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

Marek Mikulski

Department of Occupational and Environmental Health
College of Public Health
The University of Iowa

Outline

Background –History of IAAAP, exposures and health outcomes of interest, materials and methods common for all three studies

Study 1 - Risk of Beryllium Sensitization in a Low-Exposed Former Nuclear Weapons Workers Cohort from the Cold War Era (Department of Energy – DoE BeS study)

Study 2 - Prevalence of Beryllium Sensitization among Conventional Munitions Workers at Low Risk for Exposure, Department of Defense - (DoD BeS study)

Study 3 - Risk and Significance of Chest Radiograph and Pulmonary Function Abnormalities in an Elderly Cohort of Former Nuclear Weapons Workers (Department of Energy – DoE lung disease study)

Conclusions

Iowa Army Ammunition Plant (IAAAP), Burlington, IA

Built between 1941 and 1943 as a DoD conventional munitions Loading, Assembly and Packing (LAP) facility

In operation throughout today - Government Owned – Contractor Operated (GOCO) - over 19,000 acres with 1,000 buildings, 142 miles of roads and 103 miles of railroad tracks

Nuclear weapons assembled on-site (Line 1, Division B) between 1949 and mid-1975 under contractual agreement with DoE (formerly Atomic Energy Commission AEC) – production moved in July 1975 to Pantex Plant, Amarillo, TX

Also research, development, testing (conventional components only) and demilitarization of weapons

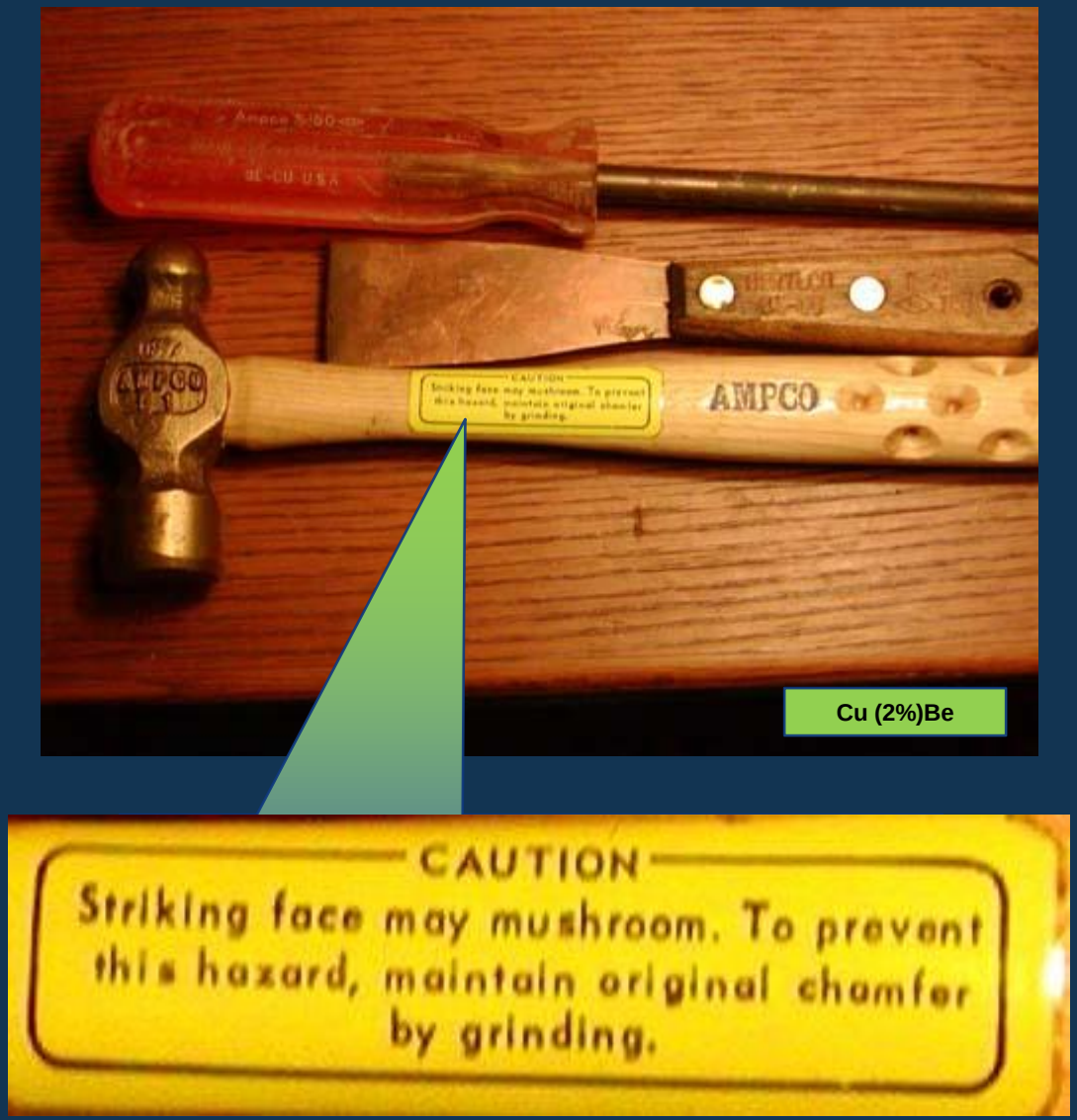
Total workforce ~ 40,000 workers between 1948 and 2004, with up to 7,000 involved in DoE activities

