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Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant

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Abstract ***Objective***: Workers at a beryllium ceramics plant were tested for beryllium sensitization and disease in 1998 to determine whether the plant-wide prevalence of sensitization and disease had declined since the last screening in 1992; an elevated prevalence was associated with specific processes or with high exposures; exposure-response relationships differed for long-term workers hired before the last plant-wide screening and short-term workers hired since then. ***Methods***: Current workers were asked to complete a questionnaire and to provide blood for the beryllium lymphocyte proliferation test (BeLPT). Those with an abnormal BeLPT were classified as sensitized, and were offered clinical evaluation for beryllium disease. Task- and time-specific measurements of airborne beryllium were combined with individual work histories to compute mean, cumulative, and peak beryllium exposures for each worker. ***Results***: The 151 participants represented 90% of 167 eligible workers. Fifteen (9.9% of 151) had an abnormal BeLPT and were split between long-term workers (8/77 = 10.4%) and short-term workers (7/74 = 9.5%). Beryllium disease was detected in 9.1% (7/77) of long-term workers but in only 1.4% (1/74) of short-term workers ($P = 0.06$), for an overall prevalence of 5.3% (8/151). These prevalences were similar to those observed in the earlier survey. The prevalence of sensitization was elevated in 1992 among machinists, and was still elevated in 1998 among long-term workers (7/40 = 18%) but not among short-term workers (2/36 = 6%) with machining experience. The prevalence of sensitization was also elevated in both groups of workers for the processes of lapping, forming, firing, and packaging. The data suggested a positive relationship between peak beryllium exposure and sensitization for long-term workers and between mean, cumulative, and peak exposure and sensitization for short-term workers, although these findings were not statistically significant. Long-term workers with either a high peak exposure or work experience in forming were more likely to have an abnormal BeLPT (8/51 = 16%) than the other long-term workers (0/26, $P = 0.05$). All seven sensitized short-term workers either had high mean beryllium exposure or had worked longest in forming or machining (7/55 = 13% versus 0/19, $P = 0.18$). ***Conclusions***: A plant-wide decline in beryllium exposures between the 1992 and 1998 surveys was not matched by a decline in the prevalence of sensitization and disease. Similar to findings from other studies, beryllium sensitization/disease was associated with specific processes and elevated exposures. The contrast in disease prevalence between long-term and short-term workers suggests that beryllium sensitization can occur after a short period of exposure, but beryllium disease usually requires a longer latency and/or period of exposure. The findings from this study motivated interventions to more aggressively protect and test workers, and new research into skin exposure as a route of sensitization and the contribution of individual susceptibility.

Key words Beryllium disease · Epidemiology · Exposure-response · Beryllium lymphocyte proliferation test · Surveillance

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Introduction

The understanding of the epidemiology of beryllium sensitization and disease has advanced with the application of screening for beryllium-specific cellular immune response among beryllium-exposed workforces. Peripheral blood is submitted for a beryllium lymphocyte proliferation test (BeLPT), and a repeatable abnormal result indicates beryllium sensitization. Sensitized individuals are referred for clinical evaluation to determine if they have granulomatous interstitial inflammation in the lungs which constitutes chronic beryllium disease. Based on this evaluation, beryllium disease can now be diagnosed in a sub-clinical stage. The BeLPT does a reasonable job of identifying who is likely to have disease. Studies at different plants have shown that from 48% to 100% of beryllium workers with an abnormal BeLPT have disease [6–10, 13].

An assumption of any screening program is that early detection of disease will improve prognosis [4]. Similar to sarcoidosis, beryllium disease with physiological abnormalities is normally treated with oral corticosteroids to arrest the progression of functional loss. While the use of corticosteroids has been shown to benefit many patients with sarcoidosis [14, 17] this treatment has not been formally validated for beryllium disease. Close clinical monitoring and a reduction or elimination of beryllium exposure is normally recommended for anyone who has an abnormal BeLPT without disease or beryllium disease without clinical symptoms. While the limiting of further exposure is a prudent recommendation, its benefit has never been explicitly demonstrated. An abnormal BeLPT without clinical disease can place a burden on the individual, since this finding often leads to job changes, a reduction in income, worry about future illness, and difficulty in subsequently obtaining health insurance [11]. Despite its limitations, the BeLPT is the best test available for screening for beryllium disease [6, 12].

Process-related risks of beryllium sensitization and disease have been identified at nearly all plants in which BeLPT screening has been the basis for surveillance. However, in the plants with usable historical exposure data, exposure-response relations have been inconsistent [9, 10, 18]. This paper presents a follow-up cross-sectional surveillance study at one of these plants, a beryllium ceramics plant first studied in 1992 [9]. From that earlier study, 5.9% (8/136) of workers had an abnormal BeLPT, and six of the eight sensitized also had beryllium disease based on the presence of granulomas in the lungs. The prevalence of sensitization was significantly higher among machinists, 14.3% of whom were affected, in comparison with 1.2% among the remaining workers. Machining exposures were slightly higher, on average, than exposures in other processes, and accounted for most of the historical exposures above the Occupational Safety and Health Administration (OSHA) 2 $\mu g/m^3$ daily 8-h average exposure limit. Lappers also had high rates of sensitization, but nearly all lappers had also done machining, precluding independent assessments of the two processes. The company lowered machining exposures over the period from 1993 to 1996 by enclosing machines, and exhausting them outside the plant through HEPA filters. Beginning in 1996, employment expanded at the plant.

