Original article

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Sensitization and chronic beryllium disease at a primary manufacturing facility, part 3: exposure–response among short-term workers

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Objectives Exposure–response relations for beryllium sensitization (BeS) and chronic beryllium disease (CBD) using aerosol mass concentration have been inconsistent, although process-related risks found in most studies suggest that exposure-dependent risks exist. We examined exposure–response relations using personal exposure estimates in a beryllium worker cohort with limited work tenure to minimize exposure misclassification.

Methods The population comprised workers employed in 1999 with six years or less tenure. Each completed a work history questionnaire and was evaluated for immunological sensitization and CBD. A job-exposure matrix was combined with work histories to create individual estimates of average, cumulative, and highest-job-worked exposure for total, respirable, and submicron beryllium mass concentrations. We obtained odds ratios from logistic regression models for exposure–response relations, and evaluated process-related risks.

Results Participation was 90.7% (264/291 eligible). Sensitization prevalence was 9.8% (26/264), with 6 sensitized also diagnosed with CBD (2.3%, 6/264). A general pattern of increasing sensitization prevalence was observed as exposure quartile increased. Both total and respirable beryllium mass concentration estimates were positively associated with sensitization (average and highest job), and CBD (cumulative). Increased sensitization prevalence was identified in metal/oxide production, alloy melting and casting, and maintenance, and for CBD in melting and casting. Lower sensitization prevalence was observed in plant-area administrative work.

Conclusions Sensitization was associated with average and highest job exposures, and CBD was associated with cumulative exposure. Both total and respirable mass concentrations were relevant predictors of risk. New process-related risks were identified in melting and casting and maintenance.

Key terms average exposure; beryllium disease; cumulative exposure; occupational respiratory disease; peak exposure.

Exposure–response relations for beryllium sensitization (BeS) and chronic beryllium disease (CBD) using various methods for estimating airborne exposure have been inconsistent (1–5). Processes or jobs worked have been used as surrogates for quantitative exposures in many studies. Process-related risks have been identified in the absence of exposure–response (1–3, 6), suggesting that predictive exposure factors do exist but may not have been adequately characterized. Possible explanations may include, among others: (i) quantification of airborne beryllium exposure using metrics that do not take into account biological relevance, rather than metrics that consider lung deposition (7–9), and (ii) inclusion of exposure periods not relevant to risk due to uncertainty regarding time of onset of BeS and CBD in cross-sectional epidemiologic studies.

Physical properties of exposure aerosols, such as aerodynamic particle size, influence deposition and distribution within the human respiratory tract, with size affecting how deeply they are likely to penetrate and

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where they will likely deposit (10). However, many epidemiologic studies to date have used estimates of total beryllium mass concentration without consideration for particle size (1–3). Some studies have shown an association between exposure to smaller-size particles and BeS or CBD (4, 11). As such, it is biologically plausible to consider beryllium particle size among the exposure factors relevant to the development of an alveolar beryllium lung burden and thus to risk of disease.

The interval between initial exposure to beryllium and the development of BeS can be as short as three months with several studies detecting a higher prevalence of BeS among workers with one year or less of employment tenure (3, 6, 12–14). The interval between initial exposure and the development of CBD is not well understood. In cross-sectional epidemiologic studies, however, it is not possible to know when an individual actually became sensitized or developed CBD. Work tenure, or time from first exposure to test date, has been used as the relevant time frame for quantitatively estimating exposure or for use as a covariate. Tenure in these studies has ranged from <1 year to >40 years (1–3, 5, 6). It is thus possible that prior cross-sectional studies have overestimated (for quantitated) or misclassified (for process/job) exposure due to uncertainty regarding the relevant exposure period.

The facility described in this report produces beryllium metal in powder, sheet, and solid forms, beryllium oxide powder, and copper-beryllium alloys in strip (sheet) and bulk (rod, bar, and tube) forms. In a cross-sectional survey conducted in 1993–1994 at this plant, no exposure–response relationships were found for either cumulative or average exposure and BeS or CBD (2). However, among the overall plant population, higher levels of BeS were identified for workers in several processes: beryllium oxide ceramics production (moved to another facility in the early 1980s), beryllium metal production, and in the extraction of beryllium metal pebbles (2).

Subsequent to the 1993–1994 survey, several changes were implemented at the facility, primarily in the beryllium metal pebbles extraction plant and oxide powder production areas (15). A second survey was conducted in 1999 in which the prevalence of BeS and CBD was ascertained. Workers hired after the earlier survey, having a maximum of six years of employment at the facility (ie, "short-term workers"), are a group in whom exposure may be estimated more accurately as a consequence of the relatively shorter timeframe between initial exposure and outcome assessment. Extensive data on historical airborne beryllium concentrations measured throughout the facility from 1994–1999 were used to estimate workers' airborne exposure. These exposure estimates and survey results were utilized to answer the following research questions among this cohort of short-term workers: (i) what was the prevalence of BeS and CBD? (ii) were estimates of total, respirable, or submicron beryllium mass concentration associated with higher risk of BeS and CBD? and (iii) which work processes were associated with elevated prevalence of BeS and CBD?

