American Thoracic Society Statement: Occupational Contribution to the Burden of Airway Disease

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As the classic mineral dust-induced pneumoconioses decrease in frequency because of the control of exposure, obstructive airway diseases have emerged as the most prevalent category of occupational respiratory disorder (1). Unlike the pneumoconioses, recognition of work-relatedness for asthma and chronic obstructive pulmonary disease (COPD) is difficult. This is the case for two reasons. First, these are multifactorial diseases that are strongly associated with nonoccupational exposures. Second, the occupational dose–response and temporal relationships for obstructive airway diseases are complex. Nonetheless, because asthma and COPD are common diseases in the general population, even a small increase in the percentage of prevalence due to occupational exposures would have major public health impact and should be preventable. The purpose of this statement is to review the evidence implicating occupational factors in the pathogenesis of obstructive airway diseases and to quantify the contribution of work-related risk to the burden of these diseases in the general population. Assessing the occupational component of the total burden of asthma and COPD can better inform preventive strategies designed to reduce the morbidity and mortality associated with these conditions.

1. CLINICAL SPECTRUM

Asthma has been defined as a chronic inflammatory disorder of the airways that causes recurrent episodes of coughing, wheezing, chest tightness, and dyspnea. Inflammation makes the airways sensitive to stimuli such as allergens, chemical irritants, tobacco smoke, cold air, or exercise. When exposed to these stimuli, the airways may become edematous, constricted, filled with mucus, and hyperresponsive to stimuli. The resulting airflow limitation is reversible (but not completely so in some patients) either spontaneously or with treatment (2). As a subset of this disorder, occupational asthma has been defined as a category of disease that is "characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment" (3). There are two major types of occupational asthma: sensitizer induced (i.e., work-caused asthma associated with exposure to one or more sensitizing agents and appearing after a latency period) and irritant induced (which may occur after single or multiple exposures to nonspecific irritants). This terminology may evolve as the mechanism(s) of irritant-induced asthma comes to be better understood. It is also important to recognize that there may be much greater morbidity and productivity loss associated with exacerbations of pre-existing asthma due to workplace exposures than due to *de novo* asthma caused by such exposures, a relationship sometimes subsumed under the rubric "work-related asthma" (4).

COPD is defined as a disease state that is characterized by the presence of airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (5). COPD can result from chronic bronchitis accompanied by hypersecretion of mucus and/or emphysema characterized by destruction of alveolar walls.

Some work-related airway disorders do not fit neatly into either asthma or COPD categories. Work-related variable airflow limitation may occur with occupational exposure to organic dusts such as cotton (byssinosis), flax, hemp, jute, sisal, and various grains. Such organic dust-induced airway disease is often classified as an "asthma-like disorder" rather than as "true" asthma (3).

2. BIOLOGIC PLAUSIBILITY FOR OCCUPATIONAL CONTRIBUTION TO ASTHMA AND COPD

2.1. Asthma: Epidemiologic Evidence

Asthma likely develops because of both a genetic predisposition and exposure to environmental factors. There is considerable epidemiologic evidence that occupational exposure to certain specific agents can lead to the development of asthma. The incidence and prevalence of occupational asthma in various occupational cohort studies depend on the agent(s) to which the workers are exposed and the levels of their exposure. Host susceptibility factors, such as atopy and cigarette smoking, may also play a role in at least some cases. There are convincing data to indicate that the level of exposure is a critical risk factor for sensitizer-induced occupational asthma (6–9).

Atopy appears to be a contributing risk factor for occupational asthma due to IgE-dependent mechanisms, such as asthma in bakers or laboratory animal handlers (9–11). Cigarette smoking may also increase risk of IgE-mediated occupational asthma and interact with atopy (12, 13), although data are more limited

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in this regard. For most sensitizing agents that cause asthma through mechanisms that do not obviously involve specific IgE antibodies, such as diisocyanates and western red cedar, atopy and smoking do not appear to be risk factors, and cigarette smoking may even change susceptibility (14, 15).

Little is known about the epidemiology of irritant-induced asthma, but it appears to be a relatively infrequent outcome of irritant exposure. Data from the Surveillance of Work-related and Occupational Respiratory Disease study in the United Kingdom suggest that less than 10% of reported inhalational injuries are followed by persistent asthma (1). Somewhat surprisingly, recent data from the Sentinel Health Notification System for Occupational Risk program in the United States indicate that exposures to irritants are reported frequently as causes of new-onset asthma (16, 17). The intensity of exposure is likely to be a risk factor for irritant-induced asthma. In a study of hospital laboratory workers exposed to a spill of glacial acetic acid, the risk of irritant-induced asthma increased with the level of exposure as assessed by distance from the spill (18). Several studies have also suggested that atopy and smoking may be risk factors for irritant-induced asthma (19, 20), although their role is less well established than it is for IgE-mediated occupational asthma.

