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Beryllium and compounds (CASRN 7440-41-7)

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Reference Dose for Chronic Oral Exposure (RfD)

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe* PDF format (94 Pages, 320 Kbytes). Similar documents can be found in the [List of Available IRIS Toxicological Reviews](#).

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to the IRIS Help page for instructions.

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Beryllium and compounds; CASRN 7440-41-7, 04/03/1998

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Beryllium and compounds

File First On-Line 01/31/1997

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	On-line	04/03/1998
Inhalation RfC Assessment (I.B.)	On-line	04/03/1998
Carcinogenicity Assessment (II.)	On-line	04/03/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

IA Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Beryllium and compounds
 CASRN -- 7440-41-7
 Last Revised -- 04/03/1998

Chronic Health Harards for Non-Carcinogenic Effects

Reference Dose for Chronic Oral Exposure (RfD)

- Oral RfD Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/Comments
- Confidence in the Oral RfD
- EPA Documentation and Review

Reference Concentration for Chronic Inhalation Exposure (RfC)

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- EPA Documentation and Review

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Quantitative Estimate of Carcinogenic Risk from Oral Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of



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The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts

- Bibliography
- Revision History
- Synonyms

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Small intestinal lesions	BMD ₁₀ : 0.46 mg/kg-day	300	1	2E-3 mg/kg-day

Dog Dietary Study

Morgareidge et al., 1976

*Conversion Factors and Assumptions -- mg/kg-day doses determined from administered doses (ppm), reported food intake of 300 g/day and TWA body weights for males and females in each dose group. This benchmark dose (BMD₁₀) is the dose at the 95% confidence limit of the dose-response model corresponding to a 10% increase in incidence of these effects compared with controls. A 10% increase was chosen as the benchmark response and calculated as probability (P) of extra risk over controls at dose (d), [P(d) - P(0)/1 - P(0)]. An exponential polynomial model was used as the dose-response model. There was good fit of the model to the data (p = 0.94), and the maximum likelihood estimate (MLE) at 10% increase in incidence is 1.4 mg/kg-day.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Morgareidge, K; Cox, GE; Gallo, MA. (1976) Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America, Alcan Research & Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc.

Morgareidge et al. (1976) conducted a long-term feeding study in which groups of 5 male and 5 female beagle dogs (aged 8 to 12 mo) were fed diets (for 1 h per day) containing 0, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate for 172 weeks. Because of overt signs of toxicity, the 500 ppm group was terminated at 33 weeks. At this time, a group of 5 male and 5 female dogs was added to the study and fed a diet containing 1 ppm beryllium; duration of exposure for this group was 143 weeks. Using estimated TWA body weights and the reported average food intake of 300 g/day, the 1, 5, 50, and 500 ppm concentrations correspond to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. The following parameters were used to assess toxicity: daily observations, food consumption, body weight, hematology and serum clinical chemistry, urinalysis, organ weights (heart, liver, kidney, brain, spleen, pituitary, thyroids, adrenals, and gonads), and comprehensive histopathology.

Two moribund animals in the 500 ppm group were sacrificed during week 26; the remainder of the animals in the 500 ppm group were killed during week 33. Overt signs of toxicity observed in the 500 ppm group included lassitude, weight loss, anorexia, and visibly bloody feces, indicating that the MTD is <500 ppm. Four other animals died during the course of the study or were killed moribund: two dogs died during parturition, and one male and one female dog in the 50 ppm group died. The appearance, behavior,

food intake, and body weight gain of the animals in the other beryllium groups did not differ from controls. No beryllium-related hematological, serum chemistry, or urinalysis alterations were observed in the 1, 5, or 50 ppm groups. In the 500 ppm group, a slight anemia (slight decreases in erythrocyte, hemoglobin, and hematocrit; statistical analysis not reported), more apparent in the females than in the males, was observed after 3 and 6 mo of exposure; however, there were no alterations in the bone marrow and none of the animals was seriously affected. No alterations in organ weights were observed. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine and to a lesser extent in the stomach and large intestine, and were regarded by the authors as treatment related. This conclusion is supported by independent review of the study report; the lesions are not considered to be related to some other cause such as intestinal worms (Goodman, 1997). All of the animals with stomach or large intestinal lesions also had lesions in the small intestine except for one animal with stomach lesions only. This animal had stomach lesions that were very localized and not very severe. Lesions in the small intestine (4/5 males and 5/5 females) considered treatment related include: desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium, and ulceration (Goodman, 1997). High-dose animals also showed moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment related (Goodman, 1997). Bile stasis and vasculitis in the liver and acute inflammation in the lymph nodes occurring in these animals is attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa. A generalized low-grade septicemia likely initiated kidney damage.

In the 50 ppm group, one female dog died after 70 weeks of treatment. This animal showed gastrointestinal lesions, but less severe, occurring in the same locations and appearing to be the same types of lesions as those in dogs administered 500 ppm. The authors stated the cause of death of this animal appeared to be related to beryllium administration. Other animals in this treatment group survived until study termination and had no remarkable gross or microscopic findings.

Dose-response modeling of the data for small intestinal lesions in male and female dogs (0/10, 0/10, 0/10, 1/10, 9/10) was conducted to derive a benchmark dose for beryllium. A BMD_{10} (the lower 95% confidence limit on the dose from the maximum likelihood estimate [MLE] of a 10% relative change) of 0.46 mg/kg-day (MLE = 1.4 mg/kg-day) was derived for this lesion and used for further quantitation in this assessment (U.S. EPA, 1995, and Conversion Factors and Assumptions, above).

An oral chronic study via drinking water was carried out by Schroeder and Mitchener (1975a) using Long-Evans rats (52 weanling rats of each sex). In addition to control animals, rats of both genders were exposed to 5 ppm beryllium as beryllium sulfate over a lifetime. No adverse effects were observed in the beryllium-exposed rats compared to controls with respect to lifespan, various organs (heart, kidney, liver, and spleen), urinalysis, serum glucose, cholesterol, or uric acid. With respect to cancer, the incidence of gross or malignant tumors in the control and beryllium-exposed rats was not significantly different. This chronic oral study served as the basis for the previous IRIS RfD of 5E-3 mg/kg-day. The new RfD derived from the Morgareidge et al. (1976) study of 2E-3 is not significantly different.

__ I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 300.

The following uncertainty factors are applied: 10 for extrapolation for interspecies differences, 10 for consideration of intraspecies variation, and 3 for database deficiencies. A partial uncertainty factor for database deficiencies is applied because while there are several chronic oral animal studies, human toxicity data by the oral route are lacking, and reproductive/developmental and immunotoxicologic endpoints have not been adequately

assessed in animals. Database gaps include lack of adequate studies for evaluation of reproductive and developmental toxicity (including multigenerational studies, studies on male reproductive toxicity, teratology, and postnatal development) owing to the possible crossing of the placenta and greater absorption of beryllium in young animals. In addition, oral studies examining immunologic endpoints, the most sensitive endpoint by the inhalation route, are lacking. Since the principal study is of chronic duration and a benchmark dose is used, there are no uncertainty factors for duration or NOAEL/LOAEL extrapolation. No modifying factor is proposed for this assessment.

MF = 1

I.A.4. Additional Studies/Comments (Oral RfD)

No human information on the oral toxicity of this compound was located.

While each of the chronic animal studies appears to have limitations (e.g., multiple elements in drinking water, no randomization of animals, not published in peer-reviewed journal, no doses showing an adverse effect, and/or lack of histological examination of all animals), collectively they establish the range of doses that is unlikely to evoke noncancer toxicity.

In a chronic toxicity study by Morgareidge et al. (1975, 1977), groups of Wistar albino rats were fed diets containing 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate. The rats were administered the beryllium-containing diet from 4 weeks of age through maturation, mating, gestation, and lactation. Fifty male and 50 female offspring were then placed on the same diets as the parents and fed the beryllium-containing diet for 104 weeks. Using estimated TWA body weights of 0.467, 0.478, and 0.448 kg for males in the 5, 50, and 500 ppm groups and 0.294, 0.302, and 0.280 kg for the females, respectively, and U.S. EPA's (1988) allometric equation of food intake, doses of 0.36, 3.6, and 37 mg/kg-day for males in the 5, 50, and 500 ppm groups and 0.42, 4.2, and 43 mg/kg-day for females in the 5, 50, and 500 ppm groups, respectively, were calculated. Clinical observations, body weight, food consumption, organ weights (liver, kidney, testes, ovaries, thyroid, pituitary, adrenal), gross necropsy, and histopathological examination of most tissues and organs (25 to 26 tissues examined) were used to assess the toxicity and carcinogenicity of beryllium in the offspring; it does not appear that the P₀ rats were examined. Tissues from 20 rats/sex/group in the control and 500 ppm groups were examined microscopically (the study authors did not state whether the animals undergoing histopathological examination were randomly selected), as well as all tissues with gross abnormalities (all groups) and tissues (excluding bone marrow, eyes, and skin) from animals found dead or sacrificed moribund (all groups).

No overt signs of toxicity were observed, and mortality appeared to be similar in the controls (30/50 males and 28/50 females died) and beryllium groups at 5 ppm (30/50 and 24/50, respectively), 50 ppm (31/50 and 18/50), and 500 ppm (24/50 and 17/50) at the end of the 104 weeks of the study. During the first 40 to 50 weeks of the study, exposure to beryllium did not appear to affect growth; slight decreases in growth (body weights of males and females in the 500 ppm group were within 10% of control body weights) were observed in the latter part of the study; however, no statistically significant alterations were observed. Alterations in organ weights were limited to statistically significant ($p < 0.05$) increases in relative kidney weight in males exposed to 50 ppm, decreases in relative kidney and adrenal weights in 500 ppm females, and decreases in relative testes weights in 5 and 50 ppm males. Histological examination of the major organs and tissues did not reveal beryllium-related noncarcinogenic alterations. This study has a NOAEL at the highest dose tested (37 mg/kg-day).

Groups of 52 male and 52 female Long-Evans rats were maintained on a low-metal diet and given drinking water containing 0 or 5 ppm beryllium as beryllium sulfate (presumably tetrahydrate) from weanling to natural death (Schroeder and Mitchener, 1975a). The water also contained 5 ppm chromium III, 50 ppm zinc, 5 ppm copper, 10

ppm manganese, 1 ppm cobalt, and 1 ppm molybdenum. Doses of 0.63 and 0.71 mg/kg-day were calculated for male and female rats, respectively. The following parameters were used to assess toxicity: body weights; blood glucose, cholesterol, and uric acid; urine protein, pH, and glucose; heart weight; gross pathology; and histopathology of heart, lung, kidney, liver, spleen, and tumors. Twenty male and eight female rats in the beryllium group died at 20 mo of age from pneumonia; a similar number of animals in the control group also died from pneumonia. At 30 days, the male and female rats exposed to beryllium weighed significantly more than the control animals. At 60, 90, 120, and 180 days, the beryllium-exposed male rats weighed significantly less than the controls; no significant alterations in body weight were observed at the other time intervals (150, 360, or 540 days). No significant alterations in mortality or longevity were observed. The results of the histological examination were not reported. Alterations in serum glucose and cholesterol levels and urine glucose levels in beryllium-treated animals were not considered adverse because the magnitude of the alterations was not sufficiently large to suggest an impairment in organ function. The NOAEL for this study is 0.63 mg/kg-day, the highest dose tested.

