/m^3$; they ranged from 0.35 to 213 $\mu g/m^3$ in the billet plant and 0.31 to 1310 $\mu g/m^3$ in the fabrication plant.

A case of beryllium skin granuloma due to beryllium oxide was reported (Williams, Lawrie, and Davies, 1967; Williams, 1971). The patient cut his finger on a grinding wheel contaminated with the compound. This led to amputation of the finger and lymphatic spread of beryllium to produce granulomata of the forearm and lung.

Cases of chronic beryllium disease have been reported in the vicinity of industrial sources (Hardy and Chamberlin, 1972). Thus far, 45 cases

TABLE 6.17. MORTALITY OF CHRONIC BERYLLIUM DISEASE BY INDUSTRY UP TO 1966

	Number		Percent dead	Total
	Living	Dead		
Extraction-smelting	57	21	27	78
Fluorescent lamp	170	79	32	249
Atomic energy	33	6	15	39
Neon tube	8	15	65	23
Ceramics	12	19	43	21
Foundry-machining	12	9	43	21
Cathode-tubes	11	8	42	19
Alloy	3	10	77	13
Tube disposal	2	7	78	9
Other	3	0	0	3
Total workers	311	164	35	475

Source: Adapted from Redding, Harding, and Gaensler, 1968, Table 11, p. 272. Reprinted by permission of the publisher.

have been reported in persons living within 1/2 mile of the source or in persons handling contaminated clothing of workers. As early as 1949, neighborhood cases were reported (Eisenbud et al., 1949). Eleven cases were observed near a processing plant; ten of the patients resided within 3/4 mile of the plant. The eleventh patient's disease was thought to result from contamination introduced into the home by worker's clothes. Lieben and Williams (1969) reported a total of 29 neighborhood cases around a beryllium refinery. Some of these patients lived more than 3 miles away but came within 1/2 mile of the refinery routinely. These neighborhood cases of beryllium disease are thought to have occurred from close contact with a contaminated person or object rather than from general air pollution (Preuss, 1975).

6.3.4.7 Treatment — Prior to treatment with steroids (Seeler, 1959) and adrenocorticotropic hormone (ACTH), chronic beryllium disease treatment consisted of bed rest and oxygen administration (Tepper, Hardy, and Chamberlin, 1961). Now, long-term therapy with daily doses of steroids in the range of 75 to 150 mg or more has proven effective (Hardy and Chamberlin, 1972).

TABLE 6.18. CLINICAL DATA ON PATIENTS WITH CHRONIC BERYLLIUM DISEASE

Patient	Age	Sex	Type of exposure	Duration of exposure (years)	Delay in onset from first exposure (years)	Smoking history	Last tests (years after first exposure)
				Interstitial group			
S.R.	48	F	Fluorescent lamp	4	8	0	28
M.D.	47	F	Fluorescent lamp	9	12	0	28
E.I.	42	F	Fluorescent lamp	7	11	0	23
F.P.	42	F	Fluorescent lamp	0.5	11	0	24
D.B.	45	F	Fluorescent lamp	2	9	+	24
J.C.	43	M	Fluorescent lamp	1	5	0	24
L.W.	66	M	Atomics	2	22	0	23
W.D.	58	M	Atomics	0.5	0.5	0	24
P.K.	54	M	Fluorescent lamp	1	5	-	26
W.G.	58	M	Fluorescent lamp	10	5	+	
S.A.	49	M	Atomics	0.5	5	0	21
F.B.	50	F	Fluorescent lamp	1	18	0	23
M.S.	48	M	Beryllium alloy	19	15	+0'60	
S.N.	35	F	Fluorescent lamp	2	12	0	20
W.J.	53	M	Ceramics	3	15	0	18
P.T.	52	F	Fluorescent lamp	2		-	37
				Restrictive group			
G.R.	58	M	Foundry	8	6	0	28
A.Z.	51	F	Fluorescent lamp	9	9	0	28
P.S.	51	M	Fluorescent lamp	1	22	0	29
E.H.	26	M	Foundry	0.5	None (immediate)	+	5
M.H.	52	F	Fluorescent lamp	3	19	0	24
M.F.	35	F	Fluorescent lamp	3	12	0	20
T.C.	44	M	Fluorescent lamp	2		+	
J.S.	57	M	Ceramics	1	13	+	18
				Obstructive group			
L.H.	45	M	Fluorescent lamp	2.5	8	+	28
M.C.	43	F	Fluorescent lamp	5	6	0	28
L.S.	43	F	Fluorescent lamp	1.5	9	+	26
H.G.	47	F	Fluorescent lamp	3	15	0	28
A.S.	47	M	Fluorescent lamp	3	3	0	26
E.W.	39	F	Ceramics	4.5	4	+	19
N.S.	45	F	Fluorescent lamp	1	24	-	25
M.B.	48	F	Fluorescent lamp	1		0	26
D.M.	47	F	Metal (beryllium)	3	8	+0	20
B.G.	38	F	Fluorescent lamp	5	8	-	20
F.G.	45	M	Ceramics	5		+0'65	
V.M.	53	M	Ceramics			-	23
K.K.	45	F	Atomics	2		0	24
J.V.	40	F	Fluorescent lamp	1		+0'58	
M.C.	40	F	Fluorescent lamp	1.5	9	-	17
				Normal group			
C.F.	51	F	Fluorescent lamp	8	23	+	24
L.R.	39	M	Atomics	1	18	0	18

Source: Adapted from Andrews, Kazemi, and Hardy, 1969, Table 1, p. 792. Reprinted by permission of the publisher.

A patient with the chronic disease received treatment with prednisone at 60 mg/day, which was reduced to 15 mg/day over a four-month period (Henderson, 1970). As a result of treatment, clinical, radiological, and lung function improvement followed. Symptoms reoccurred as the dosage decreased; hence it was necessary to keep the patient on a 15-mg/day dose. Another patient was relieved of symptoms on a maintenance dose of 20 mg/day of prednisone (Neff and Petty, 1969). Treatment with steroids on a continued basis has led to marked improvement in patients; however, because of the long duration of the disease, total cure cannot be established (U.S. Department of Health, Education, and Welfare, 1972).

Chelating agents for removal of deposited tissue beryllium have been explored. Among these, aurintricarboxylic acid proved effective in protecting mice and rats if given parenterally 1 to 8 hr after intravenous injection of an otherwise lethal dose of beryllium sulfate. The chelate tended to accumulate in the kidneys and spleen (White, Finkel, and Schubert, 1951; Schubert, White, and Lindenbaum, 1952; Schubert and Rosenthal, 1959). In the Soviet Union, organophosphorus complexons were tried in animal experiments (Arkhipova, Zel'tser, and Petushkov, 1966). However, for the alleviation of the chronic disease, chelating agents have proved thus far ineffective, and clinical trials were disappointing (Dequindt and Haguenoer, 1973).

6.3.5 Carcinogenesis

Experimental findings show that beryllium compounds are capable of producing malignant tumors in experimental animals (Vorwald, Reeves, and Urban, 1966). Of all the beryllium compounds tested, only five have been shown carcinogenic: beryllium oxide, beryllium sulfate, beryllium fluoride, beryllium phosphate, and the phosphor zinc manganese beryllium silicate (Schepers, 1961). A summary of experimental beryllium carcinogenicity is provided in Table 6.19. Tumors induced in species in the above table include adenocarcinoma, epidermoid carcinoma, mixed carcinoma, pleural mesothelioma, alveolar cell carcinoma, reticulum cell sarcoma of lymph nodes, and osteogenic sarcoma.

6.3.5.1 Human Carcinogenesis — Counterparts to cancers produced in experimental animals by beryllium have not been observed in humans (U.S. Department of Health, Education, and Welfare, 1972). Epidemiological studies to show a relationship between beryllium exposure and cancer incidence have not provided data for the existence of such a relationship (International Agency for Research on Cancer, 1972). The fact that human beryllium cancer has not been identified, however, may be a result of chemical carcinogens not remaining at the cancer site. The causative agent often cannot be identified except through work histories. Hence, beryllium may be overlooked as a causal agent.

Cancer has been reported among beryllium workers, although a direct relationship lacks proof. Mancuso and El-Attar (1969) studied the cancer incidence of workers in two beryllium companies and reported no correlation between cancer at any specific site and the worker's beryllium exposure. In contrast, two cases of delayed lung carcinoma induced by beryllium aerosol were reported by Niemöller (1963). In each case the carcinoma was detected 16 years after the last exposure. No incidence rates were given, and no correlation between beryllium and cancer rate could be concluded. In a retrospective study of employees in two beryllium companies, Mancuso (1970) reported a higher rate per 100,000 for lung cancer among the workers with prior respiratory illness than among the total workers. Mancuso suggested that prior chemical respiratory illness may influence the development of lung cancer among beryllium workers.

6.3.5.2 Pulmonary Cancer — Development of pulmonary cancer generally requires 7 to 13 months in rats and four to five years in monkeys (Vorwald,

TABLE 6.19. BERYLLIUM COMPOUNDS EXPLORED FOR CARCINOGENICITY

Substance	Animal species	Route	Concentration or dosage	Duration (months)	Carcinogenesis
Fluoride	Rat	Inhalation	48 $\mu g/m^3$	15	+
	Monkey	Inhalation	953 $\mu g/m^3$	5	
	Guinea pig	Subcutaneous	1 mg	12	
Metal	Guinea pig	Intratracheal	75 mg	3	
	Guinea pig	Intraperitoneal	200 mg	5	
	Rabbit	Intravenous	1 g	8	
Hydroxide	Rabbit	Intravenous	100 mg	2	
	Guinea pig	Intraperitoneal	200 mg	7	
	Guinea pig	Intratracheal	150 mg	4	
Oxide	Guinea pig	Intraperitoneal	200 mg	7	
	Guinea pig	Intratracheal	150 mg	9	
	Rabbit	Intravenous	1 g	12	+
	Rat	Intravenous	65 mg	8	
	Rat	Inhalation	28 mg/m^3	12	
Carbide	Guinea pig	Intraperitoneal	200 mg	5	
Phosphate	Rat	Intravenous	5 mg	2/3	
	Mouse	Intravenous	1 mg	2/3	
	Guinea pig	Intracardiac	25 mg	2/3	
	Rabbit	Intravenous	100 mg	10	
	Rat	Inhalation	3.5 mg/m^3	12	+
	Pig	Subcutaneous	1 mg	12	
	Monkey	Inhalation	0.9 mg/kg	4	+
Silicate ($ZnMnBeSiO_4$)	Rat	Intravenous	80 mg	12	
	Rat	Intratracheal	20 mg	12	
	Rat	Inhalation	25 mg/m^3	9	+
	Guinea pig	Intratracheal	150 mg	12	
	Rabbit	Intravenous	1 g	10	+
	Rabbit	Intraperitoneal	40 mg	12	
	Rabbit	Inhalation	25 mg/m^3	24	
	Dog	Intravenous	1.3 g	40	
	Guinea pig	Inhalation	25 mg/m^3	22	
	Guinea pig	Intracardial	80 mg	4	
Sulfate	Guinea pig	Inhalation	424 $\mu g/m^3$	12	
	Rat	Inhalation	424 $\mu g/m^3$	18	+
	Monkey	Inhalation	424 $\mu g/m^3$	8	
	Pig	Subcutaneous	1 mg	12	
	Rabbit	Intravenous	100 mg	25	
	Guinea pig	Intratracheal	150 mg	12	

Source: Schepers, 1961, Table 11, p. 208. Reprinted by permission of the publisher.