2.2. Asthma: Experimental Evidence

There are over 250 agents that have been adequately documented to cause sensitizer-induced occupational asthma (also known as immunologic occupational asthma or occupational asthma with latency) (21, 22). Although these sensitizing agents have been identified largely on clinical grounds, experimental data have confirmed immunologic responses that are consistent with established models of asthma pathogenesis (23–30). Recent investigations into the genetic determinants of risk for allergic occupational asthma have suggested that polymorphisms in genes encoding MHC class II proteins may be important determinants of the specificity of response to sensitizing agents (31–35).

Experimental evidence delineating the mechanisms of irritant-induced asthma is fragmentary at best. Available data suggest that an airway inflammatory response is likely involved (36–38). There are limited animal data to support the hypothesis that massive epithelial damage after irritant inhalation results in direct activation of nonadrenergic, noncholinergic pathways via axon reflexes and the onset of neurogenic inflammation (38–40).

2.3. COPD: Epidemiologic Evidence

There is consensus that cigarette smoking is a specific cause of COPD. The preponderance of data establishing this link comes from longitudinal epidemiologic studies. In these studies, a dose–response relationship between the amount smoked and an observed accelerated decline in ventilatory function have been consistently found (5, 41–44). This effect appears to be confined to a minority of smokers, however, and it is still not possible to predict based on smoking exposure alone which individual smokers will develop chronic bronchitis, emphysema, or both. In addition, an estimated 6% of persons who have COPD in the United States are never smokers (45). Cigarette smoke is analogous to a mixed inhalational exposure at a workplace because it is a complex mixture of particles and gases. Epidemiologic studies of the effects of cigarette smoke cannot pinpoint the specific etiologic role of any of its over 400 constituents.

Despite the difficulty of disentangling the effects of cigarette smoke from those of other exposures, an increasingly impressive body of scientific literature is available demonstrating that specific occupational exposures contribute to the development of COPD (46–56). Longitudinal studies documenting the association between COPD and occupational exposures have been performed in coal miners (57–60), hard-rock miners (49, 61), tunnel workers (62), concrete-manufacturing workers (63), a cohort of nonmining industrial workers in Paris (64), and several community-based populations (65–67). Most of these studies reported an annual decline in FEV_1 due to occupational exposures (after adjustment for age and smoking) of 7–8 ml/year (57–60, 64, 65). In heavily exposed workers, the effect of dust exposure may be greater than that of cigarette smoking alone (62). Quantitative pathologic assessment of emphysema as an outcome variable in epidemiologic studies has confirmed a relationship between dust exposure and degree of emphysema, independent of cigarette smoking, in several studies of coal and hard-rock miners (68–72). Overall, the magnitude of effect of occupational exposures appears consistent with that of cigarette smoking (73).

2.4. COPD: Experimental Evidence

Differing pathologic processes can contribute to COPD, most notably chronic obstructive bronchitis (with obstruction of small airways) and emphysema (with enlargement of air spaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways) (74). Experimental models have demonstrated convincingly that several agents are capable of inducing chronic obstructive bronchitis, including sulfur dioxide, mineral dusts, vanadium, and endotoxin (75–78). The clearest human model of emphysema is that of α_1-antitrypsin deficiency (5, 74). Although smoking is the most potent and well-established cofactor in emphysema related to α_1-antitrypsin deficiency, occupational exposures are linked to such disease as well (79, 80). Agents other than cigarette smoke that can cause emphysema in animals (81) include several for which there is also epidemiologic evidence of occupationally related COPD, such as cadmium, coal, silica, and endotoxin (48, 49, 51, 57–61, 82–86).

2.5. Organic Dust-induced Asthma-like Disorder

Longitudinal studies of workers chronically exposed to cotton or grain dusts have shown these workers to have an increased prevalence of cough and phlegm and an accelerated annual decline in lung function (84, 85, 87–89). The concentration of endotoxin in the inhaled dust may be more critical to the development of respiratory symptoms and airway disease than the level of total cotton or grain dust (86, 90), although the role of other cofactors has not been excluded.

The airway response to organic dust inhalation appears to be primarily mediated by nonallergic inflammatory mechanisms (89, 91). The results of in vitro studies demonstrate that grain dust can activate complement (92) and induce alveolar macrophages to release neutrophil chemotactic factors (93). Moreover, both animal and human studies have shown that inhaled grain dust can cause recruitment of neutrophils to the proximal and distal airways (93, 94–96). Animal studies have shown that responsiveness to endotoxin is critical to the development of grain dust-induced airway inflammation and airflow obstruction (96, 97). Human challenge studies with cotton dust also suggest that neutrophilic inflammation and endotoxin responsiveness are important components of acute "byssinosis" (98, 99). One epidemiologic study found that cotton mill workers with byssinosis had increased nonspecific airway hyperresponsiveness compared with coworkers without byssinosis in the same mill (100).

