Preliminary Quantitative Risk Assessment for Beryllium

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I. Introduction

An IARC working group concluded, in 1993, that there was at that time sufficient evidence for the carcinogenicity of beryllium and beryllium compounds in humans. The target organ appeared to be the lung, following inhalation exposures. In addition, it is known that occupational exposure to beryllium can cause chronic beryllium disease (CBD), a progressive respiratory condition that develops via immune response to beryllium particles deposited in the lung and leading to the formation of diffuse, interstitial granulomatous lesions.

This document reviews some of the epidemiological evidence linking beryllium exposures to lung cancer and CBD. The focus of the review was to help OSHA identify sources suitable for quantitative risk assessment of occupational exposures to beryllium. This document presents estimates for both lung cancer and CBD risks to workers following working-lifetime exposure (45 years) to beryllium at various concentrations ranging from 2 to 0.1 $\mu g/m^3$, based on some of the studies which had quantitative exposure estimates and provided enough published information to perform an analysis. Other studies with exposure information that might support quantitative risk assessment were not analyzed here, because OSHA is currently attempting to determine whether the raw data can be obtained for further analysis.

The following section provides a brief overview of the published studies that address the issue of lung cancer or CBD associated with occupational beryllium exposure. Summary information about those studies, along with synopses of their strengths and weaknesses, is provided. The third section describes the quantitative approaches that have been applied to the selected studies, as well as results of those applications. Separate estimates were derived and are presented for lung cancer and CBD; strengths and weaknesses of the studies and analyses are presented. The final section provides a conclusion based on the results of the analyses and discusses the need for follow-on work.

II. Overview of Epidemiological Studies

A. Lung Cancer Studies

The literature available concerning the potential carcinogenicity of beryllium in humans comes from occupational mortality studies, which are summarized in this section and in Table 1.

Two of these studies evaluated participants in the Beryllium Case Registry (BCR) (Infante et al. 1980; Steenland and Ward 1991). The BCR was established in 1952 at the Massachusetts General Hospital to create a basis for the evaluation of long term effects of beryllium exposure. Infante et al. (1980) evaluated the mortality patterns of white male participants in the BCR diagnosed with nonneoplastic respiratory symptoms of beryllium disease. Of the 421 cases evaluated, 7 of the participants had died of lung cancer, six of which occurred at greater than 15 years since initial beryllium exposure. The duration of exposure for 5 of the 7 participants with lung cancer was less that 1 year with the time since initial exposure ranging from 12 to 29 years. One of the participants was exposed for 4 years with a 26 year interval since the initial exposure. Exposure duration for one participant diagnosed with pulmonary fibrosis could not be determined; however, it had been 32 years since the initial exposure. Based on BCR records, the participants were classified as being in the acute respiratory group, those diagnosed with acute respiratory illness at the time of entry in the registry, or chronic respiratory group, those diagnosed with pulmonary fibrosis or some other chronic lung condition at the time of entry into the BCR. In the 7 participants with lung cancer, 5 having greater than 15 years since the initial beryllium exposure and one with less than 15 years were in the BCR because of diagnoses of acute respiratory illness. Only 1 of the 7 (with greater than 15 years since initial exposure to beryllium) had been diagnosed with chronic respiratory disease. The study did not report exposure concentrations or smoking habits. The authors concluded that the results of this cohort agreed with previous animal studies and with epidemiological studies demonstrating an increased risk of lung cancer in workers exposed to beryllium.

Steenland and Ward (1991) extended the work of Infante et al. (1980) to include females and to include 13 additional years of follow-up. Ninety-three percent of the women in the study had been diagnosed with CBD while only 50% of the men had at the time of entry in the BCR. In addition, 61% of the women had worked in the fluorescent tube industry and 50% of the men had worked in basic manufacturing industry. A total of 22 males and 6 females died of lung cancer. Of the 28 total deaths from lung cancer, 17 had been exposed for less than 4 years while 11 had been exposed for greater than 4 years. The study did not report exposure concentrations. Survey data collected in 1965 provided information on smoking habits for 223 cohort members (32%), on the basis of which the authors suggested that the rate of smoking among workers in the cohort may have been lower than U.S. rates. The authors concluded that there was evidence of increased risk of lung cancer in workers exposed to beryllium and diagnosed with beryllium disease.

Bayliss et al. (1971) performed a cohort study of approximately 8,000 former workers from the beryllium processing industry employed in the industry from 1942 - 1967. Information for the workers

was collected from the personnel files of participating companies. Of the 8,000 employees, a cause of death was known for 753 male workers. The number of observed lung cancer deaths was 36 compared to 34.06 expected for a SMR of 105.7. When evaluated by the number of years of employment, 24 of the 36 men were employed for less than 1 year in the industry (SMR = 124.3), 8 were employed for 1 to 5 years (SMR 140.2), and 4 were employed for more than 5 years (SMR = 54.4). Half of the workers that died from lung cancer began employment in the beryllium production industry prior to 1947. When grouped by job classification, over two thirds of the workers with lung cancer were in production related jobs while the rest were classified as office workers. The authors concluded that while the lung cancer mortality rates were the highest of all other mortality rates, the SMR for lung cancer was still within range of the expected based on death rates for the United States. The limitations of this study included the lack of information regarding exposure concentrations, smoking habits, and the age and race of the participants.

Mancuso (1970; 1979; 1980) and Mancuso and El-Attar (1969) performed a series of occupational cohort studies on a group of over 3000 workers (primarily white males) employed in the beryllium manufacturing industry during 1937 – 1948.[1] The beryllium production facilities were located in Ohio and Pennsylvania and the records for the employees, including periods of employment, were obtained from the Social Security Administration. These studies did not include analyses of mortality by job title or exposure category. In addition, there were no exposure concentrations estimated or adjustments for smoking. The estimated duration of employment ranged from less than 1 year to greater than 5 years. In the most recent study (Mancuso 1980), employees from the viscose rayon industry served as a comparison population. There was a significant excess of lung cancer deaths based on a total number of observed lung cancer mortalities at the end of 1976 of 80 compared to an expected number based on the comparison population of 57.06 resulting in an SMR of 140 ($p < .01$) (Mancuso 1980). There was a statistically significant excess in lung cancer deaths for the shortest duration of employment (< 12 months, $p < .05$) and the longest duration of employment (> 49 months, $p < .01$). Based on the results of this study, the author concluded that the biological effectiveness of beryllium to induce cancer in workers does not require continuous exposure, and it is reasonable to assume that the amount of exposure required to produce lung cancer can occur within a few months of exposure regardless of the length of employment.

Wagoner et al. (1980) expanded the work of Mancuso (1970; 1979; 1980) using a cohort of 3055 white males from the beryllium extraction, processing, and fabrication facility located in Pennsylvania.

[1] The third study (Mancuso et al 1979) restricted the cohort to workers employed between 1942 and 1948.

The men included in the study had been employed at the facility sometime between 1942 and 1968. The study accounted for length of employment, and the participants in this study were followed through 1976. Other factors accounted for included age, smoking history, and regional lung cancer mortality. Of the 3,055 white males included in this cohort, 47 died of lung cancer compared to an expected 34.29 based on U.S. white male rates ($p < .05$). The results of this cohort showed an excess risk of lung cancer in beryllium-exposed workers at each duration of employment (< 5 years and ≥ 5 years), with a statistically significant excess noted at < 5 years durations of employment and a ≥ 25 year interval since the onset of employment ($p < .05$). The study was criticized by several epidemiologists (MacMahon 1978, 1979; Roth 1983), by a CDC Review Committee appointed to evaluate the study, and by one of the study's coauthors (Bayliss 1980), for inadequate discussion of possible alternative explanations of excess lung cancer in the cohort. The specific issues identified include the use of 1965-1967 U.S. white male mortality rates to generate expected numbers of lung cancers in the period 1968-1975 and inadequate adjustment for smoking.

IRIS, IARC, and OEHHA all based their cancer assessment on this study with supporting data concerning exposure concentrations from Eisenbud and Lisson (1983) and NIOSH (1972), who estimated that the lower-bound estimate of the median exposure concentration exceeded 100 $\mu g/m^3$ and concentrations in excess of 1000 $\mu g/m^3$ were commonly found. The IRIS cancer risk assessment recalculated expected lung cancers based on U.S. white male lung cancer rates (including the period 1968-1975) and used an alternative adjustment for smoking. In addition, one individual with lung cancer who had not worked at the plant was removed from the cohort. After these adjustments were made, an elevated rate of lung cancer was still observed in the overall cohort (46 cases vs. 41.9 expected). However, neither the total cohort nor any of the subgroups based on duration of employment or interval since onset of employment had a statistically significant excess in lung cancer (EPA 1987). Based on their evaluation of this and other epidemiological studies, the EPA characterized the human carcinogenicity data then available as "limited" but "suggestive of a causal relationship between beryllium exposure and an increased risk of lung cancer" (IRIS database). This report includes quantitative estimates of risk that were derived using the information presented in Wagoner et al. (1980), the expected lung cancers recalculated by the EPA, and bounds on presumed exposure levels (see Section III.A.2 below).

Ward et al. (1992) performed a retrospective mortality cohort study of 9,225 male workers employed at seven beryllium processing facilities, including the Ohio and Pennsylvania facilities studied by Mancuso and El-Attar (1969), Mancuso (1970; 1979; 1980), and Wagoner et al. (1980). The men

were employed for no less than 2 days between January 1940 and December 1988. At the end of the study 61.1% of the cohort was known to be living and 35.1% was known to be deceased. The duration of employment ranged from 1 year or less to greater than 10 years with the largest percentage of the cohort (49.7%) employed for less than one year, followed by 1 to 5 years of employment (23.4%), greater than 10 years (19.1%), and 5 to 10 years (7.9%). Of the 3240 deaths, 280 observed deaths were caused by lung cancer compared to 221.5 expected yielding a statistically significant SMR of 126 ($p < .01$). Information on the smoking habits of 15.9% of the cohort members, obtained from a 1968 Public Health Service survey conducted at four of the plants, was used to calculate a smoking-adjusted SMR of 112 (not statistically significant). The number of deaths from lung cancer was also examined by decade of hire. The authors reported a relationship between earlier decades of hire and increased lung cancer risk.

Levy et al. (2002) questioned the results of Ward et al. (1992) and performed a reanalysis of the data used by Ward et al. The major differences between the Levy et al. reanalysis and that of Ward et al. were as follows. Levy et al. (2002) examined two alternative adjustments for smoking; these were based on 1) a different analysis of the ACS data used by Ward et al. (1992) for their smoking adjustment or 2) results from a smoking/lung cancer study of veterans. Levy et al. (2002) also examined the impact of computing different reference rates derived from information about the lung cancer rates in the cities in which most of the workers at two of the plants lived. Finally, Levy et al. (2002) considered a meta-analytical approach to combining the results across beryllium facilities. For all of the alternatives considered by Levy et al. (2002) except the meta-analysis, the facility-specific and combined SMRs derived were lower than those reported by Ward et al. (1992). Only the SMR for the Lorain, Ohio facility remained statistically significantly elevated in some reanalyses. The SMR obtained when combining over the plants was not statistically significant in eight of the nine approaches they examined, leading Levy et al. (2002) to conclude that there was little evidence of statistically significant elevated SMRs in those plants.

