Prevalence of Beryllium Sensitization Among Department of Defense Conventional Munitions Workers at Low Risk for Exposure

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Objective: To estimate the prevalence of beryllium sensitization among former and current Department of Defense workers from a conventional munitions facility. **Methods:** Participants were screened by using Beryllium Lymphocyte Proliferation Test. Those sensitized were offered clinical evaluation for chronic beryllium disease. **Results:** Eight (1.5%) of 524 screened workers were found sensitized to beryllium. Although the confidence interval was wide, the results suggested a possibly higher risk of sensitization among workers exposed to beryllium by occasional resurfacing of copper–2% beryllium alloy tools compared with workers with the lowest potential exposure (odds ratio = 2.6; 95% confidence interval, 0.23–29.9). **Conclusions:** The findings from this study suggest that Department of Defense workers with low overall exposure to beryllium had a low prevalence of beryllium sensitization. Sensitization rates might be higher where higher beryllium exposures presumably occurred, although this study lacked sufficient power to confirm this.

Multiple reports have been published on the prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) in the Department of Energy (DoE) nuclear weapons workforce[1–8]; however, data are lacking regarding the epidemiology of beryllium-related health effects in Department of Defense (DoD)–associated workforces. The DoD has been the major user of beryllium products either in the manufacture of conventional ordnance or in the production of electrooptical targeting systems, infrared countermeasure devices, and missile guidance and radar systems.[9] Studies estimate that some 18,400 current DoD contractor workers may be potentially exposed to beryllium.[10]

Cross-sectional studies have reported that the prevalence of sensitization, defined as confirmed double-abnormal or abnormal and borderline Beryllium Lymphocyte Proliferation Test (BeLPT), varies among occupational groups. Aluminum smelter workers exposed to very-low concentrations of beryllium through a bauxite refinery process were found to have a BeS prevalence of up to 0.5%.[11,12] Among higher-exposed beryllium-extraction, metal-production, and oxide-production workers, 14.6% were found to have BeS.[13] The CBD has been found to affect up to 8% of exposed populations,[1] but reporting of CBD rates has been complicated by the fact that most screening programs do not routinely perform diagnostic follow-up examinations.

The risk for BeS and CBD is affected by genetic predisposition,[14,15] as well as particle size, concentrations, and solubility.[1,2,4,16–23] Sensitization has been found to develop as early as a few months after initial exposure or after up to four decades.[24–26] Smoking, a known suppressant of T-cell proliferative response,[27,28] has been postulated to decrease the risk of sensitization and CBD,[24] while corticosteroids, the first line of drugs in the treatment of CBD, have been shown to potentially reverse sensitization.[29,30]

This report presents findings of a study of BeS prevalence and risk factors among former and current DoD workers from a single government-owned, contractor-operated conventional-weapons manufacture, testing, and disassembly site in the Midwest. This site has been in operation since 1941. Between 1949 and mid-1975, part of the site was used by the DoE for the assembly of nuclear weapons. Preliminary results of screenings between 2000 and 2002 of a small sample of DoD workers ($n = 65$), with no verifiable history of employment in nuclear weapons production, raised concerns for health effects of beryllium exposure in this DoD workforce, resulting in this larger cross-sectional study.

MATERIALS AND METHODS

Cohort Identification and Eligibility Criteria

Approval for the study was received from The University of Iowa institutional review board . The details of cohort identification have been described elsewhere.[31] Identification of all workers employed on site between 1948 and 2002 was based on contractor's archived paper and electronic employment records, local International Machinists and Aerospace Workers Union seniority logbooks, radiation-monitoring badge records, plant medical records, and lists of workers involved in accidents (incident reports) used to distinguish DoD from DoE employment.

