# 26 Chronic obstructive airway disease due to occupational exposure

*Paul D. Blanc, Eva Hnizdo, Kathleen Kreiss, and Kjell Toren*

## CASE SCENARIOS

The patient is a 68-year-old male presenting with progressive dyspnea of 5-year duration and shortness of breath with one flight of stairs or with carrying groceries uphill. He denies dyspnea at rest, is without paroxysmal symptoms, and has only occasional complaints of wheezing.

He was an active cigarette smoker from age 14–30 with a maximum of 1½ packs per day (24 pack-years total), quitting 40 years previously. He had done extremely dusty work with exposure to copious amounts of inorganic dust. This involved grinding large concrete display tanks as an exhibit preparator in an aquarium, work which he performed for 7 years. He reported less exposure over the following 5 years at which point he retired due to age. The work was sufficiently dusty that there was a spirometry-based workplace respirator fit testing program as part of his employment, even though he did not use any personal protective equipment on a routine basis. Because of abnormal findings on serial lung function testing, he was told at the time to consult his private physician regarding his results, but he did not do so.

On initial examination he is thin but not cachectic, with a prolonged expiratory phase but no wheezes or rhonchi. There is no increased pulmonic component to the second heart sound and no clubbing of the extremities. Initial pulmonary function testing (PFT) demonstrates obstruction without reversibility and a reduced diffusing capacity for carbon monoxide (DLco) that does not improve substantially adjusted for the observed lung volume (VA) (DLco, 59% height and age predicted; DLco/VA, 69% predicted). Follow-up PFTs after a course of systemic corticosteroids do not demonstrate any improvement. A computed tomography scan of the chest demonstrates bilateral lower lobe-predominant emphysema. A serum alpha-1-antitrypsin (A1AT) assay documents a "ZZ" phenotype and a quantified value of 24 units (normal ≥90).

Employment-based serial spirometry over 12 years of employment is available through his workplace respirator-fit surveillance program, along with nearly 5 years of subsequent follow-up data after his initial presentation for medical evaluation (following a 6-year data gap). Based on 18 serial measurements taken over 241 months, the patient's forced expiratory volume in one second ($FEV_1$) fell by 77 mL/yr. Using the US National Institute for Occupational Safety and Health (NIOSH) Spirometry Longitudinal Data Analysis (SPIROLA) software for analysis of lung function time trends, the change in $FEV_1$ during the employment exposure period (−128 mL/yr) demonstrates an accelerated decline relative to projected normal (−42 mL/yr), crossing the 95th percentile lower limit of normal (LLN) approximately midway in this dusty exposure period. After retirement and in the context of discontinued exposure, the $FEV_1$ remained below the LLN, but with a decline (−46 mL/yr) near the expected (1).

## INTRODUCTION

Long before personal cigarette smoking was widespread, medical writers recognized that "dusty trades" were associated with various lung diseases. "Miner's phthisis" was prototypical of such diseases. This and related conditions (e.g., "grinder's rot") were associated with exposure to inorganic dusts and can best be understood by today's nosology as one or another of the pneumoconioses (with or without superimposed tubercular disease). Clinical syndromes consistent with chronic bronchitis or airway obstruction, in particular among persons experiencing heavy organic dust inhalation, were already well described throughout the 19th century (2,3).

By the mid-20th century, occupational exposures in the various dusty trades were generally presumed to be contributors to chronic bronchitis specifically and, by extension, to airway disease more broadly defined. For example, a key 1953 analysis of mortality data from the 1930s found that work in dusty trades, even within the same social class, was linked to bronchitis mortality (4). In 1958, Fletcher noted that "men who work in dusty trades, especially coal miners, have a higher prevalence of symptoms of bronchitis and emphysema...." (5). In the early 1960s, the "Dutch hypothesis" was articulated, holding that bronchitis and chronic airflow obstruction fell along a spectrum, with the ultimate pathophysiological manifestations of disease dependent on a combination of host and environmental factors (6). Fletcher's landmark studies, which came to downplay the role of chronic bronchitis in the progression of airway obstruction, coincided with the ascendancy of cigarette smoking as a major independent risk factor for airflow limitation-defined chronic obstructive pulmonary disease (COPD). This fit in with the "British hypothesis," which viewed COPD and asthma as separate processes with distinct causal pathways (7). The paramount importance of smoking in COPD tended to eclipse all other potential associations. This was especially

true of consideration of possible links between occupational exposures and COPD, with or without concomitant chronic bronchitis.

Since the late 1960s and particularly throughout the 1970s, a number of industry-specific cohort studies, particularly of investigations of mining populations, accumulated data on progressive airflow decline associated with coal and inorganic dusts (predominantly silica, in particular the gold mining industry in South Africa, where COPD in this industry was recognized as work-related in the 1970s). The textile industry was also extensively studied during this period, in particular the associated disease process of byssinosis. Although this disease process was clearly manifested as airflow limitation, it has typically been approached as a variant of occupational asthma rather than a model of work-related COPD, in part because of the reversibility of obstruction in the early stages of the disease and the lack of a link between byssinosis and emphysema (8). Industry-specific occupational exposure to cadmium proved to be an important source of data relevant to emphysema pathogenesis (9).

