

Efficacy of a Program to Prevent Beryllium Sensitization Among New Employees at a Copper-Beryllium Alloy Processing Facility

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SYNOPSIS

Objectives. In 2000, 7% of workers at a copper-beryllium facility were beryllium sensitized. Risk was associated with work near a wire annealing/pickling process. The facility then implemented a preventive program including particle migration control, respiratory and dermal protection, and process enclosure. We assessed the program's efficacy in preventing beryllium sensitization.

Methods. In 2000, the facility began testing new hires (program workers) with beryllium lymphocyte proliferation tests (BeLPTs) at hire and at intervals during employment. We compared sensitization incidence rates (IRs) and prevalence rates for workers hired before the program (legacy workers) with rates for program workers, including program worker subgroups. We also examined trends in BeLPTs from a single laboratory.

Results. In all, five of 43 legacy workers (IR=3.8/1,000 person-months) and three of 82 program workers (IR=1.9/1,000 person-months) were beryllium sensitized, for an incidence rate ratio (IRR) of 2.0 (95% confidence interval [CI] 0.5, 10.1). Two of 37 pre-enclosure program workers (IR=2.4/1,000 person-months) and one of 45 post-enclosure program workers (IR=1.4/1,000 person-months) were beryllium sensitized, for IRRs of 1.6 (95% CI 0.3, 11.9) and 2.8 (95% CI 0.4, 66.2), respectively, compared with legacy workers. Test for trend in prevalence rates was significant. Among 2,159 first-draw BeLPTs during 95 months, we identified seven months when high numbers of redraws were required, with one possible misclassification in this facility.

Conclusions. Fewer workers became sensitized after implementation of the preventive program. However, low statistical power due to the facility's small workforce prevents a definitive conclusion about the program's efficacy. These findings have implications for other copper-beryllium facilities, where program components may merit application.

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Beryllium sensitization is a lymphocyte-mediated hypersensitivity response to beryllium exposure and can be detected in peripheral blood with the beryllium lymphocyte proliferation test (BeLPT). Prevalence of beryllium sensitization in cross-sectional studies of exposed workers has ranged from 1% to 14%, with chronic beryllium disease (CBD) diagnosed in 10% to 100% of the sensitized.¹ Despite efforts to comply with the air-level standard established around 1950, sensitization and CBD continue to be documented in every assessed group from facilities using traditional compliance-based approaches to prevention.²⁻¹² However, Cummings et al. recently reported that a comprehensive preventive program reduced beryllium sensitization in new workers during their first years of employment.¹³

The facility examined in this article is located in the eastern United States and first opened in the early 1950s. It receives stock copper-beryllium alloys and limited quantities of nickel-beryllium alloys from a production facility, and converts semifinished copper-beryllium alloy strip and wire into finished strip, rod, and wire. Copper-beryllium alloys, which generally contain $\leq 2\%$ beryllium, are the most commonly used form of beryllium.¹⁴ Published reports have shown that beryllium sensitization and CBD are associated with copper-beryllium alloy work.^{4,11,12,15-20} However, known or suspected concurrent or prior exposure to other sources of beryllium made it difficult to identify specific risk from the processing of copper-beryllium alloys in some studies.^{4,16}

Identified cases of CBD were rare among this workforce during the early years of operation. One case of CBD had been diagnosed among this workforce in the 1970s. In 1999, a second worker was diagnosed with CBD following an abnormal result on a BeLPT conducted to evaluate a new skin condition, prompting new interest in prevention and surveillance efforts at the plant. Prevention efforts at the facility had been limited up to that point because monitored airborne beryllium levels were predominantly below the Occupational Safety and Health Administration (OSHA) standard, suggesting little need for additional engineering controls or personal protective equipment (PPE).

In 2000, the National Institute for Occupational Safety and Health (NIOSH) assisted in conducting the first plant-wide medical survey of this facility. This survey identified 7% (10/144) of workers as sensitized to beryllium, and 4% (6/144) were diagnosed with CBD.¹¹ These prevalence rates were similar to those found in previously studied facilities with higher mean and peak airborne beryllium exposures, including a primary production facility producing pure beryllium metal, oxide powder, and alloys (7% sensitization, 4%

CBD)⁴ and a beryllium oxide ceramics facility, in 1992 (6% sensitization, 4% CBD) and 1998 (10% sensitization, 3% CBD).^{2,6} "Sensitized" was defined as two or more abnormal BeLPT results in these studies, which used similar protocols. These findings helped shape the modified preventive program.

The facility implemented an enhanced beryllium exposure preventive program in June 2000, which sought to reduce exposure through multiple pathways.²¹ The program at this facility included targeted engineering controls designed to lower respiratory exposures, as well as emphasis on reducing clothing/skin contamination and dust migration, improving workplace orderliness and cleanliness, and training and involvement of workers. The 2000 survey identified three high-risk processes, all part of the rod and wire production area, including point and chamfer, wire annealing and pickling, and wire drawing. Based on airborne beryllium concentration data, the wire annealing and pickling process was identified as the likely primary source of beryllium exposure in the rod and wire area.¹¹ This process was enclosed into a restricted access zone (RAZ) in January 2002. Figure 1 shows the evolution of the preventive program from 2000 to 2007.

