Process-Related Risk of Beryllium Sensitization and Disease in a Copper–Beryllium Alloy Facility

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Background *Chronic beryllium disease (CBD), which primarily affects the lungs, occurs in sensitized beryllium-exposed individuals. At a copper–beryllium alloy strip and wire finishing facility we performed a cross-sectional survey to examine prevalences of beryllium sensitization and CBD, and relationships between sensitization and CBD and work areas/processes.*

Methods *Current employees (185) were offered beryllium lymphocyte proliferation testing (BeLPT) for sensitization, clinical evaluation for CBD (if sensitized), and questionnaires. We obtained historical airborne beryllium measurements.*

Results *Participation was 83%. Prevalences of sensitization and CBD were 7% (10/153) and 4% (6/153), respectively; this included employees with abnormal BeLPTs from two laboratories, four diagnosed with CBD during the survey, and one each diagnosed preceding and following the survey. Potential BeLPT laboratory problems were noted; one laboratory was twice as likely to have reported an abnormal result ($P < 0.05$, all tests), and five times as likely to have reported a borderline or uninterpretable result ($P < 0.05$, first blood draw and all tests). CBD risk was highest in rod and wire production ($P < 0.05$), where air levels were highest.*

Conclusions *Sensitization and CBD were associated with an area in which beryllium air levels exceeded 0.2 $\mu g/m^3$, and not with areas where this level was rarely exceeded. Employees at this copper–beryllium alloy facility had similar prevalences of sensitization and CBD as workers at facilities with higher beryllium air levels.* Am. J. Ind. Med. 47:195–205, 2005. *Published 2005 Wiley-Liss, Inc.*[†]

KEY WORDS: beryllium; beryllium sensitization; chronic beryllium disease; copper–beryllium alloy; epidemiology

INTRODUCTION

Population-based surveys for sensitization to beryllium and chronic beryllium disease (CBD) have been conducted since 1987 [Kreiss et al., 1989, 1993a,b, 1996, 1997; Deubner et al., 2001b; Henneberger et al., 2001; Newman et al., 2001]. The beryllium lymphocyte proliferation test (BeLPT), which assesses beryllium-induced proliferation of peripheral blood lymphocytes, is used to identify sensitization [Mroz et al., 1991]. CBD is a disease in sensitized individuals that primarily affects the lungs and is characterized by non-caseating granulomas and interstitial infiltrates, leading to fibrosis. Symptoms are non-specific and include cough,

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shortness of breath, fatigue, and night sweats. Before testing for sensitization became widely used in the early 1990s, identification of CBD was dependent on recognition of symptoms, or significant radiographic and/or pulmonary function changes. Subsequent to the utilization of the BeLPT, many individuals are now diagnosed with subclinical disease.

Prevalence of sensitization in cross-sectional surveys of exposed workers has ranged from 2% to 12%; further clinical evaluation has identified CBD in 49% to 100% of workers with an abnormal BeLPT [Kreiss et al., 1989, 1993a,b, 1996, 1997; Henneberger et al., 2001; Newman et al., 2001].

Copper–beryllium alloys, which generally contain 2% or less beryllium, are the most commonly used form of beryllium [Kolanz, 2001]; they are used in the electronics, automotive, defense, and aerospace industries because of properties such as strength, electrical and thermal conductivity, and resistance to corrosion [Stonehouse and Zenczak, 1991]. This study presents the first plant-wide medical survey of a facility that primarily handles copper–beryllium alloys. Other published studies have described plants that have processed beryllium hydroxide, beryllium oxide, ceramics made from beryllium oxide, and pure beryllium metal; these facilities may or may not have also processed various alloys of beryllium. Beryllium sensitization or CBD associated with copper–beryllium alloy work has been identified previously [Israel and Cooper, 1964; Lieben et al., 1964; Lieben and Williams, 1969; Kreiss et al., 1997; Yoshida et al., 1997; Balkissoon and Newman, 1999; Tarlo et al., 2001]. In some surveys, known or suspected concurrent exposure to other beryllium-containing materials has made it difficult to identify specific risk from processing copper–beryllium alloys [Lieben et al., 1964; Kreiss et al., 1997].

The plant, which had employed more than 500 workers over its history, was located in the eastern United States and processed copper–beryllium alloys and very small quantities of nickel–beryllium alloys. The plant converted semi-finished copper–beryllium alloy strip and wire into finished strip, wire, and rod. In 1999, a plant employee was diagnosed with CBD, the second such case in the more than 40-year operational history of this facility. The company subsequently surveyed the entire workforce, offering all current employees the BeLPT and medical and work history interviews, with clinical follow-up for those who were found to be sensitized to beryllium. Airborne beryllium levels in various processes and jobs were determined from historical sampling data, collected between 1969 and 2000.

Using this information, we addressed the following research questions:

1. What were the prevalences of sensitization and CBD at this copper–beryllium alloy facility?
2. Were prevalences of sensitization and CBD related to work categories, or to specific processes or jobs within those categories?
3. If work categories, or processes or jobs within those categories, were found to be associated with higher prevalences of sensitization or CBD, then did they also have higher airborne beryllium levels?

MATERIALS AND METHODS

Study Population

All workers employed at the plant during the period December 1999 through April 2000 were eligible to participate; the employee diagnosed with CBD in 1999 was included. The study protocol was reviewed and approved by the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH), and written informed consent was obtained from each study participant.