Methods

Study population

All facility workers employed between January–August 1999 were invited to participate in a plant-wide survey. For purposes of this report, we included only those hired after 1 January 1993, who had not participated in the 1993–1994 plant survey and had no previous diagnosis of CBD. Since some prospective participants had actually begun work at the facility prior to the cutoff date, (eg, as temporary workers) or otherwise had prior beryllium exposure, we also limited the study population to those with no work onsite prior to 1 January 1993 or any known beryllium work exposure elsewhere prior to their hire date. The Human Subjects Review Board of the National Institute for Occupational Safety and Health reviewed and approved the study protocol; written informed consent was obtained from each study participant.

Evaluation for beryllium sensitization and chronic beryllium disease

Between February–November 1999, the company's medical staff collected initial split blood samples for the BeLPT, which were sent to two of three laboratories and analyzed as previously described (6). Follow-up blood testing and clinical evaluation for workers with abnormal test results were completed by February 2000. A BeLPT was interpreted as *abnormal* if ≥2 stimulation indices (ratio of proliferation rate in beryllium-exposed cells to rate in unexposed control cells) of the 6 combinations of concentration (1, 10, or 100 μM) and duration (5 or 7 days) were ≥3.0, *borderline negativ*e if a single ratio was ≥3.0, and *normal* if no ratios were ≥3.0. Additional blood was drawn and the test repeated to confirm an abnormal result (eg, if an individual's initial split blood sample returned one abnormal and one normal result), for clarification of a borderline negative result, or when the laboratory deemed the results uninterpretable. A person was considered to be *sensitized to beryllium* if two or more BeLPT were abnormal, either from separate laboratories or from repeated testing at the same lab. Participants who did not meet this definition were classified as *not sensitized*.

In 1997, the company had offered testing for BeS

to a group of employees who had worked in the metal pebbles plant. In 1997, 33 employees who were hired after January 1993 were tested with the BeLPT; 26 were still employed at the time of the 1999 survey and consented to participate. In addition, seven other participants hired after January 1993 were also offered BeLPTs prior to the 1999 survey. We included all results from this additional testing.

Workers with one or more abnormal BeLPT and others who presented to plant medical staff with indications suggestive of CBD were referred for voluntary clinical evaluation, including bronchoscopy with bronchoalveolar lavage and transbronchial biopsies. Biopsy specimens were examined for granulomas, mononuclear cell interstitial infiltrate, and fibrosis; lavage cells were tested for evidence of lung BeS with the bronchoalveolar lavage lymphocyte proliferation test. A sensitized individual was considered to have *CBD* if granulomas or any of the above pathologic abnormalities consistent with that diagnosis were present.

Medical and work history questionnaires

Trained staff at Bowling Green University's survey research unit conducted medical questionnaire interviews with workers via telephone during work hours. The questionnaire included smoking history and demographic questions. Smoking history was reduced to *ever* versus *never smoker*.

Trained company occupational health nurses conducted work history questionnaire interviews onsite during work hours. Participants reported start and end dates, days/week, and hours/week for each job held since they started work at the facility, including time spent as a temporary worker; personnel records were available as a memory aid for job titles and dates. For each job, the respondent further partitioned the workday into number of minutes spent performing specific operations or tasks. The date of first beryllium exposure was either the date of hire or the date first worked at this facility if initially hired as a contract temporary worker. Time since first exposure (*work tenure*) was calculated as the interval between the date of first beryllium exposure and the blood draw date of: (i) the first normal BeLPT in the 1999 survey for non-sensitized workers or (ii) the first abnormal BeLPT for sensitized workers. For those diagnosed with CBD, if evaluation did not directly follow identification of BeS, separate tenure calculations terminated on the date of CBD diagnosis.

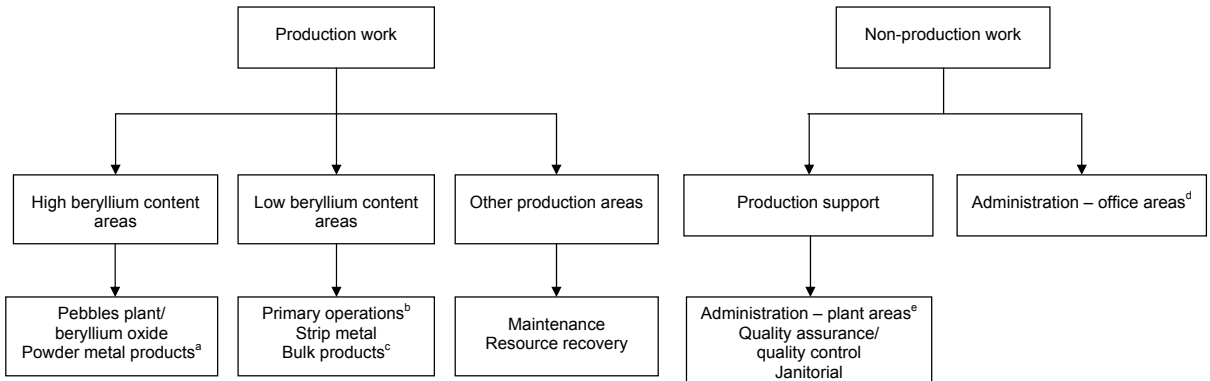
Characterizing beryllium exposure

Summarizing work histories. For purposes of evaluating process-related risk, we first classified all jobs at the facility into production and non-production work (figure 1). Production work was divided by the type of material processed: high beryllium content (pure metal and oxide), low beryllium content (alloys, typically >4% beryllium), and other production areas (potential for exposure to materials with both high and low beryllium content) including plant maintenance activities. Non-production work was divided into production support and administration-office categories; the former was assumed to have lower exposure than production work, and the latter was assumed to have the lowest exposure. Processes/jobs within each work category are shown in figure 1. To determine whether experience in a given work category (or process/job area) was associated with higher prevalence of BeS or CBD, we compared the subgroup *ever worked* (defined as two weeks or greater) in a work category or process/job area with the subgroup that had *never worked* there.

