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Cross-sectional Study of Respiratory Symptoms, Spirometry and Immunologic Sensitivity in Epoxy Resin Workers

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Keywords

lung function; sensitizers; biological monitoring; respiratory; health surveillance

Introduction

In 2007, an employee of a manufacturing facility presented with severe obstructive lung disease. Surgical lung biopsy demonstrated hypersensitivity pneumonitis (HP), likely from workplace exposure to epoxy resin system (ERS) chemicals. The diagnosis was based both on her symptom and exposure history and on an abnormal blood lymphocyte proliferation test (LPT) to an epoxy resin hardener containing a proprietary amine and a polydiamine. Despite removal from exposure and aggressive pharmacologic treatment, she required lung transplantation.

Diverse industries ranging from electronics to construction use ERSs because of their physical properties and easy curing[1]. Market analysts predict over 3.03 million tons in annual sales of epoxy resin systems by 2017, potentially placing thousands of workers at

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risk for exposure related health effects[2]. An ERS consists of several components: epoxy resins, plasticizers, adhesives, solvents, hardeners and blends of other resins. Health effects associated with ERSs vary depending on the particular components, many being pulmonary and dermatologic sensitizers and irritants[3, 4, 5]. The mechanisms for ERS health effects and risks for work-related lung disease from these exposures are poorly understood.

Similar to other forms of hypersensitivity pneumonitis, HP associated with ERS exposure likely occurs via a delayed-type hypersensitivity reaction[6]. This mechanism is important in the development of other granulomatous occupational lung diseases, such as chronic beryllium disease (CBD)[6]. CBD occurs via immunologic sensitization to beryllium, detected through *in vitro* testing of lymphocyte proliferation with beryllium salts[7]. Our sentinel patient developed abnormal lymphocyte proliferation to an epoxy thermoset hardener, suggesting sensitization as a mechanism leading to end-stage granulomatous lung disease. Findings in this patient suggested that an epoxy resin specific blood LPT might identify workers at risk for respiratory health effects associated with ERSs.

While much literature documents the epidemiology of occupational dermatitis due to epoxy resins, few systematic studies assessing occupational respiratory disease due to epoxy resins exist. Further, even though early identification of workers at risk for developing respiratory health effects from epoxies was targeted as an area for investigation in 1980, no strategies, such as identification of sensitized, but not symptomatic workers, currently exist[8]. This cohort study aimed not only to assess the prevalence of respiratory symptoms and spirometric abnormalities among ERS-exposed workers compared to demographically-similar co-workers without ERS exposure, but to explore the utility of ERS lymphocyte proliferation testing (ERLPT) as a biomarker of exposure and immunologic sensitization in ERS workers compared to unexposed workers. If ERLPT positivity correlates with exposure status and ultimately with symptoms and spirometry outcomes, then ERLPT testing could serve as a surveillance tool to prevent occupational respiratory disease morbidity.

Materials and methods

Study subjects

We recruited study participants from a Colorado-based employer with over 1100 workers between August and October, 2010. Investigators reviewed job descriptions to determine the population working directly with ERS processes or entering areas where ERS are frequently used. The plant physician and safety officer verified the at-risk population of workers. We defined exposed workers as those who work directly in the epoxy area or within 30 feet and maintenance workers who routinely enter the epoxy area for purposes of cleaning. Exposed workers were grouped into two categories. Primary users of epoxy resins were considered higher exposed workers. We classified workers who entered epoxy areas for repairs, maintenance, janitorial duties, or who worked within 30 feet of the epoxy area lower exposed workers.

We recruited unexposed subjects from production areas where workers are not exposed to epoxy resins and from non-production areas in order to attempt one to one matching with exposed workers for age, race and gender. Pregnant workers were excluded.

The study was approved by the National Jewish Health Institutional Review Board. Participants provided informed consent, and data were de-identified for analysis.

Methods

Questionnaire—We collected demographics and medical/occupational histories using a modified version of the ATS Respiratory Symptom Questionnaire[9]. Participants self-completed questionnaires, and a trained interviewer reviewed and verified results.