In 1998, the company offered all current workers screening, with a questionnaire and blood BeLPT. Workers with an abnormal BeLPT were offered pulmonary evaluations to distinguish between sensitization with and without beryllium disease. Concurrent with worker screening, industrial hygienists from the company and the National Institute for Occupational Safety and Health (NIOSH) collaborated on a supplemental characterization of current beryllium exposure, including personal monitoring and particle size differentiation. These screening, medical, and exposure characterization efforts made it possible to address the following research questions:

1 Did the plant-wide prevalence of beryllium sensitization and disease decrease since the screening 6 years earlier?
2 Did the engineering interventions lower exposures and the prevalence of beryllium sensitization for new machinists versus machinists with historical exposures?
3 Were new or persistent process-specific risks evident?
4 Did the association between sensitization/disease and beryllium exposure differ for long-term workers who had a normal BeLPT when screened 6 years earlier versus short-term workers hired since 1992?

Methods

Medical screening and diagnosis

All current employees as of 15 January 1998, at the beryllium ceramics facility who had not previously been diagnosed with beryllium disease were invited to participate. The protocol was reviewed and approved by the NIOSH Human Subjects Review Board, and written informed consent was obtained from each participant. The company medical department conducted questionnaire interviews during February through May 1998 and blood test screening during March through May 1998. The follow-up clinical examinations for subjects with an abnormal BeLPT were continued through December 1998. Trained interviewers administered a modified version of the standardized American Thoracic Society (ATS) questionnaire [3] with additional questions to assess dermatological conditions and specific occupational exposures. Self-reported respiratory symptoms were operationally defined as follows. Usual cough: usually cough, or usually cough first thing in the morning, or usually cough during the rest of the day or night. Usual phlegm: usually bring up phlegm, or usually bring up phlegm first thing in the morning, or usually bring up phlegm during the rest of the day or night. Wheeze apart from colds: chest ever sounds wheezy or whistling, occasionally apart from colds, or most days or nights. Breathlessness: have to walk slower than people of own age on level because of breathlessness, or worse.

Industrial hygienists collected job histories during October through December 1998. Due to changes in the organization of work tasks that were instituted by 1996, we coded work performed prior to 1996 differently from work performed during 1996 or later. Study participants indicated the start and end dates for each area where they had worked in the company, as well as the tasks they had performed in each area, using for reference a list of all tasks for which measurements of beryllium were available. Finally, the workers estimated the average amount of time they spent each week doing each task. To unify an individual's pre- and post-1996 working experience, we grouped all area-task codes into 11 process categories: lapping, forming, packaging, firing, machining, quality control, administration, material preparation, tape, maintenance, and metallizing.

The company medical staff collected blood samples in heparin and sent split samples overnight to laboratories A and B for the BeLPT. Lymphocytes were stimulated with 1, 10, and 100 μM concentrations of beryllium sulfate ($BeSO_4$), radiolabeled with a DNA precursor, and harvested on days 5 and 7 at laboratory A and on days 5 and 6 at laboratory B. A stimulation index, defined as the ratio of counts per minute in beryllium-exposed cultures relative to counts per minute of unstimulated cultures, was recorded at these times. An abnormal blood test was defined as two or more stimulation indices ≥3 on the same test. In the event that only one stimulation index was ≥3, a second sample was submitted to the same two laboratories for clarification of status. When abnormal test results were reported by one or both laboratories, an additional blood sample was drawn and sent for confirmation to the two labs. An abnormal BeLPT was defined as an abnormal blood test on at least two occasions, which could include abnormal results from the two laboratories based on the same sample or different samples, or abnormal results from the same laboratory upon retesting. This definition of an abnormal BeLPT was essentially the same as that used in the 1992 survey [9]. However, the actual testing of blood samples was different in 1998 compared with 1992: one of the two laboratories was changed between the two surveys, and the laboratory that was retained altered its procedures.

In addition to testing workers during plant-wide surveys, the company offers the blood BeLPT to individuals if their symptoms, annual chest radiographs, or pulmonary function tests suggest lung disease. Most of the findings used in this study are from the 1998 screening, but we also considered results of occasional tests and examinations conducted after the 1992 study to mid-2000.

Study subjects with an abnormal BeLPT were referred for clinical evaluation to the University of Pennsylvania Medical Center. The diagnostic examination included fiberoptic bronchoscopy for bronchoalveolar lavage (BAL) BeLPT, cell count and differential, and transbronchial lung biopsy. The laboratory utilized 1, 10, and 100 μM concentrations of $BeSO_4$ and beryllium fluoride (BeF_2) for stimulation of lavage cells and harvested them on days 3 and 5. An abnormal BAL-BeLPT was defined as two or more of 12 stimulation indices ≥5, while a borderline BAL-BeLPT was defined as only one stimulation index ≥5. Transbronchial biopsies were collected from the right upper lung lobe and submitted in Bouin's solution to the University of Pennsylvania Department of Pathology and Laboratory Medicine for microscopic evaluation. For the following statistical analyses, we defined beryllium disease as a borderline or abnormal BAL-BeLPT and/or characteristic granulomas on lung biopsy. That is, someone with a borderline or abnormal BAL-BeLPT but without granulomas was classified as having beryllium disease.

Environmental evaluation

The number concentration of beryllium particles might be a superior predictor of health effects than standard mass measurements [5]. Exposure assessment conducted at the ceramics plant in 1998 and 1999 revealed that the size distribution of particles varied little across processes. Since consideration of particle size and count was unlikely to change dramatically the exposure characterization based on mass alone, mass was retained as the metric of exposure.