Medical surveillance efforts were focused on workers hired after the 2000 cross-sectional survey, as new detection of beryllium sensitization in workers previously exposed to beryllium can occur despite cessation of work with beryllium.⁶ Frequent BeLPT testing early in employment tenure was used to evaluate the effectiveness of the preventive program, which is a modified version of the preventive program evaluated in the article by Cummings et al.¹³ We have assessed the program's effectiveness by comparing sensitization rates among two groups of workers: (1) those hired from 1993 through March 2000 and tested in the 2000 survey (legacy workers), and (2) those hired after the start of the preventive program in June 2000 (program workers). We also calculated rates for program worker subgroups hired before and after enclosure of the RAZ (pre-enclosure and post-enclosure program workers, respectively). In addition, we have calculated mean airborne beryllium levels in the facility before and after the preventive program and examined the quality of BeLPT results pre- and post-preventive program implementation.

METHODS

Study population

The study protocol for the 2000 survey was reviewed and approved by the NIOSH Human Subjects Review Board, and written, informed consent was obtained

from each study participant. As the BeLPT was a component of workplace medical surveillance, written, informed consent was not obtained from the program workers at the time blood was drawn. We analyzed only de-identified medical surveillance data under the terms of a confidentiality agreement between NIOSH and the company that owns and operates the facility with Institutional Review Board waivers. Due to the

relatively small number of workers hired at this facility since 2000, descriptive characteristics are limited in this article to avoid identifying individuals.

We included 82 workers hired from June 2000 to November 2006, followed through June 2007, who had undergone at least one interval BeLPT subsequent to their baseline BeLPT in the program group, which was subdivided into the pre-enclosure program group,

Figure 1. Evolution of a program to prevent beryllium sensitization and chronic beryllium disease, before and after enclosure of a restricted access zone, by year and type of control

Year	Control type	Description of control
<i>Pre-enclosure program</i>		
2000	ADM	Smoking/street clothes in production areas banned
2000	ADM	All employees: work clothes/boots kept on-site in locker rooms
2000	ADM	New employees: end-of-shift showering/clothing changes required for production-area male workers
2000	PPE	New employees: polymer gloves required in production areas
2001	PPE	All employees: facility uniforms (long-sleeve shirts, long pants) required for production-area workers, supplied and laundered by company
2001	ADM	Shower trailers installed, but use not required, for women and vendors
2001	ENG	Plastic curtains installed at entrances/exits to production floor
2001	ENG	Die grinder and polisher hooked to local exhaust ventilation
<i>Post-enclosure program</i>		
2002	ADM	Over-shoe booties, lab coats, and polymer gloves required for office workers, visitors, and vendors entering production area
2002	ENG	Wire annealing/pickling process enclosed, put under negative pressure (RAZ)
2002	ADM	Showering before leaving required for RAZ workers
2002	PPE	Required for RAZ workers: PAPRs, company clothing, outer coveralls, rubber boots, and outer gloves
2002	ADM	"RAZ only" locker room installed for changing in/out of RAZ PPE
2002	PPE	Polymer gloves required for all workers on production floor
2002	ADM	Methodic decontamination procedures: included checklist providing item/frequency/method of cleaning information
2002	ADM	Production workers clean work areas 15 minutes/shift and one hour/month
2002	ADM	All wet methods and/or HEPA-filtered vacuums implemented for cleaning
2002	ADM	Workers required to remove gloves/wash hands before eating/drinking/smoking
2002	ADM	Visibly dirty uniforms required to be changed and incident-causing potential clothing contamination to be reported to management
2003	ADM	Eating and drinking in production areas banned
2003	ENG	Tacky mats installed at production area exits
2003	ENG	Boot scrubbers installed at production area exits
2003	ENG	Boot lockers installed in area separate from locker rooms
2003	ADM	Blue/gray zone designations: tell what type of clothing/PPE is required
2004	ADM	Showering before leaving facility required for all maintenance and strip pickling workers, as well as all janitorial, mechanical, electrical, and general contracting vendors who were in production areas
2005	ENG	New operator booth for one rolling mill
2006/2007	ENG	New ventilation systems installed over one annealing furnace, a roll grinder, a slitter, more draw-on ventilation hood over one strip pickler, and new fan installed to increase number of air exchanges from five to 15/hour in RAZ

ADM = administrative

PPE = personal protective equipment

ENG = engineering

RAZ = restricted access zone

PAPR = powered air-purifying respirator

HEPA = high-efficiency particulate air

hired from June 2000 through December 2001, and the post-enclosure program group, hired from January 2002 through November 2006. To achieve a similar potential duration of employment, the comparison group comprised 43 workers participating in the 2000 survey who had been hired between January 1993 and March 2000 (legacy workers). No plant-wide BeLPT testing of workers occurred before the 2000 survey; thus, routine periodic testing was not available to the legacy workers prior to 2000.

BeLPT surveillance: program workers, 2000–2006

Data collection for the program workers was prospective in nature. Beginning in June 2000, new workers had a BeLPT at the time of hire to establish baseline sensitization status. After the baseline BeLPT, testing occurred at intervals of three, six, 12, 24, and 48 months, and then every three years. In October 2006, the three- and 12-month intervals were dropped from the testing schedule as the company felt the six- and 24-month tests were adequately identifying individuals who became sensitized within the first two years of employment. Eighteen individuals were tested following the revised schedule. The facility did not use test results to make decisions concerning workers' employment. Also, some workers were tested just before leaving employment, and one worker submitted BeLPT results after leaving employment. These tests were conducted in the same laboratories used in the company surveillance program, and the results were included in these analyses.

