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# Cumulative Sensitization and Disease in a Beryllium Oxide Ceramics Worker Cohort

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## Learning Objectives

- Review the development of beryllium sensitization and chronic beryllium disease (CBD), including diagnostic testing and efforts to reduce worker exposure.
- Discuss the short and long-term risks of beryllium sensitization among workers with past and current exposure.
- Describe an appropriate monitoring and testing plan for workers with past and/or current exposure to beryllium, including counseling for workers with exposure in different areas.

## Abstract

**Objective:** We followed a cohort of 136 beryllium oxide ceramics workers from 1992 to 2003, including those who left employment, for beryllium sensitization and chronic beryllium disease (CBD). **Methods:** We invited the cohort's participation in current worker surveys in 1992, 1998, 2000, and 2002–2003, and in former worker surveys in 2000–2001 and 2003. We calculated 11-year cumulative incidences (after 1992 initial survey) of sensitization and CBD, both crude and corrected for interval censoring; and period prevalences (including 1992 findings), crude and corrected. **Results:** In 1992, point prevalences were 6% sensitized and 4% CBD. We obtained follow-up on 83% of 128 not sensitized in 1992. Crude cumulative incidences for sensitization and CBD were 13% and 9%, respectively; corrected were 15% and 11%. Crude period prevalences for sensitization and CBD were 16% and 11%, respectively; corrected were 20% and 14%. Corrected period prevalences for pre-1992 machining work were 30% and 20%. **Conclusions:** With repeated testing over 11 years, total sensitization and CBD in this cohort were triple initial 1992 survey results. (J Occup Environ Med. 2008;50:1343–1350)

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Chronic beryllium disease (CBD) is a granulomatous disease that primarily affects the lungs; it is found in a proportion of beryllium-exposed workers who develop sensitization to the metal. Sensitization is a cell-mediated immune response detected in the peripheral blood with the beryllium lymphocyte proliferation test (BeLPT). Sensitized individuals can be evaluated for CBD using bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy.

The BeLPT has been used in surveillance of beryllium-exposed workers since the late 1980s.<sup>1</sup> Cross-sectional studies have been conducted in a variety of beryllium worker groups, both current and former workers, with sensitization identified in less than 1% to more than 14% of those tested.<sup>1–14</sup> The proportion of sensitized individuals who have CBD at the time that sensitization is identified has varied from 10% to 100%.<sup>1–14</sup> In one study, biennial testing was offered to workers at a beryllium machining facility; the initial sensitization prevalence of 6.4% increased to a cumulative level of 9.4% over a 4-year period.<sup>15</sup> CBD has been identified within the first year of exposure,<sup>7,10</sup> but also many years after cessation of exposure.<sup>3,8</sup> It is unknown what proportion of those sensitized will eventually go on to develop CBD. In one study, 55 sensitized individuals were followed for an average period of 3.8 years and 31% developed CBD during that time.<sup>16</sup>

In 1992, a cohort of 136 workers at a beryllium oxide ceramics facility

that began operations in 1981 was evaluated with the BeLPT.<sup>4</sup> Eight workers were found to be sensitized (6%), and six of those sensitized (4%) were diagnosed with CBD. Machinists were at highest risk of sensitization (14% of those who had ever worked in this process) compared with other work processes (1% of those who had never worked in machining). Lapping, a form of wet machining, also demonstrated a higher risk, but all sensitized participants who had worked in lapping also worked in machining. Historical beryllium air concentration samples (general area and task-based) ranged from non-detectable levels to over 2.0  $\mu\text{g}/\text{m}^3$ , with a median of 0.35  $\mu\text{g}/\text{m}^3$ .<sup>4</sup> Levels were highest in the machining areas, where 8% of daily weighted average estimates of exposure exceeded the Occupational Safety and Health Administration permissible exposure limit of 2  $\mu\text{g}/\text{m}^3$  (8 hour time-weighted average). This suggestion of an exposure-response relationship led to the implementation in the mid-1990s of additional engineering controls targeted to the high-risk machining processes. All of those identified as sensitized or with CBD subsequently left employment at this facility.