The company had records of 18,903 beryllium air-level measurements taken in the ceramics plant from when full production was started in 1981 through 1998, of which 42.6% were breathing zone samples and 57.4% were general area samples. High volume samplers with mixed cellulose ester filters were used, at a flow rate of 30 l per min. For most of the tasks that workers performed, sampling was done on a monthly basis for general area samples, and variably for breathing zone samples, with at least one sample taken each year. Breathing zone measurements were obtained by industrial hygiene personnel holding samplers in the worker's breathing zone while a task was being performed. Collection times were approximately 30 min for general area samples, and 1–15 min for task-specific breathing zone samples. The limit of detection for all industrial hygiene samples was 0.1 μg/m^3. We assigned half the limit of detection (i.e., 0.05 μg/m^3) to all samples that were at or below the limit of detection. When an area-task lacked beryllium measurements for a particular year, we assigned exposure values from comparable area-tasks that did have measurements. This filling-in for missing values was done in 9% of the subjects' person-time experience in the plant.

Work histories were truncated at the date of the first abnormal blood draw for individuals with sensitization or disease, and at the date of normal blood draw during the study period for all others. This was done to ensure that the exposure under consideration preceded the outcome. An exposure value was calculated for each task/time period combination using the available sampling data. Breathing zone samples accounted for the majority of data used to estimate exposures, with general area samples used only when a worker spent time away from a process, such as in an office area where no actual production process operated.

An individual's experience in the plant was characterized in several ways, including processes worked and number of years since first beryllium exposure. We calculated the prevalence of an abnormal BeLPT for each of the 11 process categories, based on ever-worked and longest-worked process. Process as a surrogate for exposure can provide an integration of the exposure experience, incorporating aspects that might be considered separately in other exposure assessments, or not addressed directly at all. By examining ever-worked versus never-worked in a particular process, we tested the hypothesis that any experience in that process is potentially harmful. The process that an individual had worked at longest might influence risk for sensitization or disease and was also considered in the analysis.

We compared the prevalence of an abnormal BeLPT among quartiles of cumulative, mean, and peak beryllium exposure. These three types of quantitative measurements of beryllium exposure were derived for each subject following the merger of work histories and area-task/time-based exposure levels. First, cumulative beryllium exposure was a sum of the products of length and intensity of exposure for each area-task, expressed in the units μg-year/m^3. Intensity was calculated on an annual basis, and was the arithmetic mean of the area-task-specific measurements for that year. A work-year comprised 50 weeks of work at 40 h per week. With overtime, it was possible for a worker to accumulate more than a work-year of exposure within a calendar year. Second, the mean beryllium exposure was the cumulative beryllium exposure divided by the number of work-years of exposure. Third, a peak exposure for each subject was achieved in two steps: (1) the maximum exposure level was determined for each area-task on an annual basis; (2) based on an individual's work history, the peak exposure was the highest of the annual maximum area-task-specific exposure values.

Short-term versus long-term workers

The current employees in 1998 comprised two distinct groups of workers defined by when they had started work at the company. One group included short-term workers hired since the last plant-wide screening in 1992. They had relatively brief histories of beryllium exposure and had not been screened as a group since they were hired. Few of them would have left employment due to work-related health problems by the time of the 1998 survey, so those available for testing should include people with varying levels of susceptibility to the harmful effects of beryllium. The second group of 1998 current employees included long-term workers hired before the 1992 screening. They had relatively long histories of beryllium exposure by the time of the 1998 survey, had already been screened as a group in 1992, and would likely experience a greater "healthy worker effect" than the short-term workers. Specifically, former co-workers of the long-term workers with work-related health problems would have already left employment by 1998, so those still employed probably would not include the people most susceptible to beryllium. We conducted analyses separately for short-term versus long-term workers because exposures needed to initiate sensitization and disease might differ for these two groups.

Statistical analyses

Statistical analyses were accomplished with SAS and Epi Info software [2, 16]. The continuity-corrected χ^2 and Fisher's exact tests were used to test for statistical significance with categorical data, while the Wilcoxon rank sum test and *t*-test were used with continuous data [1]. Least squares linear regression was used to estimate the average annual change in exposure for selected processes. *P* values less than or equal to 0.05 were considered statistically significant, unless otherwise noted.

Results

Study population

Of the 167 eligible employees, two left before the screening, six declined to participate, and eight did not complete the questionnaire. So, 90% (151/167) completed the questionnaire and submitted blood for laboratory evaluation during the 1998 survey. Slightly more than half of the 151 participants ($n = 77$) were long-term workers hired before the 1992 screening and 74 were short-term workers hired subsequently. One of the long-term workers had not been tested during the 1992 survey because he had left company employment prior to that earlier survey and had then returned after it; he had a normal BeLPT in the 1998 survey. The median years since first beryllium exposure was 14.1 (range 8.0 to 40.1) for the 77 long-term workers and 1.0 (range 0.25 to 12.75) for the 74 short-term workers. The plant began operations in 1980, so the maximum time since hire was approximately 18 years. However, eight of the long-term subjects had their first beryllium exposure before this facility opened, and their times from first exposure ranged from 18.75 to 40.1 years. All 74 short-term workers in the 1998 survey had been hired since the 1992 survey, and only two exceeded 6.1 years since first contact with beryllium because of prior occupational exposure.

