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Health Assessment Document for Beryllium

Review Draft

(Do Not
Cite or Quote)

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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Environmental Criteria and Assessment Office
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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This report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment, in consultation with other Agency and non-Agency scientists, has prepared this health assessment to serve as a "source document" for Agency-wide use. Specifically, this document was prepared at the request of the Office of Air Quality Planning and Standards.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared such that the toxicity of beryllium is qualitatively and where possible, quantitatively, identified. Observed effect levels and dose-response relationships are discussed where appropriate in order to place significant health responses in perspective with observed environmental levels.

ABSTRACT

The chemical and geochemical properties of beryllium resemble those of aluminum, zinc, and magnesium. This resemblance is primarily due to similar ionic potentials which facilitate covalent bonding. The three most common forms of beryllium in industrial emissions are the metal, the oxide, and the hydroxide.

The main routes of beryllium intake for man and animals are inhalation and ingestion. While the absorption of ingested beryllium is probably quite insignificant, the chemical properties of beryllium are such that transformation of soluble to insoluble forms of inhaled beryllium results in long retention time in the lungs. The tissue distribution of absorbed beryllium is characterized by main depositions in the skeleton where the biological half-time is fairly long.

The lung is the critical organ of both acute and chronic non-carcinogenic effects. However, unlike most other metals, the lung effects caused by chronic exposure to beryllium may be combined with systemic effects, of which one common factor may be hypersensitization. Certain beryllium compounds have been shown to be carcinogenic in various experimental animals under differing routes of exposure. Epidemiologic studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. A lifetime cancer risk for continuous inhalation exposure at 1 μg beryllium/m^3 has been estimated.

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1. INTRODUCTION

This report evaluates the effects of beryllium on human health, with particular emphasis on those effects which are of most concern to the general U.S. population. It is organized into chapters that present in a logical order those aspects of beryllium that relate directly to the human health risk. The chapters include: an executive summary (Chapter 2); background information on the chemical and environmental aspects of beryllium, including levels of beryllium in media with which U.S. populations may come into contact (Chapter 3); beryllium metabolism, where absorption, biotransformation, tissue distribution, and excretion of beryllium are discussed with reference to the element's toxicity (Chapter 4); beryllium toxicology, where the various acute, subacute, and chronic health effects of beryllium in man and animals are reviewed (Chapter 5); beryllium mutagenesis, in which the ability of beryllium to cause gene mutations, chromosomal aberrations, and sister-chromatid exchanges is discussed (Chapter 6); and information on beryllium carcinogenesis, which includes a discussion of selected dose-effect and dose-response relationships (Chapter 7).

This report is not intended to be an exhaustive review of all the beryllium literature, but is focused instead upon those data thought to be most relevant to human health risk assessment. Literature was collected and reviewed up to April, 1985. In view of the fact that this document is to provide a basis for making decisions regarding the regulation of beryllium as a hazardous air pollutant under the pertinent sections of the Clean Air Act, particular emphasis is placed on those health effects associated with exposure to airborne beryllium. Health effects associated with the ingestion of beryllium or with exposure via other routes are also discussed, providing a basis for possible use of this document for multimedia risk assessment purposes. The background information provided on sources, emissions, and ambient concentrations of beryllium in various media is presented to provide a general perspective for viewing the health-effects evaluations contained in later chapters of the document. More detailed exposure assessments will be prepared separately for use in subsequent EPA reports regarding regulatory decisions on beryllium.

2. SUMMARY AND CONCLUSIONS

2.1 BACKGROUND INFORMATION

The industrial use of beryllium has increased tenfold in the last 40 years. Despite this fact, increases in the environmental concentrations of beryllium have not been detected. Atmospheric beryllium is primarily derived from the combustion of coal.

Contamination of the environment occurs almost entirely by the deposition of beryllium from the air. Beryllium from the atmosphere eventually reaches the soil or sediments, where it is probably retained in the relatively insoluble form of beryllium oxide. Since the time of the industrial revolution, it is likely that no more than 0.1 μg Be/g has been added to the surface of the soil, which has a natural beryllium concentration of 0.6 μg/g. Distributed evenly throughout the soil column, beryllium derived from the atmosphere could account for not more than one percent of the total soil beryllium. Allowing for greater mobility of atmospheric beryllium in soil than natural beryllium, it is possible that 10 to 50 percent of the beryllium in plants and animals may be of anthropogenic origin.

The typical American adult usually takes in 400 to 450 ng Be/day, of which 50 to 90 percent comes from food and beverages. Some of this beryllium found in food may be derived from the atmosphere; however, aside from primary and secondary occupational settings, air or dust has little impact on total human intake.

2.2 BERYLLIUM METABOLISM

Inhalation and ingestion are the main routes of beryllium intake for man and animals. Percutaneous absorption is insignificant.

Due to the specific chemical properties of beryllium compounds, even primarily soluble beryllium compounds are partly transformed to more insoluble forms in the lungs. This can result in long retention times in the lungs following exposure to all types of beryllium compounds. Like other particulates, dose and particle size are critical factors that determine the deposition and clearance of inhaled beryllium particles. Of the deposited beryllium that is absorbed, part will be rapidly excreted and part will be stored in bone. Beryllium is also transferred to regional lymph nodes. Beryllium transferred from the lungs to the gastrointestinal tract is mainly eliminated in the feces with only a minor portion being absorbed.

There are no quantitative data on absorption of beryllium from the gastrointestinal tract in humans, but several animal studies indicate that the absorption of ingested beryllium is less than one percent. The absorption of beryllium through intact skin is very small, as beryllium is tightly bound in the epidermis.

Absorbed beryllium will enter the blood, but there are no data on the partitioning of beryllium between plasma and erythrocytes. In plasma, there are limited data to suggest that, at normally occurring levels of beryllium, the main binding is to various plasma proteins. In animal experiments, it has been shown that large doses of injected beryllium are found in aggregates bound to phosphate. The smaller the dose, the more beryllium will be in the diffusible form. The data are insufficient to permit an estimate of the levels of beryllium normally occurring in blood or plasma.

Absorbed beryllium is deposited in the skeleton, with other organs containing only very low levels. In the liver, beryllium seems to be preferentially taken up by lysosomes. There are not enough data to permit any definitive conclusions about the distribution and amounts of beryllium normally present in the human body. However, total body burden is probably less than 50 μg.

Based on animal studies, beryllium appears to have a long biological half-time, caused mainly by its retention in bone. The half-time in soft tissues is relatively short.

Beryllium seems to be normally excreted in small amounts in urine, normal levels probably being only a few nanograms per liter. Animal data indicate that some excretion occurs by way of the gastrointestinal tract.

2.3 BERYLLIUM TOXICOLOGY

2.3.1 Subcellular and Cellular Aspects of Beryllium Toxicity

It is not well known in what form or through which mechanism beryllium is bound to tissue. Beryllium can bind to lymphocyte membranes, which may explain the sensitizing properties of the metal. A number of reports describe various *in vivo* and *in vitro* effects of beryllium compounds on enzymes, especially alkaline phosphatase, to which beryllium can bind. Effects on protein and nucleic acid metabolism have been shown in many experimental studies; however, the doses in these studies have been large and parenterally administered. Because such administrative routes have less practical application to humans, the data from these studies have limited utility in advancing an understanding of human effects, which are mainly on the lung. Beryllium particles retained in

the lung are found in the macrophages, and the understanding of how these and other pulmonary cells metabolize beryllium is probably of most relevance to the understanding of chronic beryllium disease.

An important aspect of beryllium toxicology is that beryllium can cause hypersensitivity which is essentially cell-mediated. There are species differences; humans and guinea pigs can be sensitized to beryllium, whereas the present data indicate that no such mechanism exists for the rat. There are also strain differences among guinea pigs indicating that a genetic component may be operative. Patch tests have been used to detect beryllium hypersensitivity in humans, but these tests are no longer used since they were shown to cause a reactivation of latent beryllium disease. Presently, the lymphoblast transformation test is regarded as the most useful test to detect hypersensitivity to beryllium.

2.3.2 Pulmonary and Systemic Toxicity of Beryllium in Man and Animals

There are no data indicating that moderate beryllium exposure by oral administration causes any local or systemic effects in humans or animals. Respiratory effects, occasionally combined with systemic effects, constitute the major health concern of beryllium exposure, with hypersensitization likely playing an important role in the manifestation of the systemic effects. Respiratory effects may occur as either a nonspecific acute disease or as a more specific chronic beryllium disease.

The most acutely toxic beryllium compounds are probably beryllium oxides fired at low temperatures, e.g. 500°C, and some salts, such as the fluoride and the sulfate. The latter forms of beryllium are acidic, and part of the toxic reactions caused by these compounds may be due to the acidity of the particles. Acute effects have generally occurred at concentrations above 100 μg Be/m^3. The main feature of such effects is a chemical pneumonitis which may lead to pulmonary edema and even death. In animal experiments, concentrations of more than 1 mg/m^3 have generally been needed to produce acute effects, but effects have been reported at lower levels of exposure. In most cases, the acute disease will regress, but it may take several weeks or months before recovery is complete. If there is no further excessive exposure to beryllium, it is generally believed that acute disease will not lead to chronic beryllium disease. The amount initially deposited during acute exposure and an individual's predisposition are probably the main factors leading to later sequelae.

Acute beryllium poisoning was quite common in the 1940s, but since the present standards were established in 1949, the number of new cases reported has been relatively small.

Chronic beryllium disease occurred as an epidemic in the 1940s, which led to the establishment of the "Beryllium Case Registry" (BCR), a file for all cases of acute and chronic beryllium disease. Chronic beryllium disease is characterized by dyspnea, cough, and weight loss. It is sometimes associated with systemic effects in the form of granulomas in the skin and muscles, as well as effects on calcium metabolism. There are many similarities between chronic beryllium disease and sarcoidosis, but in sarcoidosis the systemic effects are much more prominent. In most cases of chronic beryllium disease, there are only lung effects without systemic involvement. Pathologically, the disease is a granulomatous interstitial pneumonitis in which eventually there may be fibrosis, emphysema, and also cor pulmonale. Deaths from chronic beryllium disease are often due to cor pulmonale. A long latency time is typical; sometimes there may be more than 20 years between last exposure and the diagnosis of the disease.

It has been very difficult to establish the levels of beryllium in air that may cause the disease. One reason for this difficulty is that exposure data have not always been obtainable. Another factor is that hypersensitization may cause the occurrence of the disease in people with relatively low exposures, whereas in nonsensitized people with much higher exposures there may be no effects. Diagnosis of the disease is obtained by X-ray examinations, but lung function tests of vital capacity may decrease before roentgenological changes are seen. Hypersensitization can be detected by the lymphoblast transformation test.

There are limited data on levels of beryllium found in lung tissue in cases of acute and chronic beryllium disease, and these data do not allow for conclusions about dose-effect relationships.

New cases of chronic beryllium disease are still being reported due to the fact that, in some instances, the standards have been exceeded. In industries where the average exposure generally has been below 2 $\mu g/m^3$, there have been very few new cases of chronic beryllium disease.

There have also been a large number of "neighborhood" cases of beryllium disease. Neighborhood cases are those in which chronic beryllium disease occurs in people living in the vicinity of beryllium-emitting plants. The air concentrations of beryllium in such areas at the time when the disease occurred have

probably been around 0.1 $\mu g/m^3$, but considerable exposure via dust transferred to homes on workclothes likely contributed to the occurrence of the disease. No new "neighborhood" cases of beryllium disease have occurred since standards of 0.01 $\mu g/m^3$ were set for the ambient air and the practice of washing workers' clothes in the plants was initiated. Presently, ambient air levels are generally below 1 ng/m^3.

2.3.3 Dermatological Effects of Beryllium Exposure

Contact dermatitis and some other dermatological effects of beryllium have been documented in occupationally exposed persons, but there are no data indicating that such reactions have occurred, or may occur, in the general population.

2.3.4 Teratogenic and Reproductive Effects of Beryllium Exposure

Available information on the teratogenic or reproductive effects of beryllium exposure is limited to three animal studies. The information from these studies is not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects. Further studies are needed in this area.

2.4 MUTAGENIC EFFECTS OF BERYLLIUM EXPOSURE

Beryllium has been tested for its ability to cause gene mutations in Salmonella typhimurium, Escherichia coli, yeast, cultured human lymphocytes, and Syrian hamster embryo cells; DNA damage in Escherichia coli, and unscheduled DNA synthesis in rat hepatocytes.

Beryllium sulfate and beryllium chloride have been shown to be nonmutagenic in all bacterial and yeast gene mutation assays. However, this may be due to the fact that bacterial and yeast systems generally are not sensitive to metal mutagens. In contrast, gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells, and Chinese hamster ovary (CHO) cells have yielded positive mutagenic responses of beryllium. Similarly, chromosomal aberration and sister-chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses of beryllium. In DNA damage and repair assays, beryllium was negative in pol, rat hepatocyte, and mitotic recombination assays, but was weakly positive in the rec assay. Based on available information, beryllium appears to have the potential to cause mutations.

2.5 CARCINOGENIC EFFECTS OF BERYLLIUM EXPOSURE

2.5.1 Animal Studies

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits, by inhalation exposure or by intratracheal injection of rats and monkeys, but not by oral ingestion in any animals studied to date. Carcinogenic responses have been induced by a variety of forms of beryllium including beryllium sulfate, phosphate, oxide, and beryl ore. The carcinogenic evidence in mice (intravenously injected or exposed via inhalation) and guinea pigs and hamsters (exposed via inhalation) is equivocal.

Osteosarcomas are the predominant types of tumors induced in rabbits. These tumors are highly invasive, metastasize readily, and are judged to be histologically similar to human osteosarcomas. In rats, pulmonary adenomas and/or carcinomas of questionable malignancy have been obtained, although pathological end points have not been well documented in many cases.

Although, individually, many of the reported animal studies have methodological and reporting limitations compared to current standards for bioassays, collectively the studies provide good evidence for carcinogenicity. Responses have been noted in multiple species at multiple sites and, in some cases, afford evidence of a dose response. On this basis, using EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984) to classify the weight of evidence for carcinogenicity in experimental animals, there is "sufficient" evidence to conclude that beryllium is carcinogenic in animals. Since positive responses were seen for a variety of beryllium compounds, all forms of beryllium are considered to be carcinogenic.

2.5.2 Human Studies

Epidemiologic studies provide equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early epidemiologic studies of beryllium exposed workers (see IARC, 1972, 1980; Bayliss et al., 1971; Bayliss and Lainhart, 1972) do not report positive evidence for increased cancer incidence. However, recent studies do report a significantly increased risk of lung cancer in exposed workers. The absence of beryllium exposure levels and a demonstrated concern about possible confounding factors within the workplace make the reported positive correlations between beryllium exposure and increased risk of cancer difficult to substantiate. This relegates the reported

statistically significant increases of lung cancer to, at best, an elevated incidence that is not statistically significant. Because of these limitations, the EPA (U.S. EPA, 1984) considers the available epidemiologic evidence to be "inadequate" to support or refute the existence of a carcinogenic hazard for humans exposed to beryllium.

2.5.3 Qualitative Carcinogenicity Conclusions

Using the EPA weight-of-evidence criteria for evaluating both human and animal evidence, beryllium is most appropriately classified in Group B2, indicating that, on the strength of animal studies, beryllium should be considered a probable human carcinogen. This category is reserved for chemicals having "sufficient" evidence for carcinogenicity in animal studies and "inadequate" evidence in human studies. In this particular case, the animal evidence demonstrates that all beryllium species should be regarded as probably being carcinogenic for humans.

2.6 HUMAN HEALTH RISK ASSESSMENT OF BERYLLIUM

2.6.1 Exposure Aspects

In the general U.S. population, the dietary intake of beryllium is probably less than 1 μg a day, and due to its chemical properties, very little is available in the gut for absorption. Approximately half of the absorbed beryllium enters the skeleton.

For most people, the daily amount of beryllium inhaled is only a few nanograms. However, it is likely that much of this is retained in the lungs. The available data indicate that the beryllium lung burden in the average adult ranges from 1 to 10 μg. Since beryllium occurs in cigarettes, it is possible that smokers will inhale and retain more beryllium than nonsmokers. Unfortunately, the data on beryllium concentrations in mainstream smoke are, at present, uncertain.

2.6.2 Relevant Health Effects

Occupational exposure to various beryllium compounds has been associated with acute respiratory disease and chronic beryllium disease (in the form of granulomatous interstitial pneumonitis). Some systemic effects have also been noted and a hypersensitization component probably plays a major role in the

manifestation of these effects. In the past, chronic beryllium disease was found in members of the general population living near beryllium-emitting plants, but past exposures were relatively high compared to present levels of beryllium in the ambient air. Contaminated workclothes brought home for washing contributed to these exposures. No "neighborhood" cases of chronic beryllium disease have been reported in the past several years.

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. Although some of these studies have limitations, the overall evidence from animal studies should be classified as "sufficient" using EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984). The International Agency for Research on Cancer (IARC) has also concluded that the evidence from animal studies is "sufficient." Human studies on beryllium carcinogenicity have deficiencies that limit any definitive conclusion that a true association between beryllium exposure and cancer exists. Nevertheless, it is possible that a portion of the excess cancer risks reported in these studies may, in fact, be due to beryllium exposure. Although IARC concluded that beryllium and its compounds should be classified as having "limited" human evidence of carcinogenicity, the U.S. Environmental Protection Agency's Carcinogen Assessment Group (CAG) has concluded that the human evidence is "inadequate."

2.6.3 Dose-Effect and Dose-Response Relationships of Beryllium

As previously stated, beryllium can act upon the lung in two ways, either through a direct toxic effect on pulmonary tissue or through hypersensitization. Even if reliable and detailed exposure data were available, it would still be difficult to establish dose-effect and dose-response relationships due to this hypersensitization factor. No adverse effects have been noted in industries complying with the 2 $\mu g/m^3$ standard; therefore, it appears that this level of beryllium in air provides good protection with regard to respiratory effects. It is unknown whether exposures to the maximum permissible peak standard (25 $\mu g/m^3$) can cause delayed effects.

From available data, the CAG has estimated carcinogenic unit risks for inhalation exposure to beryllium. The quantitative aspect of carcinogen risk assessment is included here because it may be of use in setting regulatory priorities and in evaluating the adequacy of technology-based controls and other aspects of the regulatory decision-making process. However, the uncertainties associated with estimated cancer risks to humans at low levels of exposure

should be recognized. The linear extrapolation procedures used (see Section 7.3) provide a rough but plausible estimate of the upper limit of risk--that is, it is not likely that the true risk would be much higher than the estimated risk, but it could be considerably lower. The risk estimates presented below should not be regarded, therefore, as accurate representations of true cancer risks even when the exposures are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-limit risks is found to be useful.

Both animal and human data are used to estimate the carcinogenic potency of beryllium. Many of the animal inhalation studies conducted on beryllium are not well documented, were conducted at single-dose levels and, in some cases, did not utilize control groups. Despite individual deficiencies, data from ten inhalation studies (eight studies of rats, one study of hamsters and one study of monkeys) have been analyzed and show that potency estimates among several studies using the same form of beryllium (beryllium sulfate) differed to only a small degree, while different forms resulted in a much greater variation in potency. The upper-bound potency estimates, calculated on the basis of animal data range from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.3/(\mu g/m^3)$, using a surface area correction. Among the four beryllium compounds examined in the ten studies, beryl ore, which is the least soluble, is the least carcinogenically potent, while beryllium sulfate, the most soluble of the compounds, is the most potent. The estimated potency values for beryllium on the basis of animal studies, except the potency value estimated with the Wagner et al., (1969) study on beryl ore, are considerably greater than those estimated from human data.

Even though the epidemiologic studies have been judged to be qualitatively inadequate to assess the potential of carcinogenicity for humans, these studies can be analyzed to determine the largest plausible risk that is consistent with the available epidemiologic data. This upper bound can be used both to estimate human risk and to evaluate the reasonableness of estimates derived from animal studies. Information from the epidemiologic study by Wagoner et al., (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to estimate a plausible upper bound for incremental cancer risk associated with exposure to air contaminated with beryllium. The upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is estimated to be 2.4×10^{-3}. This estimate is based upon occupational exposure to beryllium compounds thought to have a low degree of solubility.

Because the carcinogenic potencies of beryllium compounds derived from the animal data are much greater than the estimate derived from the human data, the animal values are judged to be less relevant to human environmental exposure and the estimate based upon human data is recommended for use with caveat. If the form of beryllium present contains more than a small fraction of the more soluble forms, then the human estimate ($2.4 \times 10^{-3}/\mu g/m^3$) may underestimate the upper limit and consideration should be given to noting the animal based estimates. The incremental upper limit risk of $2.4 \times 10^{-3}/(\mu g/m^3)$ places beryllium in the lower part of the third quartile of 55 suspect carcinogens evaluated by the CAG.

2.6.4 Populations at Risk

In terms of exposure, persons engaged in handling beryllium in occupational environments obviously comprise individuals at highest risk. With regard to the population at large, there may be a small risk for people living near beryllium-emitting industries. However, the risk for such individuals may not be from ambient air levels of beryllium, but rather from beryllium-contaminated dust within the household. There are no data that allow an estimate of the number of people that may be at such risk, but it is reasonable to assume that it is a very small group. It should be noted that no new "neighborhood" cases of beryllium disease have been reported since the 1940s.

3. BERYLLIUM BACKGROUND INFORMATION

3.1 GEOCHEMICAL AND INDUSTRIAL BACKGROUND

3.1.1 Geochemistry of Beryllium

Average crustal rock contains about 2.8 μg Be/g (Mason, 1966), but beryllium also occurs in more concentrated forms as a component of over forty different minerals. Granites are enriched by 15 to 20 μg Be/g. It is likely that most beryllium minerals were formed during the cooling of granitic magmas (Beus, 1966). The element was excluded during the early cooling stages and accumulated in the crystallization products formed during the final stages, commonly in association with quartz. The most highly enriched deposits of beryllium are in pegmatitic intrusions.

Only two beryllium minerals are of current economic importance, beryl and bertrandite. Beryl, an aluminosilicate ($Be_3Al_2Si_6O_8$), is mined largely in the USSR, Brazil, and the People's Republic of China; smaller amounts are produced in several other countries (Table 3-1). Formed by pegmatite processes, beryl is 5- to 11-percent beryllium oxide and, in its purest gem-quality form, is treasured as the green or blue emerald. Until the late 1960s, the common technique for separating beryl from associated rock was to crush the rock and hand pick the mineral crystals. By 1969, mechanical flotation separation techniques were developed, and a second mineral, bertrandite [$Be_4Si_2O_7(OH)_2$], became economically important (Anonymous, 1980). Bertrandite occurs as very tiny silicate granules that have a beryllium oxide concentration of less than one percent. The only active commercial deposit of bertrandite in the United States is at Spor Mountain, Utah. This domestic source supplies about 85 percent of the beryllium ore consumed in the United States, the rest is imported, either as beryl or bertrandite, as listed in Table 3-1 (U.S. Bureau of Mines, 1984).

Beryllium was discovered by Vauquelin in 1798. The element was isolated in metallic form in 1828 by Woehler, and perhaps independently that same year by Bussy (Beus, 1966). Beryllium is a light-grey, low-density metal with a high melting point, exceptional resistance to corrosion, and the capacity to absorb heat. In the United States, beryllium ore is processed at Delta, Utah by Brush Wellman, Inc.

Although beryllium was isolated as a metal in 1828, it was not until the 1930s that beryllium-copper alloys came into widespread use. Deposits of beryl known for gem production were the first to be exploited. In the USSR,

TABLE 3-1. GLOBAL PRODUCTION AND U.S. CONSUMPTION OF BERYLLIUM ORE (METRIC TONS)

Country	1948	1968	1980	1984
Argentina	45	593	31	15
Brazil	1617	2078	550	1252
Madagascar	8	--	10	10
Mozambique	73	95	20	15
People's Republic of China (1)	(4)	(4)	580	239
Portugal	9	128	19	18
Rwanda	40	149	108	36
U.S.S.R.	(4)	1197	1814	1905
United States (2)	82	152	6756	5469
Zimbabwe	--	88	9	50
Other Countries (3)	257	2088	--	--
World production	2131	6568	9897	9009
U.S. consumption	1787	8384	7717	8166

(1) Estimated from U.S. imports.

(2) Includes bertrandite ore, calculated as equivalent to beryl containing 11% BeO.

(3) Includes Australia, French Morroco, India, South-West Africa, and Spain in 1948, and Australia, India, Kenya, Malagasy Republic and Uganda in 1968. These countries are no longer a significant part of global beryllium production.

(4) Data not available, not included in total.

(--) No production or less than 0.5 tons.

Source: U.S. Bureau of Mines (1950, 1970, 1984)

geochemical techniques for locating beryl deposits by chemical anomalies in surrounding rock formations were used for some time, but had little success (Goldschmidt and Peters, 1932).

3.1.2 Production and Consumption of Beryllium Ore

From the ore, beryllium is extracted as the hydroxide, from which all forms of the metal and its alloys can be made. The most useful products are beryllium metal, beryllium oxide, and beryllium-copper alloys. Its stiffness-to-weight ratio and high thermal conductivity make beryllium metal useful in the aerospace industry. In the electronics industry, beryllium oxide is used to dissipate heat away from thermally sensitive components. Beryllium-copper alloys, which provide a combination of strength, electrical conductivity, and resistance

to stress relaxation, are used extensively for electrical/electronic switches, sockets, and connectors. The alloys are also non-magnetic. Other beryllium alloys are especially valuable for their resistance to oxidation or corrosion and have been used in the production of dental prostheses (Newland, 1982).

From 1930 to 1969, deposits of beryl remained the sole source of beryllium. The consumption of beryllium increased 600-percent between 1948 and 1968 (Table 3-1), a rate that was ten times that of any other common metal (Knapp, 1971). During this period, the nuclear power industry joined the aerospace and electronics industries as a consumer of beryllium products (Anonymous, 1980). Two countries, the USSR and the United States, became the primary consumers of beryllium ore and producers of beryllium products.

After the production of bertrandite became economically feasible in 1969, its production in the United States rose to the equivalent of about 6000 tons of beryl by 1981. From the domestic production of 5469 equivalent tons of beryl ore, the use of existing stocks, and the import of 1208 actual tons, the United States produced about 107 tons of contained beryllium in 1984, of which about 18 tons were exported as finished or unfinished products.

3.1.3 Industrial Uses of Beryllium

About 10 percent of the domestic beryllium hydroxide is used in the production of pure beryllium metal in sheet, rod, or wire form. Since 1979, Brush Wellman, Inc. has been the only free-world producer of beryllium metal (Anonymous, 1980). The metal is milled to desired specifications at the user facility, producing beryllium dust and scrap in the vicinity of machine shops. Because of the high cost of the metal, efficient recovery and recycling of the metal are a high priority.

About 15 percent of the raw beryllium hydroxide is consumed in the production of beryllium oxide (beryllia). It is used in the production of ceramics that have excellent thermal conductivity, especially at high temperatures (Table 3-2). These products make good electrical insulators and have a high resistance to thermal shock. The high melting point permits the use of beryllium oxide in rocket nozzles and thermocouple tubing.

The remaining 75 percent of beryllium hydroxide is used in the production of alloys, primarily beryllium-copper alloys. As a general rule, two percent beryllium in a copper alloy with a mixture of other metals can markedly increase the strength, endurance, and hardness of the alloy. Most applications for beryllium alloys are in the electronic field, although specialized uses such

TABLE 3-2. INDUSTRIAL USES OF BERYLLIUM PRODUCTS

Beryllium Metal	
Aircraft disc brakes	Nuclear reactor neutron reflectors
Navigational systems	Fuel containers
X-ray transmission windows	Precision instruments
Space vehicle optics and instruments	Rocket propellants
Aircraft/satellite structures	Heat shields
Missile parts	Mirrors
	Nuclear weapons
Beryllium Oxide	
High-technology ceramics	Military vehicle armor
Electronic heat sinks	Rocket nozzles
Electrical insulators	Crucibles
Microwave oven components	Thermocouple tubing
Gyroscopes	Laser structural components
Beryllium Alloys	
Springs	Precision instruments
Electrical connectors and relays	Aircraft engine parts
Pivots, wheels and pinions	Submarine cable housings
Plastic injection molds	Non-sparking tools

as springs, wheels, and pinions serve an indispensable industrial function. Kawecki-Berylco, Inc. at Reading, Pennsylvania and Brush Wellman at Elmore, Ohio are the major producers of beryllium alloys in the United States.

3.2 CHEMICAL AND PHYSICAL PROPERTIES OF BERYLLIUM

The chemical and physical properties of beryllium resemble those of aluminum, zinc, and magnesium (Table 3-3). Chemical similarities are due primarily

TABLE 3-3. PHYSICAL PROPERTIES OF BERYLLIUM AND RELATED METALS

	Be	Al	Zn	Mg
Metal				
Atomic number	4	13	30	12
Atomic weight	9.012	26.98	65.38	24.31
Atomic radius	1.40	1.82	1.53	1.72
Valence	2+	3+	2+	2+
Ionic radius A°	.35	.51	.74	.66
Density 25 °C	1.85	2.7	7.14	1.74
Melting point °C	1283	660.4	419.58	648.8
Boiling point °C	2970	2467	907	1107
Thermal conductivity 100°	.401	.573	1.12	.376
Electrical resistivity (μ°nm · cm @ 20°C)	4.31	2.65	5.916	4.45
Oxide				
Formula	BeO	Al_2O_3	ZnO	MgO
Molecular weight	25.01	101.96	81.37	40.31
Density	3.008	3.965	5.606	3.58
Melting point °C	2530	2072	1975	2852
Boiling point °C	3900	2980	---	3600
Thermal conductivity 725°C (cal/sec · cm^2 · °C/cm)	.111			
Hydroxide				
Formula	$Be(OH)_2$	$Al(OH)_3$	$Zn(OH)_2$	$Mg(OH)_2$
Molecular weight	43.01	78.00	99.38	58.33
Density		2.42	3.053	2.36
Solubility moles/liter	0.8×10^{-4}			
Decomposes to oxide °C	250-300	300	125	350

to similar ionic potentials, which facilitate covalent bonding (Novoselova and Batsanova, 1969).

The properties of beryllium are often considered in the context of the three most common forms of potential industrial emissions: the metal, the oxide and the hydroxide. In certain occupations, beryllium halides may also be important, but these cases are too few to merit extended discussion.

Beryllium is extracted from ores as the hydroxide and shipped in this form to commercial processing plants (Anonymous, 1980). The most common concentration process involves the leaching of 20-mesh particles with sulfuric acid followed by hydroxylation with di-2-ethylhexylphosphate in kerosene. The

beryllium hydroxide salt is then collected by filtration. The process recovers about 80 percent of the beryllium found in low-grade bertrandite ore.

From beryl, beryllium may be extracted by the Sawyer-Kjellgren process; the ore is melted at 1625°C and cooled quickly with water to form a beryllium glass. The glass is dried and ground to 200-mesh powder, then leached with sulfuric acid. Sodium hydroxide is used to convert the sulfate to beryllium hydroxide. This process is also about 80-percent efficient but can not be used to extract the small amounts of beryllium in bertrandite ore.

A third process, the Copaux-Kawecki process, uses sodium ferric fluoride to extract beryllium from low-grade, fine-grained bertrandite ores at a 90-percent efficiency. This process is no longer used in the United States or Europe, due to its expense and the toxicity of beryllium fluoride. Indeed, the first medical report of berylliosis in 1933 can be attributed to exposure to beryllium fluoride at an extraction plant (Weber and Englehardt, 1933).

3.3 SAMPLING AND ANALYSIS TECHNIQUES FOR BERYLLIUM

Beryllium occurs in environmental samples at concentrations of about 0.01 to 0.1 ng/m^3 in air, 0.05 to 0.1 µg/g in dust, 0.01 to 1.0 ng/g in surface waters, 0.3 to 6.0 µg/g in soil, and 0.01 µg/g in biological materials. Some plants, such as hickory, may accumulate beryllium as much as 1 µg/g dry weight (Newland, 1982). Two techniques, gas chromatography (GC) (Ross and Sievers, 1972) and atomic absorption spectroscopy (AAS) (Owens and Gladney, 1975), appear to offer the best combination of sensitivity and sample handling efficiency. However, colorimetry, fluorometry, and emission spectrometry are also occasionally used.

Environmental samples analyzed by atomic absorption spectroscopy and gas chromatography require pretreatment to remove interfering substances and increase sensitivity. At high concentrations (500 µg/g), aluminum and silicon interfere with beryllium analysis by AAS. Separation of these elements is achieved by chelation and extraction with an organic solvent. The limit of detection for the flame method of AAS is 2 to 10 ng/ml, and 0.1 ng/ml for the flameless method. Air samples of a few cubic meters must be concentrated after extraction to a liquid volume of less than 1 ml to enter the detection range. The high-volume sampler, which collects in the range of 1.1 to 1.7 m^3/min, is more desirable than either a low-volume sampler or a cascade impactor, which

collect at 0.001 m^3/min. Normal concentrations of dust, water, and biological materials are all at or below the detection limits of flameless AAS, so that preconcentration by wet digestion is necessary.

Using gas chromatography, Ross and Sievers (1972) reported a detection limit for beryllium in air of about 0.04 ng/m^3, making this method marginally acceptable for small sample sizes. Extensive chemical digestion and extraction are required, however.

Standard reference materials are available for each method in the form of fly ash, coal, orchard leaves, and bovine liver. Beryllium values for these standard sources have been reported by Owens and Gladney (1975).

3.4 ATMOSPHERIC EMISSIONS, TRANSFORMATION, AND DEPOSITION

Although there is little evidence for significant emissions of beryllium to the atmosphere during ore production, emissions could be significant without existing regulations. The 20 percent of beryllium lost as waste during processing (in the form of the hydroxide or the fluoride) could also represent an environmental problem. Any potential effects from these sources of exposure would be locally confined to the sole ore-processing plant in the United States, operated by Brush Wellman at Delta, Utah.

Emission of beryllium from non-metallurgical processes (coal and fuel oil combustion) accounts for 99 percent of U.S. emissions (Table 3-4). The average concentration of beryllium in coal is between 1.8 and 2.2 µg/g. In 1984, the United States burned 790 x 10^6 metric tons of coal. Had emission control measures for other pollutants not been used, 1300 tons of beryllium would have been emitted, an amount that is far greater than the 0.3 tons lost during beryllium ore processing. However, there is evidence that emission control measures capture 70 to 90 percent of beryllium in the fly ash. The actual efficiency of beryllium retention during coal combustion is a subject of controversy and a source of confusion in several published reports. Phillips (1973) presented data that suggested 86 percent of the beryllium in coal is released to the atmosphere. Gladney and Owens (1976) concluded that less than 4 percent escapes. Henry (1979) suggested that less than 1 percent escapes, but could not account for 35 percent of the beryllium in mass-balance estimates. The following calculations may explain this descrepancy.