Inclusion in the study required confirmation of employment in DoD's conventional munitions production before the end of 2002; the last-year copper–2% beryllium (Cu–2% Be) alloy tools, likely the primary source of exposure to beryllium in DoD operations, were used on this site (Robert Haines, personal verbal communication, 2004). No minimum duration of employment was required to be included in the study. Exclusion from the cohort was based on ever having been employed or directly exposed to DoE's operations on site, resulting in potential for additional exposure to beryllium from manufacture of nuclear weapons. Other exclusion criteria included employment terminating before 1948 or beginning post-2002 or lack of employment records. Selection into the study was limited to workers living within 4-hour driving distance to the screening sites.

Dates and Duration of Employment

Munitions workers at this site typically worked in multiple jobs. The contractor's employment records included information on each job code, with hire and termination dates specific to job codes. Redundant and overlapping records were eliminated to compile chronologic work-history records for the cohort. Records for employees hired before 1953 often lacked start or hire dates, presumably because of the fact that oversight of conventional munitions operations was transferred from the government to a private contractor in 1951, at which time most of the available employment data

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DOI: 10.1097/JOM.0b013e31820a408a

began to be compiled. For records lacking start dates, contractors' wage and salary schedules were used to identify and assign appropriate dates matching specific job codes and wages appearing in the subject's employment records. For subjects whose records did not include specific wage information that would define the employment era, wage and contract books were referenced to identify a given period in which specific job codes were used and an imputed 1-year term of employment was assigned. Total duration of employment was calculated for every worker, who worked on site, by summing months of employment in each job.

Beryllium-Exposure Assessment

Given the long latency between this survey and employment on site for the majority of the cohort, it was assumed that participants' recall or knowledge of beryllium-exposure potential would be problematic. A job exposure matrix was developed to assign qualitative exposure rankings for beryllium. This matrix was based on a job dictionary constructed from the compilation of all known job codes used by the site's contractors. Job titles associated with these codes were obtained from the contractor's wage and salary schedules for hourly, salaried, bargaining, and nonbargaining positions at the plant. The dictionary's entries were grouped into similar exposure-job categories on the basis of titles, known work tasks, and expected exposures, using input from current and past plant personnel and knowledge of production processes. The categories were then reviewed by a panel of current and former workers with knowledge of historic processes, exposure sources, and control technologies implemented over the years.[32]

Since no industrial hygiene-monitoring data for beryllium were found for DoD operations, the panel established qualitative beryllium-exposure rankings—ranging from category 0 to 2—on the basis of the frequency and proximity to known processes involving beryllium (Table 1). These rankings were consistent with the results of surface-wipe sampling conducted early in the study to estimate the presence and the location of beryllium in surface dust in a variety of plant locations. Higher concentrations of beryllium in surface dust were noted in proximity to sanding and grinding equipment in machine shops, where workers sanded and resurfaced Cu–2% Be alloy tools.[33] Grinding and reshaping of tools were also found to have been the main source of exposure to beryllium in DoE nuclear weapons operations on site[31]; machinists, millwrights, and tool-and-die workers had the highest exposure potential of all jobs on both the DoE and DoD production lines.

Many workers had multiple jobs over their work career at the plant. Beryllium exposure was characterized by assigning the highest beryllium-exposure category experienced by each worker during his or her tenure on site, regardless of the duration of employment.

Data Collection

The study design was cross-sectional, and participants were initially randomly selected from a cohort of living current and former conventional munitions workers. To maximize statistical power in testing for dose–response trend across the exposure strata, all living category 2 workers were selected for recruitment.

Workers were not compensated for their travel, and a geographic restriction was placed on the recruitment of study participants, as few former workers living far from the plant were expected to participate in the study. Selected workers, identified as living in the proximity of screening sites (within a 4-hour driving radius), were mailed invitations to the screenings with informational handouts, informed consents, return envelopes, and the phone number for the study's toll-free line. The study's Web site was also accessible through major search engines.

After the initial mailing, nonrespondents were recontacted by mail and exposure category 2 workers were contacted by phone, where this information was available. These presumed highest-exposed workers were more actively recruited because of the small sample size of this group and concerns about statistical power. Because of a poor initial response rate, the random-selection recruitment protocol was modified to allow volunteers to enroll in the study. This modification was followed by an extensive media campaign, including paid advertisements, and radio-station interviews, both locally and in neighboring states. In addition, members of the study's community advisory board and study participants were provided postcards with information about the study to distribute to former workers.