On-site testing was not always conducted at exact intervals. For the three-, six-, and 12-month intervals, tests were completed within approximately one month of the targeted interval. Testing for the 24- and 48-month intervals and those tests occurring after the 48-month interval were measured in ranges of months, including a range of 20–27 months for the 24-month interval, and a range of 37–48 months for the 48-month interval. Other interval ranges included tests falling at 28–36 months, 49–60 months, and 61–75 months.

The use of interval ranges in later months meant that four people had two or more tests fall into the same range. A total of six tests were excluded from the program evaluation analyses for this reason. However, the last test for an individual was never excluded, to accurately calculate person-months, and all excluded test results were normal.

A single commercial laboratory (Lab 1) performed the baseline and interval BeLPTs for new hires using published criteria.²² During the first three months of this surveillance program (June to August 2000), the blood sample for the baseline BeLPT was split and the

second sample was sent to one of two additional laboratories (Lab 2 and Lab 3), which also used published criteria.²² In August 2000, the facility dropped the split sample protocol from the baseline BeLPT testing and sent all first-draw samples only to Lab 1 thereafter. However, initial split samples were occasionally sent to Lab 1 and either Lab 2 or Lab 3, in part to assist in the assessment of laboratory performance.

Throughout surveillance, all non-normal results, including abnormal, negative borderline, and uninterpretable tests,²² were followed-up by sending split samples to Lab 1 and either Lab 2 or Lab 3. A worker with one abnormal test result at Lab 1, followed by a second abnormal test result at any laboratory at any point, met the study definition of beryllium sensitization. Additionally, follow-up testing from a negative borderline or uninterpretable result may have eventually resulted in two abnormal results from any laboratory at any point. Sensitized workers were referred for clinical evaluation for CBD, which included chest x-ray and bronchoscopy with bronchoalveolar lavage BeLPT (BALLPT) and transbronchial biopsy.

BeLPTs: legacy workers, 1993–2000

Data collection for the legacy workers was cross-sectional during the 2000 survey. Between January and June 2000, the company's medical staff collected all initial blood samples in duplicate from all employees not known to have CBD. The split samples were sent overnight to two separate laboratories, Lab 1 and Lab 2, which used similar BeLPT protocols.¹¹ The company drew additional blood to follow up any non-normal results. The individual diagnosed with CBD immediately prior to the 2000 cross-sectional survey was included as a sensitized individual for these analyses. However, to make the legacy workers' testing protocol more comparable to the program workers' testing protocol, only a worker with one non-normal test at Lab 1, followed by confirmed abnormal test results at either laboratory at any point, met the definition of beryllium sensitization. Sensitized employees were referred for clinical evaluation for CBD.

Exclusion criteria

In the legacy group, we excluded six participants from the 2000 survey who had been exposed to beryllium prior to their employment at this facility, as we were comparing program workers to legacy workers exposed only at this facility with a similar duration of exposure. No program workers were known to be exposed to beryllium prior to their employment. Four people from the legacy group were excluded from these analyses, as they had abnormal test results at only one laboratory

(Lab 2) and did not meet our criteria for sensitization, which required an initial non-normal result at Lab 1.

Airborne beryllium levels

During the study period, this facility collected 2,394 airborne beryllium full-shift personal lapel samples. We grouped these data into three time periods—1995 to May 2000, June 2000 to December 2001, and January 2002 to July 2007—to reflect the environment experienced by legacy, pre-enclosure program, and post-enclosure program workers, respectively. Personal lapel samples were attached to workers' shirt collars in the breathing zone at a flow rate of approximately 2 liters/minute for approximately eight hours. Samples were analyzed for the total mass of beryllium by either of two methods: flame atomic absorption spectrophotometry or inductively coupled plasma atomic emission spectrometry. When results were below the limit of detection (LOD), a value equal to half the LOD was assigned. LODs were 0.2 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) for flame atomic absorption spectrophotometry, and 0.02 $\mu\text{g}/\text{m}^3$ for inductively coupled plasma atomic emission spectrometry. We grouped samples into the work categories of administration, production support, and two production-area categories: (1) rod and wire processes and (2) strip processes. We assessed the percent of samples below the LOD, as well as ranges, means, standard deviations, medians, geometric means, and geometric standard deviations. We also examined the number of samples exceeding OSHA's permissible exposure limit of 2.0 $\mu\text{g}/\text{m}^3$ and the number of samples exceeding the Department of Energy's action level of 0.2 $\mu\text{g}/\text{m}^3$.^{23,24}

Statistical analyses

Study subjects. To assess whether the legacy and program groups were similar, we compared race, gender, age at time of hire, work categories, and length of employment at the time of the last BeLPT for the program group, or at the time of the 2000 survey for the legacy workers. We used SAS[®] software²⁵ to analyze the data, examining the results from χ^2 tests for categorical variables, using Fisher's exact tests when appropriate. For continuous variables, we performed nonparametric one-way analyses of variance using median scores to account for unequal variances and non-normally distributed data, and used Kolmogorov-Smirnov two-sample tests for pairwise comparisons among subgroups. We used the Cochran-Armitage test^{26,27} to test for trend among prevalence rates for the legacy and program subgroups. A test for trend was also conducted with the incidence rate (IR) data.²⁸

Work categories included administration workers,

who spent little or no time in the production areas; production support workers, who were not production workers but who spent at least part of a typical day in the production areas (e.g., supervisors, maintenance mechanics, and janitors); and production workers, who operated the production equipment and therefore spent most of a typical day in the production areas. There was little transition among work categories due to job changes or promotions in either the legacy or program group during the study period. However, we assigned workers who did change work categories to the category likely to have the higher beryllium exposure, with production workers likely to have the highest exposure, production support workers being in the second-highest exposure category, and administration workers having the lowest expected exposure.¹¹

As BeLPT data collection was prospective for program workers and cross-sectional for legacy workers, we used two approaches to analyze our data. We calculated sensitization IRs and prevalence rates, as well as incidence and prevalence rate ratios among the various groups.