Airborne beryllium exposure metrics. Exposure to airborne total, respirable, and submicron mass concentration beryllium was assigned to study participants for the entire duration of their onsite work history (16). Briefly, to obtain historical exposure estimates for all groups, we constructed a job-exposure matrix (JEM) for the years 1994–1999 by applying temporal adjustment factors to baseline exposure estimates for job groups. Baseline exposure estimates were obtained from two comprehensive exposure surveys conducted in 1999, one survey employing total mass cassette (N=4022) and the other size-separated impactor (N=198) samples. We analyzed process-level time trends in general area sample exposure data (N=76 349) from 1994–1999 to create annual temporal adjustment factors for 1994–1998, which were applied to baseline estimates to approximate changes in exposure levels in the years prior to 1999 due to changes in workplace conditions. Estimates from 1994 were used for the single individual who had worked during 1993. Job title and task-level data from work histories were linked with JEM exposure estimates to generate beryllium exposure profiles for each participant. Individual-level summary exposure metrics generated for epidemiologic analyses were: (i) *average exposure* ($\mu g/m^3$) – time-weighted average annual exposure of all jobs in the employee's work history; (ii) *cumulative exposure* ($\mu g/m^3$-year) – exposure levels for each job worked, multiplied by number of years at that job, summed over all jobs in the work history; and (iii) *highest job exposure* ($\mu g/m^3$) – the exposure level for each participant's single job with the highest mean exposure. These three indices were calculated for *total, respirable,* and *submicron* mass concentrations of beryllium.

Statistical analysis

We analyzed the data with SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA). Categorical outcomes were evaluated with continuity-corrected χ^2



[a] Includes beryllium machining.
[b] Melting and casting of beryllium alloys.
[c] Copper-beryllium alloy rod, bar, tube, and wire.
[d] Staff who spent all or almost all of their time within a specific administrative building, and who rarely went out into production areas.
[e] Included supervisors, environmental health and safety, and other non-production staff who regularly spent a portion of the work day in production areas.

Figure 1. Work categories and processes/jobs within those categories.

and Fisher's exact tests, and continuous outcomes with the Wilcoxon rank-sum (two samples) and Kruskal-Wallis (more than two samples) tests. We used the Cochran-Armitage test to evaluate trends in exposure categories. Results were reported as significant ($P<0.05$) or marginally significant ($0.05\leq P<0.10$). We used logistic regression to model exposure–response relations and obtained odds ratios (OR) with profile likelihood 95% confidence intervals (95% CI). Models were evaluated for possible confounders or effect modifiers (race, gender); model fit was evaluated with the Hosmer-Lemeshow test.

Results

Study population

Of 303 current employees without CBD hired after 1 January 1993, 276 consented to participate. Of these, 12 had work histories indicating beryllium exposure, onsite or elsewhere prior to 1993, and were excluded. The final population comprised 264 workers who were hired between January 1993 and August 1999 (90.7% of 291 eligible); 136 of them spent time working onsite prior to their hire dates (eg, as temporary workers) but not earlier than January 1993. Median work tenure was 20.9 months (range 0.2–72.7 months). Participants were mostly white (98.1%) and male (77.3%), with a median age at hire of 31.4 years (range 19.3–60 years). The 27 non-participants were not significantly different with respect to gender (85% male) or age at hire (median 34.4 years); race was not available.

Sensitization and chronic beryllium disease

Among 264 participants, 24 had ≥2 abnormal BeLPT during the 1999 survey, including one person already known to be sensitized. The latter had first been identified as part of the 1997 limited process-specific screening, but upon clinical evaluation had no evidence of CBD at that time. We regarded two other participants as sensitized because of confirmed abnormal test results in pre-1999 testing; in the 1999 survey, one had a single abnormal and a normal test, and the other had two normal results. We therefore considered a total of 26 (9.8%) of the 264 participants to be sensitized. Including the employee first evaluated in 1997, 22 (84.6%) of the sensitized consented to further clinical evaluation for CBD. Transbronchial biopsies revealed lung granulomas among 6 (2.3%) of 264 workers tested for BeS, including the employee who was first clinically evaluated in 1997. Five participants with a single (unconfirmed) abnormal BeLPT and two with normal results were also clinically evaluated; none was diagnosed with CBD.

The 26 employees with BeS and/or CBD were not significantly different from non-sensitized employees with respect to age at hire, gender, race, or smoking status (table 1). We observed a trend by years worked for CBD, but not for BeS (figure 2). The four shortest intervals between initial exposure and first abnormal test (that was later confirmed) were 51, 71, 106, and 112 days. The shortest tenure to diagnosis of CBD was 1.9 years.

Exposure–response relations

Prevalence of BeS by quartile of exposure is shown in table 2a. BeS increased significantly with increasing

average and highest job total mass exposure indices, and increased marginally significantly for average respirable exposure. Generally, the lowest exposure quartiles demonstrated the lowest prevalence of BeS. CBD was not observed in the lowest quartile of any exposure index: average, cumulative or highest job (table 2b). CBD increased significantly with increasing cumulative total mass exposure and marginally so for cumulative respirable and submicron (not shown) and highest job respirable exposure.