Screening for BeS, and Clinical Evaluation for CBD

Beryllium sensitization was evaluated by testing cultured-lymphocyte responses to beryllium sulfate, as determined by tritiated thymidine incorporation during preparation for mitosis. An individual Lymphocyte Proliferation Test was defined as abnormal if the rate of beryllium-induced cell proliferation in two or more beryllium concentrations exceeded the laboratory-specific cutoff value for beryllium-unexposed cells. A positive response to only one beryllium concentration was defined as a borderline result, while low response to positive controls or high statistical variability within the sample deemed the result uninterpretable.[34,35]

Participants' blood samples were tested by two laboratories simultaneously, and the laboratories were blinded to all personal identification. Thirty milliliters of sodium-heparinized venous blood was submitted to each laboratory, and samples were shipped unrefrigerated by overnight express to ensure delivery and setup within 24 to 48 hours of the blood draw. Half way through the screenings, one of the laboratories stopped performing the test and a third laboratory was used to test the samples.

Repeat split samples were submitted to confirm single abnormal test results or clarify initial borderline or uninterpretable tests. Only one follow-up split was performed unless the repeat test was reported as uninterpretable from both laboratories or the blood sample was damaged, lost, or otherwise unprocessable. Participants were considered beryllium sensitized if a single abnormal test result was confirmed by a second abnormal or a borderline test from either laboratory.[7,35–37]

At the time of the BeLPT screening, project staff provided participants with information on the process and interpretation of the BeLPT, collected informed consent from all participants, and answered questions. The BeLPT sample collection was scheduled for the convenience of workers at off-site locations. Home visits were performed as needed for home-bound participants. Participation in the study was voluntary, and subjects could withdraw at any time. A questionnaire was obtained from each participant to obtain information on smoking status and steroid or immunosuppressant use, as well as to both confirm employment in DoD operations and exclude those ever having worked in production of nuclear weapons. The questionnaires were reviewed with participants on arrival at the screenings by project staff familiar with the site's history.

Workers with confirmed abnormal BeLPT were offered medical follow-up, as indicated clinically to rule out an active inflammatory or granulomatous pulmonary process. Subjects were told that they had no obligation to pursue further evaluation, and clinical judgment was used in assessing the a priori likelihood of a treatable lung condition and the risk of subsequent medical evaluations, including lung function testing, high-resolution computed tomographic (HRCT) scanning of the lung, and fiberoptic bronchoscopy with lavage, and multiple transbronchial biopsies.

Spirometry was performed according to the American Thoracic Society guidelines.[38] The percentage-predicted forced vital capacity (FVC%) and forced expiratory volume in the first second (FEV1%) were calculated by using the National Health and Nutrition Examination Survey–based algorithm, recommended by

TABLE 1. Distribution of Job Categories by Exposure and Sensitization to Beryllium*

Exposure Category	Job Category	Screened	Total Beryllium Sensitization *n* (%)
0			
Virtually no exposure; lowest exposures at this plant	Administrative and office support	8	
	Automotive and equipment mechanics	7	
	Cameramen	1	
	Carpenters	1	
	Custodial	3	
	Electricians	6	
	Engineers	6	
	Expeditors, material handlers, and checkers	16	
	Equipment operators	3	
	Firefighters	1	
	Ironworkers	1	
	Inspectors	41	
	Laborers	20	
	Melt workers	10	
	Health care	1	
	Painters	2	
	Plant utilities	2	
	Plant services	1	
	Rail and transportation	1	
	Security	13	
	Sheet metal	3	
	Storage	17	1 (5.9)
	Trainees, interns general	1	
	Grounds workers	5	1 (20.0)
	Waste disposal	1	
	Radiograph	2	
1			
Rare exposures; can include bystander or indirect exposure	Production operators	274	5 (1.8)
	Explosive operators	44	1 (2.3)
	Component operators	187	1 (0.5)
	Scientists	7	
	Plumbers/pipe fitters	4	
2			
Occasional exposures; can include bystander or indirect exposures	Machinists	7	
	Tool and die	6	
	Millwrights	41	2 (4.9)
	Mechanical division supervisors	3	

*Category 0 also included food service, firing-site workers, scale/instrument repairmen, stores and safety and health. Category 1 included facilities maintenance and burn ground workers—none screened.