3. METHODS FOR ASSESSMENT OF POPULATION BURDEN

3.1. Epidemiologic Definitions of Asthma and COPD

For the purposes of this statement, obstructive airway disease is considered as falling into two general categories: asthma and COPD. In the epidemiologic context, asthma that is caused by workplace exposures has been defined in three ways: (*1*) clini-

cally recognized occupational asthma identified through physician reports or workers compensation records; (*2*) asthma meeting a working definition of occupational or work-related asthma based on a combination of exposure, symptom, and physiologic or clinical data; and (*3*) excess asthma occurrence among workers exposed to noxious agents as compared with referents (4, 8). The latter two definitions may encompass cases that do not necessarily meet the traditional definition of clinically recognized occupational asthma. These epidemiologic definitions are useful, however, for both research purposes and improved efforts at prevention (101).

COPD does not have a clinical subcategory that is clearly identified as occupational, largely because the condition develops slowly and, given that the airflow limitation is chronic, does not reverse when exposure is discontinued. Thus, a clinical diagnosis of occupational COPD, using methods similar to those employed for occupational asthma, is not feasible. Epidemiologically, therefore, the identification of occupational COPD is based on observing excess occurrence of COPD among exposed workers (55, 56, 73), analogous to the third approach for asthma listed previously here.

3.2. Defining Attributable Risk

The fraction of cases in a population that arise because of certain exposures is called the attributable fraction in the population or the population attributable risk (PAR). The PAR is a useful indicator in prioritizing efforts to reduce the burden of disease (102). This measure of attributable disease burden relates the public health importance of a given exposure to both its potency and prevalence. Thus, low-potency exposures can be important when their prevalence is high, and high-potency exposures can be important even when their prevalence is low. For this statement, studies that either calculated the PAR or presented sufficient information so that PAR could be estimated were considered.

The most straightforward approach to the calculation of PAR is to divide the number of work-related cases by the total number of cases. This method has usually been applied using surveillance data of physician-reported asthma and occupational asthma. A variation of this "case-by-case" method involves the development of a case definition for work-related disease that can be used with data obtained from chart reviews, questionnaires, and standardized physiologic testing protocols, rather than by physician reporting. The case definition can then be applied to all cases arising within a defined population (e.g., membership of a health maintenance organization) or to a case series (as from a hospital).

The second approach to PAR calculation is to estimate the excess number of cases among exposed workers as a fraction of the total in a population using information about the number exposed and the risks of disease in the exposed and unexposed. This "risk-based method" is the standard epidemiologic approach to measuring the work-related burden of disease and does not require that individual cases be recognized as due to workplace exposures. It can be used with various measures of disease occurrence (e.g., physician-diagnosed disease, symptoms, or physiological abnormality). However, it is critically dependent upon the definition of exposure that is applied (103).

In the following sections, a detailed review of the literature on the PAR of asthma and COPD due to occupational exposures is presented. The attributable risks for each report were obtained as follows. If the authors presented an attributable risk and it was clear from the reported methods that the data represented a PAR calculated by appropriate methods, we have used the reported PAR. If the report did not calculate the PAR as described previously here but did provide an adjusted RR and sufficient data to estimate the proportion of the population exposed, then we have computed the PAR. If information was sufficient to estimate the proportion of cases exposed, we used a standard formula (Equation 1; *see* Appendix) (104). Otherwise, and in most cases when only the overall prevalence of exposure could be estimated from the data presented, we used an alternate equation (Equation 2; *see* Appendix) to generate an estimate of PAR, with the recognition that these estimates could be biased if there were large amounts of confounding in the original data (104–106).

3.3. Defining Exposure

Estimates of disease burden (such as PAR) caused by occupational exposure require information on rates of exposure in the source population. The quality of the exposure information, ideally, should be such as to allow satisfactory description of between-subject differences in exposure and the accurate estimation of risks for groups that differ in exposure level, type, and/or duration (107). In community-based studies, the source population is usually a general population sample (65, 108–110). In case-control studies, it may be community based or based on the workforce that generated the cases. The following methods have been used for gathering the exposure information relevant to airway disease: work history questionnaire, expert evaluation of the job history for exposures, and job-exposure matrix (i.e., a database containing job titles on one axis linked to the associated occupational exposure(s) on the other axis) (111–115).