Exposures at IAAAP

Metals
- **Beryllium**
- **Barium**
- Aluminum
- Lead
- Mercury
- Manganese
- Depleted Uranium
- Cadmium
- Chromium
- Copper

High Explosives
Asbestos

Epoxy adhesives
Isocyanates
Solvents
Ionizing radiation



Exposures and Lung Disease

Airborne beryllium dust or fume exposure linked to pneumoconiosis:

- **Chronic Beryllium Disease (CBD) – a granulomatous, fibrotic lung disease with prevalence between 0.1% and 8% in workers' studies**
- **Elevated risk for lung cancer**

(Van Ordstrand et al., 1945; Hardy and Tabershaw, 1946; Freiman & Hardy, 1970; *Williams, 1977; Kreiss et al.,1989; Kreiss et al., 1993; Sanderson et al., 2001; Sackett et al., 2004; Cummings et al., 2009)*

CBD typically preceded by sensitization to beryllium (BeS) - an asymptomatic CD4+ T-memory cell mediated response affecting up to 15% of the exposed workforce *(Kreiss et al., 1989; Newman and Kreiss, 1992; Kreiss et al., 1993; Rosenman et al., 2005).*

BeS and CBD may develop within few months up to several decades after the initial exposure – the rate of progression from BeS to CBD - 6-8% per year *(Stange et al., 2001; Newman et al., 2005; Cummings et al., 2007; Madl et al., 2007)*

Highest prevalence of BeS and CBD in machining of Be metal but cases found in exposures to concentrations below the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) of 2 µg/m^3 of air(*Kreiss et al., 1996; Newman et al., 2001; Henneberger et al., 2001; Kelleher et al., 2001; Rosenman et al., 2005; Stanton et al. 2006)*

Limited epidemiological data available on prevalence of BeS and CBD in low-exposed nuclear weapons workers. Data lacking on prevalence in conventional munitions workers

" Pneumoconiosis is the accumulation of dust in the lungs and the tissue reactions to its presence. 'Dust' is meant to be an aerosol composed of solid inanimate particles". IVth International Pneumoconiosis Conference, International Labour Organization (ILO), Bucharest 1971 http://www.ilo.org/safework_bookshelf/english?content&nd=857170103

Exposures and Lung Disease

Asbestos exposure linked to fibrotic pneumoconiosis (asbestosis) with/without pleural involvement and asbestos related pleural disease

- **2% prevalence of CXR parenchymal abnormalities in former DoE asbestos exposed construction and trade workers; 3% for parenchymal and pleural disease; 20% for pleural disease** (Dement et al., 2003)

Barium (additive to HE) – non-fibrotic pneumoconiosis (baritosis) – CXR evidence of transient parenchymal abnormalities found in workers in barium industry (Fiori,1926, Doig, 1976)