Reeves, and Urban, 1966). Vorwald (1967) exposed 16 rhesus monkeys to $BeSO_4$ mist at an atmospheric level of 35 µg of beryllium per cubic meter of air for 6 hr daily, five days a week. The first pulmonary cancer occurred in a male exposed for 3241 hr. Over a period of the next four years, seven other monkeys developed lung cancer. One female monkey did not develop cancer after 3303 hr of exposure. The remaining monkeys died of acute chemical pneumonitis early in the study.

Numerous reports exist on the development of pulmonary cancer in beryllium-exposed rats. Wagner et al. (1969) produced pulmonary tumors in 18 of 19 rats that survived 17 months of exposure to 15 mg of beryl per cubic meter. One hundred fifty rats were exposed to $BeSO_4$ aerosol at an atmospheric concentration of 34.25 µg of beryllium per cubic meter for 72 weeks (Reeves, Deitch, and Vorwald, 1967). A proliferative response consisting of epithelial hyperplasia commenced rapidly at four weeks after initial exposure. This response progressed through metaplasia and anaplasia to lung cancer, with the first tumors found after nine months of

exposure. At 13 months the incidence rate reached 100%, vs 0% in controls. All tumors were alveolar adenocarcinomas, with focal intermixture of other kinds in some instances. Rats given 5 ppm beryllium as the sulfate in drinking water developed tumors of which 44% and 57% were malignant in males and females, respectively (Schroeder and Mitchener, 1975*a*). Data were not given concerning kind or site of tumors.

Intratracheal injections of beryllium in rats have induced cancers. Beryl ore, BeO, $Be(OH)_2$, beryllium metal, chromium-passivated beryllium metal, and beryllium-aluminum alloy produced adenomas, adenocarcinomas, and epidermoid carcinomas in rats given single injections of these substances (Groth, Stettler, and MacKay, 1976). The age of the rat and dose of the compound determine the size, number, and quality of the lesions produced. Twelve- and three-month-old rats injected with 40, 4, or 0.4 µg of beryllium as $Be(OH)_2$ had one adenocarcinoma in the oldest group receiving the highest dose. The greatest number of metaplastic foci occurred in the older rats at doses of 40 and 4 µg; none were formed at 0.4 µg exposure. Four micrograms was the lowest dose that induced mast cell and lymphocytic infiltrates, and interstitial fibrosis and proteinaceous material in the alveoli (Groth, Scheel, and MacKay, 1972). Metaplasia, produced with the 4-µg dose, is a consistent feature of low-level exposures and is probably a precursor to cancer (Groth and Mackay, 1971). Rat pulmonary tumors, bronchiolar alveolar cell tumors, and mixed adenocarcinoma-bronchiolar alveolar cell tumors have been induced by doses of 0.25 mg of $Be(OH)_2$ administered by single injection (Mackay, Groth, and Mead, 1970).

6.3.5.3 Sarcoma in Rabbits — Sarcomas in rabbits have been induced by injection of zinc beryllium silicate and beryllium oxide; histologically they are of three types: chondroblastic, osteoblastic, and fibroblastic (Vorwald, Reeves, and Urban, 1966). Osteogenic sarcomas developed in six of nine rabbits administered serial intravenous injections of $Be(OH)_2$ or a phosphor containing $Be(OH)_2$ three times a week from six to eight weeks (Dutra and Largent, 1950). Tumors appeared within a period of 16 months after the initiation of treatment (Table 6.20). Analysis of tumor tissue showed that the tumors contained little beryllium. Tumors transplanted from one animal into the anterior chamber of the eyes of guinea pigs continued to grow, thus indicating that once established, tumor growth was independent of the presence of beryllium. Higgins, Levy, and Yollick (1964) also successfully transplanted beryllium-induced chondrosarcoma tumors from the host rabbit into the anterior eye chamber of recipient rabbits.

Sarcomas formed in 4 of 12 rabbits injected with 20 mg of zinc beryllium silicate into the medullary cavity of the upper end of the right tibia (Tapp, 1966). The tumors formed 12 to 15 months after injection, and in appearance they resembled bone sarcomas found in man. All tumors metastasized to the lungs and in some cases into the parietal pleura and hilar lymph nodes. Tapp (1969*a*) also produced osteogenic sarcomas in 4 of 18 rabbits 10 to 25 months after implantation of 10 mg of zinc beryllium silicate, beryllium silicate, or beryllium oxide. These tumors metastasized into the lungs. The initial reactions to beryllium salt implantation was

TABLE 6.20. OSTEOSARCOMAS INDUCED BY BERYLLIUM

Rabbit number	Substance (1% suspension in saline solution)	Dose (ml)	Number of doses	Total amount of beryllium (g)	Date of first dose	Date of last dose	Date tumor found
Be 17	Phosphor	8	21	0.09	8/14/47	10/3/47	8/16/48
Be 24	BeO	8	23	0.66	8/14/47	10/6/47	10/16/48
Be 26	BeO	5	20	0.36	9/15/47	11/3/47	8/27/48
Be 29	BeO	7.5	26	0.70	9/15/47	11/15/47	9/14/48
Be 31	Phosphor	8	25	0.08	9/17/47	11/15/47	9/2/48
Be 27	BeO	5	20	0.36	9/15/47	11/15/47	10/13/48
Be 4	Phosphor	7	17	0.064	8/27/47	10/6/47	*a*
Be 23	BeO	6-7	21	0.50	8/14/47	10/3/47	*b*
Be 28	BeO	7.5	24	0.58	9/15/47	11/15/47	*b*

[a]No tumors found.

[b]Tumors found after paper was submitted for publication.

Source: Adapted from Dutra and Largent, 1950, Table 1, p. 198. Reprinted by permission of the publisher.

a granulomatous reaction, which was most marked with beryllium silicate and least with beryllium oxide (Tapp, 1969*b*). The granulomatous reaction decreased three to six months after administration; however, focal accumulations of beryllium-containing macrophages remained in the medullary cavity. Following intramedullary injection of zinc beryllium silicate and engulfment by macrophages, the beryllium salt crystal appears to provide a prolonged release of beryllium ions, which destroy the host cell (Schneider, Resnick, and Wellmann, 1973). This reaction seems to provide a stimulus for new bone formation following beryllium administration by intravenous or intramedullary injection.

6.3.6 Teratogenicity and Mutagenicity

No data exist concerning the teratogenic or mutagenic effects or lack of these effects by beryllium in humans or other mammals.

SECTION 6

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SECTION 7

ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

7.1 SUMMARY

Beryllium and its compounds are widely used in industry, primarily in electrical applications. There are two American beryllium producers — Brush-Wellman, Inc., of Elmore, Ohio, and KBI Industries, of Reading, Pennsylvania. United States demand for beryllium is expected to be 1500 metric tons (1660 tons) in the year 2000; U.S. reserves are estimated at 72,700 metric tons (80,100 tons). About 95% of the beryllium ore used in the United States is imported, although domestic production is expected to increase until it accounts for about half the ore consumed.

Beryllium enters the environment principally from coal combustion. World coals contain 0.1 to 1000 ppm beryllium and estimates indicate that as much as 84% of this beryllium can be released during combustion. The second major source of beryllium release is beryllium production, which accounts for about 4% of all beryllium released. Other sources include oil combustion, ceramic manufacture, rocket firing, and space vehicle heat shield evaporation. The two U.S. beryllium production plants, located in Pennsylvania and Ohio, are the sites of most U.S. emissions.

The beryllium content of common rocks and minerals ranges from less than 1 ppm to about 10 ppm, while beryllium ores may contain several thousand parts per million. The major ore is beryl, which contains about 5% beryllium metal. Major U.S. beryllium deposits are found in Kentucky, Texas, Arizona, Nevada, and Idaho. World soils average 6 ppm beryllium, with a range of 0.1 to about 40 ppm; U.S. soils average about 1 ppm beryllium or less.

Beryllium is almost nonexistent in natural waters: freshwater averages less than 0.001 ppm, and seawater contains about 0.0000006 ppm. Beryllium in water is primarily in solution rather than in suspension. Sediments contain 2 to 3 ppm. Finished U.S. waters average 0.00019 ppm beryllium and range from 0.00001 to 0.00122 ppm. The recommended provisional limit for beryllium in water is 1 ppm.

Unpolluted air usually contains less than 0.0001 $\mu g/m^3$ beryllium. Urban air generally contains more than rural air. The average daily atmospheric concentration in the United States is less than 0.0005 $\mu g/m^3$. In the past, elevated beryllium concentrations have been found in air near beryllium processing plants, but pollution control equipment is available and is now employed to meet U.S. air standards (an average of 0.01 $\mu g/m^3$ beryllium over a 30-day period).

Beryllium chemistry in the soil has not been thoroughly investigated, but it is thought to be similar to that of aluminum or zinc. The beryllium ion participates in cation exchange reactions and undergoes isomorphic substitution in secondary clay minerals. Beryllium is strongly fixed

in many soils and will displace divalent cations which share common sorption sites. Residence times for beryllium in soil were not located in the literature.

The oxide and hydroxide of beryllium are relatively insoluble at the common pH of natural waters; hence, beryllium does not readily go into solution during the weathering process. About 9600 metric tons (10,579 tons) beryllium is added to the oceans each year in water and sediments; approximately 0.00002% of this amount is retained. The residence time of beryllium in the oceans is on the order of a few hundred years.

