Association Between Spirometry Results and ILO Abnormalities in a Cohort of Former Nuclear Weapons Workers

Marek Mikulski[1], Patrick Hartley[2], Nancy Sprince[1], Wayne Sanderson[3], Spencer Lourens[4], Nicole Worden[2], Kai Wang[4], Laurence Fuortes[1]
[1]Department of Occupational and Environmental Health, College of Public Health, University of Iowa, Iowa City, IA
[2]Carver College of Medicine, University of Iowa, Iowa City, IA
[3]Department of Epidemiology, University of Kentucky, Lexington, KY
[4]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA

Abstract

Nuclear weapons industry workers are recognized as being at risk for a variety of exposures, including various radionuclides, beryllium, asbestos, high explosives and barium, all of which have been implicated in the pathogenesis of occupational lung disease. Limited epidemiological data is available on the association between pulmonary physiology and radiologic evidence of occupational lung disease in this population. Former DoE nuclear weapons workers from a nuclear weapons assembly site received spirometry and chest x-ray as part of the DOE Former Worker Medical Screening Program. Of the 757 screened workers, we found 45 (5.9%) with parenchymal abnormalities defined as ILO small opacities median profusion score =>1/0. We found 37 (4.9%) workers with isolated pleural and 19 (2.5%) with coincident parenchymal and pleural abnormalities. No statistically significant association was found between ILO abnormalities and exposures under study but in logistic regression models controlling for age, sex, race and smoking, isolated pleural abnormalities were statistically significantly associated (p<0.05) with abnormal spirometry defined based on NHANES III lower limit of normal (LLN) values. Workers with pleural abnormalities had over six-fold statistically significant increase in odds of testing below 60% of FVC%predicted, when compared to those with normal spirometry results. Coincident parenchymal and pleural abnormalities were also associated with abnormal spirometry results (p=0.05) and had a six-fold increase in odds of testing below 60% FVC%predicted. These results confirm the association of spirometric abnormality with ILO readings consistent with pneumoconiosis in medical screening programs of nuclear weapons workers

Project Background

The University of Iowa College of Public Health Project started in 2001

Funded by DoE under Public Law 102-484 Section 3162 of the 1993 Defense Authorization Act

Goal: *Identifying, locating, and providing former IAAAP DoE workers employed in the manufacture of nuclear weapons with medical evaluation of long term health effects that might have resulted from employment*

Iowa Army Ammunition Plant (IAAAP)

Located in Middletown, IA (Des Moines County) - over 19,000 acre Government Owned Contractor Operated (GOCO) facility with >1000 buildings, 142 miles of roads and 103 miles of railroad tracks

Built between 1941-1943 as a conventional munitions (DoD) Loading, Assembly and Packing (LAP) facility. Atomic weapons assembled, disassembled and repaired between 1949 and mid-1975 on **Line 1** under Atomic Energy Commission (AEC, pre-DoE) contractual agreements with Silas-Mason Company

Production terminated/moved in 1975 to Pantex, Amarillo, TX

Nuclear Weapons Workers

Approximately 7,000 workers worked on or were exposed to Line 1 operations (a.k.a. Division B) between early 1949 and mid-1975

Substantial cross-over of workforce with adjacent conventional munitions manufacturing lines (95-100% of DoE workers worked on DoD lines too during their tenure at the plant)

DoD lines are still in operation – currently approx. 600 employees

Primary exposures:

- *Ionizing radiation* — *High Explosives incl. Barium*
- *Beryllium* — *Isocyanates*
- *Asbestos* — *Epoxy adhesives*
- *Solvents* — *Curing agents*

Methods

Cohort selection based on subcontractor employment records, plant radiation dosimetry records, union seniority records and employment validation by other former workers.

Participants recruited by mail, telephone, press releases, town hall meetings and word of mouth.

All former workers participating in the screenings offered CXR and spirometry with the most recent results used for analysis.

Postero-Anterior (PA) films reviewed by 3 experienced ILO readers blinded to radiologist's reports and each other's readings. **Parenchymal abnormalities** defined as median ILO profusion score **≥1/0**. Pleural abnormalities confirmed by at least 2 out of 3 readers.

Spirometry performed according to ATS guidelines, using **NHANES III** reference population and ACOEM's recommended **lower limit of normal (LLN) algorithm for interpretation**. For comparison purposes results interpreted according to **fixed %predicted cut-off point (%Pred).**

Beryllium, asbestos, high explosives and barium exposure categories for each worker assigned based on job codes/job titles in subcontractor's and plant's employment records.

Highest exposure ever used in estimating personal exposure

Job Exposure Matrix

The only available historical exposure data – limited beryllium surface wipe sample reports for 1970-1974 - served as indicators of the presence and relative levels of beryllium on surfaces in various locations within the plant - these could not be used to directly estimate workers' inhalational exposure to beryllium at the plant.