Evaluation for CBD

Between January and June 2000, the company's medical staff collected initial blood samples for the BeLPT from all employees not known to have CBD. Follow-up (repeat or confirmatory) blood testing and clinical evaluation for employees with abnormal test results were completed by August 2000. All initial blood samples were collected in duplicate in heparinized tubes, and the split samples were sent via overnight delivery to separate laboratories. Mononuclear cells were separated from other blood components, suspended in tissue culture media, and stimulated with a positive mitogen control (phytohemagglutinin), either of two antigen controls (tetanus toxoid or candida), and three concentrations of beryllium sulfate ($BeSO_4$) or three concentrations each of $BeSO_4$ and beryllium fluoride (BeF) (1, 10, and 100 micromolar (μM)). The beryllium-stimulated cells were cultured for five and either six or seven days, radiolabeled with tritiated thymidine, and harvested. A stimulation index (SI) for each of the beryllium concentration/duration combinations was calculated as the ratio of counts per minute for stimulated relative to unstimulated cultures. A BeLPT was determined to be ‘‘abnormal’’ (if at least two of the SIs were $\geq$3.0), ‘‘borderline’’ (if a single SI was $\geq$3.0), or ‘‘normal’’ (if no SIs were $\geq$3.0). The company drew additional blood and the test was performed again for confirmation of a single abnormal test result (e.g., 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 considered a participant to be ‘‘sensitized’’ to beryllium if two or more separate BeLPTs were found to be abnormal. We defined those participants who did not meet this definition as ‘‘non-sensitized.’’

Sensitized employees were referred to one of the authors (MDR) at the Hospital of the University of Pennsylvania

(HUP) for clinical evaluation, including bronchoalveolar lavage (BAL) and fiberoptic bronchoscopy for collection of transbronchial biopsies. BAL cells were examined for lymphocytosis, and a lymphocyte proliferation test was performed on the BAL fluid (BALLPT) to determine if there was a lung response to beryllium stimulation. Biopsy specimens were collected from the right upper and lower lobes and placed in Bouin's solution. The HUP Department of Pathology and Laboratory Medicine microscopically evaluated the biopsy samples for granulomas, mononuclear cell interstitial infiltrate, and fibrosis. The clinical evaluation also included an additional BeLPT, pulmonary function testing (spirometry, lung volumes, diffusion, and airways resistance), pulmonary exercise testing (ventilatory and cardiovascular response), and chest radiography (standard postero-anterior and lateral chest films, and high-resolution computerized tomography, evaluated by a radiologist). We considered a sensitized individual to have "CBD" if granulomas or other pathologic abnormalities consistent with that diagnosis were identified.

Medical and Work History Questionnaires

Trained occupational health nurses from the company conducted medical and work history questionnaire interviews.

Medical questionnaire

The medical questionnaire comprised a modified version of the American Thoracic Society respiratory symptoms questionnaire [Ferris, 1978], a series of questions on work-related dermatological conditions, and questions to ascertain demographic information. We classified individual respiratory symptoms from positive responses to questions on cough, phlegm, wheeze apart from colds, and breathlessness. We categorized self-reported skin problems as ever/never: rash from exposure to pickling fluids; rash from exposure to coolants; rash related to other work; or presence of ulcers or small craters in skin. We reduced smoking history to ever- versus never-smoker.

Work history

The work history interview included questions about beryllium work-related job history and plant-specific occupational exposures. Study participants described, for the period of time since they started work in the plant, each process or job at which they had worked, and the start and end dates. Employees were also asked to recall any events during which they were not wearing respiratory protection that may have resulted in high beryllium exposures. Reports of very frequent (e.g., daily) exposures were excluded, as we considered those to be a customary part of that job. Employees were asked about two types of potential high exposure activities: clean-up, including area cleaning, materials spill clean-up, and decontamination of materials or equipment leaving the plant; and shutdown maintenance. Generally, at this facility the former activities occurred more frequently, and the latter took place once a year. Because this facility handled mostly copper–beryllium alloys, employees were also asked about potential exposure to other forms of beryllium, such as may have occurred from work at other facilities within this company, and/or any exposure to beryllium that took place outside employment at this company. We calculated "time since hire" as the interval between the participant's hire date and the date of the first blood draw or, for non-participants, January 2001. We calculated "time since first exposure" as the interval between date of first reported exposure to beryllium and the date of the first blood draw.

Characterization of Beryllium Exposure

Summary of work histories

We divided all work at the plant into the following work categories: production, production support, and administration (Fig. 1). We further subdivided production work by the type of metal that was processed: rod and wire, and strip metal. Specific processes or jobs within rod and wire production included: wire annealing and pickling, wire drawing, straightening, point and chamfer, rod and wire packing, die grinding, and, in the past, wire rolling. Strip metal production comprised these processes or jobs: strip rolling, slitting, strip pickling, strip annealing, degreasing, shipping and receiving, inspection, and, in the past, salt baths, cadmium plating, welding, and deburring. Production support jobs included mechanical maintenance, quality assurance (the metallurgy laboratory), and wastewater treatment. Administration was divided into staff primarily working within the plant (e.g., supervisory staff) and personnel who mostly worked within the office areas. To determine whether any experience in a given work category (or process or job) contributed to risk, we compared the subgroup of those "ever" employed in a work category or process with the subgroup who "never" worked there.