Abnormal beryllium lymphocyte proliferation test and beryllium disease

The BeLPT was abnormal for 9.9% (15/151) of the participants in the current survey, which was somewhat greater than the 5.9% (8/136) observed in the 1992 survey ($\chi^2 = 1.1$, $P = 0.30$). The fifteen sensitized subjects were split between long-term and short-term workers, with prevalences of 10.4% (8/77) and 9.5% (7/74), respectively. Twelve of the fifteen sensitized workers had their first abnormal BeLPT findings during the 1998 survey, all consented to bronchoscopy with lavage and transbronchial biopsies, and six were classified as having beryllium disease. The other three sensitized individuals were long-term workers who were first identified earlier or later than the 1998 survey. The first of the three had a single abnormal blood test result during the 1992 survey, but this was called into question since the laboratory was having trouble with the test. Subsequently, this worker had a series of six normal BeLPT findings from two different laboratories, consecutive abnormal blood test results from the same laboratory in 1995, and evidence of disease from diagnostic follow-up in 1998. A second worker had a suspicious chest radiograph in 1997 and a single abnormal blood test at that time. This was followed by two borderline blood tests over the next 2 years, including one during the 1998 screening, and a second abnormal blood test in June 2000. This worker declined clinical follow-up after the 1998 screening, and disease status is unknown to date. The third worker had a normal BeLPT during the 1998 survey, and then underwent clinical evaluation in December 1998 after a suspicious chest radiograph. This person was classified as having beryllium disease, based on findings of an abnormal BAL-BeLPT and granulomas on biopsy, and was considered to be sensitized as well, based on an abnormal blood test result and the abnormal BAL-BeLPT findings.

In total, 5.3% (8/151) of all participants and 53% (8/15) of those with an abnormal BeLPT had beryllium disease. All seven long-term workers who underwent diagnostic follow-up fulfilled the current criteria for beryllium disease ($7/77 = 9.1\%$), while only one of the seven sensitized short-term workers was classified as having disease ($1/74 = 1.4\%$) ($P = 0.06$). The long-term workers classified as having beryllium disease included four with abnormal BAL-BeLPTs and granulomas, one with a borderline BAL-BeLPT and granulomas, and two with abnormal BAL-BeLPTs but without granulomas. The one short-term worker considered to have beryllium disease had a borderline BAL-BeLPT result and no granulomas. The prevalence of granulomas in this survey was 3.3% (5/151), which was slightly less than the 4.4% (6/136) observed in the 1992 survey ($\chi^2 = 0.03$, $P = 0.86$).

We compared demographic characteristics between those with and without an abnormal BeLPT, separately for long-term and short-term workers (Table 1). In both groups of workers, those with an abnormal BeLPT were a little older and more likely to be female, although these differences were not statistically significant. Among the short-term workers, the BeLPT abnormal subjects tended to have a higher proportion of Hispanics than the BeLPT normal subjects (i.e., 71% versus 46%, respectively, $P = 0.26$). The sensitized subjects did not differ from the others in the percentage who had ever smoked cigarettes.

Process-specific prevalence of an abnormal beryllium lymphocyte proliferation test among long-term workers

Long-term subjects had worked at an average of 4.4 different processes, and based on where the participants had ever worked, several processes produced an elevated prevalence of sensitization: lapping 21% (4/19, $P = 0.10$ compared with all other long-term workers), machining

Table 1 Demographic characteristics by beryllium lymphocyte proliferation test (*BeLPT*) status, for long-term and short-term workers (none of the comparisons between workers with normal and abnormal BeLPTs was statistically significant at the $P \le 0.05$ or $P \le 0.10$ level)

Characteristics	Long-term workers		Short-term workers	
	Normal BeLPT (n = 69)	Abnormal BeLPT (n = 8)	Normal BeLPT (n = 67)	Abnormal BeLPT (n = 7)
Median age (years)	46	51	36	41
Gender (female)	30%	50%	34%	57%
Ethnicity/race				
Non-Hispanic white	65%	63%	48%	14%
Hispanic	29%	25%	46%	71%
Other	6%	13%	6%	14%
Ever smoked cigarettes	52%	50%	36%	43%

18% (7/40, $P = 0.04$), forming 16% (7/45, $P = 0.08$), firing 15% (7/47, $P = 0.10$), and packaging (4/29 = 14%, $P = 0.35$) (Table 2). Most of the eight sensitized long-term subjects had experience in several of these high-prevalence processes. In particular, seven had worked in both firing and machining, of whom six had also worked in forming, and four of those six had worked in lapping. The prevalence increased with the number of top four processes ever worked: none 0% (0/19), one 7% (1/14), two 10% (1/10), three 11% (2/19), and all four 27% (4/15, $P = 0.03$ compared with none). By longest-worked process, the sensitized subjects were spread out, with two cases each in forming and machining and one each in lapping, quality control, maintenance, and administration (Table 2). The one whose longest-worked process was administration also had over 6 work-years in other processes, including 3.7 work-years in forming and 1.2 work-years in maintenance.

Process-specific prevalence of an abnormal beryllium lymphocyte proliferation test among short-term workers

Although most short-term workers had been employed for fewer than 2 years, they still had experience in an average of 3.3 different processes. Six of the seven sensitized short-term workers had worked in forming, of whom five had also worked in firing, and two of the five had also worked in lapping. There were two sensitized short-term workers without experience in firing or lapping, and one had worked only in forming, while the other had worked longest in machining and had spent less time in metallizing. The one short-term worker with beryllium disease had worked longest in firing, and had also worked in forming, quality control, and tape.

