United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington, DC 20460

Research and Development

EPA/600/S8-84/026F July 1988

EPA

Project Summary

Health Assessment Document for Beryllium

The chemical and geochemical properties of beryllium resemble those of aluminum, zinc, and magnesium. This resemblance is primarily due to similar ionic potentials that 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 small, the chemical properties of beryllium are such that inhaled beryllium has a long retention time in the lungs and, thus, a greater potential for absorption and/or physical irritation. The tissue distribution of absorbed beryllium is characterized by depositions primarily in the skeleton where the biological half-time is fairly long.

The lung is the critical organ of both acute and chronic noncarcinogenic 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 shown carcinogenic activity in various experimental animals by various routes of exposure, but not by ingestion *per se*. Epidemiologic studies are inadequate to demonstrate or refute a human carcinogenicity potential. In terms of the weight of evidence for carcinogenicity, beryllium is judged to be in Group B2 signifying that the animal evidence for carcinogenicity is sufficient and that beryllium and its compounds are regarded as probably carcinogenic for humans.

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

The full report evaluates the effects of beryllium on human health, with particular emphasis on those effects that 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 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).

The full report is not 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 on beryllium was collected and reviewed up to January 1986. General information pertaining to the calculation of unit risk values was reviewed up to April 1987. In

view of the fact that the full 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 U.S. Environmental Protection Agency (EPA) reports regarding regulatory decisions on beryllium.

Results and Conclusions

Background

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.

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 time in the lungs following exposure to all types of beryllium compounds. Like other particulate matter, 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, except in the lung.

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

Beryllium Toxicology

Subcellular and Cellular Aspects of Beryllium Toxicity

It is not well known in what form c through which mechanism beryllium i bound to tissue. Beryllium can bind t lymphocyte membranes, which ma explain the sensitizing properties of th metal. A number of reports describ various *in vivo* and *in vitro* effects c beryllium compounds on enzyme especially alkaline phosphatase, to whic beryllium can bind. Effects on protei and nucleic acid metabolism have bee shown in many experimental studie however, the doses in these studies hav been large and parenterally administere Because such administrative routes hav less practical application to humans, th data from these studies have limite utility in advancing an understanding human effects, which are mainly on th lung. Beryllium particles retained in th lung are found in the macrophages, ar the understanding of how these and oth pulmonary cells metabolize beryllium probably of most relevance to the u derstanding of chronic beryllium diseas

An important aspect of berylliu toxicology is that beryllium can cau hypersensitivity which is essentia cell-mediated. There are species d ferences; humans and guinea pigs c be sensitized to beryllium, whereas th present data indicate that no su mechanism exists for the rat. There a also strain differences among guinea pi indicating that a genetic component m be operative. Patch tests have been us to detect beryllium hypersensitivity humans, but these tests are no long used since they were shown to cause reactivation of latent beryllium disea Presently, the lymphoblast transformati test is regarded as the most useful test detect hypersensitivity to beryllium.

Pulmonary and Systemic Toxicity of Beryllium in Man an Animals

There are no data indicating th moderate beryllium exposure by o administration causes any local systemic effects in humans or anim Respiratory effects, occasionally co bined with systemic effects, constit the major health concern of beryll exposure, with hypersensitization lik

laying 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 1940's, 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 1940's, 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 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 occupational standards have been exceeded. In industries where the average exposure generally has been below 2 $µg/m^3$, 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 $µg/m^3$, 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 $µg/m^3$ 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, although a few urban areas report values between 1 and 6 Ng/m^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.

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.

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.

Carcinogenic Effects of Beryllium Exposure

Animal Studies

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits and by inhalation exposure or by intratracheal injection of rats and monkeys. With one possible exception, beryllium carcinogenesis has not been induced by ingestion. 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 endpoints 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 reasonable 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 Guidelines for Carcinogen Risk Assessment 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.

Human Studies

Epidemiologic studies provide equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early epidemiologic studies of beryllium-exposed workers 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 considers the available epidemiologic evidence to be "inadequate" to support or refute the existence of a carcinogenic hazard for humans exposed to beryllium.

This designation of the epidemiologic data as "inadequate" differs from that of the International Agency for Research on Cancer (IARC) which concluded that the epidemiologic data provide "limited" evidence for the carcinogenicity of beryllium. In the EPA evaluation, more recent unpublished tabulations and analysis of the earlier study cohorts that correct for errors in the data base and the National Institute for Occupational Safety and Health (NIOSH) Life-Table program were included. Use of this newer data provides a basis to change the weight-of-evidence conclusion for the human data.

Qualitative Carcinogenicity

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.

Human Health Risk Assessment of Beryllium

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.

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 chron beryllium disease have been reported i the past several years.

Numerous animal studies have bee performed to determine whether or nc beryllium and beryllium-containin substances are carcinogenic. Althoug some of these studies have limitation the overall evidence from animal studie is considered to be "sufficient" usin EPA Guidelines for Carcinogen Ris Assessment. The IARC has also cor cluded that the evidence from anim studies is "sufficient." Human studies c beryllium carcinogenicity have deficie cies that limit any definitive conclusic that a true association between berylliu exposure and cancer exists. Neve theless, it is possible that a portion of th excess cancer risks reported in thes studies may, in fact, be due to berylliu exposure. Although IARC concluded th beryllium and its compounds should b classified as having "limited" huma evidence of carcinogenicity, the EPA Carcinogen Assessment Group (CA(has concluded that the direct huma evidence is "inadequate."