Airborne beryllium exposure

The company had collected samples for exposure to total mass of airborne beryllium as far back as the 1960s. We examined historical records and located reliable exposure information from data collection sheets, monthly reports, and/or quarterly reports for the period 1976 through 2000, with some additional data from 1969 and 1972. Most early samples were area and task samples; the company began regular full-shift breathing zone ("personal") sampling for total mass of beryllium in 1995, although limited numbers of

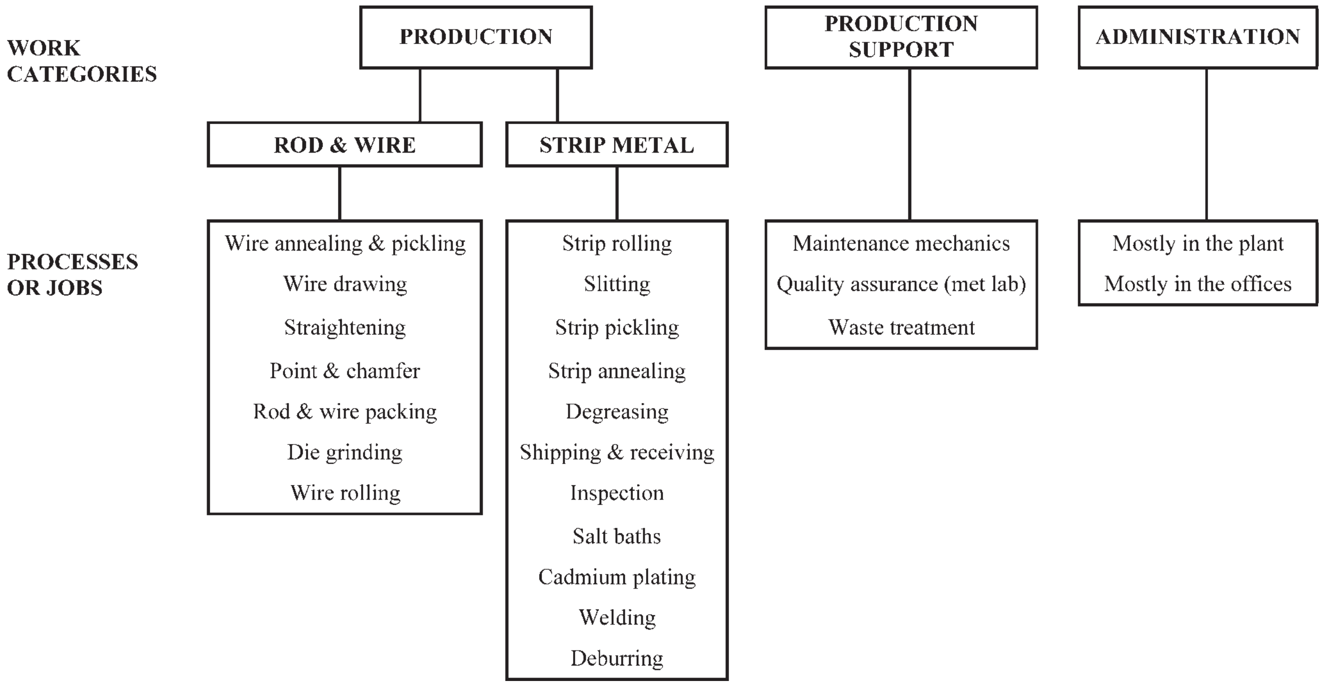

FIGURE 1. Work categories, processes, and jobs used in analyses for risk of sensitization and chronic beryllium disease (CBD).

these samples were also taken at a few processes in 1977 and 1978.

General area samples had been collected using stationary high-volume samplers located near the process. The average flow rate was 300 liters per minute (lpm) and sample duration was usually 30 minutes. Lapel samplers were used to collect personal samples, and the sampler was clipped to the employee's collar in the vicinity of his or her breathing area. Personal samples were taken with a typical sampling train used for the assessment of metal dust exposure [NIOSH, 1994]. Sample duration was customarily full-shift, or 8 hours, with a flow rate of 2 lpm. Short-duration high-volume (SD-HV) breathing zone task samples [Kolanz et al., 2001] were also collected at a limited number of processes. The average flow rate was 300 lpm and sample duration was usually 3 to 5 minutes.

All samples were analyzed for total mass of beryllium by either flame or graphite furnace atomic absorption spectrophotometry, and analytical results were presented in micrograms of beryllium per cubic meter ($\mu g/m^3$). When laboratory results were reported at or below the limit of detection (LOD), which ranged from 0.10 to 0.008 μg, we assigned a value equal to half the LOD to those samples. We partitioned beryllium sample data by work category and, within each of those categories, by individual processes or jobs.

Statistical Analysis

We used SAS software [SAS Institute, 2000] to analyze the data; categorical outcomes were evaluated with the continuity-corrected χ^2 and Fisher's exact tests, and continuous outcomes were evaluated with the Wilcoxon rank-sum (two samples) and Kruskal–Wallis (more than two samples) tests. We used the kappa statistic to calculate interlaboratory agreement on paired samples [Cohen, 1960], with agreement between laboratories defined as poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and excellent (0.81–1.00) [Landis and Koch, 1977]. For airborne beryllium total mass exposure data, we calculated descriptive statistics, including central tendency and characteristics of the upper tail of the distribution. For the latter, we calculated the upper 95% confidence limit (UCL) for the 95th percentile of the distribution (the upper tolerance limit (UTL)) and for the fraction of the distribution that exceeded two occupational exposure limits (OEL) [Hewett and Ganser, 1997]. Exceedance fractions provide information on the proportion of the distribution that exceeds a given exposure value. The uncertainty around point estimates is described by the 95% UCL. A set of exposure measurements is generally considered to be acceptable if the exceedance fraction is less than or equal to 5% [Comite Europeen de Normalisation, 1995]. We used both 0.05 and 0.10 levels of significance; *P* values for results reported as non-significant are greater than 0.10.

