

Risk of Beryllium Sensitization in a Low-Exposed Former Nuclear Weapons Cohort From the Cold War Era

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Background *The nuclear weapons industry has long been known as a source of beryllium exposure.*

Methods *A total of 1,004 former workers from a nuclear weapons assembly site in the Midwest were screened for sensitization to beryllium (BeS). The screenings were part of the Department of Energy (DOE) Former Worker Program established in 1996.*

Results *Twenty-three (2.3%) workers were found sensitized to beryllium and this prevalence was comparable to other DOE sites. Occasional, direct exposure to beryllium through machining and grinding of copper–beryllium (Cu–Be) 2% alloy tools was found to increase the risk of sensitization compared to background exposure (OR = 3.83; 95% CI: 1.04–14.03) with a statistically significant trend (P = 0.03) revealing that particular jobs are associated with sensitization. Exposure potential in this study was estimated based on job titles and not personal exposure information.*

Conclusions *These results confirm the need to screen workers using beryllium alloy tools in other industries and for consideration of altering work practices.* Am. J. Ind. Med. 54:194–204, 2011. © 2010 Wiley-Liss, Inc.

KEY WORDS: *beryllium; beryllium sensitization; beryllium exposure assessment; medical screenings; former worker program*

INTRODUCTION

Beryllium (Be) is a metal with physical, chemical, and mechanical properties that make it useful in energy, aerospace, automotive, medical, and electronics industries [Stonehouse and Zenczak, 1991]. Inhalational exposure to beryllium dust or fume has been linked to granulomatous,

fibrotic interstitial lung disease [Hardy and Tabershaw, 1946; Freiman and Hardy, 1970; Newman et al., 1989], and lung cancer [Sanderson et al., 2001a]. Lung granulomas and fibrosis are thought to be preceded by sensitization to beryllium, an asymptomatic CD4⁺ T-memory cell mediated immune response affecting up to 15% of the exposed workforce [Saltini et al., 1989; Maier, 2002; Rosenman et al., 2005].

The dose–response, latency, and mechanism of progression from beryllium sensitization to chronic beryllium disease (CBD) have not been clearly determined. Sensitization may develop in workers after few months and up to four decades following initial exposure [Stange et al., 2001; Newman et al., 2005; Cummings et al., 2007; Madl et al., 2007]. Follow-up studies among beryllium industry workers have shown that 6–8% of sensitized workers progress to lung disease per year [Newman et al., 2005]. Studies have also shown that exposures to concentrations below the Occupational Safety and Health Administration (OSHA)

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Permissible Exposure Limit (PEL) of 2 microgram per cubic meter of air ($\mu\text{g}/\text{m}^3$) carry a risk for sensitization and chronic beryllium disease (CBD) [Kreiss et al., 1993a, 1996; Kelleher et al., 2001; Taiwo et al., 2008]. The dose–response relationship is not well understood and risk of CBD is believed to be related to genetic susceptibility to exposure to beryllium [Richeldi et al., 1993; Maier, 2002].

Workers in the nuclear weapons industry have long been recognized to have beryllium exposure and to become sensitized and develop CBD. Studies of DOE (formerly Atomic Energy Commission, AEC) sites have documented beryllium use and risk of sensitization and disease from alloy tools and beryllium casings for nuclear warhead “pits” [Kreiss et al., 1993a; Stange et al., 1996b]; in the research and development departments [Kreiss et al., 1989]; in facility construction [Welch et al., 2004] and cleanup activities [Sackett et al., 2004]. The greatest potential for exposure and risk in this industry is believed to be related to beryllium machining including sawing, grinding, polishing and cutting as well as maintenance services including plumbing, ventilation and janitorial [Kreiss et al., 1993a; Stange et al., 1996b, 2001].

The reported prevalence of sensitization—defined as two abnormal peripheral blood beryllium lymphocyte proliferation tests (BeLPTs) or one abnormal and one borderline test—ranges widely: from 0.8% in cleanup and decontamination workers [Sackett et al., 2004] and 1.4% in construction workers [Welch et al., 2004] to 11.8% in a group of current production, research and development machinists [Kreiss et al., 1989] and 11.9% in health physicists, technicians and beryllium machinists [Stange et al., 2001]. Although not well studied, it is presumed that the background rate of BeS—defined either as a single or confirmed abnormal BeLPT—in the unexposed population is very low and may range between 0% and 1% [Kolanz, 2001; Silveira et al., 2003; ATSDR, 2006].