Only a small amount of the total beryllium waste produced by industry is composed of actual beryllium scrap. Beryllium users can resell virtually all scrap to producers. The major portion of beryllium wastes results from pollution control efforts. It is recommended that wastes that cannot be recycled be buried in plastic containers sealed in metal drums. These practices are judged adequate to handle beryllium wastes now and in the foreseeable future.

Data concerning the beryllium content of food are scarce. An Australian study found the beryllium content of foodstuffs to be low, ranging from 0.01 to 0.10 ppm. Oyster flesh and mushrooms contained the highest values. Zorn and Diem (1974) measured beryllium concentrations in food crops and tobacco in Western Germany. They found in polished rice 0.08, in toasted bread 0.12, in potatoes 0.17, in tomatoes 0.24, and in head lettuce 0.33 µg beryllium per gram dry substance. In three brands of cigarettes, the values were 0.47, 0.68, and 0.74 µg beryllium per cigarette, with 4.5%, 1.6%, and 10.0% of the beryllium content, respectively, escaping into the smoke during smoking. Beryllium is not known to biomagnify within the food chain.

7.2 PRODUCTION AND USAGE

Beryllium is used in industry in three main forms: beryllium metal, beryllium alloys, and beryllium oxide (Table 7.1). Two beryllium producers exist in the United States — Brush-Wellman, Inc., of Elmore, Ohio, and KBI Industries, of Reading, Pennsylvania (Ottinger et al., 1973). Production is 45.4 to 68 metric tons (50 to 75 tons) of beryllium metal per year, divided about equally between the two plants (Eilertsen, 1965).

Major uses of beryllium and its compounds are given in Table 7.1. Approximately 25% of all beryllium is used in switchgear; 30% in computer, radio, television, and electrical applications; 10% in nuclear applications; 10% in missiles and space programs; and the remainder in welding and other applications (Heindl, 1970).

Estimated supply-demand relationships for beryllium in 1968 are given in Figure 7.1. The forecast median demand for the United States in the year 2000 (Table 7.2) is 1500 metric tons (1660 tons) (Heindl, 1970). U.S. beryllium reserves are estimated at 72,667 metric tons (80,100 tons) (Table 7.3). Data concerning beryllium reserves in the rest of the world are lacking. Heindl (1970) estimates the cobbable beryl reserves of 25 countries, other than the United States, at 272,160 kg (300,000 tons, 12,000

TABLE 7.1. USES OF BERYLLIUM

Form	Use
Beryllium metal	Nuclear applications
	Gyroscopes
	Accelerometers
	Inertial guidance systems
	Rocket propellants
	Aircraft brakes
	Heat shields for space capsules
	Portable x-ray tubes
	Optical applications
	Turbine rotor blades
	Mirrors
	Missile systems
	Nuclear weapons
Beryllium-copper alloy	Springs
	Bellows
	Diaphragms
	Electrical contacts
	Aircraft engine parts
	Welding electrodes
	Nonsparking tools
	Bearings
	Precision castings
	High-strength, current-carrying springs
	Fuse clips
	Gears
Beryllium oxide	Spark plugs
	High-voltage electrical components
	Rocket-combustion-chamber liners
	Inertial guidance components
	Laser tubes
	Electric furnace liners
	Microwave windows
	Ceramic applications

Source: Adapted from U.S. Environmental Protection Agency, 1973*a*, Table 2-3, p. 2-3.

tons of beryllium). About 95% of the beryllium ore used in the United States is imported (Griffitts, 1973). Three-fourths of the imported ore comes from Brazil, the Republic of South Africa, India, Argentina, and Mozambique. Domestic production is expected to increase, however, until it accounts for at least half the ore consumed.

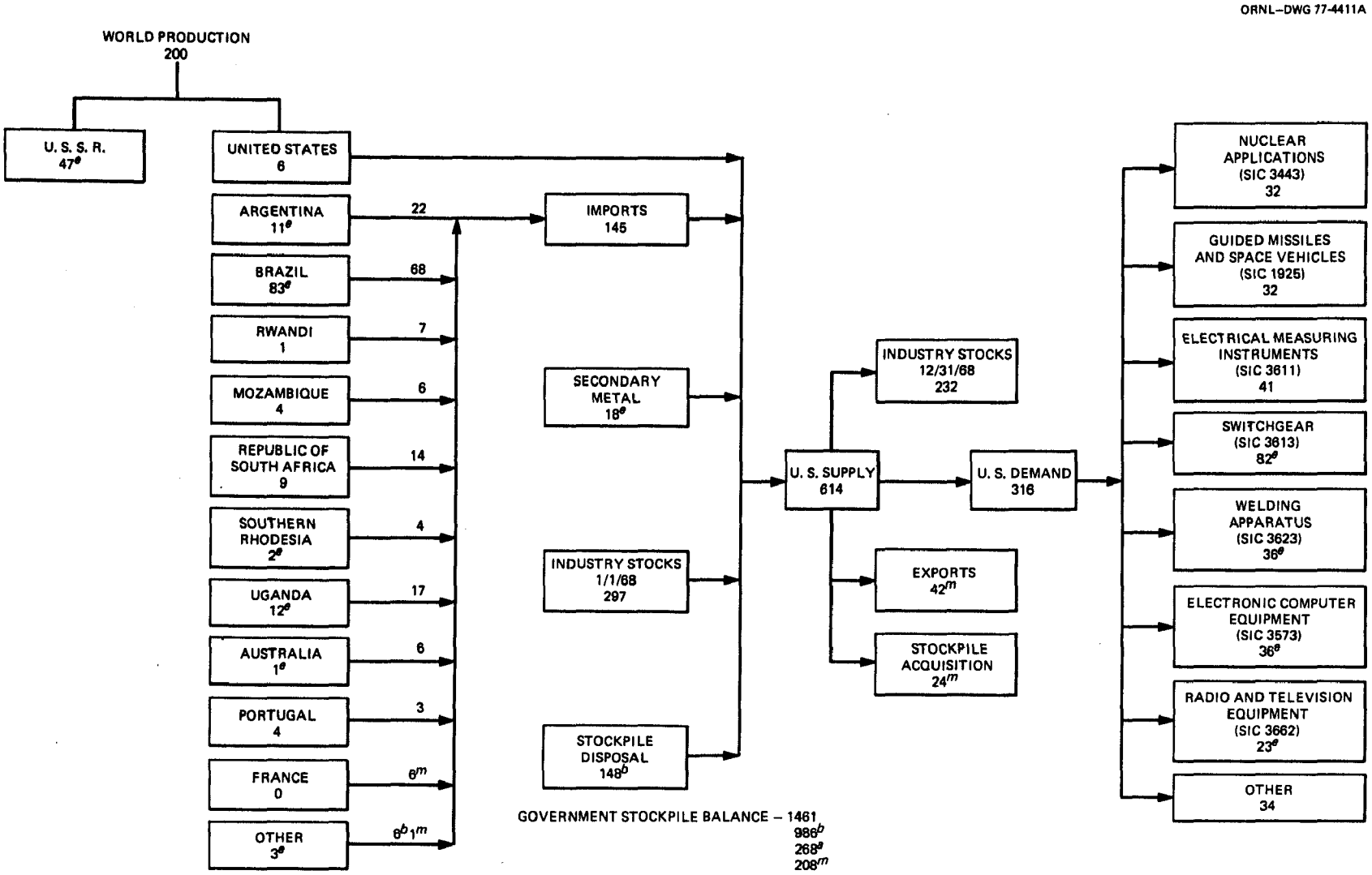

Figure 7.1. Supply-demand relationships for beryllium, 1968. Values are in metric tons of beryllium, *e* = estimate, *b* = beryl, *a* = Be-Cu master alloy, *m* = metal, SIC = Standard Industrial Classification. Source: Adapted from Heindl, 1970, Figure 1, p. 493.

TABLE 7.2. FORECAST OF BERYLLIUM DEMAND

	Forecast range of demand for beryllium (metric tons)	
	1968	2000
Total		
United States		
High	316	1750
Low		1260
Median		1500
Primary		
United States		
High	298	1580
Low		1130
Median		1350
Rest of world		
High	136	1200
Low		360
Median		770

Source: Modified from Heindl, 1970, p. 497.

TABLE 7.3. UNITED STATES RESERVES OF BERYLLIUM

Type of deposit and grade of ore (%)	Size of individual deposits (metric tons)	Beryllium content (metric tons)	Location
Pegmatites			
+1 beryl	At least 100	400	Mostly in New England and South Dakota
0.2-1 beryl	At least 100	9,800	Mostly in North Carolina
0.4 beryl		37,000	North Carolina
Nonpegmatites			
0.5 BeO		24,000	Bertrandite at Spor Mountain, Gold Hill, Utah
0.5 BeO		800	Bertrandite and phenacite in Nevada

Source: Heindl, 1970, Table 1, p. 492.

7.3 DISTRIBUTION OF BERYLLIUM IN THE ENVIRONMENT

7.3.1 Sources of Pollution

Beryllium enters the environment from a variety of sources (Table 7.4). The major source is coal combustion. World coals contain 0.1 to 1000 ppm beryllium (Bowen, 1966). Ruch, Gluskoter, and Shimp (1974) reported an average of 1.61 ppm in 101 U.S. coals, most of which came from the Illinois Basin. Colorado coal contains 2.5 ± 0.5 ppm beryllium (Phillips, 1973). Over 1300 coals were analyzed by Stadnichenko, Zubovic, and Sheffey (1961) (Table 7.5). The average beryllium in ash was 46 ppm. The highest value was 62 ppm, found in ash of coal from the Appalachian region. Overall, beryllium was primarily concentrated in the vitrain coal type.

Much of the beryllium in coal is released to the environment during combustion. Phillips (1973) calculates that 84% of the beryllium in Colorado coals is lost to the atmosphere upon combustion. The U.S. Environmental Protection Agency (1971) estimates that 0.26 kg (0.58 lb) of beryllium is released for every 907 metric tons (1000 tons) of coal burned. About 133 metric tons (147 tons) of beryllium was emitted in the United States in 1968 due to coal combustion.