Earlier, large population-based cross-industry studies of symptoms and lung function provided an important set of additional insights into the question of occupation in relation to COPD. These investigations treated occupational factors as little more than a controlling cofactor to be considered in multivariate modeling that focused on cigarette smoking and ambient air pollution. Despite this limitation, these studies yielded surprisingly consistent findings of a link between higher exposure jobs as a group and bronchitis or airflow obstruction. Thus, beginning in the mid-1980s, wider biomedical interest grew in the potential role of occupational exposures in the causation of chronic bronchitis, COPD, and emphysema. The seminal work of Dr. Margaret Becklake was critical in this regard. Early on, she had observed the association of airway obstruction of irritant gas inhalation among miners exposed to explosive blast fumes and had also shown that lung function decline among gold miners need not be linked to the extent of radiographic disease (10,11). Beginning in 1985, she authored a series of reviews and informal meta-analyses systematically compiling the epidemiological evidence that had been accumulating in the medical literature (12–16). Initially, this work relied on findings reported from industry-specific cohort studies, in particular coal miners, showing airflow decline or pathologically confirmed emphysema. It later widened to multiple large population-based studies, all showing that a longitudinal decline in airflow or a greater prevalence of airflow obstruction was associated with work-related inhalation of gases and vapors or fumes and dust or both categories of exposure.

Other reviews followed on this work (17–21). A major systematic review by the American Thoracic Society (ATS) published in 2003, for which Dr. Becklake was a coauthor, marked a turning point in the general recognition of the occupational contribution to COPD (22).

Over time, the Dutch and British hypotheses have come to be seen less as polar opposites and more as constructs that both can be applied to questions of COPD and asthma, each construct yielding its own potential insights (23). The inclusion of a chapter devoted to chronic airway disease in this book on occupational asthma, first introduced with the third edition of this text (24), underscores this more inclusive view. This chapter also takes into account the evolving recognition that along with COPD, chronic bronchitis, and emphysema, bronchiolitis is another occupationally related form of airflow obstruction, and moreover, of emerging importance. In this chapter, we will first present the epidemiological evidence linking occupation to COPD from a population-based perspective, including review of the population attributable fraction (PAF) of worked-related COPD and chronic bronchitis. Next, we will review the literature for industry-specific cohorts exposed to coal dust, inorganic dusts, and selected metal fumes. Finally, we will discuss occupationally related bronchiolitis syndromes following acute and longer term inhalation exposures. Organic dusts, such as cotton and grain, are addressed in a separate chapter in this volume (see chapter 25) that considers both asthma-like responses and less-reversible airflow obstruction in relation to such exposures.

## COPD FROM AN EPIDEMIOLOGICAL PERSPECTIVE

### Defining Disease and Measuring Risk

COPD is defined by airflow limitation that, in practical terms, requires spirometric assessment. The criteria for carrying out spirometry and the application of cut points for abnormality are discussed elsewhere in this volume and have been the focus of position papers by relevant international professional societies. A standardized definition of COPD, staged by severity, has also been attempted through the application of the Global Initiative for Obstructive Lung Disease (GOLD) criteria. Beyond lung function-based definitions of airflow limitation, emphysema can be defined by computerized tomographic (CT) or pathological criteria (although inferences can also be drawn from diffusing capacity measurements) and chronic bronchitis can be defined by standardized questionnaire responses (although pathological criteria can be applied, for example, using airway biopsies). Despite these distinctions, the label "COPD" is often applied imprecisely in clinical practice and can be driven by diagnostic biases that are particularly relevant to occupationally related COPD. The clinical diagnosis of COPD is more likely to be given if linked to a history of cigarette smoke exposure. When another respiratory condition is present that might account for fixed airflow obstruction, for example, long-standing asthma in a nonsmoker, the concomitant diagnostic label of COPD may not be applied. When emphysema is present along with airflow obstruction, a patient may simply be told of the former diagnosis but not receive a label of "COPD." Of note, occupational factors in emphysema are generally not considered in clinical practice, even in the context of A1AT deficiency (exposure that was clearly relevant to the case scenario presented). When chronic bronchitis is combined with COPD, the latter diagnosis alone is frequently applied, and chronic bronchitis may not be captured even in medical records.

For epidemiological research studies that include the direct collection of spirometric data in the field, airflow limitation can be quantified directly. In epidemiological research and clinical outcomes studies using other methods (e.g., questionnaire-based survey or interrogation of electronic medical record data), the case definition of COPD may have to take into account the clinical bases noted above, as well as the availability of ancillary data. Thus, COPD, emphysema, and chronic bronchitis, even though separate diagnostic entities, are sometimes studied together as a mixed diagnostic group, with condition-specific subcategories stratified insofar as the data allow. This is particularly relevant to the question of emphysema, given that even epidemiological studies that have carried out spirometric assessment may not have carried out systematic CT scanning. A related, more overarching category of chronic obstructive lung disease (COLD) includes asthma along with the previous three conditions. The COLD categorization will not be considered further in this discussion.