One of the most recent occupational case-control studies available evaluated lung cancer incidence in a cohort of 3,569 male workers employed at a beryllium alloy production plant in Reading, Pennsylvania from 1940 to 1969 and followed through 1992 (Sanderson et al. 2001). For each lung cancer mortality, 5 age- and race-matched controls were selected by incidence density sampling. Calendar-time-specific beryllium exposure estimates were made for every job and used to estimate workers' cumulative, average, and maximum exposure. Confounding effects of smoking were evaluated. There were a total of 142 known lung cancer cases and 710 controls. The cumulative, average, and maximum beryllium exposure concentration estimates for the 142 known lung cancer cases were 4606 ±

9.3µg/m^3-days , 22.8 ± 3.4 µg/m^3, and 32.4 ± 13.8 µg/m^3, respectively. The lung cancer mortality rate was 1.22 (95% CI = 1.03 – 1.43). Exposure estimates were lagged by 10 and 20 years in order to account for exposures that did not contribute to lung cancer because they occurred after the induction of cancer. In the 10 and 20 year lagged exposures the geometric mean tenures and cumulative exposures of the lung cancer mortality cases were higher than the controls In addition, the geometric mean and maximum exposures of the workers were significantly higher than controls when the exposure estimates were lagged 10 and 20 years ($p < .01$). Results of a conditional logistic regression analysis indicated that there was an increased risk of lung cancer in workers with higher exposures when dose estimates were lagged by 10 and 20 years. There was also a lack of evidence that confounding factors such as smoking affected the results of the regression analysis. The authors noted that there was considerable uncertainty in the estimation of exposure in the 1940's and 1950's and the shape of the dose-response curve for lung cancer. The results of this case-control study were used to estimate lifetime lung cancer risks associated with exposure to the OSHA PEL (see Section III.A.1 below).

B. Beryllium Sensitization and Chronic Beryllium Disease

The literature available regarding the potential development of CBD and beryllium sensitization in exposed workers is summarized in this section and in Table 2.

Cotes et al. (1983) investigated the effects of beryllium exposure in 130 male workers (out of an eligible 146) employed for at least six months from 1952 to 1963 in a factory that refined beryllium ore to produce beryllium hydroxide. The estimated duration of exposure ranged from 6 months to 9 years. For each participant, the investigation included a clinical interview, occupational history, chest radiograph, and assessment of lung functions performed in 1963, with a similar follow-up survey administered to 106 of the original participants in 1973. In 1977 a third survey was conducted of 47 employees and former employees, including the majority of workers hired at the plant after 1963, as well as nine individuals hired before 1963. Estimates of beryllium concentrations in the workplace were obtained from records of total airborne dust concentrations over a period from 1952 to 1960 and from information on where each employee worked during his time with the company. In 1952, the mean beryllium dust exposure concentrations measured at each of ten areas of the plant ranged from 0.1 to 2 µg/m^3 and in 1960 they ranged from 0.06 to 0.57 µg/m^3. All but one of the area-specific annual mean beryllium dust concentrations in the period from 1952 to 1960 fell below the OSHA PEL of 2 µg/m^3, and only 9% of the individual readings exceeded the PEL. Of the 130 workers examined in 1963, 4 men developed clinical,

radiographic, and physiological features of beryllium disease, 2 had abnormal chest radiographs but no other symptoms, and one had probable beryllium disease which was not confirmed at necropsy. Two of these cases were not identified in 1963, but developed features of CBD in 1976 and 1981, respectively. The 1973 and 1977 surveys did not identify any further cases. Six of the cases developed symptoms after exposure had ceased. It is not clear from the publication that all these cases were CBD. Results indicated that there was no evidence of a decline in lung function with increasing beryllium exposure among individuals without clinical or radiographic evidence of disease. However, when multiple regressors including age, stature, body mass exposure indices, and smoking habits were evaluated by multiple regression analysis the forced vital capacity decreased faster in older subjects, forced expiratory volume decreased faster in smokers compared to nonsmokers, and there was a significant association between the estimated exposure and forced expiratory volume and tidal volume during exercise. The authors did not evaluate beryllium sensitization.

Kreiss et al. (1989) evaluated beryllium-exposed workers in the nuclear industry. A company medical department identified 58 workers with beryllium exposure among a work force of 500. Of those workers exposed, 51 (88% of the exposed workers) participated in the study. The average age was 44 years old, ranging from 23 to 63 years. The mean estimated duration of exposure was 14.5 years, with a range of <1 to 35 years. The number of workers with abnormal BLPT readings was 6, with 4 being diagnosed with CBD. This resulted in an estimated 11.8% prevalence of beryllium sensitization. The study population consisted of 2 distinct groups. The first was a research and development group consisting of 24 workers who were older and had a longer tenure with a mean time from first exposure of 21.2 years. The second, a production group, consisted of 27 workers with a mean age of 38 years and a mean time since first exposure of 5 years. Age, years since first beryllium exposure and smoking habits were all accounted for in the evaluation. This study was the first to document that beryllium-exposed workers screened with a peripheral blood test for beryllium-specific lymphocytes frequently have mild beryllium disease.

Kreiss et al. (1993) expanded the work of Kreiss et al. (1989) by performing a cross-sectional study of beryllium workers in the same nuclear weapons plant to examine the relationships among beryllium sensitization, beryllium disease, job-related factors, and personal attributes. A total of 895 workers participated in the study. The mean age was 44.9 years, with a range of 26 to 69. Participants were placed in qualitative exposure groups (“no exposure”, “minimal exposure”, “intermittent exposure”, and “consistent exposure”) based on questionnaire responses. The number of workers with abnormal BLPT totaled 18 with 12 being diagnosed with CBD. Three additional sensitization cases developed

CBD over the next 2 years. Beryllium sensitized cases did not differ from noncases in age, gender, race, ethnicity, smoking, most respiratory symptoms, spirometric or radiographic abnormalities, or job tenure, but were significantly more likely to report having had cuts that were delayed in healing ($p = .02$). Beryllium sensitization occurred in all of the qualitatively defined exposure groups. Individuals who had worked as machinists were statistically overrepresented among beryllium-sensitized cases, compared with noncases. Cases were more likely than noncases to report having had a measured overexposure to beryllium ($p = .009$), a factor which proved to be a significant predictor of sensitization in logistic regression analyses, as was exposure to beryllium prior to 1970. The authors concluded that individual variability and susceptibility along with exposure circumstances are important factors in developing beryllium sensitization and CBD.

Kreiss et al. (1996) presented a third cross-sectional workforce study in which historical exposure data was available to assess the relationship between process-related risk and estimates of past beryllium exposure. The plant opened in 1980 for the production of beryllium ceramics from beryllium oxide powder manufactured elsewhere. Beryllium disease screening was conducted from February through June 1992. Industrial hygiene measurements had been collected from 1981 to 1992. Daily weighted average exposures were calculated and ranged from 1.4 to 6990.1 µg-days/m^3 with a median of 591.7 µg-days/m^3. The median average beryllium exposure of the workforce was 0.35 µg/m^3. There were a total of 136 employees that participated in the study. Of those participating, abnormal BLPT levels were found in 8. Six of the 8 employees with abnormal BLPT levels were observed to have CBD. The 14.3% rate of beryllium sensitization among machinists in this study was comparable to rates of 15.8% among dry pressers and 13.6% among process developers and engineers in another ceramics plant. The authors concluded that decreasing exposure in the machining process in this beryllium ceramics plant was important in lowering the risk of beryllium disease in workers.

Kreiss et al. (1997) presented another study, this one concerning a beryllium processing plant producing pure metal, oxide, alloys, and ceramics. Industrial hygiene measurements related to work practices taken in 1984 through 1993 were reviewed. Various types of air samples were collected including: general area samples, continuous samples, process breathing zone samples, and personal lapel samples. The median cumulative beryllium exposure for employees employed since 1984 was 1635 µg-days/m^3. The median average exposure was 1.3 µg/m^3. Quarterly job-specific daily weighted average exposures ranged from 0.05 to 63.11 µg/m^3. Alloy arc furnace workers and furnace rebuild workers had the highest median daily weighted averages. A total of 627 workers had blood drawn for the beryllium lymphocyte proliferation test (BLPT). Of these 627 workers, 59 had abnormal BLPT levels. Forty seven

employees were evaluated for CBD with 29 being diagnosed. Variables adjusted for in the analysis included: sex, race, smoking, time since first employment, work in another beryllium facility, work around or in beryllium fluoride, pebble plant, vacuum melting, alloy extrusion, ceramics, and shipping and receiving. The study had several limitations which resulted in likely misclassification of beryllium disease and sensitization status. Inconsistent results were produced from the 2 laboratories analyzing blood samples for the BLPT tests. CBD may have been underestimated because (1) not all people with abnormal blood test underwent clinical evaluation, (2) there were protocol changes in the BLP test, and (3) only four biopsies were taken (instead of the normal 8-12) in those undergoing bronchoscopy.

The Beryllium Health Surveillance Program (BHSP), established in 1991 at the Rocky Flats Nuclear Weapons Facility, served to identify beryllium sensitized individuals using the BLPT (Stange et al. 1996). The BHSP was a voluntary health surveillance program for current and former employees who believed they were exposed to beryllium. In the 29 cases of CBD and 76 cases of beryllium sensitization identified since 1991, there appeared to be cases that had only minimal exposure to beryllium. At the time of the Stange et al. (1996) publication, the BHSP included 4,397 participants tested from June 1991 to March 1995. Of these, 42.8% were current employees and 57.2% were former employees. The participants received an initial BLPT and a one and three year follow-up. The sensitization rate for the population was 2.43%. Because personal air samples were not collected in the BHSP, beryllium exposure values could not be compared to either the building or job exposure factors for the individual in the cohort. However, cases of CBD and beryllium sensitization were noted in individuals in all jobs classifications, even those considered to have very little exposure to beryllium. Therefore, the authors suggest ongoing beryllium health surveillance in employees in all jobs that have the potential for beryllium exposure.

