FINAL PROGRESS REPORT

A CASE-CONTROL STUDY OF AIRWAYS OBSTRUCTION AMONG CONSTRUCTION WORKERS

GRANT SPONSOR: National Institute for Occupational Safety and Health

GRANT NUMBER: 5R01OH009943

PROJECT TITLE: Etiology of COPD among Construction Workers

PROJECT DATES: 9/1/2011 - 8/31/2015

PRINCIPAL INVESTIGATOR:

John Dement PhD, CIH
Professor
Division of Occupational & Environmental Medicine
Department of Community & Family Medicine
Duke University Medical Center
2200 West Main Street, Suite 400
Durham, NC 27710
Phone: (919)684-8136
Fax: (919)286-1021
John.Dement@Duke.edu

CO-INVESTIGATORS:

Laura Welch MD[1], Knut Ringen Dr. PH[1, 2], Patricia Quinn, BA[1]

[1]The Center for Construction Research and Training
8484 Georgia Avenue, Suite 1000
Silver Spring, Maryland 20910
Phone: 301- 578-8500

[2] Stoneturn Consultants
2610 SW 151st Place
Seattle, WA 98166, USA
Phone: 206-444-9811

TABLE OF CONTENTS

TERMS AND ABBREVIATIONS

ANOVA -- Analysis of variance

ATS – American Thoracic Society

ATS/ERS – American Thoracic Society /European Respiratory Society

CDC – Centers for Disease Control and Prevention

COPD – Chronic obstructive pulmonary disease

DOE – Department of Energy

FEV_1 – Forced expiratory volume in on second

FVC – Forced vital capacity

NIOSH – National Institute for Occupational Safety and Health

OSHA – Occupational Safety and Health Administration

GOLD -- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease

ILO -- International Labour Office

LLN – Lower limit of normal. Refers to FEV_1/FVC ratio below the LLN using the prediction equations of Hankinson et al. [1999]

PAF – Population attributable fraction

PNOR – Particulates not otherwise regulated.

VGDF – Vapors, gases, dusts, and fumes.

ABSTRACT

Background: While smoking is the major cause of COPD, occupational exposures to vapors, gases, dusts, and fumes (VGDF) increase COPD risk. This case-control study estimated the risk of COPD associated with occupational exposures experienced by construction workers.

Methods: The study population included 834 cases and 1243 controls participating in a national medical screening program for older construction workers. A telephone questionnaire obtained a lifetime occupational and exposure history, including frequency doing 90 specific construction-related tasks known to generate VGDF exposures. Qualitative exposure indices were developed for a list of 14 specific exposures experienced by construction workers based on lifetime task-specific exposure histories in combination with task exposure intensities estimated by a panel of experienced industrial hygienists. COPD risk associated with specific agents and VGDF combined was assessed using unconditional logistic regression controlling for demographics, cigarette smoking, and other risk factors. Principal component analyses investigated correlations among exposures and effects of combined exposures on COPD risk. The joint effects of exposure agents and smoking were evaluated for departure from additive interactions between specific exposures and cigarette smoking.

Results: Cumulative exposure indices for Asbestos; Silica; Cement Dust; Engine Exhausts; Acids and Caustics; Welding, Thermal Cutting, Soldering, Brazing; Metal Cutting, Grinding, and Machining Aerosol; Isocyanates; Organic Solvents; Wood Dust; Molds and Spores; and Particulates not otherwise regulated (PNOR) were significantly associated with risk of COPD. Additionally, the exposure index for all VGDF exposures combined was a strong predictor of COPD risk. Approximately 18% (95% CI=2–24%) of COPD risk was estimated to be attributable to construction-related exposures. Among never smokers, the attributable fraction for construction-related exposures was 32% (95% CI=6-42%). The effects of smoking and the occupational exposures studied did not depart significantly from additivity.

Conclusions: Construction workers are at increased risk of COPD as a result of broad and complex effects of many exposures acting independently or interactively. The VGDF exposure metric is a reasonable exposure measure for assessment of COPD risk in complex exposure environments and regulatory approaches should take this into account. Control methods should be implemented to prevent worker exposures and smoking cessation should be promoted.

SIGNIFICANT (KEY) FINDINGS

This study had four specific aims. Significant results and findings relative to each specific aim are discussed below.

Specific Aim 1: To identify and enroll approximately 1000 COPD cases and at least 1000 matched controls.

A total of 1612 COPD cases and 2129 frequency matched controls were identified among workers participating in the Building Trades National Medical Screening Program (BTMED). A key strength of this study was ability to define COPD cases and controls objectively based on spirometry meeting acceptable technical standards established by the American Thoracic Society. A wealth of clinical, medical and exposure history data derived from BTMED examinations, allowing for assessment and control of confounders such as cigarette smoking and hobby-related exposures.

Specific Aim 2: To develop, pilot test, and administer an occupational exposure assessment questionnaire by telephone interview.

The telephone questionnaire was developed based on significant worker input and pilot testing among different construction trades. Interviewers had excellent knowledge of construction-related exposures and significant experience administering telephone-based occupational exposure histories through the BTMED program. Approximately 86% of workers contacted participated in the telephone questionnaire.

Specific Aim 3: To conduct exposure assessments for cases and controls using questionnaire task exposure frequency scores and exposure intensity scores by industrial hygienists.

Qualitative cumulative exposure indices were developed for a list of 15 *a priori* exposures frequently experienced by construction workers. These exposure indices were task-based and incorporated the dimensions of task frequency, duration, and exposure intensity. The assessment of cumulative exposures was comprehensive, including construction and non-construction work, bystander exposures, and exposures while serving in the military.

Specific Aim 4: To conduct analyses to identify exposures increasing COPD risk and evaluate interactions of occupational risk factors with personal factors such as smoking.

Unconditional logistic regression was used to assess COPD risk associated with *a priori* exposures while controlling for important confounders such as cigarette smoking. Increased COPD risk was significantly associated with exposures to all vapors, gases, dusts, and fumes (VGDF) combined as well as 13 of the 15 studied specific agents. Overall, approximately 18% of COPD cases in this population were attributable to workplace exposures and the occupational attributable fraction was 32% among never smokers. Construction exposures are many and complex; therefore, many workers had elevated cumulative exposures to multiple agents.

TRANSLATION OF FINDINGS

COPD associated disability and mortality is rising worldwide. Currently available treatments for COPD are minimally effective with regard to disease progression, making prevention critically important. This study adds to the literature concerning the risk of COPD among construction workers as well as specific exposures that contribute to this increased risk.

A key finding of this study was the strong association of COPD risk with the measure of all VGDF exposures combined. These results suggest a broad effect of workplace exposure agents acting collectively to increase COPD risk, perhaps through common biological pathways such as a chronic inflammatory reaction.

In addition to risks for all VGDF combined this study found increased risk for the category 'particulates not otherwise regulated' (PNOR), which includes all mineral and inorganic 'inert or nuisance dusts' without specific individual U.S. Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL). PNOR exposures, are currently regulated by OSHA as 'inert or nuisance dusts' with a very high PEL of 5 mg/m^3 as respirable dust. PNOR exposures result from many different construction tasks such drywall work, demolition, work with insulation materials, and cutting, drilling, or grinding concrete.

OUTCOMES/ IMPACT

The current regulatory framework, directed at individual exposures and not combined VGDF exposures may not provide adequate worker protection. A better framework would add a focus on respirable irritants regardless of source. Given the complex nature of exposures in the construction industry, more attention is needed to prevent or control exposures to all respirable particulates.

A simplistic prevention model might conclude that reduction of smoking, if smoking cessation programs were to be effective, could have a significantly greater health impact than preventing occupational exposures to VGDF exposures. However, COPD is a significant health risk even for non-smokers, and the findings from this study suggest that workplace VGDF exposures account for nearly one-third of COPD incidence among never-smokers. Smoking cessation efforts must not reduce efforts to prevent occupational VGDF exposures. A comprehensive prevention strategy is needed to reduce the risk of COPD.

SCIENTIFIC REPORT

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder that includes chronic bronchitis and emphysema [Pistolesi, 2009] and more than 13 million people in the U.S. have physician diagnosed COPD [Ford et al., 2013a; NHLBI, 2014; Welch et al., 2013]. The prevalence of obstructive impairment determined by spirometry ($FEV_1/FVC < 0.70$) was estimated to be 13.7% during 2007-2010 among adults [Ford et al., 2013b]. COPD ranked as the third leading cause of death in 2010 [Ford et al., 2013a; Johnson et al., 2014]. Currently available treatments for COPD are minimally effective with regard to disease progression, making prevention critically important [Eisner et al., 2010].

The etiology of COPD is complex and the biology of COPD is still poorly understood. Although tobacco smoking is the major risk factor for COPD with an estimated population attributable fraction (PAF) of 80 to 90% [ATS, 1995a], only 15-20% of smokers develop COPD [Barr et al., 2002; Mannino et al., 2002]. A significant fraction of all COPD cases and COPD-related mortality occurs among non-smokers [Behrendt, 2005; Eisner et al., 2010; Mannino et al., 2002; Whittemore et al., 1995]. An estimated 15-30% of COPD cases are attributable to occupational exposures; the PAF may be as high as 53% among never smokers [Balmes et al., 2003; Balmes, 2005; Eisner et al., 2010; Hnizdo, 2002; Mehta et al., 2012; Toren and Jarvholm, 2014].

Occupational exposures to particulates, and possibly to ambient particulates, are associated with COPD [Andersen et al., 2011; Eisner et al., 2010; Omland et al., 2014]. Increased COPD risk, and increased COPD mortality, has been observed among workers exposed to 'vapors, gases, dusts, and fumes' (VGDF) [ATS, 2003; Balmes, 2005; Bergdahl et al., 2004; Blanc et al., 2009a; Blanc et al., 2009b; GOLD, 2014; Hendrick, 1996; Mehta et al., 2012; Omland et al., 2014; Oxman et al., 1993; Toren and Jarvholm, 2014; Trupin et al., 2003; Weinmann et al., 2008]. Both large and small airway effects of VGDF exposures are suggested in the literature [Churg and Wright, 2002; de Jong et al., 2014a].

Increased COPD risk has been associated with some specific occupational exposure agents, including: **coal dust** [Becklake, 1989; Coggon and Newman Taylor, 1998; Hendrick, 1996; Henneberger and Attfield, 1996; NIOSH, 1995]; **asbestos** [ATS, 2004; Dement et al., 2010; Glencross et al., 1997]; **silica** [Dement et al., 2010; Hnizdo and Vallyathan, 2003; Oliver and Miracle-McMahill, 2006; Rushton, 2007b; Tse et al., 2007]; **welding and cutting gases and fumes** [Balmes, 2005; Bradshaw et al., 1998; Dement et al., 2010; Hunting and Welch, 1993; Koh et al., 2015; Mastrangelo et al., 2003; Szram et al., 2013]; **cement dust** [Abrons et al., 1988; Dement et al., 2010; Fell et al., 2010; Mwaiselage et al., 2004; Rushton, 2007a]; **diesel exhausts** [Hart et al., 2009; Hart et al., 2006; Tuchsen and Hannerz, 2000; Ulvestad et al., 2000; Weinmann et al., 2008]; s**pray painting** [Glindmeyer et al., 2004; Hammond et al., 2005; Mastrangelo et al., 2003; Pronk et al., 2007]; **organic solvents** [Heederik et al., 1989; Melville et al., 2010; Post et al., 1994]; and **possibly man-made mineral fibers** [Clausen et al., 1993; Hansen et al., 1999; Hughes et al., 1993; Hunting and Welch, 1993; Kilburn et al., 1992].

Construction workers experience a wide spectrum of exposures and are at increased risk for COPD and COPD-related mortality [Dement et al., 2009; Glencross et al., 1997; Hnizdo, 2002; NIOSH, 2014; Ringen et al., 2015; Welch et al., 2015]. Increased COPD risk among construction workers has been associated with exposures to inorganic dusts, gases and irritants, and fumes [Bergdahl et al., 2004; Toren and Jarvholm, 2014].

We have previously reported results of a cross-sectional study of airways obstruction among 7579 construction and trade workers employed at U.S. Department of Energy (DOE) sites and participating in the Building Trades National Medical Screening Program (BTMED) (https://www.btmed.org) [Dement et al., 2010]. The overall prevalence of spirometry defined airways obstruction was 13.3% and was highest among cement masons, brick masons, and plasterers (24%). Cumulative exposures to asbestos, welding/cutting, silica, cement dusts, and some tasks resulting in exposures to solvents and paints were associated with the risk of airway obstruction in sub-analyses restricted to workers with less than five years of construction work outside of DOE sites.