All three authors use a form of a mass-balance calculation in which the concentration of beryllium in the coal and the fly ash is either measured or assumed. Since beryllium output is presumed to be confined to captured fly

TABLE 3-4. NATURAL AND ANTHROPOGENIC EMISSIONS OF BERYLLIUM

Natural	Total U.S. Production[a] (10^6 t/yr)	Emission Factor (g/t)	Emission (t/yr)
Windblown dust	8.2	0.6	5
Volcanic particles	0.41	0.6	0.2
Total			5.2
Anthropogenic			
Coal combustion	640	0.28	180
Fuel oil	148	0.048	7.1
Beryllium ore processing	0.008[b]	37.5[b]	0.3
Total			187.4

[a]Units are in metric tons

[b]The production of beryllium ore is expressed in equivalent tons of beryl; the emission factor of 37.5 is hypothetical.

ash and emitted stack gases, that fraction of the coal input not found in the fly ash is considered as emitted to the atmosphere. Neither Phillips (1973) nor Gladney and Owens (1976) knew the actual mass of the ash produced. In both cases, they reported ash content published elsewhere in the literature. Phillips measured a beryllium content of the coal (2.5 μg/g) and of the ash (5.0 μg/g), and assumed an ash content of 7 percent to calculate the emitted fraction as:

$$\frac{2.5\ \mu g/g - (0.07)\ (5\ \mu g/g)}{2.5\ \mu g/g} = 0.86$$

Gladney and Owens (1976) assumed an ash content of 12 percent, which is near the upper range of the 7 to 14 percent normally found in coal. They measured a coal beryllium content of 1.89 and an ash beryllium content of 15.3 μg/g. The calculated percent loss would be:

$$\frac{1.89\ \mu g/g - (0.12)(15.3\ \mu g/g)}{1.89\ \mu g/g} = 0.0285$$

Both calculations are extremely sensitive to the assumed ash content of coal. Using the range of 7 to 14 percent, the data of Phillips would show beryllium losses of 72 to 86 percent, and the data of Gladney and Owens, 0 to 43 percent. It is also possible that errors of analysis were made in measuring the beryllium concentration of coal and ash. Coal and ash from the same plant that Phillips investigated were reported by the Southwest Energy Study (1972) to contain 0.43 and 7 μg Be/g, respectively. However, these concentrations cannot be considered typical because in the range of 7 to 14 percent ash, these data would yield a percent beryllium loss of less than zero. If the average beryllium content of western coal (1 μg/g) is used with the Phillips data, the loss to the atmosphere ranges from 30 to 65 percent.

Henry (1979) made similar measurements of coal and ash. Sixty-five percent of the beryllium was accounted for in the ash. However, measurements of beryllium at the precipitation outlet and in the stack did not account for the remainder of the beryllium. In simulation runs, Yeh et al. (1976) found 77 percent retention of the beryllium in the slag and fly ash.

Although the data range from 0 to 86 percent, it seems reasonable to conclude that between 10 and 30 percent of the beryllium in coal is emitted to the atmosphere during the coal combustion process. While not all coal burning facilities control emissions as well as power plants, the following calculation is a conservative estimate of total beryllium emissions from coal in the United States during 1984.

$$790 \times 10^6 \text{ t coal/yr} \times 1.4 \text{ g Be/t coal} \times \underset{\text{efficiency}}{(0.1 \text{ to } 0.3)} = 220 \pm 110 \text{ t Be/yr}$$

Emissions from oil-burning facilities may be calculated from the average beryllium concentrations of fuel oil (Anderson, 1973), an assumed loss of 40 percent, and a consumption of 1.1×10^8 tons residual oil per year. From this calculation, it appears that 7.1 tons of beryllium are emitted from this source.

Although no data exist, it is likely that less than 0.5 percent of the contained beryllium is emitted during the post-ore production metallurgical processes, adding a maximum of 0.12 tons/year to the atmosphere. Therefore, 187 tons/year would seem to be a reasonable estimate for anthropogenic beryllium emissions from the United States. An estimate by Flinn and Reimers (1974) that coal combustion accounts for 88 percent of the total beryllium emissions was

probably conservative and could perhaps be revised upward to 95 percent or higher.

Assuming a residence time of 10 days, an effective stratospheric volume of 2.3×10^{16} m^3, and stationary air mass above the United States, this amount of beryllium could account for an average atmospheric concentration of 0.22 ng/m^3. Because of the dispersion caused by moving global air masses, the actual air concentrations are about one-third this value.

Because most atmospheric beryllium is derived from coal combustion, it is likely that its chemical form would be beryllium oxide. Conversion to ionized salts is possible, but has not been reported. Gladney and Owens (1976) studied the particle size distribution of stack emissions and reported that most beryllium is found on particles smaller than 1 μm. Particles of this size remain aloft for about ten days.

Removal of beryllium from the atmosphere is by wet and dry deposition. The rate of dry deposition of aerosol particles is a function of particle size, windspeed, and surface roughness. The actual deposition rate for beryllium has not been measured, but can be estimated by analogy to other elements. Davidson et al. (1982) described the relationship between concentration of particles in air, particle size, and surface roughness. For vegetation surfaces, a reasonable deposition velocity would be 0.25 cm/sec. Assuming an average air concentration of 0.1 ng Be/m^3 in air, 0.002 ng of beryllium would be removed from the atmosphere per square centimeter of actual surface area.

Kwapulinski and Pastuszka (1983) have determined that in Poland, emissions of beryllium appear to be in balance with deposition. They applied the solution of the Reynolds mass-balance model described by Astarita et al. (1979) to the deposition of beryllium as a function of air concentration. The coefficient of deposition, K_1, was found to be constant during rainy periods and linearly correlated with windspeed during dry periods. This report confirms that beryllium is removed from the atmosphere by both wet and dry deposition in a manner similar to metals on particles of comparable size distribution. Values for K_1 have not yet been measured in the United States. Because K_1 varies regionally with surface roughness and windspeed, calculations based on metals associated with particles of comparable size are an acceptable substitution.

Concentrations of beryllium in precipitation have not been reported in the United States. Assuming that half of the beryllium emitted into the atmosphere

returns to earth as wet precipitation, the average concentration of beryllium in rain or snow is expected to be 0.01 ng/g. This value is below the detection limit for most analytical techniques. In a report from Australia, the actual concentration of beryllium in rain was reported to average 0.07 ng/g (Meehan and Smyth, 1967).

Beryllium oxide is very insoluble and would not be mobilized in soil or surface water at normal environmental pH ranges of 4 to 8. If this is the chemical form of beryllium at the time of deposition, the compound would not move easily along grazing food chains, but would instead be confined to soil and sediment. If, however, significant amounts of beryllium are converted to chloride-, sulfate-, or nitrate-salts during atmospheric transport, solubility upon deposition would be greatly enhanced and mobility within ecosystems could be facilitated. Beryllium is classified as a fast-exchange metal, which means that it could potentially interfere with the transport of nutritive metals, such as calcium, into eukaryotic cells (Wood and Wang, 1983). There is a need for research into the effects of pH on the mobility of beryllium in ecosystems and its subsequent effects on plants and animals. Some of the toxic effects of beryllium on natural populations of plants and animals are reviewed by Brown (1979).

3.5 ENVIRONMENTAL CONCENTRATIONS OF BERYLLIUM

3.5.1 Ambient Air

Beryllium is measured at many of the stations in the SLAMS (State and Local Air Monitoring Stations) and NAMS (National Air Monitoring Stations) networks. The data are available from the SAROAD (Storage and Retrieval of Aerometric Data) data base of the U.S. Environmental Protection Agency. The detection limit for these analyses is 0.03 ng/m^3, and most annual averages are at this concentration. Annual averages which exceeded 0.1 ng/m^3 during 1977-81 are listed in Table 3-5. The highest 24-hour observation recorded was 1.78 ng/m^3 in Atlanta, Georgia in 1977. At no sampling site did the 30-day average concentration approach the 10 ng/m^3 standard set by the U.S. Environmental Protection Agency (Federal Register, 1973).

3.5.2 Soils and Natural Waters

Shacklette et al. (1971) reported a geometric mean of 0.6 µg Be/g in soil for 847 samples taken from sites distributed evenly across the United States. Only 12 percent of the samples exceeded 1.5 µg/g. The soils were sampled at a

TABLE 3-5. CONCENTRATIONS OF BERYLLIUM IN URBAN ATMOSPHERES[a]

	1977	1978	1979	1980	1981[b]
Birmingham, AL		.11(20)			
Douglas, AZ				.25(7)	
Tucson, AZ					.11(7)
Ontario, CA				.14(11)	
Hialeah, FL					.22(1)
Miami, FL	.11(20)				
St. Petersburg, FL	.12(13)				.11(7)
Tampa, FL	.11(23)	.11(22)			
Atlanta, GA	.19(27)	.13(24)			
East Chicago, IN		.11(18)			
Gary, IN		.15(25)	.16(21)		
Hammond, IN			.12(23)		
Indianapolis, IN			.11(19)		
Des Moines, IA					.11(6)
Kansas City, KS		.14(28)			
Ashland, KY	.16(23)	.37(19)			
Baton Rouge, LA	.19(26)				
Portland, ME				.18(5)	
Baltimore, MD				.11(6)	
Fall River, MA		.11(29)			
New Bedford, MA		.12(26)			
Flint, MI				.13(10)	
Lansing, MI					.13(4)
Kansas City, MO		.12(29)			
Omaha, NB		.13(15)			
Camden Co., NJ	.22(24)			.17(14)	
Perth Amboy, NJ		.13(28)			
Trenton, NJ			.11(19)		
Albuquerque, NM					.22(6)
Niagara Falls, NY		.17(5)			
Syracuse, NY		.19(2)			
Cincinnati, OH		.11(30)		.11(16)	
Cleveland, OH		.15(26)			
Columbus, OH		.11(26)			
Dayton, OH		.21(26)			
Mansfield, OH		.15(29)			
Portsmouth, OH		.14(27)			
Steubenville, OH		.13(24)	.17(28)		
Toledo, OH				.11(11)	
Youngstown, OH		.19(27)	.14(26)	.18(10)	

(continued on the following page)

TABLE 3-5. (continued)

	1977	1978	1979	1980	1981
Guayanilla Co., PR					.15(7)
Baja Co., PR				.17(5)	.16(5)
Knoxville, TN		.11(29)			
Nashville, TN			.13(11)		
Dallas, TX		.14(25)	.40(2)		
El Paso, TX		.17(17)			
Houston, TX	.11(15)				
Lubbock, TX				.17(13)	
Pasadena, TX		.13(23)			
Seattle, WA					.11(7)
Charleston, WV		.15(23)			
Milwaukee, WI		.13(25)			

[a]Values exceeding 0.1 ng/m^3 are reported for the period 1977-81. Units are in ng/m^3. Values in parentheses are the number of 24-hour observations used to determine average annual concentrations.

[b]Values not yet available.

depth of 20 cm. These results are lower than those of previous geochemical surveys conducted by Vinogradov (1960), Hawkes and Webb (1962), and Mitchell (1964), each of whom reported a mean of 6.0 µg/g. The differences may be due to limitations in analytical techniques. The 0.6 µg/g value is more consistent with the average crustal value of 2.8 µg/g reported by Mason (1966).

Values for beryllium in surface waters range from 0.01 to 1.0 ng/g (Bowen, 1979). The lowest value (0.01 ng/g) was reported by Meehan and Smythe (1967) in Australia. These concentrations are in the same range as the expected concentration of beryllium in precipitation (0.01 ng/g) discussed above. The beryllium concentration in seawater was reported to be 0.0005 ng/g by Merrill et al. (1960) and 0.0056 ng/g by Bowen (1979). There are no available reports of beryllium concentrations in groundwater.

3.6 PATHWAYS TO HUMAN CONSUMPTION

Humans may be exposed to beryllium through air, food, water, and dust (Figure 3-1). In this section, beryllium concentrations are estimated for typical environments not exposed to extraordinary sources of beryllium. These values are combined with the consumption rates of air, food, water, and dust to estimate the typical total daily intake of beryllium.

A likely average concentration of 0.08 ng Be/m^3 in a residential environment can be projected from data collected from monitoring stations. Values are

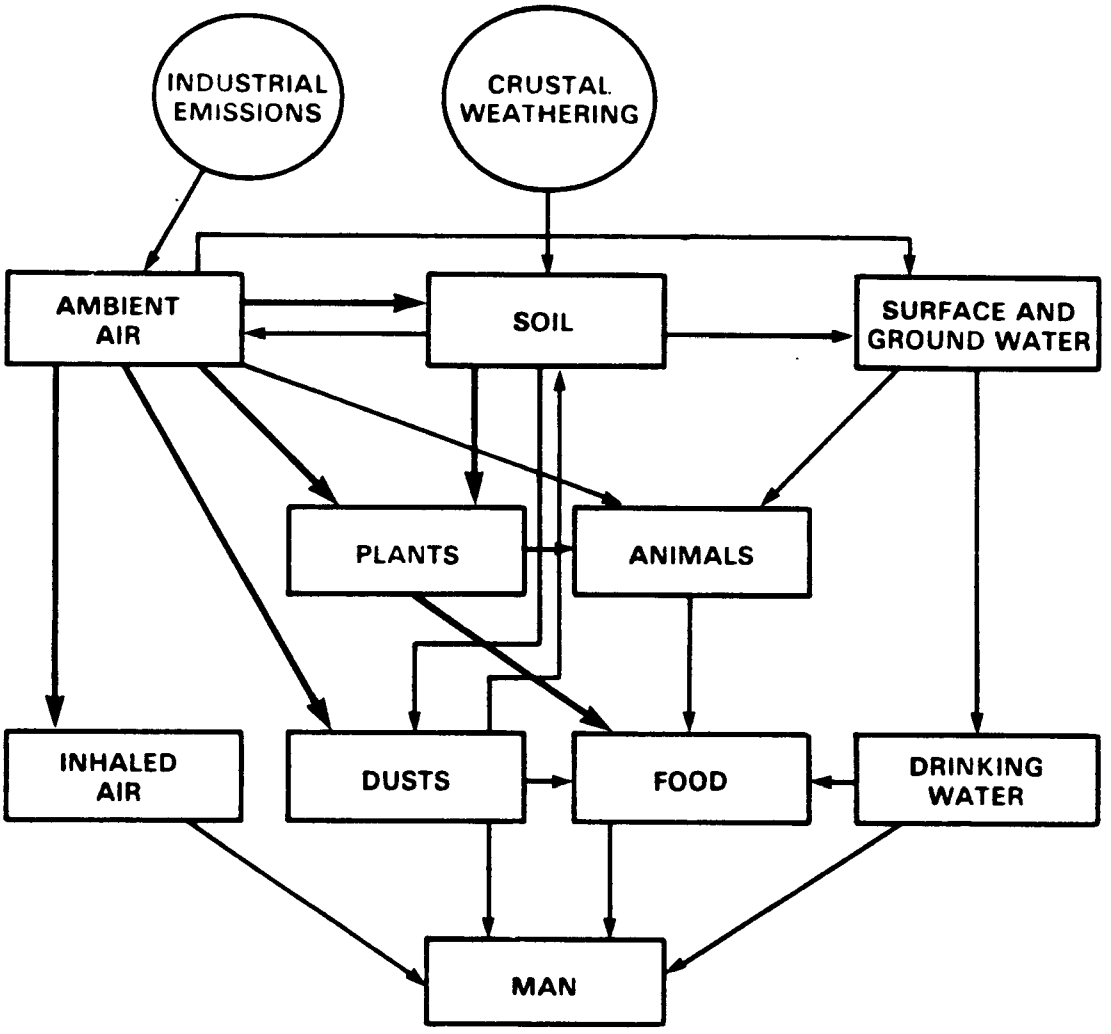

Figure 3-1. Pathways of environmental beryllium concentrations leading to potential human exposure.

undoubtedly influenced by the distance and location of monitoring stations from beryllium sources, and whether indoor or outdoor, filtered or unfiltered air is sampled. Only limited data on the beryllium content of foods are available. Meehan and Smythe (1967) analyzed a few foods from Australia, and reported values from 0.05 to 0.15 ng/g fresh weight. The reported values of beryllium in drinking water range from 0.01 to 1.2 ng/g, with an average of 0.2 ng/g. There are no reports of beryllium in household dust, but if it is assumed that such dust originates solely from the atmosphere having a beryllium concentration of 0.1 ng/m^3, and that the air/dust ratio is 600, then household dust would contain 60 ng Be/g.

The average American adult inhales 20 m^3 of air/day, and consumes 1200 g of food and 1500 g of water and beverages (Pennington, 1983). The daily consumption of dust is not well established, but a conservative estimate of 0.02 g is made here for the purpose of illustration. The typical American adult consumes 423 ng/day of beryllium, most of which comes from food and beverages (Table 3-6). It is apparent that air or dust derived from air has little impact on the total intake of beryllium. This overall determination is extremely sensitive to the average concentration of beryllium in food and water, which accounts for 99.3 percent of total daily consumption of beryllium. Variation in these numbers can be expected, depending on the types of food and beverages consumed and the atmospheric contribution to the beryllium concentrations of food and beverages.

Daily consumption from extraordinary sources, such as occupational exposures or secondary occupational exposure e.g., a non-worker's exposure to a worker's clothes, may increase the relative contribution of air and dust to overall beryllium exposure. At 2 µg Be/m^3 (the current occupational standard), a worker's exposure for an 8-hour shift would increase to more that 13,000 ng/day. Dust of beryllium metal or metal oxide consumed at a daily rate of 0.02 g (including dust consumed during the working shift and dust carried home on the clothing of the worker), could add 2,000,000 ng beryllium to the total daily consumption. There is also the possibility that certain individuals might be exposed to beryllium from implanted dental prostheses. Although the leaching of nickel and chromium from alloys used in prostheses has been reported, no studies on the leaching of beryllium are available.

Consumption of beryllium from cigarette smoking was discussed by Zorn and Diem (1974). They found an average of 630 ng Be/cigarette and an average of 35 ng Be/cigarette in the inhaled smoke. Based on these findings, a person smoking

a pack of twenty cigarettes per day would inhale about 700 ng of beryllium, which is nearly twice the daily consumption from other sources. Unfortunately, details in this study are lacking. The origin of the tobacco was not given, and the relationship between the beryllium concentration of the tobacco and the smoke was very weak.

TABLE 3-6. POTENTIAL HUMAN CONSUMPTION OF BERYLLIUM FROM NORMAL SOURCES IN A TYPICAL RESIDENTIAL ENVIRONMENT

	Environmental Concentration	Total Daily Human Intake	Consumption	Percent of Total Daily Consumption
Air	0.08 ng/m3	$20m^3$	1.6 ng/day	0.4
Food	0.1 ng/g	1200g	120	28.4
Water	0.2 ng/g	1500g	300	70.9
Dust	60 ng/g	0.02g	1.2	0.3
		Total	422.8	

4. BERYLLIUM METABOLISM IN MAN AND ANIMALS

4.1 ROUTES OF BERYLLIUM ABSORPTION

4.1.1 Beryllium Absorption by Inhalation

There are no data on the absorption of inhaled beryllium in humans. However, it can be expected that the dose, size, and solubility of beryllium particles will be important factors in determining the rates of absorption and clearance.

Beryllium has been found in the lungs of persons without known occupational exposure to the metal. Cholak (1959) analyzed 70 lungs from unexposed individuals and reported an average concentration of 3.3 µg Be/kg dry weight (range: 0.1-19.8 µg/kg). Meehan and Smythe (1967) reported a mean beryllium level of 1.3 µg/kg wet weight (range: 0.3-2.0 µg/kg) in four human lungs (a value which corresponds to about 6 µg/kg dry weight). Sumino et al. (1975) analyzed beryllium in the lungs of 12 Japanese subjects and found concentrations of up to 30 µg/kg wet weight. It should be kept in mind that smoking habits were not taken into account in any of these studies. In addition, it is difficult to validate such data, as well as other data on beryllium in tissues or body fluids, since no interlaboratory or quality control studies have been conducted, and no reference samples for beryllium in tissues or body fluids are available. The highest value recorded by Cholak (20 µg Be/kg dry weight) has been used to denote an upper normal level of beryllium in human lung tissue (Hasan and Kazemi, 1974).

Animal studies have shown that rats exposed to beryllium sulfate at an average beryllium concentration of 35 $\mu g/m^3$ for 7 hours a day, 5 days a week, for 72 weeks, reached a plateau in lung beryllium concentrations of about 13.5 µg (in whole lungs) after 36 weeks of exposure. A plateau in the tracheobronchial lymph nodes was also reached at that time. After exposure was terminated, pulmonary beryllium was initially eliminated with a half-time of two weeks, followed by a much slower elimination rate (Reeves et al., 1967; Reeves and Vorwald, 1967).

In studies of the distribution of radioactive beryllium compounds administered by intratracheal injection, Kuznetsov et al. (1974) reported a half-time of 20 days in rats given a single injection of beryllium chloride, whereas Van Cleave and Kaylor (1955) reported that beryllium citrate was rapidly eliminated in rats. Longer observation periods in rats, however, suggest a half-time of

about 325 days after inhalation of beryllium oxide (Sanders et al., 1975, 1978). Reanalysis of the latter data showed that there was an initial clearance of 30 percent of the deposited beryllium at a half-time of 2.5 days, while the rest was cleared much more slowly at a half-time of 833 days (Rhoads and Sanders, 1985). About 25 percent of the beryllium cleared from the lungs during the slow phase was translocated to regional lymph nodes (Sanders et al., 1978).

Hart et al. (1984) exposed 20 rats for one hour to beryllium oxide fired at 560°C. The average concentration of beryllium was 447 $\mu g/m^3$, and 90 percent of the particles had a mean diameter of 1 μm or less. The beryllium oxide contained a trace of carrier-free ^7Be. Four animals were killed at 2.5 hours and at 2, 5, 12, and 21 days after exposure. Lungs were lavaged and the beryllium content was determined in the lavage fluid and in the lung tissue. In the lung tissue, about 200 ng of beryllium was found 2.5 hours after exposure. This amount remained constant over the following weeks. In contrast, the amount of beryllium in the lavage fluid decreased from 280 ng to 16 ng in three weeks. The lavage fluid contained free alveolar cells (mainly macrophages).

It is not known in detail how beryllium is retained in the lungs. It is likely that soluble beryllium compounds are transformed to insoluble complexes with, for instance, phosphate, when the beryllium concentration reaches a certain level (Reeves and Vorwald, 1967). Beryllium particles in the insoluble state are apt to be taken up by macrophages as demonstrated *in vitro* (Hart and Pittman, 1980). At high *in vitro* and *in vivo* exposures, beryllium has been shown to be very toxic to alveolar macrophages (Camner et al., 1974; Sanders et al., 1975; Hart et al., 1984). Robinson et al. (1968) exposed two dogs for 20 minutes to a mixture of beryllium oxide, beryllium fluoride and beryllium chloride (average concentration 115 mg/m^3). The dogs were killed after three years. The average beryllium concentration in the lungs was 3.9 and 5.5 mg/kg wet weight. Beryllium deposits were seen in the interstitial tissue where they were in the lysosomes of histiocytes.

Zorn et al. (1977) exposed rats and guinea pigs to beryllium sulfate aerosol (with ^7Be added as the chloride) for a period of three hours. Animals (number not given) were killed at the end of 3 hours and then from 20 to 408 hours, thereafter. The total amount of beryllium inhaled was less than 3 mg of which 10 ng was ^7Be. At the end of the exposure, about 5 ng of the isotope was retained and about 0.5 ng was found in excreta. Of the retained amount of ^7Be, about 67 percent was in the lungs and 15 percent was in the skeleton,

indicating a rapid initial clearance. After 408 hours (17 days), about 80 percent of the total body burden of ^{7}Be was in the skeleton and approximately 18 percent was in the lungs. Less than one percent of ^{7}Be was in other organs. During the first four days, ^{7}Be was cleared from the lungs with a half-time of about 24 hours. This was followed by a slower clearance with a half-time of several weeks. Unfortunately, the lack of detailed information precludes a thorough evaluation of this study.

4.1.2 Gastrointestinal Absorption of Beryllium

There are no data on the absorption of ingested beryllium compounds in humans. Animal experiments, however, generally indicate that less than one percent of ingested beryllium is absorbed (Hyslop et al., 1943; Crowley, 1949; Furchner et al., 1973). The latter two studies were done using tracer amounts of ^{7}Be.

Reeves (1965) gave two groups of rats, four in each group, beryllium sulfate in drinking water. The average daily intake was about 6.6 μg Be in one group and 66.6 Be in the other. One rat in each group was killed after 6, 12, 18, and 24 weeks of exposure. Reeves found that 60 to 90 percent of the ingested beryllium was eliminated in the feces, indicating that an appreciable amount was absorbed. However, the skeletal uptake of beryllium in both groups of rats was nearly the same, averaging 1.49 μg in the low-dose group and 1.19 μg in the high-dose group. This suggests either that gastrointestinal absorption was much less in the high exposure group or that the uptake in bone was independent of absorbed dose. If it is assumed that 50 percent of gastrointestinally absorbed beryllium goes to the skeleton and that the biological half-time in the skeleton is 100 to 1000 days, the daily absorbed amount would be less than 50 ng (or less than 1 percent of the low oral daily dose).

In reporting the study, Reeves (1965) concluded that due to the low solubility of beryllium in intestinal fluid, it was precipitated as the phosphate and was not, therefore, available for absorption. Reeves surmised that most of the beryllium found in the body was absorbed from the stomach.

In contrast to Reeves' study, Morgareidge et al. (1977, abstract) found that uptake in bone was dose-dependent. They exposed rats orally to beryllium as the sulfate at concentrations of 5, 50, and 500 mg/kg for up to two years. Unfortunately, no quantitative data are given in the abstract of this study.

4.1.3 Percutaneous Absorption of Beryllium

There are no data on skin absorption in humans. Tracer studies in rats have shown that small amounts of beryllium may be absorbed from the tail (Petzow and Zorn, 1974). Belman (1969) reported that ionic beryllium applied to the skin will bind to epidermal constituents, mainly alkaline phosphatase. However, the chemical properties of beryllium in any of its different forms make it unlikely that significant absorption can occur through intact skin.

4.1.4 Transplacental Transfer of Beryllium

In a study by Bencko et al. (1979), the soluble salt of beryllium, $BeCl_2$, was evaluated for its ability to penetrate the placenta and reach the fetus of mice. Radiolabeled $^{7}BeCl_2$, injected into the caudal vein of 7 to 9 mice, crossed the placenta and was deposited in various organs of the fetus (see Chapter 5 for a detailed discussion of this study).

No other data are available on placental transfer of beryllium.

4.2 TRANSPORT AND DEPOSITION OF BERYLLIUM IN MAN AND EXPERIMENTAL ANIMALS

Ingestion studies on animals have shown that beryllium absorbed from the gastrointestinal tract accumulates mainly in the skeleton. In soft tissues, concentrations have mainly been found in the liver (Reeves, 1965; Mullen et al., 1972). Similar results have been obtained in injection studies on animals (Mullen et al., 1972; Hard et al., 1977). In the case of the injection studies, the physiochemical state of the injected compound determines the main site of deposition: soluble beryllium rapidly distributes to the skeleton, whereas colloidal forms go mainly to the liver (Klemperer et al., 1952). In rat blood, large doses of injected beryllium tend to aggregate and bind to phosphate, whereas small doses remain largely in a diffusible form (Vacher and Stoner, 1968a,b). At low doses of beryllium, the main binding in human blood was reported to be the prealbumin and α-globulin fractions of plasma (Stiefel et al., 1980). Recent data indicate that there is a binding site for beryllium in the lymphocyte membrane (Skilleter and Price, 1984).

Witschi and Aldridge (1968) found that less than 10 percent of an intravenous dose of beryllium sulfate in rats was in the liver 24 hours after dosing (dose range: 0.75-15 µg ^{7}Be/kg b.w.). In contrast, more than 25 percent was found in the liver following the administration of doses of 63 µg/kg b.w. or higher. With increasing dose, comparatively more beryllium was located in the nuclear fraction and less in the supernatant of subcellular fractions of rat

liver. At the lowest dose (0.75 μg), the light mitochondrial fraction had the highest amount of beryllium, and some evidence was presented for beryllium being located in the lysosomes. Further evidence for a role of lysosomes in the hepatic accumulation of beryllium was presented by Skilleter and Price (1979).

There are few data on beryllium levels in humans. Analysis of tissues from people occupationally exposed to beryllium showed that, generally, concentrations were highest in bone, liver, and kidney (Tepper et al., 1961). Meehan and Smythe (1967) reported that in the brain, kidney, spleen, liver, muscle, and heart, concentrations were generally less than 1 μg/kg wet weight. However, in one bone sample the concentration was 2 μg/kg, and in five vertebrae the mean was 3.6 μg/kg. The form in which beryllium is stored in bone is presently unknown.

4.3 EXCRETION OF BERYLLIUM IN MAN AND ANIMALS

In rats given intravenous injections of tracer doses of ^{7}Be, 15 percent of the dose was excreted in urine by day 1 and 64 percent was excreted by day 64 (Crowley et al., 1949). In mice, monkeys, and dogs, urinary excretion was the main route of beryllium elimination during the first days after parenteral dosing (Furchner et al., 1973). These researchers found that only later did elimination by the gastrointestinal tract equal that of urinary excretion. In early studies, Scott et al. (1950) discovered that increasing the dose in experimental animals resulted in lowering urinary excretion rates. Biliary excretion seems to play only a minor role in total beryllium excretion (Cikrt and Bencko, 1975).

With oral dosing, Reeves (1965) found that less than one percent of the administered dose was excreted in urine of rats.

Quantitative data on the excretion of beryllium in humans are scarce. In one study of persons not exposed to an occupational source of beryllium, very small amounts (<0.1 μg Be/l), as measured by emission spectroscopy, were found in the urine (Lieben et al., 1966). Much higher values (averages of 0.9 μg Be/l) were reported in two other studies, one of 120 people from California (Grewel and Kearns, 1977) and another of 20 individuals from Germany (Stiefel et al., 1980). In the latter two studies, flameless atomic absorption spectroscopy was used to measure the beryllium concentrations. Thus, the differences observed between these two studies and that of Lieben et al. (1966) may have been due to the different analytical methods used.

Since human dietary intake of beryllium is low, and animal studies suggest that gastrointestinal absorption would also be low, the total human body burden of beryllium is likely to be such that only a few nanograms would be excreted daily. Based on the limited data reported by Meehan and Smythe (1967), the soft tissue burden of an adult is likely to be less than 20 μg and the skeletal burden about 30 μg.

Presently, there are no estimates of the biological half-time of beryllium in humans. However, in dogs, mice, rats, and monkeys, the long-term biological half-times of beryllium after injection have been estimated at 1270, 1210, 890, and 770 days, respectively (Furchner et al., 1973). Some circumstantial evidence suggests that the half-time in human bone is likely to be many years.

5. BERYLLIUM TOXICOLOGY

This chapter reviews the non-mutagenic and non-carcinogenic effects of beryllium. Because of the volume of information available regarding the mutagenic and carcinogenic effects of beryllium, these topics are dealt with specifically in Chapters 6 and 7.

5.1 ACUTE EFFECTS OF BERYLLIUM EXPOSURE IN MAN AND ANIMALS

5.1.1 Human Studies

Acute lung disease from excessive exposure to beryllium compounds was first reported in Europe during the 1930s. The first case in the United States was reported in 1943 (Van Ordstrand et al., 1943). In the 1940s, many hundreds of cases occurred, but with today's improved working conditions, acute beryllium poisoning is rare.

Acute lung disease can be caused by inhalation of soluble beryllium compounds, such as the fluoride with acidic pH or the low-fired beryllium oxide. The reported symptoms have been nonspecific, with chemical pneumonitis as the most severe manifestation (Freiman and Hardy, 1970; Reeves, 1979). In a study of six fatal cases, Freiman and Hardy (1970) reported that death occurred between 17 days and 10 weeks after exposure. Interstitial edema and cellular infiltration dominated the histological tissue analyses. The beryllium concentrations in the lung ranged from 4 to 1800 µg/kg. It was not stated whether the analyses were based on wet or dry weight.

In most cases of acute poisoning, recovery is slow, taking several weeks or months (Reeves, 1979). In the U.S. Beryllium Case Registry (BCR), a file on reported cases of acute and chronic beryllium disease, 215 cases of acute poisoning were registered up to 1967 (Freiman and Hardy, 1970). Since 1967, an additional nine cases have been reported (Eisenbud and Lisson, 1983).

The fact that there still is some occupational risk for acute beryllium disease is shown by recent case reports by Hooper (1981) and Lockey and co-workers (1983). Hooper describes a case of an 18-year-old sandblaster exposed to grinding dyes containing a copper-beryllium alloy. The man developed acute respiratory disease, which was diagnosed as interstitial pneumonitis by an open lung biopsy performed six days after exposure. Beryllium concentrations in the lung tissue were 28 µg/kg dry weight compared to a normal level of 20 µg/kg or less. In the report by Lockey and co-workers, acute chemical pneumonitis in a

dental laboratory technician was attributed to the casting and grinding of dental bridges containing nickel-beryllium alloys.

Contact dermatitis caused by exposure of skin to soluble beryllium salts has also been described (Van Ordstrand et al., 1945).

5.1.2 Animal Studies

Acute chemical pneumonitis has been produced in a variety of animals exposed to beryllium as a sulfate or fluoride (Stokinger et al., 1950). Some insoluble compounds, especially low-fired beryllium oxide, have also caused acute effects in rats (Hall et al., 1950). The concentrations needed to cause acute effects have generally been on the order of several mg/m^3.

Injection of beryllium compounds can cause acute liver damage (Cheng, 1956; Aldridge et al., 1949).

5.2 CHRONIC EFFECTS OF BERYLLIUM EXPOSURE IN MAN AND ANIMALS

5.2.1 Respiratory and Systemic Effects of Beryllium

5.2.1.1 Human Studies. Hardy and Tabershaw (1946) were the first to report chronic lung disease caused by beryllium. They presented data on 17 persons employed in the fluorescent lamp manufacturing industry. The main symptoms noted were dyspnea on exertion, cough, and weight loss. In most cases, the symptoms first appeared months or even years after exposure. The patients were generally younger than 30 years of age and the majority were women. X-rays showed that an early sign of chronic beryllium poisoning was a fine diffuse granularity in the lungs. In the second stage, a diffuse reticular pattern was seen, while in the third stage, distinct nodules appeared. After generally less than two years of illness, five deaths occurred among the 17 persons. Though disability persisted in most cases, some recovery was noted in two cases. Postmortem examination of the lungs from one person showed a granulomatous inflammation characterized by central and eccentrically located giant cells of the foreign body type in the alveoli. Infiltration of plasma cells and lymphocytes was also noted.

This pioneer study by Hardy and Tabershaw led to further occupational studies, which have been documented in papers by Hardy (1980) and Eisenbud (1982). In addition, there have been reports on "neighborhood cases," i.e. beryllium disease in persons living in the vicinity of beryllium-emitting plants. In

these cases, exposure was not only to beryllium in ambient air, but also to contaminated clothing brought into the house from occupationally exposed members of the household (Eisenbud et al., 1949). At least three children, ages 7 to 14 years, were counted among such cases (Hall et al., 1959).

These and other findings led to the adoption of beryllium standards for both the industrial and natural environments. A Threshold Limit Value (TLV) of 2 $\mu g/m^3$ was set as an average for an 8-hour occupational exposure; the maximum permissible peak (not to exceed more than one 30-minute period) was set at 25 $\mu g/m^3$. For the general environment, a level of 0.01 $\mu g/m^3$ was proposed. It should be noted that the 2 $\mu g/m^3$ standard was not based on actual dose-response relationships. As stated by Eisenbud (1982), the standard was based on the molar toxicity of beryllium in relation to some heavy metals such as lead and mercury, which have TLVs around 100 $\mu g/m^3$.

While these proposed standards seemed to prevent acute poisoning, many new cases of chronic beryllium disease appeared mainly as a result of heavy exposures during the period from 1940 to 1946. This led to the foundation of the Beryllium Case Registry (BCR) in 1952. The BCR was intended to serve as a file for all cases of acute and chronic beryllium disease, from which information on the development and clinical manifestations of beryllium disease could be obtained. Since 1978, the BCR has been maintained by the National Institute for Occupational Safety and Health.

Throughout the years, many scientific reports have relied on the information found in the BCR. In 1959, Hall et al. presented data on 601 cases (Table 5-1). The authors noted that most male cases were acute. However, in later reports the number of cases of chronic disease increased and currently number more than 600. In contrast, only a few additional cases of acute disease have been reported. It should be noted that 28 of the acute cases in Table 5-1 were also classified as chronic. Between 1966 and 1974, 74 new cases of beryllium disease were reported to the BCR, of which 36 had been exposed after 1949 (Hasan and Kazemi, 1974).