No BeS was observed when total mass concentration exposures for average and highest job were <0.09 and 0.12 μg/m^3, respectively; exposures for 24 and 25% of participants were below these levels (table 2a). Similarly, no BeS was observed when respirable concentration exposures for average and highest job were each <0.04 μg/m^3; exposures for 10% of participants were below this level. No CBD was observed when total mass and respirable cumulative exposures were <0.38 μg/m^3-year and 0.33 μg/m^3-year, respectively; 44% of participants' exposures were below these levels (table 2b). Additional summary data for all exposure estimates are available in Virji et al (16).

Goodness-of-fit for logistic regression models with log-transformed exposure variables was generally superior to models with untransformed exposures; the former are presented in table 3. No confounders or effect modifiers were identified. For total mass exposure estimates and BeS, logistic models demonstrated elevated OR for average (OR 1.48) and highest job (OR 1.37) exposure; the OR for cumulative exposure was smaller (OR 1.23), with the 95% CI barely including unity. Relationships between BeS and respirable exposure estimates were similarly elevated for average (OR 1.37) and highest job (OR 1.32). Among the submicron exposure estimates and BeS, only highest job (OR 1.24) had a 95% CI that just included unity.

For CBD, we observed elevated OR only for the cumulative exposure estimates: total mass (OR 1.66) and respirable (OR 1.68). Cumulative submicron exposure demonstrated an elevated OR but the 95% CI just included one (OR 1.58). Although the OR for average exposures were of similar magnitude, 95% CI included one by relatively large margins. OR for highest job were slightly smaller.

Work category- and process-related risk

We then compared prevalences of BeS and CBD among participants who had ever worked in five work categories to those who had never worked in those categories. Those who had ever worked in processes or jobs with high beryllium content materials were more likely to be sensitized (18.5% ever worked versus 7.6% never worked, P=0.04, table 4). Work in other production tended toward higher risk for BeS (15.7% versus 7.7%, P=0.06). Work in production support areas conferred a reduced risk of BeS (3.1% versus 13.8%, P=0.005), and no administration-office workers were sensitized [not significant (NS)]. Higher prevalence of CBD was observed among those who had ever worked in processes or jobs with low beryllium content materials (4.3% versus 0.0%, P=0.04). No CBD was found among any non-production workers, either production support (P=0.08) or administration-office (NS).

Among specific work process groups, in the high beryllium content areas, pebbles/oxide demonstrated an elevated prevalence of BeS (26.9% versus 8.0%, P=0.007). In the low beryllium content areas, work in primary operations (alloy melting and casting) showed an elevated prevalence for both BeS (14.8% versus 6.4%, P=0.03) and CBD (5.2% versus 0.7%, P=0.04). Work as a maintenance mechanic suggested higher risk of BeS (18.0% versus 7.9%, P=0.06). No administrative staff who spent time in plant areas became sensitized (P=0.004).

Discussion

This survey of workers employed six years or less at a complex beryllium production facility identified one in ten (9.8%) as sensitized, with about one-fourth of the sensitized also diagnosed with CBD (2.3% of participants). A survey conducted six years earlier at this facility, among workers without known CBD and with up to 38 years of tenure, yielded prevalences of 6.9% BeS and 3.8% CBD (2). When we reanalyzed a subset of this latter cohort with ≤6 years tenure, prevalences were similar to the present survey: 9.2% BeS and 2.5% CBD (data not shown). Thus, prevalences had not changed in the intervening six years despite conventional engineering control efforts in previously identified higher-risk work processes (15).

We identified significant relations between BeS and both average and highest job exposures, for total mass and respirable concentration-based estimates. Although no significant trends were noted for the other exposure indices, the lowest prevalence was always observed in the lowest quartile. Highest prevalence of BeS tended to be in the highest quartile with the exception of highest job (second quartile). Regression analyses suggested a lesser relationship for highest job exposures in the submicron size range and for cumulative total mass concentration exposures. In contrast, Henneberger et al (3) found no BeS among short-term workers in the second quartile of mean, cumulative, or peak total mass exposure, although small numbers precluded any test for trend. Highest prevalence was observed in the highest

Table 1. Demographic characteristics by beryllium sensitization (BeS) or chronic beryllium disease (CBD) status for 1999 survey short-term workers.

	Not BeS (N=238)				All BeS [a, b] (N=26)				CBD [a] (N=6)				BeS only [a, c] (N=20)			
	Years	Months	%	Range	Years	Months	%	Range	Years	Months	%	Range	Years	Months	%	Range
Median age at hire	31.4				31.3				29.5				31.3			
Gender (male)			76.5				84.6				83.3				85.0	
Race (white)			98.3				96.2				83.3				85.0	
Ever smoked (yes)			53.2				57.7				33.3				65.0	
Median work tenure [d]		20.9		0.2–72.7		22.2		1.7–52.8		28.3 [e]		22.6–48.6		19.7		1.7–52.8

[a] Compared to the not BeS.

[b] Participants with confirmed abnormal beryllium lymphocyte proliferation tests (BeLPT), including those diagnosed with CBD.

[c] Participants with confirmed abnormal BeLPT, excluding those diagnosed with CBD.