RESULTS

Study Population

Of the 185 employees invited to participate, 153 (83%) completed the interviews and 152 provided blood samples for the BeLPT. (The employee previously diagnosed with CBD was not retested.) Most participants were male (89%, 136/153) and white or white Hispanic (95%, 146/153); their median age was 44 years (range 22–68). Non-participants were not different with respect to gender (88% male, 28/32) or race (94% white, 30/32), but were slightly older (median age 48, range 31–65, not significant (n.s.)). Median time since hire was 16 years (range <1–45) for study participants; 11 participants also reported beryllium exposure prior to hire (range 1–16 years of additional time since first exposure). Non-participants had a longer tenure at the plant (median 19 years, range 1–40) compared to participants (n.s.).

Sensitization and CBD

Among the 152 participating employees without known disease at the time of the survey, 17 had two or more abnormal BeLPT results. Eight had at least one abnormal BeLPT from each of the two testing laboratories; an additional nine had two or more abnormal results from a single lab only, which was the same laboratory in all cases. Sixteen of the 17 with multiple abnormal BeLPT results consented to further clinical evaluation for CBD. Four (25% of 16 evaluated) were found to have CBD as diagnosed by identification of granulomas on lung biopsy. In those diagnosed with CBD, all had a positive BALLPT and three had an increased percentage of lymphocytes in BAL fluid. No pathologic changes (granulomas, interstitial infiltrate, or fibrosis) were evident in those not diagnosed with CBD. One employee at this facility had been diagnosed with CBD in the year prior to the survey; BeLPTs performed during this individual's clinical evaluation for CBD were abnormal. Another employee, who had two normal BeLPTs during the survey, complained of pulmonary symptoms in the months immediately after the survey. Subsequent BeLPTs were abnormal, and the worker was diagnosed with CBD based on lung biopsy. All six individuals diagnosed with CBD had no significant lung function changes and no fibrosis apparent in biopsies or on chest radiographs.

For quality control purposes, we compared BeLPT results from separate laboratories for both split samples (initial blood draw) and for all samples (Table I). Laboratory "A" performed a total of 252 BeLPTs, comprising 152 initial blood draws and 100 redraws. Laboratory "B" performed 209 BeLPTs, comprising 152 initial blood draws and 57 redraws. Inter-laboratory variability among the split samples from the initial blood draw was poor (kappa = 0.20). Overall, Laboratory A was twice as likely to have reported an abnormal result, both overall ($P < 0.05$) and on initial draw (n.s.). Laboratory A was nearly five times more likely to have reported either a borderline or uninterpretable test result, compared to Laboratory B (among all tests, 23% vs. 5%, $P < 0.05$; on first draw, 24% vs. 5%, $P < 0.05$). On initial blood draw, of the four employees eventually diagnosed with CBD, one had an abnormal and one had a borderline BeLPT at Laboratory A; all four with CBD had abnormal results on initial draw at Laboratory B. Of eight workers with abnormal BeLPTs from both labs, four were found to have CBD (50%); none of the nine with abnormal results only from Laboratory A were found to have CBD. Based on these trends, we concluded that Laboratory A likely experienced some BeLPT-related technical problems during the time of this survey.

Based on our interpretation of the trends in laboratory results presented above we excluded the nine employees with multiple abnormal BeLPTs solely from Laboratory A from analyses for risk, from both the numerator and denominator. Thus, for purposes of risk factor analysis for CBD, we included the six known current cases: one diagnosed in the year prior to the survey, four diagnosed during the survey, and one diagnosed after the survey ended (6/144 = 4%). For purposes of risk factor analysis for sensitization, we elected to restrict the group of sensitized workers to the eight employees with abnormal BeLPTs from both laboratories (four of whom had CBD), together with the two additional workers with CBD (10/144 = 7%).

We compared the 134 non-sensitized employees (i.e., those who were not defined as sensitized and excluding the nine employees mentioned above) to all ten employees with beryllium sensitization, as well as to these ten workers subdivided by CBD status (Table II). (Case status definitions can be found in "Materials and Methods, Evaluation for CBD.") Most workers, regardless of health status, were male, white, and current or former smokers. The sensitized without CBD were younger than the non-sensitized (35 years vs. 44 years,

TABLE I. Beryllium Lymphocyte Proliferation Testing (BeLPT) Results by Laboratory

Test result	Number of tests		Abnormal test result[a]		Borderline test result[a]		Uninterpretable test result[a]	
Laboratory	A	B	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
All tests	252	209	16*	8	14*	3	9*	2
First draw	152	152	7	4	11*	4	13*	1

*$P < 0.05$.
[a]See "Materials and Methods" for definitions.

TABLE II. Characteristics of Employees at a Copper–Beryllium Alloy Facility

Characteristic	Non-sensitized (n = 134)	Sensitized[a] (n = 10)	Chronic beryllium disease (CBD)[a] (n = 6)	Sensitized (not CBD)[a] (n = 4)
Gender (% male)	89	90	83	100
Race (% white)	96	100	100	100
Ever smoked cigarettes (%)	56	70	67	75
Median age (years)	44	42*	44	35**
Median years since first exposure (range in years)	17 (0–45)	8 (0–27)	16 (5–27)	1** (0–5)

*$0.05 < P < 0.10$.
**$P < 0.05$.
[a]All comparisons were to employees defined as non-sensitized. See "Materials and Methods" for definitions.