The epidemiological perspective on COPD in relation to occupational factors focuses on associations of risk, most through estimation of relative risk (RR) and a related measure, the odds ratio (OR). The study of occupationally related COPD has also been informed by estimations of population attributable risk percent, which is also known as the population attributable fraction (PAF). This measure integrates the magnitude of the RR or OR together with the prevalence of exposure to the risk factor in question among populations. For example, a putative risk factor (Exposure I) may be associated with a markedly elevated RR/OR for COPD, but this exposure may be limited to a small proportion of the population at large. Under that scenario, the actual number of COPD cases induced by (attributed to) Exposure I may be quite small. Were another risk factor for COPD (Exposure II) to have a much lower RR in absolute terms but be far more common, the number of cases induced by it could be much greater. The epidemiological calculation of the PAF can be performed using various algebraic equations and this can be done post hoc using published risk and exposure prevalence data. Whatever the method of calculation, the PAF provides an important estimate of disease caused, at least in part, by the factor in question. Another way of considering this question is to ask what burden of disease would be removed were this factor eliminated. Further, because two factors may act upon each other to magnify risk, removing either one could reduce the burden of disease. Indeed, the PAF values estimated for multiple risk factors for the same outcome may yield a combined value of more than 100%. This is particularly relevant to considerations of combined occupational exposure and cigarette smoking in COPD causation.

### The Occupational Burden of COPD

The ATS statement, Occupational Contribution to the Burden of Airway Disease, noted previously, provided a benchmark systematic review of the occupationally associated PAF for COPD (22). Although published in 2003, it reviewed data through 2000 only, emphasizing population-based studies across populations rather than industry-specific cohorts.

Table 26.1 summarizes the ATS findings on the occupational PAF in relation to COPD based on spirometry, breathlessness by questionnaire (as a surrogate for COPD), and chronic bronchitis. As the table shows, the epidemiological cohorts analyzed included a large subject pool and all the analyses were smoking adjusted. The ATS concluded that 15% was a reasonable estimate of the work-related burden of COPD.

A number of reviews and editorials on the question of occupational factors in COPD have followed the publication of the ATS Statement (25–31). As importantly, the pace of new epidemiological research addressing this topic has increased rapidly. This led to a follow-up, 2007 systematic review of 14 additional publications, most of which had appeared since the previous ATS analysis (32). These further findings, summarized in Table 26.2, were in line with the previous literature.

Of note, additional data have emerged, specifically addressing the occupationally associated PAF for COPD among never-smokers: These estimates range from 26% to 53% (33–37). Studies have also begun to address the potential interaction between work exposures (which can be defined as regular contact with vapors, gas, dusts, or fumes in one's longest held job) and cigarette smoking. In one of the first such analyses (using a definition of disease based on physician-diagnosed COPD, emphysema, or CB and using nonsmoking, nonoccupationally exposed subjects as the referent group), the OR for COPD was 1.4 for occupational exposure alone, 2.8 for smoking alone, and 6.2 for both risk factors combined; for COPD or emphysema, excluding chronic bronchitis alone, the effect was stronger, with estimated ORs of 2.4, 7.0, and 18.4, respectively (38). In another study that yielded an occupationally associated PAF for COPD between 13% and 33% (depending on the measure of exposure

*Table 26.1* ATS Findings on the Occupationally Associated PAF for COPD

| Outcome Studied | PAF | | Subjects | Studies |
|---|---|---|---|---|
| | Median (%) | Range (%) | *n* | *N* |
| Airflow obstruction | 18 | 12–55 | >12,000 | 6 |
| Breathlessness | 13 | 6–30 | >25,000 | 6 |
| Chronic bronchitis | 15 | 4–24 | >38,000 | 8 |

*Abbreviation*: PAF, population attributable fraction.

*Table 26.2* Additional Studies on the Occupationally Associated PAF for COPD

| Outcome Studied | PAF | | Subjects | Studies |
|---|---|---|---|---|
| | Median (%) | Range (%) | *n* | *N* |
| Airflow obstruction | 15 | 1–37 | >339,000 | 8 |
| Chronic bronchitis | 15 | 0–34 | >9,000 | 8 |

*Abbreviation*: PAF, population attributable fraction.

used), there was also a step-up in risk for combined occupational and smoking exposures: relative to no occupational exposure and no smoking, occupational factors doubled the risk of COPD, smoking alone carried a sevenfold excess risk, and combined exposure carried a 14-fold increased risk, a cross-product increase that is consistent with an additive effect (39). The combined occupational exposure and smoking effect was also assessed in a 10-year COPD incidence that also suggested an additive but not synergistic relationship for the two risks combined (40).

Other risk estimates have appeared since both the ATS and the later systematic review consistently observe a substantial contribution of work-related exposures to the burden of COPD (41–45). Studies from outside of Europe and North America are contributing to this growing body of data, including from a study from South Africa estimating that, depending on the definition of disease used, the occupational PAF for COPD ranged from 8% to 45% (44). An ecological, population-level analysis from 45 sites of three international studies (the Burden of Obstructive Lung Disease study, the Latin American Project for the Investigation of Obstructive Lung Disease, and the European Community Respiratory Health Survey) included data from developing as well as developed economies, suggesting that a 20% reduction in the burden of COPD could be achieved by an 8.8% reduction in the prevalence of occupational exposures (42). Data on occupation and COPD disease severity are sparse, but suggest a potential relationship (46,47).