Spirometry—Two NIOSH-certified technicians trained in ATS/ERS criteria for standardization of spirometry performed spirometry using two EasyOne Plus™ (ndd Medical Technologies, Inc., Zurich, Switzerland) spirometers. The quality grading function was activated. We excluded unacceptable spirometry (quality grades D or F) from analysis. A pulmonologist reviewed results to assure that they met ATS/ERS criteria for acceptability and repeatability[10]. Abnormal spirometry values included FEV1 or FVC values or FEV1/FVC ratios that fell below the lower limit of normal (LLN) based on Hankinson/NHANES III predicted values[10,11].

Epoxy Resin Lymphocyte Proliferation Testing—We selected a panel of five ERS products for immunologic testing, shown in Table 1. We chose these products based on abnormal reactions in the ERLPTs performed in the sentinel case; on potential immunotoxicity of product components listed on Material Safety Data Sheets; and on reported volume of use at the worksite. The sentinel case showed abnormal reactions to the thermoset hardener, containing various amines. We performed ERLPT testing based upon the general technique used to perform LPT testing to beryllium sulfate[12].

Preparation of epoxy resins: A 1:10 vol/vol stock of the 5 different epoxy resin system components was prepared by adding 1 mL of the component to 9 mL complete RPMI-1640 medium (RPMI-1640 (Irvine Scientific) supplemented with 10% human AB serum (Gemini Biologicals), 200mcg/ml L-glutamine (Fisher Scientific) and penicillin/streptomycin (Fisher Scientific). The five ERS components varied in viscosity: the triamine hardener, a clear liquid, went readily into solution; the trade secret epoxy, thermoset hardener, black epoxy and methacrylate adhesive were viscous, and care was taken to pipette approximately 1 mL into 9 mL complete media. Tubes were vortexed and placed at 37°C overnight to permit the ERS component to solubilize in complete media. The triamine hardener was readily soluble; the other four components remained essentially undissolved in media. Prior to use, the stock solutions were vortexed and working concentrations prepared by making serial 10-fold dilutions. The resins were tested at concentrations of 1:10, 1:100 and 1:1000.

Lymphoproliferation assay: Venous blood (30 mL) was collected in 10 mL sodium heparin tubes from each participant. Mononuclear cells were isolated by Histopaques-1077 (Sigma) density centrifugation, washed in phosphate buffered saline, and re-suspended in complete medium. Mononuclear cells were cultured in triplicate at 2.5×10^5 cells/well in round-bottomed, 96-well microtiter plates (Fisher Scientific) in the presence of complete medium and dilutions of each of the 5 ERS components for 6 days. As positive controls, cells were incubated with phytohemagglutinin (5 mcg/mL) for 3 days or with Candida

albicans (20 mcg/mL) for 6 days. At the end of the incubation period, cells were pulsed with tritiated thymidine (Perkin Elmer), 1 mCi/well, and incubated for a further 6 hours before harvesting and quantification for ^{3}H incorporation by liquid scintillation. Proliferation was assessed by the degree of cellular incorporation of tritiated thymidine. Results were expressed as stimulation index (SI), the mean response observed at any concentration of component divided by the mean response of the unstimulated cells grown under the same conditions in the absence of the potential sensitizer.

SIs were calculated for three concentrations each of five epoxy resin products. An abnormal test result was determined based on an SI exceeding the product-specific cut-off point. Each cut-off point was determined by taking the mean peak SI for unexposed workers in this population and adding two standard deviations. Standard deviations and coefficients of variation (CV) were calculated for all conditions. If a calculated CV was greater than 0.5, the value was excluded from analysis.

Analysis

We used Intercooled STATA 11.2 (Stata Corp, College Station, Texas) for all analyses. In bivariate analysis, we used several tests: The chi-square test was used to determine if exposure groups differed in demographic variables or reported symptoms. Fisher's exact tests were used to compare categorical data (such as presence of comorbidities) for small numbers of responses (less than 20).

Normality was assessed using the Shapiro-Wilkes test. We assessed differences in means between the three exposure groups using analysis of variance when outcome data were normally distributed (i.e., LPT peak SIs for methacrylate adhesive, black epoxy, thermoset hardener), and the Kruskal-Wallis test when continuous outcome data were not normally distributed (i.e., LPT peak SIs for trade secret epoxy & triamine hardener).