In 1998, a second study was conducted at the same facility to determine if the engineering controls had been effective in reducing sensitization and CBD. New cases of sensitization and CBD were identified among the workforce, including those who had been tested in the 1992 survey and found not to be sensitized.<sup>7</sup> Despite a decline in airborne beryllium concentrations between 1992 and 1998, overall levels of sensitization (15/151, or 10%) and CBD (5/151, or 3%) did not drop. Risk associated with machining declined for those hired after implementation of engineering controls (6% sensitized), but higher risk (18%) persisted among machining employees who had worked in that process before 1992. Among these

longer-term workers, lapping also demonstrated a higher risk but, as in 1992, all of the sensitized who had worked in lapping had also worked in machining.

The point prevalence measure provided by a cross-sectional survey tallies all persons in a population that are detected to have a condition at that point in time. It provides no information on persons who had left the population before the study period (ie, former workers), nor does it tally persons who develop the condition in the future. Cross-sectional surveys also miss undetected cases. Thus, we sought a more complete picture of beryllium sensitization and CBD in a defined population over time, specifically by obtaining information on sensitization and CBD on multiple occasions and by contacting those workers who had left employment since 1992. Our questions included:

1. What were the cumulative incidences of sensitization and CBD among cohort members who were not sensitized in 1992 over an additional 11-year period of follow-up?
2. What were the period prevalences of sensitization and CBD in the original cohort of 136 workers?
3. Which work processes were associated with elevated levels of sensitization and CBD?

## Methods

### Study Population

The population for this study was a cohort of 136 beryllium-exposed workers defined by their employment at a beryllium ceramics facility and participation in a 1992 cross-sectional survey at the facility. The Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH) approved follow-up of this cohort of current and former workers as part of a larger longitudinal study.

### Surveys

Members of the cohort were contacted for voluntary participation in

follow-up on several occasions over an 11-year period. The company surveyed all of its current workers in 1998<sup>7</sup> and offered testing again in 2000 and 2002–2003. NIOSH surveyed former workers from the 1992 cohort in 2000–2001 and in 2003. Each survey included a questionnaire interview to update demographic data, respiratory and dermatologic questions, work history, and testing for beryllium sensitization for those not already known to be sensitized. For former workers who were unable to participate in scheduled data collection efforts, NIOSH arranged for a local blood draw (eg, public health department or personal physician) and conducted interviews via telephone.

Work history questionnaires collected descriptions of all job processes worked during an employee's tenure at the plant. Significant engineering changes were implemented at the plant in 1995 and in 2000, which resulted in changes in the work history collection instrument with respect to work processes. We recoded the 1992 (eight process categories) and 1998 (eleven categories) data to reflect 13 current process group categories. We also combined process groups into three broad work categories: production, production support, and administration. Production work included the processes of machining, firing, forming, lapping, material preparation, metallizing, and tape (eliminated in 2000). Production support work included janitorial and laundry workers, maintenance, packaging, quality control, and administrative personnel who spent a significant amount of time in production areas (eg, medical staff, engineers, and supervisors). Administration included those who primarily worked in the office, rarely entering production areas. For analysis purposes, we considered both "ever worked" in a given process and "ever worked prior to 1996," the period before the most significant changes in engineering controls were implemented at the facility.

We defined “relevant workplace exposure” as follows: for employees with sensitization or CBD that was identified while still employed—date of hire by the company to the date of the first abnormal BeLPT that was subsequently confirmed; for those with sensitization or CBD identified after leaving work—date of hire to date of employment termination; for non-sensitized workers whose last BeLPT occurred during employment—date of hire to date of last normal BeLPT; for non-sensitized workers whose last BeLPT took place after they left employment—date of hire to date of employment termination.

