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Epidemiology of beryllium sensitization and pneumoconiosis in the population of former nuclear weapons workers and current and former conventional munitions workers from the Iowa Army Ammunition Plant (IAAAP) in Burlington, Iowa

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EPIDEMIOLOGY OF BERYLLIUM SENSITIZATION AND PNEUMOCONIOSIS IN THE POPULATION OF FORMER NUCLEAR WEAPONS WORKERS AND CURRENT AND FORMER CONVENTIONAL MUNITIONS WORKERS FROM THE IOWA ARMY AMMUNITION PLANT (IAAAP) IN BURLINGTON, IOWA

by

Marek Andrzej Mikulski

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Occupational and Environmental Health
in the Graduate College of
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Thesis Supervisor: Professor Laurence J. Fuortes

ABSTRACT

Background: Nuclear and conventional weapons industry workers are at risk for exposures to beryllium, asbestos, high explosives and barium, all of which are implicated in the pathogenesis of pneumoconiosis. Beryllium has also been shown to cause sensitization (BeS) carrying a risk of progression to Chronic Beryllium Lung Disease (CBD). Data are lacking on the epidemiology of beryllium related health effects in conventional munitions workers and limited studies have been published on the prevalence of BeS in workers with minimal exposure. Data on the prevalence of pneumoconiosis in nuclear weapons workers is also lacking. The main objectives of this study were to determine prevalence and risk factors for beryllium sensitization in former nuclear and conventional munitions workers and rates of and risk factors for pneumoconiosis in former nuclear weapons workers, both cohorts from the Iowa Army Ammunition Plant (IAAAP) in Burlington, IA.

Methods: Former nuclear weapons workers were offered chest x-ray (CXR) and blood screening for sensitization with beryllium lymphocyte proliferation test (BeLPT) as part of the Department of Energy (DoE) Former Worker Medical Screening Program. Conventional munitions workers were offered BeLPT and clinical follow-up if sensitized, as part of a Department of Defense (DOD) funded study. Chest x-rays were reviewed by three readers according to the International Labour Organization's Classification system for Radiographs for Pneumoconioses (ILO system). Exposures under study were characterized qualitatively by the industrial hygiene team and based on former worker interviews and historical industrial hygiene records.

Results: The prevalence of beryllium sensitization in nuclear and conventional munitions workers was found to be slightly higher than in other workforces and weapons worker populations at low risk for exposure. The prevalence of parenchymal disease was higher in these nuclear weapons workers than in other DoE studies, while the prevalence of coincident parenchymal and pleural and isolated pleural disease was lower than in other nuclear weapons populations. Workers who occasionally dressed the copper-beryllium alloy tools were found to have an increased risk of beryllium sensitization, compared to those in administrative or other jobs with insignificant potential for exposure on site. Exposure to beryllium, asbestos, high explosives or barium was not associated with lung disease in this population.

Conclusions: The findings from this study have potential policy implications for DOE and DOD to extend or implement beryllium surveillance and lung disease screening for their workforces and better control use of the copper-beryllium alloy tools in their production processes.

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CERTIFICATE OF APPROVAL

PH.D. THESIS

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CHAPTER 1

INTRODUCTION

Nuclear and conventional weapons industry workers are recognized as being at risk for a variety of respiratory exposures associated with occupational lung disease. Beryllium has been a major focus of the nuclear weapons workers studies because of its relatively common use in this industry and the expected continuum from immune mediated sub-clinical beryllium sensitization (BeS) to Chronic Beryllium Disease (CBD), a rare but debilitating and typically progressive lung disease. Data are lacking on the epidemiology of beryllium health effects in conventional munitions workers and limited studies have been published on the prevalence of BeS and CBD in nuclear weapons workers at low risk for exposure.

Population-based data on the prevalence of work-related parenchymal and pleural disease in the weapons workers is also limited. Despite a nationwide Department of Energy (DoE) medical surveillance program for former nuclear weapons industry workers, few programs have systematically reported their findings on work-related radiological abnormalities involving lung parenchyma and pleura. The published reports have been restricted to selected exposures specifically beryllium, asbestos, silica and ionizing radiation, and included results of chest x-ray review, according to International Labour Organization's system for classification of radiographs for pneumoconioses (ILO system), among former construction, craft, trade, production and maintenance workers from five sites (Kreiss et al., 1993a; Dement et al, 2003; Makie et al., 2005; Newman et al., 2005b; Dement et al., 2010). These studies provide a reference for other nuclear weapons worker populations, however exposures across sites differ substantially and data are still lacking regarding the pulmonary effects of other exposures in this industry, such as high explosives and barium.

The specific aims for this study were:

- To determine prevalence and risk factors for BeS in former nuclear weapons assembly workers at the Iowa Army Ammunition Plant (IAAAP) in Burlington, IA.
- To determine prevalence and risk factors for BeS in current and former conventional munitions workers at the IAAAP.
- To determine prevalence and risk factors for work-related parenchymal and pleural abnormalities as evidenced by CXRs reviewed according to ILO system in former nuclear weapons workers at the IAAAP.

It is expected that fulfilling these aims will add to the knowledge on epidemiology of beryllium sensitization and work-related parenchymal and pleural lung disease among nuclear and conventional munitions weapons workers. Ultimately, the results of this study have a potential to shape the DoE and DoD policies regarding surveillance of workers in the weapons industry with particular attention on work-related lung disease and effects of beryllium exposure.

Background

The University of Iowa, College of Public Health is conducting medical surveillance projects aimed at screening former and current IAAAP workers for adverse health effects, including pulmonary effects, related to employment in nuclear and conventional weapons production. These projects have been funded by DoE and DoD.

The DoE project is part of the nationwide Former Worker Program (FWP) established in response to U.S Congress adding Section 3162 to the Public Law 102-484 of the 1993 National Defense Authorization Act. This section called for the Secretary of Energy to implement a nationwide surveillance program to identify the hazardous exposures in atomic weapons production, and provide medical screenings to detect health effects from those exposures. Since 1996, DoE established programs for 27 sites around the country under cooperative agreements with universities, labor unions and commercial health care organizations. Over 60,000 former workers have been screened throughout October 2009 (U.S. DOE - Office of Health, Safety and Security, 2010).

The DoD project is a congressionally mandated study in response to section 1078 of the Floyd D. Spence National Defense Authorization Act for Fiscal Year 2001 (Pub. L. No. 106-398), as amended by section 8172(a) of the DoD Appropriations Act (Pub. L. No. 107-117) and section 8172(e) of that Act. Section 8172 of the DoD Appropriations Act, 2002, modified section 1078, and required DoD to conduct a health study of current and former workers at the Army facility at the IAAAP.

IAAAP has been in operation since 1942 as a conventional munitions Load, Assembly and Pack (LAP) facility. Several types of conventional warheads have been produced there along with different kinds of ammunitions including mines, demolition charges, and weapons' component parts such as fuses, primers and detonators. The plant also conducts testing of weapons' components, processes tons of Trinitrotoluene (TNT) derived high explosives on a yearly basis and disposes of old and/or obsolete ordnance (Fuortes, 2001). Historically (until 2001) all the hand tools used in the facility had been copper-beryllium (Cu-Be) alloy tools (Robert Haines, personal verbal communication, 2004).

For almost three decades, from early 1949 to mid 1975 nuclear weapons were assembled, disassembled and repaired on site, on Burlington Atomic Energy Commission Plant's (BAECP) Line 1 otherwise known as Division B. This part occupied roughly one percent of the Plant's production area but adjacent areas were used for testing of weapons' components and disposal of waste products. The BAECP operated until June 1975 when production was moved to Pantex, BAECP's sister plant, in Amarillo, TX (Lemert, 1979; Fuortes, 2001).

Approximately 33,544 workers have been employed in conventional DoD munitions operations also known as workers Division A through 2002 (Mikulski et al., 2011b). An estimated 6,797 workers or roughly 18% of the plant's workforce worked on

Division B between 1949 and 1975 (Fuortes, 2001; Mikulski et al., 2011a). They were craft, trade, maintenance, utility, administration and service workers employed by the Atomic Energy Commission (AEC), its contractor and subcontractors. The same contractor, Mason & Hanger- Silas Mason Co (now American Ordnance LLC), operated the Division A conventional munitions production lines, under contract with US Army. Crossover of workers between lines was common and between 80 to 90% of atomic bomb workers also worked on Division A component lines at some time (Lemert, 1979; Fuortes, 2001).

According to interviews with former DoE and DoD workers, and review of available industrial hygiene records on file, the craft and trade workers at the plant were involved in assembly, testing and disassembly operations that potentially exposed them to beryllium from machined copper-beryllium alloy tools. Those workers were also exposed to a variety of high explosives and epoxy adhesives from melt, assembly and bonding operations; and ionizing radiation, from fissionable materials and x-ray equipment. Service and utility workers including security guards, laundry personnel, storage crews, and general laborers were less likely exposed to direct production hazards but their exposures included bystander exposure to beryllium from production operations or contaminated clothing, and ionizing radiation from nuclear warheads and geologic radon in underground production and storage spaces. Construction and maintenance personnel were at particular risk for exposures to asbestos but bystander exposure to beryllium was again possible. Exposures to beryllium, asbestos, radon and ionizing radiation have been recognized as risk factors for chronic long-term pulmonary effects in the weapons industry. Data on the epidemiology of pulmonary effects associated with exposures to high explosives and barium are lacking.