In a lifetime exposure study, groups of 54 male and 54 female Swiss mice were administered 0 or 5 ppm beryllium as beryllium sulfate in the drinking water from weaning to natural death (Schroeder and Mitchener, 1975b). The mice were fed low-metal diets and the drinking water was supplemented with 50 ppm zinc, 10 ppm manganese, 5 ppm copper, 5 ppm chromium III, 1 ppm cobalt, and 1 ppm molybdenum. The 5 ppm water concentration is equivalent to doses of 1.2 mg/kg-day for the male and female mice. In the beryllium group, statistically significant alterations in body weight were observed; the alterations included heavier male mice at 30 days and lighter female mice at 90 and 120 days. No significant alterations in mortality or survival were observed in the beryllium-exposed mice. A NOAEL of 1.2 mg/kg-day is established for this study.

Shorter term oral studies in rats fed up to 3% beryllium carbonate in the diet have shown beryllium rickets (Kay and Skill, 1934) and decreases in serum phosphate and serum alkaline phosphatase activity (480 mg/kg-day; Matsumoto et al., 1991). One hypothesis for the development of rickets has been the deprivation of phosphate in the intestines by precipitation as beryllium phosphate and not to any direct effects due to beryllium per se.

There are limited data on the reproductive and developmental toxicity of beryllium compounds following oral exposure. In the chronic dog oral exposure study conducted by Morgareidge et al. (1976), the male and female dogs exposed to 1, 5, or 50 ppm beryllium sulfate in the diet (0.024, 0.11, and 1.1 mg/kg-day for males and 0.025, 0.15, and 1.3 mg/kg-day for the females) were housed together, allowed to mate, and wean their pups (with the exception of the first litter, which was killed 5 days after whelping). Beryllium did not appear to adversely affect reproductive or developmental endpoints, but stillborn or cannibalized pups dying within the first few postnatal days were not examined. The authors reported no gross or skeletal abnormalities in the surviving first litter pups, but data were not shown. In addition, there was no visceral evaluation for terata.

Several parenteral studies (as reviewed by U.S. EPA, 1991) have observed developmental effects (increased fetal mortality, decreased fetal body weight, internal abnormalities, and delayed neurodevelopment) in the offspring of rodents following intratracheal or intraperitoneal administration of beryllium chloride, beryllium oxide, or beryllium sulfate during gestation. Clary et al. (1975) conducted a continuous breeding experiment in which male and female Sprague-Dawley rats received a single intratracheal administration of 200 µg beryllium as beryllium oxide (calcined at 960C in the first experiment and calcined at 500C in the second experiment). There were no adverse effects of beryllium in either experiment. Mathur et al. (1987) administered intravenous injections of 0.021 mg/kg beryllium as beryllium nitrate to mated Sprague Dawley rats (n = 5-8/group) (1/10th the LD₅₀) and performed laparotomies; all pups died 2 to 3 days after birth, but these effects may have been due to the repeated surgeries.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7

(PDF).

__I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Low to Medium
RfD -- Low to Medium

The overall confidence in this RfD assessment is low to medium. The confidence in the principal study is medium. Beryllium was administered by a relevant route (oral) at multiple dose levels for a chronic duration, effects were demonstrated at two dose levels, and relatively comprehensive histopathologic evaluations were conducted. However, there were small groups of animals (5/sex/dose), early mortality at the high dose level, no evidence of randomization or control for potential litter effects, and no measure of immune response or function, the critical endpoint by the inhalation. Confidence in the database is low to medium because there is only one chronic study in dogs showing adverse effect levels; other chronic studies in rodents demonstrated NOAELs at the highest doses tested. Confidence in this assessment is improved over the earlier version on IRIS because of the inclusion of additional chronic studies in rats and dogs.

The major areas of scientific uncertainty in this assessment are the lack of chronic oral studies establishing LOAELs, the lack of a chronic oral study examining immunologic endpoints, the lack of a critical effect in humans by the inhalation route as identified in dogs and the lack of sensitive indicators for rickets, the lack of reproductive and developmental studies (including multigenerational studies or male reproductive toxicity), and the lack of human toxicity information. The uncertainty factors above compensate for these areas of uncertainty. The RfD determined from the BMD₁₀ (0.46 mg/kg-day) of small intestinal lesions in dogs (2E-3 mg/kg-day) is almost identical to the previous IRIS RfD (5E-3 mg/kg-day) derived from the NOAEL (0.5 mg/kg-day) in the Schroeder and Mitchener (1975a) rat study. However, to substantiate the significance of the similarities between these two RfDs, additional dose-response rat studies would be needed to establish a LOAEL and NOAEL.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review of Beryllium and Compounds in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF).***

Other EPA Documentation -- U.S. EPA, 1987; U.S. EPA, 1991

Agency Consensus Date -- 03/26/1998

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Beryllium and compounds
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The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3 . In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (U.S. EPA, 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Beryllium sensitization and progression to CBD	LOAEL(HEC): $0.55 \mu\text{g}/\text{m}^3$ LOAEL(HEC): $0.20 \mu\text{g}/\text{m}^3$	10	1	$2\text{E}-2 \mu\text{g}/\text{m}^3$
Occupational study Kreiss et al., 1996				
Community exposure study Eisenbud et al., 1949	NOAEL: $0.01\text{-}0.1 \mu\text{g}/\text{m}^3$ NOAEL(HEC): $0.01\text{-}0.1 \mu\text{g}/\text{m}^3$ LOAEL: None			

*Conversion Factors and Assumptions: MW -- 9. The occupational LOAEL is based on 8-h TWA exposure level. $\text{Mvo} = 10 \text{ m}^3/\text{day}$, $\text{Mvh} = 20 \text{ m}^3/\text{day}$. $\text{LOAEL(ADJ)} = \text{LOAEL(HEC)} = 0.55 \mu\text{g}/\text{m}^3 \times (\text{MVo}/\text{MVh} \times 5 \text{ days}/7 \text{ days}) = 0.20 \mu\text{g}/\text{m}^3$.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

The RfC is based on beryllium sensitization and progression to chronic beryllium disease (CBD) identified in the co-principal studies by Kreiss et al. (1996) and Eisenbud et al. (1949). The Kreiss et al. (1996) occupational exposure study identified a LOAEL for beryllium sensitization in workers exposed to $0.55 \mu\text{g}/\text{m}^3$ (median of average concentrations). The Eisenbud et al. (1949) study, using relatively insensitive screening methods, suggests a NOAEL of $0.01\text{-}0.1 \mu\text{g}/\text{m}^3$ in community residents living near a beryllium plant. The LOAEL from the Kreiss et al. study was used for the operational derivation of the RfC because the screening method used in the Eisenbud et al. (1949) study was less sensitive than the method used in the Kreiss et al. (1996) study.

Chronic beryllium disease is a chronic inflammatory lung lesion that can result from

inhalation exposure to beryllium. It is characterized by the formation of granulomas (pathologic clusters of immune cells) and involves a beryllium-specific immune response. Beryllium sensitization of the immune system can be demonstrated using the beryllium lymphocyte transformation test (BeLT) (reviewed by Newman, 1996). In this test, lymphocytes obtained from bronchoalveolar lavage (BAL) fluid or from peripheral blood are cultured *in vitro* and then exposed to soluble beryllium sulfate to stimulate lymphocyte proliferation. The observation of beryllium-specific proliferation indicates beryllium sensitization.

The criteria for diagnosis of CBD have evolved with time, as more advanced diagnostic technology became available. These varying definitions of CBD should be considered in comparing results from different studies. More recent criteria have both higher specificity than earlier methods and higher sensitivity identifying preclinical effects. Recent studies typically use the following criteria: (1) history of beryllium exposure; (2) histopathological evidence of noncaseating granulomas or mononuclear cell infiltrates; and (3) a positive blood or bronchoalveolar lavage (BAL) lymphocyte transformation test (Newman et al., 1989).

A cross-sectional study (Kreiss et al., 1996) was conducted of 136/139 of the then-current beryllium workers in a plant that made beryllia ceramics from beryllium oxide powder. Measurements from 1981 and later were reviewed and included area samples, process breathing-zone samples, and personal lapel samples (the last year only). Quarterly daily-weighted average (DWA) exposures were calculated using a formula based on all of these measurements for each job title. General area and breathing zone samples were not recorded until the last quarter of 1985, soon after machining production was transferred to that plant, even though a limited amount of machining had been conducted since 1982. The median breathing zone measurements for machining was $0.6 \mu\text{g}/\text{m}^3$, and $0.3 \mu\text{g}/\text{m}^3$ for other processes. The frequency of excursions to higher exposure levels decreased with time, with the percentage of machining breathing zone measurements above $5 \mu\text{g}/\text{m}^3$ falling from 7.7% during early sampling years to 2.1% during later sampling years.

Beryllium lymphocyte transformation tests were performed by two different laboratories on blood samples collected from 136 employees. Positive results from one or both laboratories were confirmed by analyzing a subsequent blood sample. Of 136 tested employees, 5 had consistently abnormal blood BeLT results from the two laboratories and were diagnosed with CBD based on observation of granulomas in lung biopsy samples. An additional two employees had abnormal blood results from one of the two laboratories and had no granulomas in lung biopsy samples. Both employees developed abnormal blood results in the other laboratory within 2 years. One of these two employees also developed symptoms of CBD. The other employee declined clinical follow-up. An additional case of CBD was found during the study in an employee hired in 1991, who had a nonhealing granulomatous response to a beryllium-contaminated skin wound. This subject had a confirmed abnormal blood test, and after several additional months developed lung granulomas. Only one CBD case had an abnormal chest X-ray. An additional 11 former employees had CBD, for a total prevalence of 19/709. Beryllium-sensitized cases were similar to nonsensitized ones in terms of age, ethnic background, or smoking status, but did have significantly fewer pack-years of smoking. There was also no significant difference in percentage exposed to beryllium dust or mist in an accident or unusual incident, or those in areas with a posted high air count. Of the eight sensitized workers, seven had worked in machining at some point, while one case had never worked in a production job. The beryllium sensitization rate was 14.3% among the machinists, compared to 1.2% among all other employees. The individual average exposures for the six CBD cases and two sensitized cases among current employees ranged from 0.2 to $1.1 \mu\text{g}/\text{m}^3$, and the cumulative exposure ranged from 92.6 to $1,945 \mu\text{g}/\text{m}^3\text{-days}$. Two of the seven beryllium-sensitized machinists started machining prior to the systematic environmental monitoring, and exposure estimates for these two subjects may have been underestimated. The median of estimated average beryllium exposure for the sensitized cases was about $0.55 \mu\text{g}/\text{m}^3$. The sensitized cases without disease did not have lower exposures than the CBD cases. Machinists may have been more susceptible than other groups because of their higher overall exposure or because the particles produced during

machining were primarily respirable in size, while other exposures were to particles larger than the respirable range ($< 10 \mu\text{m}$). Other characteristics of the machining exposure, such as the particle morphology, particle surface properties, and adjuvants in machining fluids, may also have affected sensitization. The study authors noted that median breathing zone levels tended to be lower than the DWAs derived from these levels because much of the day was typically spent in high-exposure tasks. This study identified a LOAEL of $0.55 \mu\text{g}/\text{m}^3$ and a LOAEL(HEC) adjusted for an occupational exposure of $0.19 \mu\text{g}/\text{m}^3$.