Section 3162 to Public Law 102-484 called for the Secretary of Energy to implement nationwide surveillance to identify the hazardous exposures in atomic weapons production, and to provide medical screenings to detect health effects from those exposures. The DOE established surveillance programs for several sites around the country under cooperation with universities, labor unions and commercial health care organizations. Results of some of these studies have been described previously in the literature [Stange et al., 1996a, 2001; Dement et al., 2003; Sackett et al., 2004; Welch et al., 2004; Makie et al., 2005; Rodrigues et al., 2008]. This report presents findings of federally mandated screenings for beryllium sensitization among former DOE workers employed at a single weapons assembly plant in the Midwest. This site has been in operation since 1941 as a Load, Assembly and Pack (LAP) facility for the Department of Defense (DOD) conventional munitions operations. Between 1949 and mid-1975 it was shared with DOE for large scale

production of nuclear weapons. In 1975 DOE activities ceased at this site. Extensive testing of non-fissile nuclear weapons’ components and disposal of many tons of high-explosives waste were also performed at this facility.

MATERIALS AND METHODS

Approval for the study was received from the DOE Central Beryllium Institutional Review Board (CBeIRB) and the University of Iowa Institutional Review Board (UI-IRB).

In 2000 and 2001 a site needs assessment was performed to determine work processes and exposures, develop exposure based screening protocols, identify the cohort of former DOE workers, determine their vital status, and obtain contact information. The second phase of the study began in 2001 and included collecting medical, exposure, and work history information and recruiting and screening workers for possible health effects of occupational exposures.

The needs assessment phase involved reviewing historical documents including plant maps, building locations and line area designations, annual health and safety reports, memoranda and policies for bio-monitoring for various toxicants. These documents helped determine the possible exposures and primary locations of DOE activities on site.

Identification of the cohort was primarily based on archived paper employment records. The Local International Association of Machinists and Aerospace Workers Union (IAMAW) provided copies of seniority log books including names, seniority dates, contract dates, and job titles for DOE job codes. The main contractor’s employment records included all employees between 1948 and 2002. Other sources of DOE specific employment information included radiation monitoring dosimetry badge records for a group of scientists, supervisors and foremen, and lists of workers involved in accidents on DOE lines (incident reports) and monitoring records for employees working with specific agents.

Estimating Exposure to Beryllium

The only beryllium environmental data available were surface wipe sample reports for 1970–1974. Some data appeared to be collected to test various cleaning methods (vacuuming vs. wiping). The concentrations reported ranged from non-detectable to 1,000 μg beryllium per sample with no reference to surface area in a 1971 report; non-detectable to 4 $\mu\text{g}/100\text{ cm}^2$ in a 1973 report; and non-detectable to 112 $\mu\text{g}/100\text{ cm}^2$ in a 1974 report. These wipe samples were useful as indicators of the presence and relative levels of beryllium on surfaces of components or work areas in various locations, but could not be used for estimating workers’ exposures at the plant, nor identifying specific operations contributing to beryllium surface dust. The rationale for sampling and the length of time over which beryllium may have accumulated was not documented in survey data.

Interviews of former production, trade and health and safety workers were used to assess areas, activities, and eras for risk of beryllium exposure. The workers reported that millwrights at the plant were at risk for direct exposure to beryllium through machining copper–beryllium (Cu–Be) alloy tools with 1–2% beryllium content, such as chisels, scrapers, and screwdrivers. These tools were machined using belt sanders in one of two tool and die shops. Workers also reported that some workers occasionally honed their own beryllium tools without personal protective equipment or engineering controls. Production workers described the potential of exposure during machining of beryllium layered hemisphere shells used to enclose the nuclear warhead pits. This process was limited to two DOE buildings, only one weapon design and was conducted for a limited period of time by a group of fewer than 15 production workers.

A 2007 survey of surface contamination at this facility revealed only two samples out of one hundred collected throughout the facility which exceeded the DOE surface contamination housekeeping level of $3.0 \mu\text{g}/100 \text{ cm}^2$ and both of these were from surfaces in the area in which millwrights had used belt sanders to occasionally resurface alloy tools [Sanderson et al., 2008]. These surface contamination measurements were used, along with other available information, to estimate the potential for workers to be exposed and categories of exposure level.

Job codes, job titles, and work tasks were reviewed by two trained industrial hygienists and a group of former expert workers with extensive knowledge of the work processes and site, to develop a qualitative exposure matrix for beryllium [Sanderson et al., 2001b]. The estimates for each job were based on task frequency and proximity to potential sources of airborne beryllium and reflected the group's consensus. Workers reported that service and utility employees including laundry personnel, plumbers, and pipefitters were less likely exposed to direct beryllium hazards but may have received bystander exposures from contaminated clothing or maintenance and cleanup activities. Indirect occasional exposures also occurred in production workers and scientists.

No jobs were classified as involving frequent direct exposure, category 3. Occasional direct or indirect exposure to beryllium tool sanding or grinding by tool and die workers, millwrights, and machinists was classified as category 2 (Table I). Production workers, scientists, draftsmen, pipefitters, plumbers, and laundry operators were assigned to category 1 for rare, low indirect or bystander exposure. Administrative personnel, medical staff, storage crews, electricians, ground and security workers were classified as category 0 reflecting the lowest potential for exposure at this site. Exposures from other jobs were not incorporated in the ranking system.