Our prior study using BTMED data had two primary limitations. First, because the BTMED exposure assessment was primarily designed to identify exposures on DOE sites for selection of medical surveillance tests, the exposure questions were not optimal for assessment of COPD risk factors. Secondly, even though BTMED participants have worked a great deal outside DOE facilities, the BTMED exposure assessment was largely restricted to exposures on DOE sites and did not take into account exposures from work outside DOE employment. This report provides final results of a case-control study among construction workers which specific aims as follows:

1. To enroll approximately 1000 COPD cases and at least 1000 controls from the study base of workers completing medical examinations with spirometry.

2. To develop, pilot test, and administer an occupational exposure assessment questionnaire to cases and controls by telephone interview.

3. To conduct exposure assessments for cases and controls using data from the exposure questionnaires and qualitative exposure intensity scores for tasks using ratings by a panel of experienced industrial hygienists.

4. To conduct detailed analyses to identify exposures increasing COPD risk and evaluate interactions of occupational risk factors with personal factors such as smoking and prior respiratory history, hobby-related exposures, and family history

MATERIALS AND METHODS

Identification of Cases and Controls

Cases and controls were identified using medical examination results from the BTMED program through December 2013. Prior reports describe the work history and medical components of the BTMED program [Dement et al., 2009; Dement et al., 2003; Dement et al., 2010; Welch et al., 2004; Welch et al., 2013]. Briefly, BTMED medical examinations are performed by local medical providers who meet credentialing requirements and adhere to a detailed protocol. The respiratory examination includes: a respiratory history and symptom questionnaire; a posterior-anterior (P-A) chest radiograph, classified by a B-reader according to International Labour Office (ILO) Classification of Radiographs of Pneumoconiosis [ILO, 1980; ILO, 2002]; and spirometry. The respiratory history and symptom questionnaire was adapted from the American Thoracic Society (ATS) DLD-78 questionnaire [Ferris, 1978]. All participating medical facilities agreed to obtain spirometry according to ATS standards and quality control procedures were in place for all medical data [Dement et al., 2010].

Workers completing at least one BTMED examination with spirometry through December 2013 formed the study base for selection of cases and controls if: 1) not missing key demographic data (age, race, sex, height, and BMI); and 2) had spirometry meeting inclusion criteria of a minimum of three recorded expiratory efforts and repeatability of FVC and FEV_1 of 0.2 liters or less [ATS, 1995b]. We chose the ATS 1995 criteria as these were in effect at the start of the BTMED program in 1996, and many participants were screened prior to publication of the new ATS recommendation in 2005. The most recent examination was selected for each worker.

In this manuscript we use the term COPD to describe airways obstruction based on an epidemiologic rather than clinical case definition. In clinical practice COPD is diagnosed based on a combination of symptoms and pulmonary function, often including post-bronchodilator spirometry. However, prior studies have used the term COPD based on spirometry without bronchodilation to describe an epidemiologic case definition [Behrendt, 2005; Hnizdo, 2002; Weinmann et al., 2008]. The ATS/ERS Task Force [ATS/ERS, 2005] recommends identification of air obstruction based on an FEV_1/FVC ratio below the lower limit of normal (LLN) to avoid age-related misclassification associated with use of a fixed FEV_1/FVC ratio [Enright et al., 2008; Hansen et al., 2007; Hnizdo et al., 2006; Swanney et al., 2008]. On this basis, COPD was defined as a FEV_1/FVC ratio below the LLN using the prediction equations of Hankinson et al. [1999] without use of bronchodilation. Workers not classified as having airways obstruction by this definition but meeting all other inclusion criteria were eligible as controls.

All available cases were frequency matched to controls based on sex, race, age, and DOE site by random sampling. We oversampled controls to increase statistical power. Frequency matching by DOE site allowed some degree of control for location specific non-occupational exposures.

Exposure Assessment

Based on our experience in the BTMED program telephone interviews have been found to be an

effective approach to collecting exposure history data. This is consistent with studies that have found telephone interviews to be superior to postal surveys for respiratory symptoms and risk factors [Brogger et al., 2002]. A telephone questionnaire was developed and administered to obtain a lifetime occupational and exposure history through the date of the qualifying BTMED examination. Questionnaire data domains included:

1. Industry and jobs held for at least six months with start and stop dates (month and year). Jobs within the same industry and occupation were treated as one job. For each job, workers were asked to list the products or services produced, job title/position, and usual work hours per week.

2. For all construction-related jobs, a qualitative assessment of frequency (none to daily) of doing 90 specific construction tasks known to generate VGDF exposures (e.g. cutting concrete, insulation installation, wood sanding, etc.). Open-ended questions were included to allow workers to report other construction-related tasks that created VGDF exposures but were not included in the listed tasks in the questionnaire.

3. For non-construction jobs, workers were asked "Does/did this job expose you to vapors, gases, dusts, and fumes" as this single survey item has been shown to delineate exposures associated with COPD risk [Blanc et al., 2005; Quinlan et al., 2009]. For any job with a positive response concerning VGDF exposure, workers provided a description of tasks resulting in exposures, materials exposed to, and frequency of exposure.

4. A qualitative assessment of exposure frequency (none to daily) for an *a priori* list of other materials associated with respiratory disease in the literature (e.g. coal dust; formaldehyde; beryllium; mercury; polyvinyl chloride fumes (heating or cutting PVC); isocyanates; pesticides, insecticides, or herbicides; diesel or gasoline engine exhaust; grain dusts; and animal feed or fodder). These data were collected for control of potential confounding exposures.

5. Use of respiratory protection (always, sometimes, rarely, or never) and engineering controls such as wet methods or local exhaust ventilation (always, sometimes, rarely, or never) for reported tasks.

6. An assessment of the frequency of bystander exposures to asbestos, man-made fibers, abrasive cutting or grinding of concrete, drywall/plaster dusts, spray painting, sandblasting, welding/cutting, and wood dusts.

7. Service in a branch of the military and if their military jobs resulted in exposures to VGDF. For any military job with a positive response concerning VGDF exposure, workers provided a description of tasks resulting in exposures, materials exposed to, and frequency of exposure.

8. Exposures to passive tobacco smoke at home and at work, having a blood relative with COPD [Weinmann et al., 2008], and history of pneumonia as a child [Tager et al., 1988]. Respiratory history and smoking history were determined using data from each worker's BTMED exam and any missing data from the BTMED exam was collected.

The telephone questionnaire was developed and pilot tested in several ways. First, we assembled two separate focus groups of 10-15 experienced construction workers from DOE's Savannah River and Oak Ridge sites to review the draft questionnaire for ease of understanding (language level), question syntax, and overall questionnaire flow. We also asked focus group participants to identify any common VGDF exposures experienced by construction workers not adequately addressed in the draft questionnaire. Secondly, the draft questionnaire was pilot tested via telephone administration to approximately 25 construction workers identified by BTMED to represent the approximate age and experience range of the COPD cases and controls.

The final telephone questionnaire was administered by four trained interviewers without knowledge of case or control status. Cases and controls were randomly assigned to interviewers. Study subjects were first sent an invitation letter describing the study followed by telephone contact by the assigned interviewer to obtain informed consent and administer the questionnaire. A minimum of two telephone contact attempts were made before a second reminder letter was sent. Following the second reminder letter at least two additional telephone contact attempts were made. Study subjects were classified as 'failed to contact' due to bad addresses or telephone numbers and 'failed to respond' after no response following two letters and at least four phone calls. Information about the study was also provided on the BTMED web site and included in the BTMED Newsletter.

Qualitative cumulative exposure indices were assessed for an *a priori* list of 15 common construction-related exposures shown in Table I. The category 'particulates not otherwise regulated' (PNOR) includes all mineral and inorganic 'inert or nuisance dusts' without specific individual U.S. Occupational Safety and Health Administration Permissible Exposure Limits (PEL) [NIOSH, 2015; OSHA, 2015]. A PNOR exposure index was included to allow generation of an overall index for VGDF exposures comparable to those in the published literature. All indices were based on task frequency by job, job duration, and usual work schedule from the interviews in combination with task exposure intensity scoring by industrial hygienists.

The telephone interviews collected information concerning the frequency of performing a specified set of 90 construction-related tasks resulting in exposures to 'vapors, gases, dusts, and fumes' (VGDF). Task frequency from the questionnaire and assigned exposure days per month were as follows:

Worker Reported Task Frequency Description	**Assigned Days of Exposure Per Month**
None: Did not perform the task	0
Rarely: Performed the task less than once per month	1
Monthly: Performed task 1-2 times per month	2
Weekly: Performed task weekly or most weeks	10
Daily: Performed task daily or almost every day	20

In addition to collecting information about the frequency of performing tasks, exposure intensity for each task reported by workers for jobs held more than six months was scored by three senior American Board of Industrial Hygiene (ABIH) certified industrial hygienists, each with 40 or more years of experience. Hygienists performed intensity scoring for the 15 *a priori* agents and

90 construction tasks in the questionnaire prior to data collection following guidelines proposed by Rice and Heineman [2003]. For each agent, exposure intensities were 'calibrated' relative to NIOSH Recommended Exposure Levels (RELs), ACGIH Threshold Limit Values (TLV), or OSHA Permissible Exposure Levels (PELs) (Table I). Intensity of exposure for each agent/task combination was recorded on a four-level ordinal scale. These ordinal categories and assigned exposure intensities relative to the reference concentration were as follows:

Exposure Intensity Category and Description	**Assigned Exposure Intensity Weight Relative to Reference Concentration**
None: Not exposed	0
Low: Less than half the reference concentration	0.5
Moderate: More than half but generally not greater than the reference concentration	1.0
High: Generally higher to much higher than the reference concentration	2.0

Explicit standardization rules on exposure intensity have been shown to improve exposure ratings [McGuire et al., 1998]. In addition to recording exposure intensity, experience and familiarity of the hygienist with the task was ranked on a three-level scale (direct experience, indirect experience, or literature reference only) [Rice and Heineman, 2003].

For derivation of exposure intensity score consensus among the industrial hygienists, three rounds of scoring were used. Any differences among the three hygienists of more than one exposure intensity category were noted and hygienists were asked to further document the rational for their choice of exposure scale based on direct personal experience or published literature. This documentation and rationale was shared among the three hygienists, who were allowed to modify their score if they felt appropriate. For tasks where full consensus was not achieved, the final intensity score used a weighted average of the industrial hygienists' scores, with greater weight being given to raters most knowledgeable concerning the specific exposure and task (i.e. direct experience) [Ramachandran and Vincent, 1999]. Multi-rater kappa statistics were used to assess rater agreement [Chen et al., 2005; Fleiss et al., 2003].

Cases and controls reported a small number of tasks resulting in VGDF exposures in non-construction work and during military service. Many of these tasks were the same or similar to already scored construction tasks and were matched to construction tasks for exposure intensity assignment where appropriate. All remaining unscored tasks were scored for exposure intensity applying the same procedures used for construction tasks by one of the study industrial hygienists (JD). Workers also recorded frequency of exposure to a list of agents associated with bystander exposures in construction and non-construction work. Bystander exposures are typically much less than breathing zone exposures experienced by workers preforming tasks [Donovan et al., 2011]; therefore, bystander intensity was assigned a value of 10% (intensity weight=0.1) of the reference concentration.

Workers also were asked about the normal or usual number of hours worked each week for all jobs held 6 months or more. Cumulative exposure indices were calculated for each exposure scenario (i.e. construction, non-construction, military, and bystander) and these were summed to arrive at an overall cumulative exposure index for each agent. The following relationship was

used to generate the cumulative exposure indices by exposure scenario:

$$Agent\ Cumulative\ Exposure\ Index = \sum_{All\ Jobs\ \&\ Tasks}^{N} D * ((H)/40) * ((F) * 12)/240) * (I)$$

Where:

D = Duration of the job in years
H = Average hours of work per week for each job
F = Frequency (days per month) of performing the task or experiencing the exposure (bystander)
I = Assigned exposure intensity relative to the agent reference concentration (0 to 2.0)
N = Number of jobs and tasks contributing to the exposure index for the agent of concern

In the above expression, a full time work year consisted of 240 potential days of work. For presentation of exposure distributions for cases and controls the cumulative exposure indices were categorized using tertile break points for the exposed controls [Hsieh et al., 1991], with unexposed subjects placed in a separate category. For regression modeling cumulative exposure indices were retained as continuous variables and standardized by dividing each worker's cumulative exposure index by a value representing an exposure at the upper 95th percentile of the range for all workers. Exposures were thus expressed as a fraction of the upper 95th percentile of the exposure distribution which allowed more directed comparison of exposure-response patterns across the exposures of a priori interest. Acids and caustics were grouped together as these exposures occurred with low frequency and their mode of action (e.g. respiratory irritation) is likely similar.