By ever-worked process, the prevalence of sensitization was elevated for lapping 25% (2/8, $P = 0.16$), forming 14% (6/42, $P = 0.11$), packaging (1/8 = 13%, $P = 0.57$), and firing (5/42 = 12%, $P = 0.34$), but not for machining (2/36 = 6%) (Table 2). By longest-worked process, an elevated prevalence was observed for forming (3/16 = 19%) and firing (2/4 = 50%), and combined, the prevalence was 25% (5/20) versus 4% (2/54) for all other short-term workers ($P = 0.01$). The sensitized short-term subject who had worked longest in administration had the second longest period of employment in forming.

Environmental measurements

The beryllium measurements from 1981–1998 that exceeded the OSHA 30-min maximum peak exposure limit of 25 μg/m^3 included 28 (0.3%) breathing zone samples and 21 (0.2%) general area samples. The

Table 2 Prevalence of abnormal beryllium lymphocyte proliferation test (*BeLPT*) by process, for long-term and short-term workers

Process	Long-term workers		Short-term workers[b]	
	Ever-worked	Longest-worked	Ever-worked	Longest-worked
Lapping	4/19 = 21%*	1/1 = 100%	2/8 = 25%	0/3
Forming	7/45 = 16%*	2/11 = 18%	6/42 = 14%	3/16 = 19%
Packaging	4/29 = 14%	0/2	1/8 = 13%	0
Firing	7/47 = 15%*	0/6	5/42 = 12%	2/4 = 50%
Machining	7/40 = 18%[a]	2/13 = 15%	2/36 = 6%	1/16 = 6%
Quality control	6/53 = 11%	1/8 = 13%	3/49 = 6%	0/5
Administration	2/24 = 8%	1/10 = 10%	1/12 = 8%	1/5 = 20%
Material preparation	0/9	0/2	1/4 = 25%	0/2
Tape	1/20 = 5%	0/3	1/9 = 11%	0/7
Maintenance	3/38 = 8%	1/17 = 6%	0/13	0/5
Metallizing	1/16 = 6%	0/4	1/19 = 5%	0/11

* $0.05 < P \le 0.10$, compared with all other long-term workers
[a] $P \le 0.05$, compared with all other long-term workers
[b] For the short-term workers, none of the process-specific prevalences was statistically significant at the $P \le 0.05$ or $P \le 0.10$ levels

OSHA 5 μg/m^3 ceiling exposure limit was exceeded in 194 (2.4%) breathing zone samples and 68 (0.6%) general area samples, while the 2 μg/m^3 daily 8-h average exposure limit was exceeded in 512 (6.4%) breathing zone samples and 181 (1.7%) general area samples. Mean calculated exposures for all participants ranged from non-detectable (and assigned a value of 0.05 μg/m^3) to 4.4 μg/m^3. Only four participants had mean exposures that exceeded the 2 μg/m^3 standard, one of whom was the short-term worker classified as having disease.

Beryllium exposures for long-term versus short-term workers

Between the 1992 and 1998 surveys, the company engaged in a number of efforts to reduce exposures, and workers hired since the 1992 survey had lower mean and peak exposures. The median values for long-term and short-term workers were 0.39 μg/m^3 and 0.28 μg/m^3, respectively, for mean exposure ($P = 0.005$ by Wilcoxon test), and 14.9 μg/m^3 and 6.1 μg/m^3, respectively, for peak exposure ($P = 0.0003$ by Wilcoxon test).

The prevalence of an abnormal BeLPT result among those who had ever worked in machining was 7/40 = 18% for long-term workers and only 2/36 = 6% for short-term workers ($P = 0.16$). Consistent with the suggested decline in the effect of machining, regressing the 1986–1998 mean annual exposures for machining yielded a coefficient of −0.10 μg/m^3 per year ($P = 0.08$). At the same time, we would expect to see little change in beryllium exposure for processes such as forming, lapping, firing, and packaging, in which the prevalence of sensitization was relatively high for both recent hires and more experienced workers. This expectation was realized for forming, with an estimated annual change in mean exposure based on linear regression of +0.01 μg/m^3 per year ($P = 0.27$), but not for the other three processes. Specifically, the average annual change in mean exposure was −0.18 μg/m^3 per year ($P = 0.002$) for lapping, −0.06 μg/m^3 per year ($P = 0.10$) for firing, and −0.03 μg/m^3 per year ($P = 0.04$) for packaging.

Prevalence of an abnormal beryllium lymphocyte proliferation test by years since first beryllium exposure and by level of beryllium exposure for long-term workers

Table 3 presents the prevalence of an abnormal BeLPT by quartile of years since first beryllium exposure and mean, cumulative, and peak beryllium exposure, separately for long-term and short-term workers. The small number of subjects and cases per category discouraged statistical testing using quartiles. When we divided the long-term workers into two approximately equal-sized groups based on time since first exposure or individual mean or cumulative exposure, the prevalence of an abnormal BeLPT was not associated with greater exposure. However, six of the eight sensitized long-term workers were in the upper half of the peak exposures (6/39 = 15%) versus two in the lower half (2/38 = 5%,

Table 3 Prevalence of abnormal beryllium lymphocyte proliferation test (*BeLPT*) by years since first beryllium exposure and by mean, cumulative, and peak beryllium exposure, for long-term and short-term workers