The role of multiple exposures deserves comment (64, 66, 82, 83). Much effort has been (and continues to be) put into the evaluation of the individual components of workplace exposures, whereas the lungs of workers at risk are subjected to the total exposure burden of all airborne contaminants in any workplace. Evidence in support of applying a measure of total exposure burden comes from the strength and consistency of the association of objective markers of COPD (such as FEV_1 level or annual decline in FEV_1) with occupational exposures in community-based studies (64, 66, 82, 83). Despite the fact that these exposures are self-reported and usually described only in broad terms encompassing multiple exposures (i.e., dusts, fumes, gases, or vapors), this crude index appears to be reasonably effective in classifying exposure (82, 83, 116). By analogy, the most appropriate exposure metric for cigarette-related obstructive airway disease is pack-years, not exposure to any single component of the almost 400 found in cigarette smoke, and many epidemiologic studies use only smoking status to stratify exposure (117).

4. ESTIMATED POPULATION BURDEN OF ASTHMA AND COPD

4.1. Asthma PAR

A number of studies have attempted to address the issue of attributable risk of asthma due to occupation. A review of the published literature regarding the magnitude of the PAR (PAR%) for the occupational contribution to asthma has been conducted for this statement. All articles published before January 2000 that included PAR% calculations or presented data from which PAR% could be calculated were included in the review.

Several different types of studies were reviewed. The most common type is the cross-sectional study based on population sampling (118–127). Two studies, one from Finland and one from Israel, are of a second type, which can be characterized as involving cohorts based on a total national sample (128, 129). The third type of study reviewed involves case-control investigations, mostly based on sampling of cases and control subjects within a population-based frame (130–132). In these three study types, the risk for asthma is calculated as an odds ratio (OR) or a

TABLE 1. ASTHMA: POPULATION ATTRIBUTABLE RISK CAUSED BY OCCUPATION

Reference Number	Type of Study	Age Range	No. Subjects/ No. Cases	Sex	Asthma Diagnosis	Timing of Asthma	Type of Exposure	PAR% Reported	PAR% Calculated 1	PAR% Calculated 2
(120)	National sample	64	6,063/468	M/F	Q-SR	Ever	Self-assessed	15	–	–
(118)	Random population	18–64	1,027/17	M	Q-PD	Ever	GDF	–	30	24
			608/22	F				–	51	28
(119)	Random population	15–70	4,469/156	M/F	Q-PD	Ever asthma	Gas or dust	19	13	19
(137)	Asthma cohort	20–75	34 cases	M/F	Clinical diagnosis	Adult onset	Exposure to a recognized causing agent	5.9	–	–
			320 cases	M				9.4	–	–
			240 cases	F				1.7	–	–
(126)	Random population	40–69	3,606/137	M/F	Q-PD	Ever asthma + wheeze	GDF	17[1]	–	–
(136)	Hospital- based cohort	20–65	1,634/62	M/F	Q-SR	Ever asthma	Grain farming	–	15	15
				M				–	22	24
				F				–	4	3
(138)	Asthma cohort	20–65	94 cases	M/F	Clinical diagnosis	Current	Self-assessed	21	–	–
(131)	Case- control study	20–54	1,591/787	M/F	Clinical diagnosis	Current	Decided *a posteriori* among occupations with increased OR	33	33	34
(122)	Random population	> 64	708/27	F	Clinical diagnosis	Current	Manufacturing, construction, farming	–	51	76
(130)	Case-control study	20–65	304/79	M/F	Clinical diagnosis	Adult onset	GDF	–	36	–
(128)	Nationwide cohort	15–64	5.1 mil/8,056	M/F	Clinical diagnosis	Adult onset	Identification of the specific causative agent	5	–	–
			2.5 mil/3,334	M				6	–	–
			2.6 mil/4,717	F				4	–	–
(124)	Random population	> 65	2,355/144	M/F	Q-SR	Ever	Farmers, manual workers and domestic service employees	–	29	35
(100)	Asthma cohort	15–55	66 Cases	M/F	Clinical diagnosis	Current	Self-assessed	21	–	–
(133)	Asthma cohort	18–50	601 Cases	M/F	Clinical diagnosis	Adult onset	Reported exposure to sensitizers and irritant gases known to cause OA	13	–	–
(125)	Populationbased	> 18	899/77	M/F	Q-SR	Ever	Reported exposure to etiologic agent at work	20	–	–
(121)	Populationbased	> 55	1226/65	F	Q-PD	Adult onset	GDF	15	14	14
(135)	Asthma cohort	16–65	182 cases	M/F	Clinical diagnosis	Adult onset	Occupations known to cause OA	4	–	–
(123)	Populationbased	20–44	15,637/702	M/F	BHR+ Symptoms	Adult onset	Occupations with increased OR	10	–	–
			7,375/384	M				9	–	–
			8,262/318	F				12	–	–
(132)	Case-control study	20–65	321 cases	M/F	Clinical diagnosis	Adult onset	Exposures known to cause OA	11	–	–
			126 cases	M				14	–	–
			195 cases	F				10	–	–
(134)	Asthma cohort	18–50	150 cases	M/F	Clinical	Ever	Exposures known to cause OA	11	–	–
(129)	National cohort		59,058/588	M	Clinical diagnosis	New onset	Soldiers in combat units compared with clerks	–	44	44