High explosives – exposure to agents used /released in the manufacture of high explosives linked to interstitial fibrosis

- **aluminum powders** (Goralewski, 1947; Corrin 1963; Kraus et al., 2006)
- **nitric acid and nitric oxide** (Costa et al., 2005, Arora and Aldrich, 1980; Cordier et al., 2007),

Population based data from the nuclear weapons industry limited (asbestos) or lacking (HE and Barium)

DoE and DoD Medical Screening Projects
Data for Doctoral Studies

The Former IAAAP Nuclear Weapons Workers Program – part of the nationwide DoE Former Worker Medical Screening Program (FWP) - in response to the U.S Congress mandating DoE to evaluate the long-term health effects of employment in nuclear weapons productions. *Section 3162 to the Public Law 102-484 of the National Defense Authorization Act for FY 1993*

- **Medical screenings for work-related lung disease and malignancies**

The Former and Current IAAAP Conventional Munitions Workers Study – part of the site-specific study in response to the U.S Congress mandating DoD to conduct the study of main health hazards and health effects associated with making of conventional munitions at IAAAP. *Section 1078 to the Public Law 106-398 of the Floyd D. Spence National Defense Authorization Act for FY 2001, as amended by sections 8172(a) and 8172(e) to the Public Law 107-117, of the DoD Appropriations Act*.

- **Medical screenings for work-related lung disease (beryllium exposure)**

Materials and Methods
(Common for all three studies)

Cohort Identification

- All working on site **between 1948 and 2004** identified through contractor's (Silas and Mason) employment records including 3x5 cards + e-records, Machinists' Union seniority log books, DoE radiation badge dosimetry records, incident reports
  - **Vital status** confirmed by Social Security Administration (SSA)- Death Index
  - **Contact information** obtained from IA Driver's License records and updates by major Credit Bureaus/online search engines
  - **DoE employment confirmed** by contractor's employment records, DoE incident reports, radiation dosimetry badge records, union seniority log books or other DoE workers

Recruitment

- Targeted mailings, Toll-free line, Internet
- Local media – press releases, interviews for radio stations
- Educational meetings in Burlington area
- Community Advisory Board, workers breakfast club

Questionnaires

- Self-reported information on smoking status (DoE/DoD studies), and immunosuppressant use (DoD study)

Materials and Methods - Exposure Assessment (Common for all three studies)

No personal exposure data available for any of the exposures on-site

Job Exposure Matrix (JEM) developed by OEH IH team with input from former and current IAAAP workers (DoD/DoE expert worker panels)

Job titles/job categories grouped into Exposure Rankings (category 0,1,2,3) based on frequency of exposure and proximity to known processes involving this exposure.

Every worker assigned the highest Job-Exposure Ranking for each of the exposures under study

EXPOSURE RANKING	BERYLLIUM	ASBESTOS	HIGH EXPLOSIVES/BARIUM
Category 0 Virtually no exposure; lowest exposures at this facility	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 exposures; can include bystander or indirect exposure	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 exposures; can include bystander or indirect exposures	**MILLWRIGHT, TOOL AND DIE, MACHINIST**	Power Plant, Auto/Equipment Mechanics	Pipefitter, Plumber, Process Engineer, Firing Site
Category 3 Frequent exposures; several times weekly; can include bystander or indirect exposure	Not assigned	**PIPEFITTER, PLUMBER, CARPENTER,**	**PRODUCTION (FABRICATION) AND EXPLOSIVE OPERATOR MELT, SCIENTIST,**

Materials and Methods
Medical screening panels for DoE and DoD studies

Participants in DoE screenings offered:

1) Screening for sensitization with **Blood Beryllium Lymphocyte Proliferation Test (BeLPT)**
2) Spirometry (according to ATS guidelines, ATS 1995)
3) Chest X-ray (postero-anterior and lateral)

Participants in DoD screenings offered:

1) Screening for sensitization with **Blood BeLPT**
2) BeS +ve offered clinical evaluation for CBD – with lung function testing and high Resolution CT scan – clinical protocol based on clinical judgment with invasive testing (bronchoalveolar lavage (BAL) with transbronchial biopsy) dependent on the results of PFTs and HRCT