Many of the cumulative exposure indices were correlated. Principal component analysis (PCA) was used to identify independent factors that explained the maximum amount of mutual correlation of the individual task exposure indices and to derive combined cumulative exposure indices [Burstyn, 2004; Dement et al., 2010; Vermeulen et al., 2004]. Inputs to the PCA analyses were the estimated cumulative exposure indices for each agent found to be significantly associated with COPD in the individual logistic models. The output of principal component analyses was a set of weights or 'loadings' that were then multiplied by each worker's exposure index to derive a summary score for each principal component. Choice of principal components for logistic regression analyses was based on eigenvalues greater than one or where scree plots indicated a significant contribution to explaining the multiple correlations among the exposure indices.

Case-Control Analyses

Cases and controls were compared for demographic characteristics, health status variables, spirometry, and chest x-ray readings by ILO criteria using analysis of variance (ANOVA), Wilcoxon rank-sum tests, or chi-square test of general association as appropriate. In all tests p-values of 0.05 or less were considered statistically significant.

Our primary analytical tool was unconditional logistic regression and we first developed a baseline model prior to inclusion of occupational exposures. Age, race/ethnicity, sex, and

cigarette smoking (status and pack-years) are known risk factors for COPD and were included in the baseline model *a priori.* Univariate logistic regression was used to evaluate other analytical variables (BMI category, blood relative with COPD, history of having lived with a smoker, history of childhood pneumonia, and volunteer/hobby-related activities potentially associated with VGDF exposures) as candidates for inclusion. Body mass index (BMI) was categorized (underweight = BMI<18.5; normal=BMI 18.5-24.9; overweight= BMI 25.0-29.9; and obese= BMI $\geq$30). Volunteer/hobby-related activities included: gardening, stained glass work, silk screening, house painting or paint removal, model plane/car building, ceramics, melting of metals, volunteer firefighter, woodworking, jewelry making, mimeographing, furniture refinishing, hunting or indoor firing range practice, boat, auto or motorcycle racing, use of chain saws or other gasoline powered equipment, and operating farm equipment. Dichotomous variables for each volunteer/hobby-related activity was considered individually for inclusion in the baseline logistic model and a summary index based on the sum of positive participation responses also was considered.

We used a moderate level of statistical significance (p-value <0.25) for initial retention of parameters in the main effects logistic model [Hosmer and Lemeshow, 1989] and retained all *a priori* covariates as well as other covariates that were biologically plausible and having a reasonable degree of statistical significance (p-value < 0.10). After the baseline logistic model was developed main effects models for the 15 exposures of *a priori* interest (Table I) and our overall measure of VGDF exposures were explored. We modeled each exposure separately followed by modeling of the summary scores from the principal component analyses. Cumulative exposures were entered as continuous variables to avoid loss of statistical power caused by categorization of continuous variables [Altman and Royston, 2006; Greenland, 1995a; Greenland, 1995b; Royston et al., 2006]. We examined the possibility of a non-linear relationship between cumulative exposure indices and COPD odds-ratios non-parametrically with restricted cubic splines [Durrleman and Simon, 1989; Ruifeng et al., 2011]. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. The proportion of workers with no reported exposure was high for acids and caustics combined and for isocyanates. For these exposures two parameters were entered into the models with one being dichotomous and indicating zero versus non-zero exposure and the other representing the value of the continuous exposure index [Robertson et al., 1994].

The joint effects of exposure agents and smoking were evaluated for departure from additive. Assessment of interaction on an additive scale is often more meaningful than an assessment on a multiplicative scale [Knol et al., 2007; Richardson and Kaufman, 2009; Rothman et al., 2007]. Departure from additivity was evaluated based on calculation of the relative excess risk due to interaction (RERI); which represents the increased risk for smoking and the exposure of interest combined relative to the risk estimated for the sum of these two factors, with a value greater than 1.0 representing some degree of interaction [Richardson and Kaufman, 2009].

Assessment of potential confounding associated with exposures not included in the task-based exposure assessments was based on the questionnaire data concerning the frequency of exposure to a list of materials (previously described) associated with COPD in the literature. For each agent, a cumulative index was developed by multiplying duration and assigned exposure days

per months based reported exposure frequency. Potential confounding was evaluated in the final logistic model for VGDF exposures.

We calculated the population attributable fraction (PAF) for our overall VGDF exposure index. Very few cases or controls had a VGDF exposure index value of zero; however, many were estimated to have low cumulative VGDF exposures. In order to achieve stability in the PAF estimates workers at or below the cut point for lowest quartile of the VGDF exposure distribution for controls were classified as 'unexposed'. The VGDF attributable fraction point estimate was calculated as described by Benichou [2001] as well as approximate 95% confidence intervals [Brady, 1998; Greenland and Drescher, 1993]

Our COPD case definition was not based on post-bronchiolar spirometry so may include some individuals with asthma and not COPD. The possibility also exists that some individuals with airway obstruction and taking long-acting bronchodilator medications might have spirometry improvement sufficient to change their classification from case to control. We conducted sensitivity analyses to address potential misclassification on disease status based on these two issues. Individuals with an $FEV_1 < 65\%$ of predicted are less likely to have fully reversible airway obstruction; therefore, we restricted the logistic regression model for VGDF exposure to cases with an $FEV_1 < 65\%$ of predicted. Controls were required to have a $FEV_1 \geq 70\%$ of predicted for inclusion to reduce the probability of misclassifying COPD cases using long acting bronchodilators.

SAS Version 9.3 [SAS, 2011] or STATA Version 11.1 [STATA, 2009] were used for all analysis presented in this report.

Human Subjects Protection

Participants were contacted by mail before the telephone interview and were provided information concerning the study. At the start of the telephone interviews, the interviewers administered verbal consent using a written script and study subjects gave oral informed consent before beginning the work history questionnaire. All study procedures and materials were reviewed and approved by the Central DOE Institutional Review Board and the CPWR Institutional Review Board. All data received by Duke University investigators were stripped of personal identifiers under provisions approved by the Duke University Health System Institutional Review Board.

RESULTS

Case and Control Demographic Characteristics

A total of 3741 frequency matched COPD cases and controls were identified (Table II). Of the 3741 potential study participants 1332 could not be contacted by telephone; 375 were deceased and 957 could not be contacted due to bad address or telephone information or lack of response. Among workers not deceased the overall participation rate was 60.6% among cases and 62.5% among controls. Of those who contacted by telephone, 2079 (86.3%) participated. Participating controls were slightly older than non-participants and slightly fewer female cases participated. The percent predicted FEV_1 was slightly higher among participating cases as was the FEV_1/FVC ratio. No differences in smoking pack-years were observed. Of the 2079 study participants, only 572 (248 cases and 324 controls) were included in our prior cross-sectional study of exposures experienced while working on DOE sites [Dement et al., 2010].

Demographic and clinical characteristics of cases and controls are compared in Table III overall and by smoking status, Table IV compares by DOE site, and Table V compares by trade or job. The final analytic sample included 834 cases and 1243 controls; two workers missing data were excluded. Overall, there were no statistically significant differences between participating cases and controls for the frequency matching variables (age, gender, race/ethnicity, and DOE site). Cases were significantly more likely to report a history of physician diagnosed respiratory conditions (asthma, chronic bronchitis, emphysema, and pneumonia), prevalent respiratory symptoms (cough, phlegm, and dyspnea), hypertension, and having a blood relative with COPD. Cases were significantly more likely to have smoked and had a significantly higher mean pack-year smoking history. No significant differences were observed in prevalence of B-reader chest x-ray findings, history of childhood pneumonia, or history of having lived with a smoker. Cases and controls were significantly different by job or trade distribution (Supplemental Materials Table II-S). Among the COPD cases 52.5% had an $FEV_1 < 65\%$ of predicted, indicative of clinically significant airway obstruction.

Exposure Assessment

Results of the industrial hygienists' ratings for task exposure intensity across categories of contaminants of interest are presented in Table VI. In general, kappa values below 0.40 represent poor agreement and values greater than 0.75 represent excellent agreement [Fleiss et al., 2003]. Based on these criteria, good to excellent agreement was achieved for all exposures of interest except the category 'particulates not otherwise regulated' (PNOR) where the overall kappa was 0.41. PNOR represents a very heterogeneous category of exposures and is subject to more interpretation as to composition and level for mixed exposures such as dust from cutting cement and work with molded pipe insulation.

Except for exposure indices for acids and caustics and isocyanates, both cases and controls had a high probability of exposure for the exposure agents of *a priori* interest, with cases having a higher probability of any exposure for all agents (Table VII). Differences in exposures between cases and controls tended to be greatest in the highest exposure tertile.

Multivariate Baseline Logistic Model

The baseline model included age, gender, race/ethnicity, and cigarette smoking history *a priori*. Both cigarette smoking status and pack-years of smoking were strong predictors of COPD risk ($p=0.0011$ and $p<0.0001$, respectively). Having a blood relative with COPD and having lived with a smoker were highly correlated (chi-square=10.05, $p<0.0015$); however, only a having a blood relative with COPD was significantly associated with COPD and retained in the baseline model. A history of childhood pneumonia was not significantly associated with COPD after adjustment for demographic variables and smoking. BMI category was retained because it was significantly associated with COPD risk, with elevated risk for those underweight and a moderate protective effect among those overweight or obese.

Dichotomous covariates for the volunteer/hobby activities were evaluated separately and collectively for inclusion in the baseline model. No volunteer/hobby activity demonstrated a significant positive relationship with COPD risk whereas gardening and working with wood showed significant negative associations ($p<0.05$). A categorical summary measure based on the sum of volunteer/hobby-related activities was negatively associated with COPD risk in the baseline model ($p<0.001$). This finding was somewhat surprising and we hypothesized that this covariate reflected current activities at the BTMED examination rather that past activities. This covariate thus served as a surrogate for health status and ability to participate in volunteer/hobby-related activities rather than a negative association with hobby-related VGDF exposures. This hypothesis was supported in that participation in volunteer/hobby activities was also negatively associated with a history of congestive heart failure in a regression model adjusting for age, sex, gender, and smoking ($p= 0.0012$) (not shown). Additionally, model fit based on AIC criterion was negatively impacted by inclusion of this covariate and inclusion slightly inflated the effects of occupational exposures; therefore, volunteer/hobby-related exposures were not included in the baseline model but were considered in sensitivity analyses.

Cumulative Exposure Indices and COPD Risk

Final logistic regression model results for the exposures of *a priori* interest are summarized in Table VIII. Acids and caustics were grouped together as these exposures occurred with low frequency and their mode of action (e.g. respiratory irritation) is likely similar. Significant associations were observed for all exposures except man-made-mineral-fibers and painting aerosols. The associations were best described as a linear function in the logistic models for all exposures except wood dust where the restricted cubic spline provided a better model fit. At the upper 95^{th} percentile of the exposure distribution for each exposure the odds-ratios for the exposure indices ranged from 1.17 for wood dust to 2.15 for PNOR. The exposure index for all VGDF combined demonstrated a relatively strong association with COPD risk ranging from 1.19 at the lower range of exposures to 2.03 among those with exposures at the upper 95^{th} percentile. Wood dust demonstrated a non-linear relationship with evidence of flattening of the exposure-response relationship at higher cumulative exposures. The exposure-response relationship for acids and caustics was largely influenced by the dichotomous variable indicating exposure compared to no exposure.

In a separate model (not shown) we investigated the time period of first employment in construction (before or after 1980) as a predictor of COPD risk associated with VGDF exposures. Calendar year 1980 reflects the implementation of many permissible exposure limits by the US Occupational Safety and Health Administration (OSHA) and studies have shown declines in asbestos-related respiratory diseases among workers first employed in this timeframe [Welch et al., 2007]. After adjustment for all model parameters including VGDF exposures, the dichotomous covariate for pre versus post 1980 first employment was not significant (p=0.6459), suggesting continued risk among workers first employed in construction after 1980.

Potential confounding by exposure to other materials associated with COPD was assessed in the final model for VGDF exposures. Only exposures indices for pesticides/herbicides and grain dust were significantly associated with the risk of COPD (p=0.0154 and p=0.0336, respectively). Inclusion of these covariates changed the risk estimates for VGDF exposures negligibly, suggesting independent effects of these exposures rather than confounding of the construction-related VGDF risk estimates.

Our analyses of the interaction between cigarette smoking and the cumulative exposures of interest are presented in Table IX. While most values for the relative excess risk due to interaction (RERI) were slightly greater than 1.0, indicating some degree of smoking-exposure interaction, only the interaction between smoking and exposures to molds and spores was of borderline statistical significance (RERI=1.07, 95% CI=1.00-1.16). Overall, the analyses support the conclusion that the effects of smoking and the occupational exposures studied did not depart significantly from additivity.