Detailed review of the literature on each of the study aims is included in the next three chapters. It should be noted that this review is presented in a publishable format as two of the three doctoral studies included in this thesis, namely chapters 2 and 3, have already been published. The third study, included in chapter 4, is currently in the process of submission, expected to be undergoing peer-review at the time of the deposit of this thesis. Repetitions in literature review and methodology will be noted as these studies analyzed, in all three instances, the health effects of the exposure to beryllium and were conducted on the cohort of workers from the same weapons assembly site.

CHAPTER 2

RISK OF BERYLLIUM SENSITIZATION IN A LOW-EXPOSED FORMER NUCLEAR WEAPONS WORKERS COHORT FROM THE COLD WAR ERA

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., 2005b; 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., 2005a). Studies have also shown that exposures to concentrations below the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) of 2 microgram per cubic meter of air ($\mu g/m^3$) carry a risk for sensitization and chronic beryllium disease (CBD) (Kreiss et al., 1993a; Kreiss et al., 1996; Kelleher at 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 1996a); 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; Stange et al., 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 et al., 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; Stange et al., 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 µg/100 cm^2 in a 1973 report; and non-detectable to 112 µg/100 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 µg/100 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 1). 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.

Table 2-1 Beryllium exposure categories and jobs

Exposure category	Jobs
Category 0 Virtually no exposure; lowest exposures at this facility	Administrators, shipping and receiving workers, carpenters, computer workers, plant services workers, custodian 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 & operators
Category 1 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
Category 2 Occasional exposures; can include bystander or indirect exposures	Machinists, tool and die workers, millwrights, mechanical division supervisors
Category 3 Frequent exposures; several times weekly; can include bystander or indirect exposure	Not assigned

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 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 (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 (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 (DOE, 2001; Welch et al., 2004; Middleton et al., 2006). 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, USA, 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 was applied to the logistic regression modeling (Hosmer and Lemeshow, 2000). 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 2. 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).

Table 2-2 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[3]
Sex, n (%)				
Male	831 (82.8)	18 (78.3)	813 (82.9)	0.58[1]
Female	173 (17.2)	5 (21.7)	168 (17.1)	
Race, n (%)				
White	953 (94.9)	23 (100.0)	930 (94.8)	1.00[1]
Other or missing	51 (5.1)	-	51 (5.2)	
Smoking, n (%)				
Ever smoker	707 (70.4)	17 (73.9)	690 (70.4)	0.82[1]
Never smoker	295 (29.4)	6 (26.1)	289 (29.4)	
Missing	2 (0.2)	-	2 (0.2)	
Beryllium exposure, n (%)				
Category 0	472 (47.0)	7 (30.4)	465 (47.4)	0.03[2]
Category 1	446 (44.4)	11 (47.8)	435 (44.3)	
Category 2	62 (6.2)	4 (17.4)	58 (5.9)	
Missing	24 (2.4)	1 (4.4)	23 (2.3)	
Beryllium exposure, n, mean, range				
Total months worked	865;134;0-631	22;147;2-454	843;134;0-631	0.45[3]
Total months worked in category 1	390;97;0-569	12;114;2-362	378;96;0-569	0.13[3]
Total months worked in category 2	49;129;6-387	3; 195;73-267	46;126;6-387	0.04[3]
FVC%, n, mean (SD), median	929;90(23);89	22;90(21);91	907;90(24);89	0.85[3]

(1) Chi-square test

(2) Cochran-Armitage test

(3) Wilcoxon rank-sum test

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 3 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 compared to category 0 exposures ($P=0.03$). Those working in jobs classified as highest exposed had an almost five-fold 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).

Table 2-3 Unadjusted analysis of predictors of sensitization

Independent Variable	Sensitized n=23	Non-sensitized n=981	OR (95% CI)
Beryllium exposure, 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)	23 (95.8)	-
Beryllium exposure, 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)	23 (95.8)	-
Beryllium exposure, 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)	23 (95.8)	-
Age, n (%)			
$\leq$ 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)
$\geq$ 80	7 (3.6)	183 (96.4)	2.87 (0.74-11.82)
Sex, n (%)			
Male	18 (2.2)	813 (97.8)	1.0
Female	5 (2.9)	168 (97.1)	1.34 (0.39-3.82)
Smoking, n (%)			
Never smoker	6 (2.0)	289 (98.0)	1.0
Ever smoker	17 (2.4)	690 (97.6)	1.19 (0.46-3.04)
Missing	-	2 (100.0)	-

Results of logistic regression for beryllium exposure adjusted for potential confounders are presented in Table 4. 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 (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 2-4 Logistic regression models for beryllium sensitization

Independent variable	OR (95% CI)	p-value
Beryllium exposure		
Cat 1/0	1.64 (0.63-4.26)	0.31
Cat 2/0	3.83 (1.04-14.03)	0.04
Beryllium exposure		
Cat 2+1/0	1.91 (0.63-4.26)	0.16
Beryllium exposure		
Cat 2/1+0	2.90 (0.91-9.22)	0.07
Beryllium exposure		
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

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; Kreiss et al., 1993b; Stange et al., 1996a; Stange et al., 2001). Over 43,000 former DOE nuclear weapons workers have been screened with this test at multiple sites (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) (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 et al., 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 at 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 (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 (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., 2006; 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; Kreiss et al., 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.

Conclusion

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.

CHAPTER 3

PREVALENCE OF BERYLLIUM SENSITIZATION AMONG DEPARTMENT OF DEFENSE (DOD) CONVENTIONAL MUNITIONS WORKERS AT LOW RISK FOR EXPOSURE

Introduction

Multiple reports have been published on the prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) in Department of Energy (DoE) nuclear weapons workforce (Kreiss et al., 1989; Kreiss et al., 1993a; Stange et al., 1996a; Stange et al., 2001; Frome et al., 2003; Sackett et al., 2004; Welch et al., 2004; Arjomandi et al., 2010); however data are lacking regarding the epidemiology of beryllium-related health effects in Department of Defense (DoD) associated workforces. The Department of Defense has been the major user of beryllium products either in the manufacture of conventional ordnance or in production of electro-optical targeting systems, infrared countermeasure devices, and missile guidance and radar systems (Stonehouse & Zenczak, 1991). Studies estimate some 18,400 current DoD contractor workers may be potentially exposed to beryllium (Henneberger et al., 2004).

Cross-sectional studies have reported 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% (Taiwo et al., 2008; Taiwo et al., 2010). Among higher exposed beryllium extraction, metal, and oxide production workers, 14.6% were found to have BeS (Rosenman et al., 2005). CBD has been found to affect up to 8% of exposed populations (Kreiss et al.,1989), 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 (Richeldi et al., 1993; Maier, 2002) as well as particle size, concentrations, and solubility (Kreiss et al., 1989; Kreiss et al., 1993a; Kreiss et al., 1993b; Kreiss et al., 1997; McCawley et al., 2001; Newman et al., 2001; Stange et al., 2001; Stefaniak et al., 2003; Stefaniak et al., 2004; Schuler et al., 2005; Kreiss et al., 2007). Sensitization has been found to develop as early as a few months after initial exposure or after up-to four decades (Newman et al., 2005a; Cummings et al., 2007; Madl et al., 2007). Smoking, a known suppressant of T-cell proliferative response (Kalra et al., 2000; Kalra et al., 2002), has been postulated to decrease risk of sensitization and CBD (Newman et al., 2005a), while corticosteroids, the first line of drugs in the treatment of CBD, have been shown to potentially reverse sensitization (Deodhar et al., 1973; Rom et al., 1983).

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 (GOCO) 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 Department of Energy (DoE) for 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 (UI-IRB). The details of cohort identification have been described elsewhere (Mikulski et al., 2011a). 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 (IAMAW) seniority log books, 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 upon 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 four-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 prior to 1953 often lacked start or hire dates, presumably due to 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 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 one-year term of employment was assigned. Total duration of employment was calculated for every worker by summing months of employment in each job worked on site.

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 (JEM) 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 non-bargaining positions at the plant. The dictionary's entries were grouped into similar exposure-job categories based on 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 (Sanderson et al., 2001b).

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 - based on the frequency and proximity to known processes involving beryllium (Table 1). These rankings were consistent with results of surface wipe sampling conducted early in the study to estimate the presence and 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 (Sanderson et al., 2008). Grinding and reshaping of tools was also found to have been the main source of exposure to beryllium in DoE nuclear weapons operations on site (Mikulski et al., 2011b); machinists, millwrights, and tool-and-die workers had the highest exposure potential of all jobs on both 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 their tenure on-site, regardless of 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 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 four-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 website was also accessible through major search engines.

Following the initial mailing, non-respondents were re-contacted 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 (CAB) and study participants were provided post-cards 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 (3HTdr) incorporation during preparation for mitosis. An individual LPT test was defined as abnormal if the rate of beryllium-induced cell proliferation in two or more Be concentrations exceeded the laboratory-specific cut-off value for beryllium unexposed cells. A positive response to only one Be concentration was defined as a borderline result, while low response to positive controls or high statistical variability within the sample deemed the result uninterpretable (Frome et al., 1996; DOE, 2001).

Participants' blood samples were tested by two laboratories simultaneously and the laboratories were blinded to all personal identification. Thirty milliliters (mL) of sodium heparinized venous blood was submitted to each laboratory and samples were shipped unrefrigerated by overnight express to assure delivery and set-up within 24-48 hours of the blood draw. Halfway 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 (DOE, 2001; Welch, et al., 2004; Middleton, et al., 2006; Middleton et al., 2010).