TABLE 7.4. SOURCES OF BERYLLIUM EMISSIONS TO THE ENVIRONMENT

Source	Annual emission (metric tons)	Percent of this pollutant
Mica, feldspar mining	Negligible	Negligible
Gray iron foundry cupolas	4	2.77
Ceramic coatings	Negligible	Negligible
Beryllium alloys and compounds	5	3.64
Beryllium fabrication	Negligible	Negligible
Power plant boilers		
Pulverized coal	78	59.62
Stoker coal	9	6.93
Cyclone coal	3	2.08
All oil	2	1.39
Industrial boilers		
Pulverized coal	7	5.55
Stoker coal	12	9.01
Cyclone coal	2	1.39
All oil	2	1.39
Residential and commercial boilers		
Coal	1	0.69
Oil	7	5.55
Total	132	100.01

Source: Adapted from Duncan, Keitz, and Krajeski, 1973, Table V, p. 24.

TABLE 7.5. AVERAGE BERYLLIUM CONTENT OF COAL ASH

Region	Number of samples	Average ash content (%)	Average beryllium content of the ash (ppm)
Eastern	376	7.59	62
Interior	586	7.71	49
Northern Great Plains	189	9.83	27
Rocky Mountains	191	6.22	24
Total	1342	7.74	46

Source: Adapted from Stadnichenko, Zubovic, and Sheffey, 1961, Table 7, p. 285.

Oil combustion also results in beryllium release. Data regarding the beryllium content of crude and residual oils in the United States are scarce (U.S. Environmental Protection Agency, 1971). One electric company reported that oil used in 1968 contained less than 0.1 ppm beryllium. The U.S. Environmental Protection Agency (1971) estimates that oil used in 1968 contained 0.08 ppm beryllium, providing an emission of 7.3 metric tons (8 tons) of beryllium upon combustion.

Many forms of beryllium are emitted from extraction plants (Table 7.6). These facilities are required to limit ambient beryllium concentrations to 0.01 $\mu g/m^3$ and have demonstrated their ability to operate within this limit (U.S. Environmental Protection Agency, 1973*a*). Beryllium fabrication provides an atmospheric release of 4.5 kg (10 lb) of beryllium for every 907 metric tons (1000 tons) of beryllium processed (U.S. Environmental Protection Agency, 1971). About 6 kg (13 lb) of beryllium was emitted by this process in 1968.

Ceramic plants release some beryllium to the environment. These emissions are almost entirely in the form of dusts, fumes, and mists containing beryllium oxide (U.S. Environmental Protection Agency, 1973*a*). About 0.45 kg (1 lb) of beryllium is released for every ton of beryllium processed in the manufacture of beryllia ceramics (U.S. Environmental Protection Agency, 1971). Fourteen and one-half metric tons (16 tons) of beryllium was released to the U.S. atmosphere in 1968 as a result of ceramic manufacture.

Beryllium machining facilities produce a variety of emissions. Depending on the machining operation in use, chips, dust, mists, or fumes may be produced (U.S. Environmental Protection Agency, 1973*a*). Emissions from beryllium and beryllium oxide machine shops are generally controlled, in contrast with those from Be-Cu alloy machine shops, which use only low-efficiency filters to retain large chips for recycling.

TABLE 7.6. CHARACTERIZATION OF THE EMISSIONS OF BERYLLIUM EXTRACTION PLANTS

Extraction plant operation	Emissions	Control device
Ore crushing	Beryl ore dust	Dry cyclone, baghouse
Ore milling	Beryl ore dust	Dry cyclone, baghouse
Mulling	Beryl ore dust, Na_2SiF_6, Na_2CO_3	Baghouse
Briquetting	Briquette dust	Baghouse
Sintering	Beryl dust, sinter dust	Venturi scrubber
Briquette crushing and milling	Briquette dust	Dry cyclone, baghouse
Slurrying	Ground sinter	Baghouse
Thickening	Sinter slurry	Scrubber
Filtering	Sodium fluoroberyllate	Scrubber
Leaching	Ammonium persulfate fume	Scrubber
High-purity beryllium hydroxide production	$Be(OH)_2$ slurry, H_2SO_4 fume	Scrubber
Beryllium metal production	$(NH_4)_2BeF_4$ slurry, $PbCrO_4$, CaF_2, HF, $Be(OH)_2$, BeF_2, NH_4F fume, Mg, Be, MgF_2, BeO acid fume	Packed tower scrubber, scrubbing tower, floating bed scrubber, dry cyclone, venturi scrubber, baghouses
Beryllium oxide production	BeO furnace fume and dust, BeO dust	Packed tower scrubber, baghouse, mist collector
Beryllium-copper alloy production	Alloy furnace dust, Be, Cu, BeO	Settling chamber, cyclone, baghouse

Source: Adapted from U.S. Environmental Protection Agency, 1973*a*, Table 3-1, p. 3-12.

Foundry operations that generate beryllium fumes include (1) melting of ingots, (2) preheating of crucibles that have previously contained beryllium, (3) transfer of alloy among crucibles, (4) drossing and dross handling, (5) charging molds with alloys, and (6) finishing operations (U.S. Environmental Protection Agency, 1973*a*). Cast iron production results in particulates that contain about 0.003% beryllium (U.S. Environmental Protection Agency, 1971). The degree of emission control is about

25%. Beryllium emission to the U.S. atmosphere due to cast iron production is estimated at 3.6 metric tons (4 tons) for the year 1968 (U.S. Environmental Protection Agency, 1971).

A potential for beryllium emissions exists in the rocket propellant industry. Potential releases could occur during (1) handling, weighing, and transferring of beryllium powders to mixers; (2) mixing of ingredients; (3) casting of propellant into molds; (4) curing or polymerization of propellant; (5) release of the propellant from molds; and (6) machining of propellant (U.S. Environmental Protection Agency, 1973*a*).

Rocket motor testing involving combustion of beryllium-containing propellants can provide emissions from handling of the fuel, from exhaust fumes, and from accidental fire or explosion (Durocher, 1969). Gases that may contain beryllium oxide, beryllium nitrate, beryllium carbide, and beryllium chloride are produced during testing (Beardall and Eatough, cited in U.S. Environmental Protection Agency, 1973*a*, p. 3-26; Frame, 1972). Approximately 30% of the total metallic beryllium originally in the propellant is thought to be emitted during combustion (Durocher, 1969, p. 39). Major beryllium emissions from this source are not anticipated in the future (U.S. Environmental Protection Agency, 1971).

Additional sources of beryllium release (believed not to be very significant) are evaporation of heat shields during reentry of space vehicles and missiles into the atmosphere; incineration of municipal trash or sewage (U.S. Environmental Protection Agency, 1971); transportation (U.S. Environmental Protection Agency, 1973*a*); laundering of beryllium workers' garments (Durocher, 1969); use of camping lanterns employing beryllium-coated mantles (Griggs, 1973); and mining of beryllium ore (U.S. Environmental Protection Agency, 1971).

A total of about 148 metric tons (164 tons) of beryllium was emitted to the U.S. atmosphere in 1968 (U.S. Environmental Protection Agency, 1971). The distribution of emissions by state is given in Table 7.7. Pennsylvania and Ohio account for 25% of the total, due to the beryllium production plants in those states.

7.3.2 Distribution in Rocks and Soils

The beryllium content of rocks and minerals is given in Table 7.8. According to Bowen (1966), igneous rocks average 2.8 ppm beryllium, shales about 3 ppm, and sandstones and limestones less than 1 ppm. Representative beryllium minerals are listed in Table 7.9. All but a small percentage of beryllium is in common rock-forming minerals rather than beryllium-rich minerals (Griffitts, 1973). The main beryllium ore is beryl, which contains about 5% beryllium metal (Heindl, 1970). Major beryllium deposits may be found in Kentucky, Texas, Arizona, Nevada, and Idaho (Figure 7.2).

Due to its prevalence in rocks, beryllium occurs in most soils. World soils average 6 ppm beryllium, with a range of 0.1 to 40 ppm (Bowen, 1966; Swaine, 1955). Mineral soils contain 0.2 to 10 ppm (Murrmann and Koutz, 1972). Shacklette et al. (1971) report an average of 1 ppm and a range

TABLE 7.7. BERYLLIUM EMISSIONS BY STATE, 1968

State	Beryllium emissions (metric tons)
Pennsylvania and Ohio	37
Illinois	11
Indiana	11
Michigan	10
New York	6
Alabama and Mississippi	6
West Virginia	6
Kentucky	5
North Carolina	5
Tennessee	5
Wisconsin	4
Delaware and Maryland	4
Virginia	4
Georgia and Florida	4
All other states	22
Undistributed	9
Total	149

Source: Adapted from U.S. Environmental Protection Agency, 1971, p. 3.

of 1 to 7 ppm beryllium in surficial materials of the conterminous United States (Figure 7.3). Cholak (1959) found 0.13 to 0.88 ppm (an average of 0.37 ppm) in 15 soil samples from Ohio, West Virginia, Georgia, Maryland, North Carolina, and South Carolina. Soils from Kenya, Africa, contain 0.04 to 1.45 ppm beryllium (Chamberlain, 1959). Kenyan soils high in cobalt were usually low in beryllium, and vice versa. Soils high in beryllium usually came from areas of impeded drainage or areas receiving only slight weathering.

TABLE 7.8. BERYLLIUM IN ROCKS AND MINERALS

Rock type or mineral	Beryllium content (ppm)
Igneous	6
Ultrabasic	0.2
Basalt	0.3
Nepheline syenite	0.65
Diorites	1.6
Diorite and gabbro-diorite	1.8
Granite	3.6
Shales	3.6
Shale and clay	7
Earth's crust	10
Upper part of the lithosphere	2
Talc	0.065
Asbestos	0.24
Kaolin	7.4
Monazite	0.059
Phosphate	0.08 to 3.75
Mafic	Less than 1
Silicic	6.5
Alkalic	11.4
Meteorites	0.038

Source: Adapted from Stadnichneko, Zubovic, and Sheffey, 1961 and Meehan and Smythe, 1967, Table 1, p. 256. Data collected from several sources.