In multivariate analysis, we used linear regression to examine associations between continuous outcomes (FEV1 % Predicted, FVC % Predicted, and FEV1/FVC ratio) and exposure categories while adjusting for factors known to be associated with pulmonary function, such as age (for FEV1/FVC), smoking status (current smokers versus former or nonsmoker), and socioeconomic status. We used education status (college versus no college) as a proxy for socioeconomic status. Other factors, such as years worked for the company, were investigated and retained if they were significant predictors in the model. Due to the small number of affirmative responses in many outcomes, we used exact logistic regression to examine associations between dichotomous outcomes (such as symptoms or presence of FVC or FEV1 < LLN) and exposure categories. Smoking status was assessed as current smoker versus former or non-smoker, due to the necessity of use of a dichotomous variable with exact logistic regression. We were unable to adjust for the continuous variable of tenure in exact logistic regression models. In order to account for age in the symptom exact logistic regression model, we categorized age into two groups: younger than 50, and 50 and above. Age 50 was selected due to distribution of the data and biologically plausible expected variations in symptoms starting at age 50. Age is already accounted-for in the exact logistic regression evaluation for outcomes of FVC or FEV1 < LLN, as part of the expected values for LLN determination.

Results

Worker Characteristics

We identified 47 workers potentially exposed to epoxy resins from job description lists. All eligible workers were contacted and offered participation in the medical screening program. Of the nine workers who declined participation, none were primary users of epoxy resins. Overall, 81% of eligible workers participated in this voluntary program. Table 2 describes characteristics of 70 workers participating in the medical screening. Unexposed workers did not differ from either lower or higher exposed workers by gender, race, age, hours worked or education level. Exposed workers were more likely to currently smoke. There was also a statistically significant difference in employment tenure at the company, with the lower exposed group having the longest tenure.

Medical History and Symptoms

Table 2 also describes pertinent medical co-morbidities in this population. Higher exposed workers more often reported heart disease than lower or unexposed workers (p=0.025), though this group was also slightly older and included more current smokers. Groups did not differ for any respiratory diseases; however, there was a high prevalence of allergies for all three, ranging from 48-56%. A significantly greater percentage of higher exposed workers used inhaled medications (18%) compared to unexposed (3%).

Table 3 shows Odds Ratios for symptoms according to exposure groups. Because the presence of current smoking was low overall, and because only one subject in the unexposed group was a current smoker (See Table 2), we analyzed symptom reporting among the current non-smokers only, rather than attempting to adjust for smoking. We did adjust for age. Higher exposed workers were significantly more likely to report wheezing (OR 5.91, [1.07-41.42], p=0.041) than unexposed workers. The lower exposed workers were more likely to report achiness than unexposed workers (OR 10.86, [1.05-∞], p=0.045). Although not statistically significant, we observed a pattern of higher exposed workers more frequently reporting cough, shortness of breath, chest tightness, and producing phlegm, compared to lower exposed and unexposed workers.

Spirometry

Of 70 workers who performed spirometry, 67 (96%) achieved results meeting ATS/ERS criteria for acceptability and repeatability and were included in analysis. Among 16 higher exposed workers, five (31.3%) had an FEV1 < LLN compared to two of 20 (10%) lower exposed workers and one of 31 (3.2%) unexposed workers. Similarly, four of 16 (25.0%) higher exposed workers had an FVC < LLN compared to three of 20 (15.0%) lower exposed workers and three of 31 (9.7%) unexposed workers. Among the 10 workers with FVC below the LLN, seven had body mass indices above 30.

We found no statistically significant differences between exposure group and abnormal spirometry (Table 4). We did, however, observe a similar pattern to that seen with respiratory symptoms: higher exposed workers had a greater frequency of abnormal spirometry (FEV1 most notably) than the lower or unexposed groups after adjusting for

smoking. We found no significant differences for decreased FEV1/FVC ratio < LLN among exposure groups (p=0.537) in bivariate analysis. For all workers with spirometric values below the LLN, clinical follow-up was recommended.