$P < 0.05$) and had fewer years since first reported exposure to beryllium (1 year vs. 17 years, $P < 0.05$). Employees with CBD were similar to the non-sensitized with respect to age and years since first beryllium exposure. One of the employees with CBD had reported beryllium exposure prior to work at this facility. Thirteen percent (2/15) of workers with one year or less since first reported beryllium exposure were sensitized.

Respiratory Symptoms and Skin Problems

Employees found to be sensitized to beryllium (including those with CBD) reported levels of respiratory symptoms similar to non-sensitized individuals. Self-reported skin problems associated with exposure to pickling fluids, coolants, or other work, were not related to either sensitization or CBD. Participants with CBD were more likely to have reported ulcers or small craters in the skin, compared to employees without disease; two workers with CBD were among the five who reported ulcers or small craters, compared to four employees with CBD among 135 with no reported ulcers or craters ($P < 0.05$).

Area- and Process-Related Risk

We first examined work at the plant in each of the four general work categories (production of rod and wire materials, production of strip metal, production support, and administration) (Table III). All six employees diagnosed with CBD had worked in both rod and wire production and strip metal production. However, only in rod and wire production was prevalence of CBD significantly higher ($P < 0.05$) for those having ever worked in that category compared to those who had never worked there. Prevalence of sensitization was also highest in rod and wire production (n.s.).

We then evaluated individual processes or jobs within each of the four work categories (Table III). In rod and wire production, CBD prevalence was elevated among those who had ever worked in the point and chamfer (21% of ever worked, $P < 0.05$), wire annealing and pickling (10%, $P < 0.05$), and wire drawing (10%, $P < 0.10$) processes. Prevalence of sensitization to beryllium was also higher for these processes.

A history of work in strip metal production was not statistically associated with sensitization or CBD, nor was any individual process or job within strip metal production. The work categories of production support and administration, as well as individual processes or jobs within these categories, were also not linked with increased prevalences of sensitization or CBD. No sensitization or CBD was found among administrative staff who only worked in the office areas.

Other Beryllium Exposure

Workers who reported incidents that may have resulted in high beryllium exposures (during which they were not wearing respiratory protection) were more likely to be sensitized; five of the 28 workers who reported high exposure incidents were sensitized, compared to five of 116 who did not report high exposures ($P < 0.05$). Half of those with CBD reported high exposure incidents, compared to 17% of the non-sensitized ($P < 0.10$). All three groups—the sensitized, those with CBD, and the non-sensitized—were equally likely to have taken part in clean-up activities, including area cleaning, materials spill clean-up, and decontamination of materials or equipment leaving the plant; and shutdown maintenance. We also observed no differences among the three groups with respect to exposure to beryllium in previous employment.

Airborne Beryllium Sampling Data

The available measurements for assessing total mass of airborne beryllium, from 1969 to 2000, comprised 650 personal, 4,524 general area, and 815 SD-HV breathing zone samples. Median plant-wide values for personal and general area samples were 0.02 and 0.09 $\mu g/m^3$, respectively. The median for SD-HV breathing zone samples was 0.44 $\mu g/m^3$.

TABLE III. Prevalences of Sensitization and CBD Among Employees at a Copper–Beryllium Alloy Facility by Work Category, and by Process or Job Within Each Category

	Ever worked	
***Work category*: process or job**[a]	**Sensitized (%)**[b] **(n = 10)**	**CBD (%) (n = 6)**
Production: rod and wire	*10 (8/83)*	*7 (6/81)***
Point and chamfer	21 (3/14)*	21 (3/14)**
Wire annealing and pickling	13 (5/40)	10 (4/39)**
Wire drawing	14 (6/44)*	10 (4/42)*
Wire rolling	13 (1/8)	13 (1/8)
Rod and wire packing	10 (5/48)	9 (4/47)
Straightening	8 (2/26)	8 (2/26)
Die grinding	0 (0/3)	0 (0/3)
Production: strip metal	*8 (8/96)*	*6 (6/94)*
Strip annealing	11 (6/53)	8 (4/51)
Strip rolling	11 (6/56)	7 (4/54)
Slitting	8 (5/60)	7 (4/59)
Strip pickling	7 (4/55)	6 (3/54)
Inspection	6 (2/33)	6 (2/33)
Salt baths	4 (1/23)	4 (1/23)
Shipping and receiving	4 (2/47)	2 (1/46)
Welding	0 (0/2)	0 (0/2)
Deburring	0 (0/2)	0 (0/2)
Cadmium plating	0 (0/6)	0 (0/6)
Production support	*7 (4/58)*	*5 (3/57)*
Maintenance mechanics	6 (1/17)	6 (1/17)
Quality assurance (metallurgy lab)	4 (1/26)	4 (1/26)
Wastewater treatment	0 (0/6)	0 (0/6)
Administration	*6 (3/51)*	*4 (2/50)*
Administration (plant)	10 (3/29)	7 (2/28)
Administration (office)	0 (0/26)	0 (0/26)

*$0.05 < P < 0.10$.
**$P < 0.05$.
[a]Summary data for each work category are presented in italics, followed by individual processes or jobs within that category. Within each work category, processes or jobs are sorted by prevalence of CBD for ever worked, with significant associations listed first.
[b]Each fraction is the number of all employees with sensitization who ever worked in that category (or process or job), divided by the total number of employees who ever worked in that category (or process or job). Statistical comparisons are to employees who never worked in that category (or process or job).