TABLE 7.9. REPRESENTATIVE BERYLLIUM MINERALS

Mineral	Composition	Geological occurrence	Geographical distribution
Beryl	$3BeO \cdot Al_2O_3 \cdot 6SiO_2$	Pegmatite	Widely distributed
Beryllonite	$NaBePO_4$	Pegmatite	Maine
Bertrandite	$Be_4Si_2O_7(OH)_2$	Pegmatite	Colorado, Maine, France, Bohemia
Bromellite	BeO	Veins	Sweden
Chrysoberyl	$Be(AlO_2)_2$	Pegmatite	Brazil, Ceylon, Urals, New York
Euclase	$BeHAlSiO_5$	Pegmatite	Brazil, Urals, Austrian Alps
Hambergite	$Be_2(OH)BO_3$	Pegmatite	Norway, Madagascar
Helvite	$Mn_4Be_3Si_3O_{12}S$	Pegmatite, veins	Iron Mountain, New Mexico; Norway; Russia; Australia; Canada; Brazil
Herderite	$CsBePO_4(OH,F)$	Pegmatite	Maine
Leucophanite	$(Ca,Na)_2BeSi_2(O,OH,F)$	Pegmatite	Norway
Phenacite	Be_2SiO_4	Pegmatite	Colorado, Urals, Vosges Mountains

Source: Adapted from Krejci and Scheel, 1966, Table 4.1, p. 47. Reprinted by permission of the publisher.

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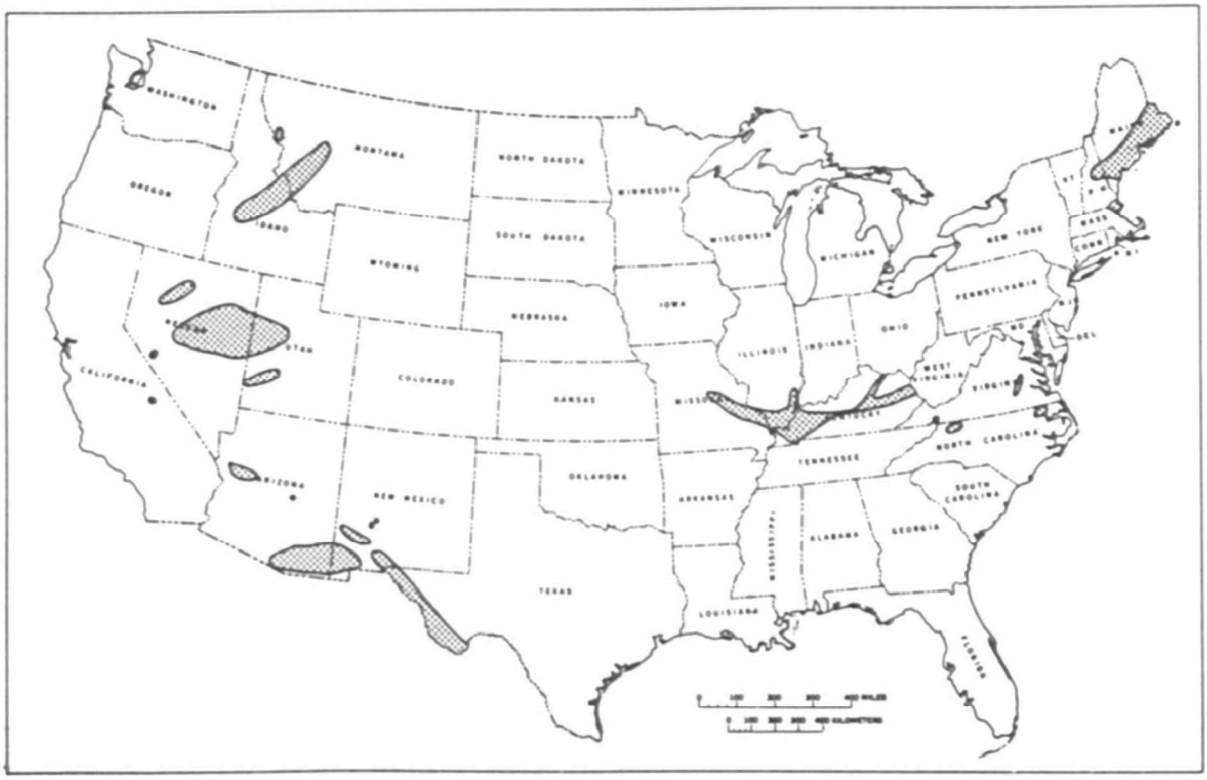

Figure 7.2. Areas of the conterminous United States in which beryllium deposits are most likely to be found. Source: Griffitts, 1978, Figure 12, p. 92.

Figure 7.3. Beryllium content of surficial materials of the United States. Source: Shacklette et al., 1971, Figure 4, pp. D16-D17.

Little information is available concerning beryllium distribution within the soil profile. Indiana losses average 6 ppm beryllium at a depth of 0.3 to 1.3 ft, 5 ppm at 1.3 to 8.8 ft, and 8 ppm at 8.8 to 17.3 ft (Leininger, 1957). Mitchell (1957) analyzed a single profile and found a decrease in beryllium content with an increase in depth. Chamberlain (1959) reported that beryllium content increased or remained stable with increased depth in seven profiles. The amount of weathering that has occurred and the type of parent material present may explain the differences in beryllium content with depth.

7.3.3 Distribution in Water and Sediments

Beryllium is almost nonexistent in natural waters (Committee on Water Quality Criteria, 1972). Bowen (1966) gave values of less than 0.001 ppm beryllium in fresh water and 0.0000006 ppm in seawater. Merrill et al. (1960) determined the average beryllium content of the Pacific Ocean to be 5.7×10^{-7} ppm. Of this, 68% was in solution and 32% in particulate form. Sediments averaged 2 to 3 ppm. According to Silker et al. (1968), the average activity of ^{7}Be in the Atlantic Ocean is 329 disintegrations per minute per 1000 liters. The particulate fraction averaged 20 disintegrations per minute per 1000 liters. Values for the beryllium content of Australian waters are listed in Table 7.10.

TABLE 7.10. BERYLLIUM IN AUSTRALIAN WATERS

Water	Range (ppb)	Mean	Number of samples
Rain			
All samples	0.01 to 0.18	0.07	20
Lucas Heights	0.01 to 0.07	0.05	5
Non-Lucas Heights	0.03 to 0.18	0.08	15
River			
Lachlan (Forbes)		0.01	1
Macquarie (Bathurst)		0.01	1
Nepean (Emu Plains)		N.D.[a]	1
Woronora (Discharge Pt.)	0.01 to 0.12	0.03	27
Woronora (Tolofin)	0.01 to 0.08	0.02	26
Sea			
Pacific Ocean		0.002	1
Indian Ocean		0.001	1
Tank[b]			
Lucas Heights area	0.002	0.002	2

[a] N.D. — not detected.

[b] Rainwater collected in tank. This value is lower than that for rainwater due to sediment settling out.

Source: Adapted from Meehan and Smythe, 1967, Table II, p. 843. Reprinted by permission of the publisher.

Analysis of over 1500 U.S. raw and finished waters revealed an average beryllium content of 0.19 µg/liter and a range of 0.01 to 1.22 µg/liter (Kopp and Kroner, 1968). The maximum concentration which occurred in the Monongahela River at Pittsburgh was thought to result from mine drainage in that area. The Atchafalaya River in Louisiana contains 0.1 to 1 ppb beryllium (Livingstone, 1963); the Delaware and Hudson rivers contain about 10^{-4} ppm (Merrill et al., 1960). The recommended provisional limit for beryllium in water is 1 ppm (Ottinger et al., 1973).

7.3.4 Distribution in Air

Beryllium is generally found in the atmosphere in minute concentrations. The beryllium content of the atmosphere is less than 0.0001 µg/m^3 (Bowen, 1966). Beryllium was undetectable in most of the over 100 cities sampled by the National Air Surveillance Network (U.S. Department of Health, Education, and Welfare, 1966; U.S. Environmental Protection Agency, 1973*b*). Chambers et al. (1955, cited in Durocher, 1969, p. 41) found a maximum of 0.003 µg/m^3 of beryllium in the air of more than 30 metropolitan areas. The variation in beryllium concentration between these urban areas and some rural areas is shown in Table 7.11. The authors acknowledged limitations in this study, including locations selected, extent of coverage, methods used, and inherent defects in analysis of data based on particulate samples. Despite such limitations, the data are useful for comparative purposes. Tabor and Warren (1958) found 0.003 µg/m^3 of beryllium in suspended particulate samples from Houston, Denver, and Louisville. Trace quantities (less than 0.003 µg/m^3) were found in Chattanooga, Chicago, Cincinnati, East Chicago, Minneapolis, Paulsboro, New Orleans, New York, Philadelphia, and Washington.

Atmospheric beryllium concentrations are often higher than normal near beryllium processing plants. Sussman, Lieben, and Cleland (1959) reported a mean concentration of 0.0155 µg/m^3 and a maximum concentration of 0.0827 µg/m^3 near a Pennsylvania plant. In comparison, background samples from different areas averaged 0.0002 µg/m^3. During a partial plant shutdown the beryllium concentration averaged 0.0047 µg/m^3; a complete two-week shutdown resulted in an average of 0.0015 µg/m^3. Similar results were reported by Watts, Walsh, and Vought (1959) and by the U.S. Environmental Protection Agency (1973*a*).

As expected, the atmospheric concentration of beryllium decreases with distance from the emission source. Eisenbud et al. (1949) studied this relationship and found that beryllium ranged from 0.2 µg/m^3 at 1/4 mile from the stack to nil (limit of detection, 0.001 µg/m^3) at 10 miles (Figure 7.4). Data were collected continuously for ten weeks at 350, 420, 650, and 750 ft from the stack. The average beryllium concentrations were 0.15, 0.1, 0.05, and 0.05 µg/m^3, respectively. A decrease in beryllium content with increased distance from the stack is also reported by Watts, Walsh, and Vought (1959) and by Sussman, Lieben, and Cleland (1959).

The recommended national emission standard for beryllium discharge is as follows: (1) the total beryllium emission shall not exceed 10 g of beryllium in a 24-hr period and (2) the total emission shall not exceed amounts which will result in an out-plant concentration of 0.01 ug/m^3

TABLE 7.11. AVERAGE BERYLLIUM CONCENTRATIONS IN URBAN AND RURAL AREAS

Area	Concentration ($\mu g/m^3$)
Cities over 2,000,000	
Los Angeles	0.0001
Detroit	0.0004
Philadelphia	0.0005
Chicago	0.0002
New York	0.0003
Cities between 500,000 and 2,000,000	
Cincinnati	0.0002
Kansas City	0.0003
Portland	0.0003
Atlanta	0.0002
Houston	0.0002
San Francisco	0.0001
Minneapolis	0.0002
Rural or suburban	
Boonsboro, Maryland	0.0001
Salt Lake City	0.0001
Atlanta	0.0002
Cincinnati	0.0001
Portland	0.0001

Source: Adapted from Chambers et al., 1955 (cited in Durocher, 1969, p. 42), Table 10, p. 42.

averaged over a 30-day period (Utidjian, 1973). Pollution control devices to limit beryllium discharge are available (Table 7.12) and are used on an industry-wide basis to meet the above standard (Ottinger et al., 1973). As a result, the overall beryllium concentration in the U.S. atmosphere does not appear to present a health hazard.