Mean values of FVC percent predicted, FEV1 percent predicted and FEV1/FVC all fell within clinically normal ranges (Figure 1). Mean FEV1 percent predicted for unexposed workers was 98.0 ±12.0, lower exposed workers was 94.8 ±10.9, and higher exposed workers was 90.6 ± 17.3. Similarly, FVC percent predicted for unexposed workers was 96.5 ± 12.3, lower exposed workers was 95.9 ±9.9, and higher exposed workers was 91.0 ± 15.5. FEV1/FVC ratio for the unexposed was 81.2 ± 4.4, lower exposed was 79.4 ± 5.4, and higher exposed was 77.5 ± 6.9.

Table 5 shows that, after adjustment for smoking, education level and age (for FEV1/FVC), there were no significant differences in mean FVC or FEV1 percent predicted or FEV1/FVC ratio among the three groups. Despite finding normal mean spirometry values, there was a pattern for all parameters, as seen in Figure 1 and in the regression coefficients by exposure categories, showing decreasing lung function associated with increasing exposure. While higher exposed workers were slightly older (mean age 50.4 years) than the unexposed group (mean age 42.9 yrs), the percent predicted values in the higher exposed workers showed a pattern of lower FEV1 (p=0.172) and FVC (p=0.176) compared to unexposed workers, even accounting for age, education and smoking. We also examined spirometry endpoints using duration of employment to assess for any additional exposure effect. Duration of employment was not a significant predictor in the linear regression models and was therefore not included in the final models.

Lymphocyte Proliferation Testing

Few workers had LPT stimulation indices exceeding the statistical cut-off points for any ERS products. For the trade secret epoxy, only two of the higher and lower exposed workers and no unexposed workers demonstrated abnormal LPTs. For the triamine hardener, only one exposed worker and one unexposed worker had abnormal results. Similarly, only one unexposed and no exposed workers had abnormal LPTs to the black epoxy. All workers had normal responses to the methacrylate adhesive and the thermoset hardener. There were no significant differences in proportion with abnormal LPTs between exposure groups.

Discussion

In this population of 70 workers, we found greater frequencies of reported respiratory symptoms, use of inhaled medications, and abnormal FEV1 and FVC results in higher exposed workers compared to unexposed workers. This remained statistically significant for symptoms of cough and wheeze when adjusted for smoking. Although not statistically significant, the pattern remained consistent across other respiratory outcomes after smoking adjustment. While mean FEV1 and FVC percent predicted values and FEV1/FVC ratios were within normal ranges, we saw an exposure-response gradient in both FEV1 and FVC percent predicted for unexposed, lower exposed and higher exposed worker populations, suggesting even in this cross-sectional study that those with higher ERS exposure may be at risk for occupational lung disease. Although we were hopeful to demonstrate a biomarker

that could identify workers at risk to develop occupational illness prior to onset of disease, epoxy resin LPT did not consistently predict exposure status in this worker population.

ERS chemicals are well-known causes of occupational asthma, particularly the acid anhydrides and aliphatic polyamines[1]. The mechanisms for ERS-related occupational asthma remain uncertain, with debate as to whether epoxy monomers can cause immune-mediated asthma[13], or whether activating agents like anhydrides and amines impart such risk exclusively. Our findings suggest that ERS-exposed workers are at risk for airflow obstruction and respiratory symptoms. An on-going longitudinal medical surveillance program for these workers will include spirometry and symptom questionnaires, with follow-up and referral of workers in whom occupational illness is suspected.

Epoxy resin system components also cause allergic contact dermatitis. Recently, thirteen epoxy resins were tested for skin-sensitization potential using a local lymph node assay, all with abnormal results[14]. Dermal absorption is an important route of exposure, conferring risk for some occupational lung diseases including those associated with beryllium and isocyanates[15]. Though our study focused on respiratory health effects, the questionnaire included queries on skin symptoms. Eight workers reported regularly experiencing skin rash, mainly on areas of skin that came in contact with chemicals and the majority reportedly occurring in relation to work. Future investigations of ERS-related lung disease should focus on elucidating skin symptoms and dermal exposure in at-risk workers.