Eisenbud et al. (1949) evaluated beryllium exposure for 11 community cases of CBD. CBD was defined based on limited radiographic and pathologic examination. Radiologic screening of 10,000 residents was conducted, with questionable cases undergoing clinical evaluation. CBD was diagnosed based on radiologic and clinical findings from a consensus of specialists, but no sensitization information. One case was exposed to beryllium dust on worker clothes and will not be discussed further. Of the other cases, five lived within 0.25 mile of a beryllium production plant and all lived within 0.75 mile of the plant. A follow-up to this study reported three additional cases at less than 0.75 miles from the plant, but no additional cases of CBD at greater than 0.75 miles (Stern and Eisenbud, 1951). Measurements downwind from the plant found that the beryllium concentration at 0.75 miles was about $0.045 \mu\text{g}/\text{m}^3$, and continuous sampling stations found that the average concentration at about 700 feet from the plant (the furthest distance within the affected area) was $0.05 \mu\text{g}/\text{m}^3$ (range 0 to $0.46 \mu\text{g}/\text{m}^3$). The emitted beryllium was primarily as beryllium oxide, although beryllium fluoride and beryl (beryllium ore) were also present. The study authors also calculated an estimated exposure, based on emissions levels, stack heights, and wind speed data. These estimates were generally in good agreement with the downwind data. Based on these calculations, the authors estimated that the average exposure levels at 0.75 miles from the plant during the period of exposure monitoring were 0.004 to $0.02 \mu\text{g}/\text{m}^3$. Averaging this value to $0.01 \mu\text{g}/\text{m}^3$, and noting that both plant production and emissions were about 10-fold higher in earlier years, the authors estimated that the concentration at 0.75 mile was 0.01 to $0.1 \mu\text{g}/\text{m}^3$. The similar prevalence of CBD in the community compared to workers exposed to much higher levels (100 to $1,000 \mu\text{g}/\text{m}^3$) was attributed to the smaller particle size of beryllium emitted to the outside air compared to beryllium particles inside the plant. This study, although limited by classification of CBD, suggest a NOAEL(HEC) of 0.01 to $0.1 \mu\text{g}/\text{m}^3$ for the development of CBD in a population exposed to beryllium in ambient air.

Few data are available on the particle characteristics of beryllium under occupational exposure conditions. However, Hoover et al. (1990) found that 5.7% of the particles released during sawing beryllium metal had aerodynamic diameters smaller than $25 \mu\text{m}$ but larger than $5 \mu\text{m}$, and 0.3% were smaller than $5 \mu\text{m}$. For milling of beryllium metal, 12% to 28% of the particles had aerodynamic diameters between 5 and $25 \mu\text{m}$, and 4% to 9% were smaller than $5 \mu\text{m}$, depending on the milling depth. More than 99% of the particles generated from operations conducted with beryllium alloys were larger than $25 \mu\text{m}$.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 10.

The available data suggest that only a small percentage of the population (1% to 5%) appears to be susceptible to CBD (Kreiss et al., 1994). Because individuals developing beryllium sensitization and CBD are the most sensitive subpopulation, an uncertainty factor of 1 was used to account for human variability. An uncertainty factor of 1 was also used to adjust for the less-than-chronic exposure duration of the Kreiss et al. (1996) study; use of this uncertainty factor is supported by the evidence that the occurrence of CBD does not appear to be related to exposure duration. Because the screening method used in the Kreiss et al. (1996) study was more sensitive than the methods used in the Eisenbud et al. (1949) study, the RfC was derived from the LOAEL (Kreiss et al., 1996) with an

uncertainty factor of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization). A database uncertainty factor of 3 was used to account for the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies that assessed the incidence of beryllium sensitization and CBD among exposed workers and community residents. Although there are no developmental studies or 2-generation reproduction studies, a limited continuous breeding study found that beryllium does not cause reproductive or developmental effects following intratracheal administration (Clary et al., 1975). In addition, systemic distribution of beryllium is less than 1% (U.S. EPA, 1987), and any systemic effects would be expected to occur at exposure levels much above the very low levels at which CBD is observed.

MF = 1.

I.B.4. Additional Studies/Comments (Inhalation RfC)

A. SUPPORTING STUDIES

Cullen et al. (1987) detected five likely cases of CBD (using the beryllium case registry definition of CBD) in workers who were exposed to beryllium oxide fumes at a precious metals refinery for 4 to 8 years before the development of symptoms. Time-weighted average personal air samples for beryllium ranged from 0.22 to 42.3 $\mu\text{g}/\text{m}^3$ throughout the plant, and 10% of the samples were greater than 2.0 $\mu\text{g}/\text{m}^3$. However, four of the cases worked predominantly in the furnace area, where beryllium exposure was measured at $0.52 \pm 0.44 \mu\text{g}/\text{m}^3$ (maximum measurement 1.7 $\mu\text{g}/\text{m}^3$). No additional cases were found in the screening of current workers, but a fifth was identified after the screen. This subject worked as a crusher, where exposure was to beryllium metal dust at $2.7 \pm 7.2 \mu\text{g Be}/\text{m}^3$. The CBD cases had the classic signs of CBD, including radiologically visible hilar adenopathy, noncaseating granuloma and pulmonary fibrosis in biopsy samples, and decreased carbon monoxide diffusing capacity (DLCO). Symptoms progressed even after removal from exposure. Beryllium sensitization was shown in vitro with BAL lymphocytes. Three of the cases were considered to have CBD, while diagnosis of two (both in the furnace area) was complicated by a history of hilar enlargement in one; the other had schistosomiasis and no BAL stimulation data. The study authors also analyzed beryllium exposure levels by job classification and screened 45 of 70 current workers for CBD, using interviews and analysis of spirometry data and chest radiographs from routine testing. No in vitro screening for beryllium sensitization was conducted on the general worker population. Noting that the prevalence of CBD was highest at a task with lower exposure levels, the study authors suggested that the beryllium oxide fumes to which workers were exposed in the furnace area were more toxic than the beryllium metal dust to which workers were exposed at other tasks. Alternative explanations for the development of disease following low-level exposure were considered unlikely. Although sampling efficiency was low for particles < 0.8 microns, these small particles were not considered to contribute significantly to the overall mass; however, because of their great surface area, they may have been much more toxic than larger particles. Although the study authors note that there were no significant changes in work practices during the previous 20 years, it is possible that the retrospective sampling conducted in a 2-week period may not accurately reflect past and present exposure conditions. The LOAEL in this study was 0.52 $\mu\text{g}/\text{m}^3$, with a LOAEL(HEC) after adjusting for occupational exposure of 0.18 $\mu\text{g}/\text{m}^3$.

CBD has resulted in death, especially in earlier years, when exposure was much higher than it is now. In a cohort mortality study of 689 patients with CBD who were included in the case registry, there was a high rate of deaths due to pneumoconiosis, primarily CBD (SMR = 34.23, 158 deaths) (Steenland and Ward, 1991). Similar results were observed in an earlier analysis of deaths due to nonneoplastic respiratory disease in the beryllium case registry (Infante et al., 1980). Deaths have also been reported in community cases of CBD, including in a 10-year-old girl (Lieben and Williams, 1969). Some of these cases have been confirmed based on histological evidence of CBD and evidence of beryllium in the lungs.

In addition, CBD has been reported in people not occupationally exposed to beryllium, including people living in communities near beryllium plants (Chesner, 1950; Dattoli et al., 1964; Lieben and Metzner, 1959) and in families of beryllium workers who wore contaminated clothing at home. These cases have been markedly reduced by better hygiene, including mandatory work clothes exchange, but nonoccupational CBD still has been reported following low-level episodic exposure of family members (Newman and Kreiss, 1992).

The onset of CBD from initial exposure (latency) ranges from a few months to an average of 23.7 years (Kreiss et al., 1993); however, at the present time there is no clear relationship between duration of exposure and the development of the disease. Some studies suggest that early stages of CBD can be reversed (Rom et al., 1983; Sprince et al., 1978), although these conclusions are weakened by methodological limitations of these studies (Kanarek et al., 1973; Kriebel et al., 1988b; Rom et al., 1983); however, beryllium sensitization was observed to progress to CBD even in the absence of continued exposure, suggesting that abnormal BeLT test findings are predictive of future development of CBD (Kreiss et al., 1994).

A number of earlier studies have characterized the signs and symptoms of CBD. Clinical, radiographic, and traditional spirometric signs of CBD are less sensitive than histologic findings and immunologic screens using the BeLT. Computed tomography (CT) can identify some CBD cases missed by chest radiography, but even CT missed 25% of histologically confirmed cases (Newman et al., 1994). Initial symptoms of early cases of CBD typically include dyspnea, cough, fatigue, weight loss, and chest pain (Aronchik, 1992; Hasan and Kazemi, 1974; Kriebel et al., 1988c; Meyer, 1994; Sterner and Eisenbud, 1951; Williams, 1993). Other symptoms included bibasilar crackles, clubbing of the fingers and skin lesions, heart failure, and an enlarged liver or spleen. Prominent diagnostic findings are diminished vital capacity, diffuse infiltrates, and radiographically visible hilar adenopathy. Fibrosis occurs at late stages in the disease. Granulomatous inflammation also has been reported in extrapulmonary organs, such as extrapulmonary lymph nodes, skin, liver, spleen, kidney, bone, myocardium, central nervous system, and skeletal muscle.

The development of fiberoptic bronchoscopy and transbronchial biopsy methods has allowed the identification of subclinical cases of CBD. Newman et al. (1989) evaluated respiratory symptoms and physical examination results in 12 cases of newly identified CBD based on (1) a history of beryllium exposure, (2) histopathological evidence of noncaseating granulomas or mononuclear cell infiltrates, and (3) a positive blood or BAL BeLT. Based on these findings, the authors suggested that CBD be classified into (1) sensitization, (2) subclinical beryllium disease (sensitized subjects with histopathological evidence, but no clinical signs), and (3) beryllium lung disease (as for [2], but with respiratory symptoms, changes on chest radiographs, or altered pulmonary physiology).

The BeLT has allowed the identification of an exposure-response relationship for beryllium sensitization (Kreiss et al., 1993a). Kreiss et al. (1989) used the peripheral blood BeLT to screen occupationally exposed populations for CBD, and found that 6/51 (11.8%) of the currently exposed workers were sensitized. No sensitized cases who had not yet developed CBD were identified, perhaps because of the long latency period. Although subjects identified based on BeLT test results may not have clinical signs of CBD, many do exhibit functional impairment (Pappas and Newman, 1993).