## EXPOSURE TO INORGANIC DUSTS, COAL DUST, AND METAL FUMES

### Overview

Occupational exposure to inorganic dust occurs in many work settings worldwide. Occupational inorganic and coal dust exposures can be broadly categorized as strongly fibrogenic dusts (silica, asbestos, and coal) and other inorganic dusts and metal fumes that may also be associated with adverse respiratory effects (e.g., iron, emery, graphite, gypsum, marble, mica, perlite, plaster of Paris, Portland cement, silicon, silicon carbide, soapstone, talc, and welding fume particles) (48). Dust-induced pneumoconioses [silicosis, asbestosis, and coal workers' pneumoconiosis (CWP)] and associated tuberculosis have been the main non-cancer causes of morbidity and mortality attributable to highly fibrogenic dust exposure. Industry-specific epidemiological studies have demonstrated, however, that exposure to inorganic dusts, primarily the more highly fibrogenic types of dusts, in addition to their links to restrictive disease, is also associated with increased levels of obstructive lung function impairment and increased prevalence of chronic bronchitis (14,15,17,49). These associations were also shown in those with lower exposures that may not lead to radiological signs of pneumoconiosis (50,51).

There may be multiple pathophysiological mechanisms by which highly fibrogenic dusts, independent of fibrosis, may potentially initiate lung injury leading to airflow obstruction, chronic bronchitis, or emphysema considered collectively under the rubric of COPD. Upon deposition, dust particles can reach two critical target cells in the lung: macrophages and epithelial cells (52,53). Macrophage ingestion of various dust particles (phagocytosis) has been shown to lead to macrophage activation, resulting in an increased release of a wide range of products that may react with various target cells in the lung to cause tissue damage. The potential mechanisms of cell injury include cytotoxicity (53–56) leading to generation of reactive oxygen/nitrogen species (56) and secretion of proinflammatory factors (57), cytokines, chemokines, elastase (56,57), and fibrogenic factors (58,59). Dusts analyzed in terms of these mechanisms and found to be toxic include not only crystalline silica and coal dust but also kaolin, talc, bentonite, and feldspar.

In addition to macrophage-mediated effects, which include cytokine networking with epithelial cells, epithelial cells may interact directly with deposited particles. This may lead to hyperplasia of mucus-producing glands and increased mucus production in the bronchus as well as inflammatory processes in conducting and peripheral airways and in alveolar tissue leading to bronchitis (53,60) and emphysema (56,57,60–64). Particulates can also cause epithelial cell injury that facilitates penetration of the particles through the walls of small airways and localized fibrosis (58,59,65).

Mineral dust airway disease (MDAD) defined by focal fibrosis in respiratory bronchioles associated with mineral dust exposure has been reported as a pathological process causing airflow limitation in mineral dust-exposed workers (66–68). Although data on direct pathological correlates of airflow obstruction in mineral dust exposure are limited, findings of emphysema have often served as a surrogate marker for the concomitant risk of COPD in mineral dust-exposed workers. The following sections provide mainly epidemiological evidence relevant to the particular type of exposure and various COPD outcomes.

### Silica

Despite the dramatic reduction of silica dust exposure levels in most developed countries during the last century, airflow limitation and associated COPD remain worldwide health issues in workers exposed to silica dust (51,69). Epidemiological studies show that silica dust exposure can lead to airflow limitation in the absence of radiological signs of silicosis (14,15,17,51) and also that airflow limitation associated with silica dust exposure can occur in many different types of industrial operations as will be discussed in the following section.

Large studies of hard rock miners demonstrated that the $FEV_1$, forced vital capacity (FVC), and $FEV_1$/FVC ratio, adjusted for age, height, and tobacco smoking, decreased with increasing cumulative respirable dust exposure in both smokers and nonsmokers (70–76). The average loss in lung function attributable to silica dust exposure, estimated for South African gold miners exposed for about 24 years to standard exposure levels was equivalent to an average excess loss of 8–9 mL/yr of $FEV_1$ and 9.0 mL/yr of FVC (51,71–73). Decreased lung function was also observed among Canadian hard rock miners

(74), Western Australian miners (75), and US molybdenum miners (76).

Further Epidemiological studies of morbidity have affirmed that silica dust exposure also constitutes a hazard for airflow limitation in many nonmining industries (general population study of silica exposure, granite crushers, tunnel workers, construction workers, brick-manufacturing workers, slate workers, stone carvers and grinders, ceramic workers, refractory ceramic fiber, molders and coremakers handling furan resin sand, silicon carbide industry, and iron foundry and smelter workers) (77–98). A dose-dependent relationship between exposure (quantified duration of employment, dust level, or cumulative dust exposure) and lung function level or lung function decline was found in some of these studies. The effect of employment in silica dust-exposed occupations was even detected in a large general population-based cross-sectional study of Norwegian men of 30–46 years of age (77). Workers with 15 or more years of silica dust exposure had a statistically significant excess loss of $FEV_1$ of 4.3 mL [95% confidence interval (CI) 1.1–7.5] with each year of exposure; the exposure–response relationship was similar among nonsmokers, ex-smokers, and smokers.