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. 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 upon 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 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 Tomography (HRCT) scanning of the lung, and fiberoptic bronchoscopy with lavage (BAL) and multiple transbronchial biopsies (TBLB).

Spirometry was performed according to the American Thoracic Society (ATS) guidelines (Miller et al., 2005). The percent predicted forced vital capacity (FVC%) and forced expiratory volume in the 1st second (FEV1%) were calculated using the National Health and Nutrition Examination Survey (NHANES III)-based algorithm recommended by Hankinson et al., (1999) and adjusted for age, sex, height and race. Percent predicted diffusing lung capacity for carbon monoxide (D_LCO%) was calculated based on equations of Miller et al., (1983). HRCT scans were reviewed within the same radiology department for evidence of Interstitial Lung Disease (ILD), including reticular changes, honeycombing, traction bronchiectasis/bronchiolectasis, interlobular septal thickening, and ground glass opacities, as well as perilymphatic nodules and mediastinal and hilar adenopathy (Hansell and Kerr, 1991; ATS/ERS, 2002; Gotway et al., 2005). Evidence of spirometric and radiologic abnormalities in combination with symptoms was required, under the clinical evaluation protocol, for BAL and TBLB.

Analysis

Data generated through this study were double-entered and stored in a secure Microsoft Access 2002-2007 database, with data queries completed periodically for update and quality assurance purposes. Personal identifiers were removed from the data prior to exporting them into PC SAS 9.2 software for statistical analyses (SAS Institute Inc., Cary, NC, USA 2002-2008). 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 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's exact test was used to evaluate the differences in frequencies of covariates and exposure levels between sensitized and non-sensitized individuals and to compare the prevalence rate of sensitization from this study to rates in other studies. The Cochran-Armitage (CA) chi-square test (Agresti, 2002) was used to assess the trend in sensitization rates by exposure to beryllium, age, date of first hire and duration of employment. Normality distribution of continuous variables was tested using the Shapiro-Wilk (SW) test and the Wilcoxon rank-sum test was used to evaluate the differences in medians of non-normally distributed continuous covariates between sensitized and non-sensitized groups.

Crude odds ratios and 95% confidence intervals 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 1,131 workers (including 212 category 2 workers) identified through records from a major credit bureau and world-wide-web sites as living within a four-hour driving distance of the screening sites were mailed invitations to participate in the study. Three hundred and 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 telephone 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: a) they had potential exposure to nuclear weapons - DoE - operations on site (n=34); b) they were employed on-site before 1948 (n=2); c) their employment started after 2002 (n=2); or d) they had no available employment records (n=2). Six additional workers were excluded because a single valid test result (i.e. 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.

Table 3-1 Distribution of job categories by exposure and sensitization to beryllium

Exposure category	Job category*	Screened	Total BeS, n (%)
Category 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	-
	Fire fighters	1	-
	Ironworkers	1	-
	Inspectors	41	-
	Laborers	20	-
	Melt workers	10	-
	Healthcare	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	-
	X-ray	2	-
Category 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/Pipefitters	4	-
Category 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.

Approximately thirty eight percent (n=197) worked multiple jobs (range 2-6) 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 (cat 0; n=1), production (cat 1; n=2), component operations (cat 1; n=1), and millwright (cat 2; n=1). Three sensitized workers worked in multiple jobs: one was first hired as a millwright (cat 2) and later rehired as a production operator (cat 1); one worked as an explosives operator (cat 1) and subsequently in production operations (cat 1); and one started as a production operator (cat 1) and was rehired for grounds maintenance (cat 0).

The non-sensitized 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 non-sensitized 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 non-sensitized workers (n=102) worked in multiple jobs that would have put them in different beryllium exposure category: 81 worked in both category 0 and 1 jobs; 8 in category 1 and 2 jobs; 11 in category 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 males (P=0.01).

Table 3-2 Characteristics of sensitized and non–sensitized workers and unadjusted predictors of BeS

Parameter	Sensitized (n=8)	Non-sensitized (n=516)	p-value	OR(95% CI)
Age, mean (SD), range	64(7); 54-74	63(10);28-88	0.85(3)	N/A
Age, n (%)				
< 55	1 (1.1)	91 (98.9)	0.97(2)	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(1)	N/A
Female	-	243 (100.0)		
Smoking, n (%)				
Ever smoker	5 (1.5)	330 (98.5)	1.00(1)	1.0
Never smoker	3 (1.6)	186 (98.4)		1.07 (0.25-4.50)
Immunosuppressant, n (%)				
Yes	-	17 (100.0)	1.00(1)	N/A
No	8 (1.6)	499 (98.4)		
Date of first hire, n (%)				
<7/1/1975 (DoE on-site)	7 (1.9)	357 (98.1)	0.45(1)	1.0
≥7/1/1975 (no DoE)	1 (0.6)	159 (99.4)		0.32 (0.04-2.63)
Employment duration (months), mean, SD, range	48(67); 0.5-194.0	103(126);0.1-855.5	0.19(3)	N/A
Employment (months),n(%)				
<12	3 (2.3)	126 (97.7)	0.19(2)	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(2)	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	-	2 (100.0)		-
Beryllium exposure, n (%)				
Category 0+1	6 (1.3)	464 (98.7)	0.19(1)	1.0
Category 2	2 (3.8)	50 (96.2)		3.10 (0.61-15.73)
Missing	-	2 (100.0)		-
Beryllium exposure, n (%)				
Category 0	1 (1.5)	66 (98.5)	1.00(1)	1.0
Category 1+2	7 (1.5)	448 (98.5)		1.03 (0.13-8.52)
Missing	-	2 (100.0)		-

(1) Chi-square test

(2) Cochran-Armitage test

(3) Wilcoxon rank-sum test

Work in category 2 jobs was associated with an almost three-fold higher rate of sensitization when compared to category 0 exposures but the result was not statistically significant (OR=2.64; 95%CI: 0.23-29.94; P=0.36). Comparing those highest exposed to individuals working in combined exposure categories 0 and 1 was still not statistically significant but revealed a higher odds ratio with a narrower confidence interval (OR = 3.10; 95% CI: 0.61-15.73; P=0.19). The algorithm for the multivariate logistic regression model did not converge.

Table 3 presents the results of clinical evaluation of sensitized individuals for CBD.

Table 3-3 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, 2mm 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 non pathologic, <1cm mediastinal and hilar lymph nodes	AB+BD
4	69	30	Never	94	114	83	89	No ILD; 3mm 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, 3mm 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 Test; DLCO%, 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 tomography; ILD, interstitial lung disease.

Of eight sensitized workers, six underwent clinical testing and two declined follow-up testing. All six were found to have normal spirometry and D_LCO with one worker having a minimally decreased FEV1/FVC ratio suggestive of mild obstructive airways physiology (Pauwels et al., 2001); testing was, however, done pre-bronchodilator. No evidence of CBD was found on 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 beryllium sensitization 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 (Rodrigues et al., 2008) and 1.4% (P=0.90) in construction workers from three nuclear weapons sites (Welch et al., 2004). The rate remains higher even after restricting the confirmed BeLPT definition to two and more abnormal tests only (1.0% in this study), as compared to studies of aluminum smelter workers from nine aluminum-producing plants (0.47%; P=0.32) (Taiwo et al., 2010). 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 (Silveira et al., 2003). The only identifiable risk of exposure was occasional resurfacing and grinding of Cu-2% Be alloy tools (Figure 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 may 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 (Newman et al., 2005b). Sensitization has also been found to regress over time (Rom et al. 1983, Duggal et al. 2010). It is unknown if 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 (Deubner et al., 2001; Stange et al., 2004; Middleton et al. 2006; Middleton et al., 2010). This study found the agreement between split-test laboratories to range from poor (weighted kappa statistic = 0.17; 95%CI: -0.02-0.35) to fair (weighted kappa statistic = 0.35; 95%CI: 0.01-0.70) (Landis and Koch, 1977). The probability of the split-testing protocol confirming sensitization was estimated, using methods suggested by other researchers, at 60% (Middleton et al., 2006). 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 non-zero 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 could also have implications for other industries using such alloy tools (Figure 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 grinding of Be containing tools in the workplace (McAtee et al., 2009).

The increase in prevalence and risk of sensitization found in those DoD workers working in category 2 beryllium exposure jobs compared to those working in category 0 jobs only, although not statistically significant, is consistent with the trend in risk of sensitization found in the previous study of former DoE nuclear weapons workers from the same site (Mikulski et al., 2011a). Beryllium exposure strata in both studies were determined based on 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; nevertheless the increase in the risk of sensitization seen in those highest exposed compared to those lowest exposed adds to the body of evidence of potential for beryllium sensitization being associated with certain tasks with the highest likelihood of beryllium exposure.

Figure 3-1 Copper beryllium alloy tools with instructions for grinding to maintain chamfer

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 only in 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 non-caseating granulomas with or without mononuclear cell interstitial infiltrates and fibrosis on biopsy (Newman et al. 1994). 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 (Duggal et al., 2010).

All confirmed abnormal BeLPT results in this study were found in workers who did not use immunosupressants 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 use of immunosuppressants including inhaled steroids; ever - smokers had over two-fold higher history of using immunosuppressants compared to never smokers (OR 2.1 95% CI 1.03-4.15). This is most likely explained by the higher rates of lung disease in ever-smokers and subsequent increase in 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 beryllium sensitization as immunosuppressant use may confound tobacco use in epidemiologic studies of BeS and lung disease.