Sensitization incidence rate comparison. We calculated the sensitization IRs for the program group/subgroups using the sum of the months of sensitization-free employment as the denominator. All interval and follow-up BeLPT results were included for each worker. Workers meeting study criteria for beryllium sensitization were considered sensitization-free until the time of the first non-normal test result. Data for the rest of the cohort were censored at the time of their final BeLPT, whether that final BeLPT was a regularly scheduled interval test or the follow-up test(s) for a non-normal result. For workers tested after termination or rehired after a period of unemployment, the months spent outside company employment were included in the calculation of sensitization-free time. If follow-up testing for negative borderline tests was not obtained, we considered the results to be normal.

As the baseline BeLPT status for the legacy workers was unknown, it was impossible to calculate a true IR for them. As an estimate of incidence, we calculated the number of sensitized workers per person-months, defining sensitization-free time as the time of hire until the 2000 survey BeLPT to estimate person-months. All sensitization comparisons were performed by calculating incidence rate ratios (IRRs). The corresponding 95% confidence intervals (CIs) were determined using a binomial probability model.²⁹

Sensitization prevalence rate comparison. We calculated the prevalence of sensitization for the legacy workers using the number of sensitized workers divided by

the total number of legacy workers tested in the 2000 survey and included in these analyses. To approximate cross-sectional survey data for the program group/subgroups, we estimated the prevalence of sensitization using only the results available from the final interval BeLPT. Therefore, for sensitized program workers who remained employed after learning they were sensitized to beryllium, results were not censored at the time of the first abnormal result, as they were in the IR calculations. Instead, we used the number of workers in the program group/subgroups who would have been identified as sensitized based on each worker's final interval BeLPT divided by the total number of workers in the program group/subgroups to estimate sensitization prevalence and calculate prevalence rate ratios. We calculated 95% CIs using a method that accounts for differing variances in both the numerator and denominator.³⁰

BeLPT analyses

Because we had had reservations about the quality of some laboratory results during the 2000 cross-sectional survey at this facility,¹¹ we examined this issue by evaluating all BeLPT results for this company's employees from August 1999 to June 2007. We included all BeLPT results from this facility, as well as from the company's largest production facility and the facility that was the focus of Cummings et al.'s 2007 publication, generated by Lab 1. We used SAS JMP 5.1³¹ software to create statistical control charts examining both the number of abnormal results and the number of tests requiring redraw (non-normal results) on a monthly basis. We used all available first-draw test results from the laboratory most frequently used during medical surveillance (Lab 1) in an effort to identify months with unexpected results. We defined these as months during which the number of abnormal/non-normal results was greater

than three sample standard errors above the expected number of abnormal/non-normal results, given the laboratory's overall performance.

In addition, we went back to the data from the 2000 survey first-draw split samples to compare both the number of abnormal results and the number of non-normal results between the two laboratories. We used SAS JMP 5.1 software to create a nominal logistic model to examine the differences between the proportion of abnormal results, as well as the proportion of non-normal results, between Lab 1 and Lab 2.

RESULTS

Study subjects

No significant racial or job category differences existed between the legacy group (*n*=43) and program group (*n*=82). However, there were significant differences in gender, age at hire, and length of employment. The legacy group had a significantly higher proportion of female employees than the program group (21% vs. 7%, *p*=0.04). Employee age at hire was significantly different whether analyzed continuously (*p*=0.006) or categorically in four groups (<30, 30–39, 40–49, ≥50) (*p*=0.01), with employees from the program group being older. Length of employment was significantly different between the legacy and program groups (*p*=0.01), with the legacy group having a longer length of employment (Table 1).

Gender, racial, or job category differences did not reach statistical significance when comparing the legacy (*n*=43), pre-enclosure program (*n*=37), and post-enclosure program (*n*=45) groups. However, there were significant differences in age at hire and length of employment (Table 1). The age at hire in the three groups differed whether analyzed continuously (*p*=0.001) or categorically in four groups (<30,

Table 1. Significantly different demographic characteristics among beryllium industry workers hired before and after implementation of a program to prevent beryllium sensitization and chronic beryllium disease

	Legacy workers		Program workers ^a		Pre-enclosure program ^b		Post-enclosure program ^b	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Age at hire (in years)	34.1	33.2	39.4	39.2 ^c	36.5	34.6	41.7	41.9 ^{c,d}
Length of employment (in months)	30.8	28.0	19.3	12.0 ^c	22.9	12.0	16.3	11.0 ^c
Gender (percent female)	21		7 ^c		NS		NS	

^aCompared with legacy workers

^bLegacy vs. pre-enclosure vs. post-enclosure workers

^c*p*≤0.05 compared with legacy workers

^d*p*≤0.05 compared with pre-enclosure workers

NS = not significant

30–39, 40–49, ≥ 50) ($p=0.0055$). Multiple comparison tests were conducted to compare the distributions for the three groups, and showed that the post-enclosure program group was significantly older than both the legacy group ($p=0.0002$) and the pre-enclosure program group ($p=0.02$), though the pre-enclosure program group was not significantly different from the legacy group ($p=0.62$). Length of employment was significantly different among the three groups ($p=0.03$) (Table 1). Multiple comparison tests showed that the difference between length of employment in the post-enclosure program and legacy groups was significantly different ($p=0.0001$). Differences in length of employment between the pre-enclosure and post-enclosure program groups ($p=0.10$), and between the pre-enclosure and legacy groups ($p=0.06$) did not reach statistical significance.