B. GENETICS OF BERYLLIUM SENSITIVITY

Evidence from a variety of sources shows that genetic susceptibility plays a role in the development of CBD. Early occupational studies proposed that CBD was an immune reaction with a genetic component, based on the extreme sensitivity of certain individuals and the lack of CBD in others who are exposed to levels several orders of magnitude higher (Sterner and Eisenbud, 1951). Animal studies support these results. Immune granulomas are observed in strain 2 guinea pigs, but not in strain 13 guinea pigs, which differ from strain 2 only at the MHC Ia locus (Barna et al., 1984a). Similarly, beryllium

inhalation caused immune granulomas in A/J mice, but not in BALB/c or C57B1 mice, which have different MHC class 2 genes (Huang et al., 1992). These studies suggest that differences in CBD susceptibility are related to differences at the MHC locus. Saltini et al. (1989) demonstrated that T cells only respond to the antigen (in this case, beryllium or beryllium plus some protein) in association with MHC class II molecules on the surface of the antigen-presenting cell. Granuloma formation has been hypothesized to result from a cytokine amplification loop involving macrophages, lymphocytes, and other factors (Newman, 1996).

Recent studies have identified a genetic marker linked to CBD susceptibility. The MHC class II region includes the HLA-DR, DQ, and DP genes. Richeldi et al. (1993) and Stubbs et al. (1996) reported associations between the presence of MHC class II alleles and the development of CBD in beryllium-exposed workers. Both studies found a biased distribution of HLA-DPB1 alleles (glutamine in position 69) in beryllium-sensitized subjects. They also found a biased distribution of the MHC class II HLA-DR gene, but found no association with specific amino acid changes. Thus, neither of these markers are completely specific for CBD, but the data do support a strong genetic contribution to CBD susceptibility, and the markers may be useful for screening for sensitive workers. It is also not clear if the association between either allele and CBD is a causal one. However, Richeldi et al. (1993) noted that structure-function studies of MHC class II molecules indicate that the amino acid change associated with CBD may affect an amino acid that plays a critical role in antigen binding. The more common allele of HLA-DP1 has a positively charged amino acid (lysine) at position 69, while the glutamate-69 variant is negatively charged at this site and could directly interact with the beryllium ion. Nonetheless, the high percentage (~30%) of exposed workers without CBD who had this allele suggests that other factors also contribute to the development of CBD. The beryllium exposure level plays at least some role, since the overall prevalence of CBD in exposed workers is 2% to 5%, while the prevalence at certain highly exposed tasks is as much as 15% (Kreiss et al., 1993a, 1996).

C. CHRONIC ANIMAL STUDIES AND MODELS

Although a number of chronic studies in laboratory animals have been conducted with beryllium compounds, few have been done using modern criteria for high-quality toxicology studies. In addition, whereas several laboratory animal species (such as mice, dogs, and monkeys) respond to beryllium exposure with several features of human CBD, no laboratory animal model fully mimics all features of human CBD. In particular, the animal models fail to demonstrate a model that has a progressive granulomatous pulmonary response with a concomitant beryllium-specific immune response. In addition, no chronic studies are available on nonneoplastic effects of beryllium oxide, the most environmentally relevant form.

Considerable research has investigated the mechanism of CBD and attempted to identify an appropriate animal model for CBD. An appropriate animal model for CBD is one that forms immune granulomas following the inhalation of beryllium dust or fume. These immune granulomas are distinct from granulomas formed by foreign-body reactions (Haley, 1991). Immune granulomas result from persistent antigenic stimulation, while foreign-body granulomas result from persistent irritation. Histologically, foreign-body granulomas consist predominantly of macrophages and monocytes and small numbers of lymphocytes. By contrast, immune granulomas are characterized by larger numbers of lymphocytes, primarily T lymphocytes, known as T-cells. The studies (Haley et al., 1990; Finch et al., 1994; Haley, 1991; Sendelbach et al., 1986; Hart et al., 1984; Sanders et al., 1975) show that acute beryllium disease occurs in the rat, but the rat is not an appropriate model for CBD because it does not mount an immune response to inhaled beryllium. Mice may be an appropriate model for CBD, although not all aspects of the disease have been replicated in this species in these studies (Haung et al., 1992; Finch et al., 1996). The guinea pig and beagle dog may be good models for CBD based on the studies by Barna et al. (1981, 1984a,b) with respect to the guinea pig and Haley et al. (1989, 1992) with respect to the dog. In the case of guinea pigs, intratracheal instillation of beryllium oxide can induce both immune granulomas containing a T lymphocyte component and a

beryllium-specific immune response. However, the effect has not yet been demonstrated under physiological conditions (inhalation exposure), and specificity for beryllium over other metals has not been demonstrated. In the case of the beagle dog, granulomatous lesions and lung lymphocyte responses consistent with those observed in humans with CBD were observed following a single exposure (perinasally; 0.01 μg beryllium/ m^3 for 5 to 40 min) to beryllium oxide aerosol generated from beryllium oxide calcined at 500 or 1,000C. However, Conradi et al. (1971) found no exposure-related histological alterations in the lungs of six beagle dogs exposed to a range of 3,300 to 4,380 μg Be/ m^3 as beryllium oxide calcined at 1,400C for 30 min, once per month for 3 mo.

Conradi et al. (1971) found no effect in monkeys (*Macaca irus*) exposed via whole-body inhalation for three 30-min monthly exposures to a range of 3,300 to 4,380 μg Be/ m^3 as beryllium oxide calcined at 1,400C. On the other hand, Haley et al. (1994) showed that beryllium can induce immune granulomas and beryllium sensitization to beryllium metal and not BeO in monkeys, although this was not shown using a physiologically relevant route, namely, intrabronchiolar instillation.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

I.B.5. Confidence in the Inhalation RfC

Study -- Medium
Database -- Medium
RfC -- Medium

The overall confidence in this RfC assessment is medium. The RfC is based on an occupational inhalation study performed with a moderate to large group size (136 subjects screened) in which sensitive measures were used to identify the affected population (Kreiss et al., 1996). No NOAEL was identified in this study, but a NOAEL slightly below the LOAEL(HEC) was suggested in a study using less sensitive methods of diagnosing CBD in a population exposed to high levels of beryllium in ambient air (Eisenbud et al., 1949). The poor quality of the exposure monitoring in the co-principal studies decreases the confidence in the principal studies to medium. The confidence in the database is also medium. A common limitation in the database is the lack of adequate exposure monitoring in the epidemiology studies and some uncertainty regarding the mechanism (and beryllium exposure levels) associated with the progression to CBD in beryllium-sensitized individuals. Several human and animal studies are currently being conducted that may provide additional information on the mechanisms of action and data that would be useful for dose-response assessment. In particular, several investigators are conducting screening and monitoring studies of workers at the Rocky Flats Environmental Technology site and Oak Ridge site. Although no inhalation developmental or multigenerational reproductive studies were available for beryllium, no reproductive effects were observed in an intratracheal reproduction study in animals at exposure levels above those causing CBD (Clary et al., 1975). In addition, the unusually low level at which CBD occurs, together with the low systemic distribution of inhaled beryllium, mean that any developmental effects would occur at levels much higher than those causing CBD. Reflecting the medium confidence in the principal studies and database, confidence in the RfC is medium.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document -- U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been

evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review of Beryllium in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). *To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF).*

Other EPA Documentation -- U.S. EPA, 1987; U.S. EPA, 1991

Agency Consensus Date-- 03/26/1998

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (301) 345-2870 (phone), (301) 345-2876 (fax) or Hotline.IRIS@epamail.epa.gov (Internet address).

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__II. Carcinogenicity Assessment for Lifetime Exposure

Beryllium and compounds
CASRN -- 7440-41-7
Last Revised -- 04/03/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per $\mu\text{g/L}$ drinking water or risk per $\mu\text{g/m}^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (U.S. EPA, 1986) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (U.S. EPA, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

B1; probable human carcinogen. Based on the limited evidence of carcinogenicity in humans exposed to airborne beryllium (lung cancer) and sufficient evidence of carcinogenicity in animals (lung cancer in rats and monkeys inhaling beryllium, lung tumors in rats exposed to beryllium via intratracheal instillation, and osteosarcomas in rabbits and possibly mice receiving intravenous or intramedullary injection), beryllium is reclassified from a B2 (inadequate human data) to a B1 probable human carcinogen (limited human data) using criteria of the 1986 Guidelines for Carcinogen Risk Assessment. Using the 1996 proposed Guidelines for Carcinogen Risk Assessment, inhaled beryllium would be characterized as a "likely" carcinogen in humans, and the human carcinogenic potential of ingested beryllium cannot be determined.

Studies regarding the potential carcinogenicity of ingested beryllium to humans were not

available. Increases in lung cancer mortality have been observed in cohort mortality studies of beryllium processing workers (Ward et al., 1992; Wagoner et al., 1980; Mancuso, 1979, 1980) and in studies of entrants on the BCR (Steenland and Ward, 1991; Infante et al., 1980). No increases in other types of cancer were found, but increases in deaths from nonmalignant respiratory disease were also observed. Newer studies, particularly the occupational study of Ward et al. (1992), have been considered as the basis for a dose-response assessment, but share a limitation with the Wagoner et al. (1980) study--lack of individual exposure monitoring or job history data that would support a more definitive exposure assessment. NIOSH has recently completed a lung cancer case-control study nested within a cohort mortality study of beryllium manufacturing workers at the Reading beryllium processing facility. The study developed an exposure matrix and calculated airborne beryllium exposure concentrations and thus may provide the best available basis for a quantitative cancer estimate. Rather than calculate an interim quantitative estimate based on the Ward et al. (1992) data and poorly defined exposure estimates, the existing unit risk based on the Wagoner et al. (1980) study is retained until the NIOSH assessment can be evaluated as the basis for a quantitative estimate.

Chronic oral studies of the potential carcinogenicity of beryllium in animals were conducted at dose levels below the MTD, and therefore are inadequate for the assessment of carcinogenicity. Beryllium has been shown to induce lung cancer in rats exposed to beryllium by both inhalation and intratracheal instillation and in monkeys by inhalation. Osteosarcomas have been produced in rabbits and possibly in mice by intravenous and intramedullary injection using a variety of beryllium compounds and beryllium metal. No tumors were produced by intracutaneous or percutaneous injections of beryllium compounds.

The majority of studies do not induce gene mutations in bacterial assays with or without metabolic activation. Gene mutations have been observed in mammalian cells cultured with beryllium chloride. Culturing mammalian cells with beryllium chloride, beryllium sulfate, or beryllium nitrate has resulted in clastogenic alterations.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

__II.A.2. Human Carcinogenicity Data

Limited. The most recently published studies are cohort mortality studies of beryllium processing workers (Ward et al., 1992) and of entrants to the beryllium case registry (Steenland and Ward, 1991). The Ward et al. (1992) is a follow-up to the studies by Mancuso (1979, 1980) and Wagoner et al. (1980) and the Steenland and Ward (1991) is a follow-up to the study by Infante et al. (1980).