A survey of surface contamination at this facility in 2007 revealed only two beryllium samples out of one hundred collected throughout the facility which exceeded the DoE surface contamination housekeeping level of 3 µg/100 cm² 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., JOEH 5(7) p.475, 2008)

Job codes, job titles, and work tasks were reviewed by industrial hygienists and a group of former workers to develop a qualitative exposure matrix (JEM) for beryllium, asbestos, high explosives and barium. The estimates for each job code/category were based on task frequency and proximity to potential sources of airborne exposures and reflected the group's consensus.

Exposure Categories/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,

Results

Table 1.Characteristics of DoE screened workforce by ILO abnormality categories (Yes ILO vs. No ILO abnormality)

Parameter	Parenchymal (PA) n=45	Parenchymal and Pleural (PP) n=19	Pleural (PL) n=37	Not Abnormal n=656	p-value
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	
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	
Beryllium sensitized, n (%)					$0.59^{PA}; 0.33^{PP}; 0.17^{PL}$ [3]
No	42 (6.3)	18 (2.8)	34 (5.1)	627	
Yes	1 (10.0)	1 (10.0)	- (0.0)	9	
Missing	2 (9.1)	- (0.0)	3 (13.0)	20	
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	
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/Barium exposure, n (%)					$0.93^{PA}; 0.21^{PP}; 0.75^{PL}$ [2]
Cat 0	17 (7.1)	5 (2.2)	13 (5.5)	223	
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	
Age, n (%)					***$<0.01^{PA}; <0.01^{PP}; <0.01^{PL}$*** [2]
≤59	3 (2.6)	2 (1.7)	2 (1.7)	114	
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 (%)					$0.56^{PA}; 0.15^{PP}; 0.20^{PL}$ [3]
Female	7 (5.0)	1 (1.0)	4 (2.9)	134	
Male	38 (6.8)	18 (3.3)	33 (5.9)	522	
Race, n (%)					$1.00^{PA}; 0.53^{PP}; 0.64^{PL}$ [3]
White	44 (6.5)	18 (2.8)	37 (5.5)	631	
Other	1 (3.8)	1 (3.8)	- (0.0)	25	
Smoking, n (%)					$0.32^{PA}; 0.45^{PP}; 0.59^{PL}$ [3]
Never smoker	11 (5.0)	4 (1.9)	10 (4.5)	210	
Ever smoker	34 (7.1)	15 (3.3)	27 (5.7)	446	
First date of 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	
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	
Spirometry (LLN), n (%)					***$0.02^{PA}; <0.01^{PP}; 0.013^{PL}$*** [3]
Normal	18 (4.3)	5 (1.2)	13 (3.2)	397	
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	
Spirometry (%Pred), n (%)					0.20^{PA}; ***$<0.01^{PP}; 0.01^{PL}$*** [3]
Normal	18 (4.9)	4 (1.1)	10 (2.8)	347	
Obstructive	11 (6.1)	10 (5.6)	15 (8.1)	170	
Restrictive	14 (10.9)	3 (2.6)	9 (7.3)	114	
Inconclusive	- (0.0)	1 (10.0)	1 (10.0)	9	
Missing	2 (11.1)	1 (5.9)	2 (11.1)	16	
FVC % predicted mean(SD),range	79(22);36-121	66(19);37-99	75(20);32-127	86(19);12-184	0.15^{PA}; ***$<0.01^{PP}; <0.01^{PL}$*** [1]
FVC % predicted, n (%)					0.18^{PA}; ***$<0.01^{PP}; <0.01^{PL}$*** [2]
≥100%	9 (6.5)	- (0.0)	3 (2.3)	129	
80-99%	14 (4.8)	6 (2.1)	12 (4.1)	280	
60-79%	13 (6.6)	5 (2.7)	12 (6.2)	183	
≤59%	7 (12.7)	7 (12.7)	8 (14.3)	48	
Missing	2 (11.1)	1 (5.9)	2 (11.1)	16	

[1]Wilcoxon rank sum test ; [2] Cochran-Armitage chi-square test; [3] Fisher's exact test

Table 2. Unadjusted analysis of predictors of ILO abnormalities

Parameter	Parenchymal OR 95% CI	Parenchymal and Pleural OR 95% CI	Pleural OR 95% CI
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)
Beryllium sensitized			
Yes	1.66 (0.21-13.40)	3.87 (0.47-32.20)	N/A
No	1.0	1.0	
Asbestos exposure			
Cat 0	-	-	-
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/Barium 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)
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)
First date of hire			
<1/1/1950	3.83 (0.40-36.91)	2.28 (0.26-19.70)	**4.21 (1.27-13.89)**
1/1/1950 -12/31/1959	2.37 (0.31-18.20)	2.41 (0.89-6.51)	1.86 (0.91-3.80)
1/1/1960 -12/31/1969	0.77 (0.10-6.24)	1.0	1.0
1/1/1970 - 6/30/1975	1.0	-	-
Spirometry (LLN)			
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)**
Spirometry (%Pred)			
Normal	1.0	1.0	1.0
Obstructive	1.25 (0.58-2.70)	**5.10 (1.58-16.51)**	**3.06 (1.35-6.96)**
Restrictive	**2.37 (1.14-4.91)**	2.28 (0.50-10.35)	**2.74 (1.09-6.91)**
Inconclusive	N/A	9.64 (0.98-95.09)	3.86 (0.45-33.42)
FVC% predicted			
≥100%	1.0	-	1.0
80-99%	0.72 (0.30-1.70)	1.0	1.84 (0.51-6.64)
60-79%	1.02 (0.42-2.45)	1.28 (0.38-4.24)	2.82 (0.78-10.19)
≤59%	2.09 (0.74-5.93)	**6.81 (2.19-21.13)**	**7.17 (1.83-28.14)**