Hankinson et al,[39] and were adjusted for age, sex, height, and race. Percentage-predicted diffusing lung capacity for carbon monoxide was calculated on the basis of the equations of Miller et al.[40] The HRCT scans were reviewed within the same radiology department for the evidence of interstitial lung disease, including reticular changes, honeycombing, traction bronchiectasis/bronchiolectasis, interlobular septal thickening, and ground glass opacities, as well as perilymphatic nodules and mediastinal and hilar adenopathy.[41–43] Evidence of spirometric and radiologic abnormalities in combination with symptoms was required, under the clinical evaluation protocol, for bronchoscopy with lavage and transbronchial biopsies.

Analysis

Data generated through this study were double-entered and stored in a secure Microsoft Access 2002 to 2007 database, with data queries completed periodically for update and quality assurance purposes. Personal identifiers were removed from the data before exporting them into PC SAS 9.2 software (SAS Institute Inc, Cary, NC) for statistical analyses.[44] The date of the last BeLPT screening was used to determine workers' age. *Never smoking* was defined as less than 20 packs of cigarettes smoked during one's lifetime and ever smokers included current and ex-smokers. *Use of immunosuppressants* was defined as the use of oral or injected derivatives of corticosteroids or other immunosuppressants, including chemotherapeutic agents at the time of the testing.

Frequencies of categorical covariates and means, standard deviations, and ranges of continuous covariates were calculated by sensitization status. Fisher exact test was used to evaluate the differences in frequencies of covariates and exposure levels between sensitized and nonsensitized individuals and to compare the prevalence rate of sensitization from this study with rates in other studies. The Cochran-Armitage chi-square test[45] was used to assess the trend in sensitization rates by exposure to beryllium, age, date of first hire, and the duration of employment. Normality distribution of continuous variables was tested by using the Shapiro-Wilk test, and the Wilcoxon ranked sum test was used to evaluate the differences in medians of nonnormally distributed continuous covariates between sensitized and nonsensitized groups.

Crude odds ratios (OR) and 95% confidence intervals (CIs) were calculated, using logistic regression methods, for unadjusted association of each explanatory variable with sensitization. Forward selection was used to build a multivariable logistic regression model, in which the risk of sensitization by exposure was assessed while adjusting for potential confounders, including all explanatory variables under study. A P value of less than 0.15 was required for possible entry into the model. All tests conducted were double-sided, and statistical significance of $P < 0.05$ was selected throughout all the analyses.

RESULTS

The study cohort included 33,544 workers employed between 1948 and 2002. A total of 1131 workers (including 212 category 2 workers), identified through records from a major credit bureau and World Wide Web sites as living within a 4-hour driving distance of the screening sites, were mailed invitations to participate in the study. Three hundred thirty-eight (30%) of contacted workers responded, and of these respondents, 210 (63%) agreed to participate in the screening. Seventy percent ($n = 793$) of contacted workers did not respond to the mailings or follow-up phone calls or their contact information was incorrect. An additional 360 workers were recruited after BeLPT sensitivity screening was opened to all workers employed between 1948 and 2002 for a total of 570 participants. Eight percent ($n = 46$) of the screened workers were excluded from the analyses because of the following reasons: (1) They had potential exposure to nuclear weapons—DoE operations on site ($n = 34$); (2) They were employed on site before 1948 ($n = 2$); (3) Their employment started after 2002 ($n = 2$); or (4) They had no available employment records ($n = 2$). Six additional workers were excluded, because a single valid test result (ie, normal, abnormal, or borderline) was not confirmed by a second valid test from either the initial or subsequent split tests. The final cohort included 524 workers.