Chronic beryllium disease often appears many years after exposure ends. In more than 20 percent of the cases recorded in the BCR before 1959, the time since last exposure was greater than 5 years, the maximum being 15 years (Table 5-2). There has been some overlap between acute and chronic disease, but generally the disease has been registered as chronic if it has lasted more than one year.

TABLE 5-1. BERYLLIUM REGISTRY CASES, 1959

	Men	Women	Total	Dead
Acute	227	20	247 (39%)	15 (6%)
Chronic	191	191	382 (61%)	121 (31%)

Source: Hall et al. (1959)

TABLE 5-2. TIME FROM LAST EXPOSURE TO FIRST SYMPTOM* IN THE BCR, 1959

Time	Cases of beryllium disease	%
Less than 1 month	126	41
1 month to 1 year	27	9
1-5 years	89	29
5-10 years	56	18
More than 10 years	12	4
	310	

*Maximum was 15 years.

Source: Hall et al. (1959)

The latest report contains 897 cases, 10 of which have been added since 1978 (Center for Disease Control, 1983). Eisenbud and Lisson (1983) reported on 888 cases, but noted that they knew of 45 other chronic cases that had not yet been included in the BCR. Therefore, the total number of cases of beryllium disease in this country may exceed 900.

Of the 888 cases reported by Eisenbud and Lisson, 224 were classified as acute. This number is smaller than the one given in Table 5-1, but as mentioned earlier, 28 acute cases in that table were also classified as chronic. The chronic cases were reported to be 622, leaving 42 cases unaccounted. Of the 622 cases, 557 occurred in individuals occupationally exposed to beryllium and 65 occurred among members of the general populace. Of the latter, 42 were attributed to ambient air exposure and 23 to dust exposure in the home.

The majority of the occupational cases cited by Eisenbud and Lisson were from the fluorescent lamp (319) or beryllium extraction (101) industries. In

62 percent of the cases, dates for first exposure and onset of disease were available. Figure 5-1 shows that up to 40 years may elapse between initial exposure and onset of disease. There is some suggestion, however, that latency times may be declining in recent years (Table 5-3). Eisenbud and Lisson urged caution when interpreting these data, as a rough correspondence between the maximum latency time and number of years elapsed since first exposure must exist. It could be argued, for instance, that among the more recent members of the cohort, not enough time has passed for them to develop the disease. Hence, a person exposed in the 1960s cannot have a latency time of more than 20 years.

Some of the common symptoms of chronic beryllium disease noted from the BCR are shown in Table 5-4 (Hall et al., 1959). These symptoms confirm those reported earlier by Hardy and Tabershaw (1946). Table 5-5 shows some of the signs of chronic beryllium disease. The cardiovascular signs can be attributed to cor pulmonale, which is a sequela of the severe forms of chronic beryllium disease. There are also signs that may be seen as pure systemic effects of beryllium exposure.

An extensive description of chronic beryllium disease was presented by Stoeckle et al. (1969). In their report, clinical findings and the results of treatment were presented. In another paper by Freiman and Hardy (1970), the pulmonary pathology was presented. Data were given for 60 patients with chronic beryllium disease who had been investigated at the Massachusetts General Hospital between 1944 and 1966. Patients came from different industries and exposure levels were unknown. Consequently, the data cannot be used for dose-response analyses. However, valuable information can be derived from the clinical findings and the diagnostic problems noted during the examination of these patients. In addition to the pulmonary effects, there was further evidence for extrapulmonary signs of beryllium disease. In some patients, granulomas were found in muscle or skin.

Some of the features of chronic beryllium disease are similar to those seen in sarcoidosis. In the paper by Stoeckle et al., as well as in an earlier paper by Israel and Sones (1959), the differentiation of these two diseases is discussed. One distinguishing characteristic between the diseases is the considerably greater systemic involvement in sarcoidosis, as noted in more than 80 percent of the sarcoidosis cases. X-rays of the lungs, however, may show very similar pictures of the two conditions.

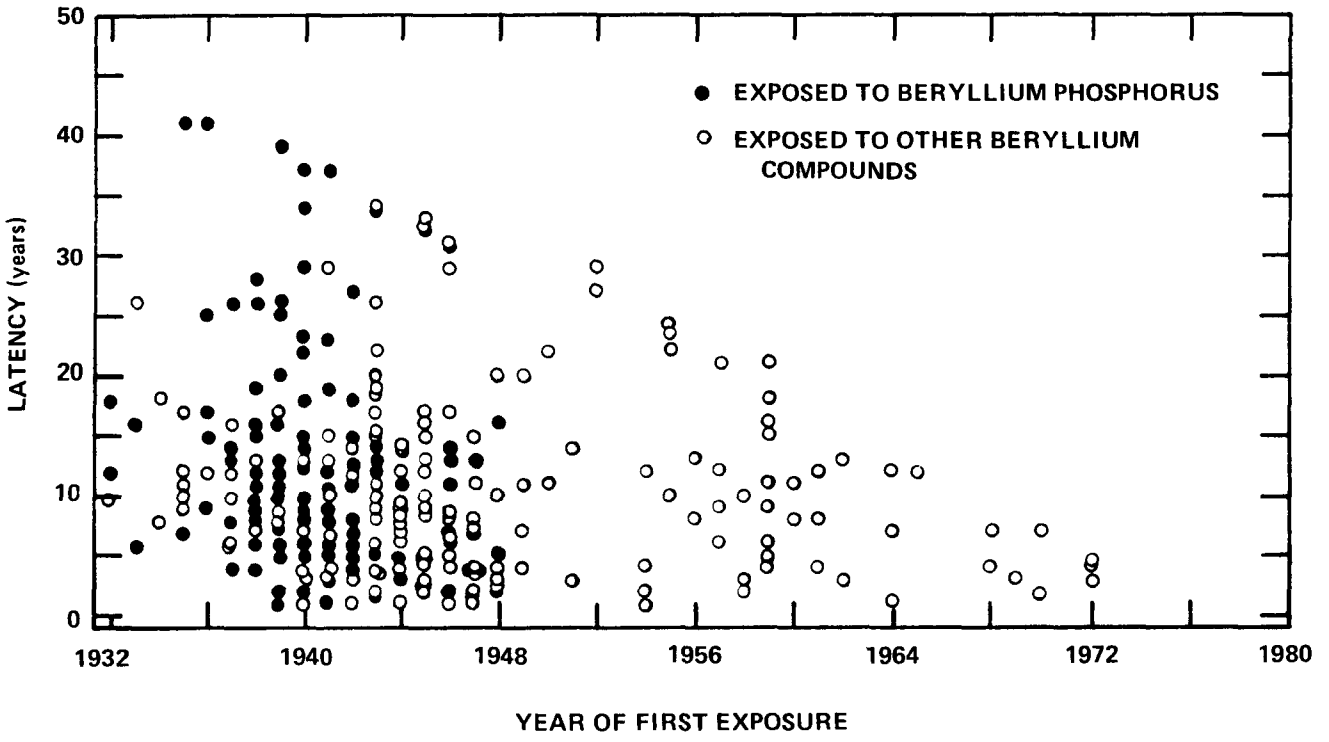

Figure 5-1. Latency of occupational berylliosis according to year of first exposure.

Source: Eisenbud and Lisson (1983).

TABLE 5-3. CHANGES OF LATENCY FROM 1922 TO PRESENT IN OCCUPATIONAL BERYLLIOSIS CASES[a]

Period of First Exposure	No. of Cases	Latency, in years	
		Mean	Range
1922-1981	347	11	1-41
1922-1937	33	16	4-40
1938-1949	264	9.8	1-39
1950-1959	32	9.6	1-25
1960-1981	18	6.6	1-13

[a]Cases were included only if both dates of first exposure and diagnosis of first symptoms were known.

Source: Eisenbud and Lisson (1983)

TABLE 5-4. SYMPTOMS OF CHRONIC BERYLLIUM DISEASE

Symptom	Percent
Dyspnea	
on exertion	69
at rest	17
Weight loss	
> 10%	46
≤ 10%	15
Cough	
nonproductive	45
productive	33
Fatigue	34
Chest pain	31
Anorexia	26
Weakness	17

Source: Hall et al. (1959)

TABLE 5-5. SIGNS OF CHRONIC BERYLLIUM DISEASE[a]

Sign	Percent
Chest signs	43
Cyanosis	42
Clubbing	31
Hepatomegaly	5
Splenomegaly	3
Complications	
Cardiac failure	17
Renal stone	10
Pneumothorax	12

[a]Signs attributable to cardiac failure are not included.

Source: Hall et al. (1959)

Among laboratory findings in cases of beryllium disease, hypercalcemia, hypercalcuria, stone formation, and osteosclerosis have been noticed (Stoeckle et al., 1969), as has hyperuricemia (Kelley et al., 1969).

In addition to studies based on the BCR, there have also been some studies within industrial populations. Balmes and co-workers (1984) reported on four cases of suspected chronic beryllium disease in a group of workers exposed to beryllium released from melted scrap metals. Wagoner et al. (1980) conducted a more extensive mortality study on a cohort of 3055 workers exposed to beryllium in a plant in Pennsylvania. (See Section 7.2 for detailed discussion of lung cancer within the cohort.) Among causes of death other than lung cancer, there was a significant excess of heart disease (396 observed versus 349 expected) and respiratory disease other than influenza and pneumonia (31 observed versus 18.7 expected). It is conceivable that some of the cardiac deaths were, in fact, caused by cor pulmonale secondary to beryllium disease. There are no data to indicate that beryllium exposure by inhalation has a direct effect on the cardiovascular system.

These data can be compared to a mortality study by Infante et al. (1980) on 421 white males listed in the BCR during the period of 1952 through 1975. Heart disease was stated to be the cause of death in 31 of these cases (29.9 were expected). Respiratory disease other than influenza and pneumonia was the cause of death in 52 cases (only 1.6 were expected). Högberg and Rajs (1980) reported granulomatous myocarditis as the cause of death in two individuals who were occupationally exposed to beryllium.

Results of studies on respiratory function have been presented by Andrews et al. (1969), Kanarek et al. (1973), and Sprince et al. (1978). Andrews et al. performed lung function tests (vital capacity and FEV_1) on 41 patients registered in the BCR as having chronic beryllium disease. In only two patients were the test results normal; 16 out of the 41 patients had airway obstruction.

The studies by Kanarek et al. (1973) and Sprince et al. (1978) were performed on workers employed in beryllium extraction and processing plants. In the first study, 214 employees were examined. They had been exposed for 1 to 14 years, and exposure had started after recommended occupational standards had been set. It was known, however, that the recommended standards of 2 and 25 $\mu g/m^3$ for 8-hour and short-term exposures, respectively, had been exceeded. In some areas of the plants, peak exposures were above 1 mg/m^3. Lung function tests including FVC, FEV_1, and gas exchange were performed. Among the 31 subjects with X-ray abnormalities of the lung, 11 had hypoxemia at rest, but these subjects were also heavy smokers. In this study, there was no control group and it is difficult, therefore, to establish whether smoking or beryllium caused the effects. However, lung biopsies were performed in two subjects, and in one of these cases a diffuse granulomatous reaction, typical of beryllium exposure, was found. The beryllium content of the lung was elevated in both cases. It is noteworthy that the case with the granulomatous reaction had a much lower beryllium concentration in the lung than did the case without tissue changes.

A follow-up was made three years later on these workers (Sprince et al., 1978). Occupational exposure levels had been reduced due to engineering changes, and peak concentrations were now less than 25 $\mu g/m^3$. For some operations, peak concentrations were less than 2 $\mu g/m^3$. Workers who had participated in 1971 and had not changed smoking habits were studied (Table 5-6). There were no major differences between the results from the two examinations, but as seen in Table 5-7, there had been some improvement of hypoxemia as indicated by the results of the Pa_{O_2} determinations. In the 13 persons who had clearly demonstrated hypoxemia in 1971, there was a highly significant rise

TABLE 5-6. COMPARISON OF 1971 AND 1974 DATA OF WORKERS SURVEYED IN BERYLLIUM EXTRACTION AND PROCESSING PLANTS[a]

Workers	Year	No.	Age (years)	Cigarette-Pack-years	Length of Employment (years)	FEV_1 (% predicted)	FVC (% predicted)	PEFR (% predicted)
Smokers	1971	55	40.9	23	10.2	92.9	96.6	96.9[b]
	1974	55	43.9	27	13.2	90.4	95.2	91.3
Ex-smokers	1971	36	43.3	25	10.6	97.9	97.8	100.0[c]
	1974	36	46.3	25	13.6	97.7	101.2	94.8
Nonsmokers	1971	20	43.4	0	10.9	105.3	98.6	104.7
	1974	20	46.4	0	13.9	102.4	102.5	99.2
Total	1971	111	42.1	23.5	10.4	96.7	97.3	99.3[d]
	1974	111	45.1	26.2	13.4	95.1	98.5	93.8

[a] FEV_1 = 1-sec forced expiratory volume; FVC = forced vital capacity; PEFR = peak expiratory flow rate. Results are mean values.

[b] $p < 0.02$

[c] $p = 0.02$

[d] $p < 0.01$

Source: Sprince et al. (1978)

TABLE 5-7. COMPARISON OF 1971 AND 1974 ARTERIAL BLOOD GAS RESULTS[a]

Workers	Year	No.	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH
Smokers	1971	55	90.9[b]	38.0[b]	7.42
	1974	55	96.1	35.1	7.42
Ex-smokers	1971	36	89.1[b]	37.9[b]	7.42
	1974	36	95.7	36.1	7.42
Nonsmokers	1971	20	93.4[c]	38.0	7.43[b]
	1974	20	100.2	36.3	7.41
Total	1971	111	90.8[b]	38.0[b]	7.43[c]
	1974	111	96.8	35.7	7.42

[a] Pa_{O_2} = arterial P_{O_2}; Pa_{CO_2} = arterial P_{CO_2} Results are mean values.

[b] $p < 0.01$

[c] $p < 0.05$

Source: Sprince et al. (1978)

in Pa_{O_2} by 1974 (average rise of 19mm Hg). Among the 98 workers who had a normal Pa_{O_2} in 1971, the average increase was 4.1 mm. Of the 31 subjects who had X-ray abnormalities in 1971, 9 now showed normal X-ray readings. These findings indicate that some minor effects might be reversible in beryllium-exposed workers if exposure is reduced. A new follow-up was conducted in 1977 and reported briefly (Sprince et al., 1979). The improvement in Pa_{O_2} remained, and there was a tendency towards normalization of lung X-rays. It is obvious, however, that due to long latency times, longer follow-ups are necessary before any final conclusions can be made with regard to prognosis.

In a recent British study, Cotes et al. (1983) presented data on workers exposed to beryllium compounds, mainly beryllium oxide. The plant in which these workers had been employed started operation in 1952. The first study of these workers was made in 1963 when 130 men out of a group of 146, who had worked for more than 6 months, were examined. Chest X-rays were taken, and in all but one case, pulmonary function was measured by a set of respiratory function tests. Airborne beryllium had been measured during the years 1952 to 1960, but it was unclear whether any measurements had been made since 1960. In a total of 3401 samples taken, only 20 exceeded the 25 $\mu g/m^3$ limit and 318 exceeded the 2 $\mu g/m^3$ limit. Concentrations were presented as geometric means, and in both 1952 and 1960 these concentrations were never above 2 $\mu g/m^3$. Generally, concentrations were far below 1 $\mu g/m^3$. The 1963 study found six cases of definite or suspected beryllium disease.

In a follow-up in 1973, 106 of the original 130 workers were examined. In another follow-up in 1977, only 8 men from the 1973 group and one ex-employee were examined, but to this new group were added 24 employees and 14 ex-employees employed since 1963. The same tests were performed on these subjects. The follow-up studies did not find any new cases of beryllium disease. However, after the 1977 study, two further cases were added. Both were men who had worked since 1952. There were also two cases of acute beryllium pneumonitis, and these two men were among a group of 17 who were deemed to have had the highest exposures. Both of these cases were normal in the 1963 study.

After adjusting for age, smoking, and other factors, the respiratory function tests showed that exposure was related only to vital capacity. In the 1963 study, a significant negative correlation between estimated total exposure to beryllium and lung compliance was shown in a subgroup of 19 workers from the

slip-casting bay. Comparison between data from 1963 and 1973 showed only changes that could be ascribed to personal factors. The conclusion of the authors was that respiratory function studies generally could not detect beryllium disease before radiographic changes appeared. Decreases in lung function were only observed in cases with clear X-ray changes. However, Preuss and Oster (1980) have noted that changes in vital capacity may occur long before X-ray changes appear.

As mentioned above, chronic beryllium disease differs from some other occupational lung diseases in that it has a systemic component. The systemic involvement suggests that there is also an immunological component to the disease, and that hypersensitivity can explain some of the findings in chronic beryllium disease.

In 1951, Curtis developed a patch test which was found to be positive for most cases of dermatitis and skin granuloma caused by beryllium. In addition, it was positive in many cases of lung disease caused by beryllium (Curtis, 1959; Nishimura, 1966). However, the patch test could also initiate the development of skin reactions or pulmonary disease in people exposed to beryllium, but who had not had previous symptoms of respiratory illness (Sneddon, 1955; Stoeckle et al., 1969; Rees, 1979; Cotes et al., 1983).

These early studies led to attempts to develop other tests suitable for studying hypersensitivity to beryllium. Of these, the lymphocyte transformation test has been the most useful (Deodhar et al., 1973; Williams and Williams, 1982a,b, 1983). This test gave a positive response in 16 patients with established chronic beryllium disease, whereas it was negative in 10 subjects with suspected disease. Only two positive responses were reported among 117 healthy beryllium workers (Williams and Williams, 1983). Similar results have also been reported by Van Ordstrand (1984). It is not clear, however, if a positive test in an otherwise healthy worker really indicates that such an individual is at a higher risk for getting pulmonary disease.

Rom et al. (1983) conducted a three-year prospective study to evaluate the relationship between lymphocyte transformation and beryllium exposure. The average beryllium exposure levels ranged from 7.18 $\mu g/m^3$ in 1979 to less than 1 $\mu g/m^3$ from 1980 to 1982. Of 11 workers with a positive test in 1979, 8 were negative in 1982. A possible reason for this change may have been the decrease in exposure levels.

In an area in Czechoslovakia where coal with a high beryllium content is burned, Bencko et al. (1980) studied immunoglobulins and autoantibodies in workers in a power plant and in people living in the vicinity of the plant. The average concentration of beryllium in the town was estimated to be 80 ng/m^3, which is 8 times higher than the suggested standard for ambient air in the United States. In both the workers and general public, levels of immunoglobulins IgG and IgA and concentrations of autoantibodies were elevated compared to a control group not exposed to beryllium. The workers had higher exposure than the town dwellers (up to 8 µg/m^3), and they also had considerably higher levels of IgM than either the town residents or the control group. Since many factors can contribute to increases in immunoglobulin levels, the significance of these findings is not clear.

5.2.1.2 Animal Studies. There have been a large number of animal studies on the acute and chronic effects of beryllium exposure by air. Much of the early work in the 1940s and 1950s has been described by Vorwald et al. (1966). A large number of the rat studies were performed by Vorwald and co-workers, but many were never fully reported. The main information source continues to be the 1966 review by Vorwald et al.

In one study, rats were exposed to beryllium sulfate aerosol in concentrations ranging from 2.8 to 194 µg/m^3 of air. The exposures were usually given 7 hours a day, for 1 to 560 days. It was stated that exposure to 2.8 µg/m^3 did not produce any specific inflammatory abnormalities, whereas 21 µg/m^3 caused significant inflammatory changes in some long-surviving rats. At 42 µg/m^3, chronic pneumonitis was produced, while an exposure level of 194 µg/m^3 caused acute beryllium disease.

The main finding of this study was that the low-exposure group had a high incidence of pulmonary cancer (13 of 21 rats). There has been some concern about the validity of the low-exposure data, however (see Section 7.1.8.3). In the group exposed to 42 µg/m^3, microscopic examination of lung tissue showed alveolar changes with a large increase in the number of macrophages. With longer exposure, diffuse pneumonitis and focal granulomatous lesions became increasingly prominent, typically occurring in patches.

Schepers et al. (1957) exposed rats to beryllium sulfate at an average concentration of beryllium of 35 µg/m^3. In one experiment, 115 animals were exposed for six months; the number of controls was 139. In this study, 46 animals died during exposure and 17 were killed at the end of exposure. Fifty-two rats were then transferred to normal air and observed for up to 18

additional months. The cause of death during exposure was mainly pleural pericarditis with a tendency to chronic pneumonitis. No bacteria were isolated, but the authors concluded that the response was caused by infection, since sulfathiazole had a beneficial effect. In further experiments, similar exposures were given, but no rats died during exposure or up to nine months afterward. Among the findings after six months of exposure were: adenomas; foam-cell clusters; focal mural infiltration; lobular septal-cell proliferations; peribronchial, alveolar-wall epithelialization, and granulomatosis.

In a study by Reeves et al. (1967), 150 rats (with an equal number of controls) were exposed to beryllium sulfate at a mean concentration of 34 $\mu g/m^3$. Exposure was for 72 weeks, 7 hours a day, 5 days a week. Control of the exposure concentrations was poor (the standard deviation of the mean level was 24 $\mu g/m^3$). Every month, three male and three female rats from the exposed and control groups were killed. Among the findings were progressive increases in lung weight in the exposed animals. At the end of the experiment, the lung weights of exposed animals were, on an average, more than four times greater than those of controls. Histological examination showed inflammatory and proliferative changes. Also, clusters of macrophages in the alveolar spaces were a common finding. Granulomatosis and fibrosis were only occasionally seen. The proliferative changes ultimately led to the generation of tumors in all of the exposed animals (43/43) (see Section 7.1.1).

Wagner et al. (1969) exposed two groups of 60 rats to the beryllium ores, beryl and bertrandite, for up to 17 months at a concentration of 15 mg/m^3. This dose corresponded to 210 μg Be/m^3 as bertrandite and 620 μg Be/m^3 as beryl. Exposure was generally for 6 hours a day, 5 days a week. A very large incidence of lung tumors was reported among rats exposed to beryl. Among the non-malignant changes, clusters of dust-laden macrophages were seen. Granulomas were seen in lungs from bertrandite-exposed rats.

Sanders et al. (1975) exposed rats to beryllium oxide particles calcined at 1000°C. Single exposures to beryllium oxide were given through the nose only. Exposure time ranged from 30 to 180 minutes, and concentrations of beryllium were from 1 mg to 100 mg/m^3. The single exposures resulted in chronic changes characterized by the appearance of foamy macrophages and some granulomatous lesions. A significant depression of alveolar clearance was also observed.

Other studies have examined the effects of beryllium exposure on monkeys (Vorwald et al., 1966; Schepers, 1964; Wagner et al., 1969; Conradi et al., 1971), dogs (Conradi et al., 1971; Robinson et al., 1968), guinea pigs (Policard, 1950; Reeves et al., 1971, 1972) and hamsters (Wagner et al., 1969).

Vorwald et al. (1966) exposed monkeys to intermittent daily administrations of beryllium sulfate (average concentration of 35 $\mu g/m^3$) for several months. Some monkeys were given intratracheal instillations of beryllium oxide. Both routes of administration led to typical chronic beryllium disease with pneumonitis and granulomatosis.

Schepers (1964) exposed three groups of monkeys, four in each group, to aerosols of beryllium fluoride, beryllium sulfate, and beryllium phosphate in concentrations of about 200 $\mu g/m^3$ beryllium. In another experiment, two groups of monkeys, four animals in each, were given higher concentrations of the beryllium phosphate, containing about 1140 and 8380 $\mu g\ Be/m^3$, respectively. Exposure was for 1 or 2 weeks in the animals exposed to the fluoride and sulfate, and from 3 to 30 days in the groups exposed to the phosphate. After exposure ceased, the animals were kept in normal air for different periods of time.

There were signs of initial general toxicity, in the form of anorexia, in the exposed animals. Dyspnea, one of the typical signs of human chronic beryllium disease, developed rapidly in the animals exposed to fluoride and to the high beryllium phosphate concentrations. Mortality was 100 percent in the animals exposed to the two highest beryllium phosphate concentrations. Examination of lungs from animals who either died during the experiment or were killed showed pulmonary edema and congestion, mainly in the animals exposed to beryllium fluoride or to the highest concentration of beryllium phosphate. Cor pulmonale was also a common finding. The histological picture was similar to that seen in other animals and humans. Notable were pigment-filled macrophages and invasion of plasma cells in the alveoli.

Wagner et al. (1969) exposed 2 groups of 12 squirrel monkeys for 23 months to beryl dust (620 $\mu g\ Be/m^3$) and bertrandite dust (210 $\mu g\ Be/m^3$). Exposure was generally for six hours a day, five days a week. While both dusts caused macrophage clusters, no other marked changes were seen compared to the controls.

The effects of beryllium oxide calcined at 1400°C were studied by Conradi et al. (1971). Five monkeys received inhalation exposures with concentrations varying between 3.3 and 4.4 $mg\ Be/m^3$. Exposure was for 30 minutes at 3 monthly intervals. After two years follow-up, histological examinations were negative and no other differences were noted between controls and exposed animals.

Conradi et al. (1971) studied six dogs exposed in the same way as the monkeys. No pathological changes were observed.

Robinson et al. (1968) exposed two dogs for 20 minutes to rocket exhaust products containing mixtures of beryllium oxide, beryllium fluoride, and beryllium chloride at average concentrations of 115 mg beryllium/m^3. The dogs were observed for a period of three years and were then killed. Immediately after exposure the dogs had some acute symptoms, but during the rest of the study they remained clinically healthy. Histological examination of the lungs showed small foci of granulomatous inflammation scattered throughout the lungs of both dogs. Beryllium deposits were also found in the lungs. The average beryllium content of the lungs of these dogs was 3.9 and 5.5 mg/kg wet weight.

Granulomatosis has also been shown in guinea pigs exposed to beryllium oxide dust (Policard, 1950; Chiappino et al., 1969). In the guinea pig, it is possible to produce beryllium sensitivity, and this is thought to have some protective effect against the development of pulmonary disease (Reeves et al., 1971; Reeves et al., 1972). Barna et al. (1981) studied two strains of guinea pigs given intratracheal injections of 10 mg of beryllium oxide. All of the animals in one strain developed granulomatous lung disease, whereas the animals in the other strain did not, indicating genetic differences in beryllium sensitivity. The latter animals also showed negative skin tests and lymphocyte transformation tests, whereas positive reactions were seen in the group with the lung reactions. Administration of the immunosuppressive drug prednisone had a beneficial effect on the animals with lung disease. However, this effect lasted only as long as treatment continued. Further studies by Barna et al. (1984a,b) have confirmed these findings. Barna and co-workers observed that beryllium exerted a more direct toxic effect on alveolar macrophages in nonsensitized animals.

Wagner et al. (1969) exposed two groups of hamsters, 48 animals in each group, for 17 months to beryl and bertrandite dust under the same exposure conditions previously described above for rats and squirrel monkeys. After six months of exposure, the bertrandite-exposed animals had a few granulomatous lesions in the lungs, and in both groups there were some atypical cell proliferations.

It is noteworthy that rats, in the various studies showing differing degrees of granulomatosis, have not developed beryllium hypersensitivity (Reeves, 1978).

There have also been some experimental studies of chronic, oral beryllium exposure. In some early studies (Guyatt et al., 1933; Jacobson, 1933; Kay and Skill, 1934), rickets was produced in young animals by giving large doses of beryllium carbonate (0.1-0.5 percent; 1000-5000 mg/kg food). This effect has since been regarded as an indirect result of the binding of phosphate to beryllium in the gut and, consequently, phosphorus depletion in the body.

Schroeder and Mitchener (1975a,b) gave rats and mice beryllium in drinking water at a concentration of 5 mg/l for the duration of their lifetimes. No consistent differences were noticed between exposed animals and controls with regard to weight or life span. In a two-year feeding study, Morgareidge et al. (1977, abstract) fed rats dietary concentrations of 5, 50, and 500 mg Be/kg. The highest dose level resulted in a slight decrease in weight. Specific details about the results were not reported.

A large number of studies have been conducted on beryllium compounds injected into animals. Some of these are mentioned in Section 7.1 on experimental carcinogenicity. Some of these studies have also been presented in earlier documents on beryllium, especially with regard to the effect of beryllium on enzymes (Drury et al., 1978). However, these injection studies are less relevant than inhalation or ingestion studies for understanding the action of beryllium in humans.

5.2.2 Teratogenic and Reproductive Effects of Beryllium

5.2.2.1 Human Studies. There are no known studies on the possible teratogenic and reproductive effects of beryllium in humans.

5.2.2.2 Animal Studies. Very few studies have investigated the teratogenic or reproductive effects of beryllium in animals. Only three such studies exist: one that evaluates the behavior of the offspring of mice exposed to beryllium sulfate during pregnancy (Tsujii and Hoshishima, 1979), one that deals with the ability of beryllium chloride to penetrate the placenta (Bencko et al., 1979), and another concerned with the effects of beryllium chloride on developing chick embryos (Puzanova et al., 1978).

Hoshishima et al. (1978) presented a brief abstract and, later, a more extensive report (Tsujii and Hoshishima, 1979) on the effects of trace amounts of beryllium injected into pregnant CFW strain mice. Six female mice were exposed to 22 compounds of metals, including $BeSO_4$ (140 ng/mouse/day). The mice received intraperitoneal injections (0.1 ml) 11 times during pregnancy. The

injections were given once daily for three consecutive days and then every other day for an additional eight treatments. The gestational days of treatment were not reported. In this study, beryllium (140 ng/day or ~ 5 μg/kg/b.w.) produced the following differences in the offspring of the metal-exposed dams as compared to the offspring from a control group: delayed response in head turning in a geotaxis test, acceleration in a straight-walking test, delayed (for a moment) bar-holding response, and acceleration of bar holding (for 60 seconds).

In a study by Bencko et al. (1978), the soluble salt of beryllium, $BeCl_2$, was evaluated for its ability to penetrate the placenta and reach the fetus. Radiolabelled $^7BeCl_2$ was injected into the caudal vein of seven to nine ICR SPF mice and was administered in three different time periods: (1) before copulation (group A), (2) the 7th day of gestation (group B), and (3) the 14th day of gestation (group C). The animals were sacrificed on the 18th to 19th day of pregnancy and the radioactivity associated with the fetal and maternal compartments was evaluated. In group C, higher levels of radioactivity were associated with the fetuses than were associated with fetuses of other exposure periods (group A, 0.0002 μg ^7Be/g fetus; group B, 0.0002 μg ^7Be/g fetus; and group C, 0.0013 μg ^7Be/g fetus). The amount of radioactivity in the various organs of the fetus was generally not influenced by beryllium exposure except in the spleen and liver. The amount of ^7Be penetrating the spleen was decreased, while in the liver it was increased when ^7BeCl was given on the 14th day of pregnancy.

Puzanova et al. (1978) conducted studies on the effects of beryllium on the development of chick embryos. $BeCl_2$ (300 to 0.00003 μg dissolved in 3 μl twice-distilled water) was injected subgerminally into chick embryos (10 embryos per dose) on the second day of embryogenesis. After a 24-hour incubation, the eggs were opened and stained with 0.1 percent neutral red so that the distance between the origin of the vitelline arteries and the caudal tip of the body could be measured. In a second part of this experiment, the same doses of $BeCl_2$ were administered subgerminally to two-day-old embryos and intra-amniotically to three- and four-day-old embryos. The surviving embryos were examined after the 6th day of incubation.

In the first part of the experiment, it was found that 300 μg $BeCl_2$ killed all of the embryos, whereas 0.3 μg was not lethal to any. Doses of 0.003 μg and less had no observable effects on the development of the embryos. When the eggs were treated on day two, the most common malformation was caudal regression, open

abdominal cavity, and ectopia cordis. When administered on the fourth day, exencephalia, mandibular malformation, and malformations described as the "straitjacket syndrome" were reported. It is not known, however, if these types of teratogenic effects in chick embryos are reflective of effects that might occur in humans. Additional studies would have to be done using mammals to determine whether beryllium has teratogenic potential.

Considered collectively, current data are not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects. It should be noted that the studies discussed above were not designed to specifically investigate the effects of beryllium compounds on reproduction or the developing conceptus. Further studies in this area are desirable.

6. MUTAGENIC EFFECTS OF BERYLLIUM

Beryllium has been tested for its ability to cause genetic damage in both prokaryotic and eukaryotic organisms. The prokaryotic studies include gene mutations and DNA damage in bacteria. The eukaryotic studies include DNA damage and gene mutations in yeast and cultured mammalian cells, and studies of chromosomal aberrations and sister-chromatid exchanges in mammalian cells in vitro. The available literature indicates that beryllium has the potential to cause gene mutations, chromosomal aberrations, and sister-chromatid exchange in cultured mammalian somatic cells.

6.1 GENE MUTATIONS IN BACTERIA AND YEAST

The studies on beryllium-induced gene mutations in bacteria and yeast are summarized in Table 6-1.

6.1.1 Salmonella Assay

Beryllium has been tested for its ability to cause reverse mutations in Salmonella typhimurium (Simmon, 1979a; Rosenkranz and Poirier, 1979).

Simmon (1979a) found that beryllium sulfate was not mutagenic in Salmonella strains TA1535, TA1536, TA1537, TA98, and TA100. Agar-incorporation assay, with and without S-9 metabolic activation, was employed. The highest concentration of beryllium sulfate tested was 250 µg/plate (12.5 µg Be). No mutagenic response was obtained in any of the above strains.

Beryllium sulfate was also not mutagenic in Salmonella typhimurium strains TA1535 and TA1538, both in the presence and absence of the S-9 activation system (Rosenkranz and Poirier, 1979). The two concentrations of the test compound used were 25 µg/plate and 250 µg/plate. No significant differences in the mutation frequencies between the experimental and the control plates were noted.

6.1.2 Host-Mediated Assay

Negative mutagenic response of beryllium sulfate was obtained in the host-mediated assay (Simmon et al., 1979). Several procedures were used. In all procedures the tester strain was injected intraperitoneally and the beryllium sulfate was given orally or by intramuscular injection. Four hours later, the Salmonella or Saccharomyces tester strain was recovered from the peritoneal

TABLE 6-1. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN BACTERIA AND IN YEAST

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Salmonella typhimurium	TA1535 TA1536 TA1537 TA100 TA98	Maximum of 12.5 µg/plate	±	Reported negative in all strains	1. Only highest concentration used.	Simmon, 1979a
Salmonella typhimurium Saccharomyces cerevisiae	TA1530 TA1538 TA1535 D_3	Unknown [Given either as i.m. injections (25 mg/kg) or by gavage (1200mg/kg beryllium sulfate)]	Host-mediated assay in mice	Reported negative in all strains by both routes of exposure		Simmon et al., 1979
Salmonella typhimurium	TA1535 TA1538	1.25 µg/plate 12.5 µg/plate	±	Reported negative		Rosenkranz and Poirier, 1979
Escherichia coli	WP2	0.9-90 µg/plate		Reported negative		Ishizawa, 1979

cavity and plated to determine the number of mutants (Salmonella) or recombinants (Saccharomyces) and the number of recovered microorganisms. Simultaneous experiments were conducted with control (untreated) mice. Using 25 mg/kg given intramuscularly, beryllium sulfate was not mutagenic with tester strain TA1530 or TA1538. Using 1200 mg/kg given orally, beryllium sulfate was not mutagenic in TA1535 and did not significantly increase the recombination frequency in S. cerevisiae D3.

6.1.3 Escherichia coli WP2 Assay

A negative mutagenic response in the Escherichia coli WP2 system was obtained with beryllium concentrations ranging from 0.1 to 10 µmol/plate (10.5-105 µg Be/plate) (Ishizawa, 1979). These results should not be taken as proof, however, that beryllium is not mutagenic. The standard test system may be insensitive for the detection of metal mutagens because of the large amount of magnesium salts, citrate, and phosphate in the minimal medium (McCann et al., 1975). Bacteria appear to be selective in which metal ions are internalized. More research is needed to select a suitable strain of bacteria to detect metal-induced mutagenesis in these prokaryotic systems.