## Beryllium Sensitization and CBD Status

To evaluate participants for sensitization, we drew blood samples for the BeLPT. All initial blood samples were split and sent to two separate laboratories. One laboratory was used for all surveys; the second laboratory varied among the 1992, 1998, and 2000–2003 efforts. Tests were performed using typical protocols.<sup>3,17</sup> For all surveys, except for one laboratory in 1992, a BeLPT was determined to be “abnormal” if at least two of the stimulation indices (SIs) were  $\geq 3.0$ , “borderline” if a single SI was  $\geq 3.0$ , or “normal” if no SIs were  $\geq 3.0$ . In 1992, the SI level for determination of abnormal results at one laboratory varied.<sup>4</sup> Additional blood was drawn and the test was performed again for confirmation of a single abnormal test result (eg, if an individual’s initial split sample blood draw returned one abnormal and one normal result), for clarification of a borderline result, or when results were determined by the laboratory to be uninterpretable. We defined beryllium sensitization as a confirmed abnormal BeLPT, which could be from the same or different laboratories; confirmatory BeLPTs could occur on redraw or at a later date.

At the time sensitization was identified, sensitized employees were referred for clinical evaluation, including

BAL and fiberoptic bronchoscopy for collection of transbronchial biopsy samples. BAL cells were examined for lymphocytosis, and a lymphocyte proliferation test was performed on the BAL fluid to determine if lymphocytes from the lung responded to beryllium ion stimulation. Biopsy samples were examined for granulomas, mononuclear cell interstitial infiltrate, and fibrosis. A sensitized individual was considered to have CBD if granulomas or other pathologic abnormalities consistent with that diagnosis were present. Individuals without CBD, and those who declined initial clinical evaluation after sensitization was identified, could elect to obtain such evaluation at a later date.

## Statistical Analysis

We used SAS software<sup>18</sup> to evaluate categorical outcomes with the continuity-corrected  $X^2$  and Fisher’s exact tests and continuous outcomes with the Wilcoxon rank-sum (two samples) and Kruskal-Wallis (more than two samples) tests. To estimate the impact of non-response, we compared demographic data among those for whom we had post-1992 follow-up with those whose participation was limited to the 1992 survey.

We calculated the crude cumulative incidences of sensitization and CBD over 11 years of follow-up for those not sensitized in 1992, and the crude period prevalences of sensitization and CBD among the entire cohort, including the 1992 findings. In addition, we used the LIFEREG procedure to estimate both cumulative incidences and period prevalences for sensitization and CBD, correcting for interval censoring,<sup>19</sup> based on the following assumptions regarding change in sensitization status. These included: that all participants were not sensitized upon hire, that anyone with normal (negative) BeLPT results was not sensitized before that date, and that anyone with abnormal (positive) BeLPT results became sensitized at some point in the interval since previous normal

(negative) testing (or since hire if abnormal in 1992).

Comparing sensitized and non-sensitized workers, we analyzed workforce demographics, smoking history, and history of lower respiratory symptoms and skin rashes or ulcers. We calculated the crude period prevalence of sensitization for workers who reported having ever versus never worked in 13 work processes, and for workers who reported working in those processes before 1996. We also separately calculated corrected period prevalences of sensitization and CBD for those who had reported ever working in the highest-risk process (machining) before the 1992 survey and for those who had reported no pre-survey work in that process. Finally, we calculated hazard ratios (HRs) with Cox proportional hazards regression models,<sup>20</sup> assessing the association between work processes and sensitization and CBD, adjusted for relevant workplace exposure duration and other processes worked.

We considered two levels of statistical significance:  $P$  less than 0.05 ( $P < 0.05$ ), and  $P$  greater than or equal to 0.05 but less than 0.10 ( $P < 0.10$ ). Both are presented. All confidence intervals (CI) are 95%.