Several mortality studies of cohorts of silica dust-exposed workers reported increased mortality from nonmalignant respiratory disease (NMRD) and COPD (99–105). Generally, NMRD combines deaths from pneumoconiosis and COPD. Some clinical studies have shown poor correlations between spirometry and profusion of nodules on the chest radiograph and CT scan, while significant inverse correlations were found between CT emphysema score and $FEV_1$ and DLCO (106–109). An exposure–response relationship between silica dust exposure and emphysema assessed on paper-mounted whole-lung sections at autopsy was also observed (110–112). Silica dust exposure appears to be associated more with emphysema than asbestos dust is (113). Nonetheless, the degree of emphysema found in silica dust-exposed miners with about 20 years of service who were never-smokers was relatively small and not correlated with lung function measured 5 years prior to death (114). However, emphysema found at autopsy was found to be the most important predictor of lung function measured 5 years prior to death in another autopsy-based study (115). In a high-resolution CT (HRCT) study of 79 construction workers, neither rounded opacities (predominant profusion of 1/0) nor cumulative dust exposure correlated with emphysema, while tobacco smoking was a significant predictor (116).

In summary, the epidemiological evidence from large studies of hard rock miners demonstrates a positive exposure–response relation for airflow limitation and silica dust exposure that is not associated with the presence of silicosis. Industry-based studies show that the silica dust-associated airflow limitation can occur in a variety of industrial settings. Any work setting associated with sufficient silica to cause pneumoconiosis should be assumed to carry risk of COPD as well. Some types or scenarios of exposure have not yet been studied well in terms of airflow limitation due to small numbers of exposed workers or because new sources of exposure have emerged only in recent years (such as sandblasting applications in the textile industry or construction work with high-crystalline silica content of artificial stone). Whatever the source of exposure, prevention in any silica dust work environment is important.

### Coal Dust

Large epidemiological studies of British, US, and Italian coal miners have established the existence of an exposure–response relationship between cumulative coal dust exposure and decreased lung function, respiratory symptoms, and mortality (50,117–130). The association has been seen among smokers, ex-smokers, and never-smokers, and across all age groups. Studies demonstrated that the severity of the impairment associated with coal mining dust exposure puts coal miners at an increased risk of clinical COPD comparable to smoking. Because of this evidence, COPD (i.e., chronic bronchitis and emphysema) became a compensable occupational disease among coal miners in some countries. Moreover, there is epidemiological evidence, showing that current permissible concentrations of coal mining dust (2 $mg/m^3$ in the USA) can increase the risk of COPD, especially in the absence of CWP (50).

Several industry-wide surveys of more than 30,000 British coal miners, initiated during 1953–1958 with follow-up studies up to 1991, have shown excessive dose-dependent losses of $FEV_1$ with cumulative dust exposure independent of the presence of CWP; the loss was found to be greatest in younger men and in men with respiratory symptoms (117–123). Investigating the severity of the impairment associated with coal dust exposure, a study reported that the risks of having symptoms of chronic bronchitis and $FEV_1$ <80% predicted and <65% predicted were almost doubled in men with the highest exposure category of 348 gram-hours per cubic meter ($ghm^{-3}$) (122). The excess loss of $FEV_1$ persisted even after dust levels were substantially reduced in coal miners employed after 1970 (50,124). British studies of miners who did not have radiological signs of pneumoconiosis also found that adjusted $FEV_1$ was on average 155 mL (95% CI 74–236 mL) lower in miners than in population controls (50).

The findings of the National Study of Coal Workers' Pneumoconiosis (NSCWP) in USA coal miners were similar (125–127); in addition, coal mining dust was also associated with higher rate of decline in lung function (126,127). Other occupational risk factors associated with excessive rate of decline in lung function included work practices such as lack of use of respiratory protection, participation in explosive blasting, roof bolting, and use of dust control sprays that used water that had been stored in holding tanks (128). Furthermore, excessive decline in $FEV_1$ of 60 mL/yr or more was associated with early retirement from coal mining, increased risk of respiratory morbidity, and increased mortality from nonmalignant respiratory disease (129). An exposure–response relationship of airflow obstruction and coal mining dust was also found in a longitudinal study of Italian coal miners (130). Relationships between exposure to coal mining dust and increased mortality from COPD have also been found in British, US, Indian, and Dutch coal miners (129,131–135). Among new Chinese coal

miners, a sharp early decline in $FEV_1$ during early ages is associated with the development of bronchitic symptoms (136). Autopsy studies of coal miners find typical focal emphysema caused by coal dust deposition forming the coal macula (137–139). Severity of emphysema in coal miners can be comparable to that of tobacco smoking (139). In summary, studies show a positive exposure–response relationship between various outcomes of COPD (morbidity and mortality) and coal mining dust exposure. It has been estimated that 8.0% (95% CI 3.4–13.7%) of nonsmoking coal miners with a cumulative respi-rable dust exposure of 123 ghm $^3$ (considered equivalent to 35 years of work with a mean respirable dust level at current allowed limits of 2 mg/m$^3$) could be expected to develop a clinically important (>20%) loss of $FEV_1$ attributable to dust (17). Among smoking miners, the estimate attributable to dust was 6.6% (95% CI 4.9–8.4%) (17). The combined effect of dust and smoking can potentially account for a large number of cases of COPD attributable to dust through the combined effect (140). Coal mining dust contains predominantly coal dust, a fossil organic material; it can, however, also contain high degree of silica from adjacent rocks. The concomitant presence of silica can complicate the analysis and interpretation of exposure–response relationships for coal dust and obstructive lung deficits.