Table 1 shows the distribution of job categories between eligible workers and those found to be sensitized. There were a total of 522 (99.6%) workers for whom at least one job title was available to estimate their exposure potential. Approximately 38% ($n = 197$) worked multiple jobs (range, two to six) during their tenure at the plant; hence, the aggregate number of workers between the job categories was greater than the actual number of workers screened. Fifteen workers (2.9%) worked in short-term jobs with undetermined exposure potential, and two (0.4%) of 524 eligible workers held jobs at the plant that had undetermined exposure potential.

Eight workers (1.5%) were identified as sensitized by a confirmed abnormal BeLPT. Sensitized workers were found in each of the three exposure strata: storage (category 0; $n = 1$), production (category 1; $n = 2$), component operations (category 1; $n = 1$), and millwright (category 2; $n = 1$). Three sensitized workers worked in multiple jobs: one was first hired as a millwright (category 2) and later rehired as a production operator (category 1); one worked as an explosives operator (category 1) and subsequently in production operations (category 1); and one started as a production operator (category 1) and was rehired for grounds maintenance (category 0).

The nonsensitized workers included 490 (93.5%) individuals with a confirmed double-normal result, three (0.6%) with a single abnormal test, and 23 (4.4%) workers with a single borderline result. The majority of nonsensitized workers worked in production and component operations, with 150 (54.7%) of the ever-production workers found to have held multiple jobs and 63 (33.7%) of ever-component operators working in other jobs as well. Altogether, almost 20% of all nonsensitized workers ($n = 102$) worked in multiple jobs that would have put them in different beryllium-exposure category: 81 worked in both categories 0 and 1 jobs; 8 in categories 1 and 2 jobs; 11 in categories 0 and 2 jobs; and 2 in every exposure category.

Table 2 presents the prevalence of sensitization and unadjusted associations of sensitization by age, sex, smoking, use of immunosuppressants, date of first hire, aggregate duration of employment, and beryllium-exposure strata. With the exception of gender, none of the variables was significantly associated with sensitization. All confirmed sensitization cases occurred in men ($P = 0.01$). Work in category 2 jobs was associated with an almost threefold higher rate of sensitization when compared with category 0 exposures, but the result was not statistically significant (OR = 2.64; 95% CI, 0.23 to 29.94; $P = 0.36$). Comparing individual highest exposed with those working in combined exposure categories 0 and 1 was still not statistically significant but revealed a higher OR with a narrower CI (OR = 3.10; 95% CI, 0.61 to 15.73; $P = 0.19$). The algorithm for the multivariate logistic regression model did not converge.

Table 3 presents the results of the clinical evaluation of sensitized individuals for CBD. Of eight sensitized workers, six underwent clinical testing and two declined follow-up testing. All six were found to have normal spirometry and diffusing lung capacity for carbon monoxide, with one worker having a minimally decreased FEV1/FVC ratio suggestive of mild obstructive airways physiology[46]; testing was, however, done before the bronchodilator intake. No evidence of CBD was found on the HRCT of any of the participants. There were no clinical indications at the time of follow-up for bronchoscopy testing in any of the participants.

DISCUSSION

The prevalence of confirmed BeS, as defined by a double-abnormal or abnormal and borderline BeLPT in this cohort of former and current conventional munitions workers, was 1.5%. This prevalence is slightly higher than expected in workers with minimal beryllium-exposure levels, including 1.3% ($P = 0.89$) in DoE workers from the Nevada test site[47] and 1.4% ($P = 0.90$) in construction workers from three nuclear weapons sites.[7] The rate remains higher even after restricting the confirmed BeLPT definition to only two and more abnormal tests (1.0% in this study), as compared with the studies of aluminum smelter workers from nine aluminum-producing plants (0.47%; $P = 0.32$).[12] This sensitization rate is also higher than the estimated 0% ($P = 0.06$) background rate of a double-abnormal BeLPT in the population of new hires in the beryllium facility.[48] The only identifiable risk of exposure was occasional resurfacing and grinding of Cu–2% Be alloy tools (Fig. 1). In addition, these activities were primarily conducted in one location, a tool-and-die shop separate from the production area, with an estimated less than 2% of the workforce working in this area as millwrights and tool-and-die workers. The beryllium-containing tools might also have been resurfaced or ground in small shops in several buildings located throughout the site, but the majority of workers at this site were employed in jobs with no or minimal bystander potential for exposure.