Exposure	Long-term workers			Short-term workers		
	Level	Prevalence of abnormal BeLPT		Level	Prevalence of abnormal BeLPT	
		Quantities	Low vs. high		Quantities	Low vs. high
Years since 1st beryllium exposure[a]	8.0 to 11	1/21 = 5%	4/38 = 11%	0.25–0.58	2/17 = 12%[c]	6/37 = 16%
	≥11 to 14	3/17 = 18%[b]		0.67–1.0	4/20 = 20%	
	≥14 to15.5	1/20 = 5%	4/39 = 10%	>1 to <2	1/19 = 5%	1/37 = 3%
	≥15.5 to 40.1	3/19 = 16%		≥2 to12.75	0/18 = 0%	
Mean (μg/m^3)	0.1–0.23	2/19 = 11%	4/38 = 11%	0.05–0.19	2/20 = 10%	2/39 = 5%
	0.24–0.37	2/19 = 11%[b]		0.20–0.28	0/19 = 0%	
	0.38–0.62	3/19 = 16%	4/39 = 10%	0.29–0.46	2/17 = 12%	5/35 = 14%
	0.63–2.16	1/20 = 5%		0.47–4.4	3/18 = 17%[c]	
Cumulative (μg-yr/m^3)	0.9–2.9	2/19 = 11%	5/38 = 13%	0.02–0.15	2/20 = 10%	2/38 = 5%
	3.0–4.5	3/19 = 16%[b]		0.16–0.32	0/18 = 0%	
	4.6–9.3	1/19 = 5%	3/39 = 8%	0.33–0.79	3/18 = 17%	5/36 = 14%
	9.4–41.2	2/20 = 10%		0.80–16.0	2/18 = 11%[c]	
Peak (μg/m^3)	0.6–5.5	0/19 = 0%	2/38 = 5%	0.05–2.4	2/19 = 11%	2/37 = 5%
	5.6–13.5	2/19 = 11%[b]		2.5–6.0	0/18 = 0%	
	13.6–64	4/20 = 20%	6/39 = 15%	6.1–13.3	2/19 = 11%[c]	5/37 = 14%
	65–307	2/19 = 11%		13.4–307	3/18 = 17%	

[a] Measured from first beryllium exposure, which might have preceded employment in the current plant, to first abnormal blood test result or time of 1998 survey
[b] The one sensitized long-term worker without beryllium disease is in this category
[c] The one short-term worker classified as having beryllium disease is in this category

$P = 0.26$). The two sensitized workers with the lower peak exposures had both worked the longest in the forming process. The prevalence of sensitization among workers either in the greater half of peak exposures or with experience in forming was 16% (8/51) versus 0% (0/26) for all others ($P = 0.05$).

Prevalence of an abnormal beryllium lymphocyte proliferation test by years since first beryllium exposure and by level of beryllium exposure for short-term workers

When divided at the median value, short-term workers with fewer years since first beryllium exposure had a greater prevalence of sensitization than those with more years (16% versus 3%, $P = 0.11$) (Table 3). The one short-term worker classified as having beryllium disease had the third highest mean exposure of 2.2 $\mu g/m^3$ (97th percentile), a cumulative exposure at the 84th percentile, and a peak exposure at the 55th percentile among short-term workers. These observations suggest that at least for those recently hired, high mean and cumulative exposures might be risk factors for disease.

The finding that all seven BeLPT-abnormal short-term workers had fewer than 2 years since first exposure suggests that some people become sensitized after little exposure (Table 3). Just how little beryllium exposure is needed was evident for two short-term workers who had mean exposures of less than 0.1 $\mu g/m^3$ (i.e., 0.05 and 0.06), cumulative exposures of less than 0.1 $\mu g\text{-year}/m^3$ (i.e., 0.04 and 0.07), and peak exposures of less than 0.4 $\mu g/m^3$ (i.e., 0.05 and 0.3). These values were in the 7th, 11th, and 7th percentiles of the respective distributions for all short-term workers. The other five sensitized short-term workers were in the upper half of the distributions of mean, cumulative, and peak beryllium exposures, which suggested that sensitization was more common among those with high exposure (14%) than low exposure (5%), although the P values in these comparisons were consistently > 0.20 (Table 3). One of the two low-exposed sensitized subjects had worked exclusively in forming, and the other had worked predominantly in machining and also in the metallizing process. All seven sensitized short-term workers can be categorized together by combining those with high mean exposures and everyone whose longest-worked process was either forming or machining. The contrast in prevalence of 13% (7/55) for the high-risk group versus 0% (0/19) for the others was not statistically significant ($P = 0.18$).

Occupational exposure to beryllium outside this plant

There were 24 individuals who had worked in at least one other beryllium facility. They were disproportionately long-term workers (20 of 24), and 42% (10/24) had ever worked in administration versus 21% (26/127) for all other subjects ($P = 0.05$). Eight percent (2/24) of the subjects with other beryllium work experience were sensitized compared with 10% (13/127) for other subjects. The two sensitized persons were both long-term workers. Given the absence of exposure data from other plants and the fact that work in other facilities was not associated with sensitization, we did not formally consider it in the analyses.