Beryllium sensitization

Table 2 shows the time of hire and interval BeLPT results for six program workers with at least one abnormal BeLPT during surveillance. Worker A (production) had an abnormal BeLPT at three months of employment from Lab 1, which was confirmed with repeat tests at Labs 1 and 3. Worker B (production) had an abnormal BeLPT at six months of employment from Lab 1, which was confirmed with a repeat test at Lab 1. Worker B left employment less than two months after being confirmed as sensitized, and no further follow-up data were available. Workers C (production) and E (production) each had a single abnormal result at 12 and six months of employment, respectively, from Lab 1. These abnormal results could not be confirmed on repeat testing performed during that interval for Workers C or E, or in subsequent intervals for Worker C

at Lab 1, Lab 2, and Lab 3. Worker E left employment before further interval BeLPTs were required. Worker D (production) had an abnormal result at three months of employment, which was confirmed at Lab 1. The confirmatory test was a split sample that resulted in a normal result at Lab 3, and an additional split sample showed normal results from Lab 1 and Lab 2.

One worker, Worker F (production), had one abnormal test result at hire from Lab 1. Because all subsequent BeLPT results from Lab 1, Lab 2, and Lab 3 were normal (two split samples sent to three laboratories, first split sample seven weeks after baseline, second split sample 18 weeks after baseline), this employee was included in the analyses as a non-sensitized worker. Thus, Workers A and B were identified as sensitized pre-enclosure program workers, and Worker D was identified as a sensitized post-enclosure program worker. No program workers were diagnosed with CBD.

Sensitization incidence rate comparison

In the legacy group, five workers (four production, one production support) developed sensitization during a total of 1,323 months of employment, for a sensitization rate of 3.8/1,000 person-months. Three of the program workers developed sensitization during a total of 1,579 person-months for an IR of 1.9/1,000 person-months. The IRR comparing the legacy group with the program group was 2.0 (95% CI 0.5, 10.1).

In the pre-enclosure program group, two workers developed sensitization during a total of 846 months of employment, for an IR of 2.4/1,000 person-months. In the post-enclosure program group, one worker developed sensitization during a total of 733 months of employment, for a sensitization IR of 1.4/1,000 person-months. Thus, the sensitization rate for the

Table 2. BeLPT results of 2000–2006 workers with at least one abnormal BeLPT result during surveillance^a

Test interval	Baseline	1 3 months	2 6 months	3 12 months	4 20–27 months	5 28–36 months
Worker A	N	A (3/3) ^{b,c}				
Worker B	N	N	A (2/2) ^{b,c}			
Worker C	N	N	N	A (1/5)	N	N
Worker D	N	A (2/3) ^{b,c}	N			
Worker E	N	NA	A (1/5) ^b			
Worker F	A (1/3) ^b	N				

^aIf initial results were uninterpretable, interpretable repeat results are shown.

^bNumbers in parentheses indicate the number of abnormal results/total number of interpretable results (including confirmatory results) associated with the interval.

^cSensitization was confirmed in the interval.

N = normal BeLPT result

A = abnormal BeLPT result

NA = not available

legacy workers was 1.6 times greater (95% CI 0.3, 11.9) than that of the pre-enclosure program workers, and 2.8 times greater (95% CI 0.4, 66.2) than that of the post-enclosure program workers. The IRR comparing the pre-enclosure and post-enclosure program groups was 1.7 (95% CI 0.1, 51.0). The worker in the post-enclosure program group with a single abnormal BeLPT result at time of hire contributed four person-months to the IR calculation. Exclusion of that individual did not change the IRs or IRRs. The test for trend among the three groups was not statistically significant ($p=0.32$).

Sensitization prevalence rate comparison

The legacy workers had a sensitization prevalence of 11.6% (5/43). One sensitized worker from the program group (Worker D, post-enclosure program subgroup) would not have been identified as sensitized using only the final interval BeLPT results. Thus, the program workers had a sensitization prevalence rate of 2.4% (2/82), providing a prevalence rate ratio of 4.8 (95% CI 1.0, 23.6).

Both individuals identified as sensitized in the pre-enclosure program workers had abnormal results on their final interval BeLPT, yielding a sensitization prevalence rate of 5.4% (2/37), while the post-enclosure program workers had an estimated prevalence of 0% (0/45). Thus, the legacy workers' prevalence rate was 2.2 times greater (95% CI 0.4, 10.4) than the pre-enclosure program prevalence. The test for trend among the three groups was significant ($p=0.02$).

Airborne beryllium levels

In general, airborne beryllium levels did decrease after the start of the preventive program, although levels experienced by the legacy group (pre-program time period) were very low (Table 3). Rod and wire processes had the highest air concentrations, medians, and upper ends of range for both the pre-program and pre-enclosure program time periods. The number of samples collected during the post-enclosure program time period was too limited to draw meaningful conclusions. However, no individual lapel samples exceeded $2.0 \mu\text{g}/\text{m}^3$ during the pre-program or post-enclosure program time periods. One of 2,211 samples exceeded this standard during the pre-enclosure program period. This sample was collected in the rod and wire area just beside the wire annealing and pickling area. Approximately 17% (27/163) and 2% (36/2,211) of samples exceeded $0.2 \mu\text{g}/\text{m}^3$ during the pre-program and pre-enclosure program time periods, respectively. The majority of those samples occurred in the rod and wire areas: 74% (20/27) and 61% (22/36) during the

pre-program and pre-enclosure program time periods, respectively. The majority of rod and wire samples exceeding $0.2 \mu\text{g}/\text{m}^3$ were collected in the RAZ: 75% (15/20) and 82% (18/22) during the pre-program and pre-enclosure program time periods, respectively. No samples exceeded $0.2 \mu\text{g}/\text{m}^3$ in the post-enclosure program period.