Abnormal BeLPT *result defined as 2 (out of 6) $BeSO_4$ wells with 3HTdR incorporation based proliferation rate of lymphocytes > rate in non-Be stimulated controls (Stimulation Index – SI > the lab's cut-off point) , Borderline BeLPT result with 1 SI > cut-off , Uninterpretable BeLPT result - no response to positive controls or any reason for non-processed.*

Confirmed Abnormal BeLPT (sensitized) *defined as (at minimum) two abnormal results or one abnormal and one borderline from any laboratory (DoE 2001; Welch et al., 2004; Middleton et al., 2006)*

STUDY 1 – DoE BeS study
Materials and Methods (study specific)

BeS screening (single BeLPT)

1) 30 mL of peripheral blood sent to one of participating DoE laboratories
2) All non-normal results repeated within 12 months with a split test (60 mL) sent to two laboratories. Normal results repeated within 3-5 years with a single test

Beryllium Exposure

1) The highest exposure ranking of all the jobs ever worked on-site for every screened worker

2) **Beryllium exposure metric** – exposure as a function of duration of employment in each exposure beryllium stratum calculated by summing up months worked for every worker in the following categories
   - Total months worked
   - Total months worked in Cat1 exposure
   - Total months worked in Cat2 exposure

Spirometry

- Knudson et al., 1983 reference standards used to calculate %predicted Forced Vital Capacity (FVC%) adjusting for age, race, sex and height

STUDY 1 – Results

N=6,797 eligible for the screenings (Former IAAAP Workers involved in DoE activities between 1948 and mid-1975) with 52% (n=3,548) confirmed deceased (SSDI) through 7/08

N=1,024 screened

- **~70% screened of all workers identified as still living in IA**
- **N=20 workers with no interpretable BeLPT result excluded**
- **Total included in analyses N=1,004 workers**

N=23 out of 1,004 (2.3%) with confirmed abnormal BeLPT (sensitized)

- **16 (70% with 2 abnormal results)**
- **7 (30% with 1 abnormal + 1 borderline result)**

STUDY 1 – Results

BeS predictor variable	Sensitized	OR (95% CI)	p-value
Beryllium exposure, n (%)* Category 0 Category 1 Category 2 Missing	**7 (1.5)** **11 (2.5)** **4 (6.9)** 1 (4.2)	N/A	**0.03***
Beryllium exposure** Cat 1/0 **Cat 2/0**		1.64 (0.63-4.26) **3.83 (1.04-14.03)**	0.31 **0.04**
Beryllium exposure (categories combined) ** Cat 2+1/0		1.91 (0.63-4.26)	0.16
Beryllium exposure (categories combined) ** Cat 2/1+0		2.90 (0.91-9.22)	0.07
Beryllium exposure (metric) *** Total months worked Total months worked in category 1 exposure Total months worked in category 2 exposure		 N/A N/A N/A	 0.87 0.44 0.10
FVC%**		N/A	0.95

** Cochran – Armitage test of trend; **adjusted for age and smoking; ***adjusted for smoking*

STUDY 1 – Conclusions

The 2.3% prevalence of BeS higher than in other DoE populations with relatively low estimates of Be exposure

- **1.4 % (p=0.03) in former DoE construction workers (Welch et al., 2004)**
- **1.3% (p=0.06) in former DoE workers from Nevada Test Site (Rodrigues et al., 2008)**

Prevalence also higher than rates in other industries

- **0.3% in current aluminum smelter workers (Taiwo et al., 2008)**
- **1.0% in current workers from Cu-Be alloy distribution center (Stanton et al., 2006)**

Background rate for BeS not well established – estimated between 0% in new hires for Be processing plant (Silveira et al., 2003) and 1% in unexposed laboratory controls (Kolanz et al., 2001)

STUDY 1 – Conclusions

Prevalence of sensitization found to increase with exposure (dose – response)

Ever- working in machining and grinding of Cu-Be alloy tools (the main source of Be exposure on-site) associated with four-fold increase in risk for sensitization (compared to office and other cat 0 work on site)

- **not related to cumulative dose as Be exposure metric was not associated with sensitization**

STUDY 2 – DoD BeS study
Materials and Methods (study specific)

BeS screening

1) 60 mL of peripheral blood sent to two participating laboratories
2) All non-normal results repeated within 12 months with another split test.