Special exposure situations, work-related skins problems, and respiratory symptoms

Subjects were asked about their participation in work activities perceived to be at higher risk of excessive beryllium exposure (i.e., clean-up of spills, shut-down maintenance, and decontamination of equipment), and whether they had ever been involved in an incident that may have resulted in high beryllium exposures. For both short-term and long-term workers, there was little difference in the percentage of positive responses when comparing workers with abnormal and normal BeLPT results (Table 4). A work-related rash or skin problem was somewhat more common among those with an ab-

Table 4 Special exposure situations, work-related skin problems, and respiratory symptoms by beryllium lymphocyte proliferation test (*BeLPT*) status, for long-term and short-term workers

Characteristics	Long-term workers		Short-term workers	
	Normal BeLPT ($n = 69$)	Abnormal BeLPT ($n = 8$)	Normal BeLPT ($n = 67$)	Abnormal BeLPT ($n = 7$)
Ever participate in clean-up, shut-down maintenance, or decontamination	88%	88%	40%	43%
Ever high beryllium exposure incident	80%	100%	63%	57%
Ever work-related rash or skin problem	32%	25%	22%	43%
Respiratory symptoms[a]				
Usual cough	29%	63%[b]	18%	29%
Usual phlegm	26%	63%[c]	22%	14%
Wheeze apart from colds	23%	63%[c]	16%	29%
Breathlessness	12%	50%[c]	6%	14%

[a] See Methods for operational definitions of self-reported symptoms
[b] $0.05 < P \leq 0.10$, compared with the BeLPT-normal subjects
[c] $P \leq 0.05$, compared with the BeLPT-normal subjects

normal BeLPT for short-term workers (43% versus 22%, $P = 0.35$) but not for long-term workers (Table 4). The eight long-term workers with an abnormal BeLPT, who included seven persons classified as having beryllium disease, exhibited higher prevalences of all respiratory symptoms than did the BeLPT-normal workers. When stratified by ever/never cigarette smoking, the effect for cough and phlegm was more apparent among never smokers, while the effect for wheeze and breathlessness was the same regardless of smoking status (data not shown). In contrast, the seven short-term BeLPT-abnormal subjects, who included only one beryllium disease case, showed little difference in prevalence of respiratory symptoms compared with the BeLPT-normal workers (Table 4).

Discussion

This cross-sectional study demonstrates the utility of surveillance approaches to company-based screening programs in identifying risk priorities and intervention efficacy. Beryllium sensitization and disease continued to have a weak association with gravimetric measurements of beryllium exposure. The overall prevalence of beryllium sensitization and granulomas in the lungs was nearly the same in the current and 1992 surveys. Beryllium-related outcomes occurred among recent hires despite efforts by the company to reduce exposures and the observation that mean and peak exposures were lower for short-term than for long-term workers. For several processes (i.e., lapping, firing, and packaging), the prevalence of sensitization did not decline despite a reduction in process-specific mean exposure. At least for the forming process, the persistence of relatively high prevalences of sensitization was associated with little change in exposures. Also, the results suggest that the considerable interventions made since 1992 to enclose and exhaust machining operations had their intended result in lowering both exposure levels and the risk of adverse outcomes. The elevated prevalence of beryllium sensitization among machinists that was observed in the 1992 survey was also seen in the 1998 survey for long-term workers, but not for short-term workers hired since the 1992 survey.

In plants with process-related risks of disease, the distribution of sensitization and disease has had similar process risks. Among nuclear workers, machinists were identified as being at high risk, with 4.7% identified as sensitized [7]. When former beryllium ceramics workers from a plant different from the current one were tested, the high-risk operations for beryllium disease were process development/engineering and dry pressing [8]. The latter operation is subsumed under the forming process in the current study. The testing of workers at a large production facility revealed excess risk for beryllium disease among those who had worked either in ceramic fabrication or in the pebble plant producing beryllium metal [10]. Findings from the large production facility also showed that not all processes conferring a sensitization risk have a disease risk.

The beryllium disease cases were almost exclusively among long-term workers whose BeLPTs were normal in the 1992 survey, while the subjects with abnormal findings from the BeLPT without disease were primarily short-term workers hired since the 1992 survey. A certain burden of beryllium in the lung may be necessary to result in disease that is evident on diagnostic follow-up. An alternative explanation is that sensitization progresses to disease with the passage of time, regardless of accumulated beryllium burden or continued exposure. The current findings for long-term workers suggest that both sufficient peak exposure and the passage of time contribute to disease development. For short-term workers, there was a suggestion that an abnormal BeLPT was more common with increased exposure, although the comparisons between high- and low-exposed were not statistically significant (Table 3).

The data from the 1992 survey at this beryllium ceramics plant were independently re-analyzed to examine what distinguishes the sensitized workers (most of whom had beryllium disease) from apparently unaffected residents who lived near another plant in Lorain, Ohio during the 1940s [19]. The researchers observed that the mean concentration and dose rate of beryllium exposure were substantially elevated among the sensitized workers, whereas cumulative exposure and cumulative dose were not. Our finding that sensitization and disease in long-term workers were associated with peak exposures but not mean exposures does not support the conclusions from the re-analysis. Also, when we computed a comparable dose rate of beryllium exposure for each participant in the current study, we found that the sensitized long-term workers were equally divided between the greater and lower half of the exposure distribution (data not shown). The researchers who conducted the re-analysis recommended an 8-h time-weighted-average (TWA) exposure limit of 0.1 $\mu g/m^3$ [19], which could possibly prevent some of the abnormal BeLPT findings and cases of disease identified in the current survey. All but two of the sensitized workers had mean exposures in excess of 0.1 $\mu g/m^3$. The two sensitized short-term workers with mean exposures of 0.05 $\mu g/m^3$ and 0.06 $\mu g/m^3$ illustrate how the recommended standard might not protect all people. Also, given that sensitization might be manifested after a relatively brief period of exposure and that it is uncertain when an individual actually converted to an abnormal BeLPT, some of the other short-term sensitized workers in the current study might have attained this status very early in their careers after rather low beryllium exposures. The recommended standard might be beneficial if the low-exposed sensitized workers do not progress to having disease. Longitudinal follow-up is currently being planned and will help to elaborate the fate of these workers.