### Asbestos

Historically, occupational exposure to asbestos dust occurred most heavily in mining and quarrying, asbestos products manufacturing, and workplaces where asbestos was used for its heat insulation properties (e.g., shipyards). In the presence of asbestosis, lung function impairment associated with asbestos dust exposure is primarily a restrictive ventilator deficit (141,142). Nonetheless, multiple epidemiological studies have shown that exposure to asbestos can be associated with obstructive as well as restrictive lung function impairment (143–150). This suggests that asbestosis-related functional changes can be coexistent with dust-related airway disease. In a longitudinal study, workers with heavy asbestos exposure had a steeper decline in both $FEV_1$ and FVC in comparison to workers exposed to cement and polyvinyl chloride; this steeper decline was found in nonsmokers and smokers (149). Other occupational groups potentially exposed to asbestos and investigated for asbestos-related lung function impairment that could include obstructive deficits were electricians (151), boilermakers (152), and plumbers and pipefitters (153) from the construction industry in Edmonton, Canada.

### Portland Cement and Other Inorganic Dusts and Fume

A variety of dusts that are less fibrogenic than coal, silica, and asbestos nonetheless have been found to be associated with airflow limitation. Some studies reported significantly lower $FEV_1$% values in workers exposed to cement in comparison to unexposed workers, suggesting that exposure to occupational factors in cement plants may lead to obstructive impairment (154–157). One of these studies also reported very high respirable dust exposure >40 mg/m$^3$. However, in two other studies, no relationship between exposure to Portland cement dust and airflow limitation was found (158,159). These results suggest that exposure levels may play an important role in disease causation with Portland cement exposure. It should also be noted that Portland cement manufacture is also associated with irritant gas (sulfur dioxide) exposure; thus, cement exposure may be as relevant to the epidemiology of irritant gas as inorganic dust exposure. Finally, it is also important not to confuse cement with concrete dust exposure, the latter being a source of silica as well; the clinical relevance of concrete dust is highlighted by the clinical case scenario presented at the outset, specific to A1AT deficiency, but also generalizable.

Airborne exposures associated with welding fume include inorganic materials such as volatilized metal and submicron particles from both the welding rod and the base metal being welded; fume from burning metal coatings, shielding gases, fluxes; and, often, dust or other airborne inorganic contaminants present in the surrounding workplace (historically, for example, asbestos from "welding blankets"). The nature and extent of exposures experienced by welders have been reviewed by many authors and have been shown to vary widely and are often in excess of regulated occupational exposure limits or guidelines (160–165). Most welding materials are alloy mixtures of metals characterized by different steels that may contain iron, manganese, chromium, and nickel. Animal studies have indicated that the presence and combination of different metal constituents is an important determinant in the potential pneumotoxic responses associated with welding fumes (164,165).

Gas inhalation can also be important in welding, especially exposure to oxides of nitrogen—this gas is addressed in a later section of this chapter in relation to bronchiolitis obliterans (OB). Some welders experience acute airflow obstruction demonstrated by changes in airflow rates over a work shift (166,167) or changes in nonspecific bronchial responsiveness in response to welding exposures (168).

Laboratory studies have provided evidence that welding exposure is linked to oxidative stress, thus providing mechanistic support for the hypothesis of inflammatory-mediated airway obstruction (169–171). Epidemiological studies have shown that welders experience increased cough and phlegm in association with measures of increased cumulative exposure to welding (172,173); however, one study found that bronchitis symptoms were reversible and not associated with lung function decline over a subsequent 3-year period (166). The possibility that the inflammatory response to welding fume components may be lessened by the development of "tolerance" has been suggested (174).

Evidence of chronic airflow obstruction in relation to measures of welding exposure has been seen in most but not all studies designed to investigate this outcome. Several investigations of shipyard welders and burners found dose-related increased chronic bronchitis symptoms and airflow obstruction, especially among welders who were current or former

smokers (175–177); one study also reported functional changes in small airways among nonsmoking welders (178), and in a longitudinal investigation of the same population of shipyard welders and burners in which welding-related functional abnormalities had been limited to smokers in cross-sectional analysis, Chinn and colleagues found airflow obstruction in both smokers and nonsmokers that was linked to the nonuse of local exhaust ventilation while welding. Functional changes appeared to be reversible only among those welders consistently using local exhaust ventilation (177). An earlier study of welders in the engineering industry found that welders were more likely to be absent from work due to upper respiratory tract infection and that welders who smoked had some evidence of small airway obstruction (reduced mid-maximal flow rates) compared to non-welders, but no differences were seen comparing nonsmoking welders and non-welders (179). Also relevant, a large cohort study observed a small but statistically significant welding-associated decline among nonsmokers but not current or ex-smokers (180).