Wagoner et al. (1980) conducted a cohort mortality study of 3,055 white males employed between 1942 and 1967 at a beryllium extraction, processing, and fabrication facility in Reading, Pennsylvania. The study cohort was followed through 1975. The total number of deaths (875) was not significantly different from the number expected on the basis of age and calendar time period for the general white male U.S. population (vital statistics data for the period 1965-1967 were assumed to be those of 1968-1975). Significant ($p < 0.05$) increases in the number of deaths due to malignant neoplasm of trachea, bronchus, and lung (47 deaths observed versus 34.29 expected, SMR = 1.37), heart disease (SMR = 1.13), and nonneoplastic respiratory disease (excluding influenza and pneumonia) (SMR = 1.65) were observed in the study cohort. When deaths from lung cancer were segregated by latency (interval since onset of employment) and duration of employment, significant increases were observed for workers with a 25-year latency employed for < 5 years (17 observed versus 9.07 expected, SMR = 1.87) and across all employment

durations (20 observed versus 10.79 expected, SMR = 1.87). (It should be noted that 83% of the cohort was employed for < 5 years.) When lung cancer mortalities were partitioned based on initial date of employment, lung cancer deaths were significantly higher in workers hired before 1950 (SMR = 1.35; $p < 0.05$); an increase in deaths in workers hired after 1950 was also found, but it was not statistically significant (SMR = 1.52). (Prior to 1950, beryllium exposures were not controlled and it is likely that the workers were exposed to high concentrations of beryllium.) Similar findings were reported when nonneoplastic respiratory disease mortalities were segregated; a significant increase in mortality was observed in the workers in the 25-year latency and < 5-year employment category (SMR = 2.13). In the workers who were hired prior to 1950, a significant increase in mortality from nonneoplastic respiratory disease was observed (SMR = 1.85). This was not observed for workers whose initial date of employment was after 1950 (0 deaths observed versus 2.03 expected).

Wagoner et al. (1980) compared cigarette smoking histories of the cohort and the U.S. population using smoking habit information collected during a medical survey in 1968 and cigarette smoking data for white males from a Public Health Service Survey conducted in 1964-1965. A smaller percentage of the cohort were current smokers (49.6% never smoked or were former smokers versus 45.2% in the U.S. population), but the percentage of current smokers smoking more than one pack per day was higher (21.4% versus 15.3%).

Limitations of the study include the following:

1. The use of U.S. white male mortality data for the period of 1941 to 1967, which resulted in an underestimation of the number of expected lung cancer deaths because lung cancer death rates in the United States were increasing during the period 1968-1975. The expected number of lung cancer deaths should have been 10% to 11% higher (U.S. EPA, 1987; Saracci, 1985).
2. The inclusion of one lung cancer death of an individual who was paid for the pre-employment physical but was not hired (U.S. EPA, 1987).
3. The exclusion of approximately 300 white males employed at the Reading facility in similar jobs as the workers included in the cohort (U.S. EPA, 1987).
4. The inadequate discussion of confounding effects from other potential lung carcinogens (U.S. EPA, 1987).

These limitations tended to exaggerate the risk of lung cancer in this population of workers potentially exposed to beryllium (MacMahon, 1994; U.S. EPA, 1987).

EPA (1987) adjusted the lung cancer SMRs from the Wagoner et al. (1980) study. The expected lung cancer deaths were increased by 11% to account for the underestimation that occurred from using older U.S. vital statistics and by 4.1% to account for differences in smoking habits between the beryllium cohort and the U.S. population. The one ineligible lung cancer death was removed from the observed deaths. Although the SMRs for latency 25 years remained elevated after this adjustment (1.42 for < 5 years employment and 1.36 across all durations of employment), they were no longer statistically significant at $p < 0.05$.

Ward et al. (1992) conducted a retrospective cohort mortality study of 9,225 men (5,681 alive and 3,240 dead) employed for at least 2 days between January 1, 1940, and December 31, 1969, and followed through December 31, 1988, at any one of seven beryllium processing facilities located in Reading, PA, Hazleton, PA, Lorain, OH, Cleveland, OH (data for Perkins and St. Clair plants combined), Lucky, OH, and Elmore, OH. Cohort members were identified from quarterly earning reports from the Social Security Administration and compared to personnel files. Workers identified from quarterly earning reports without personnel files were only included in the cohort if they appeared on at least two quarterly earning reports. Workers who worked at more than one facility were placed into a seventh category termed "multiple plant." Vital statistics for the workers were obtained from the Social Security Administration, Internal Revenue Service, post office cards mailed to the last known address, Veterans Administration,

Health Care Financing Administration, and the National Death Index. Vital statistics were not located for 304 (3.3%) individuals, and death certificates were not obtained for 46 (0.4%) individuals known to be deceased.

The workers at the beryllium processing facilities were involved in the extraction of beryllium hydroxide from beryl ore; the production of beryllium oxide, pure beryllium metal, and beryllium copper alloy; and the machining of beryllium-containing products. The beryllium compounds the workers were potentially exposed to included beryllium sulfate mists and fumes, beryllium oxide dusts, beryllium ammonium fluoride and beryllium fluoride dusts, beryllium metal, and beryllium copper alloy dusts and fumes. In addition to exposure to beryllium, the workers also were potentially exposed to ore dust, silicon dioxide fumes, lead sulfide, copper sulfide, sulfur trioxide, acid fluoride mists, hydrogen fluoride, and ammonium fluoride. In addition, according to the Beryllium Industry Scientific Advisory Committee (BISAC) (1997), exposure to sulfuric acid mists and fumes occurred in the Lorain facility. Because no occupational history data other than starting and ending dates of employment were coded, and no individual monitoring data were available, the study could not address the relationship of degree of beryllium exposure or type of beryllium compound to lung cancer risk. Ward et al. (1992) noted that prior to 1949 when controls were not mandated, air concentrations of beryllium were very high, frequently exceeding 1,000 $\mu\text{g}/\text{m}^3$.

When mortality from all causes in the entire cohort was compared to mortality rates from the U.S. population, a significant ($p < 0.05$) increase in risk was observed (SMR of 1.05, 95% confidence interval [CI] of 1.01-1.08). Excess deaths were also observed for malignant neoplasm of the trachea, bronchus, and lung (SMR = 1.26, 95% CI = 1.12-1.42), ischemic heart disease (SMR = 1.08, 95% CI = 1.01 to 1.14), pneumoconiosis and other respiratory disease (SMR = 1.48, 95% CI = 1.21-1.80), and chronic and unspecified nephritis, renal failure, and other renal sclerosis (SMR = 1.49, 95% CI = 1.00-2.12). Examination of the cause of death on a per plant basis revealed that only the Lorain and Reading facilities (the two oldest plants) had significant excesses in lung cancer: total SMRs of 1.69 and 1.24, respectively. In addition, the Cleveland and Hazleton facilities had nonsignificant excesses in lung cancer (total SMRs > 1).

A significant excess of pneumoconiosis and other respiratory disease was also observed at the Lorain facility (SMR = 1.94). Increased employment duration was not associated with an increase in lung cancer SMR; when lung cancer mortalities were stratified by employment duration category, the only significant increase in lung cancer SMRs was for workers employed < 1 year. However, there was a tendency for lung cancer SMRs to increase with increasing latency; SMRs were statistically significantly elevated in the > 30-year latency category for all employment durations combined (SMR = 1.46) and for workers employed for < 1 year (SMR = 1.52), and in the 25- to 30-year latency category for workers employed for < 1 year. Additionally, decade of hire influenced lung cancer mortality. The SMR (1.42) was statistically elevated in workers hired before 1950; this was mainly influenced by mortality in the Lorain plant, which closed in 1948. Of the other facilities in operation before 1950 (Reading and Cleveland), an increased lung cancer rate was found at the Reading facility (SMR = 1.26 for workers hired before 1950). With the exception of those hired before 1950 (total SMR = 1.42), no other significant increases in lung cancer deaths were observed when workers were grouped by decade of hire. Nonsignificant increases were seen for the 1950s decade at the Reading (SMR = 1.42), Cleveland (SMR = 1.32), Elmore (SMR = 1.42), and Hazleton (SMR = 1.86) facilities. Regression analysis (controlling for age, race, and calendar period of risk) showed that decade of hire was independent of potential latency (time since first employment).

The influence of geographic variation in lung cancer mortality was evaluated comparing lung cancer mortality found in the beryllium cohort to lung cancer rates for the cohort where most of the workers resided. Lung cancer mortality was significantly elevated in workers at the Lorain (SMR = 1.60, 95% CI = 1.21-2.08) and Reading (SMR = 1.42, 95% CI = 1.18-1.69) facilities as compared to residents of Lorain County and Berks County, respectively. The investigators noted that county residents may not serve as a better

referent group than the U.S. population because the percentage of workers at the Lorain and Reading facilities residing in an urban area was approximately 3 times higher than the percentage of county residents living in urban areas.

Data on the smoking habits of the entire beryllium cohort were not available. Some information was available from a 1968 Public Health Service survey conducted at the Reading, Hazleton, Elmore, and St. Clair facilities (it included 15.9% of the cohort members). These data were compared to smoking habits of the United States population obtained from averaging smoking surveys conducted in 1965 (National Center for Health Statistics) and 1970 (Office of Health Research, Statistics, and Technology). The estimated relative risk ratio for lung cancer for the beryllium cohort to the United States population was calculated using estimated risks of 1 for nonsmokers, 6.5 for current smokers of 1 pack per day, 13.8 for smokers of > 1 pack per day, and 6.2 for former smokers. The relative risk ratio or smoking adjustment was 1.1323, which indicates that smoking alone could account for an SMR of 1.13.

Using the smoking adjustment factor, smoking-adjusted SMRs were calculated for the entire cohort and the Lorain and Reading facilities. The resultant SMRs were 1.12, 1.49, and 1.09, respectively. One process exposure, to which BISAC (1997) attributed the excess cancer (SMR 1.49) after adjustment for smoking, and which was briefly mentioned by Ward et al. (1992), is exposure to mists and vapors from sulfuric acid and the related sulfur oxide gases. Such exposure, according to BISAC (1997), was very high in the Lorain plant. This was the only plant that used a sulfuric acid-dependent process with limited ventilation (Kjellgren, 1946); at the time, the occupational inhalation risks associated with airborne beryllium (acute pneumonitis) and airborne sulfuric acid (respiratory cancer) had not yet been established. Because the 1968 survey data are the only information available on the smoking habits of the beryllium cohort, an assumption was made that the smoking habit difference between the cohort and the United States population found in the late 1960s was the same in the 1940s and 1950s. Other investigators have shown that increased smoking is unlikely to account for SMRs greater than 1.3 for lung cancer and other smoking-related diseases (Siemiatycki et al., 1988).

Ward et al. (1992) examined the beryllium case registry (BCR) mortality study file to determine how many of the members of the cohort were registered (i.e., had a history of beryllium disease). The Lorain plant had highest percentage of registrants--8.2% (98 of 1,192 workers); 93% of these were listed as having had acute beryllium disease, which is associated with very high exposure (Eisenbud and Lisson, 1983). The lung cancer SMR for the Lorain workers on the BCR was 3.33 (95% CI = 1.66-5.95) compared to 1.51 (95% CI = 1.11-2.02) for the remaining Lorain workers.