Ninety-nine percent of all personal sample measurements were below the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 2.0 μg/m^3 averaged over an 8 hour period [Code of Federal Regulations (CFR), 1971], and 93% were below the Department of Energy's (DOE) action level of 0.2 μg/m^3 for implementation of workplace precautions and increased control measures [CFR, 1999]. All personal sample measurements greater than 2.0 μg/m^3 were from the late 1970s. Ninety-seven percent of the general area sample measurements were below the NIOSH recommended exposure limit (REL) for beryllium of 0.5 μg/m^3 [NIOSH, 1997]. Ninety percent of the SD-HV breathing zone samples were below the OSHA acceptable ceiling concentration of 5.0 μg/m^3, and 97% were below the OSHA acceptable maximum peak above the ceiling concentration of 25.0 μg/m^3 [CFR, 1971].

Among personal samples, the highest levels of beryllium were found in rod and wire production (Table IV). Median values for the four work categories were highest in rod and wire production: 0.06 μg/m^3, compared to 0.02 μg/m^3 for the other three categories. The upper 95% confidence limit for the 95th percentile of the distribution (i.e., the UTL) was much higher in rod and wire (0.68 μg/m^3), compared to strip metal production (0.10 μg/m^3), production support (0.12 μg/m^3), and administration (0.05 μg/m^3). The upper 95% confidence limit for the fraction of the data that exceeded 2.0 μg/m^3 (i.e., the OEL exceedance UCL) was less than 1% in all four work category areas. The analogous OEL exceedance UCL for 0.2 μg/m^3 was 24% in rod and wire production, and 2% or less elsewhere.

Among specific processes or jobs, wire annealing and pickling demonstrated the highest median value (0.12 μg/m^3), UTL (2.32 μg/m^3), and OEL exceedance UCL for 0.2 μg/m^3 (54%); it was the only process for which the OEL exceedance UCL for 2.0 μg/m^3 was appreciable (6%). Among processes with ten or more available measurements, exposures at the wire drawing process were second highest for these same parameters. OEL exceedance UCLs for 0.2 μg/m^3 were also slightly higher in point and chamfer (rod and wire area, 6%) and in strip annealing (7%).

The general area samples comprised the majority of samples collected historically. Among the various work categories, medians for the four groups were generally similar, ranging from 0.02 to 0.10 μg/m^3. The arithmetic mean for rod and wire production (1.75 μg/m^3), however, was much higher than the means for strip metal production, production support, or administration (0.09–0.14 μg/m^3), due to the influence of a few very high measurements. The 95th percentile of the distribution demonstrated a similar pattern, with rod and wire production (1.10 μg/m^3) much higher than either strip metal production (0.30 μg/m^3) or administration (0.20 μg/m^3). (Production support had too few observations to provide a 95th percentile). Among individual processes or jobs, wire annealing and pickling had the highest arithmetic mean (2.77 μg/m^3, compared to <0.01–0.33 μg/m^3 for other processes) and the highest 95th percentile (2.30 μg/m^3, compared to 0.20–1.00 μg/m^3 for other processes with at least ten measurements).

The other total mass exposure data were SD-HV breathing zone samples. The median values for the rod and wire and strip areas were similar (0.46 and 0.40 μg/m^3, respectively). (No SD-HV breathing zone samples were

TABLE IV. Airborne Beryllium at a Copper–Beryllium Alloy Facility—Personal Sample Total Mass Exposure by Work Category, and by Process or Job Within Each Category—1977–2000

***Work category*:** process or job[a]	n	Range ($\mu g/m^3$)	Median ($\mu g/m^3$)	95th percentile UTL[b] ($\mu g/m^3$)	OEL exceedance UCL (%)[c] 2.0 $\mu g/m^3$	OEL exceedance UCL (%)[c] 0.2 $\mu g/m^3$
Production: rod and wire	*210*	*<0.01–7.80*	*0.06*	*0.68*	*<1*	*24*
Point and chamfer	49	<0.01–1.58	0.03	0.20	<1	6
Wire annealing and pickling	78	0.01–7.80	0.12	2.32	6	54
Wire drawing	30	0.01–0.38	0.06	0.32	<1	13
Rod and wire packing	18	0.02–0.17	0.03	0.11	<1	1
Straightening	34	0.01–0.22	0.03	0.17	<1	5
Die grinding	1	—	0.02	—	—	—
Production: strip metal	*320*	*<0.01–0.72*	*0.02*	*0.10*	*<1*	*<1*
Strip annealing	71	<0.01–0.72	0.02	0.21	<1	7
Strip rolling	55	<0.01–0.31	0.02	0.09	<1	<1
Slitting	33	<0.01–0.23	0.02	0.16	<1	4
Strip pickling	73	0.01–0.28	0.03	0.14	<1	3
Inspection	30	<0.01–0.12	0.02	0.05	<1	<1
Shipping and receiving	58	0.01–0.12	0.02	0.04	<1	<1
Production support	*52*	*<0.01–0.33*	*0.02*	*0.12*	*<1*	*2*
Maintenance mechanics	44	0.01–0.10	0.02	0.07	<1	<1
Quality assurance (metallurgy lab)	5	0.01–0.13	0.06	—	—	—
Wastewater treatment	3	0.08–0.33	0.11	—	—	—
Administration	*68*	*<0.01–0.11*	*0.02*	*0.05*	*<1*	*<1*
Administration (plant)	57	<0.01–0.11	0.02	0.05	<1	<1
Administration (office)	11	<0.01–0.06	0.01	0.09	<1	<1