Workers were assigned the highest beryllium exposure category of multiple jobs they worked in during their tenure at the plant. This assignment was based on jobs documented

in the archived employment records only, as given the several decade latency from exposure to this screening survey it was suspected that workers could not accurately recall their detailed work location, time and potential beryllium exposure history. Quantitative exposure was assessed by a beryllium metric (metric) as a function of exposure to beryllium and duration of employment in each job category. This metric was calculated by adding up total months in every exposure stratum for every worker with at least one complete set of hire and termination dates in their employment records and job title/beryllium exposure information.

Recruitment of Participants

The screenings were publicized in local media and educational meetings were held to promote interest among former DOE workers. Recruitment started in 2001 with DOE approved press releases and radio interviews. A toll-free line, email address and a web-site were established and eligibility for the screenings was based upon ever having been employed or directly exposed to nuclear weapons work, and employment starting before 1975 during the DoE presence on site. No minimal duration of employment was required and there were no eligibility restrictions regarding age, current employment, or geographic location.

Contact information for the cohort was obtained from state Driver's License records and updated by major credit bureaus. The targeted mailing, including short medical and employment history questionnaire, was sent initially to known living former nuclear weapons workers with DOE employment verified by job codes and vital status confirmed by Social Security Administration (SSA). In addition, a one-page employment inquiry form was mailed between 2001 and 2003 to all living former workers from the plant with available contact information to identify those eligible for the screenings with no verifiable DOE employment history in the records. Targeted mailing to DOE workers was repeated every year to follow-up on non-responders and contact newly identified nuclear weapons workers.

Volunteers were allowed to participate in the screenings if their DOE employment could be confirmed. Workers in certain jobs including inspection, scale/instrument repairs and calibration, and cafeteria/food services were typically employed by other contractors or by the federal government directly and their employment at the plant on DOE side was verified by other former nuclear weapons workers, volunteers with the study, and/or any other employment records including old medical records from the plant.

Screening for Beryllium Sensitization and Abnormal Lung Physiology

At the screenings, staff obtained informed consent documents from all participants and interviewed the workers

TABLE I. Beryllium Exposure Categories and Jobs

Exposure category	Jobs
Virtually no exposure; lowest exposures at this facility	Administrators, shipping and receiving workers, carpenters, computer workers, plant services workers, custodial and change house workers, rail and transportation workers, electricians, engineers excluding those in category 1, fire fighters, firing site workers, inspectors, secretaries and clerks, storage operators, ironworkers, laborers, melt workers, painters, plant utilities workers, security, safety, sheet metal workers, grounds workers, automotive and equipment mechanics and operators
Rare exposures; can include bystander or indirect exposure	Production operators and supervisors, explosive operators including PBX press, engineers including draftsmen, designers and process engineers, engineer assistants, laundry operators, component operators, scientists, facilities maintenance, plumbers/pipefitters, burn ground workers
Occasional exposures; can include bystander or indirect exposures	Machinists, tool and die workers, millwrights, mechanical division supervisors

regarding their exposure history and duration of work. These interviews were conducted in the presence of volunteer former nuclear weapons workers with knowledge of the site and work processes and were aimed to confirm employment in production of nuclear weapons on site. Those workers who had not completed their medical and employment history questionnaires were allowed to complete them on site with assistance of study staff.

Participating former DOE workers received a peripheral blood BeLPT sent to one of the DOE approved laboratories. The BeLPT measures in vitro response of CD4+ T-memory cells to beryllium [Newman, 2000] and these laboratories followed DOE technical specifications for the test. An individual test was considered abnormal if the rate of beryllium induced cell proliferation—measured by radioactivity counts of cells labeled with tritiated thymidine (3HTdr)—was higher in two or more beryllium exposed wells than the lab specific cut-off value for beryllium unexposed cells. A higher response in one well was defined as a borderline result and the test was considered uninterpretable when cell quality control cultures were out of range or high statistical variability was observed within the sample [US DOE, 2001].

Initial abnormal or borderline results were repeated within 12 months with a split test sent to two laboratories in compliance with the DOE recommended protocol [US DOE, 2001]. An uninterpretable result was repeated within 12 months with the same laboratory that performed the test or with two laboratories per mid-screening protocol modification. At 3–5 years from the initial screening all participating workers with an initial normal result were offered a repeat BeLPT. Beryllium sensitization was defined as either two abnormal BeLPTs, or one abnormal and one borderline test [US DOE, 2001; Welch et al., 2004; Middleton et al., 2008]. No restrictions were placed on whether these results were produced by the same lab or by different laboratories. Additionally, the results could have

come from either a single blood draw sent to two different laboratories (a “split” draw) or separate blood draws processed by the same lab (a “repeat” draw).