## Results

### Study Population

All eight of the workers identified as sensitized in 1992 had been clinically evaluated for CBD.<sup>4</sup> Six had been diagnosed with disease; the other two had no evidence of CBD at that time and have since declined additional follow-up bronchoscopies. One of the six with CBD died of CBD-related complications 7 years after diagnosis. Mean time between hire and the 1992 survey for all participants was 7.7 years (range, 0.5 to 36 years). Although the facility began operations in 1981, eight employees working at the facility (none of whom were sensitized or diagnosed with CBD) had transferred

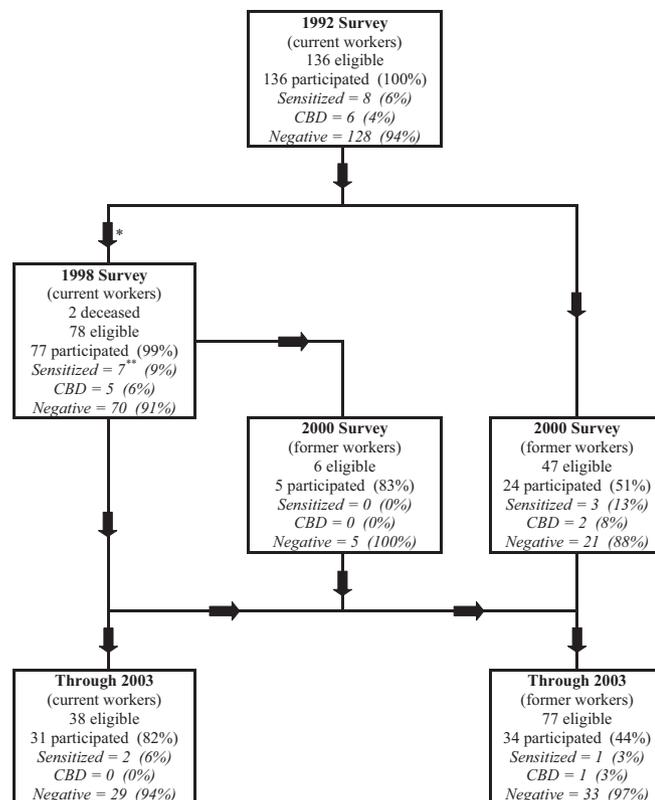
there from other beryllium facilities within the same company.

Among the 128 without sensitization or CBD in 1992, 22 (17%) did not participate in further testing: two died in the 1990s, one current worker declined further participation, and 19 former workers either declined or were unable to be located. Four who declined participation in 2000, three former and one current worker, elected to take part in 2003. Among those who participated in post-1992 testing ( $n = 106$ ), 48 were current workers and 58 were former workers at the time of their last blood test. Demographics of employees who had at least one round of post-1992 BeLPT testing did not differ from those lost to follow-up with respect to gender, age, race/ethnicity, or smoking status.

### Beryllium Sensitization and CBD

The 11-year crude cumulative incidence for sensitization was 13% (14 of 106). Nine of the sensitized were also diagnosed with CBD, eight at the time sensitization was identified and one at a later date, for an 11-year CBD crude cumulative incidence of 8%. One of the 14 sensitized had an unconfirmed positive BeLPT in 1992; a confirmatory result was obtained in the mid-1990s. The cumulative incidence for sensitization, corrected for interval censoring, was 15%, and for CBD was 11%.

Crude period prevalence of sensitization, including the 1992 results, was 16% (22 of 136 original cohort members), and of CBD was 11% (15 of 136). If the 22 lost to follow-up were excluded, the crude period prevalence of sensitization was 19% (22 of 114 cohort members either identified on first testing or who had at least one round of follow-up testing), and of CBD was 13% (15 of 114). The corrected period prevalence of sensitization, for the entire original cohort and including the 1992 results, was 20%, and of CBD was 14%.



**Fig. 1.** Participation of a beryllium oxide ceramics worker cohort in original and follow-up surveys. \*One current worker identified as sensitized between 1992 and 1998; not included in box totals. \*\*One of the sensitized was later diagnosed with CBD; not included in box totals.