Exposure potential in this study was assessed based on employment records and personal accounts of workers with health and safety qualifications and extensive job tenure on site. Exposure misclassification was possible as jobs within the same exposure category may have differed relative to exposure potential, and the accuracy of available work history records remains 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 towards the highest exposure potential misclassification would have biased the results towards 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 remains plausible (Cummings et al., 2007; Kreiss et al., 2007), 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 (Hoover et al., 1990; Tinkle et al., 2003). Those workers' higher risk of sensitization, although not statistically significant, was confirmed 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 non-screened cohort. Non-participants may 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 may have self-selected for the study based on health status.

Conclusion

In summary, this study found a non-zero 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 non-significant most likely due to lack of power.

CHAPTER 4

RISK AND SIGNIFICANCE OF CHEST RADIOGRAPH AND PULMONARY FUNCTION ABNORMALITIES IN AN ELDERLY COHORT OF FORMER NUCLEAR WEAPONS WORKERS

Introduction

Limited data are available on the epidemiology of pneumoconiosis in the Department of Energy (DoE) nuclear weapons workforce. Cross-sectional studies have reported the prevalence of parenchymal abnormalities, based on reviews of chest x-rays according to the International Labour Organization's International Classification System of Radiographs of Pneumoconioses (ILO system) (ILO, 2002), to range from 2.2% in former construction and craft workers (Dement et al., 2003) to 17.5% in former plutonium workers (Newman et al., 2005). Abnormalities of the pleura consistent with pneumoconiosis have been reported to range from 11.3% in former nuclear weapons production workers (Makie et al., 2005) to 19.9% in former construction workers, while those involving both parenchyma and pleura range between 3.2% and 3.7% in the same groups of workers (Dement et al., 2003; Makie et al., 2005).

Nuclear weapons workers are at risk for a variety of exposures known to be associated with work-related lung disease. Studies have confirmed exposure to beryllium and ionizing radiation (respirable radionuclides) in former production workers (Kreiss et al., 1993; Stange et al., 1996; Stange et al., 2001; Makie et al., 2005; Newman et al., 2005;) while exposures to asbestos and silica have been reported primarily in construction and trade workers from DoE facilities (Dement et al., 2003; Welch et al., 2004; Dement et al., 2010). High explosives and barium nitrate have been commonly used in the manufacture of nuclear weapons (DOE, 1998) but data is lacking regarding the degree and potential pulmonary effects of these exposures.

Epidemiological research on the risk factors for lung disease in nuclear weapons industry has shown that beryllium and ionizing radiation are associated with radiographic changes to lung parenchyma (Kreiss et al., 1993; Stange et al., 2001; Newman et al., 2005) while asbestos may be linked to parenchymal and pleural abnormalities in combination or individually (Makie et al., 2005). Studies of other industries have also shown parenchymal effects of aluminum powders used commonly in the manufacture of high-explosives (Jederlinic et al., 1990; Kraus, et al., 2000; Kraus et al., 2006) but population based data from the nuclear weapons industry is lacking. Also lacking is data on the effect of airborne exposure to barium dusts in this industry, the risk factor which was previously reported to result in at least transient radiographic evidence of parenchymal abnormalities in workers in barium industry (Doig, 1976).

Radiographic evidence of work-related lung disease has been found to be associated with obstructive airways impairment in former construction and trade workers from across the DoE industry (Dement et al., 2010). This finding has important implications for medical surveillance of construction trade workers but DoE sites' production processes and exposures differ dramatically. The association between the radiographic evidence of pneumoconiosis and restrictive airways physiology and the effect of changes in spirometry interpretation standards based on the lower limit of normal (LLN) on this association have not been studied well and the implications of this being a geriatric cohort have not been evaluated.

The purpose of this report is to describe the epidemiology and risk factors for and the association of radiographic evidence of parenchymal and pleural abnormalities with spirometry results in a population of former nuclear weapons workers from a single Load, Assembly and Pack (LAP) nuclear weapons assembly facility in the Midwest. Between 1949 and mid-1975 this site manufactured, refurbished and disassembled nuclear weapons under contractual agreement with DoE (formerly Atomic Energy Commission-AEC). Exposures to high explosives, beryllium and asbestos but not respirable radionuclides were common and several tons of high explosive and other non-fissile materials were tested and disposed on-site. The DoE-funded medical surveillance for work-related lung disease at this site was part of the nationwide former DoE workers screening program mandated in 1993 by U.S. Congress under section 3162 to Public Law 102-484.

Materials and Methods

Identification of the cohort

Approval for the study was received from the University of Iowa Institutional Review Board (UI-IRB). The details of the needs assessment, identification of the DoE workforce, recruitment of participants and assessment of exposure potential have been described previously (Mikulski et al., 2011a). In short, the contractor's archived employment rosters were used to identify all workers employed on-site between 1948 and 2002. DoE employment was confirmed using contract-specific job codes and job titles supported by information from the local union's seniority log books, radiation monitoring dosimetry badge records and lists of workers involved in accidents on DoE lines. Former non-contractor workers including food services workers, or inspectors and scale repairmen employed directly by the federal government were allowed to participate in the screenings following confirmation of their DoE employment by other DoE workers or records from the plant.

Workers contact information was obtained from state driver's license records and major credit bureaus with occasional updates through world-wide-web searches. Workers were contacted primarily by mail, and information about the screenings was distributed throughout the local media and the project's web-site. No minimum duration of employment was required and there were no specific restrictions that would prevent workers' participation in the medical screenings based on age, health status or geographic location.

Exposure assessment

Exposure potential to asbestos, high explosives and barium was assessed using the methods described for beryllium in the previous paper (Mikulski et al., 2011a). There were no environmental data available for these exposures, and interviews with former production, trade, and health and safety workers were queried by the project's industrial hygienists to refine the qualitative exposure estimates from a job title based exposure matrix. This matrix (Table 1) ranked jobs into those associated with virtually no exposure or lowest exposure potential at this facility (category 0); those involving rare exposures with potential for bystander or indirect exposure (category 1); those with occasional exposure potential including bystanders or indirectly exposed (category 2); and jobs with frequent exposure potential also including bystanders and indirectly exposed (category 3).

Table 4-1 Exposure categories and jobs

Exposure	Beryllium	Asbestos	High explosives/Barium
Category 0 No exposure, same as background:	Administrative, Security, Storage, Medical, Power Plant, Firing Site, Auto/Equipment Mechanics, Cafeteria, Carpenter, Custodian	Not assigned	Administrative, Security, Medical, Power Plant, Cafeteria, Carpenter, Custodian, Auto/Equipment Mechanics
Category 1 Rare/low indirect or bystander	Production and Explosive Operator, Scientist, Engineer, Pipefitter, Plumber, Electrician, Laundry,	Administrative, Security, Storage, Medical, Laundry, Custodian, Electrician, Firing site, Production and Explosive Operator, Millwright, Tool and Die, Machinist,	Production (assembly), Laundry, Millwright, Tool and Die, Machinist, Inspector, Storage
Category 2 Occasional, direct or indirect	Millwright, Tool and Die, Machinist,	Power Plant, Auto/Equipment Mechanics	Pipefitter, Plumber, Process Engineer, Firing Site
Category 3 Frequent, direct	Not assigned	Pipefitter, plumber, carpenter,	Production (fabrication) and Explosive Operator Melt, Scientist,

Every worker in the screened cohort was subsequently assigned their highest ever exposure category for all jobs worked on-site for each of the exposures under analysis. Exposure to ionizing radiation was not studied as according to former workers, most radioactive products, were shipped enclosed from other DoE sites and the risk for work-related lung disease from radionuclides would have been minimal at most except for radon progeny in the underground storage areas (Archer et al., 1998; Field et al., 2001)

Contractor's wage and salary schedules, matched on job codes and wage information, were used to fill-in the missing employment dates, particularly for workers hired before 1951 before the contractor took over the plant operations from the federal government. For workers with no wage information in the records, a one-year term of employment was arbitrarily used from the first available termination date to estimate the earliest hire date on-site.

Screening for lung disease and sensitization to beryllium

Each worker participating in the screenings signed an informed consent form prior to being offered chest x-ray, blood testing for effects of exposure to beryllium and spirometry. Chest x-rays were taken digitally and participant's most recent postero-anterior (P-A) film was reviewed in hard copy independently, for quality assurance purposes, by three occupational medicine physicians experienced in the ILO system. Workers with a CXR taken within twelve months prior to the screenings had those films reviewed instead. ILO readers used the ILO (rev. 2000) classification of radiographs (ILO, 2002) and were blinded to worker's age, smoking history, exposure information as well as radiologist's and each other's readings. No repeat readings were done to assess the intra-reader agreement due to the nature of the program, that is, federally funded surveillance aimed to provide medical testing to all eligible participants with ILO readings used as a part of the medico-legal evidence of work-relatedness of lung disease for workman's compensation purposes. Each of the readers had over twenty years of experience in ILO interpretation of radiographs for other research projects prior to beginning of this study.