Beryllium Exposure

1) The highest exposure ranking of all the jobs ever worked on-site for every screened worker

1) **Beryllium exposure metric** – exposure as a function of duration of employment in each exposure beryllium stratum calculated by summing up months worked for every worker in the following categories
   - Total months worked
   - Total months worked in Cat1 exposure
   - Total months worked in Cat2 exposure

Clinical evaluation for CBD

1) Confirmed sensitized
2) Evaluated at UIHC – with lung function testing and HRCT – clinical protocol based on clinical judgment with invasive testing (bronchoalveolar lavage (BAL) with transbronchial biopsy) dependent on the results of PFTs and HRCT

STUDY 2 – Results

N=33,544 eligible for the screenings (IAAAP DoD Workers employed between 1948-2002) with 43% (n=14,321) deceased confirmed by SSDI through 12/09

N= 570 workers screened

- **N=46 workers with no interpretable BeLPT results or with evidence of DoE employment excluded**
- **Total included in analyses N=524 workers**

N=8 out of 524 (1.5%) with confirmed abnormal BeLPT (sensitized)

- **5 (63% with 2 abnormal results)**
- **3 (37% with 1 abnormal + 1 borderline result)**

STUDY 2 – Results

Independent Variable	Total Screened (n=524)	Sensitized (n=8)	Non-sensitized (n=516)	p-value	OR (95% CI)
Age, mean (SD) , median	63(10); 63	64(7); 62	63(10); 63	0.85[3]	N/A
Age, n (%) < 55 55-59 60-64 65-69 70+	 92 (17.5) 95 (18.1) 121 (23.1) 97 (18.5) 119 (22.8)	 1 (1.1) 2 (2.1) 2 (1.7) 1 (1.0) 2 (1.7)	 91 (98.9) 93 (97.9) 119 (98.3) 96 (99.0) 117 (98.3)	0.97[2]	1.0 1.96 (0.17-21.96) 1.53 (0.14-17.13) 0.95 (0.06-15.38) 1.56 (0.14-17.42)
Sex, n (%) Male Female	 281 (53.6) 243 (46.4)	 8 (2.9) -	 273 (97.1) 243 (100.)	**0.01[1]**	N/A
Smoking, n (%) Ever smoker Never smoker	 335 (63.9) 189 (36.1)	 5 (1.5) 3 (1.6)	 330 (98.5) 186 (98.4)	1.00[1]	1.0 1.07 (0.25-4.50)
Immunosuppressant use, n (%) Yes No	 17 (3.2) 507 (96.8)	 - 8 (1.7)	 17 (100.0) 499 (98.3)	1.00[1]	N/A
Date of first hire, n (%) <7/1/1975 (during DoE operations on-site) ≥7/1/1975 (no DoE operations on-site)	 364 (69.5) 160 (30.5)	 7 (1.9) 1 (0.6)	 357 (98.1) 159 (99.4)	0.45[1]	1.0 0.32 (0.04-2.63)
Beryllium exposure, n (%) Category 0 Category 1 Category 2 Missing	 67 (12.8) 403 (76.8) 52 (10.0) 2 (0.4)	 1 (1.5) 5 (1.2) 2 (3.9) -	 66 (98.5) 398 (98.8) 50 (96.1) 2 (100.0)	0.36[2]	1.0 0.83 (0.10-7.21) 2.64 (0.23-29.94) -
Beryllium exposure (cat. combined) n (%) Category 0 Category 1+2	 67 (13.2) 455 (86.8)	 1 (1.5) 7 (1.5)	 66 (98.5) 448 (98.5)	1.00[1]	1.0 1.03 (0.13-8.52)
Beryllium exposure (cat. combined) n (%) Category 0+1 Category 2	 470 (89.7) 52 (10.3)	 6 (1.3) 2 (3.9)	 464 (98.7) 50 (96.1)	0.19[1]	1.0 3.10 (0.61-15.73)
Beryllium exposure, n, mean, range , median Total months worked Total months worked in category 1 Total months worked in category 2	 524;102;<1-856; 42 414; 89;<1-851; 32 52; 86; <1-432; 48	 8;48; <1-194; 21 5; 42; <1-97; 27 2:62; 27-97; 62	 516;103;<1-856; 42 398; 89;<1-851; 32 50; 87; <1-432; 48	 0.19[3] 0.42[3] 0.11[3]	N/A