Ward et al. (1992) concluded that a plausible explanation for the observed increased lung cancer rates is occupational exposure to beryllium. Although the results of this study are suggestive that occupational exposure to beryllium can result in an increase in lung cancer mortality, interpretation of this study is limited by a number of factors:

1. No data (including job history data) were available to associate beryllium exposure levels, exposure to specific beryllium compounds, or concomitant exposure to other chemicals with members of the cohort.
2. Because of the lack of job history data, it is possible that the cohort contained salaried workers and other nonproduction personnel who may not have been exposed to beryllium.
3. The limitations in the available smoking habit data, as discussed above, may have led to an over- or underestimation of the contribution of smoking to the lung cancer rates.
4. A large percentage (73.1%) of the workers were employed in the beryllium industry for 5 years. This is particularly true at the Lorain facility, where 84.6% of the workers were employed for < 1 year. EPA (1987) points out that there is a possibility that the workers were exposed to other potential carcinogens at jobs held before or after the beryllium job; the two facilities with the highest cancer rates (Lorain and Reading) are located in or near heavily industrialized areas.

Regardless of the shortcomings of the epidemiological studies of beryllium exposure, the results of the follow-up mortality studies on the same cohort and of the BCR cohort studies are suggestive of a causal relationship between beryllium exposure and an increased risk of lung cancer. The increased incidences of lung cancers among workers with acute beryllium disease (presumably these workers were exposed to very high concentrations of beryllium), the higher incidences of lung cancers among workers first employed when exposure levels were very high, a consistent finding of lung cancer excesses in six of seven beryllium processing facilities, and the occurrence of the highest risks for lung cancer in plants where the risk for nonmalignant respiratory disease is the highest strengthen this conclusion.

II.A.3. Animal Carcinogenicity Data

Sufficient. Lung tumors have been induced via inhalation and intratracheal administration to rats and monkeys, and osteosarcomas have been induced via intravenous and intramedullary injection in rabbits and possibly in mice. The chronic oral studies did not report increased incidences of tumors in rodents, but these were conducted at doses below the MTD.

In a chronic toxicity study by Morgareidge et al. (1975, 1977), groups of Wistar albino rats were fed diets containing 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate. The rats were administered the beryllium containing diet from 4 weeks of age through maturation, mating, gestation, and lactation. Fifty male and 50 female offspring were then placed on the same diets as the parents and fed the beryllium-containing diet for 104 weeks. Using estimated TWA body weights of 0.467, 0.478, and 0.448 kg for males in the 5, 50, and 500 ppm groups and 0.294, 0.302, and 0.280 kg for the females, respectively, and U.S. EPA's (1988) allometric equation of food intake, doses of 0.36, 3.6, and 37 mg/kg-day for males in the 5, 50, and 500 ppm groups and 0.42, 4.2, and 43 mg/kg-day for females in the 5, 50, and 500 ppm groups, respectively, were calculated. Clinical observations, body weight, food consumption, organ weights (liver, kidney, testes, ovaries, thyroid, pituitary, adrenal), gross necropsy, and histopathological examination of most tissues and organs (25 to 26 tissues examined) were used to assess the toxicity and carcinogenicity of beryllium in the offspring; it does not appear that the P₀ rats were examined. Tissues from 20 rats/sex/group in the control and 500 ppm groups were examined microscopically (the study authors did not state whether the animals undergoing histopathological examination were randomly selected), as well as all tissues with gross abnormalities (all groups) and tissues (excluding bone marrow, eyes, and skin) from animals found dead or sacrificed moribund (all groups).

No overt signs of toxicity were observed, and mortality appeared to be similar in the controls (30/50 males and 28/50 females died) and beryllium groups at 5 ppm (30/50 and 24/50, respectively), 50 ppm (31/50 and 18/50), and 500 ppm (24/50 and 17/50) at the end of the 104 weeks of the study. During the first 40 to 50 weeks of the study, exposure to beryllium did not appear to affect growth; slight decreases in growth (body weights of males and females in the 500 ppm group were within 10% of control body weights) were observed in the latter part of the study; however, no statistically significant alterations were observed. Alterations in organ weights were limited to statistically significant ($p < 0.05$) increases in relative kidney weight in males exposed to 50 ppm, decreases in relative kidney and adrenal weights in 500 ppm females, and decreases in relative testes weights in 5 and 50 ppm males. Histological examination of the major organs and tissues did not reveal beryllium-related noncarcinogenic alterations. These data suggest that the maximum tolerated dose (MTD) was not reached.

Reticulum cell sarcomas were observed in a number of tissues examined including the lungs, lymph nodes, spleen, liver, kidneys, and pancreas; the highest incidence was in the lungs. Because lymphomas (reticulum cell sarcoma is a type of lymphoma) are almost always detected grossly, reticulum cell sarcoma incidences were calculated based on the number of tissues grossly examined (all gross diagnoses were confirmed histopathologically) rather than on the number of tissues microscopically examined. In

most organs, the incidence of reticulum cell sarcomas was not significantly higher in the beryllium-exposed rats, as compared to controls. In the lung, the incidences of reticulum cell sarcoma were 10/50, 17/50, 16/50, and 12/50 in males and 5/50, 7/50, 7/50, and 5/50 in females exposed to 0, 5, 50, or 500 ppm beryllium, respectively. The incidences of lung reticulum cell sarcomas in the beryllium-exposed rats were not significantly different from controls. The incidences of reticulum cell sarcoma-bearing rats in the 0, 5, 50, and 500 ppm groups were 12/50, 18/50, 16/50, and 13/50, respectively, for males and 8/50, 11/50, 7/50, and 8/50 for the females; no significant increases in tumor-bearing rats was found. No other treatment-related increases in tumor incidence were observed.

In a lifetime exposure study, groups of 52 male and 52 female Long-Evans rats were maintained on a low-metal diet and given drinking water containing 0 or 5 ppm beryllium as beryllium sulfate (presumably tetrahydrate) from weaning to natural death (Schroeder and Mitchener, 1975a). The water also contained 5 ppm chromium III, 50 ppm zinc, 5 ppm copper, 10 ppm manganese, 1 ppm cobalt, and 1 ppm molybdenum. Doses of 0.63 and 0.71 mg/kg-day were calculated for male and female rats, respectively, using estimated TWA body weights of 0.42 and 0.26 kg and U.S. EPA's (1988) allometric equation for water consumption. The following parameters were used to assess toxicity: body weights (animals weighed at weekly and monthly intervals for the first year and at 3-mo intervals thereafter), blood glucose, cholesterol, and uric acid (blood samples collected from 12 rats/sex after an 18-h fast), urine protein, pH, and glucose, heart weight, gross pathology, and histopathology of heart, lung, kidney, liver, spleen, and tumors. Twenty male and eight female rats in the beryllium group died at 20 mo of age from pneumonia; a similar number of animals in the control group also died from pneumonia. At 30 days, the male and female rats exposed to beryllium weighed significantly more than the control animals. At 60, 90, 120, and 180 days, the beryllium-exposed male rats weighed significantly less than the controls; no significant alterations in body weight were observed at the other time intervals (150, 360, or 540 days). Overall, the weight loss of less than 10% indicates that the MTD was not achieved. No significant alterations in mortality or longevity were observed. Glycosuria (females only) and alterations in serum glucose levels were observed in the beryllium-exposed rats. The alterations in serum glucose levels consisted of significantly lower levels in males aged 475 days and higher levels in males and females aged 719 days. It should be noted that the control rats were at least 50 days older than the beryllium-exposed rats when blood samples were collected, and in the controls, blood glucose levels declined with increasing age. Significantly increased serum cholesterol levels were observed in female rats exposed to beryllium at ages 475 and 719 days. The results of the histological examination were not reported. The alterations in serum glucose and cholesterol levels and urine glucose levels were not considered adverse because the magnitude of the alterations was not sufficiently large to suggest an impairment in organ function. The incidence of gross tumors was 4/26 (15%) and 17/24 (70%) in the male and female control rats and 9/33 (27%) and 14/17 (82%) in the male and female rats exposed to beryllium. The incidences of malignant tumors (tumors were considered malignant if there were multiple tumors in the same animal) were 2/26 (7.7%) and 8/24 (33%) in the male and female controls and 4/33 (12%) and 8/57 (14%) in the male and female beryllium-exposed rats. The incidences of gross or malignant tumors in the control and beryllium-exposed groups was not significantly different. It should be noted that in an unpublished report (Schroeder and Nason, 1976), the incidence of gross tumors in the male and female beryllium-exposed rats was 4/25 and 13/20 (control data the same as reported in published paper). In the published paper, this is the tumor incidence for the tungsten-exposed male and female rats, respectively. It is difficult to determine which is the correct tumor incidence data for the beryllium-exposed rats; however, neither set of incidence data is statistically significantly different than controls.

In a similar lifetime exposure study, groups of 54 male and 54 female Swiss mice were administered 0 or 5 ppm beryllium as beryllium sulfate in the drinking water from weaning to natural death (Schroeder and Mitchener, 1975b). The mice were fed low-metal diets and the drinking water was supplemented with 50 ppm zinc, 10 ppm manganese, 5 ppm copper, 5 ppm chromium III, 1 ppm cobalt, and 1 ppm molybdenum. The 5 ppm water concentration is equivalent to doses of 1.2 mg/kg-day for the male and female mice, using an estimated TWA body weight of 0.042 and 0.035 kg and EPA's

(1988) allometric equation for water consumption. In the beryllium group, statistically significant alterations in body weight were observed; the alterations included heavier male mice at 30 days and lighter female mice at 90 and 120 days. Overall, the decrease in body weight was less than 10%, indicating that the MTD was not reached. No significant alterations in mortality or survival were observed in the beryllium-exposed mice. No alterations in tumor incidence were observed.

Reeves et al. (1967) exposed 150 male and 150 female Sprague-Dawley rats for 7 h/day, 5 days/week to $34.25 \mu\text{g Be/m}^3$ as beryllium sulfate aerosol (average particle size was $0.118 \mu\text{m}$, electron microscopy) for up to 72 weeks, with 3 of each sex sacrificed monthly during exposure. An equal number of control rats were exposed to distilled water aerosol. Lung weights were markedly increased in the exposed rats, and an inflammatory lung response (characterized as a marked accumulation of histiocytic elements and thickened and distorted alveolar septa) was noted, accumulation of alveolar macrophages. A proliferative response was also noted, progressing from hyperplasia to alveolar adenocarcinomas in 100% of the exposed rats at 13 months, compared to 0% of the controls. Histopathologic examination was limited to the lungs. The authors noted that 8 male and 4 female rats in the control group and 9 male and 17 females in the beryllium group died during the course of the study. The plateau body weight in the beryllium-exposed female rats was approximately 25% less than found in the controls (statistical significance not reported).