Multiple ILO readings were reconciled using the median profusion score, and agreement between the majority ($\geq$2/3) of readers was required to classify the positive pleural reading as consistent with pleural abnormalities. The 12-point ILO system profusion score was compressed, for the risk factor analysis, to 7 groups according to Miller et al., (1996), and the three highest groups, 4 and 5 and 6, were combined into one category due to the small number of observations. The groups were distributed as follows: 0/- and 0/0=group 0; 0/1=group 1; 1/0=group 2; 1/1=group 3; 1/2 through 3/+ = group 4. ILO abnormalities were also expressed as dichotomous outcome (Yes/No), with profusion score $\geq$1/0 used as a cut-off point. Distribution of ILO abnormalities and associations with the independent variables under study was evaluated separately for parenchymal, parenchymal and pleural, and pleural abnormalities.

Sensitization to beryllium was evaluated by blood Beryllium Lymphocyte Proliferation Testing (BeLPT) in accordance with the DoE approved standard laboratory protocol for BeLPT testing as described previously in the literature (DoE, 2001; Frome et al., 2003; Mikulski et al., 2011a). Sensitization to beryllium carries a risk for progression to chronic beryllium lung disease (CBD) (Newman et al., 2005) therefore results of BeLPT screenings were included in the analyses to assess the association between a confirmed beryllium exposure and radiographic evidence of lung abnormalities. A confirmed abnormal BeLPT result was defined according to current consensus in the literature as two abnormal results or one abnormal and one borderline result from any DoE approved laboratory (Welch et al., 2004; Middleton et al., 2006).

Spirometry was performed according to the American Thoracic Society (ATS) guidelines by trained personnel, with calibration of testing equipment prior to each screening day (ATS, 1995; Miller et al., 2005). A reasonable effort was made to obtain at least three acceptable and reproducible results but no test was rejected based on the lack of three tests (Eisen et al., 1984). The lower limit of normal (LLN) values for forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1) and FEV1/FVC ratio were calculated using formulas suggested by Hankinson et al. (1999) and based on the results from the Third National Health and Nutrition Examination Survey (NHANES III).

Spirometry results were interpreted according to the American College of Occupational and Environmental Medicine (ACOEM) recommended algorithm for use with LLN values (Townsend, 2010). A decrease in FEV1/FVC ratio (<LLN) accompanied by a decrease in FEV1 (<LLN) was interpreted as obstructive airways. A decrease in FEV1/FVC ratio without decrease in FEV1 was considered normal physiology but follow-up evaluation for borderline obstruction was recommended. Restrictive impairment was suspected in cases with FEV1/FVC ratio greater or equal to LLN and FVC <LLN. A decrease below the LLN values in all three parameters was considered a possible mixed obstructive/restrictive airways physiology. All results with FVC, FEV1 and FEV1/FVC greater or equal to LLN were considered normal and those that could not be interpreted according to the criteria set above were labeled inconclusive and repeat testing was recommended.

Every worker with abnormal results on any of the screening tests was referred for clinical evaluation but this evaluation was not part of the screening protocol and results of the follow-up care are not available

Analysis

All analyses were performed using Windows SAS 9.2 (SAS Institute Inc., Cary, NC, USA, 2002-2008) statistical software on de-identified data. Workers' age was calculated as of the date of their chest x-ray and never smokers were defined as participants with less than 20-packs of smoking history during their lifetime. Ex-smokers and current smokers were combined into one category of ever smokers in the interest of sample size.

Frequencies of ILO abnormalities were calculated for all categorical independent variables under study, and means, standard deviations and ranges were computed for continuously distributed data, such as age. The Fisher's exact test was used to evaluate the hypothesis of no-difference in frequencies of dichotomous outcome variables while trend in ILO profusion by multi-categorical covariates was tested using the Cochran-Armitage (CA) chi-square test. The Shapiro-Wilk test was applied to test the normality of the continuously distributed data, and difference in medians between those with abnormal ILO readings and those with no abnormalities was compared using the Wilcoxon rank-sum test. The unadjusted association of each of the categorical covariates with parenchymal, pleural, and parenchymal and pleural abnormalities was assessed by crude odds ratios and 95% confidence intervals, calculated using simple logistic regression methods. Kendall-tau coefficients for categorically ordered variables and Spearman's rank correlation coefficients for continuously distributed data were calculated to examine correlation between independent predictors.

Multivariable logistic regression models were tested to assess the association of ILO abnormalities with each of the exposures under study, while controlling for potential confounders. Each model was built using forward selection with an entry p-value of 0.15, and separate models were generated for parenchymal, pleural, and parenchymal and pleural abnormalities. Cases were defined by positive findings on ILO reading and each type of abnormality was modeled separately; e.g. the parenchymal model included all cases with parenchymal abnormalities but no pleural nor coincident parenchymal and pleural abnormalities. The rate ratio for parenchymal abnormalities was assessed for each of the exposures under study. Exposure to asbestos was selected as the only risk factor to be modeled in pleural, and parenchymal with pleural abnormalities models, based on the literature. All analyses were adjusted for non-collinear confounders and age was chosen as a proxy for the first date of hire. Exposure to barium was strongly correlated with exposure to high explosives ($P<0.001$) and the latter was chosen as a surrogate for both exposures. Isolated parenchymal and coincident parenchymal and pleural abnormalities were also analyzed in models with ILO profusion score strata defined according to Miller et al., (1996) and described in the methods section.

The association of ILO abnormalities with spirometry results was assessed by multivariable logistic modeling. These models were built for relevant categories of spirometry interpretations with specific type of ILO abnormality as the dependent variable, analyzed separately from the other two types and adjusted for non-linear confounders.

All statistical tests conducted were double-sided and a p-value of <0.05 was selected as a level of statistical significance in all analyses throughout the study.

Results

Prevalence and distribution of ILO radiograph abnormalities by variables under study

A total of 1,005, out of an estimated 3,617 eligible living former DoE workers, were screened and received a P-A chest x-ray, or had their most recent films submitted for ILO review. Of this total, 757 (75.0%) workers had their films reviewed by all three ILO readers and were included in the study of risk factors. There were 12 (1.2%) workers with unreadable (U/R) films, 26 (2.6%) with CXR taken over twelve months before the screenings, and 210 (21.0%) with incomplete set of one or two readings only, and all of those individuals were excluded from the analyses.

The prevalence of radiographic abnormalities and their distribution by variables under study are presented in Table 2. There were 45 (5.9%) workers identified with isolated parenchymal abnormalities, 37 (4.9%) with pleural, and 19 (2.5%) with both parenchymal and pleural.

Table 4-2 Characteristics of DoE medically screened workforce by dichotomous ILO abnormality categories

Parameter	Parenchymal (PA) n=45	Parenchymal and Pleural (PP) n=19	Pleural (PL) n=37	Not abnormal n=656	p-value
Age, n (%)					
≤59	3 (2.6)	2 (1.7)	2 (1.7)	114	<0.01^{PA};<0.01^{PP};<0.01^{PL} (2)
60-69	9 (4.1)	2 (1.0)	8 (3.7)	208	
70-79	20 (7.7)	8 (3.2)	15 (5.9)	240	
≥80	13 (12.1)	7 (6.9)	12 (11.3)	94	
Age, mean (SD), range	74(9);54-92	75(9);53-87	75(9);54-91	69(9);47-94	<0.01^{PA}; <0.01^{PP}; <0.01^{PL} (1)
Sex, n (%)					
Female	7 (5.0)	1 (1.0)	4 (2.9)	134	0.56^{PA};0.15^{PP};0.20^{PL} (3)
Male	38 (6.8)	18 (3.3)	33 (5.9	522	
Race, n (%)					
White	44 (6.5)	18 (2.8)	37 (5.5)	631	1.00^{PA};0.53^{PP};0.64^{PL} (3)
Other	1 (3.8)	1 (3.8)	- (0.0)	25	
Smoking, n (%)					
Never smoker	11 (5.0)	4 (1.9)	10 (4.5)	210	0.32^{PA};0.45^{PP};0.59^{PL} (3)
Ever smoker	34 (7.1)	15 (3.3)	27 (5.7)	446	
First date of hire, n (%)					
<1/1/1950	4 (14.3)	1 (4.0)	4 (14.3)	24	<0.01^{PA};0.06^{PP};<0.01^{PL} (2)
1/1/1950 -12/31/1959	28 (9.3)	12 (4.2)	20 (6.8)	272	
1/1/1960 -12/31/1969	11 (3.2)	6 (1.8)	13 (3.8)	328	
1/1/1970 - 6/30/1975	1 (4.2)	- (0.0)	- (0.0)	23	
Missing	1 (10.0)	- (0.0)	- (0.0)	9	
Beryllium sensitized, n (%)					
No	42 (6.3)	18 (2.8)	34 (5.1)	627	0.59^{PA};0.33^{PP};0.17^{PL} (3)
Yes	1 (10.0)	1 (10.0)	- (0.0)	9	
Missing	2 (9.1)	- (0.0)	3 (13.0)	20	
Beryllium exposure, n (%)					
Cat 0	22 (6.4)	7 (2.1)	17 (5.0)	321	0.78^{PA};0.15^{PP};0.92^{PL} (2)
Cat 1	19 (6.3)	9 (3.1)	18 (6.0)	281	
Cat 2	3 (6.7)	3 (6.7)	2 (4.5)	42	
Missing	1 (7.7)	- (0.0)	- (0.0)	12	
Asbestos exposure, n (%)					
Cat 1	39 (6.5)	15 (2.6)	27 (4.6)	558	0.67^{PA};0.19^{PP};0.01^{PL} (2)
Cat 2	3 (7.9)	1 (2.8)	2 (5.4)	35	
Cat 3	2 (3.8)	3 (5.6)	8 (13.6)	51	
Missing	1 (7.7)	- (0.0)	- (0.0)	12	
Explosives exposure, n (%)					
Cat 0	17 (7.1)	5 (2.2)	13 (5.5)	223	0.93^{PA};0.21^{PP};0.75^{PL} [2]
Cat 1	6 (4.2)	2 (1.4)	9 (6.2)	137	
Cat 2	3 (5.9)	2 (4.0)	2 (4.0)	48	
Cat 3	18 (7.1)	10 (4.1)	13 (5.2)	236	
Missing	1 (7.7)	- (0.0)	- (0.0)	12	
Barium exposure, n (%)					
Cat 0	17 (7.1)	5 (2.2)	13 (5.5)	223	0.93^{PA};0.21^{PP};0.75^{PL} (2)
Cat 1	6 (4.2)	2 (1.4)	9 (6.2)	137	
Cat 2	3 (5.9)	2 (4.0)	2 (4.0)	48	
Cat 3	18 (7.1)	10 (4.1)	13 (5.2)	236	
Missing	1 (7.7)	- (0.0)	- (0.0)	12	
Spirometry, n (%)					
Normal	18 (4.3)	5 (1.2)	13 (3.2)	397	0.02^{PA} ; <0.01^{PP}; 0.013^{PL} (3)
Obstructive	5 (13.2)	1 (2.9)	2 (5.7)	33	
Restrictive	14 (8.0)	8 (4.7)	14 (8.0)	162	
Mixed	6 (11.1)	4 (7.7)	6 (11.1)	48	
Missing	2 (11.1)	1 (5.9)	2 (11.1)	16	