Results

Table 3. Logistic regression models for exposures* as predictors of ILO radiographic abnormalities

Parameter*	Parenchymal (PA) OR (95% CI)	Parenchymal and Pleural (PP) OR (95% CI)	Pleural (PL) OR (95% CI)	p-value
Beryllium		N/A	N/A	0.90
Cat 0	1.0			
Cat 1	0.99 (0.52-1.88)			
Cat 2	0.75 (0.21-2.65)			
Asbestos				$0.43^{PA}; 0.89^{PP}; 0.19^{PL}$
Cat 1	1.0	1.0	1.0	
Cat 2	0.94 (0.27-3.24)	0.67 (0.08-5.30)	0.92 (0.21-4.06)	
Cat 3	0.38 (0.09-1.65)	1.20 (0.32-4.51)	2.21 (0.92-5.29)	
Explosives		N/A	N/A	0.69
Cat 0	1.0			
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 and smoking

Table 4. Logistic regression models for spirometry results* as predictors of ILO radiographic abnormalities

Parameter*	Parenchymal (PA) OR (95% CI)	Parenchymal and Pleural (PP) OR (95% CI)	Pleural (PL) OR (95% CI)	p-value
Spirometry (LLN)				$0.09^{PA}; 0.05^{PP}$; ***0.04^{PL}***
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)	
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)**	
Spirometry (%Pred)				0.06^{PA}; ***0.03^{PP};*** 0.05^{PL}
Normal	1.0	1.0	1.0	
Obstructive	1.11 (0.51-2.45)	**4.91 (1.51-16.00)**	**2.70 (1.16-6.30)**	
Restrictive	**2.19 (1.04-4.58)**	1.99 (0.43-9.14)	2.49 (0.97-6.34)	
FVC% Pred				0.36^{PA}; ***$<0.01^{PP}; 0.04^{PL}$***
≥100%	1.0	-	1.0	
80-99%	0.73 (0.31-1.75)	1.0	1.95 (0.54-7.08)	
60-79%	0.99 (0.41-2.41)	1.19 (0.36-4.00)	2.76 (0.76-10.07)	
≤59%	1.78 (0.62-5.13)	**5.54 (1.74-17.59)**	**6.19 (1.54-24.84)**	

* Controlled for age, sex, race and smoking

Summary of Findings/Conclusions

The 5.9% prevalence rate of parenchymal abnormalities in this study is ***higher*** than rates found in other DoE studies (2.2% in Dement et al., 2003 AJIM, 43:559-573) while the 2.4% rate of parenchymal/pleural and the 4.6% rate of pleural abnormalities is ***lower*** than rates from other nuclear weapons sites (3.2% and 19.9% in Dement et al., 2003 AJIM, 43:559-573 and 3.7% and 11.3% in Makie et al., 2005, 48:365-372).

None of the modeled exposures was statistically significantly associated with the increase in risk of ILO abnormalities. Age was a very strong confounder (p<0.01) but the effect of age could not be discriminated from cumulative exposure (age vs. asbestos or beryllium p<0.05) .

A statistically significant (or borderline) association found between isolated pleural abnormalities and coincident pleural and parenchymal abnormalities and impairment of lung function on spirometry, using currently recommended LLN based interpretation protocol and %Pred protocol – consistent with previous studies of asbestos exposed workers.

The association changed from obstructive using %Pred protocol to restrictive and mixed airways physiology using LLN interpretation.

A marked shift in spirometry characterization - the prevalence of obstructive airways is significantly lower by LLN based protocol compared to the fixed cut-off %Pred protocol (5.6% vs. 27.9%), (p<0.001), while restrictive physiology is more prevalent by LLN criteria compared to the %Pred cut-off point (26.9% vs. 19.0%), (p<0.001)

Could this be the effect of age? A marked one-way shift found in other studies (Aggarwal et al., 2006) especially in individuals >65. The mean age of participants with parenchymal and pleural abnormalities in this study 75 (±9); 13% of screened participants over the age of 80 and NHANES III equations based on population 8-80 years of age.

The results of this study confirm the need to screen former weapons workers for pulmonary health effects of airborne exposures in the manufacture of both conventional and nuclear weapons.

Further population based studies are needed to investigate the observed shift in interpretation of spirometry results especially in older populations. Linear models from NHANES population may need to be revised for the extremes of age.