In addition to welding fume, which includes a complex mix of metals as noted, certain individual metals have specific links to COPD. Vanadium is a metal that is a natural contaminant of fossil fuels and is also mined and milled for use in steel-making and other industrial applications. Vanadium appears to be a strong trigger for mucin production experimentally (181). It is associated epidemiologically with bronchitis both in vanadium plant workers and in boilermakers (182,183). Moreover, the vanadium content in oil field fires has been suspected as a contributory factor in the adverse airway effects of the acrid smoke produced in such scenarios. Cadmium exposure is causally associated with emphysema in animal exposure models (184) and is epidemiologically associated with lung function decrements consistent with emphysema in occupational exposure (9). A link between the cadmium content in cigarettes and smoking-related emphysema has been suggested (185,186).

## BRONCHIOLITIS AND RELATED CONDITIONS

### Pathological and Physiological Considerations

Bronchiolitis is an umbrella term for inflammation of the terminal airways and can subsume a spectrum of diseases. Of these, bronchiolitis obliterans (BO) is particularly relevant to occupationally related obstructive lung disease. BO involves inflammation and eventual scarring of the terminal and respiratory bronchioles. In the context of BO following exposure to toxicants, respiratory epithelial damage and sloughing are believed to be the key initial pathological events, whether the associated exposure is acute or indolent. When this evolves into fibrosis, the airways involved are obliterated, resulting in irreversible, fixed airflow obstruction that is the hallmark of BO and is poorly responsive to treatment. This is sometimes referred to as a "constrictive" BO (187). An early postacute, predominantly inflammatory cellular manifestation of bronchiolitis has been characterized as being "proliferative" and noted to be responsive to corticosteroid or other immune-modulatory interventions (188). Intermediate or transitional clinical syndromes may occur with both proliferative and constrictive manifestations.

In addition to BO in which disease of the small airways is the dominant pathophysiological manifestation of disease, there are a number of other conditions in which bronchiolitis is but one part a multicomponent process, in particular entities with prominent alveolitis or fibrosis. BO organizing pneumonia (BOOP), also referred to as cryptogenic organizing pneumonia (COP), is particularly relevant to combined airway and alveolar involvement associated with toxicant exposure. This entity includes a proliferative cellular bronchiolitis that extends into and prominently involves the alveoli. Of note, a COP-like pattern secondary to a toxicant exposure typically manifests a restrictive, rather than obstructive ventilatory deficit (the clearest example being the "Ardystil lung" syndrome) (189). The terminology as used is complicated and can be confusing, because the pathological descriptor of a "COP-like" pattern has also been applied even when the presence of proliferative inflammation is limited to the bronchioles and does not have a prominent component of organizing pneumonia.

This review of BO includes the subset of responses following acute or chronic exposures to toxicants in which a bronchiolar component is dominant. Restrictive disease in the context of an organizing pneumonia pattern characteristic of COP will not be addressed further. We will, however, address another form of bronchiolitis that is associated with a restrictive ventilatory deficit (and rarely includes alveolar damage) characterized by lymphocytic bronchiolitis, peribronchiolitis, and lymphoid hyperplasia (190). Pathologically distinct from BO or COP, lymphocytic bronchiolitis has emerged as another important occupationally related condition.

### BO Following Acute Injury

From its very first clinic-pathological descriptions, BO was associated with irritant gas inhalation scenarios best characterized by nitrogen dioxide exposure (191). Acute, high-level nitrogen dioxide exposure (which can cause fatal lung injury) leading to BO has also long been associated with explosives manufacturing or detonation (192,193). Beginning in the mid-1950s, BO as a sequela of nitrogen dioxide exposure in agriculture began to be appreciated; this scenario of nitrogen dioxide overexposure is often referred to as silo filler's disease, because it typically occurs early in the process of loading airtight silos with high nitrogen content fresh silage (acute fatal nitrogen dioxide inhalation in farming was reported even earlier, but without BO, which is a relatively uncommon aftereffect even among serious exposure events) (194–197). Nitrogen dioxide exposure leading to BO continues to be reported sporadically, including scenarios in which nitric acid interacts with metals or organic material to produce oxides of nitrogen *de novo* (198,199). Chronic airflow obstruction without documented BO has also been associated with nitrogen dioxide from explosives use, but the relationship between such occupationally related COPD and BO pathology is not clear (10).

Although nitrogen dioxide exposure has been a dominant exposure linked to acute high-level irritant inhalation and BO, there are convincing reports linking other toxicants to this pathophysiological response. These include case reports of exposure to sulfur dioxide (200), thionyl chloride (which breaks down to sulfur dioxide and hydrochloric acid) (201), bromine (202), ammonia (one case was included in a lung transplant case series) (203), and thermal breakdown by-products, including particulate fly ash (204–208). The latter heterogeneous exposure grouping underscores that gases, aerosols, and particulate exposures may each be capable of inciting a BO response. This is also consistent with a reported association between acute exposure to the heavy irritant dust environment of the World Trade Center disaster and the later development of BO (209). It should also be remembered that another obstructive airway sequela of heavy irritant exposure, in particular from thermal breakdown or combustion byproducts, is bronchiectasis. Such bronchiectasis can be combined with bronchiolitis or be an independent outcome (206,210,211). Two other exposure scenarios are also notable for their association with BO. The military use of sulfur mustard (commonly referred to as a war "gas," but actually an aerosol irritant) in the Iran–Iraq war resulted in a spectrum of respiratory tract abnormalities, including BO pathology (212,213). On the basis of epithelial sloughing and animal models, some chronic respiratory outcomes among survivors of the methyl isocyanate gassing incident in Bhopal, India, likely represent BO, even though confirmatory biopsy data have not been reported (214,215).