[d] Time (in months) from first exposure to beryllium (date began work on plant site) to date of first abnormal BeLPT (BeS) or first blood draw (not BeS). For CBD: if diagnosis was made shortly after identification of BeS, date of first abnormal BeLPT was used; if diagnosis was made at a later point in time (eg, years after BeS was first identified), date of CBD diagnosis was used.

[e] $0.05 \leq P < 0.10$.

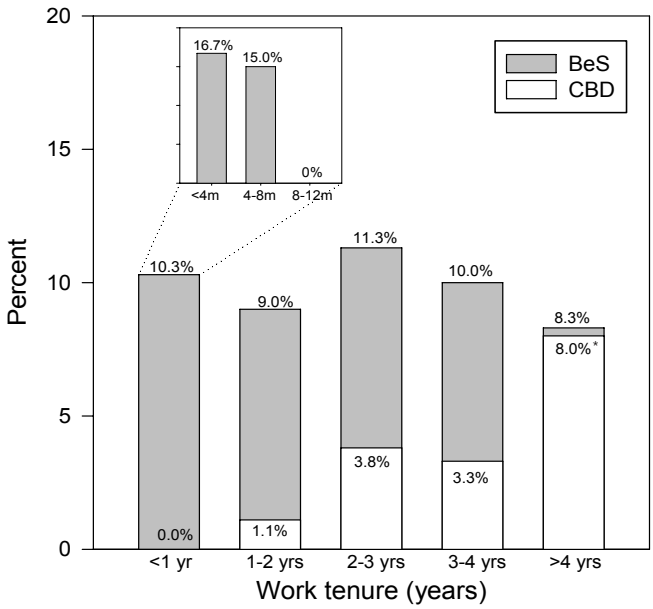


Figure 2. Work tenure by beryllium sensitization (BeS) or chronic beryllium disease (CBD) status for 1999 survey short-term workers. *CBD: $0.05 \leq P < 0.10$ for trend. *BeS (gray):* number atop each column = percent sensitized among those whose total work tenure fell into each 1 year (yr) interval. Among those with "<1 yr" worked, tenure was further divided into 4 month (mo) intervals (<4 mos, 4 to <8 mos, 8 to <1 yr). Total sensitized=26. *CBD (white):* number at bottom or within lower portion of each column=percent with CBD among those whose total work tenure fell into each 1 yr interval. Total CBD=6. *Work tenure:* time from first beryllium exposure to date of first abnormal beryllium lymphocyte proliferation test (BeLPT) (sensitized) or first blood draw (not sensitized). For CBD: if diagnosis was made shortly after identification of sensitization, date of first abnormal BeLPT was used; if diagnosis was made at a later point in time, date of CBD diagnosis was used. Work tenure intervals: <1 yr, 1 to <2 yrs, 2 to <3 yrs, 3 to <4 yrs, and ≥4 yrs (includes 1 person with >5 yrs tenure).

quartile of mean and peak exposure and next-highest quartile of cumulative exposure; the remaining cases were equally distributed among the lowest and third (mean and peak) or highest (cumulative) quartiles (3).

CBD was associated with cumulative exposure, most prominently with the total mass and respirable concentration metrics. For all metrics, we observed no CBD in the lowest exposure quartile, and the six cases of CBD were distributed across the other three quartiles. Cumulative estimates in the submicron size range were marginally important.

The similarities in results between total mass and respirable estimates for average, cumulative, and highest job are not surprising, since total mass and respirable estimates were highly correlated ($r_{Spearman}$=0.82–0.93) despite being generated from separate 1999 exposure surveys (9). It has been suggested that at least part of the reason for the observed inconsistency in exposure–response relations in prior studies was the limited current and historical sampling data available for most facilities and/or the need to use daily-weighted averages (calculated from area and task samples and time-motion studies) to estimate exposures rather than full-shift personal samples (1, 2, 4). The daily-weighted average has been shown to be poorly correlated with the personal sample, both total mass (r=0.49) and respirable

Table 2a. Percent prevalence of beryllium sensitization (BeS) by quartile of exposure, and lowest exposure at which BeS was observed.

Exposure [a]	Total mass [b]				Exposure	Respirable [c]			
	BeS (%) [d]	N [e]	Exposure level	%		BeS (%)	N	Exposure level	%
Average (μg/m³) [f]									
< 0.10	3.0	2/66			< 0.06	6.1	4/66		
0.10–0.60	10.6	7/66			0.06–0.42	7.6	5/66		
0.61–1.09	12.1	8/66			0.43–1.02	13.6	9/66		
1.10–16.26	13.6 [g]	9/66			1.03–3.56	12.1 [h]	8/66		
Lowest [i]			0.09	23.5				0.04	10.2
Cumulative (μg/m³-years) [j]									
<0.13	6.1	4/66			< 0.09	6.1	4/66		
0.13–0.63	10.6	7/66			0.09–0.51	10.6	7/66		
0.64–2.21	9.1	6/66			0.52–1.85	9.1	6/66		
2.22–34.44	13.6	9/66			1.86–15.54	13.6	9/66		
Lowest [i]			0.08	15.9				0.01	5.7
Highest job worked (μg/m³) [k]									
<0.11	0.0	0/66			< 0.08	4.7	3/64		
0.11–0.93	15.2	12/79			0.08–0.86	13.2	9/68		
0.94–1.57	9.3	5/54			0.87–1.30	10.5	7/67		
1.58–17.54	13.9 [g]	9/65			1.31–5.54	10.8	7/65		
Lowest [i]			0.12	25.4				0.04	9.8