The impetus for this study followed diagnosis of an ERS production worker with HP based on biopsy findings of poorly-formed granulomas and severe constrictive bronchiolitis, ultimately requiring lung transplantation for end-stage obstructive lung disease. This sentinel case demonstrated a high LPT SI (35.5) to a hardener containing a mono- and polydiamine and a modestly elevated SI (3.7) to an epoxy resin containing a bisphenol A epoxy resin. However, in our study population, we did not find that LPT was a useful biomarker in identifying exposed or sensitized workers.

Lymphocyte proliferation tests have been investigated clinically and experimentally in the diagnosis of hypersensitivity and drug-induced pneumonitis. LPTs have been tested to isocyanates[16,17], antibiotics[18], methotrexate[19], *Trichosporon asahi*[20], smut spores[21], pigeon serum, and feather antigens [22,23]. The ERS chemicals tested in this study were heterogeneous and included amines, epoxy resins, and methacrylates. In industrial applications, these products interact to accomplish their desired effects of bonding and adherence. In our LPT testing, each product was tested in isolation. We do not know if testing the component mixture would elicit different results, or even if such a process would be feasible in an *in vitro* cell-based testing system. Moreover, LPT may be useful primarily in those with granulomatous lung diseases such as HP, with less relevance as a biomarker in other more common ERS-related occupational diseases such as asthma.

There are several limitations to our study. This study had a small study population due to the limited nature of exposure at the facility, where only 47 out of 1100 potentially faced exposure. While the small study population did influence power to detect statistically significant differences in pulmonary function, the exposure-response patterns seen for the

symptom and pulmonary function outcomes are consistent and potentially concerning. These exposure-response patterns remained consistent after adjusting for key factors known to be associated with pulmonary function, such as smoking. Furthermore, while reporting bias could lead to differences in symptom reporting, the spirometry data supports an objective association between pulmonary function change and exposure.

In the absence of concurrent workplace exposure sampling, we focused more on exposure assessment as predicted by the job location and description with review by the plant Safety Officer and OEM Physician. Exposure sampling by the company following identification of the sentinel case showed that most ERS chemical levels were non-detectable or extremely low. Since the sentinel case was recognized, local exhaust ventilation and other engineering controls were improved, suggesting that current workplace exposures may be different from historical exposures. Misclassification in the unexposed group based on past occupational or low-level recreational exposures is possible; however, random misclassification should bias results to the null, and we still saw significant effects of exposure on cough, wheeze and use of inhaled medications.

In this exploratory research in the use of epoxy resin LPT to assess sensitization, the concentrations of epoxy materials used in the LPTs were determined by preliminary toxicity studies. A well-known challenge of LPT performance is determining the optimal concentration of antigen that is adequate to allow a proliferative response without being so high as to induce cytotoxicity. Further work is needed to explore the utility of ERS LPT, including identification of optimal antigen concentrations, feasibility of testing chemical mixtures, and culture conditions that might permit more successful antigen presentation with poorly soluble materials.

In summary, in this population where most chemical exposures appear to be well controlled, we observed a consistent pattern of workers in the higher exposed jobs more frequently reporting respiratory symptoms and showing decreased lung function compared to unexposed workers. Targeted medical surveillance along with more in-depth investigation of epoxy resin system chemical exposures and immunotoxicity, combined with improved worker hazard communication, will provide opportunities for prevention of a spectrum of potentially disabling occupational diseases.