Results from specific survey efforts are shown in Fig. 1. In 1998, 78 current workers were offered retesting, and 77 participated (99%). Seven were found to be sensitized (9%), and five (6%) of the sensitized were found to have CBD at that time; an additional sensitized worker was diagnosed with CBD 1.5 years later.<sup>7</sup> An additional current worker was tested and identified as sensitized before the 1998 survey. Between 2000 and 2003, among the 38 without sensitization who were still current workers, 31 participated (82%). Two additional workers were found to be sensitized (6%); neither had CBD. Six participants from the 1998 current workers survey left employment shortly thereafter; five were tested as former workers in 2000 and none were sensitized. By 2000–2001, 47 of the original cohort who were not sensitized had left employment, and 24 (51%) participated in testing. Three (13%) were sensitized,

and two (8%) of the sensitized were found to have CBD at that time. In 2003, 77 former workers without sensitization were offered retesting, and 34 (44%) accepted. One (3%) participant was sensitized and was also diagnosed with CBD. Some cohort members declined participation at one point and elected to take part in later surveys. Among the fourteen sensitized who were identified after 1992, four (29%), including three with CBD, were identified after leaving employment.

Overall, between 1992 and 2003, 30 workers (22% of 136) were tested only once, including those found to be sensitized in 1992 and those lost to follow-up; 46 (34%) were tested twice; 58 (43%) were tested three times; and two (1%) were tested four times. Eight of the 22 sensitized (36%) were identified on first testing in 1992, eleven (50%) on their second round of testing, three (14%) on

**TABLE 1**

Prevalences of Sensitization and CBD in a Beryllium Ceramics Worker Cohort by Number of Times Tested

Times Tested	No. Tested	All Sensitized (%)	CBD Only (%)	Percentage Sensitized with CBD	Mean Yr Since Hire (Range)	Mean Yr Since Last Test (Range)
1	136	8 (5.9)	6 (4.4)	75.0	7.7 (0.5–36.0)	—
2	106	11 (10.4)	8 (7.5)	72.7	15.0 (7.7–47.3)	6.7 (3.2–12.4)
3	60	3 (5.0)	1 (1.7)	33.1	18.3 (11.5–35.1)	3.2 (2.1–5.4)
4	2	0	N/A	N/A	20.6 (20.0–21.2)	3.2 (3.2)

**TABLE 2**

Characteristics of a Beryllium Oxide Ceramics Worker Cohort by Final Sensitization or CBD Status

Characteristic	Non-Sensitized (n = 114)	All Sensitized <sup>a</sup> (n = 22)	CBD <sup>a</sup> (n = 15)	Sensitized (not CBD) <sup>a</sup> (n = 7)
Gender (% male)	63.2	50.0	46.7	57.1
Race/ethnicity (% white)	67.5	45.5**	46.7	42.9**
Ever smoked cigarettes (%)	51.8	63.6	46.7	100.0*
Average age at hire (yr)	32.5	35.1	35.7	33.6

\*0.05 ≤ P < 0.10; \*\*P < 0.05.

<sup>a</sup>Comparisons were to non-sensitized group.

**TABLE 3**

Hazard Ratios for Demographic and Other Variables in a Beryllium Oxide Ceramics Worker Cohort

Job or Process	All Sensitized		CBD Only	
	HR <sup>a</sup>	(95% CI)	HR <sup>a</sup>	(95% CI)
Chronic cough	1.84	(0.80, 4.27)	1.94	(0.71, 5.36)
Skin problems	1.16	(0.50, 2.68)	2.16	(0.74, 6.32)
Skin ulcers	1.21	(0.47, 3.09)	1.16	(0.37, 3.65)
Race/ethnicity (white vs all other)	0.40**	(0.17, 0.93)	0.42*	(0.15, 1.15)
Race/ethnicity (Hispanic vs all other)	2.21*	(0.95, 5.11)	2.43*	(0.88, 6.70)

\*0.05 ≤ P < 0.10; \*\*P < 0.05.