6.2 GENE MUTATIONS IN CULTURED MAMMALIAN CELLS

The ability of various beryllium compounds to cause gene mutations in cultured mammalian cells has been investigated by Miyaki et al. (1979) and Hsie et al. (1979a,b) (Table 6-2).

Miyaki et al. (1979) demonstrated the induction of 8-azaguanine-resistant mutants by beryllium chloride in the Chinese hamster V79 cells. Beryllium chloride at concentrations of 2 and 3 mM (18 and 27 µg Be/ml, respectively) induced 35.01 ± 1.4 and 36.5 ± 1.7 mutant colonies per 10^6 survivors. These values were approximately six times higher than the control value of 5.8 ± 0.8 colonies per 10^6 survivors. The cell survival rates were 56.9 percent at 2 mM concentration and 39.4 percent at 3 mM. Analysis of mutant colonies revealed that they were deficient in the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) activity indicating that the mutation had occurred at the HGPRT locus.

Hsie et al. (1979a,b) also reported that beryllium sulfate induced 8-azaguanine-resistant mutants in Chinese hamster ovary (CHO) cells. However,

TABLE 6-2. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN MAMMALIAN CELLS IN VITRO

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Chinese hamster	V79 cells; resistance to 8-azaguanine	18 µg/ml 27 µg/ml	None	Reported positive 6.0 to 6.3-fold increase	1. 99 percent pure. 2. No dose response.	Miyaki et al., 1979
Chinese hamster	CHO cells; resistance to 8-azaguanine	Not stated	±	Reported mutagenic and weakly mutagenic	1. No details. 2. The authors noted variable results with noncarcinogens such as calcium.	Hsie et al., 1979 a,b

they did not provide details about the concentrations of the test compound and the number of mutants induced per 10^6 survivors.

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

6.3 CHROMOSOMAL ABERRATIONS

Beryllium sulfate was tested for its clastogenic potential in cultured human lymphocytes and Syrian hamster embryo cells (Larramendy et al., 1981) (Table 6-3). Cultured human lymphocytes (24-hours old) were exposed to a single concentration, 2.82×10^{-5}M (0.25 µg Be/ml), of beryllium sulfate, and chromosome preparations were made 48 hours after the treatment. A minimum of 200 metaphases were scored for chromosomal aberrations. In cultures treated with beryllium, there were 19 cells (9.5 percent) with chromosomal aberrations, or 0.10 ± 0.02 aberration per metaphase. In the nontreated control cells, only 3 cells (1.5 percent) had chromosomal aberrations. This sixfold increase in the aberration frequency clearly indicates that beryllium sulfate is clastogenic in cultured human lymphocytes. A beryllium concentration of 2.82×10^{-5}M was selected because it induced a maximum number of sister-chromatid exchanges in human lymphocytes in another experiment reported by the same authors (see Section 6.4).

In the Syrian hamster embryo cells the results were even more dramatic. This same concentration of beryllium sulfate induced aberrations in 38 out of 200 cells (19 percent) 24 hours after the treatment. The number of aberrations per metaphase was 0.12 ± 0.03. In control cells, only 3 cells (1.5 percent) had aberrations, or 0.01 ± 0.01 aberration per cell. In these studies, chromosomal gaps were also considered as aberrations. Even if the gaps were not included as true aberrations, the aberration frequency was still far above the control level, indicating that beryllium sulfate has clastogenic potential in cultured mammalian cells.

6.4 SISTER CHROMATID EXCHANGES

Larramendy et al. (1981) also studied the potential of beryllium to induce sister chromatid exchanges (Table 6-3). Both cultured human lymphocytes and Syrian hamster embryo cells were used in these studies.

After 24 hours of cultivation, lymphocytes were exposed to increasing concentrations of beryllium sulfate (0.05, 0.125, and 0.25 µg Be/ml) followed by 10

TABLE 6-3. MUTAGENICITY TESTING OF BERYLLIUM: MAMMALIAN *IN VITRO* CYTOGENETICS TESTS

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Chromosomal aberrations	Human lymphocytes	0.25 µg/ml	--	Reported positive	1. 6x above background level. 2. Primarily breaks.	Larramendy et al., 1981
Chromosomal aberrations	Syrian hamster embryo cells	0.25 µg/ml	--	Reported positive	1. 12x above background level. 2. Primarily breaks and gaps.	Larramendy et al., 1981
Sister chromatid exchanges	Human lymphocytes	0.05 µg/ml 0.125 µg/ml 0.25 µg/ml	--	Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al., 1981
Sister chromatid exchanges	Syrian hamster embryo cells	0.05 µg/ml 0.125 µg/ml 0.25 µg/ml	--	Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al., 1981

μg BrdUrd/ml medium. Cultures were incubated for an additional 48 hours and chromosome preparations were made and stained for sister-chromatid exchange analysis. At least 30 metaphases were scored for each concentration of the test compound. The background sister-chromatid exchange level was 11.30 ± 0.60. According to these investigators, there was a dose-dependent increase in sister-chromatid exchanges, i.e. 17.75 ± 1.10, 18.15 ± 1.79, and 20.70 ± 1.01, respectively, for the above concentrations.

In the Syrian hamster embryo cells, the same concentrations of beryllium sulfate induced 16.75 ± 1.52, 18.40 ± 1.49, and 20.50 ± 0.98 sister-chromatid exchanges. The background sister-chromatid exchange frequency was 11.55 ± 0.84. The sister-chromatid exchange assay has been extensively used in mutagenicity testing because of its sensitivity to many chemicals.

The authors stated that the results of the sister-chromatid exchange studies in human lymphocytes and Syrian hamster embryo cells demonstrated a dose-response relationship. However, in these studies, the increase was less than twofold and fell within a plateau region. Thus, the dose-response relationship suggested by the authors may be somewhat tenuous. Further experimentation to confirm the study results are advisable.

6.5 OTHER TESTS OF GENOTOXIC POTENTIAL

6.5.1 The Rec Assay

Kanematsu et al. (1980) found that beryllium sulfate was weakly mutagenic in the rec assay. Bacillus subtilis strains H17 (rec^+) and M75 (rec^-) were streaked onto agar plates. An aqueous solution (0.05 ml) of 0.01 M (4.5 μg Be/plate) beryllium sulfate was added to a filter paper disk (10-mm diameter) placed on the plates at the starting point of the streak. Plates were first cold incubated (4°C) for 24 hours and then incubated at 37°C overnight. Inhibition of growth due to DNA damage was measured in both the wild-type H17 (rec^+) and the sensitive-type (rec^-) strains. The difference in growth inhibition between the wild-type strain and the sensitive strain was 4 mm, which was considered to indicate a weak mutagenic response. Similar results were also obtained by Kada et al. (1980).

6.5.2 Pol Assay

Beryllium was tested for mutagenicity in the pol assay using Escherichia coli (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980). This assay is based on the fact that cells deficient in DNA repair mechanisms are more

sensitive than normal cells to the growth-inhibiting properties of mutagenic agents. Escherichia coli strains pol A^+ (normal) and pol A^- (DNA polymerase I-deficient) were grown on agar plates, and filter disks impregnated with 250 µg of beryllium sulfate were placed in the middle of each agar plate and incubated at 37°C for 7 to 12 hours. Experiments were conducted both in the presence and absence of an S-9 activation system. There was no difference in the diameter of the zones of growth in either strain. Positive and negative controls were used for comparison. The shortcomings of this assay are that (1) conclusions can be drawn only when measurable zones of growth inhibition occur; (2) it is possible that the test chemical may not be able to penetrate the test organisms; and (3) insufficient diffusion of chemicals from the disk can occur because of low solubility or large molecular size.

6.5.3 Hepatocyte Primary Culture/DNA Repair Test

DNA damage and repair, as reflected by unscheduled DNA synthesis (incorporation of tritiated thymidine), was examined for beryllium sulfate by Williams et al. (1982). Rat primary hepatocyte cultures were exposed to 0.1, 1, and 10 mg/ml of beryllium sulfate with 10 µCi/ml of tritiated thymidine and incubated for 18 to 20 hours. Following incubation, autoradiographs of cells were prepared. A minimum of 20 nuclei was counted for each concentration and the uptake of radioactive label was measured as grain counts in each nucleus. The compound was considered positive when the nuclear grain count was five grains per nucleus above the control value. The compound was considered negative in the assay if the nuclear grain count was less than five at the highest nontoxic dose. Cytotoxicity was determined by the morphology of the cells. According to the authors, beryllium sulfate did not induce a statistically greater grain count at any of the concentrations. Benzo(a)pyrene was employed as a positive compound.

6.5.4 Beryllium-Induced DNA Cell Binding

Kubinski et al. (1981) reported that beryllium induces DNA protein complexes (adducts) that can be measured. Escherichia coli cells and Ehrlich ascitis cells were exposed to radioactive DNA in the presence of 30 µM of beryllium. Methyl methanesulfonate (MMS) was used as a positive control. The negative control consisted of cells only and radioactive DNA. The radioactive DNA bound to cell membrane proteins was measured, and, like MMS, beryllium

induced positive results. However, the significance of beryllium-induced DNA binding to cell membranes is not clear in terms of its ability to induce mutations.

6.5.5 Mitotic Recombination In Yeast

Beryllium sulfate did not induce mitotic recombination in the yeast Saccharomyces cerevisiae D_3 (Simmon, 1979b). The S. cerevisiae strain D_3 is a heterozygote with mutations in ade 2 and his 8 of chromosome XV. When grown on a medium containing adenine, cells homozygous for the ade 2 mutation produce a red pigment. These homozygous mutants can be generated from the heterozygotes by mitotic recombination induced by mutagenic compounds. A single concentration (0.5 percent) of beryllium induced 10 mutant colonies per 10^5 survivors, while in the control the mutant frequency was 6 colonies per 10^5. In the mitotic recombination assay, there must be a threefold increase in the mutant frequency of experimental over the control in order to be considered a positive mutagenic response. The negative mutagenic response of beryllium may be due to an inability of beryllium to penetrate yeast cells.

6.5.6 Biochemical Evidence of Genotoxicity

Several in vitro experiments of the genotoxic potential of beryllium have been reported. In one study, in vitro exposure of rat liver cells to beryllium resulted in its binding to phosphorylated non-histone proteins (Parker and Stevens, 1979). Perry et al. (1982) found that exposure of cultured rat hepatosomal cells to beryllium reduced the glucocorticoid induction of tryosine transaminase activity. In a DNA fidelity assay, beryllium increased the misincorporation of nucleotide bases in the daughter strand of DNA synthesized in vitro from polynucleotide templates (Zakour et al., 1981). Beryllium has also been investigated for its effects on the transcription of calf thymus DNA and phage T_4 DNA by RNA polymerase (from E. coli) under controlled conditions. Beryllium inhibited overall transcription but increased RNA chain initiation, indicating the interaction of the metal with the DNA template (Niyogi et al., 1981).

6.5.7 Mutagenicity Studies in Whole Animals

Information on the mutagenicity of beryllium compounds in whole animal organisms, such as Drosophila and mammals, is not available in the literature.

Such studies would be highly valuable for assessing the in vivo effects of beryllium compounds, in particular to learn whether or not they induce mutations in germ cells. Metals such as cadmium and methyl mercury have been implicated in the induction of aneuploidy (numerical chromosomal aberrations) in female rodent germ cells. Aneuploidy is generally induced as a result of malfunctioning of the spindle apparatus. Such studies with beryllium compounds would yield valuable information.

7. CARCINOGENIC EFFECTS OF BERYLLIUM

The purpose of this section is to evaluate the carcinogenic potential of beryllium, and on the assumption that beryllium is a human carcinogen, to estimate its potency relative to other known carcinogens, as well as its impact on human health.

The estimation of the carcinogenic potential of beryllium relies on animal bioassays and epidemiological studies. However, studies on the mutagenicity, DNA interaction, and metabolism of beryllium are also important for the qualitative and quantitative assessment of its carcinogenicity. Because the latter are specifically dealt with elsewhere in this document, this section focuses on animal and epidemiological studies as well as the dose-response (i.e. quantitative) aspects of beryllium carcinogenicity. Summary and conclusions sections highlight the most significant aspects of beryllium carcinogenicity.

7.1 ANIMAL STUDIES

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. In these studies, metallic beryllium, salts of beryllium, and beryllium-containing alloys and ores were administered by various routes. In the discussions that follow, the studies are grouped according to the route of administration.

7.1.1 Inhalation Studies

The first report of pulmonary tumors after exposure to beryllium by inhalation was made by Vorwald (1953). Four of 8 female rats exposed to beryllium sulfate ($BeSO_4$) aerosol (at 33 µg Be/m^3, 7 hrs/d, 5.5 d/wk) for one year developed primary pulmonary adenocarcinomas. The rate was 80 percent (4/5) for animals necropsied after 420 days of exposure. This study was presented in a paper read before a meeting of the American Cancer Society, but was never published; an abstract of the presentation was printed two years later (Vorwald et al., 1955).

Schepers et al. (1957) updated the Vorwald study to include 136 rats, 78 of which survived to planned necropsy. Tumors were counted after the animals had been exposed for 6 months to beryllium sulfate aerosol followed by up to 18

months in normal air. The total number of tumors (76) -- not the number of tumor-bearing animals -- was counted. Eight histologic variants of neoplasms were observed. Intrathoracic metastases were also noted, and transplantation was successful in several cases.

During the late 1950s and early 1960s, both Schepers and Vorwald continued their experiments. Unfortunately, because these studies were never published, details are often lacking, although some of the results have been alluded to in subsequent reviews (Schepers, 1961; Vorwald et al., 1966). It can be surmised that Schepers observed 35 to 60 tumors in 170 rats (21-35%) exposed to beryllium phosphate at a concentration of 32 to 35 μg Be/m^3, and 7 tumors in 40 animals (17.5%) at 227 μg Be/m^3. After exposure to beryllium fluoride, he obtained a tumor rate of 10 to 20 in 200 animals (5-10%) exposed to 9 μg Be/m^3. With zinc beryllium manganese silicate ($ZnBeMnSiO_3$), a fluorescent phosphor in use at that time, the tumor rate was 4 to 20 in 220 animals (2-9%) exposed to 0.85 to 1.25 mg Be/m^3 (Table 7-1). No tumors were observed in similarly exposed rabbits or guinea pigs.

In all but one of his inhalation experiments, Vorwald exposed rats to beryllium sulfate aerosol at concentrations ranging from 2.8 to 180 μg Be/m^3 at exposure schedules of 3 to 24 months. In one experiment, beryllium oxide was used at 9 mg/m^3 (temperature of firing not given). Pulmonary lesions believed to be adenocarcinomas were found in all groups at frequencies ranging from 20 to 100 percent. Weak correlations were observed between tumor rate and exposure concentrations, and between tumor rate and exposure length (Table 7-2). No metastases were observed, and serial homotransplants were unsuccessful.

Reeves et al. (1967) exposed 150 rats of both sexes, and an equal number of controls, to beryllium sulfate aerosol at a mean concentration of 34.25 ± 23.66 μg Be/m^3 for 35 hours a week. Sacrifices were conducted quarterly. The first lung tumors were seen at 9 months, and by 13 months all 43 animals necropsied had pulmonary adenocarcinomas. Similar results were reported by Reeves and Deitch (1969) two years later for another animal group. In the latter study, 225 female rats of various ages were exposed for 3 to 18 months to 35.66 ± 13.77 μg Be/m^3 (35 hrs/wk) (Figure 7-1). It was found that tumor yield depended not on length of exposure but on age at exposure. Rats exposed at an early age for only 3 months had essentially the same tumor frequency (19/22; 86%) as rats exposed for the full 18 months (13/15; 86%), whereas rats receiving the 3-month exposure later in life had substantially reduced tumor

TABLE 7-1. PULMONARY CARCINOMA FROM INHALATION EXPOSURE TO BERYLLIUM

Compound	Species	Atmospheric concentration $\mu g/m^3$ as Be	Weekly exposure time (hours)	Duration of exposure (months)	Incidence of pulmonary carcinoma	Reference
$BeSO_4$	Rats	33-35	33-38	12-14	4 in 8	Vorwald, 1953
		33-35	33-38	13-18	17 in 17	Vorwald et al., 1955
		32-35	44	6-9	58 in 136	Schepers et al., 1957
		55	33-38	3-18	55 in 74	Vorwald, 1962
		180	33-38	12	11 in 27	Vorwald, 1962
		18	33-38	3-22	72 in 103	Vorwald, 1962
		18	33-38	8-21	31 in 63	Vorwald, 1962
		18	33-38	9-24	47 in 90	Vorwald, 1962
		18	33-38	11-16	9 in 21	Vorwald, 1962
		1.8-2.0	33-38	8-21	25 in 50	Vorwald, 1962
		1.8-2.0	33-38	9-24	43 in 95	Vorwald, 1962
		1.8-2.0	33-38	13-16	3 in 15	Vorwald, 1962
		21-42	33-38	18	Almost all	Vorwald et al., 1966
		2.8	33-38	18	13 in 21	Vorwald et al., 1966
		34	35	13	43 in 43	Reeves, 1967
		36	35	3	19 in 22	Reeves and Deitch, 1969
		36	35	6	33 in 33	Reeves and Deitch, 1969
		36	35	9	15 in 15	Reeves and Deitch, 1969
		36	35	12	21 in 21	Reeves and Deitch, 1969
		36	35	18	13 in 15	Reeves and Deitch, 1969
	Monkeys	35-200	42	8	0 in 4	Schepers, 1964
		38.8	15	36+	8 in 11	Vorwald, 1968

(continued on the following page)

TABLE 7-1. (continued)

Compound	Species	Atmospheric concentration $\mu g/m^3$ as Be	Weekly exposure time (hours)	Duration of exposure (months)	Incidence of pulmonary carcinoma	Reference
$BeSO_4$	Guinea pigs	35	NR	12	0	Schepers, 1961
		36	35	12	2 in 20	Schepers, 1971
		3.7-30.4	35	18-24	0 in 58	Reeves, 1972
		~15	35	18-24	0 in 110	Reeves, 1976
$BeHPO_4$	Rats	32-35	NR	1-12	35-60 in 170*	Schepers, 1961
		227	NR	1-12	7 in 40*	Schepers, 1961
	Monkeys	200	42	8	0 in 4	Schepers, 1964
		1100	42	8	1 in 4	Schepers, 1964
		8300	42	8	0 in 4	Schepers, 1964
BeF_2	Rats	9	NR	6-15	10-12 in 200	Schepers, 1961
	Monkeys	180	42	8	0 in 4	Schepers, 1964
$ZnBeMnSiO_3$	Rats	700	NR	9	4-20 in 220*	Schepers, 1961
	Rabbits	700	NR	24	0	Schepers, 1961
	Guinea pigs	700	NR	22	0	Schepers, 1961
Beryl ore	Rats	620	30	17+	18 in 19	Wagner et al., 1969
	Hamsters	620	30	17+	0 in 48	Wagner et al., 1969
	Monkeys	620	30	17+	0 in 12	Wagner et al., 1969
Betrandite ore	Rats	210	30	17+	0 in 30-60	Wagner et al., 1969
	Hamsters	210	30	17+	0 in 48	Wagner et al., 1969
	Monkeys	210	30	17+	0 in 12	Wagner et al., 1969

*Number of tumors per number of animals exposed.

NR: Not reported.

Source: Adapted from Reeves (1978)

TABLE 7-2. PULMONARY CARCINOMA FROM EXPOSURE TO BERYLLIUM VIA INTRATRACHEAL INSTILLATION

Compound	Species	Total dose (mg)	Incidence of pulmonary carcinoma	Reference
$ZnBeMnSiO_3$	Rabbits, rats, and guinea pigs	0.46	0	Vorwald, 1950
		2.3-6.9	0	Vorwald, 1950
		3.4	0	Vorwald, 1950
Be Stearate	Rabbits, rats, and guinea pigs	5.0	0	Vorwald, 1950
Be(OH)	Rabbits, rats, and guinea pigs	31	0	Vorwald, 1950
Be Metal	Rabbits, rats, and guinea pigs	54	0	Vorwald, 1950
Be O	Rabbits, rats, and guinea pigs	75	0	Vorwald, 1950
	Rats	.338	1 in 4	Vorwald, 1953
	Monkeys	18-90+	3 in 20	Vorwald, 1968

Source: Adapted from Reeves (1978)

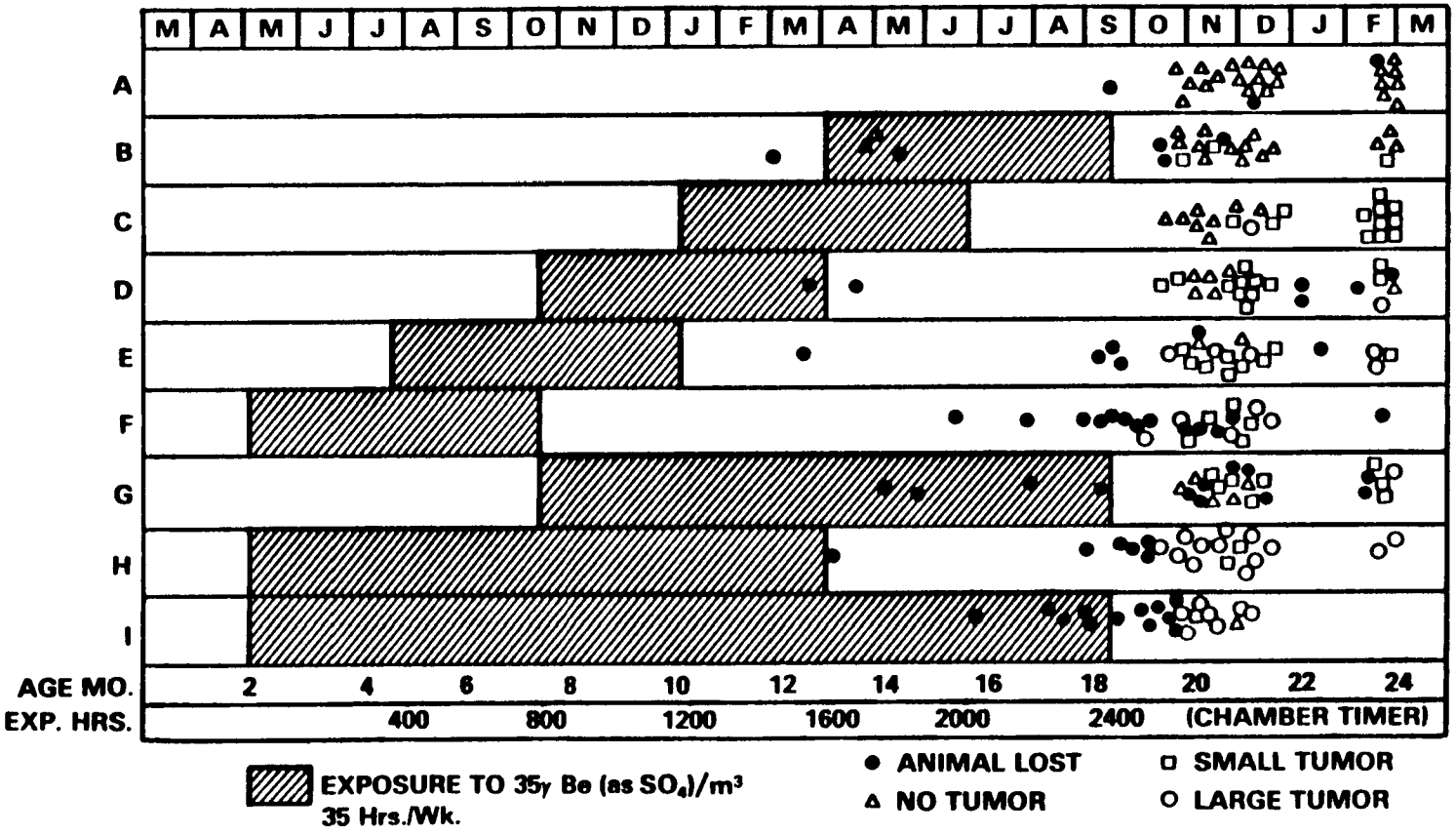

Figure 7-1. Pulmonary tumor incidence in female rats, 1965-1967.

Source: Reeves and Deitch (1969).

counts (3-10/20-25; 15-40%). Generally, an incubation time of at least 9 months after commencement of exposure was required to produce actual tumors. Epithelial hyperplasia of the alveolar surfaces commenced after about 1 month, progressed to metaplasia by 5 to 6 months, and to anaplasia by 7 to 8 months. In guinea pigs, 18 months of exposure (35 hrs/wk) to three different concentrations of beryllium sulfate (3.7 ± 1.5 μg Be/m^3, 16.6 ± 8.7 μg Be/m^3, and 30.4 ± 10.7 μg Be/m^3) produced only alveolar hyperplasia/metaplasia (associated with diffuse interstitial pneumonitis) in 23 of 144 animals. No tumors were seen. The rate of hyperplasia/metaplasia in unexposed controls was 3/55 (Reeves et al., 1971, 1972; Reeves and Krivanek, 1974). Schepers (1971) reported the occurrence of lung tumors in 2 of 20 guinea pigs exposed to beryllium sulfate (at 36 μg Be/m^3, 35 hrs/wk) for one year. While these results are suggestive of a positive effect when compared to the very low background incidence of tumors in guinea pigs, very little detail was given in the report to reach definitive conclusions.

Sanders et al. (1978) exposed female rats to submicron aerosols of medium-fired (1000°C) beryllium oxide by the nose-only method for a single exposure period of 30 to 180 minutes. Only 1 of 184 rats developed a lung tumor during the two-year observation period. Alveolar deposition of beryllium ranged from 1 to 91 μg beryllium, with a lung clearance half-time of 325 days.

Wagner et al. (1969) exposed rats, hamsters, and squirrel monkeys to aerosols of beryl ore and bertrandite ore at what was then regarded as the "nuisance limit" for all dusts (15 mg/m^3). At this particle concentration, the beryllium content of the aerosols was 620 and 210 μg Be/m^3 for beryl and bertrandite, respectively. Exposure was continued intermittently for 17 months. Of the 19 rats exposed to beryl dust, 18 had bronchiolar or alveolar cell tumors, 7 of which were judged to be adenomas, 9 adenocarcinomas, and 2 epidermoid tumors. Metastases were not observed, and transplants were not attempted. No indisputable tumors were found in either hamsters or squirrel monkeys exposed to beryl dust, although atypical proliferations were seen in the hamsters which, according to the authors, "could be considered alveolar cell tumors except for their size." There were no indisputable tumors in any of the animals exposed to bertrandite dust. However, granulomatous lesions were seen in each species and "atypical proliferations" of the cells lining the respiratory bronchioles and alveoli were seen in the rats and hamsters.

Schepers (1964) found that among 20 female rhesus monkeys exposed for eight months by inhalation to beryllium sulfate ($BeSO_4$), beryllium phosphate ($BeHPO_4$), or beryllium fluoride (BeF_2) (concentrations ranging from 0.035 to

8.3 mg Be/m^3), only one animal had a small (3 mm) pulmonary neoplasm which appeared to be an alveolar carcinoma. The animal was exposed to beryllium phosphate at a concentration of 1.1 mg Be/m^3. The tumor was discovered on day 82 of exposure; however, its association with the beryllium exposure was judged uncertain. Unfortunately, the eight-month exposure period used in the study was probably insufficient to induce lung cancer in any of the monkeys.

Vorwald (1968) reported the outcome of a three-year chamber study on rhesus monkeys intermittently inhaling beryllium sulfate aerosol, with exposures averaging 15 hours a week, at a mean atmospheric concentration of 38.8 μg Be/m^3. Eight of 11 surviving monkeys had pulmonary tumors, with adenomatous patterns predominating amid areas with epidermoid characteristics. Extensive metastases to the mediastinal lymph nodes were seen, and in some animals there were metastases to the bones, liver, and adrenals. No control animals were kept in this experiment.

Dutra et al. (1951) exposed 5, 6, and 8 rabbits to beryllium oxide aerosol (degree of firing unidentified) at 1, 6, and 30 mg Be/m^3, respectively, on a 25-hour-per-week schedule for 9 to 13 months. One rabbit in the group exposed to 6 mg Be/m^3 developed osteosarcoma of the pubic bone, with extension into the contiguous musculature. Scattered tumors which were judged to be metastases of the osteogenic sarcoma were seen in the lungs and spleen. The lungs also exhibited extensive emphysema, interstitial fibrosis, and lymphocytic infiltration. Rabbits in the other groups remained free of malignancies.

7.1.2 Intratracheal Injection Studies

Intratracheal administration of beryllium compounds was used as a substitute for inhalation in experiments by Vorwald (1953), Van Cleave and Kaylor (1955), Spencer et al. (1965), Kuznetsov et al. (1974), Ishinishi et al. (1980), and Groth et al. (1980). The fate and effects of beryllium compounds deposited by intratracheal injection are not necessarily the same as those for identical compounds deposited by inhalation. Intratracheal injection produces an unnatural deposition pattern in the lungs and permits the entry of larger particles that normally would be filtered out in the upper respiratory tract. Dusts, therefore, frequently show longer pulmonary half-times after intratracheal injection than after inhalation.

Vorwald (1953) found one lung tumor after intratracheal injection of 338 μg beryllium (as beryllium oxide) and one "sarcoma" (site unidentified) after

intratracheal injection of 33.8 μg beryllium (as sulfate). The induction of lung cancer with intrathoracic metastases in rhesus monkeys following intrabronchial injection and/or bronchomural implantation of "pure" beryllium oxide (firing temperature unknown) has been mentioned in a review, but without reference to any original publication (Vorwald et al., 1966).

Groth et al. (1980) intratracheally injected rats with dusts of beryllium metal, passivated beryllium metal (with < 1% chromium), and various beryllium alloys, as well as beryllium hydroxide. Lung tumors were observed after injection of beryllium metal, passivated beryllium metal, and a beryllium-aluminum alloy (containing 62% beryllium), but not after injection of other beryllium alloys in which the beryllium concentration was less than four percent. The injection of beryllium hydroxide into 25 rats yielded 13 cases of neoplasia, of which six were judged to be adenomas and seven adenocarcinomas (Table 7-3). The remaining animals had various degrees of metaplasia, which were regarded as precancerous lesions. Several of the tumors were successfully transplanted.

The most detailed studies of intratracheal injections of beryllium were reported by Spencer et al. (1965, 1968, 1972). High-fired (1600°C), medium-fired (1100°C), and low-fired (500°C) specimens of beryllium oxide were injected into rats. The rates of pulmonary adenocarcinomas were 3/28, 3/19, and 23/45 (11, 16, and 51%) in the three groups, respectively.

Ishinishi et al. (1980) intratracheally injected 30 rats with beryllium oxide (calcined at 900°C) in 15 weekly doses of 1 mg each. Of 29 animals examined 1.5 years later, seven (24%) had lung tumors, i.e. one squamous cell carcinoma, one adenocarcinoma, four adenomas, and one malignant lymphoma. Of the four adenomas, three had "strong histological architectures [of] suspected malignancy" (Tables 7-4 and 7-5). The malignant lymphoma was found not only in the lung, but also in the hilar lymph nodes and in the abdominal cavity, with the primary site remaining undetermined. Six extrapulmonary lymphosarcomas, fibrosarcomas, or other tumors were found in further injected animals but in only one of the 16 control animals. The frequency of clearly malignant primary pulmonary tumors in this experiment was 2/29, or seven percent.

7.1.3 Intravenous Injection Studies

In 1946, Gardner and Heslington, in a search to find the cause of an "unusual incidence of pulmonary sarcoid" in the fluorescent light tube industry, injected zinc beryllium silicate ($ZnBeSiO_3$) into rabbits. They found osteosarcomas

TABLE 7-3. BERYLLIUM ALLOYS--LUNG NEOPLASMS

Compounds	Dose of compound (mg)	Dose of Be (mg)	Total no. rats autopsied	Autopsy intervals and lung neoplasm frequencies (months)					P value[a]
				1	2-7	8-10	11-13	16-19	
Be metal	2.5	2.5	16	0/5[b]	-	-	3/5	6/6	<0.0001
Be metal	0.5	0.5	21	0/5	0/3	0/5	0/5	2/3	0.011
Passivated Be metal	2.5	2.5	26	0/5	0/2	1/5	4/10	4/4	<0.0001
Passivated Be metal	0.5	0.5	20	0/5	0/1	0/3	-	7/11	0.0001
BeAl alloy	2.5	1.55	24	0/5	0/3	2/5	0/5	2/6	0.043
BeAl alloy	0.5	0.3	21	0/5	-	0/1	0/6	1/9	0.30
4% BeCu alloy	2.5	0.1	28	0/5	0/1	0/5	0/6	0/11	
4% BeCu alloy	0.5	0.02	24	0/5	0/2	-	0/4	0/13	
2.2% BeNi alloy	2.5	0.056	28	0/5	0/1	0/5	0/5	0/12	
2.2% BeNi alloy	0.5	0.011	27	0/5	0/2	-	0/5	0/15	
2.4% BeCuCo alloy	2.5	0.06	33	0/5	0/3	0/5	0/5	0/15	
2.4% BeCuCo alloy	0.5	0.012	30	0/5	0/2	-	0/5	0/18	
Saline	-	-	39	0/5	0/3	0/5	0/5	0/21	

[a]P value (Fisher's one-tailed test) when the lung neoplasm frequency in exposed groups is compared with the lung neoplasm frequency in the saline control group at the autopsy period of 16-19 months. Because of multiple comparisons with the control group, the individual P value must be 0.008 or less to be significant.

[b]Number of rats with a lung neoplasm divided by total number of rats autopsied at the specified interval.

Source: Groth et al. (1980)

TABLE 7-4. LUNG TUMOR INCIDENCE IN RATS AMONG BeO, As_2O_3 AND CONTROL GROUPS

Group	Sex	Number of rats surviving after 15 instillations	Average	Range	Malignant tumor	Benign tumor
BeO (1 mg)*	M	30/30	545	99-791	2+(1)$^{\Delta}$	4
As_2O_3 (1 mg)*	M	19/30	546	98-820	1	0
Control	M	16	398	1-617	0	0

*Amount of one instillation Be or As.

ΔUnknown which is primary tumor or metastasis.

Source: Ishinishi et al. (1980)

TABLE 7-5. HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS AND OTHER PATHOLOGICAL CHANGES

Group	Sex	No. of rats	Malignant tumors (A) Squamous cell carcinoma	Malignant tumors (A) Adeno-carcinoma	Malignant tumors (A) Malignant lymphoma	Benign tumors (B) Ade-noma	All tumors (A + B) [tumor incidence rats]	Squamous cell meta-plasia	Osseous metaplasia	Other site tumors except the lung tumor
BeO (1 mg as Be)	M	29*	1[a]	1[b]	(1)[c]	4(3)$^{\Delta}$	21.4%	2	1	6[d]
As_2O_3 (a mg as As)	M	18*	1	0	0	0	5.6%	5	2	3[e]
Control	M	16	0	0	0	0	0	1	0	1

[a]Coexistence of squamous cell carcinoma and adenocarcinoma.

[b]Coexistence of adenocarcinoma and adenoma.

[c]Malignant lymphoma in the left lobule of the lung, the lymphatic nodules in the pulmonary hilus, and in the abdominal cavity.

[d]Lymphosarcoma or fibrosarcomas (except one).

[e]Mesothelioma in peritoneum, liver and mesentery.

*One rat was not histopathologically observed because of cannibalism.

ΔThree of four adenomas have strong histological architectures of suspected malignancy.