Stange et al. (2001) extended the previous study to determine if specific people and jobs were associated with risk of sensitization and CBD. The study evaluated participants in the Rocky Flats BHSP who were tested between June 1991 and December 1997. Of the 5173 workers participating in the study, 172 were found to have abnormal BLPT. The number of employees observed to have CBD was 74. Three-year serial testing was offered to employees who had not been tested for three years or more and did not show beryllium sensitization during the previous study. This resulted in 2891 employees being tested. Of the 63 workers found to have abnormal BLPT, 7 were diagnosed with CBD. Sensitization and CBD rates were analyzed with respect to gender, building work locations, and length of employment. Historical employee data included hire date, termination date, leave of absences, and job title changes. Exposure to beryllium was determined by job categories and building or work area codes. Personal

beryllium air monitoring results were used when available from employees with the same job title or similar job. However, no quantitative information was presented in the study. Smoking was not listed as a confounding factor that was adjusted for in the evaluation. The authors conclude that for some individuals, exposure to beryllium at levels less that the PEL could cause beryllium sensitization and CBD.

One study evaluated workers in four different beryllium manufacturing facilities between the years of 1992 and 2000 and examined laboratory performance (Deubner et al. 2001a). The facilities were located in Tucson, Arizona; Elmore, Ohio; Cleveland, Ohio; and Delta, Utah. Deubner et al. (2001a) evaluated the workers to determine the risk of developing CBD. Split blood samples were tested at two separate labs. Of the 192 cases evaluated, 86 were diagnosed as having CBD. The authors concluded that there was substantial inter- and intra-laboratory disagreement among laboratories; they suggested that the BLPT does not meet the criteria for a suitable screening test.

In a related study, concentration samples were collected from 75 workers at the beryllium mining and extraction facility in Delta, Utah (Deubner et al. 2001b). The samples were collected from 1970 to 1999. Several different procedures were used to collect the samples including general air breathing (GA), breathing zone (BA), and personal lapel (LP). The average duration of exposure for beryllium sensitized workers was 21.3 years and 27.7 years for employee with CBD. The average duration for all employees was 14.9 years. Of the 3 workers with abnormal BLPT levels, only 1 was diagnosed with CBD. The authors concluded that the results of this study indicated that beryllium ore and salts (to which these workers were exposed) may possibly pose less of a hazard than beryllium metal and beryllium hydroxide.

Henneberger et al. (2001) evaluated workers in a beryllium ceramics plant for beryllium sensitization and disease. The study was a follow-up of a previous screening performed 6 years earlier. Questionnaires and blood samples for the BLPT were collected from 151 workers. The estimated duration of exposure ranged from 8 to 40.1 years with a median of 14.1 years. The cumulative exposure concentration range for long-term workers was 0.9-41.2 μg-yr/m^3, while that of short-term workers was 0.02-16 μg-yr/m^3. A total of 15 employees were found to have abnormal BLPT (8 long-term and 7 short-term workers). Of these 15 workers, 8 were observed to have CBD. In the 8 long term workers with abnormal BLPT, 7 had CBD while 1 worker declined follow-up and his status was unknown. In this study, the authors examined possible confounding effects of age, gender, ethnicity, and smoking. The study did not follow workers that left after the 1992 survey and before the 1998 survey. Underestimation of exposure was possible because previous exposure to beryllium was not considered. On the other hand,

overestimation of exposure was possible because respirator use was not considered and because exposures were not truncated at the time of development of disease (which was unknown due to the cross-sectional nature of the study) but, rather, at the time of the survey. This is a difficulty that affects all cross-sectional studies, i.e., the inability to determine at what point in time prior to the survey the disease developed in those individuals who present with CBD.

Newman et al. (2001) performed studies on a group of 235 employees at a beryllium metal machining plant. The facility used different beryllium materials including beryllium metal, beryllium-aluminum alloy, and beryllium metal/oxide composite called E metal. Surveillance was conducted on all employees with BLPT from May 1995 through December 1997. The average estimated duration of exposure was 11.7 years. Of the 235 individuals tested, 15 had confirmed abnormal BLPT. Nine cases were observed to have CBD. A 2 year follow-up study was conducted on 187 individuals. The 15 workers originally diagnosed with abnormal BLPT were excluded from the follow-up. Of the 187 individuals participating in the follow-up, 7 were found to have abnormal BLPT. The number of observed cases of CBD was 5. All 5 were classified as normal in the original test, however; one employee had a borderline BLPT result in 1995 and another had an unconfirmed single abnormal BLPT result in 1995. These studies did adjust for smoking. Respiratory protection was not routinely used at the plant.

A nested case-control study of the 235 workers evaluated in Newman et al. (2001) was performed to study the relationship between exposure to beryllium in the beryllium precision machining industry and the presence of beryllium sensitization and CBD (Kelleher et al. 2001). Twenty workers identified in the medical surveillance program between 1995 and 1999 as having beryllium sensitization or CBD were compared to 215 workers employed during the same time period. Of the 20 workers, 7 were identified as having beryllium sensitization and 13 had CDB. One hundred air samples were collected using personal cascade impactors and the median total beryllium exposure was 0.13 $\mu g/m^3$ (range of 0.006 to 22.62 $\mu g/m^3$). A lifetime weighted (LTW) beryllium exposure for each of the 20 workers was calculated which accounted for the median estimate of job-title-specific exposure, the years in each job title, and the total years of employment. The LTW beryllium exposure in the 7 workers with beryllium sensitization ranged from 0.035 to 0.6 $\mu g/m^3$, while the LTW for workers with CBD ranged from 0.024 to 0.35 $\mu g/m^3$. Of the 20 workers with confirmed positive BLPT results, 3 declined biopsy and 11 showed signs of granulomas and/or mononuclear cell infiltrates on lung biopsy. Two of the workers had positive bronchoalveolar lavage results with positive BLPTs and lymphocytosis. The study adjusted for age, employment duration, longer work days, smoking habits, and job title. The authors concluded that there did appear to be an

increased risk of beryllium sensitization and CBD in workers performing certain tasks, specifically machining beryllium. In addition, results indicated that exposure levels in workers with sensitization and CBD were predominately below OSHA's current PEL of 2 $\mu g/m^3$.

In a case-control study of workers at the Rocky Flats Nuclear Weapons facility, 50 CBD cases and 74 beryllium sensitization cases were matched to controls of the same age, race, gender, and smoking status (Viet et al. 2000). Extensive air sampling had occurred in some portions of the plant (particularly Building 444). Because the majority of air samples were taken from fixed air head samplers in Building 444 of the facility, these air sample concentrations were used in the study to construct a job exposure matrix that included the determination of the Building 444 exposure estimates for a 30 year period, each subject's work history by job location, task, and time period, and assignment of exposure estimates to each combination of job location, task, and time period as compared to Building 444 machinists. Mean exposure concentrations ranged from 0.083 $\mu g/m^3$ to 0.622 $\mu g/m^3$. Maximum air concentrations ranged from 0.54 $\mu g/m^3$ to 36.8 $\mu g/m^3$. The mean durations of exposure for the beryllium sensitization cases and the CBD cases were 13.2 years and 19.1 years, respectively. Results indicated that the cases in the beryllium sensitization group were significantly younger than in the CBD group. The CBD cases had significantly higher numbers of years of employment, and earlier employment start dates than the sensitization cases. Limitations noted by the authors included the observation that fixed air head (FAH) samplers may have been unrepresentative of personal exposures because they were generally placed away from the operator's breathing zone. In addition, the mean exposure concentrations represented long term averages and it was noted that the daily FAH exposure sometimes exceeded 2 $\mu g/m^3$ over the history of the facility.

III. Quantitative Risk Assessment for Beryllium

In this section, preliminary quantitative risk estimates are presented for lung cancer and CBD. These estimates are considered preliminary because OSHA is in the process of determining if more data may be available to perform other analyses of such risks. In the meantime, risk estimates from three of the studies discussed above (two of lung cancer risk and one of CBD risk) are presented here as a "baseline" for comparison to future analyses. The results of the analyses reported below are expressed in terms of the extra number of cases that would be estimated to occur under various exposure concentrations or exposure scenarios.

The basis for the exposure calculations that has been used throughout the following analyses is total beryllium concentration, as opposed to alternatives based on, for example, beryllium concentration for particles of specific size ranges or concentrations of specific beryllium compounds. There has been some discussion of the possibility that particle size or compound specificity may better link beryllium exposure and disease outcome (Kelleher et al. 2001; Stefaniak et al. 2003). However, the studies that have been analyzed here did not have (or did not present) data on any other metric of beryllium exposure. The exposure metric that is the basis for all of the quantitative assessments reported below is cumulative beryllium exposure (expressed either as µg-days/m^3 or µg-yrs/m^3). Measures other than cumulative exposure (e.g., peak exposures) may be important risk factors for lung cancer or CBD, and they should be evaluated if possible in future analyses.

A further limitation of the risk estimates presented here is that they are based on the reported results of analyses that have been conducted by the study authors. As an example, in some studies (e.g., Sanderson et al. (2001)) logistic regression analyses were applied by the authors to their raw data. The risk estimates that we have completed using the author-completed analyses have taken the reported results of those analyses (e.g., model parameter estimates) and have used them as described in the methods below to obtain quantitative risk estimates. We have not been able to replicate or verify the analyses presented in the published reports, not having access to the raw data that are necessary for their implementation.

The remainder of this section describes the data and the methods that were used, as well as the results of our analyses. First, the lung cancer data and results are presented; results of the analyses applied to the studies of Sanderson et al. (2001) and of Wagoner et al. (1980) are shown. Second, CBD risk estimates are derived; those estimates were based on an analysis of the information available from Viet et al. (2000).

A. Lung Cancer

1. Sanderson et al (2001)

The case-control study reported by Sanderson et al. (2001) provided the basis for estimating the lifetime risk estimates associated with various levels of beryllium exposure. The case-control study in question examined the 142 lung cancer cases identified in a cohort drawn from workers in the Reading, Pennsylvania beryllium processing facility employed sometime between 1940 and 1969. Vital status was ascertained through 1992. As of that date, the SMR for the cohort under consideration was 122 with a 95% confidence interval of 103 to 143 (Sanderson et al. 2001). Each case that died of lung cancer was

matched to five controls; the controls had to have lived at least to the age at which the corresponding case died and had to be of the same race. These cases and controls were used to investigate the relationship between level of beryllium exposure and lung cancer.

Job exposure matrices were constructed for the cases and controls based on historical exposure estimates. Importantly, these estimates were used to estimate cumulative exposures for both the cases and the controls. Cumulative exposure estimates were also lagged 10 or 20 years to account for disease latency.

The major conclusions reported by Sanderson et al. (2001) are summarized here:

• Cases had more frequently worked in general labor and maintenance job categories, those categories where some of the highest beryllium exposures occurred.

• Cases did not differ significantly ($p > .05$) from controls with respect to unlagged cumulative exposure, but they did differ with respect to cumulative exposure lagged 10 and 20 years. In fact, geometric means of all exposure metrics reported (cumulative, average, and maximum) differed significantly only when lagged 10 or 20 years.