<sup>a</sup>Models were run separately for each variable; comparisons were to non-sensitized group.

their third round, and none on fourth round (Table 1).

Overall mean time between hire and identification of sensitization including CBD was 11 years (range, 4 to 17 years), and for CBD alone was 11 years (range, 4 to 15 years) (results not shown). The four found to be sensitized as former workers were identified an average of 4.6 years after leaving employment (range, 0.5 to 6.6 years). Among those who were not identified as sensitized, average time from hire to either last negative BeLPT or date of termination was 13 years (range, 0.5 to 40 years).

All sensitized workers (including CBD) were less likely to be white, and sensitized workers without CBD

were more likely to have smoked cigarettes at some time in their lives, compared with non-sensitized workers. The groups did not differ by gender or average age at hire (Table 2). We found no significant increase in either sensitization or CBD for those with chronic cough, skin ulcers, or other skin problems (Table 3). Sensitization was significantly decreased for whites (HR = 0.40; CI = 0.17, 0.93) and was higher among Hispanics (HR = 2.21; CI = 0.95, 5.11) compared with all other races/ethnic groups. However, Hispanics were more likely to have worked in production jobs or processes, compared with other races/ethnic groups (P < 0.05).

### Process-related Risks

In reanalysis of 1992 data consistent with current process groupings, the most significant point prevalence of sensitization was observed in machining (14% of those who ever worked, P < 0.05), followed by lapping (20%, P < 0.10) (Table 4). Cumulatively through 2003, machining continued to have the highest crude period prevalence of sensitization (24%, P < 0.05), along with firing (23%, P < 0.05). Lapping (27%) demonstrated a high prevalence but was not significantly different from those who had never lapped. Among the 22 sensitized, sixteen (73%) had ever worked in machining and at least one other process among forming, firing, and lapping. Among the six who had never worked in machining, two (9%) had worked in forming, firing, and/or lapping; one (5%) had worked in forming and firing; and three (14%) held administrative jobs with time spent in production areas.

Since machining had demonstrated the highest risk in 1992,<sup>4</sup> we separately evaluated the outcome for those who had ever (n = 51) and never machined (n = 85) between hire and 1992. In the first survey, 14% (7/51) of ever-machinists were sensitized, and 10% (5/51) had CBD (10%). Among never-machinists in the 1992 survey, one (1% of 85) was sensitized and was also diagnosed with CBD. Through 2003, the corrected period prevalence of sensitization among 1992 ever-machinists was 30%, and of CBD was 20%. The corrected period prevalences of sensitization and CBD among the 1992

**TABLE 4**

Prevalence of Sensitization by Work Process (Ever Worked) at a Beryllium Oxide Ceramics Facility During 1992 Cross-sectional Survey and Cumulatively Through 2003

Job or Process	Percentage Sensitized (No. Sensitized/No. Ever Worked) <sup>a</sup>			
	1992 Survey (n = 136) <sup>b</sup>		Through 2003 for all Participants <sup>c</sup>	
Production work				
Lapping	20*	(3/15)	27	(8/30)
Machining	14**	(7/51)	24**	(16/67)
Forming	6	(4/64)	21	(15/71)
Firing	4	(2/45)	23**	(18/78)
Metallizing	0	(0/13)	5	(1/18)
Tape	0	(0/10)	5	(1/19)
Material preparation	0	(0/8)	0	(0/13)
Production support				
Janitor/Laundry	0	(0/7)	29	(2/7)
Packaging	0	(0/12)	25	(6/24)
Admin—production areas	6	(2/33)	17	(6/36)
Quality control	3	(1/31)	15	(9/59)
Maintenance	0	(0/12)	0	(0/16)
Administration				
Admin—office areas	8	(1/12)	19	(5/27)

\*0.05 ≤ P < 0.10; \*\*P < 0.05.

<sup>a</sup>Sensitization included those diagnosed with CBD; comparisons were to those who never worked in that job or process.