Source: Ishinishi et al. (1980)

of the long bones in all seven animals which survived the treatment for seven or more months. Because this was the first instance of experimental carcinogenesis by an inorganic substance, it evoked great interest. Beryllium was clearly implicated as the causative agent because zinc oxide, zinc silicate, or silicic acid did not cause osteosarcomas in a second set of trials, whereas beryllium oxide (firing temperature unknown) did. Guinea pigs and rats, when similarly treated with both zinc beryllium silicate and beryllium oxide, failed to respond. The dose of beryllium within the two compounds injected (beryllium oxide and zinc beryllium silicate) was 360 and 60 mg, respectively, and was given in 20 divided doses during a 6-week period.

This basic experiment was repeated many times by several investigators (Tables 7-6 and 7-7). Cloudman et al. (1949) produced osteosarcomas in four out of five rabbits receiving a total dose of 17 mg beryllium (as zinc beryllium silicate). Mice were also injected with "some" tumors being produced (counts not stated). In this experiment, "substantially 100 percent beryllium oxide by spectrographic standards" (degree of firing not stated, total dose 1.54-390 mg beryllium) produced no tumors. Nash (1950) produced five cases of osteosarcomas in 28 rabbits injected with zinc beryllium silicate phosphor. The minimum effective dose appeared to be 200 mg zinc beryllium silicate (12 mg beryllium). Dutra and Largent (1950) produced osteosarcomas in rabbits with both zinc beryllium silicate (2/3) and beryllium oxide (6/6), and reported a successful transplant in the anterior chamber of the eye of a guinea pig. Barnes et al. (1950) produced six cases of osteosarcomas among 17 rabbits injected with zinc beryllium silicate and one case of osteosarcoma among 11 rabbits injected with beryllium silicate. The tumors were multicentric in origin, and blood-borne metastases were common. Hoagland et al. (1950) injected rabbits with two samples of zinc beryllium silicate phosphor, containing 2.3 and 14 percent beryllium oxide, and produced osteosarcomas in 3/6 and 3/4 rabbits, respectively. With uncompounded BeO, the tumor rate was 1/8. The osteosarcomas appeared to be highly invasive, but could not be transplanted. Beryllium phosphate produced no tumors.

Araki et al. (1954) injected 35 rabbits with zinc beryllium manganese silicate, zinc beryllium silicate, or beryllium phosphate. The rate of osteosarcoma formation was 6/24, 2/7, and 2/4 in the three groups, respectively. There were no tumors among three rabbits injected with beryllium oxide (firing temperature unstated) or among two uninjected controls. There was also a

TABLE 7-6. OSTEOGENIC SARCOMAS IN RABBITS[a]

Compound	Dose of compound (g)	Dose of beryllium (mg)	Route of injection	No. of animals with tumors	Incidence of tumors	Incidence of metastases	Reference
$ZnBeSiO_3$	1	UN	i.v.	7	7/7 (100%)	3/7 (43%)	
BeO	1	360	i.v.	1	UN	UN	Gardner and Heslington, 1946
$ZnBeSiO_3$	UN	17	i.v.	4	4/5 (80%)	3/4 (75%)	
$ZnBeSiO_3$	UN	0.264	i.v.(M)	1	UN	UN	Cloudman et al., 1949
$ZnMnBeSiO_3$	0.45-0.85	3.7-7.0	i.v.	3	$\geq$ 3/6 (50%)		
$ZnMnBeSiO_3$	0.2	10-12.6	i.v.	3	$\geq$ 3/4 (75%)	5/7 (71%)	Hoagland et al., 1950
BeO	UN	360	i.v.	1	$\geq$ 1/9 (11%)		
Be metal	0.04	40	i.v.	2	2/5 (40%)	UN	Barnes et al., 1950
$ZnBeSiO_3$	1-2.1	7.2-15	i.v.	6	6/13 (46%)	4/6 (67%)	
$BeSiO_3$	1-1.2	UN	i.v.	1	1/8 (13%)	None	Barnes et al., 1950
$ZnBeSiO_3$	UN	64-90	i.v.	2	2/3 (67%)	2/2 (100%)	
BeO	UN	360-700	i.v.	6	6/6 (100%)	6/6 (100%)	Dutra and Largent, 1950
$ZnBeSiO_3$	1	12	i.v.	5	5/10 (50%)	>2/5 (40%)	Janes et al., 1954
$ZnBeSiO_3$	1	12	i.v.	10	10/13 (77%)	UN	Kelly et al., 1961
BeO	1	360	i.v.	3	UN	2/3 (66%)	Komitowski, 1968
Be phosphate	0.103	UN	i.v.	1	UN	UN	Vorwald, 1950
BeO	0.22-0.4	79-144	IMD	7	7/9 (78%)	UN	
BeO	0.42-0.6	151-216	IMD	11	11/11 (100%)	UN	Yamaguchi, 1963
$ZnBeSiO_3$	0.02	0.144	IMD	4	4/12 (33%)	3/4 (75%)	Tapp, 1969
BeO	Inhalation 6 mg Be/m^3			1	$\geq$ 1/6 ($\geq$17%)	1/1 (100%)	Dutra et al., 1951
Totals for $ZnBeSiO_3$ + $ZnMnBeSiO_3$			i.v.	40	40/61 (66%)	$\geq$ 18/30 (60%)	

[a]UN = unknown; IMD = intramedullary; $ZnBeSiO_3$ = zinc beryllium silicate; (M) = mouse; $ZnMnBeSiO_3$ = zinc manganese beryllium silicate; BeO = beryllium oxide.

Source: Groth (1980)

TABLE 7-7. OSTEOSARCOMA FROM BERYLLIUM

Compound	Species	Total dose (mg Be)	Mode of administration	Incidence of osteosarcoma	Reference
$ZnBeSiO_3$	Rats	60	i.v. in 20 doses	0	Gardner and Heslington, 1946
	Guinea pigs	60	i.v. in 20 doses	0	Gardner and Heslington, 1946
	Mice	0.26	i.v. in 20-22 doses	"some"	Cloudman et al., 1949
	Rabbits	60	i.v. in 20 doses	7 in 7	Gardner and Heslington, 1946
		7.2	i.v. in 6-10 doses	4 in 14	Barnes et al., 1950
		16	i.v. in 6-10 doses	2 in 3	Barnes et al., 1950
		12+	i.v. repeated	5 in 28	Nash, 1950
		64-90	i.v. in 17-25 doses	2 in 3	Dutra and Largent, 1950
		12	i.v. in 20 doses	5 in 10	Janes et al., 1954
		12	i.v. in 20 doses	10 in 14	Kelly et al., 1961
		3300	i.v. in 20 doses	"many"	Higgins et al., 1964
		17	i.v. in 20 doses	4 in 5	Cloudman et al., 1949
	Splenectomized rabbits	12	i.v. in 20 doses	7 in 7	Janes et al., 1956
ZnBe silicate (BeO = 2.3%)	Rabbits	3-7	i.v. in 30 doses	3 in 6	Hoagland et al., 1950
ZnBe silicate (BeO = 14%)	Rabbits	10-12	i.v. in 30 doses	3 in 4	Hoagland et al., 1950

(continued on the following page)

TABLE 7-7. (continued)

Compound	Species	Total dose (mg Be)	Mode of administration	Incidence of osteosarcoma	Reference
BeO	Rats	360	i.v. in 20 doses	0	Gardner and Heslington, 1946
	Guinea pigs	360	i.v. in 20 doses	0	Gardner and Heslington, 1946
	Mice	0.55	i.v. in 20-22 doses	0	Cloudman et al., 1949
	Rabbits	140	i.v. in 20-22 doses	0	Cloudman et al., 1949
		180	i.v. in 6-10 doses	1 in 11	Barnes et al., 1950
		360	i.v. in 1-30 doses	1 in 8	Hoagland et al., 1950
		360-700	i.v. in 20-26 doses	6 in 6	Dutra and Largent, 1950
		360	i.v. in 20-22 doses	1 in 7	Gardner and Heslington, 1946
		1	Inhalation, 25h/wk, 9-18 mo.	0 in 5	Dutra et al., 1951
		6	Inhalation, 25h/wk, 9-18 mo.	1 in 6	Dutra et al., 1951
		30	Inhalation, 25h/wk, 9-18 mo.	0 in 8	Dutra et al., 1951
Be Phosphate	Rabbits	130?	i.v. in 1-30 doses	0 in 5	Hoagland et al., 1950

Source: Adapted from Reeves (1978)

primary thyroid tumor in the group injected with zinc beryllium manganese silicate. Liver cirrhosis and splenic fibrosis were also observed. Transplant experiments were all negative.

Several experiments reported from the Mayo Foundation confirmed the carcinogenic effects of intravenous beryllium on bone (Janes et al., 1954, 1956; Kelly et al., 1961). Twenty-two of 31 rabbits receiving zinc beryllium silicate (total dose 12 mg Be) developed osteosarcomas. New bone formation was observed in the medullary cavities of the long bones before the malignant changes became apparent. Of particular interest was the observation of splenic atrophy only in those animals which developed bone tumors. Following spelenectomy, the incidence of bone tumor or new bone formation in the medullary cavity was 100 percent, whereas the incidence of these developments in non-splenectomized rabbits receiving identical doses of beryllium was only 50 percent. The results suggest that a well-functioning spleen may serve as protection against beryllium carcinogenesis in the rabbit. Tibial chondrosarcomas were also produced, and successful transplants to the anterior chambers of the eyes of rabbits were performed (Higgins et al., 1964).

7.1.4 Intramedullary Injection Studies

Beryllium oxide or zinc beryllium silicate was directly introduced into the medullary cavity of bones of rabbits by Yamaguchi (1963), Tapp (1969), and Fodor (1977). Osteosarcomas, chondrosarcomas, and presarcomatous changes (irregular bone formation) were observed. Twenty to 30 injections (20 mg beryllium oxide per injection) gave the highest frequency of tumor formation. The tumors developed directly from the medullary bone, and were sometimes preceded by fibrosis. Tumors metastasized to the liver, kidney, lymph nodes, and particularly the lung.

7.1.5 Intracutaneous Injection Studies

Neither the intracutaneous injection of beryllium sulfate, nor the accidental introduction of insoluble beryllium compounds (beryllium oxide, beryllium phosphate, beryllium-containing fluorescent phosphors) into the skin have been found to produce tumors (Van Ordstrand et al., 1945; Reeves and Krivanek, 1974). The lesions that were produced were cutaneous granulomas, or, in the case of extensive injury, necrotizing granulomatous ulcerations.

In the immunotoxicologic experiments of Reeves et al. (1971, 1972) beryllium sulfate was administered intracutaneously in doses of 5 μg beryllium, but

there was no evidence that measurable amounts of beryllium left the sites of administration.

7.1.6 The Percutaneous Route of Exposure

No neoplasms have been observed following percutaneous administration of beryllium compounds in any species. However, eczematous contact dermatitis has been noted in humans who have worked with soluble compounds of beryllium (Van Ordstrand et al., 1945). Curtis (1951) studied the allergic etiology of these reactions and developed a beryllium patch test. In 1955, Sneddon reported that a patient with a positive beryllium patch test developed a sarcoid-like granuloma at the test site. Granulomatous ulcerations followed if insoluble beryllium compounds became imbedded in the skin. Using pigs, Dutra et al. (1951) were able to produce beryllium-induced cutaneous granulomas that resembled the human lesions. There is no record that any of these lesions underwent malignant degeneration. The fact that no neoplasms were observed could be explained by the virtual impenetrability of intact skin by beryllium (see section 4.1.3).

7.1.7 Dietary Route of Exposure

No known neoplasms have been observed following beryllium exposure by the dietary route in any species. Guyatt et al. (1933), Jacobson (1933), and Kay and Skill (1934) produced rickets in young rats fed beryllium carbonate at 0.1 to 0.5 percent dietary level. This result is attributable to the precipitation of beryllium phosphate in the intestine, leading to phosphate deprivation. Using similar dietary concentrations of beryllium, Sols and Dierssen (1951) observed a decrease in the intestinal absorption of glucose, which has been attributed to the inhibition of alkaline phosphatase (Du Bois et al., 1949). At intake levels of 5 to 500 ppm in the diet, no toxic effects of any kind were found (Reeves, 1965; Schroeder and Mitchener, 1975a,b; Morgareidge et al., 1977, abstract).

If insoluble beryllium dusts (beryllium, beryllium alloys, beryllium oxide, beryllium phosphate, or beryllium ores) are ingested, the bulk of these substances will pass through the gastrointestinal tract unabsorbed. Depending on the size of the particles, and, in the case of beryllium oxide, on the firing temperature, a minor proportion of these dusts could become dissolved in gastric juices, and traces of the resultant beryllium chloride could be absorbed from the stomach. Upon entry into the intestine, any dissolved beryllium would become precipitated again, mainly as beryllium phosphate (Reeves, 1965).

In most mammalian species, alimentary absorption of soluble beryllium salts [beryllium fluoride (BeF_2), beryllium chloride ($BeCl_2$), beryllium sulfate ($BeSO_4$), and beryllium nitrate ($Be[NO_3]_2$) is minor. Researchers have observed that 80 percent or more of an oral beryllium intake of 0.6 to 6.6 µg/day passes unabsorbed through the gastrointestinal tract of rats (Reeves, 1965; Furchner et al., 1973; Schroeder and Mitchner, 1975a,b). Upon entering the alkaline milieu of the intestine, beryllium forms a precipitate that is excreted with the feces. There is some evidence that increasing the intake concentration does not increase the amount absorbed from the intestine, because the latter is governed by the solubility of the intestinal precipitates rather than by the total amount of beryllium present.

7.1.8 Tumor Type, Species Specificity, Carcinogenic Forms, and Dose-Response

7.1.8.1 Tumor Type and Proof of Malignancy. Pulmonary neoplasms found in rats after beryllium exposure have been classified as adenocarcinomas, showing a predominantly alveolar pattern. Reeves et al. (1967) distinguished four histological variants, including focal columnar, focal squamous, focal vacuolar, and focal mucigenous. Schepers et al. (1957) distinguished several more, including some adenomas judged to be non-malignant. Wagner et al. (1969) and Groth et al. (1980) found that about half of the tumors they produced with beryllium were benign adenomas. The diagnosis of pathological lesions is complicated, and requires special expertise. The histological differentiation between adenomas and adenocarcinomas is not always well defined and may also have species-related peculiarities, so that different conclusions on the same specimen may sometimes be reached by pathologists. This is especially true when pathologists have been trained in human rather than veterinary medicine. It is also noteworthy that neoplasia in the lungs of rats was invariably associated with the purulent lesions of chronic murine pneumonia, which itself was exacerbated by inhalation of the acidic beryllium sulfate aerosol.

Metastases, as well as successful transplants, were claimed by Schepers et al. (1957). In the rat experiments of Vorwald, neither was claimed, but later reports have been ambiguous on these points (Vorwald et al., 1966; see also Lesser, 1977). In the monkey experiments of Vorwald (1968), which lacked controls, extensive metastases to the mediastinal lymph nodes and sometimes to the bones, liver, and adrenals were reported. Groth et al. (1980) performed successful transplants in experiments with intratracheal administration of beryllium metal and beryllium alloy, but metastasis to the mediastinal lymph node was observed in only one animal.

The nature of the neoplasms produced by the intravenous or intramedullary administration of beryllium in rabbits is much more certain. The osteosarcomal or chondrosarcomal character of these neoplasms has not been challenged, and metastases to all parts of the body have been observed. Transplant results have been equivocal, however. Successful transplants to the anterior chamber of the eye were reported by Dutra and Largent (1950) and Higgins et al. (1964), whereas failure with transplants was expressly admitted by Hoagland et al. (1950) and Araki et al. (1954). It is possible that the degree of malignancy of the bone tumors depends on the type of compound used in the injection.

7.1.8.2 Species Specificity and Immunobiology. Pulmonary tumors were produced after inhalation exposure and sometimes after intratracheal injection in rats (Vorwald, 1953; Vorwald et al., 1955; Schepers et al., 1957; Schepers, 1961; Vorwald et al., 1966; Reeves et al., 1967; Reeves and Deitch, 1969; Spencer et al., 1965, 1968, 1972; Wagner et al., 1969; Groth et al., 1980; Ishinishi et al., 1980) and in monkeys (Schepers, 1964; Vorwald et al., 1966; Vorwald, 1968; but see Wagner et al., 1969 for negative evidence). No pulmonary tumors were produced in rabbits (Vorwald, 1950). The evidence for hamsters (Wagner et al., 1969), and guinea pigs (Vorwald, 1950; Schepers, 1961, 1971; Reeves et al., 1972), while generally negative, was suggestive of a positive effect in some cases.

Bone tumors were produced by intravenous or intramedullary injection in rabbits (Gardner and Heslington, 1946; Dutra and Largent, 1950; Barnes et al., 1950; Hoagland et al., 1950; Araki et al., 1954; Janes et al., 1954, 1956; Kelly et al., 1961; Yamaguchi, 1963; Higgins et al., 1964; Tapp, 1969; Fodor, 1977). The single report claiming osteosarcomas in mice (Cloudman et al., 1949) needs confirmation, as does the report of osteosarcomas in rabbits after inhalation exposure (Dutra et al., 1951). Bone tumors were not observed in rats or guinea pigs.

It would appear from these data that (1) pulmonary tumors can be obtained with beryllium in rats and in monkeys, possibly in hamsters and guinea pigs, but not in rabbits, and (2) that bone tumors can be obtained with beryllium in rabbits and perhaps in mice, but not in rats or guinea pigs. The negative evidence with guinea pigs involves both the intravenous injection (Gardner and Heslington, 1946; Vorwald, 1950) and inhalation (Schepers, 1961; Reeves et al., 1972) of beryllium at levels that were definitely carcinogenic in rabbits and rats, respectively. However, in the later inhalation studies of Schepers (1971) there was suggestive evidence for the induction of lung cancer in guinea pigs.

This apparent species specificity, which might operate with other types of carcinogenesis as well (guinea pigs are generally regarded as poor models for cancer induction), has remained largely unexplored. It is certainly noteworthy that guinea pigs develop cutaneous hypersensitivity to beryllium, whereas rats do not (Reeves, 1978). In rabbits, the spleen has been found to be involved in the neoplastic response to intravenous beryllium. Gardner and Heslington (1946) observed prompt splenic atrophy in beryllium-injected rabbits, while Janes et al. (1954) found that splenic atrophy afflicted only those animals that developed the osteosarcomas. In later work, Janes et al. (1956) increased the yield of osteosarcomas in beryllium-injected rabbits twofold by performing splenectomy. These studies suggest that some form of cellular immunity, with immunocompetent cells arising from the spleen, may be a factor in determining whether beryllium is neoplastic. Various species, or perhaps individual members of a species, may have resistance to beryllium-induced cancer according to their immunocompetence.

7.1.8.3 Carcinogenic Forms and Dose-Response Relationships. There is insufficient evidence to implicate any specific chemical form of beryllium as the exclusive carcinogenic entity. Ionic beryllium changes to beryllium hydroxide upon inhalation, and both forms have caused pulmonary tumors in rats when inhaled (ionic beryllium) or injected intratracheally (beryllium hydroxide) (Vorwald, 1953; Schepers et al., 1957; Reeves et al., 1967; Groth et al., 1980). There is reason to believe that beryllium hydroxide particles can change to beryllium oxide upon aging (Reeves, in press). Beryllium oxide, when directly introduced into the lungs of rats, showed a remarkable pattern of carcinogenicity, clearly indicating that firing temperature had a definite influence on the tumor yield and that only "low-fired" (500°C) beryllium oxide was highly carcinogenic (Spencer et al., 1968, 1972). Sanders et al. (1978) observed only one lung tumor among 184 rats exposed to "medium-fired" (1000°C) beryllium oxide. Frequently, no tumors are obtained with beryllium oxide; however, in early studies, the type of beryllium oxide to which the animals were exposed was not generally identified (Cloudman et al., 1949; Dutra and Largent, 1950; Hoagland et al., 1950; Araki et al., 1954; Vorwald et al., 1966).

Experiments attempting to establish a dose-response relationship with intravenous beryllium are limited. Nash (1950) suggested 12 mg beryllium per rabbit was the minimum effective total dose to produce osteosarcomas. In the experiments of Hoagland et al. (1950), the frequency of osteosarcomas increased from 50 to 75 percent as beryllium oxide content of a fluorescent phosphor was

increased from 2.3 to 14 percent. Barnes et al. (1950) could increase the rate of rabbit osteosarcomas from 4/14 (29%) to 2/3 (67%) by doubling the dose of intravenous zinc beryllium silicate from 7.5 to 15 mg. However, in the inhalation experiment of Dutra et al. (1951) and in the intramedullary experiments of Yamaguchi (1963), no clear-cut relation between dose and tumor yield was found.

Vorwald et al. (1966), citing results of their own unpublished studies, claimed that "almost 100 percent of a large number of rats" developed lung cancer after 18 months of exposure to 42 or 21 μg Be/m^3 (as sulfate). After exposure to 2.8 μg Be/m^3 (as sulfate), their reported rate of lung cancer was 13/21 (62%). These figures came under considerable scrutiny during the beryllium hearings at the Occupational Safety and Health Administration (Lesser, 1977). It was pointed out that these experiments were poorly controlled and that the exposure data of 2.8 μg Be/m^3 deserved no confidence. Wagner et al. (1969) obtained pulmonary tumors in rats with beryl ore (beryllium content 4.14%) but not with bertrandite ore (beryllium content 1.4%). Similarly, Groth et al. (1980) obtained pulmonary tumors with beryllium metal, beryllium hydroxide, and a beryllium-aluminum alloy, with beryllium content ranging from 62 to 100 percent. They obtained no tumors with other alloys, ranging in beryllium content from 2.2 to 40 percent. Thus, the evidence points to the existence of a definable dose-response relationship in experimental beryllium carcinogenesis.

Reeves (1978) examined this relationship by the probit method. For the induction of osteosarcomas in rabbits following intravenous injection of zinc beryllium silicate, the median effective total dose per animal was 11.0 mg beryllium. The dose-response curve intersected the 1 percent incidence level at 3.8 mg, the 0.1 percent incidence level at 2.7 mg, and the 0.01 percent incidence level at 2.0 mg. For the induction of pulmonary carcinoma in rats after inhalation of beryllium sulfate (a 35-hr/wk chamber exposure lasting 3 or more months), the median effective concentration was 18.0 μg Be/m^3, and the curve intersected the 1 percent incidence level at 12.0 μg Be/m^3, the 0.1 percent incidence level at 10.5 μg Be/m^3, and the 0.01 percent incidence level at 9.0 μg Be/m^3. Obviously, these estimates are subject to considerable uncertainty.

7.1.9 Summary of Animal Studies

The results of the studies that have been reviewed in this section are summarized in Table 7-8.

TABLE 7-8. CARCINOGENICITY OF BERYLLIUM COMPOUNDS

Year	Species	Compound	Route of Administration	Tumor	Reference
1946	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Gardner and Heslington
1949	Mouse	Zinc beryllium silicate	Intravenous	"Malignant bone tumors"	Cloudman et al.
1949	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Cloudman et al.
1950	Rabbit	Zinc beryllium silicate and beryllium metal	Intravenous	Osteosarcoma	Barnes et al.
1950	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Hoagland et al.
1950	Rabbit	Beryllium oxide and zinc beryllium silicate	Intravenous	Osteosarcoma	Dutra and Largent
1951	Rabbit	Beryllium oxide	Inhalation	Osteosarcoma	Dutra et al.
1953	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	Vorwald
1954	Rabbit	Beryllium phosphate beryllium oxide	Intravenous	Osteosarcoma	Araki et al.
1954	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Janes et al.
1957	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	Schepers et al.
1961	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Kelly et al.
1964	Rabbit	Zinc beryllium silicate	Intravenous	Chondrosarcoma	Higgins et al.

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TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1966	Monkey	Beryllium oxide	Intratracheal instillation	Pulmonary cancer (anaplastic)	Vorwald et al.
1966	Monkey	Beryllium sulfate tetrahydrate	Inhalation	Pulmonary cancer	Vorwald et al.
1967	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung-cancer (alveolar-adeno Ca)	Reeves et al.
1968	Rabbit	Beryllium oxide	Intravenous	Osteosarcoma	Komitowski
1969	Rat	Beryl ore Bertrandite ore	Inhalation	Lung cancer (adeno) No tumors	Wagner et al.
1969	Hamster	Beryl ore Bertrandite ore	Inhalation	None None	Wagner et al.
1969	Monkey	Beryl ore Bertrandite ore	Inhalation	None None	Wagner et al.
1969	Rabbit	Zinc beryllium silicate Beryllium silicate Beryllium oxide	Subperiosteal injection	Osteosarcoma Osteosarcoma Osteosarcoma	Tapp
1971	Rat	Beryllium hydroxide	Intratracheal	Pulmonary tumors	Groth and Mackay
1975 a,b	Rat	Beryllium sulfate tetrahydrate	Ingestion	? No greater than controls	Schroeder and Mitchener
1975	Rat	Beryllium fluoride Beryllium chloride	Inhalation	Lung cancer (adeno and squamous)	Litvinov et al.

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TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1975	Rabbit	Zinc beryllium silicate	Intramedullary	Osteosarcoma	Mazabrau
1977	Rat	Beryllium sulfate tetrahydrate	Ingestion	? No greater than controls	Morgareidge et al.
1978	Rat	Beryllium oxide	Inhalation	Single lung cancer (adeno)	Sanders et al.
1980	Rat	Beryllium metal Beryllium alloy Passivated beryllium metal Beryllium hydroxide	Intratracheal instillation	Lung cancer (adeno and squamous) " "	Groth et al.
1980	Rat	Beryllium oxide	Intratracheal instillation	Lung cancer (squamous, adeno, lympho)	Ishinishi et al.

Source: Adapted from Kuschner (1981)

Tumors have been successfully induced by intravenous or intramedullary injection of beryllium into rabbits and, possibly, mice, and by inhalation exposure or intratracheal injection into rats, monkeys, and possibly guinea pigs. Attempts to induce tumorigenesis by the dietary route have proven unsuccessful in any species tested. This failure to induce tumors is probably attributable to minimal absorption resulting from the precipitation of beryllium compounds in the intestine. Guinea pigs and hamsters appear to have a low degree of susceptibility to beryllium carcinogenesis. This species specificity appears to be connected with immunocompetence.

In rabbits, osteosarcomas and chondrosarcomas have been obtained. The tumors are highly invasive and metastasize readily, but transplant with variable success. They have been judged to be histologically similar to corresponding human tumors. In rats, pulmonary adenomas and/or adenocarcinomas of questionable malignancy have been obtained. The tumors are less invasive, and their metastatic and transplant potential are variable. They appear to be histologically associated with the purulent lesions of chronic murine pneumonia.

There is some evidence that the carcinogenicity of beryllium oxides is inversely related to their firing temperature, with only the "low-fired" (500°C) variety presenting a substantial hazard. Limited dose-response evidence indicates that approximately 2.0 mg beryllium (as beryllium oxide) is the minimum intravenous dose for production of osteosarcomas in rabbits, and approximately 10 μg Be/m^3 (as sulfate) is the minimum atmospheric concentration for the production of adenocarcinomas in rats.

Although some studies involving beryllium clearly have limitations, the combined data, using EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984) to classify weight of evidence for carcinogenicity in experimental animals, suggest there is "sufficient evidence" to conclude that beryllium and beryllium compounds are carcinogenic in animals.

7.2 EPIDEMIOLOGIC STUDIES

7.2.1 Bayliss et al. (1971)

The first in a series of government-sponsored studies of cancer in workers exposed to beryllium was conducted by Bayliss et al. (1971). This cohort mortality study consisted originally of 10,356 former and current employees of the beryllium-processing industry (the Brush Beryllium Company of Ohio and Kawecki-Berylco Industries of Pennsylvania.) Some 2153 workers were excluded

because of insufficient data. Records consisted only of names of workers and approximate years of employment of workers employed at the Brush Beryllium Company prior to 1942. Company employment records provided no additional information despite an intensive search. These lists were prepared by a former Brush Beryllium Company physician, now deceased. After further removal of 1130 females, the cohort totaled 6818 males. In this group, 777 members died during the period from January 1, 1942 to the cutoff date, December 31, 1967. This was less than the 842.4 expected deaths based upon U.S. male death rates--a shortfall attributable to the "healthy worker effect." No elevated risk of lung cancer (International Classification of Diseases [ICD] 160-164) was evident overall (36 observed versus 34.06 expected). No significant excess risk of lung cancer was found to exist in relation to length of employment, beginning date of employment, or kind of employment (office versus production), nor were significant risks of other forms of cancer evident from these data.

This study suffers from several deficiencies. Over 2000 individuals had to be eliminated from the cohort because birth date, race, and sex were not available. The authors indicated that this reduction in the size of the study necessitated the elimination of some 251 deaths, and represented a loss of over 20 percent of the cohort and 25 percent of the known deaths, a circumstance that had the potential for introducing considerable bias into the results.

A second major problem with the study is the fact that the authors did not analyze the data according to length of time since initial employment in the industry. The lack of such an analysis meant that questions dealing with latency could not be addressed.

A third deficiency is that the populations of several different plants were combined into one cohort for the study. As a result, the study failed to consider the many potential differences of exposure levels at different plants. Individuals were studied in groups according to beginning date and duration of employment, despite the fact that their exposure histories may have been totally dissimilar.

For the above-cited reasons, this study is not adequate for the evaluation of cancer mortality in beryllium-exposed workers.

7.2.2 Bayliss and Lainhart (1972, unpublished)

In an attempt to remedy the deficiencies of the 1971 study, Bayliss and Lainhart (1972), in an unpublished report presented at the American Industrial Hygiene Association meeting on May 18, 1972, narrowed the scope of the original

study by focusing only on data from Kawecki-Berylco Industries (KBI) which had seemingly complete employment records for two locations in Pennsylvania. This change effectively reduced the size of the cohort to some 3795 white males while retaining the same starting and cutoff dates as were used in the earlier study. In the 1972 study, Bayliss and Lainhart found that 601 members of the cohort had died, compared to 599.9 expected deaths based on period- and age-specific U.S. white male death rates. Again, no significant excess of unusual mortality from any cause was evident. For lung cancer (ICD 160-164) overall, 25 deaths were observed versus 23.69 expected. Even when latency was considered, no significant excess risk of lung cancer was apparent after a lapse of 15 years from initial exposure, at which time 14 deaths were observed versus 13.28 expected. In addition, no significant risks were apparent in relation to intensity of exposure, duration of exposure, or beginning date of employment.

The Bayliss and Lainhart (1972) study was criticized by Bayliss and Wagoner (1977) in a third version of the study, which was submitted to the Occupational Safety and Health Administration (OSHA) as part of the beryllium standards development process. In this criticism, the 1972 study was said to have multiple limitations, among which were the following: (1) the study included clerical and administrative workers who presumably had not been exposed to beryllium; (2) the data were obtained from industrial representatives, which precluded an independent assessment of plant employment files to ensure that all potentially exposed workers were included; and (3) the study did not assess latency 20 or more years after initial employment, although it did examine mortality after a 15-year lapse.

7.2.3 Bayliss and Wagoner (1977, unpublished)

In the third attempt to remedy the deficiencies of the two previous studies, Bayliss and Wagoner (1977) reduced the size of the cohort to include workers employed at only one plant site of the KBI. This particular plant site in Pennsylvania was considered to be the best choice for a cohort mortality study for the following reasons: (1) this plant had, according to the authors, the most complete and detailed set of personnel records of any of the companies and sites examined; (2) it had been in continuous operation producing beryllium prior to 1940, thus, allowing an analysis of latent effects; and (3) it provided a large group of employees from which valid inferences could be made. Other plant sites were deficient in one or more of these respects. The cohort was composed of 3070 white males who were followed until January 1, 1976. Vital

status was unknown for only 80 members of the cohort (3%), and these individuals were considered to be alive until the study's cutoff period. Altogether, 884 deaths were observed, compared to 829.41 expected (based on period- and age-specific U.S. white male death rates). A significant excess of lung cancer was noted (ICD 162-163), with 46 cases observed versus 33.33 expected ($p < 0.05$). A significant excess of heart disease was also noted (399 observed versus 335.15 expected, $p < 0.05$), as was a significant excess of nonmalignant respiratory disease (32 observed versus 19.02 expected, $p < 0.01$). Irrespective of duration of employment, a significant excess was noted in bronchogenic cancer following a lapse of 25 or more years since initial employment.

In this study, the authors discussed for the first time the impact of cigarette smoking as a possible confounding agent contributing to the excess risk of lung cancer. An examination of the results of a cross-sectional health examination survey conducted at the plant by the U.S. Public Health Service (PHS) in 1968 revealed some differences in the cigarette-smoking patterns of the surveyed employees, compared to smoking patterns in the United States as a whole (determined from a health interview survey conducted by the PHS from 1964 to 1965). A greater percentage of heavy smokers was indicated in the 1968 survey as compared with national data (21.4 versus 15.3%). However, Wagoner et al. (1980) later dismissed the results as a possible cause of the increased risk of bronchogenic cancer and other diseases in the study cohort. Dismissing the role of cigarette smoking as a contributing cause of the excess risk of lung cancer may have been premature for several reasons. First, the smoking patterns of the 379 current employees surveyed in 1968 were probably not the same as those of the entire cohort of 3795, which included both current and past workers employed as early as 1942. Second, the first national reports of smoking as a cause of lung cancer were published in 1964 and were accompanied by a great deal of media attention. By 1968, intense media coverage dealing with the health consequences of smoking probably produced a diminution of cigarette smoking among various subgroups of the population in the 4-year interim period between surveys. Furthermore, while the 1968 survey at the plant did speak of current cigarette-smoking patterns, the issue of prior cigarette smoking was not addressed, nor was the issue of pipe or cigar smoking. Additional criticisms of the Bayliss and Wagoner (1977) study, as well as the final version of the study (Wagoner et al., 1980), follow.

7.2.4 Wagoner et al. (1980)

Wagoner et al. (1980) slightly reduced the cohort of Bayliss and Wagoner (1977) to a smaller cohort mortality study of 3055 white males employed some time between January 1, 1942 and December 31, 1967, in the same beryllium-processing facility. This version of the study did not differ markedly from the Bayliss and Wagoner (1977) study except in minor respects. Thirteen persons who had been included in the earlier cohort were found to be salespersons who had never appeared in the plant; thus, they were removed from the cohort. In addition, three individuals who were nonwhite and therefore also ineligible for inclusion were removed. One individual with a definite diagnosis of lung cancer but questionable employment credentials was added. The results showed a significantly high risk of lung cancer (47 observed versus 34.29 expected, $p < 0.05$) for those individuals followed until December 31, 1975. This excess extended to members of the cohort followed for more than 24 years since initial employment (20 observed versus 10.79 expected, $p < 0.01$). When the analysis was confined to those whose initial employment occurred prior to 1950, but who were followed for 15 years or more from date of initial employment, a significantly high risk of lung cancer was apparent (34 observed versus 22.46 expected, $p < 0.05$). For those whose initial employment occurred after 1950, 4 deaths from lung cancer were observed versus 2.4 expected. The authors concluded that this excessive risk of lung cancer "could not be related to an effect of age, chance, self-selection, study group selection, exposure to other agents in the study facility, or place of residence."

This study has received severe criticism from several sources: an internal Center for Disease Control (CDC) Review Committee appointed to investigate defects in the study, several professional epidemiologists (MacMahon, 1977, 1978; Roth and Associates, 1983), and also one of the study's co-authors (Bayliss, 1980). These researchers criticized Wagoner et al. for inadequately discussing all qualifiers that might explain any of the significant findings of the study.