Beryllium participates in cation exchange reactions and undergoes isomorphic substitution in secondary clay minerals (Romney and Childress, 1965). The beryllium ion is strongly fixed in some soils and will displace divalent cations which share common sorption sites. Under batch equilibrium conditions, however, magnesium, barium, and calcium will effectively

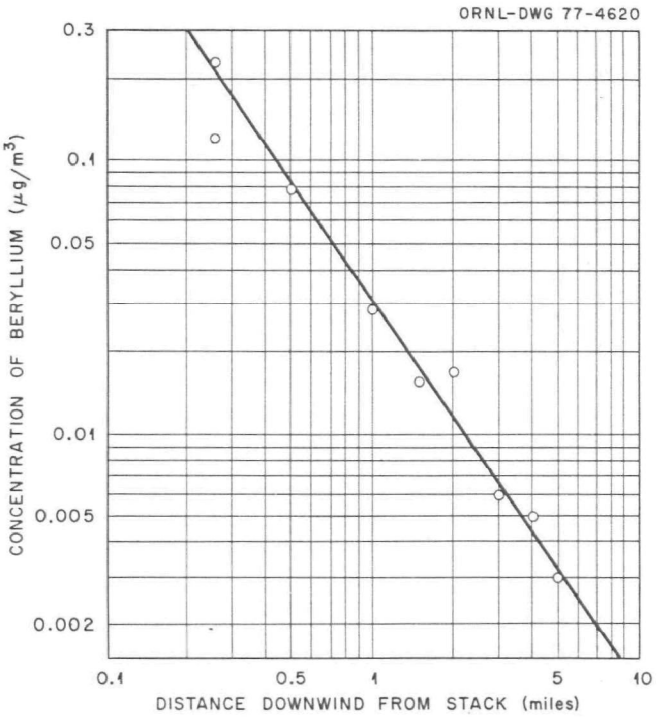

Figure 7.4. Falloff of ground beryllium concentration with distance away from a beryllium production plant. Source: Adapted from Eisenbud et al., 1949, Figure 1, p. 284. Reprinted by permission of the publisher.

TABLE 7.12. RECOMMENDED CLEANERS FOR BERYLLIUM HANDLING OPERATIONS

Operation or process phase	Type of cleaner	Estimated loading (g/m^3)	Expected efficiency by weight (%)
Ore handling, crushing ball milling, etc.	Reverse-jet or shaking bag filter	0.2-57	99[a]
Sinter furnace	Wet cell or spray scrubber	0.2	80[a]
Leaching and hydroxide filter	Same	0.02	80[a]
Sodium fluoride handling (NoBe)	Same	1.1	80[a]
Beryllium hydroxide dryer	Reverse-jet or shaking bag filter	2.3	99[a]
Beryllium hydroxide dryer and calciner	Wet spray unit for cooling, then to above unit	1.6	99[a]
Beryllium fluoride mixer	Wet cell or spray tower	0.02	80[a]
Beryllium fluoride furnace	Venturi or orifice scrubber or packed tower and wet Cottrell unit	11.4	95[a]
Reduction furnace	Same	2.3	95[a]
Ball mill	Wet cell washer	0.02	80[a]
Magnetic separator			
Pickling			
Leach tank			
Machining, powder metals handling	Small cyclone units plus bag filter with asbestos filter aid	0.2-2.3	99.9
Welding, heat treating	Bag filter with filter aid and dilution air to bring temperature to 180°F	0.2-2.3	99.9
Miscellaneous laboratory hoods	Roughing filter plus high-efficiency AEC-type filter	0.002-0.02	99.95

[a]Estimated for single-stage cleaning to be followed by overall final bag collector with asbestos floats filter aid.

Source: Adapted from Silverman, 1959, Table 4, p. 258. Reprinted by permission of the publisher.

compete with beryllium for adsorption sites in soils but not bentonite. Kaolinite adsorbs beryllium less strongly than soils; in this medium, therefore, beryllium can be displaced by the above cations. Residence times for beryllium in the soil were not located in the literature.

7.4 ENVIRONMENTAL FATE

7.4.1 Mobility and Persistence in Soils

Beryllium chemistry in the soil solution has not been thoroughly investigated (Murrmann and Koutz, 1972), but it is probably similar to that of aluminum or zinc (Bohn, 1972; Romney and Childress, 1965). Reactions of beryllium in nutrient solution and soil are responsive to pH. At low pH, Be^{2+} and $Be_3(OH)_3^{3+}$ are present; at higher pH, precipitates of $Be(OH)_2$ are formed. With further pH increase, $(BeO_2)^{2-}$ should appear (Mesmer and Baes, 1967; Murrmann and Koutz, 1972) (Section 2.2.1.2).

7.4.2 Mobility and Persistence in Water

Beryllium is found in natural waters only in small amounts due to the low solubility of its oxide and hydroxide at the common pH of such waters (Kopp and Kroner, 1968). The chloride and nitrate of beryllium are highly soluble in water, the sulfate is moderately soluble, and the carbonate is nearly insoluble in cold water (Committee on Water Quality Criteria, 1972).

Beryllium does not go into solution to an appreciable degree during the weathering process. About 9600 metric tons (10,579 tons) of beryllium are added to the oceans each year in water and sediments (Schroeder, 1974); approximately 0.00002% of this amount is retained. Merrill et al. (1960) have calculated the residence time of beryllium in seawater to be 150 years. Using the same equation but different numerical values from Arnold (1958), a residence time of 570 years was determined. Thus, both methods indicate a beryllium residence time in seawater of a few hundred years.

7.4.3 Mobility and Persistence in Air

Residence times for beryllium in the atmosphere were not located in the literature. Beryllium in the atmosphere probably returns to earth as dry fall or in precipitation.

7.5 WASTE MANAGEMENT

Only a small amount of the total beryllium waste produced is composed of beryllium scrap. This is because beryllium users can resell virtually all scrap to the producers at $10 to $20 per pound of contained beryllium (Ottinger et al., 1973). The major portion of beryllium waste results from pollution control efforts. These wastes are in the form of either solid particulates or a dilute aqueous solution (e.g., scrubber liquor).

The most desirable method of handling beryllium wastes is recycling them to producers, a situation that is expected to continue (Ottinger et al., 1973). For wastes not recycled, burial is recommended. The wastes

can first be burned to produce the chemically inert beryllium oxide, provided the exhaust gases are scrubbed to remove particulates. Both burned and unburned wastes are preferably placed in plastic containers and sealed in metal drums prior to burial (U.S. Environmental Protection Agency, 1973*a*). These practices are deemed adequate to handle beryllium wastes now and in the foreseeable future.

7.6 BERYLLIUM IN FOODS

Data concerning the beryllium content of foods are scarce. The results of Meehan and Smythe (1967) are presented in Table 7.13. The samples they studied were collected in New South Wales, Australia. Values for foodstuffs were generally low and ranged from 0.01 to 0.10 ppm. Oyster flesh and mushrooms contained the highest values. The results of Zorn and Diem (1974), obtained in West Germany, are shown in Tables 7.14 and 7.15. It seems, from these results, that beryllium content of crops in Europe is appreciably higher than in Australia.

7.7 BIOMAGNIFICATION IN FOOD CHAINS

Beryllium does not biomagnify within food chains. Beryllium ingested by higher animals is not absorbed through the digestive tract but is readily excreted (Section 6.2). Thus, human consumption of animals that have ingested beryllium presents no health hazard under normal circumstances.

TABLE 7.13. BERYLLIUM IN AUSTRALIAN FOODS

Sample	Survey figures			
	Beryllium level (ppm in ash)		Ash fresh weight (%)	Number of samples
	Range	Average		
Foodstuffs				
Beans (Lucas Heights area)	N.D.[a] to 0.01	0.01	0.65	3
Cabbage (Lucas Heights area)		0.03	0.78	1
Hen eggs				
Yolk		0.01	1.75	1
Yolk plus whites		0.006	1.01	1
Shells		0.014	77.44	1
Milk				
All samples	N.D. to 0.09	0.02	0.83	50
Lucas Heights area	N.D. to 0.04	0.02	0.81	17
Hawkesbury and Campbelltown	N.D. to 0.09	0.02	0.86	33
Mushrooms				
Lucas Heights area		0.12	1.32	1
Nuts				
Peanut kernels	0.01 to 0.03	0.02	2.6	2
Peanut shells	0.41 to 0.52	0.47	2.5	2
Almond kernels		0.01	2.9	1
Almond shells		0.01	2.9	1
Tomatoes (Lucas Heights area)		0.02	1.05	1
Yeast (bakers)		0.02	1.62	1
Marine				
Crabs				
Woronora River	0.07 to 0.13	0.10	15.4	6
Non-Woronora River		0.17	15.4	1
Eels		N.D.	5.0	1
Whole fish				
Woronora River				
Mullet	0.03 to 0.36	0.21	5.2	8
Blackfish	0.08 to 0.39	0.23	4.6	4
Non-Woronora River, mullet		0.01		1

(continued)

TABLE 7.13. (continued)