(1) Fisher's exact test; (2) Cochran-Armitage chi-square test of trend; (3) Wilcoxon rank-sum test

STUDY 2 – Results

RESULTS OF CLINICAL EVALUATION FOR CBD OF BE 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.

STUDY 2 – Conclusions

Non-zero rate of BeS in DoD workers with low overall exposure to beryllium

Increase in prevalence and risk of sensitization in workers with jobs associated with increased potential for exposure (consistent with statistically significant findings from DoE study from the same site)

No CBD found based on clinical evidence, pulmonary function testing and high resolution CT but the funding agency approved protocol less sensitive than bronchoscopy/biopsy/lavage)

STUDY 3 – DoE lung disease study
Materials and Methods (study specific)

Chest X-ray

1) Films reviewed in hard copy for evidence of work-related parenchymal and pleural abnormalities by three occupational medicine physicians, independently, according to ILO Classification System for Pneumoconioses
2) Median profusion score (0/- to 3/+) for parenchymal opacities used to reconcile multiple readings; Agreement between ≥2 of 3 readers to classify reading as +ve for pleural abnormalities
3) Profusion score ≥1/0 used as a cut-off to define parenchymal abnormalities

Spirometry

- Hankinson et al., (1999) NHANES III based formulas used to calculate the lower limit of normal (LLN) for FVC and Forced Expiratory Volume in 1 sec (FEV1)
- Results interpreted according to American College of Occupational and Environmental Medicine (ACOEM) recommended algorithm for use with LLN values (Townsend, 2010)

Beryllium, Asbestos, High Explosives and Barium Exposure

The highest exposure ranking of all the jobs ever worked on-site for every screened worker

STUDY 3 – Results

N=6,797 eligible for the screenings (Former IAAAP Workers involved in DoE activities between 1948 and mid-1975) with 58% (n=3,910) deceased confirmed by SSDI through 10/11

N=1,005 received CXR (or had an exam within 12 months prior to screen)

- **N=248 with incomplete set of 3 ILO readings or U/R films excluded**
- **Total included in analyses N=757 workers**