Analyses of Combined Exposures

Cumulative exposure indices found to be significantly associated with COPD in the logistic models were included in the principal component analyses. The first four components were retained based on selection criteria, accounting for 78% of the total exposure index variance and 63 to 93 percent of the variance of the individual cumulative exposure indices (Table X). The first three components were significant predictors of COPD risk and component four was of borderline significance. The first component was heavily loaded by welding and thermal cutting exposures as well as metal cutting, grinding and machining exposures. Asbestos, cement dust, silica, and solvent exposures also contributed to component one. Component two was heavily loaded by exposures to wood dust as well as molds and spores, with lesser loading for asbestos, cement dust, and silica. PNOR exposures were loaded on components one and two. Isocyanates, engine exhausts, and organic solvents loaded component three while only acids and caustics loaded component four.

Occupational-Attributable COPD

The overall PAF due to occupational VGDF exposures was estimated to be 18% (95% CI=2–24%) based on a model adjusted odds-ratio of 1.29 (95% CI=1.02-1.63) and a case VGDF exposure fraction of 0.784. In a logistic model restricted to never smokers (136 cases and 473 controls) a PAF of 32% (95% CI=6-42%) was estimated based on a model adjusted odds-ratio of 1.72 (95% CI=1.05-2.83) and a case VGDF exposure fraction of 0.772. It should be noted that

for PAF calculations, workers in the lowest quartile of the entire distribution of VGDF exposures were classified as unexposed whereas results in Table VI were derived based on continuous exposure variables and standardized to a proportion of the upper 95th percentile of the VGDF distribution.

Sensitivity Analyses

Sensitivity analyses that restricted cases and controls based on percent predicted FEV_1 demonstrated negligible changes in the exposure-response pattern for VGDF exposures. VGDF exposures were significantly associated with COPD in these sub-analyses (p=0.0030) and the slope parameter differed from the overall study results by less than five percent.

Hobby-related VGDF exposures were not included in the final logistic regression models. Sensitivity analyses which included the hobby-related exposure index in the final model for VGDF exposures did not change risk estimates for occupational VGDF exposures in any meaningful way.

DISCUSSION

This study supports the general hypothesis that COPD is strongly associated with occupational exposures during construction work and confirmed the increased COPD risk associated with exposures to asbestos, welding, silica, and cement dust observed in our prior cross-sectional study [Dement et al., 2010]. Other agents significantly associated with the risk of COPD included engine exhausts, acids/caustics, metal cutting and grinding aerosols, isocyanates, organic solvents, wood dust, and molds/spores.

We observed an association between COPD risk and exposure to cement dusts. Prior studies of cement dust exposures have largely involved workers producing Portland cement whereas construction workers are exposed primarily through tasks such as cutting, grinding, and drilling of concrete and masonry materials resulting in high exposure levels to mixed dusts of cured Portland cement and silica [Croteau et al., 2002; Flanagan et al., 2003; OSHA, 2009]. Exposure to cement dust has been shown to be associated with airway irritation [Fell et al., 2010].

Exposure to paint-related aerosols was not significantly associated with COPD risk in this study although an upward trend with increasing exposure was observed. Our exposure metric included surface preparation and cleaning tasks as well as spray painting. Painting also results in exposures to organic solvents and isocyanates and indices for both of these components of paints were associated with the risk of COPD in this study. Prior studies associating risk of COPD with painting exposures have included workers using paints containing isocyanates [Glindmeyer et al., 2004; Hammond et al., 2005; Pronk et al., 2007]. Additionally, exposure to organic solvents has been associated with COPD and/or chronic bronchitis in some studies [Ebbehoj et al., 2008; Heederik et al., 1989; Melville et al., 2010; Post et al., 1994; Suadicani et al., 2001; Valcin et al., 2007]. The current study results are reasonably consistent with the published literature.

The construction work environment is complex resulting in multiple and mixed exposures to many agents. A strong relationship between COPD risk and all VGDF was observed, consistent with the published literature [Omland et al., 2014]. The current study adds to prior research in finding a nearly uniform exposure-response pattern for various *a priori* exposures and COPD. The principal component analyses provide further support for consideration of all VGDF exposures collectively in assessing the risk of COPD among construction workers. The VGDF exposure metric is a reasonable exposure measure for assessment of COPD risk in complex exposure environments.

In addition to risks for all VGDF combined we observed increased risk for PNOR exposures, which are currently regulated by OSHA as 'inert or nuisance dusts' with a very high PEL of 5 mg/m^3 as respirable dust. PNOR exposures result from many different construction tasks such drywall work, demolition, work with insulation materials, and cutting, drilling, or grinding concrete. While a reasonably strong gradient in COPD risk with increasing PNOR exposures was observed, the PNOR exposure index was correlated with several exposure indices including asbestos, cement dust, and silica making determination of the independent contribution of PNOR problematic. None-the-less, our data suggests increased COPD risk associated with materials considered 'inert or nuisance dusts'. Others have recommended that use of the term "nuisance dust" should be discontinued in scientific and regulatory contexts [Christiani, 2005] and our

findings support this recommendation.

We observed associations between COPD and exposures to pesticides/herbicides and grain dusts. These results are consistent with the published literature showing associations between chronic bronchitis and/or COPD and exposures to these agents [Christiani, 1996; de Jong et al., 2014b; de Jong et al., 2014c; Dosman et al., 1980; Hansell et al., 2014; Hoppin et al., 2007; Post et al., 1998; Salameh et al., 2006; Valcin et al., 2007; Ye et al., 2013].

Our study population was relatively old (mean age at entry was about 62 years), and we conducted analyses to determine if the risks for COPD were the result of exposures prior to 1980 when occupational safety and health precautions were weaker than in subsequent years. Statistical models that adjusted for all model parameters including VGDF exposures found that workers first employed in construction after 1980 continued to experience increased COPD risk.

Reporting a blood relative with COPD was significantly associated with COPD risk in this study. We hypothesized that our measure of familial aggregation was acting as a surrogate measure of common household and/or environmental exposures, including environmental tobacco smoke (ETS), rather than an indication of a genetic influence [Eisner et al., 2010]. We have no data to directly test this hypothesis; however, we did observe a high degree of correlation between variables for having lived with a smoker and reporting a blood relative with COPD. Our hypothesis seems plausible as a family history of obstructive lung disease was not a risk factor for incident COPD in a large longitudinal study [Lindberg et al., 2005] and prior research has shown ETS exposure to increase COPD risk [Eisner et al., 2010; Hagstad et al., 2014].

We observed an inverse relationship between COPD risk and increasing BMI. While BMI was associated with COPD risk it did not confound the association between VGDF and COPD, as risk estimates for VGDF exposures changed little with or without BMI in the final logistic model. The finding of increased COPD risk among those underweight is consistent with other published data [Collins et al., 2015; Harik-Khan et al., 2002; Johannessen et al., 2005].

Our overall estimated PAF for occupational VGDF exposures of 18% is within the range observed in other studies [Balmes, 2005; Eisner et al., 2010]. Some prior studies have observed a higher occupational PAF with an upper range of approximately 30% [Balmes, 2005; Blanc et al., 2009b; Weinmann et al., 2008]. The PAF of 32% among workers who never smoked also is similar to some prior estimates [Hnizdo, 2002] but lower than found in other studies where a PAF as high as 53% has been observed among never smokers [Toren and Jarvholm, 2014]. Our PAF estimates are likely conservative as workers in lowest quartile of the VGDF exposure distribution were classified as ‘unexposed’ in the PAF calculations.

Analyses of interactions between occupational exposures and cigarette smoking in this study suggested that the effects of smoking and the exposures studied did not depart significantly from additivity. A recent COPD incidence study also found an additive effect [Pallasaho et al., 2014]. The level of interaction between occupational VGDF exposures and cigarette smoking has been variable in the literature, ranging from additive to greater than additive [Blanc et al., 2009b; Boggia et al., 2008; de Meer et al., 2004; Humerfelt et al., 1993; Trupin et al., 2003].

Sensitivity analyses which addressed possible disease misclassification due to use of spirometry without bronchodilation and possible use of long-acting bronchodilators did not show study results to be sensitive to exclusion of cases and controls based on the percent predicted FEV_1. Although research has demonstrated that airway obstruction prevalence based on spirometry post bronchodilator may be 25-35% lower than found without use of bronchodilators [Tilert et al., 2013], this effect is stronger in younger individuals, decreases in individuals between 60 and 74 years of age [Johannessen et al., 2005], and decreases in high risk populations. A recent study among individuals with a high risk for COPD found that only 9% had some reversal of airway obstruction with bronchodilators, and 60% of those still had an $FEV_1<70\%$ (the definition used in that specific study) [Kjeldgaard et al., 2015]. Our results are also consistent with other studies that found COPD risk factors to be consistent with or without post bronchodilator testing [Johannessen et al., 2005].

STRENGTHS AND LIMITATIONS

This study has several strengths: an objective COPD case definition based on spirometry, inclusion of a large number of COPD cases and controls, and assessment of lifetime occupational exposures for jobs held more than six months. Additionally, the qualitative cumulative exposure indices were task-based and incorporated the dimensions of task frequency, duration, and exposure intensity. The assessment of cumulative exposures was comprehensive, including construction and non-construction work, bystander exposures, and exposures while serving in the military. This study also benefitted from a wealth of clinical, medical, and exposure history data derived from BTMED examinations, allowing for assessment and control of important confounders.

This study also has a number of limitations. Our results were not based on post-bronchodilator spirometry; however, sensitivity analyses found study results to be robust with respect to potential disease misclassification. Occupational exposures and cigarette smoking histories were self-reported and undoubtedly resulted in exposure misclassification. Assessment of exposures to health hazards in construction is extraordinarily difficult, because these exposures occur in an uncontrolled environment where job tasks are subject to frequently unique work situations, including the work practices of each worker and type and model of tools used. Over a working life, construction workers are exposed to a myriad of hazards, either as part of the work tasks they perform or as bystanders to work tasks performed by other workers.

An additional limitation is lack of unexposed reference population due to the nature of construction-related exposures. However, a broad spectrum of construction crafts as well as security and administrative workers were included in this study, which allowed reasonable exposure contrasts for most specific exposures. None-the-less, effects of occupational exposures are likely to be underestimated due to exposure misclassification and absence of a non-exposed referent group.

CONCLUSIONS

We estimate that approximately 18% of COPD risk among construction workers can be attributed to occupational exposures; the fraction among those who never smoked may be as high as 32%. The risks contributed by occupational exposures add to the smoking-related risk. All VGDF exposures combined were a strong and consistent predictor of COPD risk. Increased COPD risk persisted among those first employed in construction after 1980. Appropriate control methods should be implemented to prevent worker exposures to VGDF as a whole. In this study, although only 13.2% of all subjects were current smokers, 28.3% of workers with COPD were current smokers, and they would greatly benefit from smoking cessation advice and support.

ACKNOWLEDGMENTS

We are grateful to Drs. Carol Rice and Robert Herrick for their assistance with the exposure intensity scoring and their valuable inputs. We also thank Dr. Eula Bingham for her advice and guidance. We are most grateful to Ron Bush, Andy Noel, Johnny Ballinger, and Dan Obray for their stamina in conducting the participant interviews and collecting the data. Their dedication to the project was invaluable. Study participants were selected from a cohort of participants in the Building Trades National Medical Screening Program (BTMED). BTMED is funded by the Department of Energy (cooperative agreement number DE-FC01-06EH06004). We extend a special thank you to Patricia Worthington (DOE) and Mary Fields (DOE) for their support of this project. We also thank both the Central DOE Institutional Review Board (Jim Morris, Chair; Becky Hawkins, Administrator) and the CPWR Institutional Review Board (Jim Platner, Chair) for their review of the project.

CUMULATIVE INCLUSION AND ENROLLMENT REPORT

Study Title: Etiology of COPD among Construction Workers

Comments: Final Study Enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	4	13	0	0	0	0	0	0	0	17
Asian	0	10	0	0	0	0	0	0	0	10
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	33	133	0	0	0	0	0	0	0	166
White	124	1719	0	0	0	0	0	0	0	1,843
More Than One Race	1	14	0	0	0	0	0	0	0	15
Unknown or Not Reported	0	0	0	0	28	0	0	0	0	28
Total	162	1,889	0	0	28	0	0	0	0	2,079

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015)

Page 1

OMB No. 0925-0001/0002
Cumulative Inclusion Enrollment Report

PUBLICATIONS

Dement J, Welch L, Ringen K, Quinn P, Chen A, Haas S: [2015] A case-control study of airways obstruction among construction workers. Am J Ind Med 58:484-508.