[a]Summary data for each work category are presented in italics, followed by individual processes or jobs within that category. No data were available for: wire rolling, salt baths, welding, deburring, and cadmium plating.
[b]95th percentile upper tolerance limit (UTL)—upper 95% confidence limit about the 95th percentile of the distribution.
[c]Occupational exposure limit (OEL) exceedance fraction upper confidence limit (UCL)—upper 95% confidence limit for fraction of samples that exceed a given OEL.

taken in production support or administration.) However, the 95th percentile was higher in rod and wire (19.3 $\mu g/m^3$) compared to strip metal (6.3 $\mu g/m^3$). Two processes provided the majority of SD-HV breathing zone samples: wire annealing and pickling in the rod and wire area, and slitting in strip operations.

DISCUSSION

Results from this population-based cross-sectional study demonstrated prevalences of sensitization (7%) and CBD (4%) associated with copper–beryllium alloy processing comparable to those found in beryllium production (7% sensitization, 5% CBD; Kreiss et al., 1997) and beryllium oxide ceramics facilities (6% and 10% sensitization, 4% and 3% CBD; Kreiss et al., 1996; Henneberger et al., 2001) with higher average airborne beryllium exposures. As in other studies, specific processes or jobs were identified that conferred apparent increased risk. At this facility, statistically significant relationships were limited to the rod and wire production area, and included the point and chamfer, wire annealing and pickling, and wire drawing processes. Although median values were very low across all areas of the plant, airborne beryllium measurements in the upper tail of the distribution were higher in the rod and wire production area; the individual process with the highest measurements was wire annealing and pickling. Approximately one-fourth of personal sample exposures in the rod and wire production area may have exceeded the DOE action level of 0.2 $\mu g/m^3$. None of the individual processes or jobs where fewer than 5% of samples may have exceeded 0.2 $\mu g/m^3$ had a statistically significant risk of either sensitization or CBD. The process-related risks we identified provide an opportunity to further investigate beryllium exposure metrics that may better predict health hazards than historical total mass airborne beryllium measurements.

We also found an elevated prevalence of sensitization among employees with one year or less since first exposure (13%), none of whom had CBD. Other studies have also identified individuals who have developed sensitization within months of first exposure. A survey of workers exposed to beryllium oxide revealed that 16% of workers with one year or less since first exposure were sensitized [Henneberger et al., 2001]. Among a group of new employees at a beryllium machining plant who were tested within one year of hire, 7% were found to be sensitized [Newman et al., 2001].

The plant layout, in which the rod and wire production processes had been segregated from strip metal production since the late 1980s, suggested that the increased risk of sensitization and disease associated with work at several rod and wire processes could have originated from a single source. The wire annealing and pickling process area had the highest airborne beryllium measurements and may have been a source of exposure for work in other rod and wire processes located nearby.

Since the late 1980s, wire annealing and pickling had been sampled as a single process, which made it difficult to discriminate which of the two component processes may have been the more important source of exposure. The strip annealing and strip pickling processes were not co-located and had always been sampled separately. Airborne mass exposure levels, as well as prevalences of sensitization and CBD, were higher in wire annealing and pickling, compared to the analogous processes for strip metal. In many respects, annealing wire and annealing strip in nitrogen–hydrogen atmospheres were similar processes, as were wire pickling and strip pickling. However, process differences between annealing the two forms suggested that wire annealing may have been more important than wire pickling as a source of beryllium exposure. These differences included the relative level of containment and the way in which the material was handled after annealing. Strip annealing was a completely enclosed process, in which a coil of strip metal was unrolled, fed into the furnace, and rerolled as it exited the furnace. In wire annealing, wire coils were inserted and retrieved through a large furnace door, without unrolling or rerolling the coil. Upon removal, the coils were quenched with water, which was not part of the strip annealing process. Oxygen exposure, both when the furnace was opened and when coils were quenched, led to formation of a loose black oxide scale when some alloy formulations were removed from the furnace [Shewmon, 1969]. Subsequent handling of wire coils dispersed this oxide scale into the air and onto surfaces. Shortly after the survey, when it became apparent that elevated levels of sensitization and CBD were associated with wire annealing and pickling, this operation was enclosed with walls and placed under negative pressure relative to adjacent areas. Access to this area was restricted, and powered-air purifying respirators, protective overgarments, and gloves were required for entry.

Although the number of administrative employees identified as office personnel was relatively small ($n = 26$), it is important to note that none were found to be sensitized or to have CBD. Office personnel in this facility included plant management, human resources, secretarial staff, accountants, engineers, and production planners. Although most of their time was spent in the office areas, office personnel periodically entered production areas. Similarly, production employees accessed the office areas. No systems were in place to prevent migration of beryllium from production areas into support areas. Other plant-wide studies have identified CBD among non-production groups of workers [Kreiss et al., 1993a, 1996, 1997; Henneberger et al., 2001], although administrative or office groups in those reports may have been defined differently and may have included workers we described as ‘‘administration—plant area’’ workers.