All participating workers were offered lung physiology testing. Spirometry was performed according to the American Thoracic Society guidelines [ATS, 1995] by technicians who completed the National Institute of Occupational Safety and Health (NIOSH) approved spirometry training course. Equipment was volume calibrated with a 3-L syringe before every screening day. An effort was made to obtain three reproducible and acceptable forced vital capacity (FVC) maneuvers however no test was excluded from the analyses based on the lack of reproducible results alone [Eisen et al., 1984]. The percent predicted FVC (FVC%) was calculated using the algorithm recommended by Knudson et al. [1983] adjusting for age, sex, height, and race.

Beryllium sensitized workers were referred for clinical evaluation to rule out CBD; however, this follow-up was not part of the DoE screening program hence those data are not available. Neither available are the follow-up data on non-sensitized participants with abnormal spirometry all of whom were referred for evaluation to their family care providers.

Analysis

All data generated through the screenings and/or obtained from the plant were stored in Microsoft Access (2000–2007) relational databases. Data queries were run periodically for quality assurance and reporting purposes. All personal identifiers were removed from the data before exporting it into PC SAS 9.1.3 software for statistical analyses [SAS Institute, Inc., Cary, NC, 2002–2008].

The workers’ age was calculated as of the date of their last BeLPT screening. Never smokers were classified as those with no history of smoking at all or occasional smoking for a

total less than 6 months or less than 20 packs smoked during lifetime.

Frequency distribution of independent variables including age, race, sex, smoking, and beryllium exposure was examined to describe the screened population. Age, FVC% and beryllium exposure metric were further described by measures of central tendency. The Chi-square test or Fisher's exact test were used to compare the frequency distribution of beryllium sensitized and non-sensitized for categorically ordered variables and to compare the prevalence of sensitization with other populations in the literature. The Cochran-Armitage test was used to test for trend in beryllium sensitization by exposure categories and age strata. The Kolmogorov-Smirnov test was used to test for normality of distribution of continuous variables and the Wilcoxon rank-sum test was calculated to evaluate non-parametric variables including age, FVC%, and beryllium metric. Crude odds ratios (OR) and 95% confidence intervals were calculated to assess unadjusted associations of explanatory variables including stratified beryllium exposure, age sex, and smoking with beryllium sensitization.

Unconditional logistic regression was used to explore the risk for sensitization by exposure to beryllium, while adjusting for potential confounders including age and smoking. Logistic regression modeling was also used to evaluate the risk of sensitization by quantitative estimates of beryllium exposure, and FVC%, while controlling for smoking. The predicted value of FVC was adjusted for age, race, and sex at the time of testing thus the effect of variable was controlled for smoking only in the analyses. To avoid issues related to collinearity in the analyses, a rule of thumb of 1 independent variable for each 10 cases of sensitization, suggested by Hosmer and Lemeshow [2000] was applied to the logistic regression modeling. Significance level of 0.05 was selected throughout all analyses as the probability of a Type I error, rejecting the null hypothesis when in fact no association exists.

RESULTS

A total of 6,797 former employees, 18% of the plant's 37,937 total workforce, were identified as having been involved in nuclear weapons production activities and eligible for screening based on DOE specific job codes, radiation dosimetry records, incident reports, union log books and self-report confirmed by coworkers. Fifty two per cent ($n=3,548$) have been identified as deceased by Social Security Administration (SSA) through July 2008.

As of August 2008, 3,617 workers living at the time were mailed invitations to the screenings. The overall mailing response rate was 28% ($n=1,005$). An additional 20 individuals responded independently to media releases and

95% ($n=19$) of these volunteers were confirmed as DOE workers by other nuclear weapons workers and/or additional employment records. Altogether, 1,024 workers—32% of the living cohort—were screened and received at least one BeLPT. Of those, 20 workers (2.0%) had no interpretable result and were excluded from subsequent analyses.

The majority of the screened population ($n=677$, 67.4%) worked in more than one job at the plant. Nuclear weapons operations ceased in mid-1975, but over one third of the screened group ($n=348$, 35.0%) continued to work in conventional munitions production. Twenty-four (2.4%) workers had no documented job code in the archived employment records or their exposure category was unknown and they were excluded from exposure-risk analysis.

The demographic characteristics of the screened DOE workforce and distribution of sensitization by age, sex, smoking history, beryllium exposure and FVC% are presented in Table II. Of 1,004 workers screened, 23 (2.3%) were confirmed sensitized; 16 by two abnormal BeLPTs and seven by one abnormal and one borderline test. The non-sensitized included all workers with normal results, 15 workers with a single, not confirmed abnormal test and four with two borderline results.