DISSEMINATION OF RESULTS

The study publication was made open access to allow for more widespread dissemination of study findings. In addition to publication of study results in the American Journal of Industrial Medicine (AJIM), study results were disseminated through a number of different presentations, publications, and informational channels.

A summary of key findings with linkage to the full AJIM publication was published on the CPWR website (http://www.cpwr.com/sites/default/files/publications/DementCOPD%2BWorkExposureKF.pdf) and disseminated by CPWR to individuals and organizations on the CPWR list serve ('Clearing the Air about COPD' CPWR Update, August 2015) (http://campaign.r20.constantcontact.com/render?ca=37c28249-a1bd-4363-bc31-ab6b1969d12c&c=89552410-deed-11e2-8453-d4ae529a7b12&ch=895a0610-deed-11e2-8453-d4ae529a7b12).

Study summaries also were included in the CPWR silica web pages (http://www.silica-safe.org/know-the-hazard/whats-the-risk) and (http://www.silica-safe.org/plan/studies-and-data-on-silica-exposure-and-the-use-if-dust-controls). The study summary will also be added to CPWR's Electronic Library of Construction Safety and Health (eLCOSH).

Results of this study were presented through a CPWR Webinar on October 14, 2015 (COPD among Construction Workers: Case-Control Study Results Presented by: John M. Dement, PhD, CIH). The study was presented at an international scientific conference held by the Collegium Ramazzini in Italy on October 23, 2015 (Ramazzini Days 2015: Living in a Chemical World IV).

News media coverage included an article in Occupational Safety and Health on September 17, 2015 (https://ohsonline.com/articles/2015/09/17/cpwr-study-assesses-copd-among-construction-workers.aspx) and coverage in industry trade publications (Durability + Design, August 17, 2015; Safety + Health, August 12, 2015; Industrial Safety and Hygiene News; August 19, 2015; The Safety Brief, September 4, 2015, OSHA QuickTakes September 15, 2015.

The study was also included in the National COSH Studies, Reports, and Testimony section http://www.coshnetwork.org/osh-studies-reports-testimony .

This study was highlighted in numerous Twitter posts with linkage to key study findings on CPWR web pages. The twitter posts (listed below) generated 1690 impression, which means that the tweet was delivered to the Twitter stream of a particular account.

- **August 6 -** COPD is a significant health risk for construction workers, even for non-smokers
- **August 11 -** New study finds nearly 1/5 of construction worker #COPD attributable to

work exposures

- **August 12** - Learn about your risk of #COPD from vapors, gases, dusts and fumes at:
- **August 14** - Do you know what can cause #COPD? Hint: Smoking isn't the only possibility!
- **August 14** - Approximately 18% of #COPD risk can be attributed to construction-related exposures, case study finds.
- **August 19** - Help prevent #COPD by using proper controls for vapors, gases, dusts and fumes on construction sites.

This study was also highlighted in numerous Facebook and LinkedIn posts with linkage to key study findings on CPWR webpage. Posts are listed below.

- **August 6 -** New study finds that nearly 1/5 of construction worker COPD is attributable to work exposures. Occupational exposures to vapors, gases, dusts and fumes on construction sites can cause COPD. Use proper controls to help prevent this disease. FB – Reach – 278; 6 clicks; 2 likes; 2 shares - FB eLCOSH – reach: 192; 1 like; LinkedIn: 81 impressions, 1 click.
- **August 12** - Occupational exposures to vapors, gases, dusts and fumes increase your risk for COPD. FB – Reach – 247; 9 clicks; 12 likes; 4 shares; FB eLCOSH – Reach: 224; 8 clicks; 10 likes; LinkedIn: 68 impressions.
- **August 17** - Do you know what can cause COPD? Hint: Smoking isn't the only possibility! FB – Reach – 362; 8 clicks; 8 likes; 7 shares; FB eLCOSH – Reach 243; 1 click; 5 likes; LinkedIn: 110 impressions.
- **August 21** - Help prevent COPD by using proper controls for vapors, gases, dusts and fumes on construction sites. FB – Reach 333; 5 clicks; 6 likes; 1 comment; 3 shares; FB eLCOSH – Reach: 301; 4 clicks; 5 likes; 1 comment; LinkedIn: 210 impressions, 3 clicks, 1 like.

The dissemination of the result of this study will continue for a long time. The findings of this study and a substantial body of scientific information support the need for public health changes in the control VGDFs and PNORs. The investigators are engaging the scientific community in a discussion about how to improve protective factors and strengthen the evidence base for enhanced methods to prevent VGDF and PNOR exposures. CPWR in conjunction with major stakeholders who are concerned about occupational safety and health and construction safety and health in particular will promote new and stronger regulatory approaches to preventing VGDF and PNOR exposures, and will work with health plans to more effectively promote smoking cessation.

INCLUSION OF CHILDREN

Not applicable.

MATERIALS AVAILABLE TO OTHER INVESTIGATORS

Study subjects gave informed consent before participating in this study. All study procedures and materials were reviewed and approved by the Central DOE Institutional Review Board and the CPWR Institutional Review Board. Any release of data from this study would require consent of

participants and approval of the Central DOE Institutional Review and the CPWR Institutional Review Boards. Questionnaires and analytical programs are available upon request to the PI.

REFERENCES

Abrons HL, Petersen MR, Sanderson WT, Engelberg AL, Harber P: [1988] Symptoms, ventilatory function, and environmental exposures in Portland cement workers. Br J Ind Med 45: 368-375.

Altman DG, Royston P: [2006] The cost of dichotomising continuous variables. BMJ 332: 1080.

Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, Tjonneland A, Overvad K, Raaschou-Nielsen O: [2011] Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am J Respir Crit Care Med 183: 455-461.

ATS: [1995a] Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152: S77-121.

ATS: [1995b] Standardization of spirometry, 1994 Update. Am J Respir Crit Care Med 152: 1107-1136.

ATS: [2003] Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 167: 787-797.

ATS: [2004] Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 170: 691-715.

ATS/ERS: [2005] ATS/ERS Task Force: Standardisation of lung function testing. Eur Respir J 26: 319-338.

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G: [2003] American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 167: 787-797.

Balmes JR: [2005] Occupational contribution to the burden of chronic obstructive pulmonary disease. J Occup Environ Med 47: 154-160.

Barr RG, Herbstman J, Speizer FE, Camargo CA, Jr.: [2002] Validation of self-reported chronic obstructive pulmonary disease in a cohort study of nurses. Am J Epidemiol 155: 965-971.

Becklake MR: [1989] Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 140: S85-91.

Behrendt CE: [2005] Mild and moderate-to-severe COPD in nonsmokers: Distinct demographic profiles. Chest 128: 1239-1244.

Benichou J: [2001] A review of adjusted estimators of attributable risk. Stat Methods Med Res 10: 195-216.

Bergdahl IA, Toren K, Eriksson K, Hedlund U, Nilsson T, Flodin R, Jarvholm B: [2004] Increased mortality in COPD among construction workers exposed to inorganic dust. Eur Respir J 23: 402-406.

Blanc PD, Eisner MD, Balmes JR, Trupin L, Yelin EH, Katz PP: [2005] Exposure to vapors, gas, dust, or fumes: Assessment by a single survey item compared to a detailed exposure battery and a job exposure matrix. Am J Ind Med 48: 110-117.

Blanc PD, Eisner MD, Earnest G, Trupin L, Balmes JR, Yelin EH, Gregorich SE, Katz PP: [2009a] Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. J Occup Environ Med 51: 804-810.

Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD: [2009b] Occupational exposures and the risk of COPD: Dusty trades revisited. Thorax 64: 6-12.

Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U: [2008] Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. J Occup Environ Med 50: 366-370.

Bradshaw LM, Fishwick D, Slater T, Pearce N: [1998] Chronic bronchitis, work related respiratory symptoms, and pulmonary function in welders in New Zealand. Occup Environ Med 55: 150-154.

Brady AR: [1998] Adjusted population attributable fractions from logistic regression (sbe21). Stata Technical Bulletin STB-42: 8-12.

Brogger J, Bakke P, Eide GE, Gulsvik A: [2002] Comparison of telephone and postal survey modes on respiratory symptoms and risk factors. Am J Epidemiol 155: 572-576.

Burstyn I: [2004] Principal component analysis is a powerful instrument in occupational hygiene inquiries. Ann Occup Hyg 48: 655-661.

Chen B, Zaebst D, Seel L: [2005] A macro to calculate kappa statistics for categorizations by multiple raters. SAS Users Group International (SUGI 30) 2005 Philidelphia, Pa.: SAS Institute.

Christiani DC: [1996] Organic dust exposure and chronic airway disease. Am J Respir Crit Care Med 154: 833-834.

Christiani DC: [2005] Occupation and COPD. Occup Environ Med 62: 215.

Churg A, Wright JL: [2002] Airway wall remodeling induced by occupational mineral dusts and air pollutant particles. Chest 122: 306S-309S.

Clausen J, Netterstrom B, Wolff C: [1993] Lung function in insulation workers. Br J Ind Med 50: 252-256.

Coggon D, Newman Taylor A: [1998] Coal mining and chronic obstructive pulmonary disease: A review of the evidence. Thorax 53: 398-407.

Collins BF, Feemster LC, Rinne ST, Au DH: [2015] Factors predictive of airflow obstruction among veterans with presumed empirical diagnosis and treatment of COPD. Chest 147: 369-376.

Croteau GA, Guffey SE, Flanagan ME, Seixas NS: [2002] The effect of local exhaust ventilation controls on dust exposures during concrete cutting and grinding activities. Am Ind Hyg Assoc J 63: 458-467.

de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM: [2014b] Pesticides and other occupational exposures are associated with airway obstruction: The LifeLines cohort study. Occup Environ Med 71: 88-96.

de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM: [2014c] Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. Am J Epidemiol 179: 1323-1330.

de Jong K, Boezen HM, Kromhout H, Vermeulen R, Vonk JM, Postma DS: [2014a] Occupational exposure to vapors, gases, dusts, and fumes is associated with small airways obstruction. Am J Respir Crit Care Med 189: 487-490.

de Meer G, Kerkhof M, Kromhout H, Schouten JP, Heederik D: [2004] Interaction of atopy and smoking on respiratory effects of occupational dust exposure: A general population-based study. Environ Health 3: 6.

Dement JM, Ringen K, Welch LS, Bingham E, Quinn P: [2009] Mortality of older construction and craft workers employed at Department of Energy (DOE) nuclear sites. Am J Ind Med 52: 671-682.

Dement JM, Welch L, Bingham E, Cameron B, Rice C, Quinn P, Ringen K: [2003] Surveillance of respiratory diseases among construction and trade workers at Department of Energy nuclear sites. Am J Ind Med 43: 559-573.

Dement JM, Welch L, Ringen K, Bingham E, Quinn P: [2010] Airways obstruction among older construction and trade workers at Department of Energy nuclear sites. Am J Ind Med 53: 224-240.

Donovan EP, Donovan BL, Sahmel J, Scott PK, Paustenbach DJ: [2011] Evaluation of bystander exposures to asbestos in occupational settings: A review of the literature and application of a simple eddy diffusion model. Crit Rev Toxicol 41: 52-74.

Dosman JA, Cotton DJ, Graham BL, Li KY, Froh F, Barnett GD: [1980] Chronic bronchitis and decreased forced expiratory flow rates in lifetime nonsmoking grain workers. Am Rev Respir Dis 121: 11-16.

Durrleman S, Simon R: [1989] Flexible regression models with cubic splines. Stat Med 8: 551-561.

Ebbehoj NE, Hein HO, Suadicani P, Gyntelberg F: [2008] Occupational organic solvent exposure, smoking, and prevalence of chronic bronchitis-an epidemiological study of 3387 men. J Occup Environ Med 50: 730-735.

Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR: [2010] An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 182: 693-718.

Enright P, Skloot G, Herbert R: [2008] Standardization of spirometry in assessment of responders following man-made disasters: World Trade Center worker and volunteer medical screening program. Mt Sinai J Med 75: 109-114.

Fell AK, Sikkeland LI, Svendsen MV, Kongerud J: [2010] Airway inflammation in cement production workers. Occup Environ Med 67: 395-400.

Ferris BG: [1978] Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 118: 1-120.

Flanagan ME, Seixas N, Majar M, Camp J, Morgan M: [2003] Silica dust exposures during selected construction activities. AIHA J (Fairfax, Va) 64: 319-328.

Fleiss JL, Levin B, Paik MC: [2003] Statistical Methods for Rates and Proportions. Third Edition ed. New York: John Wiley & Sons, Inc.

Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH: [2013a] COPD surveillance--United States, 1999-2011. Chest 144: 284-305.

Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB: [2013b] Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. Chest 143: 1395-1406.

Glencross PM, Weinberg JM, Ibrahim JG, Christiani DC: [1997] Loss of lung function among sheet metal workers: Ten-year study. Am J Ind Med 32: 460-466.

Glindmeyer HW, Lefante JJ, Jr., Rando RJ, Freyder L, Hnizdo E, Jones RN: [2004] Spray-painting and chronic airways obstruction. Am J Ind Med 46: 104-111.

GOLD: [2014] Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Global Initiative for Chronic Obstructive Lung Disease, Inc., Available from: http://www.goldcopd.org/.

Greenland S: [1995a] Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis. Epidemiology 6: 450-454.

Greenland S: [1995b] Dose-response and trend analysis in epidemiology: Alternatives to categorical analysis. Epidemiology 6: 356-365.

Greenland S, Drescher K: [1993] Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 49: 865-872.

Hagstad S, Bjerg A, Ekerljung L, Backman H, Lindberg A, Ronmark E, Lundback B: [2014] Passive smoking exposure is associated with increased risk of COPD in never smokers. Chest 145: 1298-1304.

Hammond SK, Gold E, Baker R, Quinlan P, Smith W, Pandya R, Balmes J: [2005] Respiratory health effects related to occupational spray painting and welding. J Occup Environ Med 47: 728-739.

Hankinson JL, Odencrantz JR, Fedan KB: [1999] Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 159: 179-187.

Hansell A, Ghosh RE, Poole S, Zock JP, Weatherall M, Vermeulen R, Kromhout H, Travers J, Beasley R: [2014] Occupational risk factors for chronic respiratory disease in a New Zealand population using lifetime occupational history. J Occup Environ Med 56: 270-280.

Hansen EF, Rasmussen FV, Hardt F, Kamstrup O: [1999] Lung function and respiratory health of long-term fiber-exposed stonewool factory workers. Am J Respir Crit Care Med 160: 466-472.

Hansen JE, Sun XG, Wasserman K: [2007] Spirometric criteria for airway obstruction: Use percentage of FEV1/FVC ratio below the fifth percentile, not < 70%. Chest 131: 349-355.

Harik-Khan RI, Fleg JL, Wise RA: [2002] Body mass index and the risk of COPD. Chest 121: 370-376.

Hart JE, Laden F, Eisen EA, Smith TJ, Garshick E: [2009] Chronic obstructive pulmonary disease mortality in railroad workers. Occup Environ Med 66: 221-226.

Hart JE, Laden F, Schenker MB, Garshick E: [2006] Chronic obstructive pulmonary disease mortality in diesel-exposed railroad workers. Environ Health Perspect 114: 1013-1017.

Heederik D, Pouwels H, Kromhout H, Kromhout D: [1989] Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix: the Zutphen Study. Int J Epidemiol 18: 382-389.

Hendrick DJ: [1996] Occupational and chronic obstructive pulmonary disease (COPD). Thorax 51: 947-955.

Henneberger PK, Attfield MD: [1996] Coal mine dust exposure and spirometry in experienced miners. Am J Respir Crit Care Med 153: 1560-1566.

Hnizdo E: [2002] Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the third National Health and Nutrition Examination Survey. Am J Epidemiol 156: 738-746.

Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS: [2006] Case definitions for chronic obstructive pulmonary disease. COPD 3: 95-100.

Hnizdo E, Vallyathan V: [2003] Chronic obstructive pulmonary disease due to occupational exposure to silica dust: A review of epidemiological and pathological evidence. Occup Environ Med 60: 237-243.

Hoppin JA, Valcin M, Henneberger PK, Kullman GJ, Umbach DM, London SJ, Alavanja MC, Sandler DP: [2007] Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study. Am J Ind Med 50: 969-979.

Hosmer DW, Lemeshow S: [1989] Applied Logistic Regression. Second ed. New York: John Wiley & Sons, Inc.

Hsieh CC, Maisonneuve P, Boyle P, Macfarlane GJ, Roberston C: [1991] Analysis of quantitative data by quantiles in epidemiologic studies: Classification according to cases, noncases, or all subjects? Epidemiology 2: 137-140.

Hughes JM, Jones RN, Glindmeyer HW, Hammad YY, Weill H: [1993] Follow up study of workers exposed to man made mineral fibres. Br J Ind Med 50: 658-667.

Humerfelt S, Gulsvik A, Skjaerven R, Nilssen S, Kvale G, Sulheim O, Ramm E, Eilertsen E, Humerfelt SB: [1993] Decline in FEV1 and airflow limitation related to occupational exposures in men of an urban community. Eur Respir J 6: 1095-1103.

Hunting KL, Welch LS: [1993] Occupational exposure to dust and lung disease among sheet metal workers. Br J Ind Med 50: 432-442.

ILO: [1980] Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconiosis Geneva: International Labour Office.

ILO: [2002] Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconiosis, 2000 Edition. 2000 ed. Geneva: International Labour Office.

Johannessen A, Omenaas ER, Bakke PS, Gulsvik A: [2005] Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. Thorax 60: 842-847.

Johnson NJ, Hayes LD, Brown K, Hoo EC, Ethier KA: [2014] National Health Report: Leading causes of morbidity and mortality and associated behavioral risk and protective factors—United States, 2005–2013. Morbidity and Mortality Weekly Report 63: 3-27.

Kilburn KH, Powers D, Warshaw RH: [1992] Pulmonary effects of exposure to fine fibreglass: irregular opacities and small airways obstruction. Br J Ind Med 49: 714-720.

Kjeldgaard P, Dahl R, Lokke A, Ulrik CS: [2015] Detection of COPD in a high-risk population: should the diagnostic work-up include bronchodilator reversibility testing? Int J Chron Obstruct Pulmon Dis 10: 407-414.

Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI: [2007] Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol 36: 1111-1118.

Koh DH, Kim JI, Kim KH, Yoo SW: [2015] Welding fume exposure and chronic obstructive pulmonary disease in welders. Occup Med (Lond) 65: 72-77.

Lindberg A, Jonsson A, Ronmark E, Lundgren R, Larsson L, Lundback B: [2005] Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 127: 1544-1552.

Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC: [2002] Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. Respir Care 47: 1184-1199.

Mastrangelo G, Tartari M, Fedeli U, Fadda E, Saia B: [2003] Ascertaining the risk of chronic obstructive pulmonary disease in relation to occupation using a case-control design. Occupational Medicine-Oxford 53: 165-172.

McGuire V, Nelson LM, Koepsell TD, Checkoway H, Longstreth WT, Jr.: [1998] Assessment of occupational exposures in community-based case-control studies. Annu Rev Public Health 19: 35-53.

Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, Curjuric I, Kromhout H, Rochat T, Rothe T, Russi EW, Schikowski T, Schindler C, Schwartz J, Turk A, Vermeulen R, Probst-Hensch N, Kunzli N: [2012] Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Am J Respir Crit Care Med 185: 1292-1300.

Melville AM, Pless-Mulloli T, Afolabi OA, Stenton SC: [2010] COPD prevalence and its association with occupational exposures in a general population. Eur Respir J 36: 488-493.

Mwaiselage J, Bratveit M, Moen B, Mashalla Y: [2004] Cement dust exposure and ventilatory function impairment: An exposure-response study. J Occup Environ Med 46: 658-667.

NHLBI: [2014] Data Fact Sheet, Chronic Obstructive Pulmonary Disease: National Institutes of

Health, National Heart, Lung, and Blood Institute.

NIOSH: [1995] Criteria for a Recommended Standard: Occupational Exposure to Respirable Coal Mine Dust In: Department of Health and Human Services CfDCaP, National Institute for Occupational Safety and Health editor Atlanta, GA: National Institute for Occupational Safety and Health.

NIOSH: [2014] Work-Related Lung Disease Surveillance System (eWoRLD) Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH: [2015] NIOSH Pocket Guide to Chemical Hazards: Particulates not otherwise regulated Atlanta, GA.

Oliver LC, Miracle-McMahill H: [2006] Airway disease in highway and tunnel construction workers exposed to silica. Am J Ind Med 49: 983-996.

Omland O, Wurtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, Pedersen OF, Schlunssen V, Sigsgaard T, Ulrik CS, Viskum S: [2014] Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health 40: 19-35.

OSHA: [2009] Controlling Silica Exposures in Construction In: Occupational Safety and Health Administration USDoL editor Washington, DC.

OSHA: [2015] Chemical Sampling Information: Particulates Not Otherwise Regulated (Total Dust) Washington, DC.

Oxman AD, Muir DC, Shannon HS, Stock SR, Hnizdo E, Lange HJ: [1993] Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. Am Rev Respir Dis 148: 38-48.

Pallasaho P, Kainu A, Sovijarvi A, Lindqvist A, Piirila PL: [2014] Combined effect of smoking and occupational exposure to dusts, gases or fumes on the incidence of COPD. COPD 11: 88-95.

Pistolesi M: [2009] Beyond airflow limitation: another look at COPD. Thorax 64: 2-4.

Post W, Heederik D, Houba R: [1998] Decline in lung function related to exposure and selection processes among workers in the grain processing and animal feed industry. Occup Environ Med 55: 349-355.

Post WK, Heederik D, Kromhout H, Kromhout D: [1994] Occupational exposures estimated by a population specific job exposure matrix and 25 year incidence rate of chronic nonspecific lung disease (CNSLD): the Zutphen Study. Eur Respir J 7: 1048-1055.

Pronk A, Preller L, Raulf-Heimsoth M, Jonkers IC, Lammers JW, Wouters IM, Doekes G, Wisnewski AV, Heederik D: [2007] Respiratory symptoms, sensitization, and exposure response relationships in spray painters exposed to isocyanates. Am J Respir Crit Care Med 176: 1090-

1097.

Quinlan PJ, Earnest G, Eisner MD, Yelin EH, Katz PP, Balmes JR, Blanc PD: [2009] Performance of self-reported occupational exposure compared to a job-exposure matrix approach in asthma and chronic rhinitis. Occup Environ Med 66: 154-160.

Ramachandran G, Vincent JH: [1999] A Bayesian approach to retrospective exposure assessment. Appl Occup Environ Hyg 14: 547-557.

Rice C, Heineman EF: [2003] Application of a method to evaluate the quality of work histories and document the exposure assessment process. Am J Ind Med 44: 94-106.

Richardson DB, Kaufman JS: [2009] Estimation of the relative excess risk due to interaction and associated confidence bounds. Am J Epidemiol 169: 756-760.

Ringen K, Dement J, Welch LS, Bingham E, Quinn P, Chen A, Haas S: [2015] Mortality of older construction and craft workers employed at Department of Energy (DOE) nuclear sites: Follow-up through 2011. Am J Ind Med 58: 152-167.

Robertson C, Boyle P, Hsieh CC, Macfarlane GJ, Maisonneuve P: [1994] Some statistical considerations in the analysis of case-control studies when the exposure variables are continuous measurements. Epidemiology 5: 164-170.

Rothman KJ, Greenland S, Lash TL: [2007] Modern Epidemiology. Third ed. Philidelphia, PA: Lippincott Williams & Wilkins.

Royston P, Altman DG, Sauerbrei W: [2006] Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 25: 127-141.

Ruifeng L, Hartzmeak E, Louie M, Chen L, Spiegelman D: [2011] The SAS LGTPHCURV9 Macro.

Rushton L: [2007a] Occupational causes of chronic obstructive pulmonary disease. Rev Environ Health 22: 195-212.

Rushton L: [2007b] Chronic obstructive pulmonary disease and occupational exposure to silica. Rev Environ Health 22: 255-272.

Salameh PR, Waked M, Baldi I, Brochard P, Saleh BA: [2006] Chronic bronchitis and pesticide exposure: A case-control study in Lebanon. Eur J Epidemiol 21: 681-688.

SAS: [2011] SAS/STAT® 9.3 User's Guide Cary, NC: SAS Institute Inc.

STATA: [2009] STATA Statistics/Data Analysis. 11.1 ed. College Station, TX: StataCorp.

Suadicani P, Hein HO, Meyer HW, Gyntelberg F: [2001] Exposure to cold and draught, alcohol

consumption, and the NS-phenotype are associated with chronic bronchitis: an epidemiological investigation of 3387 men aged 53-75 years: the Copenhagen Male Study. Occup Environ Med 58: 160-164.

Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL, Stocks J, Quanjer PH: [2008] Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax 63: 1046-1051.

Szram J, Schofield SJ, Cosgrove MP, Cullinan P: [2013] Welding, longitudinal lung function decline and chronic respiratory symptoms: A systematic review of cohort studies. Eur Respir J 42: 1186-1193.

Tager IB, Segal MR, Speizer FE, Weiss ST: [1988] The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 138: 837-849.