The presence of two short-term sensitized workers with very low exposures is consistent with the idea that individual susceptibility is likely to influence strongly how a person responds to beryllium [15, 20]. Independently of the company, NIOSH is conducting genetic research to examine individual susceptibility and its interaction with beryllium exposure. Also, the failure of lower air concentrations to consistently control sensitization rates has raised concern that skin exposure might play a role in the development of sensitization. In the current study, short-term sensitized workers were more likely to report an occupational dermal problem, although the contrast with workers who tested normal was not statistically significant (Table 4). Among the long-term workers, those with beryllium disease were not more likely to report such problems. The 1992 survey at this same plant found no significant difference in work-related skin problems between sensitized workers and others [9]. From medical screening conducted at a large beryllium production facility, the 35 workers with abnormal blood tests but no evidence of disease were compared with those who had normal blood test results. The group with abnormal blood test findings was more likely to report a job change due to a rash, and more likely to have had a rash in the month prior to being interviewed [10]. The possible contribution of skin exposure, especially to sensitization, is now being investigated both in the laboratory and in production facilities.

The findings on exposure-response relationships have varied by study. In the current study, sensitization and disease among long-term workers were associated with peak exposure but not with mean or cumulative exposure, while sensitization among short-term workers was associated with mean, cumulative, and peak exposure. However, the positive associations were not statistically significant. From the 1992 screening at the same facility, the high-risk machining operation had greater general area and breathing-zone measurements and greater daily weighted average (DWA) estimates of exposure than other processes, and accounted for most of the DWAs that exceeded the 2.0 $\mu g/m^3$ OSHA standard [9]. While average beryllium exposures were greater for sensitized workers than for other workers, and for sensitized machinists than for other machinists, these contrasts were not statistically significant. In a case-control study of beryllium-exposed workers at a nuclear weapons facility [18], the researchers found chronic beryllium disease associated with cumulative exposure, mean exposure, and years of employment, but no statistically significant relationships were observed for sensitization. Among workers at a large beryllium production plant who were screened in the early 1990s, there were no statistically significant differences in average and cumulative exposures among sensitized workers with disease, sensitized workers without disease, and those who tested normal [10].

Different workforces have manifested disease rates among the sensitized ranging from 48% to 100% [6–10, 13], with findings from the current study at 53%. Interestingly, the highest prevalence, in which all sensitized workers had beryllium disease, was in a plant in which beryllium ceramic production had ceased 15 years before screening [8]. No analyses are yet available to distinguish the relative contributions of time since sensitization, exposure metrics, and time courses of exposure. This is a goal of longitudinal follow-up for this and similar cohorts, including former workers. Until the effect of exposure amount or exposure cessation is better understood, it is prudent to suggest that sensitized workers avoid further beryllium exposure.

As a consequence of the continuing risk for sensitization identified in the 1998 testing of workers, the plant management instituted several changes: universal respiratory protection; restricted access to and from all production areas without company clothing, showers, air showers, and designated clean areas; and mandatory frequent BeLPT screening of new hires for ascertainment of any ongoing failure to protect against sensitization. The plant management has also instituted several measures to limit or prevent skin contamination. For example, in the lapping operation these measures include: a more efficient filtration system for re-circulated lapping fluid; changes in pumps and holding buckets to reduce splashing and overflowing in the lapping fluid re-circulating system; redesigned product carrier scoops to reduce dripping on the floors; splash barriers to reduce splashing while lapping tables are being cleaned; protective covering to prevent contact of contaminated fluid with skin or clothes; and enclosure of the area and air conditioning to reduce heat stress associated with the increased occlusive clothing requirements. Efforts to reduce dermal exposure in the forming process have included enclosure of the operations to reduce material leaving the area and prevention of skin contact with beryllium oxide powder through increased use of personal protective clothing.

Limitations

There are a number of limitations to the current data. The cross-sectional study design did not allow for surveying workers who left employment after the 1992 survey and before the 1998 survey. Since people with health problems differentially leave work, the current findings are probably an underestimate of the extent of beryllium-related health effects in this population, particularly among those with longer tenure. NIOSH is attempting to locate former employees who participated in the 1992 survey in order to provide a more comprehensive longitudinal survey of that cohort. Surveying former workers will help to address not only the healthy worker effect but also some of the sample-size limitations confronted in the current analyses.

We likely misclassified exposure for some subjects. For example, we might have overestimated exposure by not considering respirator use, although such devices were not employed systematically until December 1998. It is unlikely that sensitized persons converted from a normal to an abnormal result for the BeLPT exactly at the time of the 1998 screening, but we still considered their entire work history up to that point. This would result in an overestimate of exposure, although truncating work histories of sensitized subjects did not dramatically change the findings reported (data not shown). We probably underestimated exposure for those people who had worked with beryllium at other facilities since that part of their exposure history was not included in the calculation of measured exposures.

Conclusions

The possibility that risk can be decreased with engineering controls was demonstrated by the partial efficacy of enclosure and exhausting of machining operations for newly hired machinists. However, in the setting of uncertainty about both safe levels of exposure and routes of sensitization, only surveillance efforts such as this study can guide policy and expenditures for prevention. Sample size limits what can be learned from summary statistics in plants as small as that studied here. Nevertheless, we suggest that in every screening effort for sensitization conducted in the beryllium industry, consideration should be given to the incorporation of information from each employee on job history, practices, and respiratory and skin exposures, in order to understand plant-specific risks that need prevention efforts and to evaluate whether interventions have had their intended consequences.

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