<sup>b</sup>Point prevalence in 1992 survey; these data were reclassified into process categories consistent with current data and reanalyzed.

<sup>c</sup>Crude period prevalence—included sensitized from all prior surveys, including 1992.

**TABLE 5**

Hazard Ratios for Ever Worked in Each Job or Process Category for a Beryllium Oxide Ceramics Worker Cohort

Job or Process	All Sensitized		CBD Only	
	HR <sup>a</sup>	(95% CI)	HR <sup>a</sup>	(95% CI)
Production work				
Lapping <sup>b</sup>	1.72	(0.68, 4.36)	1.33	(0.42, 4.16)
Machining	3.13**	(1.21, 8.06)	4.65**	(1.30, 16.61)
Forming <sup>b</sup>	2.38*	(0.91, 6.20)	2.10	(0.66, 6.65)
Firing <sup>b</sup>	2.97*	(0.93, 9.48)	2.37	(0.62, 9.06)
Metallizing	0.41	(0.06, 3.13)	0.62	(0.08, 4.88)
Tape	0.44	(0.06, 3.42)	0.66	(0.08, 5.50)
Material preparation	0.00	—	0.00	—
Production support				
Janitor/Laundry	1.97	(0.45, 8.64)	2.90	(0.63, 13.42)
Packaging	2.57	(0.93, 7.08)	2.52	(0.74, 8.58)
Admin—production areas	0.92	(0.35, 2.39)	0.95	(0.30, 3.02)
Quality control	1.01	(0.41, 2.50)	0.74	(0.24, 2.31)
Maintenance	0.00	—	0.00	—
Administration				
Admin—office areas	0.54	(0.19, 1.54)	0.29	(0.06, 1.35)

\*0.05 ≤ P < 0.10; \*\*P < 0.05.

<sup>a</sup>Models were run separately for each process, comparing ever to never worked, adjusted for months employed.

<sup>b</sup>Also adjusted for work in machining.

never-machinists, through 2003, were 16% and 12%, respectively.

Through 2003, we observed sensitization more frequently in those who had ever worked in the machining processes (HR = 3.13; CI = 1.21, 8.06), forming (HR = 2.38; CI = 0.91, 6.20), or firing (HR = 2.97; CI = 0.93, 9.48) (Table 5). All models were adjusted for time worked, and those for lapping, forming, and firing were also adjusted for having worked in machining. When individual analyses were limited to those who worked in a process before 1996, at which point engineering controls were implemented, sensitization was higher for machining (HR = 3.35; CI = 1.30, 8.62), forming (HR = 2.58; CI = 1.00, 6.63), and packaging (HR = 3.02; CI = 1.06, 8.61) (results not shown). Sensitization was not elevated for pre-1996 firing (HR = 1.76; CI = 0.63, 4.88). CBD was more frequently observed with work in the machining areas, both for ever worked and work before 1996 (HR = 4.65; CI = 1.30, 16.61 and 4.93; CI = 1.38, 17.57, respectively). Additionally, pre-1996 administrative work in the office areas was associated with a lower risk of CBD (HR = 0.13; CI = 0.02, 1.06).

## Discussion

In a longitudinal follow-up of a cohort of beryllium oxide ceramics workers, defined by their participation in a 1992 workplace survey, we found additional sensitization and CBD among both current and former workers. The post-1992 11-year crude cumulative incidences and overall period prevalences of sensitization and CBD were well above the levels observed in any single cross-sectional study at this facility.<sup>4,7</sup> Cumulative incidences and period prevalences of sensitization and CBD, corrected for interval censoring, were triple the point prevalences found in the initial cross-sectional survey.

Since we were unable to obtain BeLPT results on everyone who was

not sensitized in 1992, the crude results likely represent an underestimate of the true period prevalence. Seventeen percentage of the cohort did not participate in follow-up testing. The company is aware of two additional members of this cohort who were found to be sensitized and subsequently diagnosed with CBD, but for whom consent for release of information to NIOSH was not obtained. Were these workers included, the period prevalences presented here would be higher. In addition, it is also possible that some of those currently categorized as sensitized may have developed CBD, since five of the seven workers we have listed as sensitized without CBD have not undergone recent clinical evaluation with bronchoscopy.