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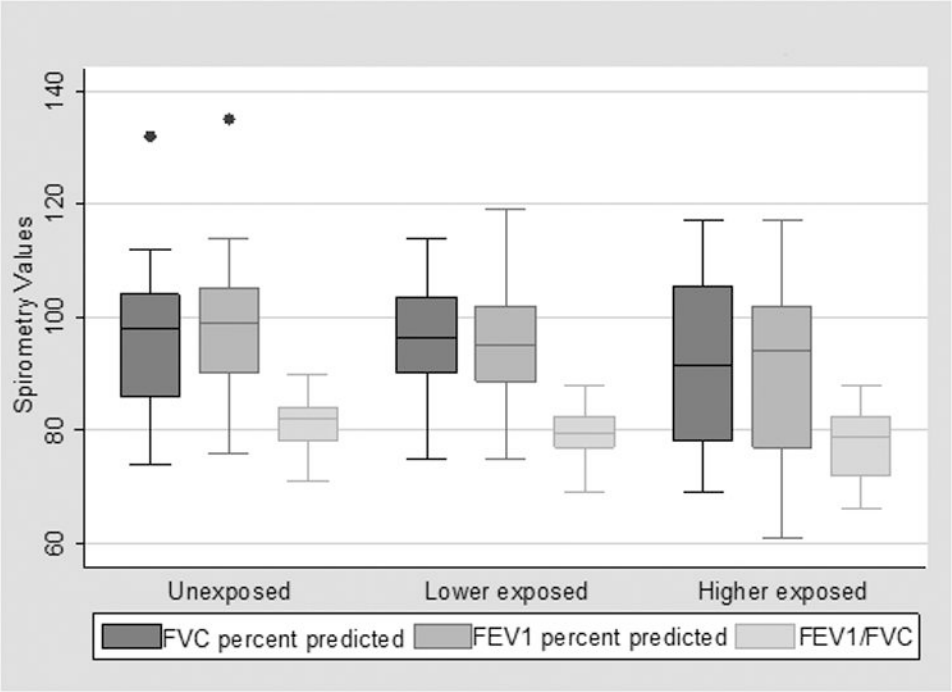

Figure 1. Exposure-response in spirometry values for Epoxy Workers

Table 1

Selected Epoxy Resin System components chosen for Lymphocyte Proliferation Testing (LPT)

Product type	Components listed on MSDS
trade secret epoxy	*Proprietary Epoxy Resin, unknown %* Proprietary Alkyl Glycidyl Ether, unknown % Microcrystalline silica, 51-60%
triamine hardener	*Polyoxypropylenetriamine, 81-90%* *Alkyl Amine Mixture, unknown %*
methacrylate adhesive	*Cyclohexyl methacrylate, 30-60%* *Poly (butadiene-co-styrene), 30-60%* *Methacrylic acid, 5-10%* Amorphous silica, 1-5% *Acrylic acid, 1-5%* *1,3-Butylene glycol dimethacrylate, 1-5%*
black epoxy	*Proprietary Epoxy Resin, ≤50%* Crystalline silica, ≤50% *Proprietary Epoxy Resin, ≤5%* Carbon Black, ≤1%
thermoset hardener	Crystalline silica, ≤50% *Proprietary Polydiamine, ≤15%* *Proprietary Amine Compound, ≤15%* 4-Nonyl phenol, ≤10%

Components in italics most likely immunologically active.

Table 2
Characteristics & Medical History of 70 Workers at an Industrial Manufacturing Facility

Characteristic	Higher exposed (n=17)	Lower exposed (n=21)	Unexposed (n=32)	p-value (for overall group difference)
		mean (SD)		
Age (years)	50.40 (14.12)	41.07 (12.08)	42.86 (13.51)	0.081
Tenure at company (years)	6.59 (3.81)	10.36 (9.97)	4.19 (4.99)	**0.007**
Hours worked/week	44.65 (5.28)	41.90 (2.84)	42.84 (7.41)	0.357
		n (%)		
Gender				
Male	11 (64.71)	16 (76.19)	22 (68.75)	0.728
Female	6 (35.29)	5 (23.81)	10 (31.25)	
Race				
White	16 (94.12)	18 (85.71)	28 (87.50)	0.796
Latino	1 (5.88)	3 (14.29)	4 (12.50)	
Current Smoking Status				
Current smoker	6 (35.29)	5 (23.81)	1 (3.13)	**0.005**
Non-smoker	11 (64.71)	16 (76.19)	31 (96.88)	
Education Level				
High School only	9 (52.94)	9 (42.86)	7 (21.88)	0.069
College +	8 (47.06)	12 (57.14)	25 (78.13)	
History of:				
• **Allergies**	9 (52.94)	10 (47.62)	18 (56.25)	0.827
• **Asthma**	3 (17.65)	4 (19.05)	2 (6.25)	0.303
• **Chronic bronchitis, mphysema, COPD**	2 (11.76)	2 (9.52)	0 (0.00)	0.104
• **Sinus trouble**	3 (17.65)	5 (23.81)	8 (25.00)	0.874
• **Hay fever**	3 (17.65)	5 (23.81)	9 (28.13)	0.726
• **Pneumonia**	3 (17.65)	4 (19.05)	5 (15.63)	0.999
• **Heart Disease**	3 (17.65)	1 (4.76)	0 (0.00)	**0.025**
• **Tuberculosis**	0 (0.00)	1 (4.76)	0 (0.00)	0.543
• **Other Lung Disease**	0 (0.00)	1 (4.76)	1 (3.13)	0.999
• **Currently taking medications**	10 (58.82)	7 (33.33)	18 (56.25)	0.186
• **Taking breathing medications****	3 (30.00)	3 (42.86)	1 (5.56)	**0.047**
• **Taking corticosteroids**	0	0	0	