The implications of this prevalence rate for the DoD workforce at large should be further explored. It has been estimated that between 6% and 8% of those with a confirmed abnormal BeLPT progress to CBD per year.[24] Sensitization has also been found to regress over time.[30,49] It is unknown whether this regression in sensitization may be caused by removal from exposure or age-related waning of immune response. It is also unclear to what degree the reported between- and within-laboratories disagreement on the BeLPT serial testing may affect the estimates of progression.[36,37,50,51] This study found the agreement between split-test laboratories to range from poor (weighted κ statistic = 0.17; 95% CI, −0.02 to 0.35) to fair (weighted κ statistic = 0.35; 95% CI, 0.01 to 0.70).[52] The probability

TABLE 2. Characteristics of Sensitized and Nonsensitized Workers and Unadjusted Predictors of Beryllium Sensitization

Parameter	Sensitized (*n* = 8)	Nonsensitized (*n* = 516)	*P* Value	Odds Ratio (95% Confidence Interval)
Age; mean (SD), range	64(7), 54–74	63(10), 28–88	0.85*	NA
Age (yrs); *n* (%)				
< 55	1 (1.1)	91 (98.9)	0.97†	1.0
55–59	2 (2.1)	93 (97.9)		1.96 (0.17–21.96)
60–64	2 (1.7)	119 (98.3)		1.53 (0.14–17.13)
65–69	1 (1.0)	96 (99.0)		0.95 (0.06–15.38)
70+	2 (1.7)	117 (98.3)		1.56 (0.14–17.42)
Sex, *n* (%)				
Male	8 (2.8)	273 (97.2)	0.01‡	NA
Female		243 (100.0)		
Smoking, *n* (%)				
Ever smoker	5 (1.5)	330 (98.5)	1.00‡	1.0
Never smoker	3 (1.6)	186 (98.4)		1.07 (0.25–4.50)
Immunosuppressant use, *n* (%)				
Yes		17 (100.0)	1.00‡	NA
No	8 (1.6)	499 (98.4)		
Date of first hire, *n* (%)				
<7/1/1975 (during DoE operations on site)	7 (1.9)	357 (98.1)	0.45‡	1.0
≥7/1/1975 (no DoE operations on site)	1 (0.6)	159 (99.4)		0.32 (0.04–2.63)
Employment duration (mo); mean (SD), range	48(67), 0.5–194.0	103(126), 0.1–855.5	0.19*	N/A
Employment duration (mo), *n* (%)				
<12	3 (2.3)	126 (97.7)	0.19†	1.0
12–40	3 (2.2)	128 (97.8)		0.99 (0.20–4.97)
41–169	1 (0.7)	132 (99.3)		0.32 (0.03–3.15)
170+	1 (0.8)	130 (99.2)		0.32 (0.03–3.20)
Beryllium exposure, *n* (%)				
Category 0	1 (1.5)	66 (98.5)	0.36†	1.0
Category 1	5 (1.2)	398 (98.8)		0.83 (0.10–7.21)
Category 2	2 (3.8)	50 (96.2)		2.64 (0.23–29.94)
Missing (no available job data)		2 (100.0)		
Beryllium-exposure categories combined, *n* (%)				
Category 0+1	6 (1.3)	464 (98.7)	0.19‡	1.0
Category 2	2 (3.8)	50 (96.2)		3.10 (0.61–15.73)
Missing (no available job data)		2 (100.0)		
Beryllium-exposure categories combined, *n* (%)				
Category 0	1 (1.5)	66 (98.5)	1.00‡	1.0
Category 1+2	7 (1.5)	448 (98.5)		1.03 (0.13–8.52)
Missing (no available job data)		2 (100.0)		