BeLPT analyses

Employees from three of this company's beryllium facilities submitted 2,159 first-draw blood samples to Lab 1 for BeLPT analysis during 95 months (August 1999 to June 2007). We identified four months (months 35, 78, 87, and 90) during which the number of abnormal results was greater than three sample standard errors above the expected number of abnormal results during the eight years included in our analyses, adjusting for the number of tests per month (Figure 2). These four months included the month (87) when the most recently sensitized person was identified as such (Worker D, Table 2). This is the post-enclosure program individual who was included in the IR calculation, but excluded from the prevalence calculation because the last interval BeLPT results were normal. We also identified seven months with high numbers of overall non-normal results (Figure 3). Months 22, 27, 87, and 88 were greater than three sample standard errors above the expected number of non-normal results during the eight years included in our analyses, adjusting for the number of tests per month. Months 21, 24, and 26 were 2.92, 2.93, and 2.91 sample standard errors above the expected number of non-normal results, respectively, but are noteworthy because they occur close to months with unexpectedly high numbers of non-normal tests (months 22 and 27). Two of these seven months (87 and 88) included the two months when Worker D was identified and confirmed as sensitized.

Our results from the nominal logistic models showed that no significant difference existed in the proportion of abnormal results between Lab 1 and Lab 2 (6/152 vs. 11/152, $p=0.21$) during the 2000 survey. However, there was a significant difference between Lab 1 and Lab 2 when comparing the proportion of non-normal results (13/152 vs. 46/152, $p<0.0001$), with Lab 2 having significantly more non-normal results than Lab 1 during the 2000 cross-sectional survey.

DISCUSSION

Previous efforts to prevent beryllium sensitization and CBD within this copper-beryllium facility were limited, as there was believed to be low risk for CBD because the airborne beryllium levels associated with the

Table 3. Airborne beryllium concentrations at a copper-beryllium alloy facility: personal sample total mass exposure, 1995–2001

Time period: process group ^a	N	<LOD (percent)	Range ($\mu\text{g}/\text{m}^3$)	Mean ($\mu\text{g}/\text{m}^3$)	SD ($\mu\text{g}/\text{m}^3$)	Median ($\mu\text{g}/\text{m}^3$)	GM ($\mu\text{g}/\text{m}^3$)	GSD ($\mu\text{g}/\text{m}^3$)
<i>Pre-program (1995 to May 2000)</i>	163	19 (12)	(<0.010–1.580)	0.137	0.195	0.073	0.079	2.833
Rod and wire processes	68	4 (6)	(<0.010–1.580)	0.202	0.261	0.113	0.119	2.837
Wire annealing and pickling	36	0 (0)	(0.054–1.185)	0.252	0.243	0.149	0.172	2.407
Other rod and wire areas	32	4 (13)	(<0.010–1.580)	0.146	0.274	0.078	0.078	2.904
Strip processes	83	10 (12)	(<0.010–0.716)	0.092	0.108	0.060	0.063	2.455
Production support	11	4 (36)	(<0.010–0.333)	0.081	0.093	0.061	0.046	3.215
Administration: office areas	1	1 (100)	<0.01	NA	NA	NA	NA	NA
<i>Pre-enclosure program (June 2000 to December 2001)</i>	2,211	1,309 (59)	(<0.010–2.470)	0.030	0.100	0.015	0.017	2.303
Rod and wire processes	467	127 (27)	(<0.010–2.470)	0.061	0.160	0.029	0.031	2.687
Wire annealing and pickling	96	12 (13)	(0.010–0.594)	0.127	0.113	0.101	0.083	2.835
Other rod and wire areas	371	115 (31)	(<0.010–2.470)	0.044	0.166	0.021	0.024	2.218
Strip processes	908	651 (72)	(<0.010–0.533)	0.018	0.028	0.011	0.014	1.823
Production support	646	386 (60)	(<0.010–1.975)	0.030	0.116	0.012	0.016	2.301
Administration: office areas	190	145 (76)	(<0.010–0.186)	0.016	0.019	0.009	0.012	1.848
<i>Post-enclosure program (January 2002 to July 2007)</i>	20	5 (25)	(<0.010–0.054)	0.017	0.012	0.017	0.013	2.212
Rod and wire processes	4	0 (0)	(<0.010–0.0170)	0.011	0.004	0.009	0.010	1.403
Wire annealing and pickling	0	NA	NA	NA	NA	NA	NA	NA
Other rod and wire areas	4	0 (0)	(<0.010–0.0170)	0.011	0.004	0.009	0.010	1.403
Strip processes	16	5 (31)	(<0.010–0.0540)	0.018	0.013	0.018	0.014	2.392
Production support	0	NA	NA	NA	NA	NA	NA	NA
Administration: office areas	0	NA	NA	NA	NA	NA	NA	NA

^aSummary data for each time period are in italics, followed by process groups within that period.