Vorwald and Reeves (1959) exposed Sherman rats (number and sex not reported) via the inhalation route to aerosols of beryllium sulfate at 6 and $54.7 \mu\text{g Be/m}^3$ for 6 h/day, 5 days/week for an unspecified duration. Animals were sacrificed periodically and examined histopathologically. Initially, inflammation consisted of histiocytes, lymphocytes, and plasma cells scattered throughout the lung parenchyma. Following more prolonged exposures, more focal lesions consisting primarily of histiocytes were observed. Multinucleated giant cells were also observed. Thickened alveolar walls and fibrotic changes were also observed. Lung tumors, primarily adenomas and squamous cell cancers, were observed in the animals sacrificed after 9 months of this exposure regime.

Similar results to those of Vorwald and Reeves (1959) were observed in a study by Reeves and Deitch (1969, as reviewed by U.S. EPA, 1987). In this study, groups of 20 to 25 Charles River CD rats were exposed to $35.66 \mu\text{g Be/m}^3$ as beryllium sulfate for 35 h/week; the mean particle size was $0.21 \mu\text{m}$ (d_{ae}). The exposure durations were 800 h (5 groups), 1,600 h (2 groups), and 2,400 h (1 group). Age at the initiation of exposure appeared to be a more important variable for tumor development than was exposure duration. The lung tumor incidence (19/22, 86%) for young rats exposed for 3 mo was the same as in rats exposed for 18 mo (13/15, 86%), but was higher than in older rats exposed for 3 mo (3-10/20-25, 15-40%). Tumors were typically observed after a latency period of 9 mo. In the beryllium-exposed rats, the epithelial hyperplasia observed at 1 mo progressed to metaplasia at 5 to 6 mo, and anaplasia by 7 to 8 mo.

In a study to test the carcinogenicity of beryllium ores, Wagner et al. (1969) exposed groups of 12 male squirrel monkeys (*Saimiri sciurea*), 60 male CR-CD rats, 30 male Greenacres Controlled Flora (GA) rats, and 48 male Golden Syrian hamsters to 0 or 15 mg/m^3 bertrandite or beryl for 6 h/day, 5 days/week for 17 mo (rats and hamsters) or 23 mo (monkeys). The test atmospheres generated from the bertrandite ore ($\text{Be}_4\text{Si}_2\text{O}_7[\text{OH}]_2$; 1.4% beryllium) and beryl ore ($\text{B}_3\text{Al}_2\text{Si}_6\text{O}_{18}$; 4.14% beryllium) contained 210 and $620 \mu\text{g Be/m}^3$, respectively, and the geometric mean diameters of the particles were $0.27 \mu\text{m}$ (geometric standard deviation of 2.4) and $0.64 \mu\text{m}$ (geometric standard deviation of 2.5). Both ores contained very high silicon dioxide levels (63.9% by weight). Exposed and control monkeys, rats, and hamsters were serially sacrificed on completion of 6 and 12 mo of exposure; rats and hamsters at 17 months, and monkeys at 23 mo. Five control rats and five rats from the 12- and 17-mo exposure groups were sacrificed in order to determine the free-silica content of the lung tissue. At exposure termination, beryllium concentrations in the lungs were 18.0 and $83 \mu\text{g/g}$ fresh tissue in the bertrandite- and

beryl-exposed rats, 14.1 and 77.4 $\mu\text{g/g}$ fresh tissue in the bertrandite- and beryl-exposed hamsters, and 33 and 280 $\mu\text{g/g}$ fresh tissue in the bertrandite- and beryl-exposed monkeys. Free silica (SiO_2) levels in the rat lungs were 30 to 100 times higher in the beryllium ore-exposed rats than in the controls. Increased mortality was observed in the monkeys (11%), rats (13%), and hamsters (25%) exposed to either bertrandite or beryl ore, with the highest mortality rates in the bertrandite ore-exposed animals (no further details provided). No significant alterations in body weight gain were observed in the monkeys or hamsters.

In the rats, decreased body weight gains (terminal body weights were 15% lower compared to controls) were observed beginning after 6 mo of exposure, and from 12 mo to exposure termination at 17 mo. In the beryl-exposed rats, small foci of squamous metaplasia or tiny epidermoid tumors were observed in the lungs of 5/11 rats killed after 12 mo of exposure. At exposure termination, lung tumors were observed in 18/19 rats (18 had bronchiolar alveolar cell tumors, 7 had adenomas, 9 had adenocarcinomas, and 4 had epidermoid tumors). Additional alterations in the lungs included loose collections of foamy macrophages and cell breakdown products, lymphocyte infiltrates around the bronchi, and polymorphonuclear leukocytes and lymphocytes present in most of the bronchiolar-alveolar cell tumors. In the bertrandite-exposed rats, granulomatous lesions composed of several large, tightly packed, dust-laden macrophages were observed in all rats exposed for 6, 12, or 17 mo. No tumors were observed. Neoplastic or granulomatous pulmonary lesions were not observed in the control rats. In the beryl- and bertrandite-exposed monkeys, the histological alterations consisted of aggregates of dust-laden macrophages, lymphocytes, and plasma cells near respiratory bronchioles and small blood vessels. No tumors were found. In the bertrandite-exposed hamsters, granulomatous lesions consisting of tightly packed, dust-laden macrophages were observed after 6 mo, and the number did not increase after 17 mo. These alterations were not observed in the beryl-exposed or control hamsters. Atypical proliferation and lesions, which were considered bronchiolar alveolar cell tumors except for their size, were observed in the hamsters after 12 mo of exposure to beryl or bertrandite. After 17 mo of exposure, these lesions became larger and more adenomatous in the beryl-exposed hamsters. It should be noted that silicosis was not observed in any of the animals exposed to the beryllium ores, which contained a large amount of free silica. No significant gross or histologic alterations were observed in the thymus, spleen, liver, or kidneys of the beryllium-exposed rats, hamsters, and monkeys.

In a monkey carcinogenicity study (Vorwald, 1968), a group of 7 male and 9 female rhesus monkeys (*Macaca mulatta*) (aged 18 months) were exposed to 35 $\mu\text{g Be/m}^3$ beryllium sulfate mist 6 h/day, 5 days/week. The author notes that the "exposure was interrupted, often for considerable periods of time, in order to maintain the best possible overall well-being of the animal, to prevent a threatening acute beryllium pneumonitis, and to favor survival to old age or at least long enough for the inhaled beryllium to exert its maximal chronic effects in terms of epithelial proliferation, metaplasia, and cancer." The exposure schedule was presented in a figure, but it was difficult to determine the exposure protocol from this figure. The longest exposure was for 4,070 h, with most of the exposure occurring during the first 4.5 years of the study with an approximate 6-mo exposure 2.5 years later. Four animals died within the first 2 mo of the study; the cause of death was acute chemical pneumonitis. Lung cancer was observed in 8 of the 12 remaining animals. The first tumor was observed in a monkey 8 years of age exposed for 3,241 hours. The tumors were described as a gross mass located in either the hilar area or more peripheral portions of the lung or as small and large tumors scattered irregularly throughout the pulmonary tissue.

A single-exposure inhalation study of beryllium metal in F344/N rats resulted in a 64% incidence of lung carcinomas over the lifetime of the animals (Nickell-Brady et al., 1994). Groups of 30 males and 30 females were administered a single, nose-only exposure to a beryllium metal aerosol (MMAD = 1.4 μm , GSD = 1.9) at 500 mg/m^3 for 8 min, 410 mg/m^3 for 30 min, 830 mg/m^3 for 48 min, or 980 mg/m^3 for 39 min. Control rats were exposed to filtered air alone. Mean lung burdens resulting from these exposures were 40,

110, 360, and 430 µg of beryllium, respectively. Tumors became apparent by 14 mo after exposure, and the incidence (apparently for all groups combined) was 64% over the lifetime of the rats. Multiple tumors were frequently found, the majority were adenocarcinomas, and some were > 1 cm.

Lung tumors have been observed in rats following a single intratracheal instillation of beryllium metal, passivated beryllium metal (99% beryllium, < 1% chromium), beryllium-aluminum alloy (62% beryllium), and beryllium hydroxide. Beryllium alloys containing 4% beryllium did not result in increases in lung tumors. Lung tumor incidences of 11% to 51% were observed in rats following intratracheal instillation of beryllium oxide fired at high, low, and medium temperatures. The types of lung tumors found in animals receiving intratracheal instillations of beryllium included adenocarcinomas, adenomas, squamous cell carcinoma, and malignant lymphoma. Osteosarcomas have been induced by intravenous and intramedullary injection of various beryllium compounds into rabbits, and possibly mice. The osteosarcomas in rabbits are histologically similar to human osteosarcomas (U.S. EPA, 1987, 1991).

__II.A.4. Supporting Data for Carcinogenicity

The genotoxicity of beryllium has been previously reviewed by EPA (1987) and recently reviewed by IARC (1993). Most studies have found that beryllium chloride, beryllium nitrate, beryllium sulfate, and beryllium oxide did not induce gene mutations in bacterial assays with or without metabolic activation. In the case of beryllium sulfate, all mutagenicity studies (Ames [Simmon, 1979; Dunkel et al., 1984; Arlauskas et al., 1985; Ashby et al., 1990]; *E. coli* pol A [Rosenkranz and Poirer, 1979]; *E. coli* WP2 uvr A [Dunkel et al., 1984]) and *Saccharomyces cerevisiae* (Simmon, 1979) were negative with the exception of results reported for *Bacillus subtilis* rec assay (Kada et al., 1980; Kanematsu et al., 1980) and *E. coli* rec assay (Dylevoi, 1990). Beryllium sulfate did not induce unscheduled DNA synthesis in primary rat hepatocytes and was not mutagenic when injected intraperitoneally in adult mice in a host-mediated assay using *Salmonella typhimurium* (Williams et al., 1982).

Beryllium nitrate was negative in the Ames assay (Tso and Fung, 1981; Kuroda et al., 1991) but positive in a *Bacillus subtilis* rec assay (Kuroda et al., 1991). Beryllium chloride was negative in a variety of studies (Ames [Ogawa et al., 1987; Kuroda et al., 1991]; *E. coli* WP2 uvr A [Rossman and Molina, 1986]; and *Bacillus subtilis* rec assay [Nishioka, 1975]). In addition, beryllium chloride failed to induce SOS repair in *E. coli* (Rossman et al., 1984). However, positive results were reported for *Bacillus subtilis* rec assay using spores (Kuroda et al., 1991), *E. coli* KMBL 3835; *lacI* gene (Zakour and Glickman, 1984), and *hprt* locus in Chinese hamster lung V79 cells. Beryllium oxide was negative in the Ames assay and *Bacillus subtilis* rec assays (Kuroda et al., 1991).

Gene mutations have been observed in mammalian cells (V79 and CHO) cultured with beryllium chloride (Miyaki et al., 1979; Hsie et al., 1979a,b), and culturing of mammalian cells with beryllium chloride (Vegni-Talluri and Guiggiani, 1967), beryllium sulfate (Brooks et al., 1989; Larramendy et al., 1981), or beryllium nitrate has resulted in clastogenic alterations.