• Conditional logistic regression analyses found significant effects attributable to the log of cumulative exposure, the log of average exposure, and the log of maximum exposure when lagged 10 or 20 years.

• When determining which types of beryllium compounds might be associated with lung cancer, lagged exposures to beryllium oxide and beryllium-copper alloy (exposures which were highly correlated with one another) appeared to show the same pattern as for beryllium in general, i.e., cases had greater lagged exposures to those compounds than did controls, with the greatest odds ratios occurring in the middle ranges of lagged exposure quartiles.

• Cases tended to be more frequently exposed to acid aerosols, fluorides, copper, and welding fume, but odds ratios were significant only for lagged exposures to fluorides and copper. These exposures were common throughout the plant.

• The subset of workers included in the case-control study for whom smoking information was available was small (consisting of those who participated in a 1968 USPHS study). Therefore, only an indirect assessment of the potential for confounding of the beryllium-lung cancer relationship by smoking was possible. It appeared that professional and nonprofessional workers in the plant differed with respect to smoking habits, so Sanderson et al. (2001) used job status (professional/nonprofessional) as a surrogate for smoking status. They then compared the geometric means and odds ratios by quartiles of exposure, when they excluded the professionals, to those obtained for the full case-control set. Since they observed

very little difference in the results, they concluded that professional status (as a surrogate for smoking status) was not a confounder.

Our risk analysis of this case-control study was based on the results reported in the publication (Sanderson et al. 2001). Thus, for example, it was not possible to perform a separate risk assessment based on summary data provided in tables within the paper. The estimates of lifetime risk associated with various levels of beryllium exposure have been estimated as follows. Only the results for 10- and 20-year lagged cumulative exposure have been used; these were the cumulative exposure metrics that appeared to be significantly different between cases and controls. The results of the logistic regression analysis presented in Sanderson et al. (2001) that used log cumulative dose as the explanatory variable were used.

The logistic regression model (using log cumulative exposure) was

$$\text{logit}[p(D)] = \ln[p(D)/(1-p(D)] = \alpha_k + \beta * \ln[D], \qquad \text{Eq. 1}$$

where p(D) is the probability of lung cancer death as a function of the cumulative exposure D. There is an α_k term for each of the K = 142 "strata" defined by each case and its matched set of controls, and it consists of all terms constant within stratum k (Hosmer and Lemeshow, 1989). The α_k parameters are often considered "nuisance" parameters, i.e., their estimation is not of interest. Furthermore, the estimate of β is biased when of all the parameters in the fully stratified model are estimated and the number of α parameters increases with the sample size, as in this 1-5 matched study. This bias can be avoided by adopting a "conditional" modeling approach (Hosmer and Lemeshow, 1989). Sanderson et al. (2001) employed such a conditional logistic regression approach in estimating (and reporting) the value of the parameter β for their case-control set.

Sanderson et al. (2001) presented estimates of the parameter β (equal to 0.60 and 0.041 for cumulative exposure lagged 10 years and 20 years, respectively, and when cumulative exposure was expressed in terms of μg-days/m^3). They also presented the "Wald statistics" associated with each of those estimates, from which the standard errors associated with those estimates (and subsequently confidence intervals for those estimates) could be derived; the following table summarizes those derivations

Lag for Cumulative Exposure (years)	Estimated Log-odds Ratio (β) Parameter (per μg-days/m^3)	Standard Error (SE) for β	95% Confidence Interval for β[a]
10	0.060	0.011	(0.038, 0.082)
20	0.041	0.0073	(0.027, 0.055)

[a]The confidence intervals were calculated assuming normality of the estimates, β. The interval was estimated to be $\beta \pm 1.96*SE$.

A common measure of the effect of a variable (such as cumulative exposure) on the risk of an adverse outcome (such as lung cancer death) is based on the odds ratio, which is defined as the odds of the outcome occurring under one set of exposure conditions, say d_1, relative to the odds of the outcome occurring under another set of exposure conditions, say d_2, and is expressed as

$$OR(d_1, d_2) = p(d_1)/(1 - p(d_1)) \,/\, p(d_2)/(1 - p(d_2)), \qquad \text{Eq. 2}$$

where p(x) is the probability of the outcome under conditions x.
The parameter β in the case of the logistic regression model in Eq. 1 is related to the odds ratio as follows:

$$OR(D_1, D_2) = \exp\{\beta*\ln(D_1) - \beta*\ln(D_2)\} = \exp\{\beta*[\ln(D_1) - \ln(D_2)]\}, \qquad \text{Eq. 3}$$

where here the exposure conditions are considered completely characterized by the cumulative exposure values (D_i). When both D_1 and D_2 are positive, there is no problem in determining the odds ratio for the difference between those exposure levels. But it is most common to express the odds ratio relative to a non-exposure situation ($D_2 = 0$), in which case the odds ratio is infinite because $\ln(0) = -\infty$. This is a difficulty imposed by the fact that Sanderson et al. (2001) chose to model the probability of response using the logarithm of dose, which implies that "0" log(Be) exposure corresponds to a Be exposure of μg-days/m^3. In the case of lung cancer, however, the probability of response is known to be positive even in the absence of Be exposure, because of other (e.g., environmental or inherent) causes of lung cancer.

We propose here an ad hoc correction for this aspect of the modeling; such an ad hoc procedure is necessary because we must rely on the reported results from Sanderson et al. (2001) as opposed to having the case-control data to perform an independent analysis. The unit of cumulative exposure used by Sanderson et al. (2001) was μg-days/m^3. It is not an unreasonable assumption that the probability of

response at 1 µg-days/m^3 would be indistinguishable from the probability of response in the absence of exposure. If that is the case, then Eq. 3 can be used to estimate OR(D, 0):

$$OR(D, 0) \cong OR(D, 1) = \exp\{\beta*[\ln(D) - \ln(1)]\} = \exp\{\beta*\ln(D)\}. \quad \text{Eq. 4}$$

The goal of this treatment of the logistic modeling results from Sanderson et al. (2001) is to estimate the relationship between the annual, age-specific, background probability of a lung cancer death and the corresponding probability when cumulative exposure (lagged either 10 or 20 years) is D. Then life-table methods can be applied to calculate the lifetime risk of lung cancer for exposure scenarios of interest. Given the approximate odds ratio OR(D, 0) derived above and shown in Eq. 4, the following assumptions and adjustments were made to derive the annual, age-specific probabilities desired.

First it was assumed that the annual, age-specific probabilities of interest, $p_a(D)$, could be expressed in terms of the annual age-specific background probabilities as follows:

$$p_a(D) = r(D)*p_a(0),$$

where r(D) (some function of exposure, D) is constant over age when D is held constant. The relevant $p_a(0)$ values were assumed to be those obtained from the US rates for lung cancer deaths (e.g., all races and both sexes combined when predicting the response for a group of otherwise unspecified workers exposed to Be under the conditions described above). This is the usual relative risk assumption applied using an accepted reference population; the probability of response with exposure D is a constant times the background probability and that constant is independent of age. This allows us to use relative risk estimates derived from Sanderson et al. (2001) for all the age categories in the life-table calculations.

The odds ratio results from Sanderson et al. (2001), and the approximation derived from them in Eq. 4 above, can be used as follows to get those relative risk estimates. It is often assumed that the odds ratio is a good approximation to the relative risk. The validity of this approximation can be seen from Eq. 2 above; when the probabilities $p(d_1)$ and $p(d_2)$ are both small the odds ratio is essentially equal to $p(d_1)/p(d_2)$, i.e., the risk for exposure situation d_1 relative to the risk for exposure situation d_2. If d_2 corresponds to no exposure (D = 0), then OR(D, 0) is approximately equal to p(D)/p(0), when d_1 corresponds to exposure equal to the cumulative metric D. This approximation of the relative risk by the odds ratio was applied in the conversion to annual rates.

However, another issue that must be dealt with when using the logistic regression results and the estimates derived from them to apply a life-table method relates to the fact that the life-table requires annual probabilities of response (denoted $p_a(D)$ above) in order to calculate lifetime risk. But the results (odds ratio estimates) from Sanderson et al. (2001) relate to the entire period of observation rather than to specific yearly intervals. Consider the following by way of illustration. If the annual probability of response is $p_a(D)$ for a fixed D, that probability is constant for each year, and there are n years of observation, then the probability of response over those n years is

$$p(D) = 1 - (1 - p_a(D))^n,$$

i.e., one minus the probability that there was no response in each year of observation. Now, if $p_a(D)$ is small, then $(1 - p_a(D))^n$ is approximately equal to $[1 - n*p_a(D)]$ so that p(D) is approximately equal to $n*p_a(D)$. Similarly, p(0) is approximately equal to $n*p_a(0)$. So, p(D)/p(0) is approximately equal to $n*p_a(D)/ [n*p_a(0)] = p_a(D)/p_a(0) = r(D)$ as defined above. In other words, the annual relative risk is approximately equal to the overall relative risk approximation discussed above that is estimated from the results of Sanderson et al. (2001), i.e., using Eq. 4.

A life-table approach (where the age-dependent accumulation of cumulative exposure is matched to the age-dependent probability of survival and of dying from lung cancer) is one way in which the accumulation of exposure over time can be incorporated with the age-specific annual rates of lung cancer death derived above to estimate risks associated with various exposure scenarios. The life-table approach also accounts for the likelihood of survival up to any point in time when determining the lifetime risk. Because the relevant estimates (the β parameter values) based on the results from Sanderson et al. (2001) are expressed per μg-day/m^3 the relevant lagged cumulative exposure up to any particular age (used to calculate the exposure-related probabilities of lung cancer and survival) was the number of years of exposure, times the hypothesized exposure concentration, times 250 working days per year.

In our applications of the life-table approach, the year 2000 all-cause and lung cancer mortality rates (both sexes, all races) were used. The life-table calculations were completed for an exposure scenario starting at age 20, ending at age 65, with follow-up to age 100. The following table presents the results obtained for the two choices of lag on cumulative exposure calculations and for the best estimate, lower bound estimate, and upper bound estimate for the β parameter obtained from Sanderson et al. (2001), as a function of the assumed constant Be concentration.

Lag for Cumulative Exposure (years)	Exposure Concentration ($\mu g/m^3$)	Estimated Additional Lung cancer Deaths per 1000 Workers Exposed[a]
10	2	47 (27 – 71)
	1	43 (25 – 64)
	0.5	39 (22 – 58)
	0.2	34 (20 – 50)
	0.1	30 (18 – 44)
20	2	28 (17 – 40)
	1	26 (16 – 37)
	0.5	24 (15 – 33)
	0.2	21 (13 – 29)
	0.1	18 (12 – 16)

[a]Workers assumed to be exposed for 45 years starting at age 20. Best estimates and bounds (in parentheses) are shown, corresponding to the estimates presented by Sanderson et al. (2001) and the 95% confidence interval bounds derived above using the Wald statistics.