N=45 out of 757 (5.9%) with ILO parenchymal abnormalities

- **60% with ILO 1/0**
- **22% with ILO 1/1**
- **18% with ILO ≥1/2 (1/2 -3/2)**

N=19 out of 757 (2.5%) with ILO parenchymal and pleural abnormalities

- **47% with ILO 1/0**
- **26% with ILO 1/1**
- **27% with ILO ≥1/2 (1/2-2/2)**

N=37 out of 757 (4.9%) with ILO pleural abnormalities

STUDY 3 – Results

Independent Variable	Parenchymal (PA) n=45	Parenchymal and Pleural (PP) n=19	Pleural (PL) n=37	Not abnormal n=656	p-value	PA OR (95% CI)	PP OR (95% CI)	PL OR (95% CI)
Age, mean (SD)	74(9); 76	75(9); 76	75(9); 78	69(9); 70	**<0.01^{PA}; <0.01^{PP}; <0.01^{PL}** (1)	N/A	N/A	N/A
Age, n (%)					**<0.01^{PA};<0.01 ^{PP};<0.01^{PL}** (2)			
≤59	3 (2.6)	2 (1.7)	2 (1.7)	114		1.0	1.0	1.0
60-69	9 (4.1)	2 (1.0)	8 (3.2)	208		1.64 (0.44-6.19)	0.55 (0.08-3.94)	2.19 (0.46-10.50)
70-79	20 (7.7)	8 (3.2)	15 (5.9)	240		3.17 (0.92-10.88)	1.90 (0.40-9.09)	3.56 (0.80-15.84)
≥80	13 (12.1)	7 (6.9)	12 (11.3)	94		**5.26 (1.45-18.99)**	4.25 (0.86-20.92)	**7.28 (1.59-33.33)**
Sex, n (%)					0.56^{PA};0.15^{PP};0.20^{PL} (3)			
Female	7 (5.0)	1 (1.0)	4 (2.9)	134		1.0	1.0	1.0
Male	38 (6.8)	18 (3.3)	33 (5.9	522		1.39 (0.61-3.19)	4.62 (0.61-34-92)	2.12 (0.74-6.08)
Race, n (%)					1.00^{PA};0.53^{PP};0.64^{PL} (3)			
White	44 (6.5)	18 (2.8)	37 (5.5)	631		1.0	1.0	N/A
Other	1 (3.8)	1 (3.8)	- (0.0)	25		0.57 (0.08-4.33)	1.40 (0.18-10.93)	
Smoking, n (%)					0.32^{PA};0.45^{PP};0.59^{PL} (3)			
Never smoker	11 (5.0)	4 (1.9)	10 (4.5)	210		1.0	1.0	1.0
Ever smoker	34 (7.1)	15 (3.3)	27 (5.7)	446		1.46 (0.72-2.93)	1.77 (0.58-5.39)	1.27 (0.60-2.68)
Date of first hire, n (%)					**<0.01^{PA}**;0.06^{PP};**<0.01^{PL}** (2)			
<1/1/1950	4 (14.3)	1 (4.0)	4 (14.3)	24		3.83 (0.40-36.9)	2.28 (0.26-19.69)	**4.21 (1.27-13.89)**
1/1/1950 -12/31/1959	28 (9.3)	12 (4.2)	20 (6.8)	272		2.37 (0.31-18.2)	2.41 (0.89-6.51)	1.86 (0.91-3.80)
1/1/1960 -12/31/1969	11 (3.2)	6 (1.8)	13 (3.8)	328		0.77 (0.09-6.24)	1.0	1.0
1/1/1970 - 6/30/1975	1 (4.2)	- (0.0)	- (0.0)	23		1.0		
Missing	1 (10.0)	- (0.0)	- (0.0)	9				
Beryllium sensitized, n (%)					0.59^{PA};0.33^{PP};0.17^{PL} (3)			
No	42 (6.3)	18 (2.8)	34 (5.1)	627		1.0	1.0	N/A
Yes	1 (10.0)	1 (10.0)	- (0.0)	9		1.66 (0.21-13.40)	3.87 (0.47-32.20)	
Missing	2 (9.1)	- (0.0)	3 (13.0)	20				
Beryllium exposure, n (%)					0.78^{PA};0.15^{PP};0.92^{PL} (2)			
Cat 0	22 (6.4)	7 (2.1)	17 (5.0)	321		1.0	1.0	1.0
Cat 1	19 (6.3)	9 (3.1)	18 (6.0)	281		0.99 (0.52-1.86)	1.47 (0.54-4.00)	1.21 (0.61-2.39)
Cat 2	3 (6.7)	3 (6.7)	2 (4.5)	42		1.04 (0.30-3.63)	3.28 (0.82-13.15)	0.90 (0.20-4.03)
Missing	1 (7.7)	- (0.0)	- (0.0)	12				
Asbestos exposure, n (%)					0.67^{PA};0.19^{PP};**0.01^{PL}** (2)			
Cat 1	39 (6.5)	15 (2.6)	27 (4.6)	558		1.0	1.0	1.0
Cat 2	3 (7.9)	1 (2.8)	2 (5.4)	35		1.23 (0.36-4.17)	1.06 (0.14-8.28)	1.18 (0.27-5.17)
Cat 3	2 (3.8)	3 (5.6)	8 (13.6)	51		0.56 (0.13-2.39)	2.19 (0.61-7.81)	**3.24 (1.40-7.51)**
Missing	1 (7.7)	- (0.0)	- (0.0)	12				
Explosives exposure, n (%)					0.93^{PA};0.21^{PP};0.75^{PL} [2]			
Cat 0	17 (7.1)	5 (2.2)	13 (5.5)	223		1.0	1.0	1.0
Cat 1	6 (4.2)	2 (1.4)	9 (6.2)	137		0.57 (0.22-1.49)	0.65 (0.12-3.40)	1.13 (0.47-2.71)
Cat 2	3 (5.9)	2 (4.0)	2 (4.0)	48		0.82 (0.23-2.91)	1.86 (0.35-9.86)	0.71 (0.16-3.27)
Cat 3	18 (7.1)	10 (4.1)	13 (5.2)	236		1.0 (0.50-1.99)	1.89 (0.64-5.62)	0.94 (0.43-2.08)
Missing	1 (7.7)	- (0.0)	- (0.0)	12				
Spirometry, n (%)					**0.02^{PA} ; <0.01^{PP}; 0.013^{PL}** (3)			
Normal	18 (4.3)	5 (1.2)	13 (3.2)	397		1.0	1.0	1.0
Obstructive	5 (13.2)	1 (2.9)	2 (5.7)	33		**3.34 (1.17-9.58)**	2.41 (0.27-21.20)	1.85 (0.40-8.55)
Restrictive	14 (8.0)	8 (4.7)	14 (8.0)	162		1.91 (0.93-3.92)	**3.92 (1.26-12.17)**	**2.64 (1.21-5.74)**
Mixed	6 (11.1)	4 (7.7)	6 (11.1)	48		**2.76 (1.04-7.28)**	**6.62 (1.72-25.49)**	**3.82 (1.39-10.51)**
Missing	2 (11.1)	1 (5.9)	2 (11.1)	16				