Definition of abbreviations: BHR = bronchial hyperreactivity; F = females; GDF =gas, dust, and fume; M = males; OA = occupational asthma; OR = odds ratio; PAR% = magnitude of the population attributable risk; PD = physician diagnosed; Q = questionnaires; SR = self-reported.

PAR% Calculated 1 and 2 refer to Equations 1 and 2, which are used to compute the PAR (*see* APPENDIX for the actual equations).

relative risk (RR), and these values can be used for the calculation of PAR%. A fourth study type is that of clinical cohorts of asthmatic patients drawn from hospitals or registries where the PAR is calculated directly without an OR or RR (133–138).

If PAR% was reported in the published article, the reported value is presented here. In addition, PAR% has been calculated according to two different equations as described previously in the section 3.2. DEFINING ATTRIBUTABLE RISK. For cross-sectional studies and cohort studies, the PAR% has been calculated, if possible, using both equations. For case-control studies, Equation 1 has been used. In the asthma cohort studies, the PAR% has been estimated as the fraction of persons with asthma classified as having occupational asthma, either based on self-attribution or based on expert classification (depending on the methods used in the investigation).

Twenty-one articles were identified in which PAR% for asthma due to occupational factors was either reported or data were presented from which it could be calculated (Table 1) (118–138). A more thorough review of the literature on this topic that also included data from other sources has recently been published (139). The reported or calculated PAR% listed in Table 1 range from 4% to 58%, with a median value of 15%. There are major differences among the reviewed studies in their design features, including study population, characterization of exposure, and definition of asthma. These differences may contribute to the wide range in the estimated PAR%. Nonetheless, the median value of 15% is a reasonable estimate of the occupational contribution to the population burden of adult asthma. It is further supported by two recent studies from Canada and one from Finland published after the review presented here was completed (109, 140, 141). Moreover, the recently published review cited previously here (139), which included a wider range of methodologies (e.g., extrapolations from registry data and theoretical estimates), arrived at a similar range of values, as did a subsequent independent review (142).

4.2. COPD PAR

As noted earlier in this document, the lack of standardization of definition for COPD complicates the determination of the PAR% due to occupational exposures. Although a number of documents on the assessment and management of COPD have been published recently, there has been a lack of standardization

TABLE 2. CHRONIC BRONCHITIS: POPULATION-ATTRIBUTABLE RISK DUE TO OCCUPATION

Reference Number	Type of Study	Age Range	Sex	Number of Subjects/ Number of Cases	Disease Definition	Type of Exposure	PAR% Reported	PAR% Calculated 1	PAR% Calculated 2
(108)	Population study of six cities in the United States	25–74	M/F	8,515/963	Chronic phlegm	Dusts	26	11	12
			M/F	8,515/961	(3+ months of the year)	Gases/fumes	19	8	7
			M/F	8,515/1,015	Chronic cough	Dusts	24	9	8
			M/F	8,515/1,066	(3+ months of the year)	Gases/fumes	23	11	10
(146)	Population study of seven French cities, PAARC	29–59	M	8,692/508	Chronic phlegm (Phlegm 3 months every year)	Dusts, gases/fumes		16	15
			F	7,772/161		Dusts, gases/fumes		17	20
			M	8,692/1,036	Chronic cough (cough 3 months every year)	Dusts, gases/fumes		11	11
			F	7,772/407		Dusts, gases/fumes		8	8
(148)	Population study of Cracow followed for 13 years	19–70	M	920/350	Chronic phlegm (most days 3 months ⩾ 2 years)	Dusts		19	19
			F	1,280/175	Chronic bronchitis (as chronic phlegm + chronic cough)	Dusts		9	8
(118)	Population study of Po Delta area in North Italy	18–64	M	1,027/150	Chronic phlegm	Dusts, gases, fumes		14	17
			M	1,027/159	Chronic cough	Dusts, gases, fumes		15	18
			M	1,027/29	COLD (emphysema and/or chronic bronchitis)	Dusts, gases, fumes		24	29
(119)	Population study of Hordaland county in Norway	15–70	M/F	4,469/887	Phlegm when coughing, morning cough (cough or clear throat in morning)	Dusts or gases	15	18	21
			M/F	4,469/895		Dusts or gases	17	19	14
			M/F	4,469/409	Chronic cough (cough 3+ months in a year)	Dusts or gases	11	16	15
(126)	Population study of three Chinese areas	40–69	M/F	3,606/877	Chronic phlegm (3 months of the year)	Dusts		8	8
			M/F	3,606/876	Chronic cough (3 months of the year)	Gases/fumes		4	4
			M/F	3,606/632		Dusts		9	9
(112)	Cohort study of Zutphen (Dutch contribution to the Seven Countries Study)	40–59	M/F	796/233	CNSLD (cough or phlegm 3+ months, or wheezing and shortness of breath reported to the physician, or diagnosis of CNSLD by physician)	Dusts, gas, fumes		15	15
(113)	Population study of 5 Spanish areas (ECRHS)	20–44	M/F	1,735/206	Chronic phlegm (> 3 months)	High gases/fumes		9	20
			M/F	1,735/259	Morning cough	High mineral dusts		9	18
			M/F	1,735/248	Chronic cough (> 3 months)	Low biologic dusts		6	8