LOD = limit of detection

$\mu\text{g}/\text{m}^3$ = micrograms per cubic meter

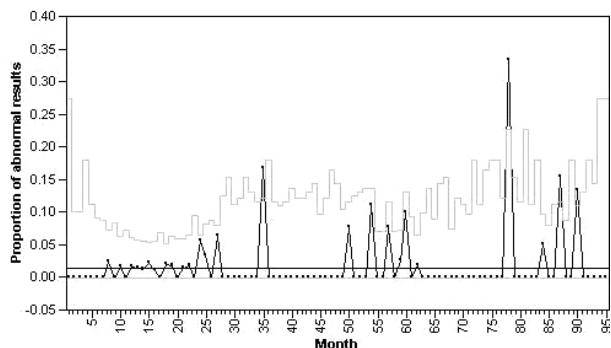
SD = standard deviation

GM = geometric mean

GSD = geometric standard deviation

NA = not applicable

Figure 2. Control chart of the proportion of abnormal BeLPT results vs. total BeLPT results during a 95-month period, Lab 1



Straight black line = average number of abnormal tests during all 95 months
 Upper gray line = upper control limit: three sample standard errors above the expected number of abnormal results for each month, adjusting for total number of tests that month
 Straight gray line = lower control limit
 BeLPT = beryllium lymphocyte proliferation test

copper-beryllium alloy manufacturing operations at this plant were predominantly below the 2.0 µg/m³ OSHA standard.²³ Also, risk was considered low due to the fact that only one worker had ever been diagnosed with (symptomatic) CBD between 1958 and 1999. These prevention efforts focused on maintaining airborne levels of beryllium below the OSHA standard. The 2000 survey showed the ineffectiveness of the traditional compliance-based efforts implemented at this facility in an effort to prevent beryllium sensitization and CBD detectable through BeLPT surveillance. The enhanced preventive program launched in 2000 appears to have been more effective. Comparing program workers with those hired prior to the preventive program implementation, we found a reduction in sensitization during the early years of employment. Although these results were not statistically significant, likely due to a lack of power related to the small sample size, they warrant consideration, especially in light of the significant results obtained at the beryllium ceramics facility.¹³

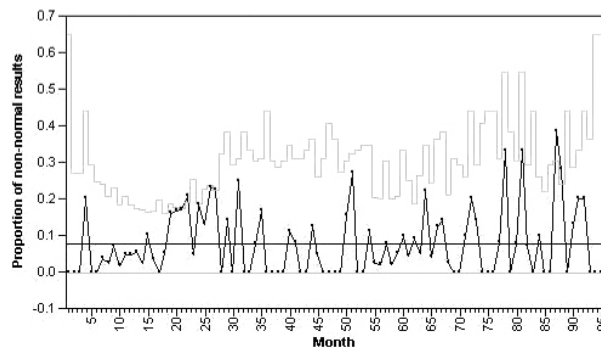
These results complement those found at this company's beryllium oxide ceramics manufacturing facility,¹³ to which the company's enhanced preventive program was also applied.²¹ Both facilities' preventive programs included multiple components that may have contributed to the program's efficacy. Components common to both facilities include improved workplace orderliness and cleanliness, enhanced dermal protection in the form of polymer gloves and long-sleeve uniforms, dust migration control measures (e.g., tacky

mats at entrances/exits and company clothing and boots that do not leave the facility), administrative controls (e.g., routine decontamination procedures in work areas, limiting airborne beryllium concentrations through engineering upgrades, such as the enclosure and ventilation of high-risk processes to reduce airborne exposures to predominantly <0.2 µg/m³), and extensive training and involvement of workers.

The concern that sensitization to beryllium might occur as a result of transdermal exposure led to the introduction of dermal protection measures at this facility. It has previously been shown that skin exposure to soluble beryllium salts can induce sensitization experimentally.³² More recently, researchers have demonstrated that fine (non-beryllium) particles can penetrate human skin with motion, and that topical application of relatively insoluble fine beryllium oxide particles induced sensitization in mice.³³ The intermediate decline in sensitization rates from the legacy workers to the pre-enclosure program workers provides some support for the possible role of dermal exposure in sensitization. The preventive measures experienced by the pre-enclosure program workers consisted mainly of particle migration control (e.g., using tacky mats and boot scrubbers), the separation of production and nonproduction areas, and the use of dermal protection (e.g., polymer gloves and company uniforms with long-sleeve shirts and long pants) (Figure 1).

There were differences in the application of the enhanced preventive program in the two facilities based on facility-specific process-related risks,^{2,6,11} materials

Figure 3. Control chart of the proportion of non-normal BeLPT results vs. total BeLPT results during a 95-month period, Lab 1



Straight black line = average number of tests requiring redraw during all 95 months
 Upper gray line = upper control limit: three sample standard errors above the expected number of abnormal results for each month, adjusting for total number of tests that month
 Straight gray line = lower control limit
 BeLPT = beryllium lymphocyte proliferation test

and manufacturing processes, and the ability to maintain airborne beryllium levels below the company's own action level of $0.2 \mu\text{g}/\text{m}^3$ with engineering controls. The most notable difference is the use of respiratory protection, which is required in all production areas in the beryllium oxide ceramics facility, but only in the wire annealing and pickling area at the copper-beryllium facility. Although half-mask respirators are worn during some maintenance work at the copper-beryllium facility, the vast majority of employees do not wear any form of respiratory protection due to very low airborne beryllium concentrations.