These estimates were obtained using the spreadsheet, "lung cancer lifetable.xls," which accompanies this report.

2. Wagoner et al. (1980)

Wagoner et al. (1980) published a follow-up of workers employed at the same Reading plant studied by Sanderson et al. (2001). The Wagoner et al. (1980) results lacked any presentation of exposure levels, but USEPA (1998) used those results and assumptions about the concentrations (they assumed an average concentration for the Wagoner et al. cohort members of either 100 $\mu g/m^3$ or 1000 $\mu g/m^3$ based on earlier NIOSH estimates of the range of median exposures) to derive unit risk estimates for inhalation exposures to beryllium. USEPA (1998) used alternative (including smoking-adjusted) reference rates to calculate the expected number of lung cancers among the cohort members whose initial exposure was at least 25 years before the end of follow-up; depending on the reference population used, the expected number was between 13.9 and 14.7 (as opposed to 20 observed), for SMRs of between 136 and 144 (upper bounds for those relative risks were determined by USEPA (1998) to be 198 and 209, respectively).

In order to derive their risk estimates, which were intended to be for ambient (lifetime) exposure to the general population, not just for workers, USEPA (1998) needed to estimate the relative fraction of the lifetime over which exposure occurred. Without additional information directly from Wagoner et al. (1980), USEPA (1998) bracketed that fraction by 1.0 above and 0.25 below. However, for the worker exposure scenario of interest for this risk assessment, we did not need to adjust for the fraction of the lifetime over which exposure occurred – the exposure pattern from the occupational cohort included in the Wagoner et al. (1980) study was assumed to be the one relevant to this occupational risk analysis. Therefore, only those estimates derived by USEPA (1998) for which the fraction of 1.0 was used were considered here.

Combining the two mean concentration estimates (100 or 1000 $\mu g/m^3$) and two upper bound estimates of relative risk (1.98 and 2.09), four "unit risk" estimates were derived (considering only those with the exposure/lifetime fraction set equal to 1.0). Those estimates ranged from 1.6E-4 to 1.8E-3 with a geometric mean of 5.4E-4. That is, the geometric mean increase in the number of lung cancers was 0.54 per 1000 people exposed to 1 $\mu g/m^3$. The unit risk calculations from USEPA (1998) included adjustments to the concentration levels to get environmental exposure levels corresponding to occupational exposures. The adjustments corresponding to the daily exposure duration (24 hours versus 8 hours) and to number of days per year (365 versus 240) were removed to obtain estimates appropriate to the occupational setting. When this was done, the 0.54 per 1000 estimate of additional lung cancers corresponds to an occupational exposure of 4.6 $\mu g/m^3$ (= 1 * 24/8 * 365/240). Extrapolating linearly, this was equivalent to an additional 0.23 lung cancers per 1000 workers exposed to 2 $\mu g/m^3$.

When the point estimates rather than the upper bound relative risk estimates were used (1.36 and 1.44 rather than 1.98 and 2.09), the unit risk estimates were 5.9E-4 and 1.8E-3 if a mean exposure level of 100 $\mu g/m^3$ was assumed for the Wagoner et al. (1980) cohort, and 5.9E-5 and 1.8E-4 if a mean exposure level of 1000 $\mu g/m^3$ was assumed for that cohort. These estimates led to additional lifetime risk estimates for the OSHA PEL of 0.25 to 0.78 per 1000 (assuming the 100 $\mu g/m^3$ mean exposure in the Wagoner et al. (1980) cohort) or 0.025 to 0.078 per 1000 (assuming the 1000 $\mu g/m^3$ mean exposure). The geometric mean of the unit risk point estimates (3.3E-4) yielded an additional risk estimate of 0.14 lung cancers per 1000 workers exposed to the OSHA PEL. The values derived from the USEPA analysis of the Wagoner et al. (1980) study for additional risk are considerably lower than those derived from use of the case-control logistic regression results of Sanderson et al. (2001).

3. Strengths and Limitations of the Lung Cancer Analyses

Both the Wagoner et al. (1980) and Sanderson et al. (2001) studies were of individuals exposed to Be in occupational settings. This is a strength of those studies with respect to estimating the risk associated with occupational exposures. It should be noted that both studies were of employees at a single facility. It is likely that other plants and other types of occupational exposures to Be may differ from those encountered by the subjects of these two studies with respect to particle size distributions and/or Be compounds. Thus, generalization to other exposure conditions is associated with uncertainties, to the extent that such characteristics are related to Be-induced lung cancer.

The Sanderson et al. (2001) study appears to have benefited from a much more complete exposure reconstruction effort, relative to that for the Wagoner et al. (1980) study. In the analysis of the Wagoner et al. (1980) cohort, a fixed concentration of either 100 or 1000 $\mu g/m^3$ was assumed (see description of the estimates derived by USEPA above). These were intended as bounding estimates, but even the lower value is greater than the average estimated by Sanderson et al. (2001) for their study participants (about 20 $\mu g/m^3$ on average). Sanderson et al. (2001) used a time-specific exposure matrix to derive their estimates of cumulative exposure based on job assignment. This is a much superior method for deriving cumulative exposure estimates relevant for risk assessment. However, Sanderson et al. (2001) raise the possibility that the earliest exposures (occurring in the 1930s and early 1940s) may have been underestimated by the linear extrapolation method they used to estimate concentrations in time periods prior to actual collection of samples (in 1947 to 1953).

Concerns have been expressed about the appropriate reference rates for the workers studied by Wagoner et al. (see, for example, USEPA, 1998). Those concerns relate to the fact that the county in which the plant is located had lower lung cancer rates than those of the overall US population, while the cities within that county where many workers resided had higher than the US average rates of lung cancer. Thus, the appropriate comparison rates for computing expected values are not clear. A strength of the case-control design used by Sanderson et al. (2001) is that no external reference rates are required for the logistic regression analyses that have been used to derived odds ratio estimates.

The case-control design of the Sanderson et al. (2001) study also makes it less susceptible to error due to limited information on workers' smoking habits than are studies that rely on comparison with external populations. Since the study compared workers with other workers in the same plant, smoking

could only have confounded the analysis if there was a correlation between the workers' smoking habits and their amount of beryllium exposure. Sanderson attempted to evaluate the extent of correlation between smoking and exposure using a tangentially related surrogate (professional status). The analysis of the Wagoner et al. (1980) data had an indirect control for smoking, via use of reference rates for a population that was only assumed to have similar smoking habits as the workers in the study. In fact USEPA (1998) reported that their estimates of lung cancer risk used adjusted rates that accounted for, among other things, differences between the assumed smoking pattern for the Wagoner et al. (1980) cohort (estimated based on a small sample of smoking history data collected from some cohort members) and the pattern observed for US white males generally. Thus, while the estimates reported above do include that smoking adjustment, the appropriateness of the adjustment is not clear. A possible confounding effect of smoking can not be completely ruled out for either of the studies analyzed here.

Other possible confounders include exposures to other potential lung carcinogens. Acid mists, welding fumes and gases, as well as other metals (including nickel, cadmium, and chromium) were present at some locations and for some jobs. Sanderson et al. (2001) appear to have considered these possible confounders carefully, although the ability to detect their confounding effect is limited by the relatively small size of the study and the correlations that exist among those exposures and with Be exposure. Exposures to copper and fluorides were statistically associated ($p < .05$) with lung cancer risk in their analysis, a relationship which could be due to the high association noted by the authors between copper and fluoride exposures in the plant and several beryllium compounds. Sanderson et al. also note that the available toxicological and epidemiological literature on copper and fluorides do not suggest these exposures as contributors to the lung cancers observed in the study population. Of the other exposures evaluated, to acid mists, aluminum, cadmium, nickel, and welding fumes, exposures were higher among cases than controls for acid mists and welding fumes, but the associations were not statistically significant.

The use of a log-transformed Be cumulative dose term in the logistic regression analysis of the Sanderson et al. (2001) case-control data entails the model artifact mentioned above, that of predicting a background lung cancer risk of zero. While this leads to some uncertainty and an ad hoc procedure for dealing with that difficulty, the procedure employed (assuming that 1 µg-day/m^3 of exposure gives essentially the same risk as no exposure) is not likely to bias the risk estimates severely. There is some uncertainty associated with the assumption that relative risk estimate derived from Sanderson et al. (2001) results can be applied in a life-table approach to all age categories. But that is an assumption that is routinely made in epidemiologically based cancer risk assessments. Similarly, the assumption that

cumulative exposure is an appropriate measure for relating Be exposure and lung cancer risk is one that is common to epidemiologically based assessments of most other carcinogens.

Finally, it should again be noted that the reliance on the results of analyses summarized for publication limits our ability to more fully explore and understand the impact of some of these issues. The availability of the raw data would allow us to do sensitivity and uncertainty analyses and to better characterize the quantitative effect of our assumptions and decisions on the resulting estimates of lung cancer risks.

B. CBD

1. Viet et al. (2000)

Viet et al. (2000) described a case-control study of individuals who had enrolled in the Rocky Flats Beryllium Health Surveillance Program (BHSP). The BHSP was initiated in 1991 to monitor the health status of Rocky Flats employees; the Viet et al. study identified 50 qualifying CBD cases from the BHSP as of October 1994. The controls (one per case) were randomly selected from the BHSP data base to match the cases based on age, smoking status, sex, and race.

Viet et al. (2000) completed a detailed exposure reconstruction based on fixed airhead (FAH) samples. This reconstruction, based on samples dating back to 1960, was based primarily on sample data for a single building (Building 444) but it included evaluation by knowledgeable industrial hygienists of the relationships among exposure levels in different building areas over time. Specific job categories were also considered, relative to the exposure levels expected for a machinist in Building 444, again with evaluation by the industrial hygienists.

From the exposure reconstructions, cumulative exposures were estimated for each individual in the case-control study. A conditional logistic regression with log-transformed cumulative exposure was completed for the case-control set, similar to the analysis performed by Sanderson et al. (2001) in their case-control study of beryllium exposure and lung cancer. Importantly however, Viet et al. (2000) also conducted an unconditional logistic regression analysis, using an equation of the form

$$\text{logit}[p(D)] = \ln[p(D)/(1-p(D)] = \alpha + \beta * \ln[D], \qquad \text{Eq. 5}$$

where p(D) is the probability of CBD as a function of the cumulative exposure D. In this model, a single "intercept" term, α, was estimated and could be used in our analyses, because in that case, the probability of CBD as a function of cumulative exposure can be derived from Eq. 5 and shown to be

$$p(D) = \exp\{\alpha + \beta*\ln[D]\} / (1 + \exp\{\alpha + \beta*\ln[D]\}) \quad \text{Eq. 6}$$

Viet et al. (2000) discussed the use of the unconditional logistic regression approach. They acknowledged that the conditional analysis is the most appropriate method for their matched case-control study, but determined that the biases that might be introduced with the unconditional analyses would not be appreciable if the matching factors were not confounded with exposure. Viet et al. (2000) thought that such confounding was probably not a problem because exposure differences among matched pairs were not statistically significant and because the slopes estimated from the unconditional and conditional analyses were similar (and the confidence intervals for them overlapped considerably). The analyses that follow are based on the unconditional logistic regression results from Viet et al. (2000), which are summarized in the following table.