Definition of abbreviations: ECRHS = European Community Respiratory Health Survey; PAARC = Pollution Atmosphérique et Affections Respiratoires Chroniques/Air Pollution and Respiratory Diseases; PAR% = magnitude of the population attributable risk.

of definition of airways obstruction in terms of a set reduction of FEV_1/VC or FEV_1/FVC (5, 143–145). Moreover, relatively few studies have been conducted with the specific purpose of determining the occupational contribution to COPD in the general population. Of the studies that have been reported, there has been no consistency in terms of a strict definition of COPD. Some have presented data on symptoms and diseases. Others have presented data on lung function, and a few have done both. Although a certain degree of standardization has been accomplished for cough and phlegm, dyspnea is defined more variably among the studies. As noted previously for asthma, occupational exposures were characterized in different ways, although most commonly through a very broad definition of exposure. Given that COPD is a very important cause of mortality in the United States and Europe (and thus an important endpoint for estimating total burden of disease), the lack of mortality studies is an unfortunate gap in the knowledge base.

Very few studies reviewed actually reported COPD PAR% due to occupational exposures. Most studies have reported ORs or RR of symptoms, a reported condition, or lung function abnormalities estimated in association with occupational exposures. As was done previously for asthma, the PAR% was calculated using Equation 1 when the prevalence of occupational exposure among cases was known and Equation 2 when the prevalence of occupational exposure in the population was known.

Eight articles were identified in which PAR% for chronic bronchitis was either reported or data were presented from which it could be calculated (Table 2) (67, 108, 112, 113, 118, 146–148). Of the eight articles, only two reported a PAR%, calculated by methods different than the equations given previously here (108, 146). Six of the studies were cross-sectional, and two were longitudinal. The definition of disease and exposure varied among the eight studies. Reported PAR% estimates ranged between 11% and 26% (median 19%), whereas PAR% calculated with Equation 1 ranged between 4% and 24% (median 15%) and with Equation 2 between 4% and 29% (median 15%). For the Zutphen study (112), the PAR% values were also calculated for the association of chronic nonspecific lung disease with these exposures: solvents, 6%; dust, 9%; high dust exposure, 6%; at least one exposure, 15%.

Five publications were identified in which the PAR% for

TABLE 3. LUNG FUNCTION IMPAIRMENT: POPULATION ATTRIBUTABLE RISK CAUSED BY OCCUPATION

Reference Number	Type of Study	Age Range	Sex	Number of Subjects/ Number of Cases	Lung Function	Type of Exposure	PAR% Reported	PAR% Calculated 1	PAR% Calculated 2
(108)	Population study of six cities in the United States	25–74	M/F	8515/137	$FEV_1/FVC < 60\%$	Dusts	34	14	14
			M/F	8515/135		Gases, fumes	12	NS	
(118)	Population study of Po Delta area in North Italy	18–64	M	763/180	$FEV_1/FVC < 70\%$ or $FEV_1 < 70\%$	Dusts, gases, fumes		9	12
(149)	Population study of four areas in New Zealand (phase of ECRHS survey)	20–44	M/F	1132/24	$FEV_1/FVC < 75\%$ and chronic bronchitis symptoms	Dusts, gases, fumes	19	56	55
(113)	Population study of five Spanish areas (phase of ECRHS survey)	20–44	M/F	1735/34	$FEV_1/FVC < 70\%$	High mineral dusts		19	35
(156)	Population study of Tucson area	>18	M	1195/96	FVC < 75% predicted or FEV1/FVC ratio < 80% predicted	Dusts, gases, fumes		19	19

Definition of abbreviations: ECRHS = European Community Respiratory Health Survey; NS = not significant; PAR% = magnitude of the population attributable risk.

lung function impairment consistent with COPD was either reported or data were presented from which it could be calculated (Table 3) (108, 113, 118, 149, 150). Of the five studies, only two reported PAR%, calculated by methods different than the equations given previously here (108, 149). All five of the studies were cross-sectional. The definition of lung function impairment and exposure varied among the five studies. Reported PAR% ranged between 12% and 34% (median 19%), whereas the PAR% calculated with Equation 1 ranged between 9% and 56% (median 19%) and with Equation 2 between 12% and 55% (median 18%).