We found no relationship between self-reported respiratory symptoms and sensitization or CBD in this facility. We did find a relationship between self-reported ulcers or small craters in the skin and CBD. However, while these skin problems could have been due to beryllium exposure, they could alternatively have been due to concurrent exposure to acids or caustic materials. We also have no information about the temporal order of development of these conditions; it is unknown whether the ulcers or small craters predated development of CBD, occurred simultaneously, or arose subsequent to CBD. Prior research among beryllium workers has not found a significant relationship between beryllium-related skin problems and either sensitization or CBD [Kreiss et al., 1996, 1997; Henneberger et al., 2001].

Potential Limitations of This Survey

This plant had a relatively small number of employees, 83% of whom participated, which limited statistical power to detect differences among groups. The comparatively small number of employees in our ‘‘administration—office area’’ group, in which no sensitization or CBD were found, raises the possibility that the true risk among this group may not be zero.

There are several ways in which we could have misclassified exposure. Since we did not know when affected individuals' sensitization or CBD first developed, we based our identification of higher-risk categories or processes on having ever worked in each category or process. We may therefore have included some work that may have been performed after development of sensitization or CBD. Many employees had worked at multiple jobs during their employment, which ranged from a few months to 45 years. Complex work histories may have resulted in some workers neglecting to mention one or more jobs during the work history interview.

Eleven participants also reported that they had had beryllium exposure prior to hire; ten of these eleven had worked elsewhere in the beryllium industry, and one had worked with beryllium in a college research laboratory. All had worked with beryllium alloys, although four also reported possible exposure to other chemical forms, such as pure beryllium metal or beryllium oxide, because they worked at facilities where other forms were handled. We did not attempt to include such prior exposure in our analyses. One among this group was found to have CBD in this study; the employee's earlier work was with copper–beryllium alloys in a plant with processes similar to the present facility, but which also performed prior production processes that included hot rolling and melting and casting.

Employees' respirator use was limited, mostly to specific tasks where high exposure had been found or could potentially occur; these types of tasks typically took place on an intermittent basis, for example, during the plant's annual shutdown maintenance. Thus, we believe it unlikely that we misclassified exposures by not considering respirator use.

It is also possible that we misclassified sensitization or CBD status. The technical problems that we believe occurred at one of the laboratories that performed BeLPTs for this study led us to remove a group of nine employees with multiple abnormal BeLPTs (only from this laboratory) from our analyses of risk for sensitization. However, additional subsequent BeLPTs performed on this group of nine employees supports our contention that they were unlikely to be truly sensitized. No abnormal BeLPT or BALLPT results were found among eight of the nine during testing for sensitization that accompanied clinical evaluation for CBD; one of the nine refused this evaluation. In addition, in the years following the survey the company conducted follow-up testing for sensitization on eight of the nine; one employee, not the one who refused clinical evaluation, had left employment prior to any follow-up testing. None of the nine had been relocated to different work environments after this survey. In this follow-up testing, no abnormal BeLPTs were found. However, the possibility of transient immunoresponsiveness to beryllium may merit exploration.

Inter- and intra-laboratory variability in the BeLPT has long been recognized [Kreiss et al., 1997; Deubner et al., 2001a]. Epidemiologic studies that use the BeLPT to identify sensitization often use split samples on the initial blood draw to maximize the likelihood of identifying all sensitized individuals and minimize the likelihood of false negative results. On the other hand, false positive results can also occur, which has led to the common practice of requiring confirmation of a single abnormal test result. Over time in surveillance of beryllium-exposed workforces, most of the laboratories in the United States who perform this test have had one or more months—long periods of aberrant results. Clues to quality assurance breaches include failure to re-identify abnormal tests in known CBD patients with previous confirmed abnormal BeLPTs; high rates of abnormal results not corroborated by repeat tests, an alternate laboratory, or anticipated proportion of abnormals on clinical evaluation; and high rates of uninterpretable or borderline results. Laboratory A now uses statistical–biological positive criteria for interpretation of test results as abnormal [Frome et al., 2003], and this method accounts for internal variability.

Excluding the nine with questionable test results did not affect our overall conclusions. When we re-analyzed the data including these nine employees, prevalences of sensitization in work categories paralleled the findings for those with abnormal results from two labs (n = 10): rod and wire = 18% (16/91, $P < 0.05$), compared to 10% (8/83); strip metal = 15% (16/104, n.s.), compared to 8% (8/96); production support = 10% (6/60, n.s.), compared to 7% (4/58); and administration = 8% (4/52, n.s.), compared to 6% (3/51). However, with respect to median years since first exposure, the nine we excluded (16 years) were not similar to the sensitized without CBD (1 year), but were similar to employees with CBD and to the non-sensitized (16 and 17 years, respectively—see Table II).

A cross-sectional study such as this one provides information about a single point in time and is likely to underestimate true disease burden in a population. Regular surveillance has been demonstrated to identify new cases [Newman et al., 2001], and follow-up of the workers in this study will enable a better understanding of risk associated with beryllium exposure.

Summary

The prevalences of beryllium sensitization and CBD in this copper–beryllium alloy facility were comparable to prevalences associated with work at other beryllium facilities with higher overall airborne beryllium exposure concentrations, and highest apparent risk was associated with work in rod and wire production. This was the area most likely to exceed the DOE action level of 0.2 $\mu g/m^3$. Areas or processes which were unlikely to exceed 0.2 $\mu g/m^3$ more than 5% of the time appeared to have lower risk of either sensitization or CBD.

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