The majority of those screened were white males ($n=831$; 82.8%) and the average age at last screening was 71 years (± 9). No cases of sensitization were found in African-American ($n=30$, 3.0%), Hispanic ($n=16$, 1.6%), and Native American ($n=3$, 0.3%) workers. Smoking was common with over 70% of workers reporting ever smoking. Women were less likely than men to have ever smoked (51% vs. 75%, $P < 0.01$). Of all the screened workers six per cent were determined to have had the potential for occasional, direct inhalational exposure to beryllium (exposure category 2) and those were tool and die workers, machinists, and millwrights who resurfaced Cu-Be alloy tools. The mean employment duration was 134 months (11.2 years). The average FVC was 90% predicted but half of the screened workforce tested below 89% of predicted.

No statistically significant differences were found in distributions of age, sex, smoking, FVC%, total duration of employment and duration of employment in category 1 exposure between sensitized and non-sensitized workers. Exposure to beryllium in category 2 and duration of employment in that category, as determined by archived employment records and job titles, were associated with sensitization to beryllium and both results were statistically significant ($P=0.03$ and $P=0.04$).

Table III provides crude odds ratios for risk of beryllium sensitization by exposure strata, age, sex, and smoking history. No cases of confirmed abnormal BeLPT were found in non-Caucasians and the variable race was excluded from further analyses. A statistically significant increase in prevalence of sensitization was observed among category 2

TABLE II. Characteristics of the Screened DOE Workforce

Parameter	Total screened (n = 1,004)	Sensitized (n = 23)	Non-sensitized (n = 981)	P-Value
Age, mean (SD)	71 (9)	74 (11)	71 (9)	0.24 ^a
Sex, n (%)				
Male	831 (82.8)	18 (78.3)	813 (82.9)	0.58 ^b
Female	173 (17.2)	5 (21.7)	168 (17.1)	
Race, n (%)				
White	953 (94.9)	23 (100.0)	930 (94.8)	1.00 ^b
Other or missing	51 (5.1)	—	51 (5.2)	
Smoking, n (%)				
Ever smoker	707 (70.4)	17 (73.9)	690 (70.4)	0.82 ^b
Never smoker	295 (29.4)	6 (26.1)	289 (29.4)	
Missing	2 (0.2)	—	2 (0.2)	
Beryllium exposure—stratified, n (%)				
Category 0 (background)	472 (47.0)	7 (30.4)	465 (47.4)	0.03 ^c
Category 1 (rare/low indirect/bystander)	446 (44.4)	11 (47.8)	435 (44.3)	
Category 2 (occasional direct/indirect)	62 (6.2)	4 (17.4)	58 (5.9)	
Missing (no available job data)	24 (2.4)	1 (4.4)	23 (2.3)	
Beryllium exposure—metric, n, mean, range				
Total months worked	865, 134, 0–631	22, 147, 2–454	843, 134, 0–631	0.45 ^a
Total months worked in category 1 exposure	390, 97, 0–569	12, 114, 2–362	378, 96, 0–569	0.13 ^a
Total months worked in category 2 exposure	49, 129, 6–387	3, 195, 73–267	46, 126, 6–387	0.04 ^a
FVC%, n, mean (SD), median	929, 90 (23), 89	22, 90 (21), 91	907, 90 (24), 89	0.85 ^a

^aWilcoxon rank-sum test.^bChi-square test.^cCochran–Armitage test.

compared to category 0 exposures ($P = 0.03$). Those working in jobs classified as highest exposed had an almost fivefold increased risk of beryllium sensitization compared to non-exposed workers (OR = 4.58; 95% CI: 1.09–18.13) and this result was also statistically significant. Category 1 exposure was associated with increased prevalence of sensitization compared to category 0—2.5% versus 1.5% sensitized workers respectively—but comparison of proportions was not statistically significant (OR = 1.68; 95% CI: 0.60–4.84). The comparison of beryllium sensitization in categories 1 and 2 combined to category 0 was also not statistically significant (OR = 2.02; 95% CI: 0.82–5.00) but comparing category 2 to category 1 and 0 combined provided with a statistically significant result (OR = 3.45; 95% CI: 1.13–10.52).

Age in this study was used instead of the poorly documented first hire date to estimate the potential for exposure to beryllium by era worked in the nuclear weapons production. The oldest workers had an almost threefold higher rate of confirmed abnormal test compared to 60–69 year olds, however this increase was not statistically significant (OR = 2.87; 95% CI: 0.74–11.82). The overall trend for LPT positivity by age was also not statistically significant ($P = 0.26$). Female workers had minimally higher

prevalence of confirmed abnormal BeLPT than men but again this was not statistically significant (OR = 1.34 95% CI: 0.39–3.82 $P = 0.58$). Smoking was not statistically significantly associated with sensitization (OR = 1.19; 95% CI: 0.44–3.71, $P = 0.82$).