[a] Quartile of exposure (rounded).
[b] Estimated total mass concentration beryllium exposure.
[c] Estimated respirable concentration beryllium exposure.
[d] Percent sensitized: sensitized = 26, not sensitized = 238.
[e] Number sensitized/number in quartile.
[f] Average exposure in micrograms of beryllium per cubic meter.
[g] P<0.05. Cochran-Armitage test for trend (exact) among four exposure quartiles.
[h] 0.05 ≤P<0.10. Cochran-Armitage test for trend (exact) among four exposure quartiles.
[i] Lowest exposure at which BeS was observed (percent of study population with exposure below that level).
[j] Cumulative exposure in micrograms of beryllium per cubic meter of air per work year.
[k] Highest job worked exposure in micrograms of beryllium per cubic meter.

(r=0.33) (17). We believe that the quality and quantity of full-shift personal samples (4022 samples across 269 job titles) available for generation of the JEM used for this study contributed to the precision and validity of the estimates. In the only other study that attempted to estimate participants' exposures to smaller particles, Kelleher and colleagues (4) discerned that median cumulative exposure, both for total mass and for particles <6 μm, was higher for cases (BeS and CBD, inclusive) than for controls, although results were not statistically significant. It has also been suggested that submicron particles need to be considered (18). Our submicron estimates were marginally associated with BeS (highest job) and CBD (cumulative exposure). It should be noted that particle size is just one physicochemical factor affecting exposure; other potentially relevant factors include surface area (7), chemical composition (19), and solubility (20, 21).

Among total mass concentration estimates, the lowest level at which BeS was observed for this population of short-term workers was 0.09 μg/m³ (average), 0.08 μg/m³-year (cumulative), and 0.12 μg/m³ (highest job). Considerable proportions of our study population were exposed below these lowest levels (24%, 16%, and 25%, respectively). The comparable lowest levels for cases (sensitized and CBD combined) in Kelleher et al (4) for total mass, derived from full-shift impactor samples, were 0.11 μg/m³ (lifetime-weighted average) and 1.18 μg/m³-year (cumulative); however, work tenure for cases in that study ranged from 3–19 years and maximum tenure in this study was 6 years. In addition, the use of different sample analysis methods for the cassette and impactor samples in our study may also have resulted in a truncation of the lower end of the distribution for mass concentration estimates. When the impactor sample analysis results were below the limit of detection (LOD), those samples were reanalyzed such that the ultimate LOD was much lower (0.003 μg for impactor samples, compared to 0.02 μg for cassette samples); cassette samples below the LOD were not reanalyzed (9).

With respect to BeS, it has been hypothesized that peak exposure may be more relevant to the nature of a cell-mediated immunologic response, while for CBD an accumulated lung burden as indicated by cumulative exposure may be a better predictor of risk (22). The eight-hour full-shift personal sample, which is the basis for the exposure estimates summarized in this study, by definition integrates exposure over an entire work shift. The highest-

Table 2b. Percent prevalence of chronic beryllium disease (CBD) by quartile of exposure and lowest exposure at which CBD was observed.

Exposure [a]	Total mass [b]				Exposure	Respirable [c]			
	CBD (%) [d]	N [e]	Exposure level	%		CBD (%)	N	Exposure level	%
Average (µg/m³) [f]									
< 0.09	0.0	0/61			< 0.05	0.0	0/61		
0.09–0.55	3.3	2/61			0.05–0.39	3.3	2/61		
0.56–1.07	3.3	2/61			0.40–1.00	3.3	2/61		
1.08–16.26	3.3	2/61			1.01–3.56	3.3	2/61		
Lowest [g]			0.20	34.4				0.17	41.0
Cumulative (µg/m³-year) [h]									
< 0.12	0.0	0/61			< 0.09	0.0	0/61		
0.12–0.63	1.6	1/61			0.09–0.50	3.3	2/61		
0.64–2.20	3.3	2/61			0.51–1.83	1.6	1/61		
2.21–34.44	4.9 [i]	3/61			1.84–15.54	4.9 [j]	3/61		
Lowest			0.38	43.8				0.33	44.3
Highest job worked (µg/m³) [k]									
< 0.10	0.0	0/60			< 0.07	0.0	0/61		
0.10–0.92	2.7	2/75			0.07–0.86	3.3	2/61		
0.93–1.57	3.9	2/51			0.87–1.34	1.6	1/61		
1.58–17.54	3.5	2/58			1.35–5.54	4.9 [j]	3/61		
Lowest			0.22	33.2				0.19	34.8

[a] Quartile of exposure (rounded).
[b] Estimated total mass concentration beryllium exposure.
[c] Estimated respirable concentration beryllium exposure.
[d] Percent with CBD: CBD = 6, not sensitized = 238.
[e] Number with CBD/number in quartile.
[f] Average exposure in micrograms of beryllium per cubic meter.
[g] Lowest exposure at which CBD was observed (percent of study population with exposure below that level).
[h] Cumulative exposure in micrograms of beryllium per cubic meter of air per work year.
[i] P <0.05. Cochran-Armitage test for trend (exact) among four exposure quartiles.
[j] 0.05≤P<0.10. Cochran-Armitage test for trend (exact) among four exposure quartiles.
[k] Highest job worked exposure in micrograms of beryllium per cubic meter.

job-worked exposure metric, representing the highest intensity job a worker held, was intended as one approach to peak exposure, a *relative* peak (23). It represents a greater likelihood for higher exposure periods within full-shift samples and removes the "dilution" by lower exposure jobs found when all exposures are averaged (ie, average and cumulative). While highest-job-worked and average exposure were highly correlated, our observed relationship between highest job and BeS supports the conjecture that more intense/peak exposure may be sensitizing. With respect to CBD, the relatively short window of time for potential exposure in this cohort, up to six years, did not allow for a substantial number of CBD diagnoses; however, this limited power reinforces the importance of our CBD-cumulative exposure findings.