The cohort studied by Wagoner et al. (1980) was composed of workers at the facility who had been employed prior to December 31, 1967, based on the facility's employment records and the results of a 1968 cross-sectional medical survey of the plant. The cohort excluded employees who were not directly engaged in the extraction, processing, or fabrication of beryllium, or in on-site administrative, maintenance, or support activities. The numbers of expected deaths used in the study were based on U.S. white male death rates that had been

generated by an analytic life table program designed by the National Institute for Occupational Safety and Health (NIOSH). As a basis for these calculations, the program used actual U.S. deaths recorded by cause, age, race, sex, and year through 1967, together with census population data from 1941 to 1967. These data were provided by the Bureau of the Census and the National Center for Health Statistics. Unfortunately, at the time of this study and subsequent studies on beryllium, cause of death information was not available from these agencies on a year-to-year basis after 1967. As a result, the NIOSH life-table program could not generate death rates during this period without certain assumptions. In order to estimate expected deaths during the period from 1968 through 1975, death rates were assumed by the authors to be unchanged from those generated by the NIOSH life-table program for the period from 1965 through 1967. The result was that for causes of death with declining death rates, expected deaths were overestimated, with a resultant underestimate of risk. Similarly, for those causes with increasing death rates during the interval studied, expected deaths were underestimated, with a resultant upward risk bias, which was the case for all of the lung cancer risk calculations made by the authors. After this problem had been corrected by the inclusion of actual lung cancer mortality data for the period in question, expected lung cancer deaths were recomputed by Bayliss (1980) prior to the Wagoner et al. (1980) publication. The result was an increase from 34.29 to 38.2 expected lung cancer deaths, or an excess of 11 percent. This correction in itself was enough to eliminate the statistical significance calculated by Wagoner et al. in their overall lung cancer tabulation. With respect to latency, the risk of lung cancer remained significant in the subgroup of the cohort that was observed for 25 years or more after initial employment (20 observed versus 13.36 expected, $p \cong 0.05$). These corrections have been confirmed by Richard Monson (MacMahon, 1977, 1978), following a reanalysis of the NIOSH data tapes in an independent Monson life-table program at Harvard University.

In attempting to assess the impact of cigarette smoking on the risk of developing lung cancer in this cohort, Axelson's method (1978) was applied to the meager cigarette smoking data that were available from Wagoner et al. (Table 7-9).

The problems with these data have been discussed in the earlier critique of the Bayliss and Wagoner (1977, unpublished) paper. However, in the interest of adjusting the expected lung cancer deaths by the contribution due to cigarette smoking, one must first assume as valid the risks of lung cancer by level

TABLE 7-9. PERCENTAGE DISTRIBUTION OF BERYLLIUM-EXPOSED WORKERS AND OF AGE-ADJUSTED U.S. WHITE MALE POPULATION BY CIGARETTE SMOKING STATUS

Cigarette Smoking Status	Beryllium Production Workers (%)	U.S. Population[a] (%)
Never smoked	27.2	24.7
Former smokers	22.4	20.5
Current smokers	50.4	54.7
< 1 pack a day	29.0	39.4
≥ 1 pack a day	21.4	15.3

[a]National Center for Health Statistics, 1967.

Source: Wagoner et al. (1980)

of smoking that are given in the American Cancer Society's 25 State Study (Hammond, 1966). These data are given in Table 7-10.

Next, a number of different assumptions about the data must be made in order to produce a range of estimates that will presumably include the best estimate of the contribution due to smoking. Four calculations were done based on varying the assumptions as follows: for the first calculation, the former smokers were grouped with the nonsmokers, and the lower risk ratios were used (i.e., 4.62 and 14.69); second, the former smokers were again grouped with the nonsmokers, but the higher risk ratios were used (i.e., 8.62 and 18.77); third, the former smokers were grouped with the moderate smokers, and the lower risk

TABLE 7-10. LUNG CANCER MORTALITY RATIOS FOR MALES, BY CURRENT NUMBER OF CIGARETTES SMOKED PER DAY, FROM PROSPECTIVE STUDIES

American Cancer Society 25-State Study	Cigarettes Smoked per Day	Mortality Ratio
Nonsmokers	0	1.00
Moderate	1-9	4.62
	10-19	8.62
Heavy	20-39	14.69
	40+	18.77

Source: Hammond (1966)

ratios were used; and for the fourth calculation, the former smokers were grouped with the moderate smokers, and the higher risk ratios were used. Using this method, the increase in expected lung cancer deaths ranges from 4.1 to 9.8 percent. This procedure is described below.

Let I_g = the incidence in the comparison population (U.S. males),

I_o = the incidence in any nonsmoking population,

R_1, R_2, and R_3 = the relative risks in nonsmokers, moderate smokers, and heavy smokers, respectively, and

p_1, p_2, and p_3 = the percentage of the population who are nonsmokers, moderate smokers, and heavy smokers, respectively.

Then, the incidence of lung cancer in the comparison population is:

$$I_g = (R_1 \cdot p_1 \cdot I_o) + (R_2 \cdot p_2 \cdot I_o) + (R_3 \cdot p_3 \cdot I_o)$$

Similarly, if I_p = the incidence of lung cancer in the plant study population and I_o, R_1, R_2, and R_3 are the same as above, but p_1, p_2, and p_3 are the percentages of the plant population who are nonsmokers, moderate smokers, and heavy smokers, respectively, then the incidence of lung cancer in the plant or study population is:

$$I_p = (R_1 \cdot p_1 \cdot I_o) + (R_2 \cdot p_2 \cdot I_o) + (R_3 \cdot p_3 \cdot I_o)$$

and finally, the contribution to the increase (or decrease) in the expected deaths is the ratio of I_p to I_g. Hence, $(I_p/I_g) \cdot$ (expected lung cancer deaths) is the adjustment due to the confounder cigarette smoking.

When the calculation is completed which produces the least change (+4.1 %) in the expected lung cancer deaths in the 25+ latent category, the new adjusted expected number of lung cancer deaths is

$$13.36 \times 1.041 = 13.91$$

which when compared with 20 observed deaths in this latent category is no longer statistically significant. Repeating this calculation and assuming the highest effect (i.e., +9.8%), the number of expected deaths is

$$13.36 \times 1.098 = 14.67$$

which, also, is not statistically significant.

A number of assumptions must be made in order to apply this crude method to adjust for the contribution to lung cancer due to cigarette smoking. These are outlined below:

1. Smoking levels in Table 7-9 are similar to those of the entire cohort. This is not necessarily true. Although most former employees began work prior to 1950, a smaller proportion of those current workers in 1967 who participated in the smoking survey began work prior to 1950. Smoking among blue-collar employees was thought to be greater in the 1940s.
2. Smoking levels at the plant in 1968 are similar to those of the United States in 1964. The survey on smoking in the U.S. population was completed in 1964 at about the same time as the release of the report on smoking and health by the Surgeon General, while the survey of the plant was completed in 1968. The ensuing national publicity engendered by the Surgeon General's report helped to produce a reduction in smoking levels in the U.S. population, and probably in this plant, during the three-year period from 1964 to 1968. Therefore, these levels are not strictly comparable because of a lack of concurrence of the two events.
3. In each smoking category (heavy, moderate, and nonsmoking), the age distributions are similar. This is not necessarily the case. It was impossible to age-adjust the plant population in each smoking category to the U.S. male population in the same smoking category because of the lack of age-specific smoking data in each category of both populations.
4. The assignment of persons into specific smoking categories by quantity smoked assumes that such persons always belonged to the category to which they were classified. This may not be the case in either population. No time factor could be used to classify persons as to the category of smoking to which they were assigned, since such information was not available.

Unfortunately, these estimates are by necessity based on the only data available to the U.S. Environmental Protection Agency's Carcinogen Assessment Group (CAG). Table 7-11, which is adapted from the Wagoner et al. (1980) study, has been corrected to eliminate the 11-percent underestimate of expected deaths

TABLE 7-11. OBSERVED AND EXPECTED DEATHS DUE TO LUNG CANCER ACCORDING TO DURATION OF EMPLOYMENT AND TIME SINCE ONSET OF EMPLOYMENT AMONG WHITE MALES EMPLOYED SOMETIME DURING JANUARY 1942 THROUGH DECEMBER 1967 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWED THROUGH 1975 (REVISED)

Interval Since Onset of Employment (yrs)	Duration of employment (years)[a,b]					
	< 5 years		> 5 years		Total	
	obs.	vs. exp.	obs.	vs. exp.	obs.	vs. exp.
< 15	7	8.88	1	1.76	8	10.64
15 - 24	15	13.44	3	3.15	18	16.59
> 25	17	12.00	3	2.67	20	14.67
Total	39	34.32	7	7.58	46	41.90

[a]Employment histories were ascertained only through 1967.

[b]No comparison is statistically significant at $p < 0.05$; obs. = observed, exp. = expected.

caused by the failure to use the appropriate lung cancer death rates in the comparison population and has been adjusted upward another 4.1 percent (minimum effect) to account for the smoking contribution based on the information provided in Table 7-9. One ineligible lung cancer death has been removed from the observed deaths.

Wagoner et al. found 875 deaths in their cohort. The vital status of 79 members of the cohort remained unknown as of December 31, 1975. The authors' assumption was that these individuals would be counted as alive until the end of the study, and that because of their added person-years, any finding of increased cause-specific mortality would tend to be underestimated. Actually, these 79 individuals represented only two percent of the total cohort, and any additional person-years included from the time when they were last known to be alive would have added little to the number of expected deaths. Furthermore, given the intense scrutiny afforded this population in determining vital status by both Wagoner and Mancuso in their own studies of the same workers, and considering the fact that these researchers shared information on newly found lung cancer deaths, it is questionable whether any additional lung cancers would have been found either in the 79 individuals with unknown vital status or in the 15 known dead for whom causes of death were not known by the cutoff date of the study. The latter number was reduced to ten in subsequent tabulations, after information on causes of death was located for five individuals (Bayliss, 1980). None of these was lung cancer.

Additional factors that could have contributed to the finding of an excess risk of lung cancer in Wagoner et al. (1980) are as follows:

1) One lung cancer victim was added to the cohort based on a single 4 by 7 inch personnel card that listed the same day (June 1, 1945) as the "starting date" and "release date" in the plant. In actuality, the individual, according to company sources, never reported for work because a preemployment chest X-ray revealed a lung abnormality. The company paid him for the time he was being examined, which is why his name and social security number appeared on a social security earnings report. Bayliss excluded him from his original cohort based on the information on the same personnel record that said "did not pass chest X-ray."

2) In a supplemental summation on the epidemiology of beryllium with respect to the proposed occupational safety and health standard for exposure to beryllium (January 13, 1978; prepared by Roth and submitted by Brush Wellman), it is stated that 295 white males, who were employed at the Reading plant of Kawecki-Berylco Industries (KBI) in jobs similar or identical to those of the Wagoner et al. cohort, were not included in the study cohort. Of that group, the report states that 199 employees had a known vital status: 181 were alive and 18 were deceased by the close of the study period. Dr. Roth's post hearing statement indicated that the inclusion of these additional employees would have increased the cohort by about ten percent.

3) In researching the medical files of the 47 lung cancer victims, David Bayliss, one of the co-authors, discovered that 23 files contained information to the effect that the individuals in question were smokers. In addition, the company from which the cohort was derived provided data indicating that 36 of the 47 lung cancer victims (77%) smoked cigarettes. These data were based on a company-sponsored survey by Hooper-Holmes and reported in a KBI interoffice memorandum (Butler, 1977). Bayliss determined that of the 47 cases, a total of 42, or nearly 90 percent, smoked cigarettes, based on a combination of smoking information gathered by the company and smoking information from the medical files. If this information is accurate, it could indicate the presence of a confounding effect due to cigarette smoking. Bayliss further established that one of the remaining five cases died from another cause of death. This victim actually died from a glioblastoma multiforme (astrocytoma) of the brain, according to medical data. However, his death certificate incorrectly listed lung cancer as an underlying cause of death. If the 47 cases are reduced to 46, then 91 percent smoked cigarettes.

4) An inadequate discussion was presented on the confounding effects of exposure to potential carcinogens prior to and following employment in the

beryllium industry. These factors are especially important since the authors maintained that only short-term employees were affected. Evidence from employment records, medical files, questionnaires administered during the 1968 NIOSH-sponsored medical survey of the plant, and death certificates indicated a distinct possibility that these factors are significant in the cohort under study (Bayliss, 1980).

Another problem with the Wagoner et al. (1980) study, as stated by the authors, is that the expected deaths were overestimated by 19 percent because of the use of death rates for white males in the United States as a whole, rather than those for Berks County, Pennsylvania, where the plant was located. This statement was based on a comparison by Mason and McKay (1973) of the 1950 to 1969 age-adjusted lung cancer death rate for white males in Berks County, Pennsylvania, with that of the 1950 to 1969 age-adjusted lung cancer rate for white males in the United States. This reference by Wagoner et al. to "lower" Berks County rates as a justification for the position that the expected deaths based on national rates are overestimated, has been criticized by Roth and Associates (1983) as well as by Bayliss (1980). Bayliss cited the fact that the periods of observation were different, i.e. the Mason data covered the period from 1950 through 1969, while those of Wagoner et al. (1980) covered the period from 1942 through 1975. Bayliss also pointed out that to derive reliable county death rates from the existing data would be extremely difficult to do with any confidence. Roth and Associates criticized the use of Berks County rates as not being reflective of greatly elevated lung cancer death rates for the City of Reading, which they maintained were 12 percent higher than the national rates. According to Roth and Associates (1983), 46 percent of the workers employed by the plant in 1968 resided within the city limits, whereas only 34 percent of Berks County residents (1970) resided within the city. Therefore, death rates calculated for Berks County should be weighted toward the relatively higher City of Reading rates. This adjustment would have the effect of generating comparison lung cancer rates that are perhaps greater than U.S. rates and, consequently, would increase the number of estimated expected deaths.

Wagoner et al. (1980) also claimed to have noted an unusual histopathologic distribution of cell types in 27 of the 47 lung cancer deaths for which pathologic specimens could be obtained. Adenocarcinomas were noted in 8 of 25 individuals (32%) histologically confirmed to have died from bronchogenic carcinoma (Smith and Suzuki, 1980). Wagoner et al. apparently

disregarded the conclusion of Smith and Suzuki that "the prevalence of histopathologic cell types of bronchogenic carcinomas among beryllium-exposed workers could not be presently defined." Smith and Suzuki attributed their conclusion to the fact that there was "an inadequate response rate for the submission of pathology specimens for review," since tissue specimens were not available for 20 (43%) of the total number of lung cancers. Wagoner et al., however, citing data from earlier studies (Haenszel et al., 1962; Axtell et al., 1976) to the effect that the frequency of adenocarcinomas in U.S. white males was 15 or 16 percent, concluded that a significant "shift" of histologic cell types was apparent in lung cancer deaths in beryllium workers. However, an internal NIOSH memorandum (Smith, 1978) stated that more recent data by Vincent et al. (1977) indicated that a shift in the prevalences of histopathological cell types of lung cancer in the general population over time has led to an increase in the prevalence of adenocarcinoma to 24 percent, and therefore the prevalence of adenocarcinomas in the lung cancer deaths of beryllium workers is not significantly different from that expected. Smith suggested in his memorandum that any mention by Wagoner et al. of the histopathological examination of lung tumor specimens that does not take into consideration the unrepresentative nature of the specimens should be deleted from the paper.

To summarize, it appears that the authors of the Wagoner et al. (1980) study tended to exaggerate the risk of lung cancer in a population of workers potentially exposed to beryllium, and underemphasized or did not discuss sufficiently the shortcomings of the study. The net effect was to turn a "nonsignificant association" of lung cancer with beryllium exposure into a questionable "significant association." Despite the study's problems, there still remains a possibility that the elevated risk of lung cancer reported therein was due in part to beryllium exposure, and although the CAG considers the study inadequate to assess the risk of lung cancer from exposure to beryllium at this time, it recommends further refinement and follow-up of this cohort to determine if the reported increase associated with lung cancer becomes statistically significant.

7.2.5 Infante et al. (1980)

In a companion paper by Infante et al. (1980), which appeared in the same journal as the Wagoner et al. (1980) study, lung cancer mortality was studied by the retrospective cohort method in white males for whom data had been

entered into the Beryllium Case Registry (BCR) with diagnoses of beryllium disease. A person was judged to have beryllium disease and thus to be eligible for inclusion into the BCR if three or more (two were mandatory) of the following five criteria were met (Hasan and Kazemi, 1974).

Mandatory -- (1) Establishment of significant beryllium exposure based on sound epidemiologic history.
(2) Objective evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease.
Mandatory -- (3) Chest X-ray films with radiologic evidence of interstitial fibronodular disease.
(4) Evidence of restrictive or obstructive defect with diminished carbon monoxide diffusing capacity by physiologic studies of lung function.
(5) 1 - Pathologic changes consistent with beryllium disease on examination of lung tissue.
2 - Presence of beryllium in lung tissue or thoracic lymph nodes.

At the time of the studies, close to 900 individuals had been entered into the BCR, based on evidence of nonmalignant respiratory disease objectively determined by appropriate and established medical procedures (Mullan, 1983).

According to Mullan (1983), the criteria listed above are characterized by high sensitivity but low specificity. Hence, while they are able to identify cases of actual beryllium disease, they can also lead to the inclusion of non-beryllium disease cases, in particular, cases of sarcoidosis.

Infante et al. (1980) eliminated from their cohort all nonwhite and female subjects because of their lack of "statistical sensitivity." They also eliminated all subjects who were deceased at the time of the BCR entry. The authors maintained that this constraint was necessary in order to ensure that no bias would result from the "selective referral of individuals with the outcome still under investigation", i.e. individuals with lung cancer. The use of the above procedure, however, raises the question that such a self-imposed constraint may not have prevented the "selective referral" of lung cancer victims prior to their deaths. This possible effect might have been eliminated if the above-referenced limitation had been applied to such cases as well. Or, alternatively, it should perhaps have been assumed that no potential bias existed, and that all BCR cases added posthumously should have been retained.

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

ascertained for 15 individuals. These were placed in an "undetermined cause of death" category. The authors ceased accumulating person-years on the group of 64 with unknown vital status at the time each was last known to be alive instead of to the end of the study. This procedure served to slightly reduce expected mortality in every cause category. This reduction was offset, however, by the fact that no potential deaths that might have occurred up to the cutoff date were included. With the intense scrutiny given the issue of lung cancer and beryllium by Infante and the many research investigators who have worked with the BCR since its inception (including Wagoner, Bayliss, and Mancuso), it is questionable whether any of the 15 deaths from undetermined causes, or any of the 64 cases with unknown vital status, were lung cancer deaths. Hence, it is probable that the estimated lung cancer risk is somewhat overestimated by this procedure.

Additionally, since the same National Institute for Occupational Safety and Health (NIOSH) life-table program that was used to calculate lung cancer deaths in the Wagoner et al. study was the method used to derive expected lung cancer deaths in the Infante et al. study, it was subject to the same problems as mentioned previously, i.e. an 11-percent deficit in the calculated expected lung cancer deaths. If it is assumed that this distortion is of the same magnitude as that described in the discussion of the Wagoner et al. (1980) study, the SMR of the Infante et al. (1980) study would also be inflated by 11 percent.

As expected, Infante et al. (1980) found a significantly high excess risk of "non-neoplastic" respiratory disease (52 observed deaths versus 3.17 expected). In terms of total cancer, 19 deaths were observed versus 12.41 expected. With respect to lung cancer, 6 deaths occurred more than 15 years after the onset of beryllium exposure versus 2.81 expected ($p < 0.05$). If the expected deaths are adjusted upwards by 11 percent to compensate for the overestimate produced by the NIOSH life-table program, the results are 6 deaths versus 3.12 expected ($p > 0.05$).

Infante et al. divided their cohort on the basis of "acute" versus "chronic" beryllium disease. Subjects were considered "acute" if the BCR records indicated a diagnosis of chemical bronchitis, pneumonitis, or other acute respiratory illness at time of entry into the registry. Subjects were called "chronic" if BCR records indicated a diagnosis of pulmonary fibrosis or some recognized chronic lung condition at time of entry into the registry. All other cases, if they could not be designated as chronic, were considered by

Infante et al. to be acute if the onset of the disease occurred within one year of initial exposure. These definitions should not be confused with the medically accepted definitions of acute and chronic beryllium disease, in which cases of beryllium disease lasting one year or less are termed "acute," while those lasting longer than one year are termed "chronic." The authors found no significant lung cancer, not even an excess in their "chronic" respiratory disease group of 198 persons (1 observed death versus 1.38 expected). However, in their "acute" respiratory disease group, they found 6 observed lung cancer deaths versus 1.91 expected ($p < 0.05$), and in the interval of more than 15 years since initial onset of beryllium exposure, 5 observed lung cancer deaths were found versus 1.56 expected ($p < 0.05$). These findings, however, suffer from the same problems previously discussed regarding the NIOSH life-table program and must therefore be regarded as questionable with respect to their implications.

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

Any one of the factors referred to above could have been of sufficient magnitude to produce a significant excess lung cancer risk in the group under study. The authors' treatment of these confounders serves to exaggerate this risk without presenting any compensating negatives. It appears likely that correcting or controlling the influence of two or more of these factors could reduce the estimated risk calculated to nonsignificance. The findings of Infante et al. (1980) are thus seen to be, at best, only suggestive of an increased risk of lung cancer from exposure to beryllium.

7.2.6 Mancuso and El-Attar (1969)

The first in a series of four epidemiologic studies of mortality in workers exposed to beryllium was conducted by Mancuso and El-Attar (1969) on the same study population used in the Bayliss and Wagoner studies. The names and social security numbers of individuals who made up the cohort in the Mancuso and El-Attar study, however, were derived from quarterly earnings reports provided by the Social Security Administration. Quarterly earnings reports on every employee of a given company covered by social security are filed four times a year by all companies included under the Social Security Act. These reports generally consist of lists of names, social security numbers, dates of birth, and reported earnings during the quarters for which filing is done. With respect to beryllium, Mancuso and El-Attar obtained quarterly earnings reports for both companies studied by Bayliss et al. (1971) and Wagoner et al. (1980), but limited their study to the period of employment from 1937 to 1948. Altogether, they identified 3685 white males from two beryllium plants. Only 729 white males were found to have died through the year 1966. Included in this group were 31 lung cancers (ICD 162-163). The authors contrasted internally generated age-, plant-, and period-specific death rates by cause with internally generated age-specific death rates by cause from an "industrial control." Unfortunately, because of the small numbers involved, the authors did not include any employees aged 55 or over. The industrial cohort used for purposes of comparison was not identified. The 729 deaths were distributed into 160 narrow subcategories, based on four broad age groups, two companies, four periods of time, and five broad death categories. Internal death rates were computed in each subcategory. Because the numbers from which these internal rates were derived are so small (in some instances nonexistent) from one subcategory to another, the comparisons with 20 rates generated from the industrial control are shaky at best and appear to vary considerably. No trends are evident. No significance tests were done. The data are open to interpretation. The authors themselves conclude, based on their analysis, that their data are "severely limited" with respect to answering the question of carcinogenic risk.

7.2.7 Mancuso (1970)

In a second study of the same cohort, Mancuso (1970) added duration of employment as a variable, and divided the cohort into a 1937 to 1944 component and a 1945 to 1948 component, by dates of initial employment. Both subgroups

were followed until 1967, and internal death rates were computed based on a technique the author termed "the generation cohort method." Each cohort was classified into 10-year age groups, beginning with 1940. An average annual mortality rate was calculated by age as of 1940. Age adjustment was done through the direct method, using the 1950 standard million as a base population (presumably the U.S. 1950 standard million, although the author does not specifically identify his comparison population). Comparisons were internal by gradient of exposure as defined by duration of employment and by evidence of prior chemical respiratory disease.

A higher rate of lung cancer was noted by the author among workers whose first employment occurred during the period 1937 to 1944 in age category 25 to 64, and who were employed for five or fewer quarters (99.9 per 100,000) compared to those employed six quarters or longer (33.2 per 100,000) based on 16 and 4 lung cancers, respectively. In one company, the author also found a higher rate of lung cancer among a group of workers with histories of chemical respiratory illness than in those who did not have this condition. During the 1940 to 1948 period, 142 white males with respiratory illness were identified in this plant. Out of a total of 35 deaths occurring in this group, 6 were due to lung cancer. Based on these 6 lung cancers, an age-adjusted lung cancer death rate of 284.3 per 100,000 was calculated, compared to an age-adjusted rate of 77.7 per 100,000 (based on 9 lung cancer deaths) in the total cohort of this company's workers employed from 1937 to 1948. These calculations were confined to individuals who were in the 25 to 64 age group in the year 1940. For some unknown reason, the author neglected to include the 15 to 24 age group. Had he done so, the lung cancer death rate in individuals without prior respiratory illness would have increased by the addition of two lung cancer deaths, leaving the rate unchanged in those with respiratory illness and narrowing the difference between the two rates. No significance tests were done, and, as noted by the author, the observations were based upon small numbers.

Although Mancuso (1970) found elevated risks in these groups, the results are subject to considerable variability. Mancuso criticized his own study for several alleged deficiencies. Some of these criticisms seem inappropriate, while others appear valid for this study and also for later studies by Mancuso on this same population. The deficiencies, according to Mancuso, consisted of "the marked influence of labor turnover on duration of employment, perhaps induced by the presence of respiratory disease; the inability to define the specific populations by department, process, or by type or form of beryllium

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

7.2.8 Mancuso (1979)

In a third update, Mancuso (1979) conducted a cohort mortality study in which he divided the cohort into two subgroups, each consisting of former and current employees of the two beryllium manufacturing companies. Employees were included in the study if they had worked at any time during the period from 1942 to 1948. The original source documents, from which names and social security numbers were derived to form the cohort, consisted of quarterly earnings reports submitted to the Social Security Administration. The Ohio cohort consisted of 1222 white males, of which 334 were deceased. The Pennsylvania cohort consisted of 2044 white males, of which 787 were deceased. A life-table analysis was performed by NIOSH, utilizing U.S. white male age- and period-specific rates (5-year age groupings) to generate expected lung cancer deaths (ICD 162, 163) through 1974 for the Ohio cohort, and through 1975 for the Pennsylvania cohort. An excess risk of lung cancer appeared in the Ohio employees after a lapse of 15 years from the onset of employment (22 observed versus 9.9 expected, $p < 0.01$). The same was true for the Pennsylvania employees (36 observed versus 22.0 expected, $p < 0.01$) following a similar latent period. The author noted that this risk occurred to workers with less than one year's duration of employment in the industry. No significant excess risk was noted in workers of either plant who were employed for more than five years in the industry. The author concluded on the basis of this study and the Wagoner et al. (1980) study that "there is evidence that beryllium causes cancer in man."

Several questions must be considered before these conclusions can be accepted as valid. These data, although derived from social security quarterly earnings reports and not from personnel records, are not independent of the data set utilized in the Wagoner et al. (1980) study. Both sets of data were

analyzed through the use of the NIOSH life-table program. The expected deaths generated in both studies are subject to the same influences introduced by the use of the same life-table program, and by the use of the same comparison rates (U.S. white male lung cancer rates). In addition, the extensive cooperation between Mancuso (at the University of Pittsburgh) and Wagoner (at NIOSH) in the search for causes of death in the respective cohorts for study, contributed to the inclusion of lung cancer deaths known to one but not the other in both studies. As mentioned previously, because of the use of the NIOSH life tables in the Mancuso study, the calculation of expected lung cancer deaths was on the low side (approximately 11%) because of the same artifact involving the calculation of lung cancer rates for which the Wagoner et al. (1980) study was criticized. Hence, these results should not be considered independent of the results of the Wagoner study.

Another problem with this cohort is the use of social security quarterly earnings reports to constitute a cohort of potentially exposed employees. These files, for the most part, are limited with respect to the data available. Only the full name, social security number, and amount paid into the system each quarter of any given year are provided, and only for covered employees. An examination of microfilm records of the reports maintained by the Social Security Administration shows that there is no possibility of determining from the reports what jobs these individuals performed for the companies, where their job stations were located, whether their jobs were on or off the premises, or whether they had actually been exposed to beryllium, or even precisely when during the three-month period they actually started work. And, of course, these records give no information on workers who were not covered by the Act. Furthermore, in the period prior to 1942, the social security system was in the process of being established, and tremendous logistic problems in setting up the system were being encountered during this time. Because the system was not fully functional until 1942, millions of employees throughout the country did not get social security numbers until after that date. Large numbers of employees refused to join the system because they considered it to be "welfare," and many more simply reported their social security numbers inaccurately if at all when applying for work. Thus, questions remain concerning the validity of this cohort.

Another difficulty with the Mancuso (1979) study, as with his earlier studies, is a lack of discussion of other exposures these workers may have received. The author observed that the main effect (lung cancer) occurred in

short-term employees more than 15 years after initial employment. These workers had an opportunity to be exposed to other potential carcinogens at jobs they may have held prior to or immediately following their short employment in the beryllium industry. This is a distinct possibility because the beryllium-manufacturing companies are located in or near heavily industrialized areas of Ohio (Cleveland, Toledo) and Pennsylvania (Reading). Roth and Associates (1983) report the presence of several industries in the Lorain, Ohio area in the period from 1942 to 1948 that conceivably could have provided an opportunity for short-term employees to receive exposure to potential carcinogens (Table 7-12).

TABLE 7-12. INDUSTRIES IN THE LORAIN AREA 1942-1948

Company	Operations	Approx. No. Employees
National Tube (now U.S. Steel)	Foundry, rolling, extruding, coke ovens	12,000
Thew Shovel	Foundry, machining, fabricating	2000
Lorain Products	Electrical conductors, fabricating, nonferrous foundry	500
American Crucible	Structural steel parts, machining, fabricating, foundry	200
Iron Ore Ship Dock	Unloading ore	?

Source: Roth and Associates (1983)

Another serious omission of the Mancuso (1979) study is the lack of a discussion of the effect of cigarette smoking on the target organ of interest, i.e. the lung. With respect to the question of smoking, it would appear likely that since there was considerable overlap between this study and the Wagoner study, it is probable that most of the lung cancer victims in the Pennsylvania cohort of the Mancuso study were smokers. Hence, it is possible that cigarette smoking contributed to the increased risk of lung cancer in the Pennsylvania cohort. No information was provided in the Ohio portion of the Mancuso study regarding the smoking influence, an exposure of considerable importance in lung cancer. The findings of significant excesses of lung cancer in both plants must be seen as limited because of the inadequate consideration of the confounding effects of these two likely exposures, the problem with the NIOSH

life-table programs, and the inadequate nature of social security quarterly earnings reports in defining an occupationally exposed cohort for study.

7.2.9 Mancuso (1980)

In the fourth update to his study of workers potentially exposed to beryllium in two beryllium-manufacturing facilities, Mancuso (1980) found statistically significant elevated risks of lung cancer in 3685 white males employed during the period from 1937 to 1948 and followed until the end of 1976, when contrasted with viscose rayon workers. The beryllium cohort, as mentioned earlier, was derived from quarterly earnings reports filed with the Social Security Administration by the two companies. The only new addition to this latest update was the introduction of a new comparison population, that of viscose rayon workers. The source or location of these workers, however, is not mentioned by the author, who states that the "viscose rayon cohort" was derived from one company's "complete" file of microfilmed employment data on employees first hired during the period from 1938 to 1948 and followed until 1976 (a period which began one year later than that of the beryllium cohort). The origin and description of this group of workers is inadequately discussed.

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

four or more years by the beryllium companies. No basis was given for choosing four years of total employment as the point at which short-term workers should be separated from long-term workers. In his earlier versions, the author utilized different durations of employment, i.e. five quarters (1 1/4 years) and five-year duration of employment categories.

An interesting omission from this study is any consideration of the effects of latency according to duration of employment. It seems unusual that a discussion of this topic was not included by Mancuso, since the major output of the NIOSH life-table program, which was utilized by Mancuso, is a set of tabulations by time since onset of employment. Lung cancers diagnosed within ten years of initial exposure probably were not a consequence of that exposure. Furthermore, the designation "duration of employment" is not necessarily uninterrupted continuous employment. In reality, what is meant is "total employment", that is periods of time when the employee was not exposed or not actually working. Layoffs and terminations, sickness, vacations, and leaves of absence between initial employment and final day of employment are not counted by the NIOSH life-table program in the category "duration of employment." Therefore, it is possible that included in the observed deaths are the deaths of individuals who had worked only a few days for the companies and who died from lung cancer 20 years later, as well as individuals who worked for the companies for several years continuously, but who died within five years of initial employment.

Additionally, the viscose rayon cohort appears to have been a somewhat younger population by age at hire than was the beryllium cohort (47.2% in the viscose rayon cohort were under age 25 when hired, compared to the beryllium cohort in which 38.4% were under age 25 when hired). Whether or not the author adjusted for age differences is questionable. Indeed, at the Peer Review Workshop on the Health Assessment Update for Beryllium (February, 1984) sponsored by the U.S. Environmental Protection Agency, an epidemiologist from NIOSH, Dr. Jean French, expressed concern that the age adjustment in Mancuso's comparison of expected mortality based on viscous rayon workers with that of actual mortality from Mancuso's beryllium cohort was "inadequate." Dr. French reported that NIOSH reanalyzed the data and found serious problems with Mancuso's analysis. Efforts to resolve this issue have not been successful through official NIOSH channels. Unsuccessful attempts to obtain the results of the analysis from NIOSH have made it difficult to determine the magnitude of impact of the required adjustment on risk estimates. Since the viscous rayon

cohort was younger than the beryllium cohort, the net impact of an adjustment would be to decrease the gap between observed lung cancer deaths based on the beryllium cohort and expected deaths based on the viscous rayon cohort.

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

As in the earlier studies by the same author, a further difficulty with this study is its lack of discussion of the confounding effects of smoking and its disregard of potential exposures received not only while working for the beryllium companies, but also in jobs prior and subsequent to employment in the beryllium industry. This represents a particular problem because a large majority of this cohort worked for less than one year. Because the towns in which the beryllium companies were located were considerably industrialized, work in these industries could potentially have produced exposures to other known or suspected carcinogens. As an example, one of the major employers in the Lorain, Ohio area in the period from 1942 to 1948 was the National Tube Company (now U.S. Steel), whose operations involved extensive exposure to coke ovens. Nothing is revealed in the study of the origin or makeup of the viscous rayon cohort. What is known about its location comes from the Wagoner et al. (1980) study in which the authors stated that Mancuso's viscous rayon cohort was located in the vicinity of the beryllium companies.

Furthermore, since both cohorts utilized the NIOSH life-table program, both suffer from the previously discussed 11-percent underestimation of expected lung cancer deaths.

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

7.2.10 Summary of Epidemiologic Studies

Although several studies claim a statistically significant excess risk of lung cancer in individuals exposed to beryllium, all of the studies cited have

deficiencies that limit any definitive conclusion that a true association exists. Support for a finding of an excess risk of lung cancer in beryllium-exposed persons consists of evidence from cohort mortality studies of two companies (Table 7-13) and one cohort mortality study of cases admitted to the Beryllium Case Registry. None of these studies can be said to be independent, since all are studies of basically the same groups of workers. Extensive cooperation existed between the authors of all of these studies, even to the extent of running all cohorts through a NIOSH computer-based life-table program known to produce an 11-percent underestimate of expected lung cancer deaths at the time. This problem has since been remedied. Furthermore, the authors could not adequately address the confounding effects of smoking or of exposures received during prior and subsequent employment in other non-beryllium industries in the area known to produce potential carcinogens (especially in beryllium workers with short-term employment). Problems in the design and conduct of the studies further weaken the strength of the findings. There appeared to be a tendency on the part of the authors to overemphasize the positive nature of their results and minimize the contribution of qualifying factors. A list of these problems is presented in Table 7-14. If the errors detailed in the preceding paragraphs were corrected and proper consideration given to addressing the problems described above, the finding of a significant excess risk would probably no longer be apparent, although the possibility, nevertheless, remains that a portion of the remaining excess lung cancer risk may be partially due to beryllium exposure. Thus, the CAG feels that the findings of these studies must be considered to be at least suggestive. The International Agency for Research on Cancer (IARC) has concluded that beryllium and its compounds should be classified as "limited" with respect to the human epidemiologic evidence of carcinogenicity. The CAG, however, regards the epidemiologic evidence of beryllium carcinogenicity in beryllium-exposed workers as inadequate.