Tilert T, Dillon C, Paulose-Ram R, Hnizdo E, Doney B: [2013] Estimating the U.S. prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007-2010. Respir Res 14: 103.

Toren K, Jarvholm B: [2014] Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: A longitudinal cohort study. Chest 145: 992-997.

Trupin L, Earnest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, Katz PP, Blanc PD: [2003] The occupational burden of chronic obstructive pulmonary disease. Eur Respir J 22: 462-469.

Tse LA, Yu IT, Leung CC, Tam W, Wong TW: [2007] Mortality from non-malignant respiratory diseases among people with silicosis in Hong Kong: exposure-response analyses for exposure to silica dust. Occup Environ Med 64: 87-92.

Tuchsen F, Hannerz H: [2000] Social and occupational differences in chronic obstructive lung disease in Denmark 1981-1993. Am J Ind Med 37: 300-306.

Ulvestad B, Bakke B, Melbostad E, Fuglerud P, Kongerud J, Lund MB: [2000] Increased risk of obstructive pulmonary disease in tunnel workers. Thorax 55: 277-282.

Valcin M, Henneberger PK, Kullman GJ, Umbach DM, London SJ, Alavanja MC, Sandler DP, Hoppin JA: [2007] Chronic bronchitis among nonsmoking farm women in the Agricultural Health Study. J Occup Environ Med 49: 574-583.

Vermeulen R, Li G, Lan Q, Dosemeci M, Rappaport SM, Bohong X, Smith MT, Zhang L, Hayes RB, Linet M, Mu R, Wang L, Xu J, Yin S, Rothman N: [2004] Detailed exposure assessment for a molecular epidemiology study of benzene in two shoe factories in China. Ann Occup Hyg 48: 105-116.

Weinmann S, Vollmer WM, Breen V, Heumann M, Hnizdo E, Villnave J, Doney B, Graziani M, McBurnie MA, Buist AS: [2008] COPD and occupational exposures: A case-control study. J Occup Environ Med 50: 561-569.

Welch L, Dement J, West G: [2015] Mortality among sheet metal workers participating in a respiratory screening program. Am J Ind Med Accepted 12-4-2014.

Welch L, Ringen K, Bingham E, Dement J, Takaro T, McGowan W, Chen A, Quinn P: [2004] Screening for beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med 46: 207-218.

Welch LS, Haile E, Dement J, Michaels D: [2007] Change in prevalence of asbestos-related disease among sheet metal workers 1986 to 2004. Chest 131: 863-869.

Welch LS, Ringen K, Dement J, Bingham E, Quinn P, Shorter J, Fisher M: [2013] Beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med 56: 1125-1136.

Whittemore AS, Perlin SA, DiCiccio Y: [1995] Chronic obstructive pulmonary disease in lifelong nonsmokers: Results from NHANES. Am J Public Health 85: 702-706.

Ye M, Beach J, Martin JW, Senthilselvan A: [2013] Occupational pesticide exposures and respiratory health. Int J Environ Res Public Health 10: 6442-6471.

TABLES

Table I: Exposures with Cumulative Lifetime Exposure Assessments

Agent or Exposure	Reference Concentration for Intensity Scoring
Asbestos	2 f/cc
Silica	0.1 mg/m^3 respirable
Cement Dust	5 mg/m^3 respirable
Man-Made-Mineral-Fibers	1 f/cc
Engine Exhausts	100 µg/m^3 respirable elemental carbon
Acids	Ceiling 5 ppm as HCL
Caustics	Ceiling 2 mg/m^3 as sodium hydroxide
Welding, Thermal Cutting, Soldering, or Brazing	5 mg/m^3 as total aerosol
Metal Cutting, Grinding, and Machining Aerosol	5 mg/m^3 as total aerosol
Paint-Related Aerosols	1 mg/m^3 as total aerosol
Isocyanates	0.02 ppm
Organic Solvents	100 ppm as toluene
Wood Dust	1 mg/m^3 as total aerosol
Molds and Spores	Exposure above typical background
Particulates not otherwise regulated (PNOR)	10 mg/m^3 as total aerosol

Table II: Study Participation Summary and Comparison by Participation Status

Participation Measure	Cases		Controls	
Sent Invitation Letters	1612		2129	
Contacted, Completed Interview	834		1245	
Contacted, Declined Interview	130		200	
Not Contacted	648		684	
Reasons for No Contact				
Deceased	238		137	
No Telephone Contact[1]	410		547	
Overall Participation Rate among Living	60.6%		62.5%	
Overall Participation Rate among those Contacted	86.5%		86.3%	
Demographic Variable [2]	**Participants (n=834)**	**Non-Participants (n=778)**	**Participants (n=1245)**	**Non-Participants (n=884)**
Mean Age (Std Err)	62.3 (0.37)	62.0 (0.48)	62.7 (0.30)	60.2 (0.44)*
Male Sex (%)	764 (91.6)	734 (94.3)*	1153 (92.6)	823 (93.1)
Non-White race or Hispanic ethnicity (%)	94 (11.3)	87 (11.2)	142 (11.4)	124 (14.1)
Spirometry, Mean (Std Err)				
% Predicted FVC	81.3 (0.70)	79.4 (0.76)	87.7 (0.46)	87.0 (0.54)
% Predicted FEV_1	62.9 (0.67)	60.3 (0.75)*	89.7 (0.49)	88.8 (0.57)
FEV_1/FVC Ratio	0.58 (0.003)	0.56 (0.004)*	0.77 (0.002)	0.77 (0.002)
Mean Cigarette Pack-Years (Std Err)	31.3 (0.88)	32.8 (1.04)	15.6 (0.56)	16.7 (0.76)

[1] Includes those with bad address or telephone information and those who did not respond after two reminder letters and up to six telephone contact attempts.

[2] Continuous data expressed as means and standard errors. Categorical data expressed as number and percent.

*Parameter significantly different for participants compared to non-participants, $p<0.05$.

Table III: Demographic and Clinical Characteristics of Cases and Controls by Cigarette Smoking Status

Characteristic[1]	Current or Former		Never Smokers		All Subjects	
	Cases (n=698)	Controls (n=770)	Cases (n=136)	Controls (n=473)	Cases (n=834)	Controls (n=1243)[2]
Mean Age (Std Err)	62.8 (0.39)	63.8 (0.36)	59.4 (0.98)	60.7 (0.53)	62.3 (0.37)	62.7 (0.30)
Male Sex (%)	641 (91.8)*	730 (94.8)	123 (90.4)	422 (89.2)	764 (91.6)	1152 (92.7)
Non-White race or Hispanic ethnicity (%)	50 (7.2)	67 (8.7)	26 (19.1)*	51 (10.8)	76 (9.1)	118 (9.5)
Respiratory History (%)						
Asthma (N=2076)	155 (22.2)*	61 (7.9)	37 (27.2)*	53 (11.2)	192 (23.1)*	114 (9.2)
Chronic Bronchitis (N=2076)	155 (22.2)*	77 (10.0)	14 (10.3)*	26 (5.5)	169 (20.3)*	103 (8.3)
Emphysema (N=2076)	180 (25.8)*	39 (5.1)	5 (3.7)	10 (2.1)	185 (22.2)*	49 (3.9)
Pneumonia (N=2076)	219 (31.4)*	158 (20.5)	23 (16.9)	83 (17.6)	242 (29.1)*	241 (19.4)
Respiratory Symptoms (%)						
Cough (N=2074)	375 (53.8)*	232 (30.2)	43 (31.6)	121 (25.6)	418 (50.1)*	353 (28.4)
Phlegm (N=2074)	350 (50.2)*	238 (31.0)	43 (31.6)*	99 (20.9)	393 (47.1)*	337 (27.2)
Dyspnea (N=2074)	422 (60.6)*	258 (33.6)	47 (34.6)	128 (27.1)	469 (56.3)*	386 (31.1)
Spirometry, Mean (Std Err)						
% Predicted FVC	80.0 (0.74)*	86.5 (0.60)	87.7 (1.80)	89.6 (0.73)	81.3 (0.70)*	87.7 (0.46)
% Predicted FEV_1	61.2 (0.71)*	88.3 (0.64)	71.4 (1.71)*	92.1 (0.76)	62.9 (0.67)*	89.7 (0.49)
FEV_1/FVC Ratio	0.57 (0.003)*	0.77 (0.002)	0.62 (0.006)*	0.78 (0.003)	0.58 (0.003)*	0.77 (0.002)
FEV_1/FVC < LLN & FEV_1 < 65% Pred. (%)	393 (56.3)	--	45 (33.1)	--	438 (52.5)	--
Chest X-ray B-Reader Prevalence (%)[3,4]						
Pleural Changes Only	105 (15.2)	116 (15.2)	15 (11.3)	63 (13.4)	120 (14.6)	179 (14.5)
Parenchymal Changes Only (Profusion ≥ 1/0)	17 (2.5)	19 (2.5)	3 (2.3)	4 (0.85)	20 (2.4)	23 (1.9)
Both Pleural and Parenchymal	22 (3.2)	24 (3.1)	1 (0.75)	4 (0.85)	23 (2.8)	28 (2.3)
History of hypertension (%) (N=2076)	223 (32.0)*	207 (26.9)	39 (28.6)	124 (26.2)	262 (31.5)*	331 (26.6)
History of congestive heart disease (%) (N=2074)	21 (3.0)*	13 (1.7)	2 (1.5)	13 (2.8)	27 (2.8)	23 (2.1)
History of severe childhood pneumonia (%)	27 (3.9)	31 (4.0)	4 (2.9)	16 (3.4)	31 (3.7)	47 (3.8)
Cigarette Smoking Status at Exam (%)[4]						
Current Smoker	236 (33.8)	138 (17.9)	--	--	236 (28.3)*	138 (11.1)
Past Smoker	462 (66.2)	632 (82.1)	--	--	462 (55.4)	632 (50.8)
Never Smoker	0 (0.0)	0 (0.0)	136 (100)	473 (100)	136 (16.3)	473 (38.1)
Mean Cigarette Pack-Years (Std Err)	37.4 (0.88)	25.2 (0.71)*	--	--	31.3 (0.88)*	15.6 (0.56)
Mean Body Mass Index (Std Err)	29.0 (0.21)	30.5 (0.19)*	29.9 (0.56)	30.6 (0.25)	29.2 (0.20)*	30.5 (0.15)
Blood Relative with COPD (%)	181 (25.9)*	139 (18.1)	31 (22.8)	91 (19.4)	212 (25.4)*	230 (15.5)
History of Living with a Smoker (%)	78 (11.2)	85 (11.0)	13 (9.7)	28 (5.9)	91 (10.9)	113 ((9.1)
Childhood History of Pneumonia (%)	27 (3.9)	31 (4.0)	4 (2.9)	16 (3.4)	31 (3.7)	47 (3.8)

[1] Continuous data expressed as means and standard errors. Categorical data expressed as number and percent. [2] Two controls were dropped from the analyses due to missing smoking pack years or BMI. [3] B-reader data was available for 2057 workers. [4] Smoking and chest X-ray categories compared using an overall chi square measure of association. *Parameter significantly different for cases compared to controls, $p<0.05$.