Among processes, elevated BeS was observed in all three production groupings. A process area already known to have higher risk (2), pebbles plant/beryllium oxide, was confirmed in this population, despite efforts in the years preceding the study to reduce these workers' exposure to beryllium through additional engineering control improvements and process isolation. Primary operations, principally the melting and casting of beryllium alloys, had not been previously identified as a higher-risk work process, but risk in the previous study may have been disguised by work in other higher-risk areas since those participants reported having worked at an average of 4.4 processes over longer work tenures (2). The bulk products processes, involving production of alloy rod, bar, tube, and wire, showed no elevated risk for either BeS or CBD. However, a survey at a copper-beryllium alloy finishing facility identified higher risks for both BeS and CBD in wire annealing and pickling and in wire drawing, among others, processes that are included in this facility's bulk products operations (6). Some differences that exist between this facility and the copper-beryllium finishing facility, such as the manual handling of the coiled wire between the annealing and pickling stages and the smaller gauge of the wire at the latter, may explain the different findings. It was not possible in this study to disentangle the various individual bulk products jobs due to small numbers and overlapping work. A significantly lower prevalence of BeS was observed in production support jobs, especially in administration work in production areas (eg, supervisors). No one who had worked in administrative jobs with little or no time in production areas was found to be sensitized. Other surveys conducted at this facility and

Table 3. Logistic regression models for beryllium sensitization (BeS) and chronic beryllium disease (CBD) among 1999 survey short-term workers, with log-transformed exposures. [OR=odds ratio; 95% CI=profile likelihood 95% confidence interval.]

Metric	BeS [a]		CBD [b]	
	OR	95% CI	OR	95% CI
Average (µg/m^3) [c]				
Total mass [d]	1.48	1.09–2.07	1.56	0.87–3.09
Respirable [e]	1.37	1.03–1.90	1.56	0.86–3.49
Submicron [f]	1.25	0.96–1.66	1.48	0.86–2.99
Cumulative (µg/m^3-year) [g]				
Total mass	1.23	0.99–1.56	1.66	1.02–2.99
Respirable	1.18	0.95–1.49	1.68	1.02–3.28
Submicron	1.13	0.93–1.40	1.58	1.00–2.83
Highest job worked (µg/m^3) [h]				
Total mass	1.37	1.06–1.82	1.45	0.88–2.63
Respirable	1.32	1.02–1.77	1.53	0.88–3.33
Submicron	1.24	0.98–1.62	1.46	0.89–2.79

[a] Analyses included 26 sensitized (including those with CBD), 238 not sensitized (N=264).
[b] Analyses included 6 with CBD, 238 not sensitized (N=244).
[c] Average exposure in micrograms of beryllium per cubic meter.
[d] Estimated total mass concentration beryllium exposure.
[e] Estimated respirable concentration beryllium exposure.
[f] Estimated submicron concentration beryllium exposure.
[g] Cumulative exposure in micrograms of beryllium per cubic meter of air per work year.
[h] Highest job worked exposure in micrograms of beryllium per cubic meter.

elsewhere found cases of BeS and CBD among office and administrative workers (1–3, 5, 6, 24, 25).

These results also confirm findings from other studies that BeS can be identified very early after initial exposure (3, 6, 12–14, 26). Here, four workers had confirmed abnormal BeLPT within four months of first reported beryllium exposure. We did not, however, identify a higher level of BeS in the overall first year of employment, compared to other yearly intervals, as prevalence varied little in cohort members subdivided by years of work tenure.

The strengths of this study lie in its design and in the detailed data that were available, both from workers (eg, work histories) and existing historical sampling data (full-shift personal cassette, full-shift size-separated impactor, and general area samples) (16). The availability and use of these full-shift samples, collected systematically and averaging about 14 samples per job title, provided a decided advantage in creating these exposure estimates. We designed the study to have a relatively short duration between first exposure and testing for BeS in order to minimize the possibility of including a period of irrelevant exposure, often a weakness of cross-sectional studies with diverse employment duration. In addition, the high participation rate mitigated the possibility of non-representativeness of the participants.

Several limitations to this study should also be considered. This was, as stated above, a cross-sectional study, and even though misclassification of exposure or inclusion of irrelevant exposure was likely reduced by limiting work tenure, it was not eliminated. It is unknown when those found to be sensitized actually became sensitized, as we were dependent upon blood test dates. Workers were not tested prior to beginning employment, so it is not known whether any may have already been sensitized at hire. Testing for BeS was not done on a regular, periodic basis. Truncating the cohort to those employed ≤6 years, which limited the number of CBD cases detected, may also limit the generalizability of our findings.