Results of logistic regression for beryllium exposure adjusted for potential confounders are presented in Table IV. There were 979 workers with categorical beryllium exposure, age, and smoking information available, to include in this analysis.

The increase in risk for the highest exposed workers (category 2) remained statistically significant after controlling for age and smoking (OR = 3.83 95% CI: 1.04–14.03) and those workers were almost four-times as likely to be sensitized as non-exposed workers. A suggestion of increased risk was also noted in category 1 workers but this result was not statistically significant (OR = 1.64 95% CI: 0.63–4.26).

No statistically significant results were found for those ever working in beryllium exposure—again defined as category 2 and 1 jobs combined—compared to non-exposed workers in category 0 (OR = 1.91 95% CI: 0.63–4.26, $P = 0.16$) and for those working in direct exposure (category 2) compared to bystanders (category 1) and non-exposed

TABLE III. Unadjusted Analysis of Predictors of Sensitization

Independent variable	Sensitized n = 23	Non-sensitized n = 981	OR (95% CI)
Beryllium exposure—stratified n (%)			
Cat 0	7 (1.5)	465 (98.5)	1.0
Cat 1	11 (2.5)	435 (97.5)	1.68 (0.60–4.84)
Cat 2	4 (6.9)	58 (93.1)	4.58 (1.09–18.13)
Missing	1 (4.2)	24 (95.8)	—
Beryllium exposure—stratified n (%)			
Cat 0	7 (1.5)	465 (98.5)	1.0
Cat 1 + 2	15 (3.0)	493 (97.0)	2.02 (0.82–5.00)
Missing	1 (4.2)	24 (95.8)	—
Beryllium exposure—stratified n (%)			
Cat 0 + 1	18 (2.0)	900 (98.0)	1.0
Cat 2	4 (6.9)	58 (93.1)	3.45 (1.13–10.52)
Missing	1 (4.2)	24 (95.8)	—
Age n (%)			
≤59	3 (2.7)	111 (97.3)	2.03 (0.35–10.90)
60–69	4 (1.3)	300 (98.7)	1.0
70–79	9 (2.3)	387 (97.7)	1.74 (0.49–6.79)
≥80	7 (3.6)	183 (96.4)	2.87 (0.74–11.82)
Sex n (%)			
Male	18 (2.2)	831 (97.8)	1.0
Female	5 (2.9)	173 (97.1)	1.34 (0.39–3.82)
Smoking n (%)			
Ever smoker	6 (2.0)	707 (98.0)	1.0
Never smoker	17 (2.4)	295 (97.6)	1.19 (0.46–3.04)
Missing	—	2 (100.0)	—

Cat, category.

(category 0) combined (OR = 2.90 95% CI: 0.91–9.2, $P = 0.07$).

Exposure information was missing for one worker. Analyzing the associations of beryllium sensitization with job or exposure strata assuming that this worker worked in

category 0 resulted in the highest exposed workers still having an over threefold higher risk of sensitization compared to category 0 exposures but the confidence interval included the value of one (OR = 3.36 95% CI: 0.94–11.98). Assigning this worker category 1 exposure did not change the risk estimates for category 1 workers as compared to category 0 (OR = 1.79 95% CI: 0.94–11.98) and placing this worker in the category 2 exposure stratum resulted in an almost fivefold statistically significant increase of risk of sensitization compared to category 0 workers (OR = 4.93 95% CI: 1.45–16.71).

The purpose of the beryllium metric was to evaluate the risk of sensitization by a more quantitative measure of exposure taking into account duration of work in each exposure category. There were 865 workers for whom this metric could be calculated because they had sufficiently complete work history records including start and termination dates for at least one of the jobs held. None of the metrics was found to be significantly predictive of sensitization, although the total duration of employment in category 2 exposure, that is, work tenure in grinding and machining of Cu–Be alloy tools—had the strongest of all three, yet still non-significant effect ($P = 0.10$).

TABLE IV. Logistic Regression Models for Beryllium Sensitization

Independent variable	OR (95% CI)	P-Value
Beryllium exposure—stratified		
Cat 1/0	1.64 (0.63–4.26)	0.31
Cat 2/0	3.83 (1.04–14.03)	0.04
Beryllium exposure—stratified		
Cat 2 + 1/0	1.91 (0.63–4.26)	0.16
Beryllium exposure—stratified		
Cat 2/1 + 0	2.90 (0.91–9.22)	0.07
Beryllium exposure—metric		
Total months worked	N/A	0.87
Total months worked in category 1 exposure	N/A	0.44
Total months worked in category 2 exposure	N/A	0.10

Cat, category.

Modeling of the association between beryllium sensitization and lung physiology revealed no statistically significant associations. There were 929 subjects for whom both spirometry and smoking information was available. Sensitization was not found to be statistically significantly associated with FVC% after controlling for the effect of smoking ($P = 0.95$).