7.3 QUANTITATIVE ESTIMATION

This quantitative section deals with estimation of the unit risk for beryllium as a potential carcinogen in air, and compares the potency of beryllium to other carcinogens that have been evaluated by the CAG. The unit risk for an air pollutant is defined as the incremental lifetime cancer risk to

TABLE 7-13. COMPARISON OF STUDY COHORTS AND SUBCOHORTS OF TWO BERYLLIUM COMPANIES

	Company where employed[a]	Source	Period of employment	Comparison population	Termination date of follow-up	Chief lung cancer results[b]
Bayliss et al. (1971)	KBI, BRUSH 6818 males	Personnel records	1942-1967	U.S. males	1967	Total 36 (O), 34.1 (E)
Bayliss and Lainhart (1972)	KBI only 3795 white males	Same as above	1942-1967	U.S. white males	1967	Total 25 (O), 23 (E) Latency 15 yrs + 14 (O), 13.3 (E)
Bayliss and Wagoner (1977)	KBI-Reading Facility only 3070 white males	Same as above	1942-1967	U.S. white males	1975	Total 46 (O), 33 (E) ($p < 0.05$) Latency 15 yrs + 37 (O), 24 (E) ($p < 0.05$)
Wagoner et al. (1980)	KBI-Reading Facility only 3055 white males	Same as above	1942-1967	U.S. white males	1975	Total 47 (O), 34.3 (E) ($p < 0.05$) Latency 15 yrs + 38 (O), 24.86 (E) ($p < 0.05$)
Mancuso and El-Attar (1969)	KBI, BRUSH 3685 white males	Social Security Quarterly Earnings Reports	1937-1948	Industrial Control (Unidentified)	1966	Equivocal

(continued on the following page)

TABLE 7-13. (continued)

	Company where employed[a]	Source	Period of employment	Comparison population	Termination date of follow-up	Chief lung cancer results[b]
Mancuso (1970)	KBI, BRUSH 3685 white males	Social Security Quarterly Earnings Reports	1937-1944 and 1945-1948	Internal Control	1966	Duration of employment (rate) ≥ 1 1/4 yrs 33.2/10^5 < 1 1/4 yrs 99.9/10^5 Prior respiratory disease only with 284.3/10^5 without 77.7/10^5
Mancuso (1979)	KBI-2044 BRUSH-1222 white males	Same	1942-1948	U.S. white males	BRUSH 1974 KBI 1975	Latency 15 yrs + only Ohio - 22 (O), 9.9 (E) ($p < 0.01$) Pennsylvania - 36 (O), 22 (E) ($p < 0.01$)
Mancuso (1980)	KBI 3685 white males	Same	1937-1948	Viscous rayon workers	1976	Mobility (deaths) Among departments 80 (O), 57.1 (E) ($p < 0.01$) Remained in same department 80 (O), 50.6 (E) ($p < 0.01$)

[a]KBI = Kawecki-Berylco Industries (Pennsylvania).

BRUSH = Brush Beryllium Co. (Ohio).

[b](O) = observed

(E) = expected

TABLE 7-14. PROBLEMS WITH BERYLLIUM COHORT STUDIES

Bayliss et al. (1971)	A. Loss of 2000 individuals because of insufficient data. B. No latency considerations. C. Combined study populations of several plants from two companies.
Bayliss and Lainhart (1972)	A. Includes clerical and administrative personnel with no exposure. B. No independent assessment plant employment files. C. Latency after 20 years not assessed.
Bayliss and Wagoner (1977) and Wagoner et al. (1980)	A. Cigarette smoking a possible confounder. B. Underestimate of expected lung cancer deaths in comparison population by 11 percent. C. Inclusion of 1 lung cancer victim who did not fit definition for inclusion. D. Loss of 295 individuals from study cohort. E. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso and El-Attar (1969)	A. Unidentified comparison population. B. Internal rates based on small numbers. C. Tremendous variability and impossible to test significance. D. No smoking consideration as possible confounder.
Mancuso (1970)	A. Internal rates based on small numbers. B. Inappropriate comparison (age group 15-24 left out of comparison). C. No consideration of smoking as a possible confounder. D. No consideration of latency. E. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1979)	A. Underestimate of expected lung cancer deaths in comparison population by 11 percent. B. No consideration of smoking as a possible confounder. C. Incomplete delineation of cohort from use of Social Security Quarterly Earnings reports. D. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1980)	A. No consideration of latent effects. B. Probable lack of age adjustment. C. No consideration of effects of smoking. D. No description of origin or makeup of comparison cohort except for age. E. Underestimate of expected lung cancer deaths in comparison population by 11 percent.

humans from daily exposure to a concentration of 1 $\mu g/m^3$ of the pollutant in air by inhalation.

The unit risk estimate for beryllium represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons, the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis.

At the present time, the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that a quantal response characteristic of mutagenesis is associated with a linear (at low doses) nonthreshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at high doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear (at low doses) nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g. radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g. the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the nonthreshold model, which is linear at low doses, has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing a plausible

upper limit for the risk, i.e. the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution and elimination of carcinogens, as well as species differences in target-site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans as compared to animals on a mg/surface area basis is virtually without experimental verification with respect to the carcinogenic response. Finally, genetic constitution, diet, living environment, activity patterns, and other cultural factors are quite varied among different human populations.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, for example, in setting regulatory priorities, evaluating the adequacy of technology-based controls, and so forth. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear-extrapolation model used here provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented in subsequent sections should not be regarded, therefore, as accurate representations of the true cancer risks, even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

7.3.1 Procedures for the Determination of Unit Risk

7.3.1.1 Low-Dose Extrapolation Model. Two dose-response models, which are derivatives of the theory of multistage carcinogenesis, are used to calculate the unit risk of beryllium on the basis of animal data. The selection of these

two models is dictated by the nature of the data available for quantitative risk assessment. The first model, a multistage model that allows for a time-dependent dose pattern, was developed by Crump and Howe (1984), and uses the theory of multistage carcinogenesis developed by Armitage and Doll (1961). The Armitage-Doll multistage model assumes that a cell is capable of generating a neoplasm when it has undergone k changes in a certain order. The rate, r_i, of the i^{th} change is assumed to be linearly related to D(t), the dose at age t, i.e. $r_i = a_i + b_i D(t)$, where a_i is the background rate, and b_i is the proportionality constant for the dose. It can be shown that the probability of cancer by age t is given by

$$P(t) = 1 - \exp[-H(t)]$$

where

$$H(t) = \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} \{[a_1 + b_1 D(u_1)] \cdots [(a_k + b_k D(u_k)]\}\, du_1 \cdots du_k$$

is the cumulative incidence rate by time t.

When H(t) or the risk of cancer is small, P(t) is approximately equal to H(t). When only one stage is dose-related, all proportionality constants are zero except for the proportionality constant for the dose-related stage.

This model will be applied to the data in Reeves and Deitch (1969) where the dose D(t) is constant for t in an interval $[S_1, S_2]$ and is zero elsewhere. Under this particular exposure pattern and the assumption that only a single stage is dose-related, the term H(t) can be written as the sum of two components $H_1(t)$ and $H_2(t)$ where $H_1(t) = a_1 \cdot a_2 \cdots a_k\, t^k/k!$ represents the background cumulative incidence and $H_2(t)$ is the incremental cumulative incidence due to exposure. Three special cases of H_2 which are often used to interpret a given set of data are given below.

$$H_2(t) = \begin{cases} 0 & t < s_1 \\ \dfrac{db_1(\pi a_i)}{k!\, a_1} \times (t - s_1)^k & s_1 \le t < s_2 \\ (t - s_1)^k - (t - s_2)^k & s_2 \le t \end{cases}$$

if the first stage is affected (r = 1),

$$H_2(t) = \begin{cases} 0 & t < s_1 \\ \dfrac{db_{k-1}(\pi a_i)}{k!\,a_{k-1}} \times \left[t^k - s_1^{k-1}[kt - (k-1)s_1] \right] & s_1 \le t < s_2 \\ s_2^{k-1}[kt - (k-1)s_2] - s_1^{k-1}[kt - (k-1)s_1] & s_2 \le t \end{cases}$$

if the penultimate stage is affected (r = k - 1), and

$$H_2(t) = \begin{cases} 0 & t < s_1 \\ \dfrac{db_k(\pi a_i)}{k!\,a_k} \times \left[t^k - s_1^k \right] & s_1 \le t < s_2 \\ s_2^k - s_1^k & s_2 \le t \end{cases}$$

if the last stage is affected (r = k).

A computer program, ADOLL1-83, has been developed by Crump and Howe (1984) to implement the computational aspect of the model. In this program, the model is generalized to include tumor induction time I by replacing the time factor t by t-I. The best-fit model is identified as the one that has the maximum likelihood among various models with different numbers of stages and the stage affected by the exposure.

The second model used to calculate the carcinogenic potency of beryllium is the one-hit model with zero background rate. This model is used because all the experiments, except that of Reeves and Deitch (1969), had only one data point and did not have a control group. The slope, b, of the one-hit model, P(d) = 1 - exp(-bxd), is calculated by the formula

$$b = [-\mathrm{Ln}(1-P)]/d$$

Since the background rate is zero, the least-square estimate b, as calculated above, is also a maximum-likelihood estimate.

7.3.1.2 Selection of Data. For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e. dose and tumor incidence) used in the model is the set where the incidence is significantly higher statistically than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A_m, is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

7.3.1.3 Calculation of Human Equivalent Dosages. Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species unless adequate evidence is presented to the contrary. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere,

the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e. during l_e), and

W = average weight of the experimental animal.

Then, the lifetime exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

7.3.1.3.1 Inhalation Exposure. Often it is necessary to convert given exposures into mg/day. When exposure is via inhalation, the calculation of dose can be considered for two cases where (1) the carcinogenic agent is either a completely water-soluble gas or an aerosol, and (2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of poorly water-soluble gases is expected to be proportional to the metabolic rate, which is proportional to the rate of oxygen consumption, itself a function of surface area. Only the case of aerosols will be considered here.

7.3.1.3.1.1 Case 1. Agents that are in the form of aerosols can reasonably be expected to be deposited proportionally to the breathing rate and deposition fraction. In this case the dosage in mg/day may be expressed as

$$m = I \times v \times de$$

where I = inhalation rate in m^3/day, v = mg/m^3 of the agent in air, and de = the deposition fraction.

If exposures are given in terms of ppm in air, the following calculation may be used:

$$1 \text{ ppm} = 0.041/\text{molecular weight } (mg/m^3)$$

This relationship is based on sea level barometric pressure and a temperature of 24°C. For other pressures and temperatures, an appropriate correction must be made. Clearance rates may also influence dosage, but cross-species comparisons are seldom available for making such adjustments.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB, 1974) that 25-g mice breathe 34.5 liters/day and 113-g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

Respiratory values for most other laboratory species are also reported in FASEB (1974). For humans, the value of 20 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977). The equivalent dose in $mg/W^{2/3}$ for these agents can be derived from the air intake data using an empirically derived factor for the air intake per kg per day, i = I/W. These are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

*From "Recommendation of the International Commission on Radiological Protection," page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

Therefore, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivde}{W^{2/3}} = \frac{iWvde}{W^{2/3}} = iW^{1/3}vde$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction deposited, de, is assumed to be the same for all species.

7.3.1.4 Calculation of the Unit Risk from Animal Studies. The risk associated with d $mg/kg^{2/3}/day$ is obtained from GLOBAL79, and for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. This value is estimated by finding the number of $mg/kg^{2/3}/day$ that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of $\mu g/m^3$ in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ $mg/kg^{2/3}/day$, and for case 2, d = 1, when $\mu g/m^3$ is the unit used to compute parameters in animal experiments.

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and to use mg/kg equivalents for the unit risk values.

7.3.1.4.1 Adjustments for Less Than Life Span Duration of Experiment. If the duration of experiment L_e is less than the natural life span of the test animal L, the slope q_1^*, or more generally the exponent g(d), is increased by multiplying by a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the second power of the age and often by a considerably higher power, as demonstrated by Doll (1971). Thus, it is expected that the cumulative tumor rate would increase by at least the third power of age. Using this fact, it is assumed that the slope q_1^*, or more generally the exponent g(d), would also increase by at least the third power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, it is expected that if the experiment had been

continued for the full life span L at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Daffer et al. (1980), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp [-f(t) \times g(d)]$$

7.3.1.5 Model for Estimation of Unit Risk Based on Human Data. If human epidemiologic studies and sufficiently valid exposure information are available for a compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor B_H. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study. An upper limit to the cancer incidence is calculated, assuming hypothetically that the true incidence is below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that permits extrapolation from high-exposure occupational studies to exposures at low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals as compared with the control group. The mathematical model employed for low-dose extrapolation assumes that for low exposures the lifetime probability of death from cancer, P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in units such as ppm. The factor B_H is the increased probability of cancer associated with each unit increase of x, the agent in air.

If it is assumed that R, the relative risk of cancer for exposed workers as compared to the general population, is independent of length of exposure or age at exposure, and depends only upon average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H x_1}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible exposure.

Substituting $P_0 = A + B_H (x_1)$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from epidemiologic studies. The value P_0 is derived by means of the life-table methodology from the age- and cause-specific death rates for the general population found in U.S. vital statistics tables.

7.3.2 Estimation of the Carcinogenic Risk of Beryllium

In extrapolating from animal data, the equivalent human dose may be influenced by a variety of factors. An important variable for inhalation studies is measurement (or estimation) of lung ventilation during exposure. In general, differences in metabolic rate for animals of different sizes are adjusted by variations in minute volume respiration rather than by lung volume per unit body weight. It has been shown by McMahon et al. (1977), for example, that minute volume respiration varies with the 0.66 power of body weight. On this basis, it could be concluded that ventilation is almost perfectly adjusted for variations in metabolic rate, and if effective concentrations of a toxic chemical

vary directly with metabolic rate, then equivalent concentrations could be considered the same in humans and experimental animals.

More commonly, however, dose conversions are carried out by using estimated values for inspiratory volumes per unit time in combination with metabolic rate conversion based on body weight to the two-thirds power. If the generally accepted value of 20 m^3/day is used for humans, the human equivalent concentration is decreased to slightly greater than one-third the value for rats. This occurs primarily because the equivalent concentrations for rats are based on respiratory levels measured for animals at rest. The human value, however, represents a daily minute volume based on normal 24-hour activity levels. While such a method of conversion is probably somewhat conservative, it is not unreasonable, since rodent species normally sleep and therefore respire less during the hours when exposure typically occurs.

The efficiency of deposition may also influence the equivalent human dose. For small particles, such as those used in the beryllium inhalation studies, the fraction deposited in the alveoli and smaller conducting airways would be predicted to be somewhat less in rats than in humans (Raabe et al., 1977; Lippman, 1977; Schlesinger, 1985). Within these studies, however, deposition varied greatly within species due to breathing patterns and experimental techniques. For most studies, the standard error of the means overlapped for humans and rats exposed to comparable particle sizes. Furthermore, McMahon et al. (1977) reported that for 0.75 μm diameter particles deposition percentages were independent of species for animals ranging in size from mice to dogs.

Due to the variability in deposition efficiency, an adjustment in dose at this time was not considered to be appropriate. Futhermore, even though deposition may be slightly more efficient in humans, any small increase in the human dose due to this factor is likely to be compensated for by the relatively large estimate of human ventilation in comparison with laboratory species.

Retention of particles can be an important factor for determining dose to the lung, since the degree of solubilization and absorption is related to residence time. Rhoads and Sanders (1985) reported a clearance half-time for beryllium in rats of 833 days. This is an exceptionally slow rate. Rats normally clear even quite insoluble particles much more rapidly. Since 833 days exceeds the expected lifetime of the rat, it is doubtful that clearance rate differences between rodents and humans will significantly influence absorbed dose.

In calculating exposure levels, a separation of total dose between the fraction deposited in the tracheobronchial region and the alveolar region could be considered. The Science Advisory Board suggested such an approach in comments dated July 20, 1985. Such a separation would be of interest because most human cases of lung cancer originate in the conducting airways. While total deposition in this region is much less than in the alveoli, the surface area is also less, so dose per unit of surface area may be as great or even greater than in alveolar regions, especially at airway junctions where impaction occurs.

Oberdoerster (personal communication) calculated an equivalent human concentration in both alveolar and tracheobronchial regions using the data of Reeves and Deitch (1969) as follows:

$$Ch = Cr \frac{(Ir/Ih)\ (Fr/Fl)}{(Wr/Wh)^{2/3}}$$

where Ch = equivalent human concentration, Cr = exposure concentration for the rat, I = the volume of air inspired per day (Ir = 0.223 m^3/day for rats and Ih = 20 m^3/day for humans), W = body weight (Wr = 0.35 kg for rats and Wh = 70 kg for humans), and F = the fraction of inhaled particles deposited in the respiratory tract. For the tracheobronchial region, Fr = 0.01 for rats and Fh = 0.02 for humans, and for the alveolar region, Fr = 0.1 for rats and Fh = 0.2 for humans.

For a concentration of 35 $\mu g/m^3$ in the rat studies, the human equivalent concentration was calculated to equal 6.7 $\mu g/m^3$ in both the alveolar and the tracheobronchial regions. The values were identical because the ratios of relative deposition efficiency between rats and humans was considered to be the same for both regions of the lungs.

This method did not take into account possible differential deposition at airway junctions, which are considered likely areas for the origin of many human lung cancers. This method also failed to account for differential absorption efficiencies based on much more rapid clearance of deposited particles from the conducting airways (less than one day) than from alveolar regions. Unfortunately, little data are available to accurately estimate differential absorption between alveoli and conducting airways.

Human equivalent concentrations using Oberdoerster's calculations differ slightly from those appearing in this document for two reasons: lung deposition in humans was assumed to be twice that of the rat, and no adjustment was made for less than 18-months exposure duration.

Finally, consideration should be given to the appropriateness of a surface area versus a body weight correction of inhaled dose. Dose corrections compensating for metabolic rate differences are largely based on the belief that a smaller animal, with a correspondingly more rapid metabolic rate, will inactivate or eliminate potentially harmful xenobiotics more rapidly.

Several lines of evidence indicate that beryllium may be sequestered in the cells lining the alveoli and bronchioles and is inactivated or eliminated slowly, if at all. For example, as mentioned earlier, beryllium oxide is cleared very slowly. Rhoads and Sanders (1985) attributed this to low solubility, but even beryllium compounds, such as beryllium sulfate, which is considered to be quite soluble, are cleared slowly (Reeves and Vorwald, 1967). Moreover, compounds such as titanium oxide, which are known to be highly insoluble, are cleared with half times of only two to three months (Ferin and Leach, 1977). The very slow rate of clearance of beryllium suggests that most of it enters the intracellular compartment following deposition. This possibility is supported by studies of Wagner et al. (1969), in which it was shown that less than one percent of the deposited dose was transferred to the liver, kidneys, or bone. Since lung cancer was induced in this study, the solubilized beryllium most likely remained in the lung cells rather than moving into the blood with transport to other organs.

According to Vorwald et al. (1966), inhaled beryllium aerosols are precipitated by lung fluids, but then hydrolysis results in a supply of beryllium ions that enter the cell and react with macromolecules, possibly DNA and RNA. Vorwald and Reeves (1959) found that 85 percent of subcellular beryllium sedimented in the nuclear fraction. Any conclusions were limited, since the actual localization of beryllium could not be shown by biochemical means. Firket (1953), however, was able to identify beryllium histochemically in the nucleolus, an organelle made up of macromolecules including RNA. If beryllium reacts with macromolecules and no mechanism is available for elimination or deactivation, then toxic dose levels are not likely to correlate well with metabolic rate.

Although the data suggest that beryllium is bound intracellularly and is eliminated very slowly, the evidence is not sufficiently conclusive to show that a dose adjustment based on metabolic rate is incorrect. Moreover, Vorwald and Reeves (1959) reported that clearance of beryllium was initially quite rapid following cessation of exposure to beryllium sulfate, with the remainder cleared at a much slower rate. If the slowly cleared fraction is bound to macromolecules, then the size of this fraction would be limited by potential reactive sites. Little is known of possible differences between humans and laboratory animals in this respect.

The direct experimental evidence available to compare effective dose with body size, or to determine if the rat is uniquely susceptible to the carcinogenic effects of beryllium, is quite limited. While no definitive positive results are available for hamsters, Wagner et al. (1969) reported atypical proliferations in animals of this species exposed to beryl ore at beryllium levels of 620 $\mu g/m^3$, a dose producing tumors in 18 of 19 rats. The authors would have considered these proliferations to be broncho-alveolar tumors except for their size. It is quite possible that these proliferations would have progressed to tumors if the hamsters had a longer life span. Other investigators, such as Dontenwill et al. (1973), reported a progression of effects in hamsters' lungs from hyperplasia through metaplasia, anaplasia, and leucoplakia, but not to overt cancer, following exposure to a known carcinogen, cigarette smoke. They also suggested that the life span of the hamster may be too short to allow full development of lung cancer.

Although statistically significant positive responses were not seen in guinea pigs, Schepers (1971) reported the occurrence of lung tumors in 2 of 20 animals exposed to beryllium sulfate and in 1 of 30 males and 1 of 20 females exposed 12 months to beryllium oxide. Since lung tumors are extremely rare in guinea pigs, this response is suggestive even if exposure conditions were not well described and control values were not reported.

The only species other than rats in which a clear-cut response occurred was the rhesus monkey. In these studies, reported by Vorwald et al. (1966) and Vorwald (1968), the mean beryllium concentration was 38.8 $\mu g/m^3$. The monkeys were exposed an average of 15 hours a week, compared with 30 to 35 hours a week during most of the rat studies. If the exposure duration is adjusted to be comparable to rats, the monkeys could have been exposed to about 15 $\mu g/m^3$ of beryllium. Eight of 11 monkeys (76%) in this study developed tumors. At 35 $\mu g/m^3$,

the response in rats to soluble beryllium compounds was generally 90 percent or more, while in one study conducted at 2.8 $\mu g/m^3$ beryllium, 62 percent responded positively. Based on this limited evidence, monkeys appear to be about as sensitive as rats.

While data on hamsters, guinea pigs, and monkeys are individually weak, taken collectively the data suggest that the rat is not uniquely sensitive to beryllium. In fact, rhesus monkeys, much closer relatives of man, appear to be as sensitive as rats. The very limited data for monkeys also indicate that, since a comparable concentration results in a similar response to that of rats, a surface area correction for dose remains plausible.

7.3.2.1 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Animal Data. Only the data from inhalation studies are used for risk assessment because that route of administration is the exposure route of interest to humans. Although there are many animal studies showing carcinogenic effects of beryllium by inhalation, the data that can be used for estimating the carcinogenic risks associated with beryllium are very limited. In order to provide some comparison among species, potency values were estimated for guinea pigs and rhesus monkeys, as well as for rats, even though the studies using the former two species were poorly documented and, in the case of guinea pigs, only suggestive of an effect. Except for Reeves and Deitch (1969), the studies were conducted at single dose levels and/or did not include control groups. In Reeves and Deitch (1969), animals were exposed to nine different dose patterns, varying in the duration of exposure and the time at which exposure was begun and terminated. The data from Reeves and Deitch (1969) and nine other studies that had only single dose levels are used herein to calculate the carcinogenic potency of beryllium. For the Reeves and Deitch data, the multistage model with time-dependent dose patterns is used as the low-dose extrapolation model. The data and the calculations are presented in the Appendix. For the studies with single dose levels, the one-hit model, as described in section 7.3.1.1, is used as the low-dose extrapolation model. The data for the nine studies with single dose levels and potency estimates on the basis of all ten of the data sets are presented in Table 7-15. Both body weight and surface area corrections have been used to arrive at an equivalent human dose.

In all of these calculations, the equivalent concentrations are arrived at by the following procedure, using ventilatory values arrived at as described in section 7.3.1.3.1.1. For an experimental exposure concentration of 1 $\mu g/m^3$, where 0.224 m^3/day is assumed to be the volumetric breathing rate for a rat

TABLE 7-15. BERYLLIUM DOSE-RESPONSE FROM TEN INHALATION STUDIES ON ANIMALS AND THE CORRESPONDING POTENCY (SLOPE) ESTIMATIONS

Investigator	Beryllium compound	Mean beryllium concentration exposure pattern	Standardized experimental concentration[a] ($\mu g/m^3$)	Pulmonary tumor incidence rate	Surface area correction	Human equivalent concentration ($\mu g/Be/m^3$)	Maximum likelihood estimate slope[b] $(\mu g/m^3)^{-1}$
			RATS				
Vorwald (1953)	$BeSO_4$	33 $\mu g/Be/m^3$ 35 hr/wk for 13 months	5.0	4/8	+	1.9	3.7×10^{-1}
					-	11.2	6.3×10^{-2}
Schepers et al. (1957)	$BeSO_4$	33.5 $\mu g/Be/m^3$ 35 hr/wk for 7.5 months	2.9	58/136	+	1.1	5.0×10^{-1}
					-	6.5	8.6×10^{-2}
Schepers (1961)	$BeHPO_4$	227 $\mu g/Be/m^3$ 35 hr/wk for 6.5 months	17.1	7/40	+	6.5	3.0×10^{-1}
					-	39.6	5.0×10^{-3}
Schepers (1961)	BeF_2	9 $\mu g/Be/m^3$ 35 hr/wk for 10.5 months	1.1	11/200	+	0.42	1.4×10^{-1}
					-	2.5	2.4×10^{-2}
Vorwald et al. (1966)	$BeSO_4$	2.8 $\mu g/Be/m^3$ 35 hr/wk for 18 months	0.58	13/21	+	0.22	4.3×10^{0}
					-	1.30	7.4×10^{-1}
Reeves and Deitch (1969)	$BeSO_4$	35.7 $\mu g/Be/m^3$ 35 hr/wk for 18 months	7.4	13/15	+	2.8	7.1×10^{-1}
					-	16.6	1.2×10^{-1}

(continued on the following page)

TABLE 7-15. (continued)

Investigator	Beryllium compound	Mean beryllium concentration exposure pattern	Standardized experimental concentration[a] ($\mu g/m^3$)	Pulmonary tumor incidence rate	Surface area correction	Human equivalent concentration ($\mu g/Be/m^3$)	Maximum likelihood estimate slope[b] $(\mu g/m^3)^{-1}$
Wagner et al. (1969)	beryl ore	620 $\mu g/Be/m^3$ intermittently for 17 months	585.6	9/19	+	223.4	2.9×10^{-3}
					-	1306.4	4.9×10^{-4}
Reeves and Deitch (1969)	$BeSO_4$	35.7 $\mu g/Be/m^3$ 35 hr/week for varying durations[c]			+		8.1×10^{-1}
					-		1.4×10^{-1}
			GUINEA PIGS				
Schepers (1971)	$BeSO_4$	36 $\mu g/Be/m^3$ 35 hr/wk for 12 months	5.1	2/20	+	1.7	6.5×10^{-2}
					-	8.8	1.2×10^{-2}
			RHESUS MONKEYS				
Vorwald (1968)	$BeSO_4$[d]	38.8 $\mu g/Be/m^3$ 15 hr/wk for 3 years	0.69	8/11	+	0.36	3.6×10^{0}
					-	1.04	1.2×10^{0}

[a]Standardized experimental dose is calculated by d x (h/168) x (6/18) where d is the mean experimental concentration, h is the number of hours exposed per week (168 hours), and L is the number of months exposed.

[b]Estimated by assuming that the control response is zero.

[c]See appendix for details.

[d]A life span of 15 years is assumed.

weighing 0.35 kg, and 20 m^3/day is assumed for a 70-kg man, the human equivalent concentration ($\mu g/m^3$) satisfies the equation

$$C = (0.244/20)\ m^3/day \times (70/0.35)^{2/3}\ kg$$

or C = 0.38 $\mu g/m^3$ assuming a surface area correction. For potency estimates not assuming a body weight correction, the human equivalent concentration satisfies the equation

$$C = (0.224/20)\ m^3/day \times (70/0.35)\ kg$$

or C = 2.24 $\mu g/m^3$. Therefore, the human equivalent concentration in $\mu g/m^3$ is obtained by multiplying the experimental dose by either 0.38 if a surface area correction is used, or 2.24 if corrected only for body weight.

A quantitative assessment of risk can also be carried out using guinea pigs and rhesus monkeys. For a 466-g guinea pig with a reported daily breathing volume of 0.23 m^3 (Handbook of Biological Data, 1971), using a surface area correction, the human equivalent concentration satisfies the equation

$$C = (0.23/20)\ m^3/day \times (70/0.466)^{2/3}\ kg = 0.32\ \mu g/m^3$$

If only a body weight correction is made, the human equivalent concentration satisfies the equation

$$C = (0.23/20)\ m^3/day \times (70/0.466)\ kg = 1.73\ \mu g/m^3$$

For a 2.68-kg rhesus monkey with a reported daily breathing volume of 1.24 m^3/day (Handbook of Biological Data, 1971), using a surface area correction, the equivalent concentration satisfies the equation

$$C = (1.24/20)\ m^3/day \times (70/2.68)^{2/3}\ kg = 0.55\ \mu g/m^3$$

If only a body weight correction is made, the human equivalent concentration satisfies the equation

$$C = (1.24/20)\ m^3/day \times (70/2.68)\ kg = 1.61\ \mu g/m^3$$

The last column of Table 7-15 represents the carcinogenic potency of beryllium as calculated from each of the inhalation studies. The maximum likelihood slope estimates range from 4.9×10^{-4} to 4.3. The magnitude of the potency appears to depend upon the form of the beryllium used in the experiment. Beryl ore is the least potent compound among the four compounds studied, while beryllium sulfate ($BeSO_4$) is the most potent. Using a surface area correction, four of the five rat studies on beryllium sulfate have potency values that approximate $0.5/(\mu g/m^3)$. The carcinogenic potency of beryllium sulfate calculated from the rhesus monkey study is $3.6/(\mu g/m^3)$, which approximates the largest value calculated using rats. Using guinea pigs, the potency is about one order of magnitude less than that obtained from the rat studies in which beryllium sulfate was used.

7.3.2.2 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Human Data. Given the need to estimate the cancer risk of beryllium and the uncertainty inherent in the use of animal data, it is desirable to use the available human data in some way to estimate the carcinogenic potency of beryllium. Data from Wagoner et al. (1980) are considered appropriate for this purpose. This study is selected because the cohort consisted of beryllium workers employed prior to 1949, when controls on beryllium in the workplace began. The workers' exposures to beryllium before 1949 were very high. A 1947 study reviewed by NIOSH (1972) reported beryllium concentrations in a beryllium extraction plant in Pennsylvania of up to 8840 $\mu g/m^3$. In more than 50 percent of the determinations reviewed, beryllium concentrations were in excess of 100 $\mu g/m^3$. According to NIOSH (1972), the levels of environmental exposure to beryllium in the workplace were markedly reduced after control measures were instituted in 1949. In one Ohio extraction plant, the beryllium exposure levels were recorded at 2 $\mu g/m^3$ or less during almost all of a seven-year period. The information available about beryllium exposure levels in the workplace and the excess cancer risk observed among workers employed in beryllium production plants is summarized below.

7.3.2.2.1 Information on Exposure Levels. The beryllium plant studied by Wagoner et al. (1980) was a major beryllium extraction, processing, and fabrication facility located in Pennsylvania. The workplace concentrations of beryllium in various beryllium production plants in Pennsylvania and Ohio were found to be comparable (Eisenbud and Lisson, 1983). Based on the NIOSH (1972)

report described previously, the lower-bound estimate of the median exposure concentration exceeded 100 $\mu g/m^3$, since more than 50 percent of the determinations exceeded that level. According to Eisenbud and Lisson (1983), it is likely that this value (100 $\mu g/m^3$) is an underestimation of the actual median exposure level in the workplace, and thus should be considered to be a lower-bound estimate of median level. Eisenbud and Lisson (1983) stated "...published studies of conditions in the Pennsylvania production plant indicate that the levels of exposure prior to installation of dust controls were comparable to conditions in the Ohio plants. Concentrations in excess of 1000 $\mu g/m^3$ were commonly found in all three extraction plants during the late 1940s." On the other hand, it is unlikely that the median level could greatly exceed 1000 $\mu g/m^3$, since at that level almost all of the exposed workers developed acute respiratory diseases (Eisenbud, 1955). Thus, it is reasonable to assume that the median level of beryllium concentration did not exceed 1000 $\mu g/m^3$. In the risk calculation, the median level of beryllium concentration is assumed to range from 100 to 1000 $\mu g/m^3$. This is the narrowest range for median exposure that could be obtained on the basis of available information.

7.3.2.2.2 Information on Excess Risk. Wagoner et al. (1980) conducted a cohort study of 3055 white males who were initially employed in a plant in Pennsylvania from 1942 to 1967, and who were followed to December 30, 1975. Of particular interest to the present risk assessment is a subcohort of workers who were initially employed prior to 1950, and who were followed for at least 25 years from the date of initial employment. The elevation of lung cancer mortality was originally shown by Wagoner et al. (1980) to be statistically significant ($p \leq 0.05$). However, the significant elevation of lung cancer mortality disappears after making an adjustment for differences in cigarette smoking between cohort and control populations. For the subcohort of workers who were followed at least 25 years since their initial employment, the smoking-adjusted expected lung cancer deaths are found to range from 13.91 to 14.67, in comparison with the 20 observed lung cancer deaths. The relative risk estimates are 20/13.91 = 1.44 and 20/14.67 = 1.36, which are not statistically significant ($p > 0.05$). Although the epidemiologic study did not show carcinogenic effects, the data can be used to calculate an upper limit of lung cancer risk.

Assuming that the observed cases follow a Poisson distribution and the expected value is constant, the 95 percent confidence limits for the two relative risk estimates, 1.36 and 1.44, are respectively 1.98 and 2.09. The

values 1.98 and 2.09 are used to estimate the lifetime lung cancer risk due to 1 $\mu g/m^3$ of beryllium in air.

7.3.2.2.3 Risk Calculation on the Basis of Human Data. To calculate the lifetime cancer risk on the basis of information described previously, the median level of beryllium exposure must be converted to the "effective" dose, through multiplying by a factor of (8/24) x (240/365) x (f/L), to reflect that workers were exposed to beryllium 8 hours/day, 240 days/year, for f years out of a period of L years at risk (i.e. from the onset of employment to the termination of follow-up). Two values of f/L are used in the calculation: f/L = 1 and f/L = 0.25. The use of f/L = 1 would avoid overestimating the risk (but could underestimate the risk) if the observation by Reeves and Deitch (1969)--that tumor yield depends not on length of exposure but on age at exposure--is valid. Table 7-16 presents a range of cancer potency estimates calculated under various assumptions about relative risk estimates and level of exposures. The upper-bound estimate of the cancer risk associated with 1 $\mu g/m^3$ of beryllium ranges from 1.6×10^{-4} to 7.2×10^{-3}, with a geometric mean of 2.4×10^{-3}.

7.3.2.3 Risk Due to Exposure to 1 $\mu g/m^3$ of Beryllium in Air. The positive tumorigenic response in rhesus monkeys, along with suggestive responses in guinea pigs and hamsters, indicates that the rat is not uniquely sensitive to the carcinogenic effects of beryllium. The responsiveness of the rhesus monkey, a close relative of man, also suggests that it is unlikely that the humans would be insensitive to beryllium under similar exposure conditions, despite the uncertain response in the workplace environment. The most likely reason for the large difference in potency estimates between animals and humans relates to the form of beryllium present during exposure. All of the animal potency estimates derived from exposure to beryllium sulfate were much greater than the estimates derived from human exposures to forms of beryllium present in the workplace. Beryllium phosphate was less potent but still gave a greater potency estimate than that derived from human exposure. Only beryl ore resulted in a potency estimate in the same range as those for humans.