*No one reported lung surgery, sarcoidosis, hypersensitivity pneumonitis, or a previous chest injury.

**Among 35 workers reported currently taking medications.

Table 3

Respiratory & systemic symptoms among current non-smokers by exposure groups, adjusted for age (n=58)*

Symptom	Higher exposed OR (95% CI)	p-value	Lower exposed OR (95% CI)	p-value	Unexposed (reference group) OR
• **Usually have a cough****	6.00 (0.44-∞)	0.177	5.81 (0.433-∞)	0.180	1.0
• **Chest ever sound wheezy or whistling**	**5.91 (1.07-41.42)**	**0.041**	2.70 (0.63-12.12)	0.216	1.0
• **Frequently feel achy****	2.09 (0.05-∞)	0.647	**10.86 (1.05-∞)**	**0.045**	1.0
• **Regularly experience skin rash**	2.39 (0.03-206.39)	1.000	7.56 (0.53-443.52)	0.178	1.0
• **Shortness of breath when hurrying on level surface or walking up slight hill**	3.65 (0.40-34.05)	0.31	2.02 (0.24-17.21)	0.694	1.0
• **Ever have chest tightness**	4.88 (0.76-34.80)	0.106	2.47 (0.38-16.62)	0.445	1.0
• **Usually bring up phlegm**	4.50 (0.42-64.75)	0.278	1.09 (0.02-23.12)	1.000	1.0
• **Regularly experience eye, nose, or throat irritation**	3.83 (0.42-36.35)	0.292	3.91 (0.63-29.88)	0.172	1.0
• **Frequently feel feverish**	2.83 (0.03-232.00)	0.927	1.93 (0.02-157.68)	1.000	1.0

*Determined using exact logistic regression

**Median unbiased estimates (MUE)

Table 4

Odds Ratios (ORs) for abnormal FVC or FEV1 based on exposure status, adjusted for smoking*

Abnormal Spirometry	Higher exposed OR (95% CI)	p-value	Lower exposed OR (95% CI)	p-value	Unexposed (reference group) OR
FVC < LLN	1.92 [0.21, 17.75]	0.770	1.21 [0.13, 10.98]	1.00	1.00
FEV1 < LLN	10.51 [0.86, 589.90]	0.071	2.98 [0.14, 191.85]	0.748	1.00

* 3 individuals with a “D” or “F” quality score for spirometry were excluded from analysis.

Note: In analysis of FEV1/FVC < LLN, only one worker in the low exposed group had an abnormal ratio, representing 5% of the low exposed group. In univariate analysis (without adjustment for smoking), this yielded no significant difference among the exposure categories, p=0.537.

Table 5

Linear Regression Coefficients (β) for the predictive value of exposure variables on mean spirometry value

	FVC % Pred β [95% CI]	p-value	FEV1 % pred β [95% CI]	p-value	FEV1/FVC β [95% CI]	p-value
Lower exposed	-0.82 [-8.26, 6.62]	0.826	-2.36 [-10.14, 5.43]	0.547	-1.42 [-4.42, 1.58]	0.348
Higher exposed	-5.71 [-14.06, 2.64]	0.176	-6.04 [-14.77, 2.6]	0.172	-1.40 [-4.88, 2.08]	0.423
Smoker	-4.36 [-13.05, 4.34]	0.320	-7.68 [-16.78, 1.41]	0.096	-2.51 [-6.02, 0.99]	0.157
Higher education	-5.21 [-11.90, 1.48]	0.125	-3.57 [-10.56, 3.43]	0.312	0.33 [-2.37, 3.04]	0.805