Sample	Survey figures			
	Beryllium level (ppm in ash)		Ash fresh weight (%)	Number of samples
	Range	Average		
Fish gut				
Woronora River				
Mullet	0.42 to 0.71	0.54	9.2	6
Blackfish	0.46 to 1.78	0.99	5.6	5
Leatherjacket	0.48 to 0.63	0.56	3.2	2
Non-Woronora River				
Mullet	0.04 to 1.33	0.43	4.2	4
Blackfish	0.80 to 1.25	1.03	5.7	2
Fish fillets				
Woronora River				
Mullet	N.D. to 0.07	0.04	3.7	2
Blackfish		0.01	3.6	1
Perch and bream		N.D.	3.7	1
Non-Woronora River				
Blackfish	0.01	0.01	4.4	2
Bonita		0.01	2.4	1
Perch		0.01	1.6	1
Redfin		0.01	5.7	1
Mullet		0.02	3.3	1
Homosira Banks II				
Bubble weed (coast south of Sydney)	0.01 to 0.05	0.03	16.5	5
Catostylus mosaicus (jelly blubber)		N.D.	1.2	1
Oyster flesh				
All samples	0.01 to 0.27	0.03	2.0	59
Woronora River	0.02 to 0.14	0.03	2.0	41
Hawkesbury River	0.01 to 0.27	0.10	2.0	18
Oyster liquid				
All samples	0.01 to 0.03	0.02	2.7	2
Woronora River	0.01 to 0.03	0.02	2.5	2
Hawkesbury River		0.02	2.9	1
Oyster shells				
All samples	0.01 to 0.08	0.04	94.9	20
Woronora River	0.01 to 0.08	0.04	93.8	14
Hawkesbury River	0.02 to 0.06	0.04	96.5	6
Plankton preparations		N.D.	13.5	1
Prawns (green)		0.03	3.5	1
Cunjevoi flesh, Pyura stolonifera				
Mixture from Cronulla and Coalcliff		0.53	3.6	1
Cronulla	0.10 to 0.26	0.18	9.1	2
Coalcliff		0.42	4.1	1
Cunjevoi tunics, Pyura stolonifera				
Mixture from Cronulla and Coalcliff		0.30	35.4	1
Cronulla	0.05 to 0.08	0.07	38.5	2
Coalcliff		0.26	33	1
River solid particles				
Woronora (Discharge Point)		N.D.		1
Woronora (Tolofin)		N.D.		1
Rockweeds (algae)				
Cronulla		0.01	4.2	1
Coalcliff	0.02 to 0.54	0.28	5.2	2
Scallops, Tasmanian		0.02	1.7	1
Seaweed, Woronora River	0.29 to 1.02	0.66	5.5	3
Shellfish flesh				
Mixture from Cronulla and Coalcliff		0.04	8.8	1
Cronulla	0.07 to 0.09	0.08	8.1	2
Coalcliff	0.30 to 1.15	0.73	14.0	2
Shellfish shells				
Cronulla	N.D. to 0.01	0.01	96.4	2
Coalcliff	N.D. to 0.01	0.01	96.3	2
Starfish, whole, Coalcliff		0.02	37.1	1
Zostera				
All samples	0.28 to 1.12	0.60	5.5	28
Woronora River	0.28 to 1.12	0.61	5.5	27
Hawkesbury River		0.41	5.5	1

[a] N.D. — nondetectable.

Source: Adapted from Meehan and Smythe, 1967, Table II, pp. 841-843. Reprinted by permission of the publisher.

TABLE 7.14. BERYLLIUM IN WEST GERMAN FOOD CROPS

Crop	Be/g dry substance
Toasted bread ("knackebrot")	0.12
Green head lettuce	0.33
Tomatoes	0.24
Rice, polished	0.08
Potatoes	0.17

Source: Adapted from Zorn and Diem, 1974, Table 1, p. 5. Reprinted by permission of the publisher.

TABLE 7.15. BERYLLIUM IN WEST GERMAN CIGARETTES

	Be/cigarette in tobacco	Be/cigarette in smoke
Brand A	0.74	0.074
Brand B	0.68	0.011
Brand C	0.47	0.021

Source: Adapted from Zorn and Diem, 1974, Table 2, p. 5. Reprinted by permission of the publisher.

SECTION 7

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SECTION 8

ENVIRONMENTAL ASSESSMENT OF BERYLLIUM

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8.1 ENVIRONMENTAL OCCURRENCE

8.1.1 Natural Background

Beryllium occupies the 44th place in the terrestrial abundance list of elements. Its overall concentration in the lithosphere is estimated at 6 μg/g. Most of it is present in localized deposits of the mineral beryl ($Be_3Al_2Si_6O_8$) and bertrandite [$Be_4Si_2O_7(OH)_2$], two commercially exploitable beryllium ores. The highly treasured gemstones, emerald and aquamarine, are colored variants of beryl. Other beryllium-containing minerals number about 30 and include such other semiprecious stones as euclas [$Al(BeSiO_4)OH$], phenakite (Be_2SiO_4), and chrysoberyl (Al_2BeO_4).

In ordinary rocks and soils, as well as in bituminous coals, the concentration of beryllium ranges from 0.1 to 3 μg/g. The beryllium content of mineral oils is estimated below 100 μg/liter and of natural waters below 1 μg/liter. The atmosphere in uncontaminated locations is estimated to contain less than 0.1 ng/m^3 of beryllium.

8.1.2 Contribution by Human Activities

The baseline of background atmospheric beryllium has been exceeded to some degree in most inhabited places because of fuel burning. Already in the 1940s (i.e., before large-scale technical exploitation of beryllium), atmospheric concentrations in U.S. cities were 0.3 to 3.0 ng/m^3 of beryllium.

Industrial emissions that have added to the atmospheric beryllium burden are discharges from beryllium mining, extracting, and machining; foundry operations; ceramic plant operations; space vehicle and rocket fuel manufacture; nuclear reactor and classified weapons manufacture; and such associated activities as laundering beryllium workers' clothes. These facilities are currently required to limit the ambient beryllium concentration to 10 ng/m^3 in the immediate vicinity of the plant.

A potential for beryllium emissions exists from certain rocket propellants; therefore, separate U.S. standards apply to rocket firing. Emissions to the atmosphere from the latter source must not exceed 75 μg/min/m^3 for "low-fired" (<500°C) beryllium oxides and 1.5 mg/min/m^3 for "high-fired" (∿1500°C) beryllium oxides, both measured within 10 to 60 min, accumulated during any two consecutive weeks, at the property line or nearest place of human habitation. Equivalent standards, if any, of other nations are not in the public information domain. Some observers believe

that global atmospheric beryllium concentrations may have increased somewhat during recent decades. The extent of increase is controversial and at this time probably not significant.

8.2 TOXICITY

8.2.1 From Skin Contact

The handling of water-soluble beryllium salts [BeF_2, $BeCl_2$, $Be(NO_3)_2$, and $BeSO_4$] causes eczematous contact dermatitis which is of allergic origin and based on "delayed" (cell-mediated) hypersensitivity. Once hypersensitivity is established, elicitation of skin reaction can occur after contact with very dilute (less than 1 mg beryllium per liter) solutions. Dermatitis is not known to occur after handling insoluble beryllium compounds [BeO, $Be(OH)_2$, $BeHPO_4$, and Be_2SiO_4], the metal, or its alloys. However, the latter substances can cause granulomatous ulceration of the skin if they become imbedded after trauma. Systemic adsorption from the skin is minimal for all beryllium compounds, including the soluble, and not known to have toxic effects.

8.2.2 From Ingestion

Beryllium compounds are not well absorbed from the gastrointestinal tract because at intestinal pH the beryllium ion tends to form insoluble precipitates, mainly the phosphate. Massive beryllium feeding to experimental animals led to rickets due to induced phosphorus deficiency, but no other harmful consequences were observed. Such quantities of beryllium that are absorbed are partly excreted through the urine and partly deposited in the skeleton. There is no significant biomagnification.

8.2.3 From Inhalation

The high toxicity of beryllium compounds is manifested only after inhalation. Two separate clinical entities were observed in humans: (1) acute chemical pneumonitis, resulting promptly from inhalation of aerosols of soluble beryllium compounds in high concentrations (>1 mg/m^3) and (2) chronic pulmonary granulomatosis ("berylliosis"), developing slowly (in the course of years) after inhalation of either soluble or insoluble compounds, sometimes in very low concentrations ($\sim$10 $\mu g/m^3$).

The acute pneumonitis was seen mainly in beryllium extraction plants and often involved all segments of the respiratory tract. The acidity of beryllium salt solutions was the probable etiologic factor and there appeared to be a definite dose-response relation with respect to rapidity of onset, severity, and duration of the inflammation. Although there were some fatalities resulting from the acute syndrome, recovery after several weeks or months was the rule and no nonoccupational cases were observed.

Chronic berylliosis has been frequently described as a "systemic" intoxication because of eventual involvement of the adrenals, liver, kidney, and heart. However, the essential original lesion is pulmonary granulomatous inflammation resembling sarcoidosis. It may develop insidiously

up to 20 years after exposure, with or without previous history of the acute syndrome, and can result in considerable mortality. This condition appeared to be most often caused by insoluble beryllium compounds, especially "low-fired" BeO which has more extensive internal surfaces and therefore much more biological activity than "high-fired" BeO. A dose-response relation between extent of exposure and severity of disease is emphatically absent, with workers from the cleanest plants and "neighborhood cases" sometimes showing the worst clinical forms. The syndrome is apparently a manifestation of an "auto-immune" response to beryllium as a hapten (a substance with capability to combine with normal body constituents and render them antigenic).

Beryllium sulfate inhalation has caused pulmonary tumors in rats and monkeys, but not in guinea pigs. The epidemiological evidence in humans is controversial; the preponderance of evidence indicates that beryllium is probably not carcinogenic, or at most very weakly carcinogenic, in man.

8.3 SAFE LEVELS

8.3.1 Air

The occupational exposure standard for beryllium in the United States is presently 2 $\mu g/m^3$; this figure is a "time-weighed average" for an 8-hr workday, allowing short-term excursions over the limit up to 25 $\mu g/m^3$ for up to four 15-min periods daily, provided that there is at least 1 hr elapsed time between the excursions and that there are compensatory excursions under the limit. Western European countries and Japan have also adopted the U.S. standard. Reduction of the U.S. standard to 1 $\mu g/m^3$, with a short-term excursion limit of 5 $\mu g/m^3$, is presently pending with the U.S. Occupational Safety and Health Administration. In the Soviet Union, the maximum allowable concentration for beryllium is 1 $\mu g/m^3$.

The margin of safety incorporated in these limits is not known with certainty. Before adoption of the U.S. occupational exposure standard of 2 $\mu g/m^3$ in 1949, acute pneumonitis and chronic berylliosis prevalence in the beryllium industry was 1% to 3%, but in-plant concentrations at that time were retrospectively estimated to have been in the 1 mg/m^3 area. There were also "neighborhood cases" in the population living within about one mile from the plant; these cases were originally attributed to air pollution of about 0.1 $\mu g/m^3$ of beryllium originating from stack gases, but it now seems probable that afflicted patients may have had direct contact with a contaminated person or object and were in fact occasionally exposed to substantially higher concentrations.