DISCUSSION

The BeLPT has been used as a diagnostic tool for approximately 20 years. The test has been used predominantly in workplace screening programs to identify sensitized workers and to target screening for chronic beryllium disease [Kreiss et al., 1993a,b; Stange et al., 1996b, 2001]. Over 43,000 former DOE nuclear weapons workers have been screened with this test at multiple sites [US DOE, 2009] and other employers have used it extensively in their medical surveillance and CBD prevention programs [Deubner et al., 2001; Cummings et al., 2007]. The test is also accepted by the U.S. Department of Labor (DoL) in establishing the medico-legal diagnosis of beryllium sensitivity and as a diagnostic criterion for CBD under the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) [US DOL, 2005].

The prevalence rate of beryllium sensitization of 2.3% in this cohort is lower than the 4.5% sensitization rate reported in a cohort of former and current DOE workers involved in a full scale manufacture of beryllium containing nuclear weapons' triggers/pits from the cold war era [Stange et al., 2001]. Despite what was thought to be a low risk of exposure, the observed rate of sensitization was higher than sensitization rates in other DOE populations with a relatively low exposure using the same definition of confirmed abnormal BeLPT as the one used in this study: 1.4% ($P = 0.03$) in nuclear weapons facilities construction workers, most of whom did not have a significant risk of exposure or worked with protective measures [Welch et al., 2004]; and higher, but not statistically significantly so, than the sensitization rate of 1.3% ($P = 0.06$) in workers from the Nevada Test Site [Rodrigues et al., 2008]. It was also higher than rates in other industries including 0.3% in aluminum smelters exposed to low concentration beryllium fumes and dusts through the bauxite refinery process [Taiwo et al., 2008] and 1% in workers from a beryllium copper-alloy distribution facility [Stanton et al., 2006]. Finally, it was higher than the 0% [Silveira et al., 2003] to 1% [Kolanz, 2001] background rate suggested in unexposed populations. The rate of beryllium sensitization in unexposed populations has not been well described as BeLPT testing is not performed routinely and the only estimates come from studies of non-exposed occupational cohorts, control groups used by the laboratories or community based surveys.

The 2.3% rate of confirmed sensitization in this cohort of former nuclear weapons assembly workers is particularly interesting given that this workforce was deemed at low risk for exposure compared to other nuclear weapons production sites from the cold war era as there was no pure beryllium metal processed on site. There were two production workers—neither found sensitized—who reportedly handled encapsulated beryllium layered hemispheres used to enclose the nuclear weapons pits, and a small group of 18 welders—none with a confirmed abnormal result—who may have occasionally used Cu-Be weld rods. The greatest potential for generating airborne beryllium based on industrial hygiene assessment and former workers' descriptions was the occasional resurfacing of the Cu-Be (2%) alloy tools by millwrights. Previous studies suggested that machining of beryllium alloys results in lower potential for exposure to respirable particles compared to machining or processing of beryllium metal possibly due to lower brittleness of the alloys [Hoover et al., 1990]. A study of Cu-Be alloy wire production facility documented similar rates of sensitization to other beryllium exposed cohorts and found the highest rate of sensitization among machinists [Schuler et al., 2005]. In this facility, the grinding processes were performed with belt sanders and limited to two small tool and die shops. Using a liberal algorithm for exposure assessment based on job codes, roughly 6% of the screened population was deemed at risk of potential occasional, direct exposures to beryllium. The sensitization rate in this group has broader implications for recommending beryllium sensitization screening of tool and die and production workers using such alloy tools in other industries and for consideration of altering work practices, that is, not grinding such tools on site or using particulate control measures in other industries using beryllium alloy tools.

In their recent summary of the Former Worker Program, the DOE reported a 3.1% average prevalence of at least one abnormal LPT in the population of former DOE workers from 23 sites around the country [US DOE, 2009]. A single abnormal test is viewed as an indicator of immune response to beryllium and the probability of a false positive result has been estimated at approximately 1 in 10,000 [US DOE, 2001]. Many question the validity of a single abnormal LPT in establishing the diagnosis of sensitization and recommend confirmatory retesting. This argument has been primarily based on the reports of variable intra- and inter-laboratory reproducibility of the test [Deubner et al., 2001; Stange et al., 2004]. The current consensus is for sensitization to be confirmed by either a second abnormal test or borderline result [Welch et al., 2004; Middleton et al., 2008; National Research Council of the National Academies, 2008].