Data on the *in vivo* genotoxicity of beryllium are limited to a single study that found beryllium sulfate (1.4 and 2.3 g/kg, 50% and 80% of median lethal dose) administered by gavage did not induce micronuclei in the bone marrow of CBA mice, although a marked depression of erythropoiesis suggestive of bone marrow toxicity was evident 24 h after dosing. No mutations were seen in *p53* or *c-raf-1* and only weak mutations were detected in *K-ras* in lung carcinomas from F344/N rats given a single nose-only exposure to beryllium metal (Nickell-Brady et al., 1994). The authors concluded that the mechanisms for the development of lung carcinomas from inhaled beryllium in the rat do not involve gene dysfunctions commonly associated with human non-small-cell lung cancer.

Regarding human exposure, beryllium particles produced from anthropogenic processes

almost always enter the atmosphere as BeO. Depending on the particle size, they can be deposited near the source or transported long distances. The inhalation toxicity of insoluble beryllium oxide, which appears to be the chemical form more likely than beryllium salts to be present in the atmosphere, depends to a great extent on its physical and chemical properties, which can be altered considerably, depending on production conditions. It is well known that the toxicity of beryllium oxide is dependent on the particle size, with smaller particles ($< 10 \mu\text{m}$, d_{ae}) able to penetrate beyond the larynx.

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II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

The oral database is considered inadequate for the assessment of carcinogenicity. The chronic oral studies did not report increased incidences of tumors in rodents, but were conducted at doses below the MTD. The oral database, including the Schroeder and Mitchener study (1975a) previously used in the development of the oral slope factor on IRIS, is considered inadequate for the assessment of carcinogenicity. The basis for not using the Schroeder and Mitchener rat study (1975a) is that the incidences of gross or malignant tumors in the control and beryllium-exposed groups were not significantly different.

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II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

The cancer dose-response assessment based on the occupational study of Wagoner et al. (1980) that is presented in this section was derived by EPA (1987), was verified in 1988, and loaded on IRIS. Newer studies, particularly the occupational study of Ward et al. (1992), have been considered as the basis for a dose-response assessment, but share a limitation with the Wagoner et al. (1980) study--lack of individual exposure monitoring or job history data that would support a more definitive exposure assessment. NIOSH has recently completed a lung cancer case-control study nested within a cohort mortality study of beryllium manufacturing workers at the Reading beryllium processing facility. The study developed an exposure matrix and calculated airborne beryllium exposure concentrations and thus may provide the best available basis for a quantitative cancer estimate. The study is currently in peer review. Rather than calculate an interim quantitative estimate based on the Ward et al. (1992) data and poorly defined exposure estimates, it is recommended that the existing unit risk based on the Wagoner et al. (1980) study be retained until the NIOSH assessment can be evaluated as the basis for a quantitative estimate.

II.C.1. Summary of Risk Estimates

II.C.1.1. Air Unit Risk -- $2.4\text{E-}3$ per $(\mu\text{g}/\text{m}^3)^*$

II.C.1.2. Extrapolation Method -- Relative Risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-2 per $(\mu\text{g}/\text{m}^3)$
E-5 (1 in 100,000)	4E-3 per $(\mu\text{g}/\text{m}^3)$
E-6 (1 in 1,000,000)	

4E-4 per ($\mu\text{g}/\text{m}^3$)

*The unit risk should not be used if the air concentration exceeds $4 \mu\text{g}/\text{m}^3$, since above this concentration the unit risk may not be appropriate.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type: Lung cancer
 Test animals: Human, male
 Route: Inhalation, occupational exposure
 Reference: Wagoner et al., 1980

Beryllium concentration in workplace ($\mu\text{g}/\text{m}^3$)	Ratio of years of exposure to years at risk (f/L)	Effective dose ($\mu\text{g}/\text{m}^3$)	95 percent upper-bound estimate of relative risk	Unit risk per ($\mu\text{g}/\text{m}^3$)
100	1.00	21.92	1.98	1.61E-3
			2.09	1.79E-3
	0.25	5.48	1.98	6.44E-3
			2.09	7.16E-3
1,000	1.00	219.18	1.98	1.61E-4
			2.09	1.79E-4
	0.25	54.79	1.98	6.44E-4
			2.09	7.16E-4

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The epidemiology study by Wagoner et al. (1980) is used to estimate the lifetime cancer risk from exposure to beryllium oxide based on the estimated lower and upper bounds of exposure estimated by NIOSH; namely, 100 and 1,000 $\mu\text{g}/\text{m}^3$. The effective dose was determined by adjusting for duration of daily (8/24 h) and annual (240/365) exposure and the ratio of exposure duration to duration at risk, i.e., f years out of a period of L years at risk (from onset of employment to termination of follow-up). Two values of f/L were used in the calculations, f/L = 1 and 0.25. An f/L of 1.0 would avoid overestimating the risk (but could underestimate the risk) if the observation by Reeves and Deitch (1969)--that tumor yield depends not on the length of exposure but on age at exposure--is valid. For a given "effective" dose d and a relative risk R, the carcinogenic potency (q_1^*) is calculated by the formula $B = (R - 1) \times 0.036/d$, where 0.036 is the estimated lung cancer mortality rate in the U.S. population. The risk estimates were based on the data of Wagoner et al. (1980) in which the smoking- adjusted, expected lung cancer deaths were found to range from 13.91 to 14.67, in comparison to 20 observed. Relative risk estimates of 1.36 ($p > 0.05$) and 1.44 ($p > 0.05$) were derived and the 95% upper confidence limits of these estimates, 1.98 and 2.09, respectively, were used to estimate the lifetime cancer risk (unit risk).

With the possible exception of the Wagner et al. (1969) study, the results of the animal carcinogenicity studies are incompletely reported and the studies are not of sufficient quality to be used as the basis of quantitative cancer risk estimates. Because Wagner et al. (1969) exposed the rats to beryllium ores with relatively low beryllium levels and high levels of silica dioxide, this study would not be an appropriate basis for a risk estimate for general population exposure to beryllium.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

The estimate for risk for inhalation was based on an epidemiologic study having several confounding variables. The estimate of exposure levels and duration of exposure by

NIOSH were also somewhat uncertain. While a quantitative estimate based on several animal studies (U.S. EPA, 1987) resulted in a similar estimate of risk, the epidemiological data are considered a better basis for quantitating risk; the assessment based on the animal data is, however, supportive of the assessment based on the human data.

The results of the epidemiological studies have been criticized (BISAC, 1997; MacMahon, 1994; U.S. EPA, 1987; Saracci, 1985). EPA (1987, 1991) considered the studies conducted prior to 1987 to be insufficient to assess the carcinogenic potential of beryllium in humans. Although the design of the Ward et al. (1992) study corrected a number of the shortcomings of the older studies, the interpretation of the study results is limited by the assumption used to account for lung cancer deaths due to cigarette smoking, the lack of job history data that would support quantitative exposure assessment, the lack of control for potential exposure to other carcinogens, including coexposure to sulfuric or hydrofluoric acid mists during employment in the beryllium industry or nonconcurrent exposure to other carcinogens during employment outside of the beryllium industry, and the relatively small increases in lung cancer risks. Exposure to sulfuric acid mists, however, has not been strongly associated with lung cancer, but rather with laryngeal cancer (IARC, 1992; Sathiakumar et al., 1997). Limitations in the evidence for an association between exposure to sulfuric acid mist and lung cancer include poor or no quantitation of exposure, possible confounding by other occupational exposures and smoking, and low SMRs. The majority of lung cancer SMRs in the studies that reported a positive association between exposure to sulfuric acid mists and lung cancer were in the range of 1.18 to 1.39. The studies of lung cancer in workers exposed occupationally to beryllium and/or sulfuric acid or other acid mists do not, for the most part, categorize the type of cancer. Thus, the data are insufficient to determine whether different types of lung cancer may be associated with beryllium exposure versus sulfuric acid exposure. Exposures to hydrofluoric acid and hydrogen fluoride are potential confounders at some of the beryllium processing facilities, including the Reading plant (Ward et al., 1992; BISAC, 1997). Information regarding the potential carcinogenicity of these compounds was not available. IARC (1992) considered hydrofluoric acid to be a weak inorganic acid and did not assess it in the monograph on strong inorganic acids.

IARC (1993; Vainio and Rice, 1997) considered the epidemiological data as sufficient evidence in humans for the carcinogenicity of beryllium and compounds. IARC (1993) concluded that the issue of adjustments for smoking had been handled adequately, and stated that a limitation of the most recent cohort studies was the absence of discussion of potential exposure to other lung carcinogens, although "there is no evidence that other lung carcinogens were present." The U.S. EPA, however, considers that the issues of incomplete smoking data and exposure to other potential lung carcinogens are not completely resolvable with the data currently available, and therefore concludes that the evidence of carcinogenicity of beryllium and compounds is limited in humans.

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II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review of Beryllium in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 1998). *To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF).*

Other EPA Documentation -- U.S. EPA, 1987, 1991

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date -- 03/26/1998

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (301) 345-2870 (phone), (301) 345-2876 (fax), or Hotline.IRIS@epamail.epa.gov (Internet address).

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_VI. Bibliography

Beryllium and compounds
CASRN -- 7440-41-7
Last Revised -- 04/03/1998

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_VII. Revision History

Beryllium and compounds
CASRN -- 7440-41-7

Date	Section	Description
03/01/1988	I.A.1.	Reference dose table clarified
03/01/1988	I.A.2.	Text added

09/07/1988	II.	Carcinogen summary on-line
01/01/1990	II.A.2.	References clarified
01/01/1990	II.A.3.	Text revised
01/01/1990	II.B.	Quantitative estimate for oral exposure section added
01/01/1990	II.C.3.	Text revised
01/01/1990	II.D.2.	Work group review dates and verification date added
01/01/1990	VI.	Bibliography on-line
02/01/1990	VI.A.	Puzanova et al. 1978 citation corrected
02/01/1990	VI.C.	Wagner et al. 1969 citation corrected
09/01/1990	I.A.	Morgareidge ref. now Cox (same study-authors reversed)
09/01/1990	IV.F.1.	EPA contact changed
09/01/1990	VI.A.	Morgareidge ref. now Cox (same study-authors reversed)
01/01/1991	II.	Text edited
01/01/1991	II.C.1.	Inhalation slope factor removed (global change)
01/01/1992	IV.	Regulatory actions updated
09/01/1992	II.A.3.	U.S. EPA citation year corrected, paragraph 3
09/01/1992	II.D.1.	Source document year corrected
09/01/1992	II.D.1.	Review statement revised
09/01/1992	VI.C.	U.S. EPA reference year corrected
02/01/1993	I.A.7.	Primary contact changed
08/01/1995	II.D.2.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
04/03/1998	I.A.	Oral RfD Assessment
04/03/1998	I.B.	Inhalation RfC Assessment
04/03/1998	II.	Carcinogenicity Assessment

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VIII. Synonyms

Beryllium and Compounds
CASRN -- 7440-41-7
Last Revised -- 04/03/1998

7440-41-7
Beryllium
Beryllium-9
Glucinum
RCRA waste number P015
UN 1567

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe* PDF format (94 Pages, 320 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.



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