Dose-Effect and Dose-Response Relationships of Beryllium

As previously stated, beryllium c act upon the lung in two ways, eith through a direct toxic effect on pu monary tissue or through hype sensitization. Even if reliable and detail exposure data were available, it wou still be difficult to establish dose-effe and dose-response relationships due this hypersensitization factor. No adver non-cancerous effects have been not in industries complying with the 2 μg/r standard set by the Occupational Safe and Health Administration (OSHA therefore, it appears that this level beryllium in air provides good protecti with regard to non-cancer respirato effects. It is unknown whether exposur to the maximum permissible pe standard (25 $\mu g/m^3$) can cause delay effects.

From available data, the Agen assessment document has discussed t estimation of carcinogenic unit risks inhalation exposure to beryllium. T quantitative aspect of carcinogen r assessment is included here because may be of use in setting regulato priorities and in evaluating the adequa of technology-based controls and ot aspects of the regulatory decisio making process. However, the meth ologic uncertainties associated w estimating cancer risks to humans at

evels of exposure should be recognized. The linear extrapolation procedures used typically 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. In the case of beryllium, the uncertainty introduced by specific characteristics of the data base may be best thought of as affecting the confidence in the upper-limit estimates. These risk estimates should not be regarded, therefore, as accurate representations of true cancer risks. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-limit risks are found to be useful.

Both animal and human studies have been used to examine the carcinogenic potency of beryllium. For quantitative risk assessment purposes the animal data present some difficult analytical problems because of weaknesses in the design and the reporting of the studies. Despite the weaknesses of the individual studies, however, there is little doubt that beryllium induces cancer in laboratory animals.

An additional difficulty in the use of animal data for quantitative assessment is that not only did many of the animal studies utilize different forms of beryllium than those commonly present in the ambient environment, but the carcinogenic response varied with the beryllium compound used. Moreover, the form most common in ambient air is beryllium oxide and, although all the animal studies were deficient in some respects, the ones utilizing beryllium oxide were more deficient, as a group, than those utilizing beryllium salts. Nevertheless, it was felt that the quantitative analysis should focus upon the form of beryllium humans are most likely to be exposed to.

While the available beryllium oxide studies were individually weak, a correlation of estimates from several data sets would be expected to increase confidence in the results. Potency factors were thus calculated using data from eight beryllium oxide animal studies. The results were reasonably consistent and the geometric mean of all eight potency factors was $2.1 \times 10^{-3}/(\mu g/m^3)$, which agreed quite well with the potency factor derived from the human epidemiologic data.

The question of beryllium potency by ingestion is debatable due to the equivocal or negative results from ingestion studies. From a weight-of-evidence point of view, the potential for human carcinogenicity by this route cannot be dismissed given the knowledge that some beryllium (< 1%) would be absorbed from the gastrointestinal tract, and intravenous injection of beryllium produced distant site tumors. For practical purposes, however, the potency of beryllium via ingestion must be considered as largely unknown, although an upper bound risk estimate is provided.

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 is a risk estimate and can be used to evaluate the reasonableness of estimates derived from animal studies. Information from a published epidemiologic study and the industrial hygiene reviews by NIOSH and other investigators have been combined to estimate a plausible upper bound for incremental cancer risk associated with exposure to air contaminated with beryllium oxide. The epidemiologic data, while being useful for estimating the cancer potency of beryllium, nevertheless, also has interpretative limitations because of the uncertainties regarding exposure levels. In the occupational exposure studies upon which the risk analysis is based, the narrowest range for median exposure that could be obtained on the basis of available information was 100 to 1,000 $\mu g/m^3$. Furthermore, an assumption was made that the ratio of exposure duration to years at risk ranged from 0.25 to 1.0. The geometric mean of the potency factors derived using these assumptions equals $2.4 \times 10^{-3}/(\mu g/m^3)$.

The unit risks from the animal data sets are best viewed as a sensitivity analysis, as opposed to a collection of reasonable upper-bound risk values. The sensitivity relates to the beryllium species tested, and for beryllium oxide, perhaps to firing temperature. Because of the need to assume exposure levels, the risk estimate derived from the human epidemiology data is, in effect, also the result of a sensitivity analysis.

With these noted caveats, the CAG feels that a recommendation for a specific upper-bound estimate of risk is warranted, even though it does evolve from less than ideal data, in order to provide a crude measure of the potential for public health impact if, in fact, beryllium is a human carcinogen. Taken together the notable comparability of the animal and human based estimates encourages one to consider these estimates as being of some utility. Given the correlation of animal and human estimates, the upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium, after rounding to one significant figure, is 2×10^{-3}. This value is based on the assumption that beryllium is present in the environment in the oxide form. If, however, the form of beryllium present includes more than a small fraction of beryllium salts, then this potency value may underestimate the upper limit and consideration should be given to the animal estimates based on exposure to beryllium sulfate. The incremental upper-limit risk, $2 \times 10^{-3}/(\mu g/m^3)$, places beryllium in the lower part of the third quartile of 58 suspect carcinogens evaluated by the CAG.

Populations at Risk

In terms of exposure, persons engaged in handling beryllium in occupational environments obviously have a higher potential for risk than the general public. With regard to the population at large, there may be some 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.

***Donna Sivulka** is the EPA Project Officer (see below).*
The complete report, entitled "Health Assessment Document for Beryllium," (Order No. PB 88-179 205/AS; Cost: $25.95, subject to change) will be available only from:

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EPA/600/S8-84/026F