Among the entire cohort of 136 workers, additional cases of sensitization were identified on the individuals' second and third rounds of testing; limited participation in a fourth round may have precluded finding additional cases. Within individual rounds of testing, we found the highest prevalences for both sensitization and CBD in the second round. Although this is a small population from which to draw conclusions, these results emphasize that providing multiple opportunities for testing enables additional sensitization to be identified. These cases could be newly developed sensitization or sensitization not detected on earlier testing through false negative BeLPT results. Although most sensitization and CBD were identified while workers were still employed, more than one-fourth of the post-1992 cases were identified after leaving work. Since BeLPTs were not specifically offered before leaving employment, we do not know if sensitization or CBD truly developed after cessation of exposure, but it does reinforce the idea that beryllium-exposed workers should be educated that their risk of disease persists long after they leave the workplace.

Some individuals demonstrate abnormal BeLPT results at one point in time, but later have normal test results<sup>16,21</sup>; some individuals diagnosed with CBD also have normal blood BeLPTs.<sup>3,16,22</sup> Possible explanations for these phenomena include variation in the concentration of beryllium-specific CD4+ T-cells capable of proliferation, maturation of circulating memory T-cells, or both,<sup>23</sup> and variation in BeLPT results between laboratories,<sup>21,24</sup> and over time.<sup>25</sup> Cross-sectional surveys detect those who are currently exhibiting beryllium sensitization in circulating immune cells, but they may not detect all of those who are truly sensitized, eg, who would have demonstrated abnormal BeLPT results in the past and/or who will have abnormal results in the future, contributing to misclassification of sensitization status in a given population when such a population is only tested once.

The 1992 survey identified machining as the highest-risk process.<sup>4</sup> When the corrected period prevalences through 2003 for those who had ever worked in machining before the 1992 survey were compared with those who had never worked there, these cumulative results reinforced the risk found associated with pre-1992 machining: 30% sensitization for pre-1992 machinists compared with 16% for non-machinists, and 20% compared with 12% for CBD. Analyses in other studies which may have only suggested a relationship may also benefit from reanalysis if additional cases are identified.

Subsequent to the 1992 survey, the facility targeted additional engineering controls to the machining areas, which were implemented in 1995. When those who were still employed at the facility in 1998 were surveyed, the highest prevalence of sensitization continued to be found among those who had ever worked in machining; lapping, forming, and firing work were also associated with increased sensitization.<sup>7</sup> Most of the sensitized had worked in multiple

processes. Through 2003, we saw persistent risk of sensitization and CBD associated with having ever performed machining work. When participants whose only machining work occurred after 1996 were excluded, levels of sensitization and CBD were similar to levels for ever worked, indicating a persistence of pre-1996 risk. When we adjusted for machining work, higher levels of sensitization were seen for forming and firing, and when limited to pre-1996 work, forming remained elevated but firing did not.

This 1992 cohort of beryllium oxide workers was exposed to historically higher levels of beryllium than the current workforce. In 2000, subsequent to the mid-1990s installation of targeted engineering controls and the failure of those controls to reduce overall disease levels,<sup>7</sup> the company implemented a comprehensive enhanced preventive program that was established on the premise that all routes and pathways of potential worker exposure that might contribute to sensitization and CBD must be addressed. The principles of the model include keeping: beryllium out of the lungs, off of the skin and clothing, at the source, in the work area, on the plant site, work areas clean and shipshape, and workers prepared to work safely.<sup>26</sup> Workers hired in the period 2000–2004 showed a marked reduction in sensitization when compared with workers hired in the 5 years before the 1998 survey.<sup>27</sup> Continued follow-up of those hired since implementation of the preventive program will provide a useful comparison to the historical 1992 cohort presented here.

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