*Wilcoxon rank-sum test.
†Cochran-Armitage test.
‡Fisher exact test.

of the split-testing protocol confirming sensitization was estimated, using methods suggested by other researchers, at 60%.[36] An additional uncertainty in the interpretation of beryllium-sensitization surveys is that both false positives and false negatives can only be discerned through invasive testing. Given these estimates and the average latency of the last potential exposure to beryllium of 25 years (range, 3 to 56 years), this population may have had an undetermined number of previously sensitized individuals.

The results of this study reveal a nonzero prevalence of sensitization in a low-exposed, previously unstudied industry and an increase in prevalence of sensitization in those workers with job titles associated with increased potential for exposure. Given the widespread use of beryllium and its products by the munitions industry, these findings may have implications for recommendations of surveillance of defense industry and other workforces who process beryllium products or who are potentially exposed to resurfacing of beryllium tools. These findings can also have implications for other industries using such alloy tools (Fig. 1) to consider improvements in control measures, including replacing damaged tools as opposed to resurfacing same and reevaluation of industrial hygiene and engineering control measures to prevent exposure to beryllium from the grinding of beryllium-containing tools in the workplace.[53]

The increase in prevalence and risk of sensitization found in those DoD workers working in category 2 beryllium-exposure jobs compared with those working in only category 0 jobs, although not statistically significant, is consistent with the trend in the risk of sensitization found in the previous study of former DoE nuclear weapons workers from the same site.[31] Beryllium-exposure strata in

TABLE 3. Results of Clinical Evaluation of Sensitized Workers

ID	Age	Age at First Hire	Smoking	FVC%	FEV1%	FEV1/ FVC%	D_LCO%	HRCT Findings	BeLPT
1	58	18	Ex-smoker	90	98	77	81	No ILD, calcified granulomas, 2-mm nodules	AB + AB
2	59	18	Ex-smoker	96	100	73	102	No ILD, calcified granulomas	AB + AB
3	64	22	Never	100	103	77	NA	Multiple nonpathologic, <1-cm mediastinal and hilar lymph nodes	AB + BD
4	69	30	Never	94	114	83	89	No ILD; 3-mm pleural-based nodule	AB + AB
5	72	30	Never	128	120	68	83	No ILD, minimal apical scarring and punctuate lymphadenopathy	AB + AB
6	74	18	Ex-smoker	94	113	79	101	No ILD; nodular intralobular septal thickening, 3-mm nodule	AB + AB
7	54	34	Ex-smoker	Declined clinical follow-up					AB + BD
8	60	18	Current	Declined clinical follow-up					AB + BD

AB, abnormal; BD, borderline; BeLPT, Beryllium Lymphocyte Proliferation Testing; D_LCO%, percentage-predicted diffusing lung capacity for carbon monoxide FEV1%, percentage-predicted forced expiratory volume in the first second; FVC%, percentage-predicted forced vital capacity; HRCT, high-resolution computed tomographic; ILD, interstitial lung disease.

FIGURE 1. Copper-beryllium alloy tools with instructions for grinding to maintain chamfer

both studies were determined on the basis of employment records, with the highest individual exposure job potential used as a proxy for personal exposure. The DoE workers at this site, as their DoD counterparts, had minimal risk for exposure to beryllium. Those highest exposed in both operations worked occasionally in grinding and reshaping of Cu–2% Be alloy tools. The lack of significance in the current study most likely resulted from insufficient power; however, the increase in the risk of sensitization seen in those highest exposed compared with those lowest exposed added to the body of evidence of potential for BeS being associated with certain tasks with the highest likelihood of beryllium exposure.