In general, airborne beryllium concentrations decreased after the start of the preventive program but were still highest in the rod and wire area. These findings led to the enclosure of the wire annealing and pickling process. Unfortunately, post-RAZ lapel sample data were sparse. Only four samples were taken in the rod and wire area after the enclosure. These samples showed airborne beryllium concentrations of 0.0170 , 0.0087 , 0.0080 , and $0.0100 \mu\text{g}/\text{m}^3$ in the other rod and wire areas, which are located just outside the RAZ. These data, while extremely limited, suggest airborne beryllium concentrations post-RAZ were lower than the median airborne beryllium concentrations in those areas before the RAZ enclosure, providing some justification for considering enclosure of the process a sentinel event in this preventive program.

The results of our BeLPT analyses lead us to believe that one possible misclassification may exist in this facility (Worker D), as the proportion of non-normal results at Lab 1 were greater than three standard deviations above the overall mean number of non-normal results during the time this individual was identified and confirmed as sensitized. However, the results of these BeLPT analyses did not influence our results concerning sensitization IRs and prevalence rates. The potentially misclassified individual was still considered sensitized for our incidence calculations, as outlined previously. Had the potentially misclassified individual been excluded, the preventive program would have been judged to be even more effective. Ongoing surveillance may help clarify whether or not this individual was truly misclassified.

Our BeLPT analyses also showed that there was a significantly higher proportion of non-normal results at Lab 2 during the 2000 survey than at Lab 1, indicating possible laboratory quality problems, which triggered the need for redraws to verify test results. Inclusion of legacy workers with an abnormal BeLPT result at either laboratory on initial testing would have increased, and may have overestimated, the apparent effectiveness of the preventive program. Our results showed that both

laboratories examined in these analyses experienced periods during which laboratory quality may have been questionable. These findings support others' conclusion that laboratories would benefit from a statistical approach, such as statistical control charts, to improve quality management.³⁴

The available data on the rate of false positives and false negatives among BeLPT results suggest that these rates may vary among labs. Stange et al. reported a false positive rate of nearly 2% and a false negative rate of 32%.³⁵ All medical screening tests can have false positive or false negative results. A second, confirmatory abnormal BeLPT result is often required for a person to be considered sensitized to beryllium. Despite its limitations, the BeLPT is currently the best available tool to identify individuals who are sensitized to beryllium and therefore at risk for developing CBD.¹

Strengths

Our analyses have several noteworthy strengths. The longitudinal design of the data collection for the program groups allowed us to calculate a true sensitization IR. We were then able to compare these data to BeLPT results from an earlier cohort, the legacy workers, which provided a relatively rare opportunity in occupational intervention evaluations. The legacy workers were similar to the program workers with respect to race and job category distributions, which limits potential differences between the two groups. Despite differences in testing protocol between the legacy and program workers, the same laboratories were used, which allowed us to identify (and recategorize) workers in each group for the various comparisons we made.

Limitations

The first limitation of this article involves the differences in the testing protocols for the legacy and program workers. The legacy workers' data were collected cross-sectionally, while the program workers' BeLPT results were collected longitudinally. These data provide sensitization prevalence and incidence respectively and are not directly comparable. We compensated for this limitation by using two approaches designed to make the data from the two groups as similar as possible. First, we approximated an IR for the legacy workers. For the second comparison, we estimated a prevalence rate for the program workers. Both sets of comparisons allowed us to draw similar conclusions, in that both sets of results showed decreases in estimated prevalence rates and IRs between the legacy and program workers, as well as steadily decreasing estimated prevalence rates and IRs among the legacy, pre-enclosure, and post-enclosure program workers.

A second limitation was the small sample size, which limited the power to find statistically significant differences. However, we feel that the decreases in sensitization observed in this study are notable for two reasons. First, the legacy workers' prevalence rates and IRs were probably underestimated. We excluded four sensitized individuals from this group because their initial abnormal test results were from Lab 2. Even though there may have been technical difficulties at the laboratory during that period, it does not rule out the possibility that at least one of these individuals was truly sensitized. The legacy workers' IR was also underestimated due to the cross-sectional data collection methods. By testing everyone at the same time, we had no way of knowing when they had become sensitized. Some of the sensitized legacy workers may have become sensitized months, if not years, before they were tested in the 2000 survey. Therefore, sensitized legacy workers likely contributed more sensitization-free time to the denominator than they would have had they undergone the same serial testing as the program workers. Unfortunately, we had no better way of estimating person-months than using time between hire and the survey.

Second, we may have overestimated the incidence in the program/post-enclosure program worker groups by including Worker D as a sensitized employee. However, we felt it prudent to be as conservative as possible, despite the fact that these approaches may have contributed to our limited power. Also, the significant trend test among the prevalence rates is promising. These findings are important and more relevant to certain downstream copper-beryllium manufacturing/processing workers, a population we know little about, than the results from the beryllium ceramics facility. The lack of statistical significance for the trend test among the IRs may have been due to the greater amount of person-months contributed by the legacy workers.

CONCLUSIONS

This article suggests that the combination of dermal protection, enclosure and improved ventilation of high-risk processes, targeted full-time use of respiratory protection in high-risk processes (e.g., the RAZ), and/or dust migration control measures may be useful in reducing sensitization in a facility with relatively low airborne concentrations of beryllium, although it is not possible to determine the contribution of individual factors. Given the expected similarities in terms of exposure between this facility and downstream users, these findings have important implications for the prevention of beryllium sensitization and CBD among workers at

facilities performing similar work activities with copper-beryllium alloys. The limited power of these analyses, as well as the limited follow-up time, indicate a need for further longitudinal study of these employee cohorts to confirm and extend our findings.

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