(1) Wilcoxon rank sum test

(2) Cochran-Armitage test

(3) Fisher exact test

Among those with isolated parenchymal abnormalities there were 27 workers with profusion score 1/0, ten with 1/1, three with 1/2, two with 2/1 and one of each in 2/2, 2/3 and 3/2 category. Of those with parenchymal and pleural abnormalities there were nine workers with profusion score 1/0, five with 1/1, four with 1/2 and one with 2/2. On average, workers with ILO abnormalities were 5 to 6 years older than those with no abnormalities consistent with pneumoconiosis and a statistically significant trend in increasing prevalence with age was noted for all three types of abnormalities. Age was strongly correlated with the first date of hire ($P<0.001$) and there was a statistically significant association found between earlier hire date and presence of parenchymal abnormalities alone and pleural abnormalities alone. Spirometry results were significantly associated with each type of radiographic abnormalities under study.

Associations with measures of exposure and other independent variables under study

The results of unadjusted analysis of associations of ILO abnormalities with all the a-priori selected independent variables are presented in Table 3. Ever working in highest exposure class to asbestos (category 3 exposure) was associated with a statistically significant increase in likelihood of pleural abnormalities on CXR, when compared to employment in jobs with lowest exposure potential – JEM category 1 exposures. The oldest workers had statistically significant increases in rates of isolated parenchymal and pleural abnormalities, when compared to the youngest group and abnormal spirometry results were found to be associated with the increased likelihood of all types of ILO abnormalities.

Table 4 presents results of multivariable logistic regression analyses of association of occupational exposures with all types of ILO abnormalities separately, and defined as dichotomous outcomes. Each model was adjusted for age, sex, race and smoking, and none showed a statistically significant association of exposures under study with ILO abnormalities. There was a suggestion of an increased likelihood of coincident parenchymal and pleural and isolated pleural abnormalities with exposure to asbestos but the results were not statistically significant. The algorithm for ILO readings stratified into five major profusion groups according to Miller et al., (1996) did not converge and no models were built.

Table 4-3 Unadjusted analysis of predictors of ILO radiographic abnormalities

Predictor, n (%)	Parenchymal, OR (95% CI) n=45	Parenchymal and Pleural, OR (95% CI) n=19	Pleural, OR (95% CI) n=37
Age			
≤59	1.0	1.0	1.0
60-69	1.64 (0.44-6.19)	0.55 (0.08-3.94)	2.19 (0.46-10.50)
70-79	3.17 (0.92-10.88)	1.90 (0.40-9.09)	3.56 (0.80-15.84)
≥80	5.26 (1.45-18.99)	4.25 (0.86-20.92)	7.28 (1.59-33.33)
Sex			
Female	1.0	1.0	1.0
Male	1.39 (0.61-3.19)	4.62 (0.61-34-92)	2.12 (0.74-6.08)
Race			
White	1.0	1.0	N/A
Other	0.57 (0.08-4.33)	1.40 (0.18-10.93)	
Smoking			
Never smoker	1.0	1.0	1.0
Ever smoker	1.46 (0.72-2.93)	1.77 (0.58-5.39)	1.27 (0.60-2.68)
Beryllium sensitized			
Yes	1.66 (0.21-13.40)	3.87 (0.47-32.20)	N/A
No	1.0	1.0	
Beryllium exposure			
Cat 0	1.0	1.0	1.0
Cat 1	0.99 (0.52-1.86)	1.47 (0.54-4.00)	1.21 (0.61-2.39)
Cat 2	1.04 (0.30-3.63)	3.28 (0.82-13.15)	0.90 (0.20-4.03)
Asbestos exposure			
Cat 1	1.0	1.0	1.0
Cat 2	1.23 (0.36-4.17)	1.06 (0.14-8.28)	1.18 (0.27-5.17)
Cat 3	0.56 (0.13-2.39)	2.19 (0.61-7.81)	3.24 (1.40-7.51)
Explosives exposure			
Cat 0	1.0	1.0	1.0
Cat 1	0.57 (0.22-1.49)	0.65 (0.12-3.40)	1.13 (0.47-2.71)
Cat 2	0.82 (0.23-2.91)	1.86 (0.35-9.86)	0.71 (0.16-3.27)
Cat 3	1.0 (0.50-1.99)	1.89 (0.64-5.62)	0.94 (0.43-2.08)
Spirometry			
Normal	1.0	1.0	1.0
Obstructive	3.34 (1.17-9.58)	2.41 (0.27-21.20)	1.85 (0.40-8.55)
Restrictive	1.91 (0.93-3.92)	3.92 (1.26-12.17)	2.64 (1.21-5.74)
Mixed	2.76 (1.04-7.28)	6.62 (1.72-25.49)	3.82 (1.39-10.51)

Table 4-4 Logistic regression models for exposures as predictors of ILO radiographic abnormalities

Exposure predictor*	Parenchymal (PA) OR (95% CI)	Parenchymal and Pleural (PP) OR (95% CI)	Pleural (PL) OR (95% CI)	p-value
Beryllium				
Cat 0	1.0	N/A	N/A	0.90
Cat 1	0.99 (0.52-1.88)			
Cat 2	0.75 (0.21-2.65)			
Asbestos				
Cat 1	1.0	1.0	1.0	0.43[PA]
Cat 2	0.94 (0.27-3.24)	0.67 (0.08-5.30)	0.92 (0.21-4.06)	0.89[PP]
Cat 3	0.38 (0.09-1.65)	1.20 (0.32-4.51)	2.21 (0.92-5.29)	0.19[PL]
Explosives				
Cat 0	1.0	N/A	N/A	0.69
Cat 1	0.60 (0.23-1.58)			
Cat 2	0.70 (0.20-2.51)			
Cat 3	1.01 (0.50-2.02)			

*Controlled for age, sex, race, smoking

Associations with spirometry results

Table 5 presents results of multivariable logistic regression analyses of associations of spirometry results, adjusted for age, sex, race and smoking with ILO abnormalities. The results of these analyses confirmed the unadjusted findings of Table 3, showing associations of lung function abnormalities with radiographic findings.

Table 4-5 Logistic regression models for spirometry results as predictors of ILO radiographic abnormalities

Spirometry results*	Parenchymal (PA) OR (95% CI)	Parenchymal and Pleural (PP) OR (95% CI)	Pleural (PL) OR (95% CI)	p-value
Normal	1.0	1.0	1.0	
Obstructive	2.96 (1.01-8.71)	2.03 (0.23-18.27)	1.68 (0.36-7.93)	0.09[PA]
Restrictive	2.00 (0.96-4.15)	4.14 (1.32-13.01)	2.82 (1.28-6.20)	0.05[PP]
Mixed	2.35 (0.87-6.39)	1.36 (1.36-22.11)	3.25 (1.16-9.08)	0.04[PL]

*Controlled for age, sex, race, smoking

Discussion

The 5.9% prevalence rate of parenchymal abnormalities in this study is comparable to the 5.4% rate of parenchymal abnormalities found in another population of former DoE production workers from a single nuclear reservation (Makie et al., 2005), but higher than the 2.2% rate reported in construction and trade workers from three former DoE sites combined (Dement et al., 2003). Although based on a different protocol, with multiple instead of single ILO readers, this increase is somewhat surprising given the low overall potential for exposure to beryllium, the main hazard evaluated in the pathogenesis of parenchymal disease in this population (Mikulski et al., 2011a). Also exposure to inhaled radio-nuclides would likely have been insignificant for this workforce, as most of the radioactive materials handled on-site were enclosed and ready-to-assemble into the weapon, shipped from other DoE sites. Exposure to asbestos, although widely used at this facility with hundreds of miles of asbestos-fitted steam pipes and all workers potentially exposed to levels above background, was not found to be associated with increase in prevalence of parenchymal abnormalities, and the 4.9% rate of pleural, and 2.5% of parenchymal and pleural abnormalities in this study were lower than in any of the other DoE studies. Direct exposure to high explosives and barium additives, as subsets of this workforce were potentially exposed to a variety of trinitrotoluene (TNT) derived high energy nitrate explosive compounds, was found to be associated with higher prevalence of combined parenchymal and pleural abnormalities, but the result was not statistically significant. Collapsing exposure categories for any of the exposures under study did not reveal different results.