No evidence of definite CBD was found in clinically evaluated sensitized workers in this study. The clinical evaluation protocol, with bronchoalveolar lavage and transbronchial lung biopsy performed in only those sensitized individuals with other evidence of lung disease, was negotiated and agreed upon with the funding agency. This protocol may have missed cases of CBD, as up to 25% of those confirmed sensitized without radiologic evidence of lung disease have been found to have noncaseating granulomas with or without mononuclear cell interstitial infiltrates and fibrosis on biopsy.[54] Recent studies, however, show that those sensitized with no histopathologic evidence of lung disease are less likely to progress to a clinically symptomatic disease than those with a biopsy-confirmed diagnosis of CBD.[49]

All confirmed abnormal BeLPT results in this study were found in workers who did not use immunosuppressants at the time of the testing, but this association lacked statistical significance. No statistically significant association was seen between smoking history and sensitization. A statistically significant association was found between smoking and the use of immunosuppressants, including inhaled steroids; ever smokers had more than twofold higher history of using immunosuppressants compared with never smokers (OR = 2.1; 95% CI, 1.03 to 4.15). This is most likely explained by the higher rates of lung disease in ever smokers and subsequent increase in the use of inhaled steroids, but there were no spirometry data available to confirm this finding. Nevertheless, this finding should be considered in future studies of BeS, as immunosuppressant use may confound tobacco use in epidemiologic studies of BeS and lung disease.

Exposure potential in this study was assessed on the basis of employment records and personal accounts of workers with health and safety qualifications and extensive job tenure on site. Exposure misclassification was possible because jobs within the same exposure category might have differed relative to exposure potential, and the accuracy of available work history records remained unknown. Exposure to beryllium from other jobs was ruled out, and the exposure assessment for this workforce was blinded to the results of BeLPT screenings. Since uncertainties in exposure classification were consistently resolved toward the highest exposure, potential misclassification would have biased the results toward the null hypothesis.

This study did not assess the potential for skin exposure in the development of sensitization. No personal exposure data were available, and individual exposure estimates were based on employment history under the assumption of airborne exposures. While dermal exposure remained plausible,[23,25] there was no history of risk for beryllium splinters obtained from former workers at this facility. The group with the highest potential for skin exposures would include the category 2 millwrights and tool-and-die workers occasionally working with the Cu–2% Be alloy tools and probably exposed to larger beryllium particles than those suggested in other studies.[55,56] Those workers' higher risk of sensitization, although not statistically significant, was confirmed by using the qualitative exposure estimates from the job exposure matrix.

Finally, there were no medical records available to estimate the prevalence of sensitization and lung disease in the nonscreened cohort. Nonparticipants might have differed from the screened workers in several characteristics, including, most importantly, gender, start and duration of employment, as well as exposure status; however, this information was not available to measure the potential selection bias. In addition, participants might have self-selected for the study on the basis of health status.

In summary, this study found a nonzero prevalence of a confirmed abnormal BeLPT in the cohort of former and current DoD conventional munitions workers, with an overall low risk for beryllium exposure. The only group with episodic exposures to Cu–2% Be alloys were the millwright and tool-and-die-workers occasionally resurfacing tools; their risk for sensitization was possibly higher, although this result was nonsignificant most likely because of the lack of power.

ACKNOWLEDGMENTS

This study was funded by the DoD with oversight from the US Army Public Health Command-Provisional (USAPHC-Provisional), formerly US Army Center for Health Promotion and Preventive Medicine. The authors thank Dr Deanna Harkins and others of the USAPHC-Provisional, Robert Haines, and the DoD workers who participated in the screenings. They thank Suzanne Sinift, Christina Nichols, Phyllis Scheeler, Sandra Reese, Kerry Krause, Nicholas Hoeger, and Jill Welch for their contribution to the screening program. They also thank Drs Leon Burmeister, Patrick Hartley, and Kai Wang for reviewing a previous version of this article, as well as members of the DoD study community advisory board for their assistance with the study. They also thank the National Institute for Occupational Safety and Health's Occupational Epidemiology Training Program within the Heartland Center for Occupational Health and Safety (grant T42 OH008491) at The University of Iowa for its support.

This study did not receive funding from any of following organizations: National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute. This study did not receive any pharmaceutical or industry support.

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