Table IV: COPD Cases and Controls by DOE Site

DOE Site Description[1]	Cases (n=834)	Controls (n=1243)	Total (n=2077)
Brookhaven National Laboratory	19	29	48
Fernald Feed Materials Production Center (FMPC)	137	183	320
General Electric Company, Cincinnati	23	39	62
Hanford	167	224	391
Idaho National Engineering and Environmental Laboratory	55	66	121
Kansas City Plant	37	53	90
Mallinckrodt Chemical/Weldon Spring	10	14	24
Oak Ridge (All Sites)	114	195	309
Paducah Gaseous Diffusion Plant	44	58	102
Portsmouth Gaseous Diffusion Plant	54	92	146
Rocky Flats Plant	62	101	163
Savannah River Site	112	189	301

[1] Case and control distribution by site not significantly different, Chi-Square=7.47, p=0.76

Table V: COPD Cases and Controls by Trade or Job Category

Trade Group or Job[1]	Cases (n=834)	Controls (n=1243)	Total (n=2077)
Asbestos Worker or Insulator	25	37	62
Boilermaker	16	27	43
Carpenter	55	77	132
Cement Mason/Brick Mason/Plasterer	23	12	35
Electrician	128	226	354
Ironworker	50	64	114
Laborer	115	152	267
Mechanical Trades	7	8	15
Millwright	14	19	33
Operating Engineer	53	81	134
Painter	29	30	59
Plumber, Steamfitters, Pipefitter	130	200	330
Roofer	13	9	22
Sheet Metal Worker	45	82	127
Sprinkler Fitter	8	8	16
Teamster	32	34	66
All Other Construction and Non-Construction	91	177	268

[1] Case and control distribution by trade significantly different, Chi-Square= 33.09, p=0.033

Table VI: Exposure Intensity Scoring Results

Agent or Exposure	Multi-Rater Kappa
Asbestos	0.71
Silica	0.66
Cement Dust	0.82
Man-Made-Mineral-Fibers	0.67
Engine Exhausts (Diesel or Gasoline)	0.71
Acids	0.49
Caustics	0.58
Welding, Thermal Cutting, Soldering, or Brazing	0.80
Metal Cutting, Grinding, and Machining Aerosol	0.80
Paint-Related Aerosol	0.78
Isocyanates	0.66
Organic Solvents	0.69
Wood Dust	0.70
Molds and Spores	0.78
Particulates not otherwise regulated (PNOR)	0.41

Table VII: Cumulative Exposure Index Distributions for COPD Cases and Controls

Cumulative Exposure Index	Cases or Controls	Mean (Std Err)	No Reported Exposure[1]	Number (%) of Workers by Tertile[2]		
				Tertile #1 Low	Tertile #2 Medium	Tertile #3 High
Asbestos	Cases	39.3(1.3)	41 (4.9)	240 (28.8)	222 (26.2)	331 (39.7)
	Controls	31.1 (1.0)	81 (6.5)	383 (30.8)	395 (31.8)	384 (30.9)
Silica	Cases	45.7 (1.4)	35 (4.2)	236 (28.3)	240 (28.3)	323 (38.7)
	Controls	38.1 (1.0)	71 (5.7)	388 (31.2)	396 (31.9)	388 (31.2)
Cement Dust	Cases	32.1 (1.1)	48 (5.8)	261 (31.3)	226 (27.1)	299 (35.9)
	Controls	27.9 (0.8)	103 (8.3)	398 (32.0)	365 (29.4)	377 (30.3)
Man-Made-Mineral-Fibers	Cases	17.9 (0.7)	68 (8.2)	233 (27.9)	232 (27.8)	301 (36.1)
	Controls	16.4 (0.6)	115 (9.3)	374 (30.1)	382 (30.7)	372 (29.9)
Engine Exhausts (Diesel or Gasoline)	Cases	10.5 (0.5)	136 (16.3)	171 (20.5)	239 (28.7)	288 (34.5)
	Controls	8.1 (0.4)	236 (19.0)	331 (26.6)	343 (27.6)	333 (26.8)
Acids and Caustics	Cases	0.9 (0.1)	689 (82.6)	46 (5.5)	43 (5.2)	56 (6.7)
	Controls	0.7 (0.1)	1082 (87.1)	53 (4.3)	53 (4.3)	55 (4.4)
Welding, Thermal Cutting, Soldering, or Brazing	Cases	17.3 (0.8)	42 (5.0)	259 (31.1)	247 (29.6)	286 (34.3)
	Controls	15.5 (0.6)	78 (6.3)	384 (30.9)	396 (31.9)	385 (31.0)
Metal Cutting, Grinding, and Machining Aerosol	Cases	39.9 (1.7)	103 (12.4)	227 (27.2)	225 (27.0)	279 (33.5)
	Controls	36.3 (1.4)	165 (13.3)	357 (28.7)	364 (29.3)	357 (28.7)
Paint-Related Aerosols	Cases	6.0 (0.3)	128 (15.4)	229 (27.4)	225 (27.0)	252 (30.2)
	Controls	5.6 (0.2)	209 (16.8)	340 (27.4)	352 (28.3)	342 (27.5)
Isocyanates	Cases	1.3 (0.1)	625 (74.9)	57 (6.8)	64 (7.7)	88 (10.6)
	Controls	1.0 (0.1)	985 (79.2)	85 (6.8)	87 (7.0)	86 (6.9)
Organic Solvents	Cases	28.1 (1.0)	38 (4.6)	249 (29.9)	219 (26.3)	328 (39.3)
	Controls	23.4 (0.8)	84 (6.8)	382 (30.7)	394 (31.7)	383 (30.8)
Wood Dust	Cases	5.0 (0.2)	74 (8.9)	224 (26.9)	240 (28.8)	296 (35.5)
	Controls	4.4 (0.2)	129 (10.4)	363 (29.2)	383 (30.8)	368 (29.6)
Molds and Spores	Cases	14.2 (0.6)	137 (16.4)	193 (23.1)	222 (26.6)	282 (33.8)
	Controls	12.1 (0.4)	237 (19.1)	332 (26.7)	338 (27.2)	336 (27.0)
Particulates not otherwise regulated (PNOR)	Cases	89.4 (2.7)	28 (3.4)	232 (27.8)	237 (28.4)	337 (40.4)
	Controls	74.2 (2.0)	67 (5.4)	389 (31.3)	398 (32.0)	389 (31.3)
ALL VGDF	Cases	367.0 (11.2)	12 (1.4)	237 (28.4)	249 (29.9)	336 (40.3)
	Controls	310.4 (8.3)	31 (2.5)	398 (32.0)	410 (33.0)	404 (32.5)

[1] Number and percent of workers not reporting exposures included in the cumulative index.

[2] Tertile cut points were based on the distribution of exposures for exposed controls. The percent ( ) represents the percent of the total distribution of exposures, including workers with no reported exposure.

Table VIII: COPD Odds-Ratios by Cumulative Exposure Index

Cumulative Exposure Index[1]	Restricted Cubic Spline p-value[2]	Exposure Index p-value[3]	Odds-Ratio (95% CI) by Fraction of Upper 95th Percentile[4]			
			0.25	0.50	0.75	1.00
Asbestos	0.1157	0.0038	1.15 (1.05-1.26)	1.31 (1.09-1.58)	1.50 (1.14-2.00)	1.72 (1.19-2.48)
Silica	0.5963	<0.0001	1.21 (1.11-1.32)	1.46 (1.23-1.74)	1.77 (1.36-2.30)	2.13 (1.50-3.03)
Cement Dust	0.4216	0.0017	1.16 (1.05-1.25)	1.31 (1.11-1.56)	1.51 (1.17-1.94)	1.73 (1.23-2.43)
Man-Made-Mineral-Fibers	0.1764	0.1829	1.06 (0.97-1.16)	1.13 (0.94-1.35)	1.20 (0.92-1.57)	1.28 (0.89-1.82)
Engine Exhausts	0.1577	0.0021	1.15 (1.05-1.26)	1.33 (1.11-1.74)	1.53 (1.17-2.00)	1.76 (1.23-2.52)
Acids and Caustics[6]	0.2281	<0.0001	1.46 (0.91-2.32)	1.49 (1.09-2.04)	1.51 (1.16-1.98)	1.54 (1.07-2.22)
Welding, Thermal Cutting, Soldering, Brazing	0.2015	0.0254	1.11 (1.01-1.21)	1.23 (1.03-1.46)	1.36 (1.04-1.77)	1.50 (1.05-2.14)
Metal Cutting, Grinding, and Machining Aerosol	0.1869	0.0364	1.09 (1.00-1.19)	1.20 (1.01-1.42)	1.31 (1.02-1.68)	1.43 (1.02-2.00)
Paint-Related Aerosols	0.1436	0.2873	1.05 (0.96-1.15)	1.10 (0.92-1.31)	1.15 (0.89-1.50)	1.21 (0.85-1.72)
Isocyanates[6]	0.5335	<0.0001	1.09 (0.83-1.42)	1.22 (0.97-1.52)	1.36 (1.03-1.80)	1.52 (1.04-2.23)
Organic Solvents	0.1869	0.0008	1.16 (1.07-1.26)	1.34 (1.13-1.59)	1.55 (1.20-2.01)	1.80 (1.28-2.53)
Wood Dust[7]	0.0434	0.0420	1.36 (1.07-1.74)	1.46 (1.10-2.00)	1.36 (1.02-1.80)	1.17 (0.80-1.69)
Molds and Spores	0.3965	0.0018	1.12 (10.3-1.22)	1.25 (1.05-1.49)	1.40 (1.08-1.82)	1.57 (1.11-2.23)
Particulates not otherwise regulated (PNOR)	0.6489	<0.0001	1.21 (1.11-1.32)	1.47 (1.23-1.74)	1.78 (1.37-2.30)	2.15 (1.52-4.04)
All VGDF[5]	0.9148	<0.0001	1.19 (1.09-1.30)	1.42 (1.20-1.69)	1.70 (1.31-2.20)	2.03 (1.43-2.87)

[1] Cumulative exposure indices generated as function of task frequency, exposure intensity, and duration. Each index summed exposures from construction and non-construction work, bystander exposures, and military exposures. The fraction represents the proportion of the upper 95 percentile for each exposure.
[2] Likelihood ratio test for non-linearity of the exposure index comparing the adjusted model with only the linear term to the adjusted model with the linear and the cubic spline terms.
[3] Likelihood ratio p-values for the cumulative exposure indices.
[4] Increase in the COPD odds-ratio for an exposure at each proportion of the maximum for the exposure index compared to those unexposed. Logistic regression model adjusted for age, gender, race/ethnicity, smoking status (Current, Past, Never), cigarette pack-years, blood relative with COPD, and BMI.
[5] VGDF is an overall measure for all vapors, gasses, dusts, and fumes combined.
[6] Many workers reported no exposures to acids and caustics and isocyanates; therefore, models for acids and caustics and isocyanates included two exposures variables as described in the text. The p-value represents the change in the -2 log likelihood with these two parameters in the model.
[7] The restricted cubic spline model provided a better fit for wood dust and was retained as the final model.

Table IX: Assessment of Cigarette Smoking and Exposure Interactions

Cumulative Exposure Index	RERI[1] (95% CI)
Asbestos	1.03 (0.95-1.11)
Silica	1.03 (0.95-1.12)
Cement Dust	1.01 (0.95-1.09)
Man-Made-Mineral-Fibers	1.00 (0.94-1.08)
Engine Exhausts	1.01 (0.92-1.10)
Acids and Caustics	1.06 (0.99-1.16)
Welding, Thermal Cutting, Soldering, Brazing	1.01 (0.95-1.09)
Metal Cutting, Grinding, and Machining Aerosol	0.99 (0.93-1.06)
Paint-Related Aerosols	1.02 (0.96-1.09)
Isocyanates	1.01 (0.95-1.10)
Organic Solvents	1.02 (0.95-1.10)
Wood Dust	1.05 (0.98-1.13)
Molds and Spores	1.07 (1.00-1.16)
Particulates not otherwise regulated (PNOR)	1.03 (0.96-1.12)
All VGDF	1.03 (0.95-1.12)

[1] Relative excess risk due to interaction (RERI) based on a linear odds-ratio model. RERI represents the increased risk for a 10% increase in cumulative VGDF exposure and 10 pack-years of smoking compared to the sum of risks for smoking and VGDF exposure. Likelihood-based 95% confidence estimates for each RERI are shown.

Table X: Principal Component Analysis Rotated Factor Pattern, Final Communality Estimates, and Logistic Model Results

Cumulative Exposure Index	Principal Component Number[1]				Final Communality Estimates[2]
	#1	#2	#3	#4	
Metal Cutting, Grinding, and Machining Aerosol	**0.89**	0.17	0.07	0.06	0.84
Welding, Thermal Cutting, Soldering, Brazing	**0.88**	0.12	0.07	0.02	0.79
Particulates not otherwise regulated (PNOR)	**0.69**	**0.56**	0.37	0.13	0.93
Silica	**0.67**	**0.59**	0.28	0.15	0.89
Cement Dust	**0.60**	**0.63**	0.10	0.13	0.78
Asbestos	**0.53**	**0.65**	0.14	0.08	0.73
Organic Solvents	**0.44**	0.25	**0.71**	0.13	0.77
Molds and Spores	0.31	**0.74**	0.17	-0.10	0.68
Engine Exhausts	0.15	0.18	**0.77**	-0.18	0.68
Acids and Caustics	0.13	0.11	0.09	**0.90**	0.91
Wood Dust	0.00	**0.77**	0.12	0.15	0.63
Isocyanates	-0.07	0.07	**0.82**	0.24	0.74
Component Proportion of Total Variance	0.50	0.12	0.08	0.08	
Logistic Regression Model p-value[3]	0.0211	0.0381	0.0045	0.0536	

[1] Exposures with a rotated factor loading ≥ 0.40 are shown in bold.
[2] Communality refers to the percent of variance in a given cumulative exposure index that was accounted for by the four retained principal components.
[3] Type 3 Wald p-values for principal components in a logistic regression model that adjusted for age, gender, race/ethnicity, smoking status (Current, Past, Never), cigarette pack-years, blood relative with COPD, BMI and all selected principal components.