Table 4 lists six publications in which PAR% for other respiratory symptoms was either reported in the individual articles or calculated for this review (67, 108, 118, 146, 147, 149). Of these six articles, only two reported PAR%, calculated by methods different than the equations given previously here (108, 146). All six studies were cross-sectional ones. The definition of symptoms and exposure varied among the six studies. The reported

TABLE 4. OTHER RESPIRATORY SYMPTOMS: POPULATION ATTRIBUTABLE RISK CAUSED BY OCCUPATION

Reference Number	Type of Study	Age Range	Sex	Number of Cases	Symptom Definition	Type of Exposure	PAR% Reported	PAR% Calculated 1	PAR% Calculated 2
(108)	Population study of six cities in the United States	25–74	M/F	8,515/579	Breathlessness (shortness of breath when walking slower than others of one's own age on level ground)	Dusts	36	15	16
			M/F	8,515/582		Gases/fumes	28	11	11
			M/F	8,515/511	Persistent wheeze (wheezing on most days or nights)	Dusts	33	14	14
			M/F	8,515/521		Gases/fumes	27	9	8
(146)	Population study of seven French cities, PAARC	29–59	M	8,692/651	Dyspnea 2+ (breathlessness when walking with other people of the same age on level ground)	Dusts, gases/fumes		14	13
			F	7,772/959		Dusts, gases/fumes		12	13
			M	8,692/1,442	Wheezing (any time)	Dusts, gases/fumes		17	18
			F	7,772/938		Dusts, gases/fumes		13	14
(118)	Population study of Po Delta area in North Italy	18–64	F	608/18	Dyspnea 2+ (shortness of breath when walking on level ground with persons of the same age or stopping for a breath while walking at the subject's own pace on level ground)	Dusts, gases, fumes		29	30
(119)	Population study of Hordaland county in Norway	15–70	M/F	4,469/479	Breathlessness 2+ (definition not reported)	Dusts or gases	15	15	21
			M/F	4,469/886	Occasional wheezing (definition not reported)	Dusts or gases	16	19	21
(126)	Population study of three Chinese areas	40–69	M/F	3,606/806	Breathlessness (shortness of breath when walking with other people of one's own age on level ground)	Dusts		10	11
			M/F	3,606/807		Gases/fumes		5	6
			M/F	3,606/244	Wheeze (wheezing on most days or nights)	Gases/fumes		10	11
(149)	Population study of four areas in New Zealand (phase of ECRHS survey)	20–44	M/F	1,609/227	Shortness of breath 1+ (shortness of breath when hurrying on level ground or walking up a slight hill)	Dusts, gas, fumes		22	23

Definition of abbreviations: ECRHS = European Community Respiratory Health Survey; PAARC = Pollution Atmosphérique et Affections Respiratoires Chroniques/Air Pollution and Respiratory Diseases; PAR% = magnitude of the population attributable risk.

PAR% ranged between 15% and 36% (median 28%) for dyspnea and between 16% and 33% (median 27%) for wheezing. The PAR% calculated using Equation 1 ranged between 5% and 29% (median 14%) for dyspnea and between 9% and19% (median 14%) for wheezing; the PAR% using Equation 2 ranged between 6% and 30% (median 13%) for dyspnea and between 8% and 21% (median 14%) for wheezing.

Based on the results of the community or general population studies summarized in Tables 2–4, the occupational exposures account for a substantial proportion (i.e., from 10–20%) of either symptoms or functional impairment consistent with COPD. There are major differences among the reviewed studies in their design features, including study population, characterization of exposure, and definitions of symptoms and functional impairment. These differences may contribute to the range in the estimated PAR%. Because there are fewer studies providing data for our estimate of the PAR of COPD due to occupation than for the similar estimate for asthma (21 versus 10), there is relatively greater uncertainty about the former estimate. Nonetheless, a value of 15% is a reasonable estimate of the occupational contribution to the population burden of COPD.