(1) Wilcoxon rank-sum test (2) Cochran-Armitage chi-square test of trend; (3) Fisher's exact test;

STUDY 3 – Results

ILO abnormality predictor variable	Parenchymal (PA) OR (95% CI)	Parenchymal and Pleural (PP) OR (95% CI)	Pleural (PL) OR (95% CI)	p-value
Beryllium*				
Cat 1/0	0.99 (0.52-1.88)	N/A	N/A	0.90
Cat 2/0	0.75 (0.21-2.65)			
Beryllium*				
Cat 2+1/0	0.95 (0.51-1.76)	N/A	N/A	0.87
Beryllium*				
Cat 2/1+0	0.75 (0.22-2.57)	N/A	N/A	0.65
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}
Asbestos*				
Cat 2+3/1	0.59 (0.22-1.58)	0.95 (0.53-1.70)	1.71 (0.78-3.75)	0.30^{PA} 0.86^{PP} 0.18^{PL}
Asbestos*				
Cat 3/2+1	0.38 (0.09-1.65)	1.06 (0.54-2.11)	2.23 (0.94-5.29)	0.20^{PA} 0.86^{PP} 0.07^{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)			
Explosives*				
Cat 3/2+1+0	1.21 (0.65-2.27)	N/A	N/A	0.55
Explosives*				
Cat 3+2/1+0	1.11 (0.60-2.06)	N/A	N/A	0.74
Spirometry*				
Normal	1.0	1.0	1.0	0.09^{PA} 0.05^{PP} **0.04^{PL}**
Obstructive	**2.96 (1.01-8.71)**	2.03 (0.23-18.27)	1.68 (0.36-7.93)	
Restrictive	2.00 (0.96-4.15)	**4.14 (1.32-13.01)**	**2.82 (1.28-6.20)**	
Mixed	2.35 (0.87-6.39)	**1.36 (1.36-22.11)**	**3.25 (1.16-9.08)**	

* Adjusted for age, sex, race and smoking

STUDY 3 – Conclusions

Prevalence rate of ILO parenchymal abnormalities higher than in other DoE studies but the effect of age and minimal variability between the ILO readers could not be ruled out

ILO abnormalities including isolated pleural were associated with abnormal spirometry

Conclusions

Confirmed cases of beryllium sensitization in population with low overall potential for exposure

Confirmed increased risk of sensitization in machinists and millwrights occasionally redressing Cu-2%Be alloy tools

Implications for DoE, DoD and other industries to:

- **continue or introduce beryllium surveillance programs for their workforces**
- **alter work practices for workers working with Cu-2%Be alloys/tools**

Need for further research on issues related to reproducibility of BeLPT and spirometry in elderly populations

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