Humans are generally exposed to different forms of beryllium than those used in most of the animal inhalation experiments. In mining operations the primary forms of beryllium present are beryl, which has a low potency in animals, and bertrandite, which failed to induce tumors in animals despite exposure to high concentrations. In the extraction process, the primary product is beryllium oxide, which is then reduced to the metallic form. In operations

TABLE 7-16. UPPER-BOUND CANCER POTENCY ESTIMATES CALCULATED UNDER VARIOUS ASSUMPTIONS

Beryllium concentration in workplace ($\mu g/m^3$)	f/L	"Effective" dose[a] ($\mu g/m^3$)	95 percent upper-bound estimate of relative risk	Cancer potency[b] $(\mu g/m^3)^{-1}$
100	1	21.92	1.98	1.61×10^{-3}
			2.09	1.79×10^{-3}
	0.25	5.48	1.98	6.44×10^{-3}
			2.09	7.16×10^{-3}
1,000	1	219.18	1.98	1.61×10^{-4}
			2.09	1.79×10^{-4}
	0.25	54.79	1.98	6.44×10^{-4}
			2.09	7.16×10^{-4}

[a]"Effective" dose is calculated by multiplying the beryllium concentration in the workplace by the factor (8/24) x (240/365) x (f/L).

[b]For a given "effective" dose d and a relative risk R, the carcinogenic potency is calculated by the formula B = (R-1) x 0.036/d, where 0.036 is the estimated lung cancer mortality rate in the U.S. population.

such as melting, pouring, or welding of beryllium, fumes consisting of fine particles of beryllium oxide are produced by condensation from the vapor phase. Other sources of workplace contamination result from metallic dusts generated by a variety of operations such as crushing, grinding, or cutting of beryllium-containing material. For further details regarding industrial processing of beryllium, refer to Tepper et al. (1961). Beryllium is also found in the ambient air as a trace metal component of fly ash emitted from coal-burning electric power plants. While other forms of beryllium are undoubtedly present, those described are expected to be present in greatest concentrations.

All of the above described forms of beryllium are likely to have a much lower carcinogenic potency than beryllium fluoride or sulfate, based on differences in solubility. The beryllium ores have already been shown to be much less potent than beryllium sulfate. When instilled intratracheally into rats, beryllium oxide calcined at 1100°C or 1600°C is less soluble and much less potent than beryllium oxide calcined at 500°C (Spencer et al., 1968). According

to Tepper et al. (1961), temperatures during the formation of beryllium oxide in the extraction process are near 1600°C, thus favoring the formation of a relatively insoluble form. Beryllium is present in fly ash as a trace metal (Fisher et al., 1980). Since it is bound to silicates, its bioavailability is quite low. Even very high concentrations of fly ash failed to induce lung tumors in experimental animals (Wehner, 1981).

If one adopts the most conservative approach, the upper-bound potency estimate of $4.3/(\mu g/m^3)$ would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of data observed in an experiment in which the level of exposure was very similar to the occupational exposure. Thus, the high potency estimate is not simply due to the use of a particular extrapolation model. The use of such a potency estimate would overestimate the human risk and is not consistent with the human experience in the beryllium industry. Therefore, the CAG recommends that the estimate of $2.4 \times 10^{-3}/(\mu g/m^3)$ be used as the carcinogenic potency of beryllium. This value is the geometric mean of eight potency estimates calculated on the basis of human data under various assumptions. On this basis, the incremental risk associated with 1 $\mu g/m^3$ of beryllium in air is estimated to be 2.4×10^{-3}. This estimate could be considered to be an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation and the 95 percent upper confidence limits of the relative risks are used in the calculations.

7.3.3 Comparison of Potency With Other Compounds

One of the uses of quantitative potency estimates is to compare the relative potencies of carcinogens. Figure 7-2 is a histogram representing the frequency distribution of potency indices for 55 suspect carcinogens evaluated by the CAG. The actual data summarized by the histogram are presented in Table 7-17. The potency index used herein was derived from the carcinogenic potency of the compound and is expressed in terms of $(mmol/kg/day)^{-1}$. Where no human data were available, animal oral studies were used in preference to animal inhalation studies, since oral studies have constituted the majority of animal studies.

To calculate the potency index, it is necessary to convert the potency estimate $2.4 \times 10^{-3}/(\mu g/m^3)$ into 8.4/(mg/kg/day), a potency estimate in a different dose unit. The new potency estimate, 8.4/(mg/kg/day), is obtained by

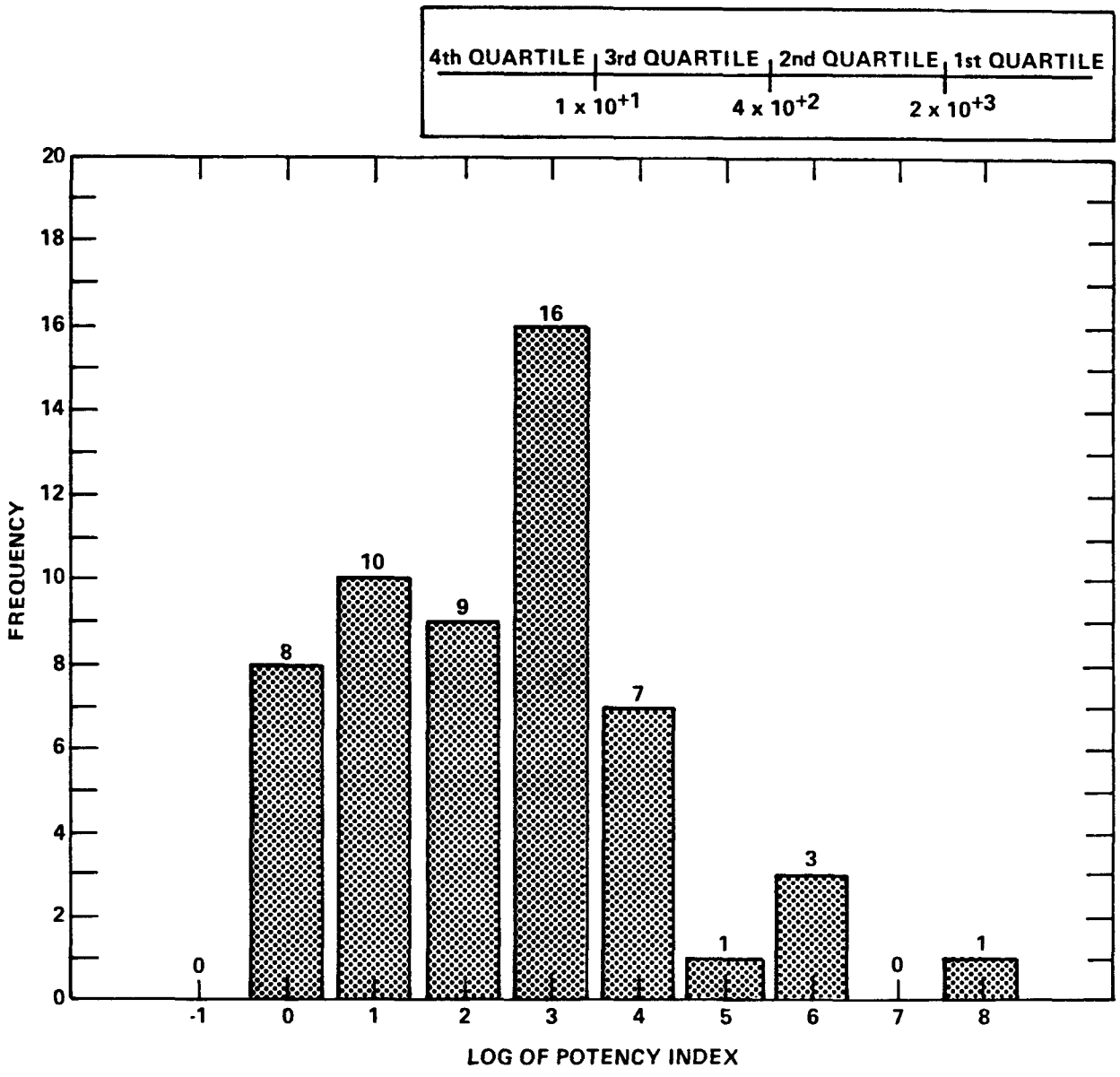

Figure 7-2. Histogram representing the frequency distribution of the potency indices of 55 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 7-17. RELATIVE CARCINOGENIC POTENCIES AMONG 55 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS

Compound	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
Acrylonitrile	107-13-1	L	S	2A	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	1162-65-8	L	S	2A	2900	312.3	$9x10^{+5}$	+6
Aldrin	309-00-2	I	L	3	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	107-05-1				$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	7440-38-2	S	I	1	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	50-32-8	I	S	2B	11.5	252.3	$3x10^{+3}$	+3
Benzene	71-43-2	S	S	1	$2.9x10^{-2}$(W)	78	$2x10^{0}$	+0
Benzidene	92-87-5	S	S	1	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	7440-41-7	L	S	2A	8.4(W)	9	$8x10^{+1}$	+2
1,3-Butadiene	106-99-0	I	S	2B	1.8(I)	54.1	$1x10^{+2}$	+2
Cadmium	7440-43-9	L	S	2A	6.1(W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	56-23-5	I	S	2B	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	57-74-9	I	L	3	1.61	409.8	$7x10^{+2}$	+3
Chlorinated ethanes								
1,2-Dichloroethane	107-06-2	I	S	2B	$9.1x10^{-2}$	98.9	$9x10^{0}$	+1
hexachloroethane	67-72-1	I	L	3	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,2,2-Tetrachloroethane	79-34-5	I	L	3	0.20	167.9	$3x10^{+1}$	+1
1,1,2-Trichloroethane	79-00-5	I	L	3	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1

(continued on the following page)

TABLE 7-17. (continued)

Compound	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
Chloroform	67-66-3	I	S	2B	$8.1x10^{-2}$	119.4	$1x10^{+1}$	+1
Chromium VI	7440-47-3	S	S	1	41(W)	100	$4x10^{+3}$	+4
DDT	50-29-3	I	S	2B	0.34	354.5	$1x10^{+2}$	+2
Dichlorobenzidine	91-94-1	I	S	2B	1.69	253.1	$4x10^{+2}$	+3
1,1-Dichloroethylene (Vinylidene chloride)	75-35-4	I	L	3	1.16(I)	97	$1x10^{+2}$	+2
Dichloromethane (Methylene chloride)	75-09-2	I	S	2B	$1.4x10^{-2}$(I)	84.9	$1x10^{0}$	0
Dieldrin	60-57-1	I	S	2B	30.4	380.9	$1x10^{+4}$	+4
2,4-Dinitrotoluene	121-14-2	I	S	2B	0.31	182	$6x10^{+1}$	+2
Diphenylhydrazine	122-66-7	I	S	2B	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	106-89-8	I	S	2B	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	111-44-4	I	S	2B	1.14	143	$2x10^{+2}$	+2
Bis(chloromethyl)ether	542-88-1	S	S	1	9300(I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	106-93-4	I	S	2B	41	187.9	$8x10^{+3}$	+4
Ethylene oxide	75-21-8	L	S	2A	$3.5x10^{-1}$(I)	44.1	$2x10^{+1}$	+1
Heptachlor	76-44-8	I	S	2B	3.37	373.3	$1x10^{+3}$	+3
Hexachlorobenzene	118-74-1	I	S	2B	1.67	284.4	$5x10^{+2}$	+3

(continued on the following page)

TABLE 7-17. (continued)

Compound	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
Hexachlorobutadiene	87-68-3	I	L	3	7.75×10^{-2}	261	$2 \times 10^{+1}$	+1
Hexachlorocyclohexane								
technical grade					4.75	290.9	$1 \times 10^{+3}$	+3
alpha isomer	319-84-6	I	S	2B	11.12	290.9	$3 \times 10^{+3}$	+3
beta isomer	319-85-7	I	L	3	1.84	290.9	$5 \times 10^{+2}$	+3
gamma isomer	58-89-9	I	L	3	1.33	290.9	$4 \times 10^{+2}$	+3
Hexachlorodibenzodioxin	34465-46-8	I	S	2B	$6.2 \times 10^{+3}$	391	$2 \times 10^{+6}$	+6
Nickel refinery dust		S	S	1	1.05(W)	240.2	$2.5 \times 10^{+2}$	+2
Nickel subsulfide	0120-35-722	S	S	1	2.1(W)	240.2	$5.0 \times 10^{+2}$	+3
Nitrosamines								
Dimethylnitrosamine	62-75-9	I	S	2B	25.9(not by q_1^*)	74.1	$2 \times 10^{+3}$	+3
Diethylnitrosamine	55-18-5	I	S	2B	43.5(not by q_1^*)	102.1	$4 \times 10^{+3}$	+4
Dibutylnitrosamine	924-16-3	I	S	2B	5.43	158.2	$9 \times 10^{+2}$	+3
N-nitrosopyrrolidine	930-55-2	I	S	2B	2.13	100.2	$2 \times 10^{+2}$	+2
N-nitroso-N-ethylurea	759-73-9	I	S	2B	32.9	117.1	$4 \times 10^{+3}$	+4
N-nitroso-N-methylurea	684-93-5	I	S	2B	302.6	103.1	$3 \times 10^{+4}$	+4
N-nitroso-diphenylamine	86-30-6	I	S	2B	4.92×10^{-3}	198	1×10^{0}	0
PCBs	1336-36-3	I	S	2B	4.34	324	$1 \times 10^{+3}$	+3
Phenols								
2,4,6-Trichlorophenol	88-06-2	I	S	2B	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	I	S	2B	$1.56 \times 10^{+5}$	322	$5 \times 10^{+7}$	+8

(continued on the following page)

TABLE 7-17. (continued)

Compound	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
Tetrachloroethylene	127-18-4	I	L	3	5.1×10^{-2}	165.8	8×10^{0}	+1
Toxaphene	8001-35-2	I	S	2B	1.13	414	$5 \times 10^{+2}$	+3
Trichloroethylene	79-01-6	I	L/S	3/2B	1.1×10^{-2}	131.4	1×10^{0}	0
Vinyl chloride	75-01-4	S	S	1	1.75×10^{-2}(I)	62.5	1×10^{0}	0

[a]S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

[b]Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear nonthreshold model. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available. The slope value is an upper bound in the sense that the true value (which is unknown) is not likely to exceed the upper bound and may be much lower, with a lower bound approaching zero. Thus, the use of the slope estimate in risk evaluations requires an appreciation for the implication of the upper bound concept as well as the "weight of evidence" for the likelihood that the substance is a human carcinogen.

[c]The potency index is a rounded-off slope in $(mmol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(m/kg/day)^{-1}$ by the molecular weight of the compound.

dividing $2.4 \times 10^{-3}/(\mu g/m^3)$ by a factor of $(1\ \mu g/m^3) \times (20\ m^3/day)/70\ kg = 2.86 \times 10^{-4}$ mg/kg/day, under the assumption that the volumetric air intake for a 70-kg person is 20 m^3/day. The potency index for beryllium is $8 \times 10^{+1}$, calculated by multiplying the potency estimate, 8.4/(mg/kg/day), and the molecular weight of beryllium (9). This calculation places the relative potency of beryllium in the lower part of the third quartile of the 55 suspect carcinogens evaluated by the CAG.

The ranking of relative potency indices is subject to the uncertainties involved in comparing a number of potency estimates for different chemicals, based on varying routes of exposure in different species, by means of data from studies whose quality varies widely. All of the indices presented are based on estimates of low-dose risk, using linear extrapolation from the observational range. These indices may not be appropriate for the comparison of potencies if linearity does not exist at the low-dose range, or if comparison is to be made at the high-dose range. If the latter is the case, then an index other than the one calculated above may be more appropriate.

7.3.4 Summary of Quantitative Assessment

Both animal and human data have been used to calculate the carcinogenic potency of beryllium. Many of the animal studies conducted on beryllium are not well documented, were conducted at single dose levels, and in some cases did not utilize control groups. Nevertheless, because positive effects were seen in multiple species, at multiple sites, and often at very low doses, these studies collectively provide sufficient evidence for carcinogenicity. In the present report, data from ten animal inhalation studies (using rats, guinea pigs, or rhesus monkeys) have been used to calculate the upper bounds for the potency of beryllium. Both surface area and body weight corrections were used in these calculations. The maximum likelihood slope estimates, calculated on the basis of animal data, vary from 4.9×10^{-4} to 4.3, a range of four orders of magnitude.

The magnitude of the potency appears to depend primarily on the beryllium compound used in the experiment, although some variability in sensitivity among species was also seen with guinea pigs responding to a lesser degree than rats or monkeys. Among the beryllium compounds examined in the ten animal studies, beryl ore is the least carcinogenically potent, while beryllium sulfate ($BeSO_4$) is the most potent. The potency is most likely related to solubility. Beryl ore is less soluble than beryllium sulfate. Further support for the importance of solubility is provided by intratracheal instillation studies of Spencer et

al. (1968, 1972). Beryllium oxide calcined at 1100°C and 1600°C was much less potent than the more soluble form of beryllium oxide which was calcined at 500°C. If one adopts the most conservative approach, the maximum potency estimate, $4.3/(\mu g/m^3)$, would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of animal data (Vorwald et al., 1966) obtained in an experiment in which the level of exposure was very similar to occupational exposure conditions. Thus, the high potency estimate is not due to the use of a particular low-dose extrapolation model. Since most beryllium compounds present in ambient air or the workplace environment are much less soluble and thereby less potent than beryllium sulfate, the use of such a potency estimate would clearly overestimate the human risk and would be inconsistent with the human experience in the beryllium industry.

Data from the epidemiologic study by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to calculate the cancer risk associated with exposure to air contaminated with beryllium. Two upper-bound relative risk estimates, 1.98 and 2.09, have been used by the CAG to calculate the carcinogenic potency of beryllium. In recognition of the greater uncertainty associated with the exposure estimation, four different "effective" levels of exposure that reflect various uncertainties, along with two relative risk estimates, have been used in the present calculations. As a result, eight potency estimates have been calculated, ranging from $1.6 \times 10^{-4}/(\mu g/m^3)$ to $7.2 \times 10^{-3}/(\mu g/m^3)$, with the geometric mean of the eight estimates being $2.4 \times 10^{-3}/(\mu g/m^3)$. The incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is thus estimated to be 2.4×10^{-3}. This estimate could be considered an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation and the 95 percent upper confidence limits of the relative risks are used in the calculations. This calculation places the relative carcinogenic potency of beryllium in the lower part of the third quartile of the 55 suspect carcinogens evaluated by the CAG.

7.4 SUMMARY

7.4.1 Qualitative Summary

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits, and by inhalation exposure or intratracheal instillation of rats and monkeys.

Osteosarcomas were induced in rabbits by intravenous injection of zinc beryllium silicate (9 studies), beryllium oxide (2 studies), metallic beryllium (1 study) and by intramedullary injection of zinc beryllium silicate and beryllium oxide (1 study each). Lung tumors were induced in rats by intratracheal instillation of beryllium oxide (4 studies), beryllium hydroxide (2 studies), metallic beryllium (2 studies), beryl ore (1 study) and in monkeys by beryllium oxide (1 study). Lung tumors were also induced in rats by inhalation of beryllium sulfate (5 studies), beryllium phosphate, beryllium fluoride, and beryl ore (1 study each), and in monkeys by beryllium sulfate (1 study). No significant neoplastic responses were observed via the intracutaneous, percutaneous, or dietary routes. This was considered to be due to low absorption efficiency resulting from precipitation of beryllium compounds in the small intestine.

The beryllium-induced osteosarcomas in rabbits were shown to be highly invasive and to readily metastasize. They were judged to be histologically indistinguishable from non-beryllium-induced human osteosarcomas, although the sites may be different.

As noted above, positive carcinogenic responses in animals were obtained in multiple species and through various routes of exposure. In studies using either inhalation or the intravenous injection route, positive results were obtained in multiple experiments. For several of the beryllium compounds tested, such as beryllium sulfate, significant responses were obtained at low dose levels. Based on the above findings, the overall evidence for carcinogenicity of beryllium in animals is convincing despite the lack of controls, the use of only one dose level, and the inadequate documentation of many of the studies. According to EPA's criteria for evaluating the weight of evidence for carcinogenicity (U.S. EPA, 1984), the evidence for carcinogenicity of beryllium in animals is considered to be "sufficient".

Although several studies (Wagoner et. al., 1980; Mancuso, 1979; Manusco, 1980) claim a statistically significant excess risk of lung cancer in individuals exposed to beryllium, all of the studies cited have deficiencies that limit definitive conclusions regarding a true carcinogenic association. Support for finding an excess risk of lung cancer in beryllium-exposed persons consists of evidence from cohort mortality studies of two beryllium production facilities. None of these studies are independent as they are all based on the same groups of workers. Extensive collaboration existed between the authors of these studies. The expected lung cancer deaths used in all of these

studies were based on a NIOSH computer-based life-table program known to produce an 11-percent underestimation of expected lung cancer deaths. Furthermore, the studies did not adequately address the confounding effects of smoking or of exposures received during prior or subsequent employment in other non-beryllium industries in the area. Many of these industries were known to produce other potential carcinogens. Problems in the design and conduct of the studies further weaken the strength of the findings. After correcting the life-table error and adjusting for some of the problems described above, the finding of a significant excess risk is no longer apparent. While the possibility remains that the portion of the reported excess lung cancer risk remaining in these studies may, in fact, be due to beryllium exposure, the epidemiologic evidence is, nevertheless, considered to be "inadequate" according to EPA's criteria for evaluating the weight of evidence provided by epidemiologic data.

Limited testing has shown beryllium sulfate and beryllium chloride to be nonmutagenic in bacterial and yeast gene mutation assays. In contrast, gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells, and Chinese hamster ovary (CHO) cells have yielded positive mutagenic responses for beryllium. Beryllium increased the infidelity of DNA and RNA polymerase in prokaryotes. Chromosomal aberration and sister chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses for beryllium. In DNA damage and repair assays, beryllium is negative in the pol, rat hepatocyte, and mitotic recombination assays but is weakly positive in the rec assay. Based on the information available, beryllium appears to have the potential to cause mutations.

Using the EPA criteria for evaluating the overall weight of evidence for carcinogenicity in humans, beryllium is most appropriately classified as group B2, a probable human carcinogen. This category is reserved for those chemicals having sufficient evidence for carcinogenicity in animals but inadequate evidence in humans.

7.4.2 Quantitative Summary

Both animal and human data are used to estimate the carcinogenic potency of beryllium. Among the animal studies, only data from inhalation exposures are used because the intravenous or intramedullary exposure routes are not considered to be directly relatable to human exposures, and all dietary ingestion studies yielded negative results. Many of the animal inhalation studies

for beryllium are not well documented, were conducted at single-dose levels, and, in some cases, did not utilize control groups. Collectively, however, the studies provide a reliable basis for estimating potency (at least for beryllium sulfate), as exemplified by the consistency of response in rats and rhesus monkeys. Data from ten studies (8 studies of rats, 1 study of guinea pigs, and 1 study of monkeys) using beryllium sulfate, phosphate, fluoride and beryl ore have been used to calculate the upper bounds for the carcinogenic potency of beryllium. Both surface area and body weight corrections were used in the calculations. While some data suggest that body weight corrections may be more appropriate for calculating the potency of beryllium, the overall weight of evidence supports the use of surface area corrections. The upper-bound potency estimates calculated on the basis of the animal data, using only surface area corrections, vary from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.3/ (\mu g/m^3)$, a range of over three orders of magnitude. If potency estimates are based on only one compound, such as beryllium sulfate, the variation is decreased to only one order of magnitude.

The magnitude of the potency estimates from animal data depends to a large extent on the beryllium compound used in the experiment, although some variability in sensitivity among species is also seen, with guinea pigs responding to a lesser degree than rats or monkeys. Among the beryllium compounds examined in the ten animal studies, beryl ore is the least carcinogenically potent, while beryllium sulfate ($BeSO_4$) is the most potent. The potency is most likely related to solubility. Beryl ore is less soluble than beryllium sulfate. Further support for the importance of solubility is provided by the intratracheal instillation studies of Spencer et al. (1968; 1972). Beryllium oxide calcined at 1100°C or 1600°C was much less potent than the more soluble form of beryllium oxide which was calcined at 500°C. If one adopts an approach which selects data from the most sensitive experimental animal species and the most potent compound as being representative of risk to humans, the maximum potency estimate, $4.3/(\mu g/m^3)$, would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of data from rats exposed by inhalation (Vorwald et al., 1966). The level of beryllium exposure used by Vorwald and co-workers is very similar to occupational exposure conditions, although the form of beryllium used ($BeSO_4$) is more soluble than forms likely to be present in ambient air or occupational environments.

Information from the epidemiologic studies by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983)

have been used to estimate the cancer risks associated with exposure to workplace air contaminated with beryllium. Even though the epidemiologic evidence does not demonstrate a causal association between beryllium and cancer, that does not mean that no risk exists. The size of the study population, the background risk, and a variety of other factors limit the ability of a study to detect small risks. Each study has a level of sensitivity, and the study population may be too small to show a statistically significant association if the true risk is below this level. An upper-bound risk estimate can be calculated from an inconclusive, or even negative, study to describe the study's level of sensitivity. Risk levels below that upper bound are completely compatible with the study data. The upper bound may be thought of as indicating the largest plausible risk that is consistent with the available data. Thus, the epidemiologic studies can be used to estimate a plausible upper bound for the increased cancer risk from human exposure to beryllium.

In the Wagoner et al. (1980) study, 20 lung cancer deaths were observed in a cohort of workers followed for at least 25 years compared with 13.91 to 14.67 expected ($p < 0.10$). Using the revised estimates of relative risk from this study, two upper-bound relative risk estimates, 1.98 and 2.09, have been used by the CAG to calculate the carcinogenic potency of beryllium. In recognition of the greater uncertainty associated with the exposure estimation, four different "effective" levels of exposure that reflect various uncertainties, along with the two relative risk estimates, have been used in the present calculations. As a result, eight unit risk estimates have been calculated, ranging from $1.6 \times 10^{-4}/(\mu g/m3)$ to $7.2 \times 10^{-3}/(\mu g/m^3)$, with the geometric mean of the eight estimates being $2.4 \times 10^{-3}/(\mu g/m^3)$. The incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is thus estimated to be 2.4×10^{-3}. This estimate could be considered an upper-bound estimate of cancer risk because low-dose linearity is assumed in the extrapolation and the 95 percent upper confidence limits of the relative risk are used in the calculations. The estimate $2.4 \times 10^{-3}/(\mu g/m^3)$ is about three times greater than the previous unit risk estimate reported in the Review Draft of Beryllium (December, 1984).

The reasons that the updated unit risk estimates are higher are as follows:

1. A statistical upper confidence limit for the relative risk, rather than a point estimate, has been used in the calculation.

2. The median concentration in the workplace is estimated to range from 100 to 1000 ppm, rather than from 160 to 1000 ppm (as was previously used). In a 1947 study reported by NIOSH (1972), more than 50 percent of air concentrations in the workplace exceeded 100 ppm. If it is assumed, as was in the earlier risk estimate, that the concentration measurements followed a log-normal distribution, then a median value of 160 ppm could be calculated. Since there are no data to substantiate (or to deny) a log-normal assumption, 100 ppm is used as the low median concentration in the workplace.

The discrepancy in potency estimates derived from rat versus human data is not likely to be due to lower sensitivity in humans, since rhesus monkeys also showed a high degree of responsiveness at beryllium concentrations not greatly different from those found in the workplace environment. While a dose extrapolation based upon body weight results in smaller differences in potency estimates between animal and human data, the weight of evidence still favors a dose extrapolation based upon surface area, despite some theoretical arguments to the contrary. There is some indication that the percentage of inhaled beryllium deposited in the human lung may be as much as twice that of the rat lung. However, any adjustment for this possibility could not account for the discrepancy between estimates from human and animal data, since such an adjustment would increase the differences in potency estimates calculated from these two data bases.

The greater potency values estimated from animal data are probably due to the different forms of beryllium. In the epidemiology studies, humans were generally exposed to relatively insoluble, and thereby less potent, compounds than were used in most of the animal experiments. In the occupational environment upon which human potency estimates are based, beryllium oxide and beryllium metal are most commonly present, while beryllium sulfate was used in most of the animal experiments. When animals are exposed to a less soluble form of beryllium, such as beryl ore, the potency estimates agree very closely with those derived from human exposures. This can be seen by comparing the risk estimate based upon human data, $2.4 \times 10^{-3}(\mu g/m^3)$, with the risk estimate of $2.9 \times 10^{-3}(\mu g/m^3)$ derived from animal data in which exposures were to relatively insoluble beryl ore.

A major uncertainty of the risk estimate based on human data comes from the derivation of exposure levels in the workplace and the temporal effect of the patterns of exposure. To account for these uncertainties, the "effective" exposure level of beryllium is derived in several ways, and the geometric mean

of different potency estimates thus calculated is used to represent the carcinogenic potency of beryllium.

Another uncertainty concerns the use of potency values derived from exposures in the workplace environment to estimate potency from exposure in ambient air. The types of sources which emit beryllium to the ambient air are limited. There is little evidence that ore production is a significant source of beryllium emissions. Metallurgical processing is likewise considered an insignificant source. As much as 95 percent of atmospheric beryllium emissions are estimated to come from coal-fired electric power plants, with most of the remainder resulting from fuel oil combustion (see Chapter 3). During coal combustion beryllium is likely emitted as an insoluble oxide, generally as a trace contaminant of fly ash particles which are even more insoluble. On this basis, the potency of beryllium from this source would be expected to be quite low. Beryllium emissions from fuel oil combustion are similarly likely to occur primarily in the oxide form. Experimental evidence also indicates that beryllium in fly ash has a low degree of potency, since even very high concentrations of fly ash containing other known carcinogens have failed to induce cancer in laboratory animals. On this basis, it is unlikely that values derived from exposure in the workplace will significantly underestimate the potency of beryllium in ambient air, unless soluble beryllium compounds such as fluoride, phosphate, or sulfate are known to be present.

Because of the apparently greater carcinogenic potency of the beryllium compounds used in animal data than those reported from human data, the estimates derived from animal data are judged to be less relevant to human environmental exposure. Despite some uncertainties concerning exposure levels in the workplace and possible differences in the forms of beryllium found in ambient air compared with the workplace environment, the CAG-revised relative risks from the Wagoner et al. (1980) epidemiologic study were considered to be the best choice for estimating the upper-bound incremental cancer risk for inhalation exposure to mixtures of beryllium compounds likely to be present in ambient air.

The upper-bound incremental unit risk of $2.4 \times 10^{-3}/(\mu g/m^3)$ results in a potency index of $8 \times 10^{+1}$, which places beryllium in the third quartile of the 55 suspect carcinogens evaluated by the CAG. The low molecular weight of beryllium is at least partially responsible for its relatively low potency index.

7.5 CONCLUSIONS

Using EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984) to classify the weight of evidence for carcinogenicity in experimental animals, there is sufficient evidence to conclude that beryllium and beryllium compounds are carcinogenic in animals. This evidence is based upon the induction of osteosarcomas and chondrosarcomas by intravenous and intramedullary injection in rabbits and upon the induction of lung tumors in rats and monkeys by inhalation and intratracheal instillation. Due to limitations in methodology, the epidemiological evidence is considered to be "inadequate", even though significant increases in lung cancer were seen in some epidemiology studies of occupationally exposed persons.

A potency of $2.4 \times 10^{-3}/(\mu g/m^3)$ was calculated from occupational studies involving human exposure to relatively insoluble beryllium compounds commonly present in the workplace.

The carcinogenic potency of inhaled beryllium derived from animal studies depends on the form of beryllium, with more soluble forms being more potent. A range of potencies calculated from the animal studies varied from a high of $4.3/(\mu g/m^3)$ for the relatively soluble beryllium sulfate to $2.9 \times 10^{-3}/(\mu g/m^3)$ for the less soluble beryl ore. Another ore, bertrandite, which failed to induce lung cancer in rats, would have yielded an even lower value if an upper-bound potency estimate had been calculated. Because studies in which rhesus monkeys were exposed to beryllium sulfate also yielded a potency estimate similar to that of the rat, the CAG believes that humans would also be quite sensitive to the more soluble forms of beryllium.

Recognizing that the carcinogenic potency of inhaled beryllium varies according to the form of beryllium present, an upper-bound incremental lifetime cancer risk for continuous inhalation exposure at 1 $\mu g\ Be/m^3$ is estimated to be 2.4×10^{-3} for general ambient conditions. This presumes that ambient air is characterized by relatively insoluble forms such as beryllium oxide and metallic beryllium. This means that the actual unit risk is not likely to be higher, but could be lower, than 2.4×10^{-3}. This also places beryllium in the lower part of the third quartile of 55 suspect carcinogens evaluated by the CAG. It should be cautioned, however, that if compounds such as beryllium fluoride, phosphate, and sulfate are known to be present in other than a small percentage of total beryllium in the ambient air, this potency estimate will

likely underestimate the potential carcinogenic risk. Conversely, since beryllium has not been shown to induce neoplasms via oral ingestion in any studies to date, this potency estimate is likely to overestimate risk by this route.

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APPENDIX
ANALYSIS OF INCIDENCE DATA WITH TIME-DEPENDENT DOSE PATTERN

Table A-1 presents time-to-death data with or without lung tumors. These data are reconstructed from Figure 1 in Reeves and Deitch (1969), in which study animals were exposed to beryllium by inhalation at a concentration of 35 $\mu g/m^3$, 35 hours/week, for specific durations during the 24-month observation period.

The computer program ADOLL1-83, developed by Crump and Howe (1984), has been used to fit these data. Models with one to seven stages, and with one of the stages affected by the dose, have been calculated. The model with the maximum likelihood has been selected as the best-fitting model. The identified best-fitting model has six stages, with the fifth stage dose-affected. Using this model, the maximum likelihood estimate of the slope (linear component), under the assumption of constant exposure, is $0.81/(\mu g/m^3)$. The 95 percent upper confidence limit for the slope is $1.05/(\mu g/m^3)$.

TABLE A-1. TIME-TO-DEATH-DATA[a]

Exposure period[b]	Time-to-death
1. Control	19^-, $20^-(2)$, $21^-(6)$, $22^-(8)$, $24^-(8)$
2. 14th - 19th month	$14^-_+(2)$, 15^-, $20^-(4)$, 20^+, $21^-(5)$, 21^+, $22^-(5)$, $24^-(3)$, 24^+
3. 11th - 16th month	$20^-(2)$, $21^-(5)$, 21^+, 22^-, $22^+(3)$, $24^+(9)$
4. 8th - 13th month	13^-_+, 14^-, $20^+(2)$, $21^-(5)$, 21^+, $22^+(6)$, $23^-(2)$, $24^-(4)$, $24^+(3)$
5. 5th -10th month	13^-, $19^-(3)$, $20^+(3)$, $21^-(2)$, $21^+(4)$, $22^-(4)$, 23^-, $24^+(3)$
6. 2nd - 8th month	16^-_+, 17^-, 18^-, $19^-(4)$, $20^-(2)$, 20^+, $21^-(3)$, $21^+(3)$, 22^-, $22^+(6)$, 24
7. 8th - 19th month	$15^-_-(2)$, 17^-_+, 19^-, $20^-(3)$, $21^-(3)$, $21^-(5)$, $21^+(3)$, $22^+(2)$, $24^-(2)$, $24^+(4)$
8. 2nd - 13th month	14^-, 18^-, $19^-(4)$, $20^+(3)$, $21^-(6)$, $22^+(4)$, $24^+(2)$
9. 2nd - 19th	16^-, $18^-(4)$, $19^-(2)$, $20^-(5)$, $20^+(3)$, $21^+(3)$, 21^-, 22^+

[a] $t^{+(n)}$ and $t^{-(n)}$ indicate, respectively, the time-to-death with and without lung tumor; n is the number of replications.

[b] All animals were exposed to beryllium at a concentration of 35 $\mu g/m^3$, 35 hours/week.