The results of two recent studies published after the review presented here was completed have confirmed that occupational exposures contribute to chronic bronchitis (151, 152). A longitudinal analysis of European Community Respiratory Health Survey data from 14 industrialized nations showed that chronic bronchitis was associated with occupational exposures to irritating dusts, fumes, gases, or vapors (prevalence ratios: 1.3 in nonsmokers, 1.8 in ex-smokers, and 1.7 in current smokers) (151). Although an association between occupational exposures and fixed airflow limitation was not evident in these data, there was also little effect of smoking alone on lung function. The authors noted that the lack of effects on lung function can probably be explained by the relatively young age of their subjects, among whom substantial declines in lung function were not yet evident. Another recently published cross-sectional analysis of data from approximately 3,400 Copenhagen men confirmed associations between chronic bronchitis and smoking (OR, 2.4), occupational smoke inhalation (OR, 1.7), long-term dust exposure (OR, 1.5), and long-term exposure to organic solvents (OR, 1.5) (152). The results of these two studies are consistent with the estimated PAR for occupational contribution to COPD presented previously here.

5. PERSPECTIVE: RESEARCH, POLICY, AND CLINICAL PRACTICE

The preceding sections have delineated the extent and impact of the occupational contribution to the burden of obstructive airway disease. A careful review of the literature demonstrates that approximately 15% of both asthma and COPD is likely to be work related, and a conservative estimate of the annual costs of this occupational asthma and COPD is nearly $7 billion in the United States alone (153). The implications of this substantial occupational contribution to asthma and COPD must be considered in the setting of research agendas, in public policy decision-making, and, above all, in clinical practice.

The agendas of both epidemiologic and bench investigation should address the critical research needs in the arena of work-related airway diseases. Better understanding of the biologic mechanisms and better quantification of the risk factors involved in occupational asthma and COPD are vital to their prevention. Moreover, many of the key occupational exposures associated with obstructive airway disease may actually serve as models from which to derive basic insights of asthma and chronic obstructive lung disease. Examples include high molecular weight antigens in IgE-mediated allergic asthma, low molecular weight antigens in non-IgE dependent sensitization, acute irritant exposures in nonallergic asthma, cotton and grain dust in COPD, cadmium in emphysema, and vanadium in bronchitis. A specific recommendation of this committee is that one or more multisponsored workshops be convened to develop research agendas for both occupational asthma and occupational COPD.

Public policy needs to be better informed about the roles of occupational factors in obstructive airway disease. This will require active education and outreach on the part of the medical–scientific community. Specific public policy issues to be re-examined in light of the magnitude of the occupational contribution to the burden of airway disease include standard setting for exposure in and out of the workplace, attribution criteria for compensation, health care costs and their assignment, and health care resources allocation.

The clinician must be aware of the potential occupational etiologies for obstructive airway disease and consider them in every patient with asthma or COPD. Identifying occupational risk factors on the individual level is important for prevention of disease before it is advanced and for modifying disability risk once disease is established (154–156). In addition, the clinician has a critical role in case identification for the purposes of public health surveillance and appropriate work-related insurance compensation. Thus, the modern clinician would be wise to heed the following admonition by Ramazzini from the 16th century: "When a physician visits a patient, he ought to inquire into many things, by putting questions to the patient and bystanders . . . to which I would presume to add . . . what trade is he of . . . But I find it very seldom minded in the common course of practice, or if the physician knows it without asking he takes little notice of it: Though at the same time a just regard to that, would be of great service in facilitating a cure" (157). Researchers and policy makers would do well to develop an equivalent question to be asked in the language of their respective disciplines.

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6. APPENDIX: METHODS USED FOR CALCULATION OF THE PAR

If a report did not present the PAR but did provide an adjusted RR and sufficient data to estimate the proportion of the population exposed, then we have computed the PAR. If information was sufficient to estimate the proportion of cases exposed (p_c), we used the preferred formula:

$$\mathrm{PAR} = \frac{p_c(\mathrm{RR} - 1)}{RR} \quad (1)$$

The second approach to PAR calculation is to estimate the excess number of cases among exposed workers as a fraction of the total in a population using information about the number exposed and the risks of disease in the exposed and unexposed. The ratio of the excess cases among the exposed, $N_1(R_1 - R_0)$, to the total number of cases, $N_1R_1 + N_0R_0$, is usually estimated from the proportion of the population exposed ($p = N_1/[N_1 + N_0]$) and their RR, where N_0 and N_1 are the number of unexposed and exposed persons, respectively, and R_0 and R_1 are their risks of disease (115). Thus, the PAR can be calculated from the following formula:

$$\mathrm{PAR} = \frac{N_1(R_1 - R_0)}{N_1R_1 + N_0R_0} = \frac{p(RR - 1)}{p(RR - 1) + 1} \quad (2)$$