The job-exposure matrices were based on a full-shift cassette sampling survey of all jobs and an impactor sampling survey, both conducted in 1999, with adjustment backwards to 1994 based on annual variability in general area samples (16). Despite the expertise required to interpret these data, the large quantity of sampling data (personal cassette and general area) provides a more stable basis for creation of estimates than any other study to date. However, separate datasets were used to create the baseline exposure estimates: cassette samples for total mass concentration estimates, and size-separated samples for respirable and submicron concentration estimates. The size-separated samples were much fewer in number, necessitating a broader grouping of jobs in completing the JEM. The methods used to collect the latter samples (9) resulted in our being unable to create an analogous set of inhalable concentration estimates for evaluating the role of "large" particles (ie, >4 µm) in development of BeS or CBD (27). The absence of an advantage in the smaller size fractions may be real or it may reflect the smaller database of size-separated samples used to estimate the respirable and submicron concentrations. Finally, our exposure estimates do not account for event-related expo-

Table 4. Percent prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) by work categories and processes/jobs within each category for 1999 survey short-term workers.

Work category	Ever worked [a]			
	BeS [b]	N [c]	CBD [d]	N [e]
Production work	12.0 [f]	25/209	3.2	6/190
High beryllium content areas	18.5 [f]	10/54	4.4	2/46
Pebbles plant/beryllium oxide [g]	26.9 [f]	7/26	5.0	1/20
Powder metal products	8.6	3/35	3.0	1/33
Low beryllium content areas	11.3	17/151	4.3 [f]	6/140
Primary operations	14.8 [f]	16/108	5.2 [f]	5/97
Strip metal	12.9	4/31	3.6	1/28
Bulk products	7.3	4/55	3.8	2/53
Other production areas	15.7 [h]	11/70	1.7	1/60
Maintenance	18.0 [h]	9/50	2.4	1/42
Resource recovery	10.7	3/28	0.0	0/25
Non-production work	3.0 [f]	3/99	0.0 [h]	0/96
Production support	3.1 [f]	3/97	0.0 [h]	0/94
Administration – plant areas	0.0 [f]	0/54	0.0	0/54
Quality assurance/quality control	0.0	0/14	0.0	0/14
Janitorial	11.8	2/17	0.0	0/15
Laundry	8.3	1/12	0.0	0/11
Other production support [i]	0.0	0/12	0.0	0/12
Administration – office areas	0.0	0/8	0.0	0/8

[a] P-value from χ^2 analysis comparing those who had ever worked in a category/process to those who had never worked there.
[b] Percent of all sensitized, including those with CBD, who ever worked in that category/process; total sensitized=26.
[c] Number sensitized/total number ever worked in that category/process.
[d] Percent of all CBD who ever worked in that category/process; total CBD=6.
[e] Number with CBD/total number ever worked in that category/process.
[f] $P<0.05$.
[g] These processes were combined as workers often worked both areas during same shift.
[h] $0.05 \leq P < 0.10$.
[i] Other production support jobs (shipping and receiving, outside maintenance and security) were combined because of small numbers.

sure excursions, and we were unable to obtain reliable information about respiratory protection although available evidence suggests that use was generally limited to half-mask respirators which were often used irregularly.

The sensitivity of the BeLPT for detection of BeS is difficult to determine, as there is no criterion standard against which to assess it, but is likely greater for those with CBD. Any non-normal test result led to follow-up testing, as many as four times, to determine BeS status. However, we did have one individual who had two abnormal BeLPT in 1997 but had two normal results in 1999. Laboratory performance has been shown to vary over time and within and between labs (14, 28); test results from this study had been included in those analyses. The use of split sampling on first blood draw mitigates the impact of using any one laboratory, increasing the ultimate yield of confirmed abnormal results. In this study, the yield was increased by 20%. Additionally, not everyone with confirmed abnormal BeLPT agreed to follow-up clinical evaluations for CBD; 4 of the 26 sensitized (15.4%) elected not to have further testing. It is thus possible, given the approximate one in four CBD/all sensitized ratio among those evaluated (6/22), that one of the sensitized who was not clinically evaluated actually had CBD. This lack of complete evaluation is a common occurrence in these studies, with anywhere from 42–100% of the sensitized undergoing clinical evaluation (29), so it should not bias results when comparing studies. However, misclassification of CBD status may have diminished power to detect associations with exposure indices.

In conclusion, we believe that the use of a workplace population with limited employment duration has allowed for evaluation of the exposure–response relationship with a more accurate assessment of the relevant period of exposure, especially for BeS. We were able to identify noteworthy exposure–response relations for both total mass and respirable concentration for BeS (average exposure and highest job) and for CBD (cumulative). While these results support efforts to revise occupational exposure limits, it should be noted that our exposure estimates were based on measures of central tendency and occupational risk management strategies are often based on the upper tail of the distribution. In addition, the limited power to detect an effect for CBD, due to the truncated period of exposure, may have precluded identification of additional exposure–response patterns. Fur-

ther exploration of other exposure metrics, such as other indices of peak exposure, potential dermal exposure, and inclusion of information about physical, chemical, and/or physicochemical characteristics, such as chemical form of beryllium and solubility of process materials, may provide additional useful information about this population.

Ethics

David C Deubner and Michael S Kent are employed by Materion Brush Inc, the owner of the beryllium manufacturing facility described in this report.

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