After adoption of the 2 $\mu g/m^3$ standard, acute beryllium pneumonitis cases have become very rare and confined to accidental exposures. Chronic berylliosis incidence also declined but did not altogether disappear: 76 new cases have been reported during the last ten years, of which about one-half received exposure since promulgation of the standard. It should be added, however, that the new cases appear to have originated during construction periods in beryllium plants or from newly installed operations, suggesting temporary noncompliance with the standard. The best

judgment of informed specialists at this time is that the existing in-plant standard of 2 $\mu g/m^3$, if enforced, is adequate to prevent acute and chronic beryllium disease in the plant population.

The recently announced intent of the U.S. Occupational Safety and Health Administration to reduce the beryllium standard from 2 to 1 $\mu g/m^3$ is based largely on the carcinogenic suspicion. Experimental animal exposures have caused lung tumors in some (not all) of the species tested, but some of the work is equivocal and the degree of malignancy of the tumors is uncertain. The human epidemiologic evidence for beryllium cancers is also controversial at present and is regarded by some (not all) observers as essentially negative. Even if the carcinogenic evidence were stronger, there are no good quality research data at present to suggest a safe threshold for this assumed effect and the suggestion to tighten the standard is made in conformity with the general policy to reduce exposure to the limit of technical feasibility.

Short-term public limits (STPLs) and public emergency limits (PELs) have been recommended by the U.S. National Research Council. For beryllium, the recommended figures were STPL = 5 $\mu g/m^3$ for 10 min and PEL = 100 $\mu g/m^3$ for 10 min. Both of these are "ceiling" values, which may be extrapolated on a concentration x time basis to longer, but not to shorter, exposure times. The STPLs are applicable to predictable and possibly repeatable exposures, but not more often than one per quarter year. On the basis of present knowledge, the STPLs were expected to produce no adverse health effects even in the most sensitive population group. The PELs are applicable only to unpredictable exposures of the public and no more than one exposure in a lifetime was assumed in setting this limit.

Both the STPL and the PEL for beryllium are extrapolations of the current air quality standard of 10 ng/m^3 of beryllium for limited exposure times on a concentration x time basis. The validity of this extrapolation is untested and it is possible that the PEL of 100 $\mu g/10\ min/m^3$, or even the special air quality standard for rocket firing of 75 $\mu g/min/m^3$, would cause untoward effects especially in sensitized individuals.

8.3.2 Water

The recommended provisional limit for beryllium in waters in the United States is presently 1 mg/liter. Since beryllium salts do not remain in soluble form at neutral pH, it is unlikely that directly hazardous concentrations could build up even in contaminated waters. Experimental rats remained essentially unaffected by up to 1.66 mg beryllium per liter in the drinking water over a period of six months. However, 0.5 to 1.0 mg beryllium per liter inhibited the growth and biologic oxygen demand of saprophytic bacteria and 3 to 5 mg/liter in the irrigating water appeared to have adverse effects on garden vegetables. According to presently available knowledge, no biologic effects of any kind would be expected from beryllium in concentrations up to 100 μg/liter water. A suitable standard, with some margin for safety and not difficult to meet under normal conditions, appears to be about 50 μg/liter in public waters.

8.3.3 Foods

The highest beryllium level in food was obtained in 1974 in Germany for green head lettuce (0.33 µg/g dry substance; the water content of fresh vegetables averages about 90%). Potatoes, tomatoes, bread, and rice had somewhat less beryllium (0.08 to 0.24 µg/g dry substance), but all of these levels were almost two orders of magnitude higher than what was reported for similar food crops from Australia (0.01 to 0.1 µg beryllium per gram of ash; ash content of vegetables averages about 1% of fresh weight). Seafood was found to have 0.1 to 1.0 µg beryllium per gram of ash in the Australian tests.

The discrepancy between the Australian and German analytical figures for beryllium in food crops may be either artifactual or real. An artifactual difference would exist if there was loss of beryllium during ashing which could make the Australian figures too low, or errors due to background contamination which could make the German figures too high. If the difference is real, it would have to be attributed to higher fallout of beryllium from the air in the northern hemisphere, possibly due to rocket firings.

In any case, there is no indication that beryllium levels in food anywhere today are near hazardous concentration. If a standard needs to be set, it appears feasible to use the level recommended for public waters (about 50 ng beryllium per gram of fresh food).

8.3.4 Cigarettes

The only figures for beryllium in cigarettes originate from the same work cited above for German vegetables, and it may be subject to the same uncertainties. In three brands of West German cigarettes, 0.47, 0.68, and 0.74 µg beryllium per cigarette were found, with 4.5%, 1.6%, and 10.0% of the beryllium content, respectively, escaping into the smoke during smoking.

Calculations show that for a 2.5 pack per day cigarette smoker (50 cigarettes per day) with 10 liter/min respiratory volume, and assuming 10% of beryllium content escaping into the smoke during smoking, cigarettes with an average of 2.0 µg beryllium per cigarette would provide an exposure equivalent to the present U.S. occupational exposure limit. However, in view of the other toxic substances in cigarette smoke with which beryllium may act synergistically, and of the possibility that persons occupationally exposed to inhalation of beryllium may smoke as well, it appears essential to reduce beryllium exposure from cigarettes to much below this figure. A limit of 0.2 to 0.3 µg beryllium per cigarette appears desirable and in view of the figures cited above, it is possible that such a limit may already have been exceeded in certain cigarettes. Since cigarette smoke, unlike water or food, enters the lung directly, the promulgation of a standard for cigarettes should have much higher priority than standards for public waters or food.

8.4 MONITORING OF SAFE LEVELS

8.4.1 Direct Analysis

Modern methods of beryllium analysis are gas chromatography and atomic absorption spectrophotometry. The former method has the greatest sensitivity of all analytical procedures for beryllium and provides a limit of detection of 0.0004 to 0.01 ng of beryllium per sample. Atomic absorption spectrophotometry is appealing for its simplicity and has a limit of detection of about 40 ng of beryllium per sample.

The classical methods of beryllium analysis by colorimetric, fluorometric, or spectrographic techniques are losing popularity because of the requirement of cumbersome preparatory procedures, interference by other metals, or inferior precision. Their limit of detection is in the range of 0.01 to 100 ng per sample of beryllium.

Since the levels of beryllium which may be encountered in biological materials or air are likely to be low, extreme precautions to avoid contamination or loss must be observed. Borosilicate glassware should be used exclusively, freshly cleansed for each determination with chromate-sulfuric acid, followed by rinsing with deionized water. Beryllium solutions, including urine specimens collected for analysis, must be acidified even for short periods of storage in order to avoid adsorption of beryllium on the vessel wall. Even well-qualified chemists, if they have no specific experience in microanalysis, are likely to experience difficulties, and the widely discrepant data on the beryllium content of foods and other consumer products in the literature must be viewed with caution.

8.4.2 Biological Monitoring

In human pulmonary tissue, amounts less than 20 ng/g of beryllium (dry weight basis) are not regarded as indicative of occupational exposure; in exposed workers, the levels may be as high as several micrograms per gram. However, there is no quantitative correlation between pulmonary beryllium and severity of berylliosis. Often, various segments of the same lung exhibited widely differing levels.

Urinary excretion of measurable quantities of beryllium (0.02 to 3.0 µg/liter) is indicative of occupational exposure but is not consistently observed and may occur in healthy workers as well as in workers suffering from beryllium poisoning. Thus, urine levels are not suitable as dependable monitors of a hazardous exposure or as diagnostic acids in berylliosis.

8.5 SUMMARY OPINION AND RESEARCH NEEDS

Beryllium compounds are present in the normal atmosphere at levels of 0.1 to 3.0 ng/m^3; in natural waters at levels of 0.1 to 1.0 µg/liter; and in ordinary soils at levels of 0.1 to 3.0 µg/g. Foods were reported to contain up to 33 ng/g of beryllium in fresh substance, and tobacco smoke up to 74 ng beryllium per cigarette.

Ingested beryllium compounds at these levels, or even at several times these levels, are harmless. A suitable standard for beryllium in fresh foods and public waters, based on present knowledge, is about 50 ng/g.

Inhaled beryllium compounds have acute as well as considerable chronic toxicity, and perhaps carcinogenicity, in the several micrograms of beryllium per cubic meter concentration range. The toxicity of beryllium oxides is inversely related to their firing temperatures during production, due to the varying area of internal surfaces in the powders. Only "low-fired" (<500°C) beryllium oxide appears to pose a high degree of toxic hazard. The thresholds of harmful concentrations are not known with certainty. An occupational exposure standard of 2 $\mu g/m^3$ of beryllium, promulgated in 1949, has prevented acute and perhaps chronic berylliosis; the carcinogenesis evidence is controversial. United States air quality standards are presently set at 10 ng/m^3 of beryllium with the exception of rocket firings, where 75 $\mu g/min/m^3$ for low-fired beryllium oxide and 1.5 $mg/min/m^3$ for high-fired beryllium oxide are permitted. Reduction of the occupational exposure limit from 2 to 1 $\mu g/m^3$ is presently pending with the U.S. Occupational Safety and Health Administration.

The limits presently in force or pending appear to be adequate, with the possible exception of the special limits for rocket firings which could produce untoward effects in sensitized individuals. The most serious problem of rocket firings, even at high altitudes, appears to be beryllium fallout on crops, specifically tobacco. The presently measured beryllium content of tobacco could cause beryllium inhalation exceeding the threshold limit equivalent in a heavy smoker. It is recommended to establish a standard for smoking tobacco at about 25 ng/g.

Outstanding research needs are to resolve the suspected carcinogenicity of beryllium in various species with better definition of the degree of malignancy of the obtained tumors; to investigate the relative biological responses to low- and high-fired beryllium oxides in the immunological area; to obtain dose-response information for short-term exposures and for long-term low-level exposures; and to survey worldwide incidence of conditions diagnosed as sarcoidosis and correlate it to local beryllium content of air, water, and crops.

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16. ABSTRACT

This is a review of the scientific literature on the biological and environmental effects of beryllium. Included in the review are a general summary and a comprehensive discussion of the following topics as related to beryllium and specific beryllium compounds: physical and chemical properties; occurrence; synthesis and use; analytical methodology; biological aspects in microorganisms, plants, wild and domestic animals, and humans; distribution, mobility, and persistence in the environment; assessment of present and potential health and environmental hazards; and review of standards and governmental regulations. More than 300 references are cited.

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