Previous studies have shown that smoking is a risk factor for pulmonary fibrosis (Baumgartner et al., 1997) and adds to the risk of development of parenchymal opacities in workers with history of heavy exposure to asbestos (Barnhart et al., 1990). Ever-smoking was found to be associated with increased prevalence of all types of ILO abnormalities in this study but the results were not statistically significant. A detailed smoking history was not available for the whole cohort, but restricting the exposure models' analyses to a sample of 407 workers with available pack-year smoking history did not affect the lack of significance. These results most likely lacked significance due to insufficient power but the suggestion of increased prevalence and risk for all types of ILO abnormalities among ever-smokers adds to the body of evidence on effects of smoking on occupational lung disease.

Other studies of DoE workers have shown a strong age effect, with increase in rates of both parenchymal and pleural abnormalities especially at the upper extreme of age (Dement et al., 2003; Makie et al., 2005). This study also found increase in rates of ILO abnormalities with age ($P<0.001$) and age was the strongest predictor of all types of ILO abnormalities in every regression analysis with p-value consistently below 0.05. Although age has been previously shown to correlate with prevalence of ILO abnormalities in unexposed populations (Meyer, et al., 1997), its strong association with exposure to asbestos ($P<0.0001$), and beryllium ($P=0.0329$), as well as that with the first date of hire ($P<0.001$) in this study makes it difficult to discriminate the effects of age from cumulative exposure.

No medical records were available to assess the rates of ILO abnormalities in those workers who did not participate in the screenings. Non-participants may have differed from the screened workers in many characteristics including age, sex, race, smoking and most importantly date of first hire and exposure potential. In addition, those who enrolled in the screenings may have self-selected themselves based on their health status and concerns about the long-term effect of exposures. As this was a federally funded screening program widely advertised in the media, the screenings were opened to all confirmed former DoE workers without the opportunity to implement the traditional research design.

Exposure potential in this study was assessed based on industrial hygiene estimates and input from former weapons workers with extensive knowledge of site's history and exposures. A misclassification of exposures was possible, especially since those exposures occurred several decades prior to the study and there were no industrial hygiene records available to quantitatively estimate exposures. The potential for bias was minimized however as all of those involved in estimating the exposure were blinded to individual and group screening results. In addition, all uncertainties in exposure categorization were resolved towards the highest exposures in each exposure category and as such a potential misclassification would have biased the results towards the null hypothesis.

Between and within reader variability in interpretation of radiographs for pneumoconioses has long been recognized as a potential issue for epidemiological studies (Fletcher and Oldham, 1949; Attfield et al., 1992; Bourbeau and Ernst, 1988; Parker et al., 1989). The National Institute for Occupational Safety and Health (NIOSH) recommends using multiple ILO trained readers, with median reading as a preferred reconciliatory protocol, to increase accuracy and precision in film classification (NIOSH, 2010). This study employed three experienced ILO readers and the agreement between them ranged from moderate to substantial for both parenchymal (simple kappa statistic k =0.57; 95% CI 0.47-0.67 for reader 1 vs. reader 2, k=0.67; 95% CI 0.59-0.76 for reader 1 vs. reader 3 and k=0.56; 95% CI 0.46-0.66 for reader 2 vs. reader 3), and pleural abnormalities (simple kappa statistic k=0.61; 95% CI 0.50-0.72 for reader 1 vs. reader 2; k=0.53; 95% CI 0.41-0.64 for reader 1 vs. reader 3 and k=0.56; 95% CI 0.43-0.69 for reader 2 vs. 3) expressed as dichotomous outcomes. The agreement in ordinal profusion scoring was substantial between all three readers (weighted kappa statistic k=0.68; 95% CI 0.57-0.78 for reader 1 vs. 2; k=0.72; 95% CI 0.64-0.80 for reader 1 vs. 3 and k=0.70; 95% CI 0.59-0.81 for reader 2 vs. 3). Although minimal variability between readers is a desirable outcome, it is unknown whether and what direction this could have biased the prevalence estimates of ILO abnormalities in this study.

A statistically significant association was found in this study between isolated pleural abnormalities and impairment of lung function on spirometry. This finding is consistent with previous findings of studies of asbestos exposed workers (Oliver et al., 1988; Kilburn and Warshaw, 1991; Miller et al., 1992; Miller et al., 1996). Interestingly however this association remained significant regardless of the spirometry interpretation protocol used. Using different reference values and protocols to interpret spirometry results has been shown to potentially lead to discrepancy in reporting of obstructive and restrictive airways physiology, but LLN is accepted as a more valid method of characterizing spirometric abnormalities compared to the clinically used percent predicted fixed cut-off values (Oliver et al., 1986; Aggarwal et al., 2006; Collen et al., 2008; Swanney et al., 2008). This study used the currently recommended NHANES III based equations to calculate the predicted and LLN values for those workers tested with spirometry. The prevalence of obstructive airways was found, as expected, to be statistically significantly lower ($P <0.001$) when LLN based protocol was used (5.6%) compared to the fixed cut-off percent predicted values protocol (27.9%). Restrictive airways were however statistically significantly ($P<0.001$) more prevalent when LLN criteria were used (26.9%) compared to the traditional clinical approach (19.0%). It is not clear why such a reverse in trend occurred, but studies have found a marked shift in discordant results between the two protocols with age, in particular in those individuals over 65 (Aggarwal et al., 2006), and the mean age of participants with parenchymal and pleural abnormalities in this study was 75 ($\pm$9). In addition, the NHANES III equations have been generated based on the population of individuals 8-80 years old and 13% of participants in this study were over this age limit at the time of testing. As age is becoming a growingly important issue in occupational studies, further research is needed into spirometry reference values for older individuals.

Conclusion

In summary, this study found an elevated prevalence of ILO parenchymal abnormalities in the population of former nuclear weapons workers at overall low risk for exposure to beryllium, compared to other DoE populations. Work in high explosive and barium fabrication and melt operations was associated with higher prevalence of combined parenchymal and pleural abnormalities compared to administrative and office jobs but the result was not statistically significant. Conversely, the rates of ILO coincident parenchymal and pleural, and isolated pleural abnormalities were lower than in other DoE populations but pipefitters and plumbers had an increase, although statistically non-significant, in risk of these abnormalities compared to office personnel. The isolated pleural abnormalities were associated with abnormalities on spirometry. This study also found a substantial agreement between ILO readers in all aspects of film review.

CHAPTER 5

DISCUSSION AND CONCLUSIONS

The main objectives of this doctoral study were to determine the prevalence and risk factors for health effects associated with exposures common in the production of nuclear and conventional weapons at the Iowa Army Ammunition Plant in Burlington, IA. For the purposes of all three studies included in this dissertation, we defined prevalence as a proportion of total number of cases to the total number of eligible and screened workers, but we recognize the limitations of this definition: the true prevalence rate is a population parameter and as such could not be accurately determined due to lack of medical records for non-participants, and non-random selection for the federally funded screening program opened to all former workers. However, this approach and terminology have been accepted by reviewers of our manuscripts submitted from this thesis, and allowed us to compare the rates of health effects in this doctoral study to other weapons workers studies using the same research methodology.

Two of the studies included in chapters 2 and 3 of this thesis, looked specifically at the effects of exposure to beryllium in nuclear (DoE BeS study) and conventional (DoD BeS study) munitions production. The prevalence of beryllium sensitization in the screened cohorts was found to be minimally to moderately higher than in other low exposure populations, including nuclear weapons workers, and using the same definition of sensitization as the one used in this doctoral study. The reasons for this increase remain unknown, as discussed previously in each of the respective chapters, but we have found this particularly surprising given that the only identifiable exposure on-site was occasional redressing of copper-beryllium alloy tools done by a small group of craft and trade workers. In addition, this exposure would have occurred, for the most part, several decades prior to the study, leaving many questions regarding latency of this effect. Regardless of these limitations this increase raises concerns for the effects of low overall exposure to beryllium and has potential for policy implications for DoE and DoD as well as other industries still using such tools, to extend or implement beryllium surveillance programs for their workforces and discontinue use of the aforementioned tools in their production processes.

The third study included in chapter 4 of this thesis looked at the association of exposures common in the nuclear weapons industry, namely beryllium, asbestos, high explosives and barium, with radiographical evidence of lung abnormalities (DoE lung disease study). This study also found an increase in the prevalence of parenchymal abnormalities compared to other published reports of DOE screenings, but rates of coincident parenchymal and pleural, and pleural abnormalities only were lower than those in other nuclear weapons workers populations reported to-date. Part of this discrepancy may be explained by a different CXR review protocol as we used multiple instead of single ILO CXR reviewers and this is discussed further in the text; however effects of different exposures between these populations cannot be ruled out. This study found a strong correlation between workers' age and all types of ILO abnormalities, far more pronounced than the correlation between age and exposure (with the exception of exposure to asbestos). These findings add to the growing body of evidence on non-exposure dependent increase in prevalence of ILO abnormalities in aging populations and need to be taken into account in future studies of occupational cohorts.