The dose-response relationship between exposure and sensitization to beryllium remains unclear. Several authors postulate this relationship is likely influenced by genetic

susceptibility, such as persons with HLA-DPB1 Glu-69 [Richeldi et al., 1993; Maier, 2002]. Studies have confirmed statistically significant increase in risk of sensitization in high exposure jobs [Kreiss et al., 1993a; Stange et al., 2001] and sensitization has been reported to occur in exposures below the current OSHA-PEL [Kreiss et al., 1993a, 1996; Maier et al., 2008; Taiwo et al., 2008]. The fourfold increase in risk of sensitization in directly exposed workers (category 2) compared to non-exposed (category 0) in this study, and an overall statistically significant trend of increasing prevalence by exposure ($P = 0.03$) reveals particular jobs are associated with sensitization. This effect appears to be related to the highest ever exposure job category as opposed to cumulative dose, as the beryllium metric incorporating duration of exposure was not statistically significantly associated with sensitization.

It should be noted that exposure may have been misclassified in this study as a result of inaccuracies intrinsic to the job exposure matrix such as variability of exposure within categories, in particular occasionally exposed bystanders, incompleteness of employment records used to estimate exposure or lack of information on exposure potential from other jobs and military service. Over one third of all sensitized workers were classified as category 0 reflecting the lowest potential for exposure at this site. Those workers may have had potential for exposure, bystander exposure at this facility or through other jobs, sufficient to induce immune response (especially in genetically susceptible individuals). All exposure classification in this study was done blinded towards individual and group BeLPT results. The default assumption for uncertainty in exposure classification was always to the higher exposure category, thus misclassification ought to have biased the results towards the null hypothesis.

The prevalence of beryllium sensitization was limited to living workers. No medical records were available to investigate rates of disease suggestive of CBD in those deceased. Age, gender, race, and exposure characteristics of non-participants may have differed from the screened workers. Without such information on non-responders selection bias cannot be measured. Some participants may have selected themselves for the screenings based on their health status or out of concern regarding health effects from exposures. Conversely as this facility began operations six decades ago it is possible that cases of occupational lung disease occurred years ago but did not survive to participate in the screenings. As this was a federally mandated surveillance program open to anyone with confirmed DOE employment participation bias would have most likely affect generalizability of lung disease and non-respiratory disease rates. Rates of beryllium sensitization, unless accompanied by clinical lung disease, would be less affected. The lack of association with spirometry results suggests this bias may have been small.

This study did not address the clinical significance of beryllium sensitization in the diagnosis of CBD, as this was not part of the DoE screening program and the clinical follow-up data were not available. The latency of several decades between last exposure and the survey suggests that the participants would not be typical of current workforces or more recently exposed cohorts. It is expected that workers who became sensitized and developed symptoms of CBD may have died or otherwise been lost to follow-up for this screening effort. The strongest, yet not statistically significant, associations noted with beryllium sensitization were with subject's age which would be consistent with the expectation that work practices likely resulted in greater exposures in the earliest eras of work. As age is also strongly associated with higher beryllium exposure ($P < 0.0001$) it is likely, in part, a surrogate for exposure.

The results of this study did not confirm the suggested immunosuppressive effect of smoking [Kalra et al., 2000]. In fact, ever smoking was found to minimally increase the risk of sensitization however this increase was not significant. This result may be partially explained by confounding effect of sex, with female risk of sensitization slightly higher than male (OR = 1.34 95% CI 0.39–3.82) and likelihood of smoking significantly lower than males (OR = 0.34 95% CI 0.24–0.49). Testing for the effect of an interaction of sex by smoking on sensitization did not reveal any significant interaction.

This study used Knudson recommended equations for spirometry reference [Knudson et al., 1983]. Most data was collected before the Third National Health and Nutrition Examination Survey (NHANES III) based standards were recommended [Pellegrino et al., 2005; Townsend, 2005].

An interesting observation was made with regards to subcontractors on site. According to former plant employees interviewed through the study, contracting of cafeteria/food services jobs to outside vendors was common on site during 1960s and 1970s. Those workers typically worked shorter shifts and were escorted on line by security cleared personnel. Three cafeteria workers with no plant employment records came to the screenings and their employment was confirmed by other DOE employees. One of those workers was eventually found sensitized and the other had a single, not confirmed abnormal test. Their employment history was otherwise insignificant for exposure to beryllium and they worked on site from 3 to 6 months. This group could not be further investigated as there were no records available to locate the workers, but this finding has important implications for screening of subcontractors' workers employed temporarily in nuclear weapons production or any other beryllium processing facility. It also has legal implications for a compensation system as those workers are currently excluded from the federally mandated Energy Employees Occupational Illness Compensation Program.

This study has found an elevated rate of sensitization in a population of nuclear weapons workers at low risk for exposure compared to other low exposed populations. This workforce was unique in that exposures were rare and occurred on average several decades prior to the screenings. Sensitization was also found in subcontractor workers with limited exposure potential. The findings from the study have important implications for workers using beryllium alloy tools in any industry and call for altering of work practices to reduce occupational exposure to beryllium.

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