Parameter	**Estimates**[a]
Intercept (α)	0.714 (0.18, 1.25)
Slope (β)	0.578 (0.29, 0.86)

[a]The 95% confidence intervals for the parameter estimates are shown in parentheses. The units for the cumulative dose metric associated with these parameter estimates are μg-yrs/m^3.

Hosmer and Lemeshow (1989) have shown that the intercept term from an unconditional logistic regression analysis of case-control data is not the intercept that should be used for predicting the probability of response as a function of the explanatory variables. The intercept that should be used depends also on the sampling fractions of the cases and the controls, θ_1 and θ_0, the fraction of all eligible cases or controls, respectively, that were included in the analysis. They show that the desired intercept term is equal to

$$\alpha' = \alpha - \ln(\theta_1/\theta_0)$$

In the case of the Viet et al (2000) study, the sampling fraction for cases was $\theta_1 = 1$; all the cases identified in the BHSP were included in the study. However, only about 1 in 100 (50 out of

approximately 5000) potential controls were included. Thus $\theta_2 = 0.01$, and the best estimate of the intercept that was used in the subsequent analyses was

$$\alpha' = 0.714 - \ln(1/0.01) = -3.89.$$

Confidence interval bounds for α' were calculated in the same manner, using the bounds for α shown in the table above.

As in the case of the interpretation of the Sanderson et al. (2001) results, it is noted that the probability of response obtained from the Viet et al. (2000) study using Eq. 6 with the adjusted intercept term is the probability of developing CBD over the entire period of "observation" associated with this study. The period of observation for the case-control set appeared to be only from sometime in 1991 (when the BHSP was initiated) to October, 1994 (the date of initiation of the Viet et al. study, and the time period over which they identified their cases). An observation period of 3.5 years was assumed for the following analyses, but that is only an approximation and other uncertainties associated with that value (related to the potential that prevalent rather than only incident cases might be included among the cases assumed to have appeared in that time period) are discussed further below. Operationally, the probability obtained from the logistic regression analysis was divided by 3.5 to yield annual rates for use in the life-table analyses.

The estimates of lifetime risk of CBD (number of cases per 1000 workers exposed for 45 years starting at age 20, derived using the parameters presented above, are shown in the following table for various FAH-estimated concentration levels, assumed to be constant over the 45 year work period. These estimates have been derived for FAH-estimated concentration levels only, because the best way to convert to other measurements (e.g., personal breathing zone, PBZ, concentrations) is not clear. The concentration reconstruction completed by Viet et al. (2000) was based on FAH samples; the estimates presented here, therefore, use that "unit" of exposure. The conversion of FAH to PBZ concentrations was noted by Viet et al (2000) to be quite uncertain, for the facilities that they were investigating. The FAH concentrations shown in the following table are some that may be consistent with cumulative exposures that could relate to CBD development in exposed workers.

Input Concentration[a] ($\mu g/m^3$)	Best Estimate (CBD Cases per 1000 Workers)	Limited Bounds[b] (CBD Cases per 1000 Workers)	Extreme Bounds[c] (CBD Cases per 1000 Workers)
2.0	893	601 – 972	430 – 982
1.0	815	535 - 945	372 – 970
0.5	707	471 – 878	319 – 940
0.2	539	391 – 694	257 – 832
0.1	415	336 – 509	217 – 676

The year 2000 all-cause mortality rates (all races, both sexes) were used in the above calculations.
[a]Input concentration is an FAH concentration.
[b]Limited bounds use the confidence interval endpoints for the slope parameter given by Viet et al. (2000), but not the confidence interval for the adjusted intercept.
[c]Extreme bounds use the confidence interval endpoints for the slope parameter and for the adjusted intercept given by or derived from Viet et al. (2000).

Based on the results available to us from those reported in Viet et al. (2000), we can not calculate true 95% confidence intervals for the risk associated with any input dose. Such a calculation would require joint confidence intervals for both parameters, α and β, but we only have intervals reported for each parameter separately. In the above table, the "limited bounds" correspond to using the confidence interval endpoints for β from Viet et al. (2000). These probably underestimate a 95% confidence interval for the risk associated with the exposures of interest. The "extreme bounds" use the confidence interval endpoints for both α and β from Viet et al. (2000); they probably overestimate a 95% confidence interval for the risk associated with the exposures of interest. All of these estimates have been calculated using the accompanying spreadsheet, "Viet reanalysis3.xls."

2. Strengths and Limitations of the CBD Analysis

The Viet et al. (2000) study was of individuals exposed to Be in an occupational setting; this is a strength with respect to estimating the effects of occupational exposures. As discussed in the context of the lung cancer analysis, occupational exposures to Be that differ from those represented by the Viet et al (2000) subjects may exist. Understanding of the dose-response relationship between Be exposure levels and CBD development will be strengthened further by investigation and analysis of exposure conditions and subsequent CBD response in other facilities.

The exposure reconstruction effort underlying the Viet et al. (2000) study appears to have been very thorough and extensive. Because exposure information is so often the limiting feature of epidemiologically based risk assessments, this is a definite strength of the study. The job-exposure matrix that Viet et al. (2000) created allows examination of a variety of dose metrics and therefore facilitates comparisons of alternative exposure indices to the standard cumulative dose measure. Of course, access to the raw data would be necessary for such alternative analyses to be completed.

As in the case of the lung cancer analyses, this assessment has been limited by reliance on the results of analyses summarized in the peer-reviewed publication. In fact, the estimates that have been presented above are based on the reported parameter estimates from an unconditional logistic regression analysis, even though a conditional analysis is known to be the more appropriate approach. In order to obtain estimates of probability of response suitable for a life-table analysis, as was desired to assess the impact of various exposure patterns on lifetime CBD risk, the best information available was the reported unconditional analysis parameter estimates. As noted above, the summarization of those parameter estimates did not allow us to calculate true 95% confidence intervals for the risk estimates.

Another limitation of using the results as summarized in Viet et al. (2000) is that the analysis of those results assumed that all of the cases identified by the BHSP and included as cases by Viet et al. (2000) were incident cases. This was an assumption implicit in the calculation of the annual rates from the overall rates estimated in their logistic regression analysis. But, thinking about the observed cases on an annual basis, the first year of observations from the BHSP would have included some unknown proportion of prevalent cases; whereas in the second and subsequent years the cases would all be truly incident cases. Thus estimating an annual rate is confounded by the fact that some years contain only incident cases while the first year contains both incident and prevalent cases. Operationally one might examine the impact of this issue by increasing the observation time used to convert the overall rate to the annual rates desired (reflecting the assumption that is was not just 3.5 years of "observation" that contributed the cases, but some longer period). But the magnitude of such an extension to the observation period is unclear. Sensitivity analyses could be performed; informally it was observed that increasing the observation period from the assumed 3.5 years to 5 years decreased the CBD risk associated with the model input dose of 0.2 $\mu g/m^3$ from 539 to 423 per 1000 exposed workers, and increasing the observation period to 10 years dropped the risk even further to 244. The extension to ten years of observation is probably more than sufficient to cover the issue of prevalent cases; and still the results predict a substantial CBD risk associated with exposure to an FAH concentration of 0.2 $\mu g/m^3$. A better solution to

this limitation would be access to the data so that, for example, one could base the analysis on cases known to be truly incident.

This preliminary analysis was based on cumulative exposure and an assumption of age-independent probability of response for fixed cumulative dose. The assumption that probability of response is independent of age or time since exposure for a fixed dose is a common one; it is often difficult to consider alternative assumptions when the age range of subjects and the length of follow-up in occupational studies may be relatively small. It is also unclear whether a cumulative measure of exposure is the most appropriate metric to relate Be exposure and development of CBD. The relatively short period of observation underlying the Viet et al. (2000) study (we have estimated the observation period to be about 3.5 years) makes it difficult to distinguish between alternatives, even if the raw data were available.

IV. Conclusion

Based on the information available about the beryllium exposures and lung cancer responses in workers employed in the Reading , Pennsylvania beryllium facility (the one facility for which quantitative estimates of cumulative exposure have been derived here), there was great variability in the lung cancer risk estimates that were derived. That variability was observed across the studies of Sanderson et al. (2001) and Wagoner et al. (1980), both of which investigated that single facility, albeit differently defined cohorts from that facility. Concentration estimates were very limited, especially before 1970 or so, when the bulk of the worker histories occurred. The basis for the USEPA concentration estimates that they used in the analysis of the Wagoner et al. (1980) data has not been presented or described in sufficient detail. Certainly the averages that USEPA examined (100 and 1000 $\mu g/m^3$) were greater than the average exposure levels reported by Sanderson et al. (2001) for their cases and controls (on the order of 20 $\mu g/m^3$), a difference that could account for the much lower risk estimates derived from the Wagoner et al. (1980) study compared to those based on Sanderson et al. (2001) publication. Levy et al. (2002) have stated their belief that the concentrations at the Reading plant were overestimated, due to the fact that the measurements would reflect nonrespirable particles. Overestimation of exposures, either for the analysis of the Wagoner et al. (1980) cohort data or for the Sanderson et al. (2001) case-control data would lead to underestimation of the risks.

With respect to CBD, the modeling approach investigated here has not considered the fact that sensitization appears to be a requisite precursor to CBD has not been. Much more information about exposures and the timing of both sensitization and CBD would need to be available in order to develop

models that considered the two-stage nature of the relationship between beryllium exposure, sensitization, and CBD. The cross-sectional studies that make up the bulk of the CBD literature pose difficulties with respect to understanding timing and sequence of events.

Nevertheless, the logistic regression analysis results reported by Viet et al. (2000) suggest that even when average FAH Be concentrations are as low as 0.2 $\mu g/m^3$, more than half of the workers exposed at that level for an entire working lifetime may be afflicted with CBD. When some bounding estimates associated purely with statistical uncertainty are considered, that fraction may be as high as about two thirds or more of workers so exposed. Those results are based on the life-table approach using the Viet et al. (2000) estimates of the regression coefficients for cumulative exposure; the other uncertainties mentioned previously were not considered in those calculations.