Dose-response is an important toxicological concept illustrating the change in health effect with different exposure levels. This effect has been well characterized for exposure to asbestos (Sheers and Templeton, 1968; Jakobsson et al., 1995; Green et al., 1997; Paris et al., 2009) but not for beryllium nor high explosives or barium. Our studies of beryllium related health effects found an increase in the prevalence of beryllium sensitization with increase in the intensity of exposure to beryllium among former weapons workers. However, only in the DoE BeS study was this association statistically significant and showed that workers occasionally exposed to redressing copper-beryllium alloy tools were at higher risk for sensitization than those working in the administrative and office jobs with very low or background exposure. The DoD BeS study found a similar trend suggestive of dose-response effect, but lacked sufficient power to detect a statistically significant difference with the exposure levels. No statistically significant changes were found in the prevalence of radiographic parenchymal abnormalities with increasing intensity in exposure to beryllium, asbestos, high explosives and barium in the DoE study of lung disease. A suggestion of trend was observed for coincident parenchymal and pleural and isolated pleural abnormalities with the increasing exposure to asbestos but this association lacked statistical significance. While insufficient sample size is suspected to have played a role in the lack of statistically significant differences in these studies (see further discussion in the text), the potential for misclassification of exposure could not be completely ruled out. Nonetheless, it needs to be stressed that the exposure assessment for this doctoral study, although retrospective and based on workers' accounts, job titles and limited historical industrial hygiene data, was done blinded to screening results and uniformly towards the highest estimated exposure in every job category on-site. As such, a potential bias would have misclassified the study findings towards the no association hypothesis.

The effect of sample size on a study's ability to reject the null hypothesis has been extensively addressed in the epidemiological literature. Our DoE BeS study found a statistically significant increase in risk for sensitization for workers exposed to highest beryllium concentrations compared to background exposures. The a-priori estimates of sample size for the DoD BeS study showed we needed at minimum 1,160 workers screened to provide 80% power to detect a 2.7% difference in BeS rates between the unexposed workers, with an estimated 0.3% background rate of sensitization (Taiwo et al., 2008), and a conservatively estimated 3.0% rate in the exposed workers, at the 0.05 significance level. This goal was not achieved as the study suffered from low participation in the highest exposed category and was obliged to cease recruitment. Given the wide 95% Confidence Intervals (95% CI) in the risk factor analyses, the limited sample size and insufficient power may explain the lack of significant results. No prospective sample size estimates were obtained for the DoE lung disease study as that project was not designed de- novo as a research project but was part of the federally mandated screening service program open to all eligible former nuclear weapons workers. Most researchers disagree with using post-hoc power analyses to explain non significant results (Smith and Bates, 1992; Goodman and Berlin, 1994; Hoenig and Helsey, 2001; Matcham et al., 2007), but the combination of wide and narrow 95% CIs in the risk factor analyses indicate a possible mix of small sample size, misclassified exposure or are true indicators of no effect.

Use of different protocols often prevents researchers from making meaningful comparisons of findings between the studies. In this doctoral study, the issue of protocol choice has become particularly challenging with regards to confirmation of beryllium sensitization and reconciliation of multiple chest x-ray readings. Beryllium Lymphocyte Proliferation Test has been in use for over two decades in detecting sensitization but researchers still disagree whether a single abnormal test is sufficient to establish evidence of immune response to beryllium metal. This argument stems from the fact that no non-invasive “gold standard” test is readily available to compare the results and establish BeLPT’s sensitivity and specificity. In lieu of this, studies have employed the concept of quantitative evaluation of inter- and intra-rater agreement, only to observe a varying degree of reproducibility of a single abnormal test both within and between laboratories (Deubner et al., 2001, Stange et al., 2004, Middleton et al., 2006). As a result, recommendations have been made to confirm single abnormal tests by either a repeat abnormal test (a two abnormal tests definition), as is the case of most pre-2004 beryllium sensitization studies, or at least one more borderline result (one abnormal and one borderline test definition); the majority of the post-2003 studies used this latter definition. Data are lacking on inter- and intra-lab comparisons of individual test wells i.e. the beryllium sulfate test wells that labs use to calculate the actual rate of proliferation of lymphocytes, as well as the effect of labs using different positive controls and testing intervals. The DoD BeS study included in chapter 3 of this dissertation was particularly well suited to further examine these issues, as the same blood draw samples were split and sent to two laboratories at the same time. This study found the agreement between labs to range between poor and fair but its power suffered from having one of the laboratories terminate their lymphocyte proliferation laboratory services halfway through the screenings. As a result no statistically conclusive comparisons could be made. It is anticipated that results from this DoD study, combined with results from DoE BeS study, and possibly a greater dataset of BeLPTs from one of the DoE accredited laboratories, as discussed with Dr Donna Cragle the current director of that laboratory, will allow examination of this issue in much greater detail.

Another challenging protocol issue involved the use of multiple readers for each chest X-ray with subsequent reconciliation of their readings, to evaluate the presence, characteristics and extent of radiographic abnormalities consistent with pneumoconiosis. Although NIOSH recommends using a multiple trained B-reader protocol with median as a reconciliatory method to increase accuracy and precision of readings, most studies still utilize a single-reader making between studies comparisons problematic. In the DoE lung disease study we obtained CXR readings from three experienced, although non-B certified ILO readers. Their relatively high agreement and higher than expected prevalence of pneumoconiosis raise several questions. These findings could be explained by a potential reader bias as all three came from the same clinical center with similar experience in reading films for research studies. There may be a true increase in interstitial fibrosis from exposure to specific pneumoconiotic agents. Lastly effects of age and technical effects of reading hard copies of electronic films, often in reduced size could all be potential explanations. Unfortunately, the funding agency did not provide resources for consistent evaluation of all screened workers with a more sensitive High

Resolution Computed Tomography scan (HRCT scan) but efforts have been made to arrange for evaluation of a sample of films by two independent and NIOSH certified ILO B-readers. In addition, we have been exploring the possibility of comparing a sample of ILO readings to a sample of chest CT scans, available to our project as part of individual, post-screening follow-up examination, with results of both studies to be reported on in future publications.

Smoking is well documented to affect pulmonary health outcomes in epidemiological studies but it has also been shown to confound effects of exposure and pulmonary health association in workers' studies from various industries. In this doctoral study, we evaluated the effects of smoking status on beryllium sensitization and risk of ILO lung abnormalities, along with its potential for association with each of the exposures under study. In none of the studies, was smoking statistically significantly associated with the health effect under study, but a suggestion of increased risk for current and former smokers compared to those who never smoked was noted in DoE beryllium sensitization and lung disease studies. On the contrary, the DoD BeS study found a minimally increased yet still non-significant protective effect of ever smoking on the results of BeLPT. The lack of significance in these results may be potentially explained by misclassification of smoking history as those who smoked very little or quit a long time ago were combined, in the interest of power, into one category with current smokers. In general however, smoking status was not found to confound any of the exposure – health effect associations under study, which indicates its' effect may have been negligible or largely overwhelmed by the effect of other variables like age or first date of hire. This issue was further investigated in the DoE lung disease study which looked at the potential confounding effect of a detailed pack-years smoking history, available for a small group of screened workers, on the risk of ILO lung abnormalities by exposure status. No significant changes were however found in this analysis, except for the increased risk of pleural abnormalities in those workers exposed to highest levels of asbestos compared to those exposed to background levels. These findings show the importance of gathering detailed smoking information and should be considered in future occupational studies.

A particularly interesting observation was made with regards to the analysis of spirometry data for the DOE lung disease study. Recent recommendations call for use of NHANES III study data along with Hankinson et al., (1999) formulas to determine the reference values for the screened individuals. These formulas are based on a population of individuals younger than 81 and when applied to older workers in our study, resulted in predicted selected lung function parameters nearing values of 0 or even negative, especially in individuals at the extremes of age and with short heights. This result was cross-checked for accuracy with reference values provided by commercially available spirometry equipment and no new information on possible correction factors or reference formulas for this population was found through exhaustive search of literature. This issue, along with an unexpected reversal of trends in characterization of spirometry abnormalities as obstructive versus restrictive after adjusting the fixed cut-off percent predicted values to lower limit of normal predicted, was discussed with Dr Eva Hnizdo from NIOSH and potential collaboration on investigating this further is expected to result from this communication..

In summary, this doctoral study found an increase in the prevalence of beryllium sensitization in former nuclear and conventional munitions workers compared to other weapons worker populations at presumed low risk for exposure. Those working in highest exposed jobs were found to have increased risk of sensitization compared to those with only minimal bystander or background exposures on site. The study also found an increase in the prevalence of parenchymal abnormalities with a relative decrease in the rates of coincident parenchymal and pleural and isolated pleural abnormalities compared to other nuclear weapons workers populations. Comparison of these rates is problematic as the rates in this study were based on a multiple as opposed to single ILO reader protocol. No association with exposures was found for the ILO abnormalities under study, except for the suggestion of increased risk for pleural abnormalities amongst workers exposed to high levels of asbestos compared to those exposed to background levels. The results of this study have policy implications for both DoE and DoD as regards implementation or expansion of their screening efforts to evaluate health effects of employment in production of nuclear and conventional munitions.

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