Of course, the usual uncertainties (about exposure reconstruction, about modeling choices, and about correct identification of all cases) affect the results of the analyses presented above and the studies on which they are based. A full examination of those uncertainties has not been included in this assessment because 1) the analyses shown here should be considered preliminary, i.e., as setting the stage for more complete analyses that should follow and be based on more complete information to the extent possible; and 2) the information most appropriate for a more complete evaluation of these uncertainties is not available from the published summaries.

The results of this preliminary assessment are suggestive enough of both a lung cancer and a CBD dose-response relationship with Be exposure to suggest that more complete analyses be attempted. In particular, those analyses should be based on information closer to the raw data than has been possible here. This will enable alternative choices (for models and for dose metrics) to be examined. The issue of dose metrics may be particularly important for Be. It was noted above that characterizations of exposure not based on total Be, but rather on specific Be compounds or Be particles within certain size ranges, have been suggested to be more appropriate measures to relate to subsequent disease development (Kelleher et al. 2001; Stefaniak et al. 2003). These alternatives should be investigated when possible. Moreover, it is not necessarily clear that cumulative dose is the only relevant or the most appropriate metric for relating Be exposure to CBD response. It is also possible that the time elapsed since exposure affects the risk of developing CBD. Little is known about the impact of early Be exposures on the risk of developing CBD at older ages, for example, and the short observation period of the Viet et al. (2000) study would shed little light on that issue. It is possible that after a certain period of time, an exposure to Be might have

reduced impact on the likelihood that an exposed individual would develop CBD, and future analyses should examine that possibility if at all possible.

Thus, the conclusion of this assessment is that the results so far indicate that there are lung cancer and CBD risks associated with working-lifetime exposures to the concentrations investigated (down to 0.1 $\mu g/m^3$). The exact magnitude of those risks is not known because of uncertainties associated with the preliminary analyses. Additional analyses, preferably using better sources of data, are recommended as a way to provide better risk estimates.

V. References

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TABLE 1

SUMMARY OF BERRYLIUM CANCER STUDIES (CASE STUDIES AND COHORTS)

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Observed	Expected	Study Strengths and Weaknesses	Reference
Be Case Registry	421[1]	July 1, 1952 – December 31,1975	<15 yrs	ND	1	0.49	**Strengths:** For the 7 lung cancer cases, information was presented for type of BE work, length of exposure, year of first exposure, and interval since initial exposure. **Weaknesses**: No exposure data. No information available on smoking habits of the individuals included in the study.	(Infante et al. 1980)
Be Case Registry	421[1]	July 1, 1952 – December 31,1975	>15 yrs	ND	6	2.81	**Strengths**: For the 7 lung cancer cases, information was presented for type of BE work, length of exposure, year of first exposure, and interval since initial exposure. **Weaknesses**: No exposure data. No information available on smoking habits of the individuals included in the study.	(Infante et al. 1980)

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Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Observed	Expected	Study Strengths and Weaknesses	Reference
Be Case Registry data	689[2]	1952 - 1988	Person yrs at risk = 13,899 Average number of years for follow-up for total cohort = 20. Mortality results based on < 4 yrs of exposure and > 4 years of exposure	ND	Total lung cancer deaths = 28 (22 males, 6 females)[3] Exposure < 4yrs = 17; exposure > 4 yrs = 11 SMR = 2% (CI = 1.33-2.89)	ND	**Strengths**: This was a follow-up to Infante et al. (1980) and included information on females in the Be Case Registry and extended the follow-up period by 13 years to 1988. Duration of exposure defined. Confounding effects of smoking were evaluated. **Weaknesses:** No monitoring data were available for this study; therefore, no exposure estimates were given. No estimate of observed vs. expected cases of lung cancer.	(Steenland and Ward 1991)
Record of former workers in Be processing industry from the Public Health Service	753 males with known cause of death	Employed from 1942-1967	<1 year to >5 years	ND	36	34.06	**Strengths:** Information was available for time of employment. **Weaknesses**: No exposure data. No information available on smoking habits of the individuals included in the study. No age or race considerations.	(Bayliss et al. 1971)

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Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Observed	Expected	Study Strengths and Weaknesses	Reference
Be production facilities in Ohio and PA	3685 white males	1937-1948	≤12 months to ≥48 months.	ND	80	57.06	**Strengths**: Large comparison population of workers not exposed to Be (5929 employees of the viscoe rayon industry) from the same geographical region. **Weaknesses**: No estimate of exposure concentrations given. No adjustments for smoking.	(Mancuso 1980)
Be production facilities in Ohio and PA	3266 white males	1942-1948[4] (follow–up through 1975)	< 1 yrs to > 5 yrs	ND	25	12.52	**Weaknesses**: This study did not include analyses of mortality by job title or exposure category. No estimate of exposure concentrations given. No adjustments for smoking.	(Mancuso 1979)
Be production facilities referred to as Company A and Company B	2313 white males (age 15 to 64 yrs)	1937-1948 (follow-up through 1968)	1 year to > 15 yrs	ND	20	ND	**Strengths**: Includes the time period prior to the initiation of more stringent control measures for Be and therefore includes highly exposed workers. **Weaknesses**: This study did not include analyses of mortality by job title or exposure category. No estimate of exposure concentrations given. No adjustments for smoking. No expected numbers of deaths given.	(Mancuso 1970)

TABLE 1

SUMMARY OF BERRYLIUM CANCER STUDIES (CASE STUDIES AND COHORTS)

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Observed	Expected	Study Strengths and Weaknesses	Reference
Be production facilities referred to as Company A and Company B	3685 white males; 196 non-white males; 684 white females; 59 non-white females	1937-1948 (22 yr latent period)	ND	ND	31 (white males) 2 (non white males); 1 (white females)	ND	**Strengths**: Includes the time period prior to the initiation of more stringent control measures for Be and therefore includes highly exposed workers. **Weaknesses**: This study did not include analyses of mortality by job title or exposure category. No estimate of exposure concentrations given. No adjustments for smoking. No expected numbers of deaths given.	(Mancuso and El-Attar 1969)
Be extraction, processing, and fabrication facility in PA	3055 white males	Jan. 1, 1942 – Sept. 1968	Median duration of employment: 7.2 yrs	ND[5]	47	34.29	**Strengths**: Expanded study of workers in the PA plant evaluated in Mancuso (1970; 1979; 1980). The study accounted for length of employment, and followed-up was conducted through 1976. Considered possible other causes of lung cancer . **Weaknesses**: The exposure concentration was estimated based on estimates from Eisenbud and Lisson (1983) and NIOSH (1972).	(Wagoner et al. 1980)
Seven beryllium processing facilities in PA and Ohio	9,225 males 8905 (white); 320 (nonwhite)	Jan. 1 1940 – Dec. 31 1988	49.7% <1year; 23.4% 1-5 yrs; 7.9% 5-10 yrs; 19.1% >10 yrs	ND	289	233.8	**Strengths:** The study accounted for age, sex, race, regional lung cancer mortality rates, and smoking habits. The study also accounted for duration of employment, and person-years-at-risk by latency and plant location.	(Ward et al. 1992)

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SUMMARY OF BERRYLIUM CANCER STUDIES (CASE STUDIES AND COHORTS)

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Observed	Expected	Study Strengths and Weaknesses	Reference
Be processing facility in Reading, PA	3569 males (age-race matched)	Jan. 1, 1940 – Dec. 31, 1969[6]	Mean tenure: 202.1±9.4 days	Cumulative exposure: 4606±9.3 μg/m^3-days Average exposure: 22.8±3.4 μg/m^3 Maximum exposure: 32.4±13.8 μg/m^3	ND	ND	**Strengths**: Each of the 142 lung cancer cases were age-race matched to 5 controls. Calendar-time-specific Be exposure estimates were made for every job and used to estimate workers cumulative, average, and maximum exposure. Attempted to evaluate confounding effects of smoking. Exposure and duration were well defined. **Weaknesses**: Case-control study results difficult to use in lifetime risk estimation, especially because log-transformed cumulative exposure was used in the reported logistic regression analyses.	(Sanderson et al. 2001)

[1] - Study participants were white males participating in the Be Case Registry, that had been diagnosed with Be-related, nonneoplastic respiratory symptoms or disease.
[2] – An earlier study included 421 of these patients. This study was extended to include females and 13 years of follow-up.
[3] – 93% of the women in the study had chronic Be disease, approximately 50% of the males had chronic Be disease. 61% of the women had worked in the fluorescent tube industry, 50% of the males worked in basic manufacturing.
[4] – In terms of production schedules for Be, production was more compatible for both the OH and PA plants during 1943-1948.
[5] – Exposure concentrations were calculated based on Eisenbud and Lisson (1983) and NIOSH (1972) which estimated that the lower-bound estimate of the median exposure concentration exceeded 100 μg/m^3 and concentrations in excess of 1000 μg/m^3 were commonly found. The available literature concerning occupational exposure to beryllium process workers was dependent on the facility where they worked, the decade they were employed, and the type of work performed.
[6] – For the purpose of the case control study, vital status follow-up was extended through Dec. 31, 1992.
ND – No data presented in the study or not applicable.

TABLE 2

SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
From 1952 to 1963 the factory refined Be ore to produce Be hydroxide. Since 1963 the main raw material was Be oxide.	130 (102 of these men were followed up in 1973)	1952 – 1963 Follow-up from 1963 to 1973	6 months - 9 years (19 years for follow-up)	In 1952 exposure concentration ranged from 0.1 to 1 µg/m^3 and in 1960 ranged from 0.06 top 0.57 µg/m^3	ND	6 (no new cases in follow-up studies in 1973 and 1977)	130	**Strengths:** Exposure and duration data reported. **Weaknesses:** Sensitization was not evaluated in this study. Small study population	(Cotes et al. 1983)
Be ceramics plant	51	1980 - 1992.	Mean = 14.5 yrs (range of <1 to 35 yrs)	ND	6	4	5	**Strengths:** 2 distinct groups in the study population: a research and development group consisting of 24 workers (who were older and had longer tenure with a mean time from first exposure of 21.2 yrs), and a production group consisting of 27 workers (mean age of 38 yrs and mean time since first exposure of 5 yrs). Factors accounted for in the evaluation included: age, years since first Be exposure, smoking habits. **Weaknesses**: Small study population.	(Kreiss et al. 1989)

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SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Stratified random sample of nuclear weapons workers.	895	1970 - 1990	ND	Exposure based on questionnaire responses. Groups included no exposure, minimal exposure, intermittent exposure, consistent exposure.	18	12 (3 additional cases developed CBD over the succeeding 2 yrs)	18	**Strengths**: Different exposure groups investigated. **Weaknesses:** Insufficient exposure and duration information.	(Kreiss et al. 1993)
Be ceramics plant	136	1980-1992	ND	DWAs were calculated and ranged from 1.4 to 6990.1 $\mu g/m^3$-days with a median of 591.7 $\mu g/m^3$-days. [2] The median average Be exposure of the workforce was 0.35 $\mu g/m^3$	8	6	8	**Strengths**: For the Be sensitized patients, the job process duration, hire date, cumulative exposure, average exposure, and diagnosis are given. **Weaknesses**: Small study population. Duration of exposure was not well documented for all employees	(Kreiss et al. 1996)

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SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Be processing plant producing pure metal, oxide, alloys, and ceramics.	627	1984-1993	Median cumulative Be exposure for employees employed since 1984 was 1635 µg/m^3-days (with a median average exposure of 1.3 µg/m^3	Quarterly job specific Daily weighted averages (DWA) ranged from 0.05 to 63.11 µg/m^3	59	29	47	**Strengths:** Air samples included general area samples, continuous samples, process breathing zone samples, and personal lapel samples. Study reported exposure and duration data. Variables adjusted for in the analysis included: sex, race, smoking status, pack years of smoking, time since first employment, work in another Be facility, work around or in Be fluoride, pebble plant, vacuum melting, alloy extrusion, ceramics, and shipping and receiving. **Weaknesses**: Inconsistent results from the 2 laboratories analyzing blood samples for the BLPT tests.	(Kreiss et al. 1997)

TABLE 2

SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Rocky Flats Environmental Technology Site	4397	June 1991 - March 1995	ND	ND	106	29	106	**Strengths:** Large study group of Rock Flats employees that took part in Be Health Surveillance Program. **Weaknesses:** Other than being current or former employees no estimates of duration were specified. Exposure to Be was determined by job categories relative to a factor of 10 for the main Be production building.	(Stange et al. 1996)
Rocky Flats Environmental Technology Site	5173	June 1991 - December 1997	< 5yrs up to and greater than 30 years.	ND	172	74	172	**Strengths:** Sensitization and CBD rates were analyzed with respect to gender, building work locations, and length of employment. Included 171 individuals with no known exposure to BE that served as controls. Historical employee data collected included hire date, termination date, leave of absences, job title changes. **Weaknesses:** Exposure to Be was determined by job categories and building or work area codes. No quantitative information was presented in the study. Smoking was not listed as a confounding factor that was adjusted for in the evaluation.	(Stange et al. 2001)

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SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Rocky Flats Environmental Technology Site	2891 (offered to employees who had not been tested for 3 years or more and did not show Be sensitization during previous study)	Three year serial testing on Rocky Flats employees	< 5yrs up to and greater than 30 years.	ND	63	7	63	**Strengths:** Sensitization and CBD rates were analyzed with respect to gender, building work locations, and length of employment. Included 171 individuals with no known exposure to BE that served as controls. Historical employee data collected included hire date, termination date, leave of absences, job title changes. **Weaknesses:** Exposure to Be was determined by job categories and building or work area codes. No quantitative information was presented in the study. Smoking was not listed as a confounding factor that was adjusted for in the evaluation.	(Stange et al. 2001)
Brush Wellman Be workers in plants in Tucson, AZ; Elmore, OH; Cleveland, OH; and Delta, UT.	1510	1992-2000	ND	ND	ND	86	192	**Strengths**: Three different labs were used (A, B, and C). Split blood samples were tested at 2 separate labs. **Weaknesses**: Samples were collected from workers at 4 different Brush Wellman facilities at different times. The study does not report a total number of abnormal BLPT cases.	(Deubner et al. 2001a)

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SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Be mining and extraction facility in Delta, UT	75	1970-1999 for general area (GA), breathing zone (BA), personal lapel (LP), and calculations of job-specific quarterly daily-weighted averages (DWA).	Mean duration of employment for Be sensitized workers = 21.3 years; for employee with CBD = 27.7; for all employees = 14.9	Annual median air concentrations for GA = 0.1-0.6 µg/m^3; BZ = < DL – 806.3 µg/m^3; DWA = 0.08 – 0.2 µg/m^3; LP = 0.05 – 0.8 µg/m^3	3	1	3	**Strengths:** A variety of airborne monitoring data were routinely collected in different areas of the facilities. Good exposure and duration of employment data. Adjusted for smoking. **Weaknesses:** Very small number of participants in the study. Authors noted some limitations in the exposure assessment because medians and means of historical data samples in different areas of different plants were used.	(Deubner et al. 2001b)

TABLE 2

SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Be ceramics facility	151	Questionnaire: Feb – March 1998 Blood test: March – May 1998 Follow up for abnormal BLPT continued through Dec. 1998	Median was 14.1 years (range 8 to 40.1 years)[3]	Cumulative[4] Long-term workers (0.9-41.2 ug-yr/m^3); short-term workers (0.02-16 ug-yr/m^3)[5]	15 (8 long term and 7 short term)	8 (7 of the 8 long term workers with abnormal BLPT had CBD, 1 worker declined follow- up and status is unknown)	15	**Strengths**: Be air samples were available from 1981 through 1998. Confounding factors adjusted for included age, gender, ethnicity, smoking. **Weaknesses**: Small sample size. The cross sectional study did not allow for surveying workers that left after the 1992 survey and before the 1998 survey. Could have overestimated exposure by not considering respirator use. Previous exposure to Be was not included in the calculation of measured exposures and could have underestimated exposure for some employees.	(Henneberger et al. 2001)

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SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Be metal machining plant. Same plant as in (Kelleher et al. 2001)	235 (187 completed the 2 year follow-up study)	Production at the plant began in 1969. Medical surveillance was from 1995-1997 (with follow–up in 1997, 1998, and 1999)	Average = 11.7 yrs (range of 1 month to 29 yrs)	See (Kelleher et al. 2001)	15[6] (7 in follow-up)	9 (5 in follow-up)	15 (7 in follow-up)	**Strengths**: Facility used different Be materials including Be metal, Be-Al alloy, and Be meal/Be oxide composite called E metal. Medical surveillance was performed in conjunction with environmental sampling for total Be and particle size related exposure. Adjusted for smoking. **Weaknesses**: Small study population.	(Newman et al. 2001)

TABLE 2

SUMMARY OF BERYLLIUM NONCANCER STUDIES (SENSITIZATION AND CDB)[1]

Location and Type of Facility	# of workers	Dates included in study	Estimated Duration of exposure	Exposure concentration	Number of workers with abnormal BLPT	Observed cases of CBD	Total evaluated for CBD	Study Strengths and Weaknesses	Reference
Be metal machining plant. Same plant as in (Newman et al. 2001)	235 (20 with Be sensitization or CDB) and controls consisted of 206 employees with complete job history data.	Production at the plant began in 1969. Medical surveillance was from 1995-1997	Cases: 14.2 yrs (range of 3-19.7 yrs) ; controls: 10.5 yrs (range of 0.5-16.5yrs)	Median total Be exposure = 0.13 µg/m^3 (range of 0.006 to 22.62 µg/m^3)[7]	20	13	20	**Strengths**: Facility used different Be materials including Be metal, Be-Al alloy, and Be meal/Be oxide composite called E metal. Medical surveillance was performed in conjunction with environmental sampling for total Be and particle size related exposure. Adjusted for smoking. **Weaknesses**: This was a case-control study, so difficult to use for estimating lifetime risk. Suitable quantitative results not included in report. Small study population.	(Kelleher et al. 2001)

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Rocky flats Nuclear Weapons facility	74 Be-sensitized cases and 74 controls, and 50 CBD cases with 50 controls.	June 1991 - December 1997	Means for each group ranged from 13.2 yrs for Be sensitized cases to 19.1 yrs for CBD cases.	Mean concentrations ranged from 0.083 µg/m^3 (1987) to 0.622 µg/m^3 (1964) Mean and max air concentrations for 1960-1988 are presented in Table II of study. [8]	74 Be sensitization cases matched with 74 controls	50 CBD cases matched with 50 controls	Be sensitization cases did not have CBD.	**Strengths:** Controls were matched for age group, race, gender, and smoking status. Exposure concentrations and duration of employment, as well as cumulative exposure, were defined for study subjects. Both conditional and unconditional logistic regression results reported. **Weaknesses**: This was a case-control study so use in lifetime risk estimation is difficult. Fixed air head (FAH) samples may have been unrepresentative of personal exposures because they are generally placed away from the operator's breathing zone.	(Viet et al. 2000)

[1] – Chronic Beryllium Disease (CDB) develops via immune response to beryllium particles deposited in the lung, leading to the formation of diffuse, interstitial, non-caseating, granulomatios lesions. The distinguish CBD from similar conditions such as sarcoidosis, its diagnosis requires the presence of beryllium sensitization in addition to non-caseating granulomatous lesions. To perform beryllium lymphocyte proliferation tests (BLPT), lymphocytes are incubated in a mixture containing a beryllium salt ($BeSO_4$). After incubation, ^{3}H-Thymidine (^{3}H-TdR) is added to the mixture. The amount of ^{3}H-TdR taken up by lymphocytes reflects lymphocyte activation (in preparation for proliferation) and is measured in disintegrations per minute, commonly expressed as counts per minute (cpm). The test is replicated six times using three concentrations of BeSO4, and the response is expressed as a stimulation index (SI) where,

SI = CPM of cultures with Be sulfate / CPM of cultures without Be sulfate

[2] – DWA exposures were calculated quarterly using a formula incorporating average general area, full-shift area, and breathing zone measurements based on time studies for most jobs.

[3] - Work histories were truncated at the date of the first abnormal blood draw for individuals with sensitization and at the date of the normal blood draw for all others.

[4] –Three types of exposure measurements were derived for each subject following the merger of work histories and area-task/time-based exposure levels:

(1) Cumulative beryllium was the sum of the products of length and intensity of exposure foe each are-task in µg-year/m^3. Intensity was the arithmetic mean of the area-task specific measurements for each work year which comprised 50 weeks at 40 hours per week plus overtime.

(2) Mean beryllium exposure was the cumulative exposure divided by the number of work-years of exposure.

(3) Peak exposure achieved in 2 steps (1) the max exposure level was determined for each area-task on an annual basis; (2) based on an individual's work history, the peak exposure was the highest of the annual maximum area-task-specific exposure values.

[5] – Short-term workers included those hired since the last plant-wide screening in 1992. Long term workers were those hired before 1992.

[6] – Four of these 15 employees were diagnosed within the first 3 months of exposure.

[7] - 100 personal samples for Be exposure were collected during 2 time periods using cascade impactors designed to characterize beryllium aerosol exposure . Analysis of particle size included particles < 6 µm and <1 µm for which the masses for the appropriate stages were summed and divided by the number of cubic meters of air supplied during the sampling period to yield a time-weighted average exposure for the respective particle size fraction for each sample.

[8] – Because the majority of air samples were taken from fixed air head samplers in Building 444 of the facility, these air sample concentrations were used in the study.