**Bronchiolitis Without Acute Injury**

Since 1996, three causes of occupational bronchiolitis emerged that had gone undetected for decades. These were butter flavoring-associated BO, lymphocytic bronchiolitis and peribronchiolitis in nylon flock workers, and lung disease in US military personnel exposed to sulfur mine fires in Iraq and burning of solid and human wastes in Iraq and Iran. With all of these new causes of disease, no accidental overexposures or acute injury occurred, onset was usually insidious, and no evident change in exposure was recognized (216). Even more important in obscuring potential occupational causes was the absence of work-related symptoms by either worsening of symptoms on workdays or over a workweek or improvement following prolonged absence from work. The only way these new occupational associations could be suspected was the recognition of disease clustering in a workforce. When occupational respiratory disease risk is not suspected, workplace surveillance is not undertaken, and the likelihood of a physician associating sporadic indolent cases over years with a particular workplace is low, even if the disease is rare. With recognition of disease clusters from a particular workplace, the physician must take the step of mobilizing public health authorities to investigate exposure–response relations in a worker population to substantiate that a workplace risk exists. The likelihood of a physician triggering a multidisciplinary investigation from a government entity with authority to investigate a workplace is itself low. An environmental cause of indolent OB related to ingestion of *Sauropus androgynus* for weight control presented a similar challenge for linking exposure and effect (217).

**Flavoring-Related BO**

BO in microwave popcorn workers was recognized following the report of an eight-person cluster of former workers at a small microwave popcorn manufacturing plant in 2000 (216). The cases had occurred indolently with onset over several years, and had no close temporal pattern of symptoms in relation to work or exposure cessation. A cross-sectional evaluation of the current workforce documented that 25% of workers had abnormal spirometry, with a 3.3-fold excess of obstructive and mixed obstructive and restrictive abnormalities. Cumulative exposure to the butter flavoring ingredient, diacetyl, was associated with decrements in $FEV_1$. Laboratory animal work confirmed the plausibility of diacetyl being a causative agent (218). Subsequently, industry-wide hazards of clinical BO were recognized in both microwave popcorn production and flavoring manufacture (219,220). The early epidemiological work focused on fixed obstruction and mixed obstruction and restriction, but some flavoring-exposed workforces have predominantly pure restrictive abnormalities (221). Whether other flavoring chemicals account for restrictive lung disease or whether diacetyl causes a spectrum of lung disease and spirometric physiologies from obstruction to restriction is not known. Rats exposed to 2,3-pentanedione (a common alpha-diketone diacetyl substitute) develop both intramural fibrosis (constrictive bronchiolitis) and intraluminal polypoid proliferation (222). Thus, an experimental basis exists for a spectrum of physiologies associated with flavorings exposure, as seen in microwave popcorn workers, flavoring workers, and case reports of workers with BO.

**Synthetic Flock-Related Lymphocytic Bronchiolitis**

The possibility of an occupational etiology for interstitial lung disease in two young workers making velvet-like upholstery from nylon fibers was recognized by an occupational medicine physician in Rhode Island who saw the cases at a 15-month interval (223). The cross-sectional study of the workforce identified eight cases of histologic abnormalities consistent with interstitial lung disease or having bronchoalveolar lavage inflammation. He suggested that the company contact NIOSH for a health hazard evaluation that later documented work-related risks of respiratory and systemic symptoms associated with working on a flocking range, with departmental category, and with days and hours worked per week (224). A study in five additional flock plants documented that, controlling for smoking, respiratory symptoms and repeated flu-like illnesses were associated with cleaning with compressed air and respirable dust exposure (225). A pathologist research panel reviewed biopsy material from 15 cases from five nylon flock plants in three US states and a Canadian province and documented a unique pathology of lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia represented by lymphoid

aggregates (226). The clinical presentation was of restrictive interstitial disease, and at least partial resolution over months away from work occurred in some cases. This new occupational disease was indolent in presentation over months to years of exposure and sometimes slowly reversible after exposure cessation. Workplace air contained respirable nylon particles that were much smaller than the flock used in making the product and came from the shearing off of nylon fragments during cutting of long nylon filaments into flock. Animal toxicology documented the pro-inflammatory nature of the respirable particulate from the plant, as well as lab-created nylon dust not treated with finish or dyes used in the flock plant (227). The presumption that the bronchiolitis was nylon-specific was not borne out by subsequent reports of subclinical abnormalities or cases in Turkey due to polypropylene dust (228), in Spain due to polyethylene dust (229), and in the USA in workers applying rayon flock to greeting cards (230).

### Constrictive Bronchiolitis in US Veterans of the Iraq and Afghanistan Wars

Evaluation of US soldiers with documented decrease in exercise tolerance after service in Iraq or Afghanistan yielded 38 cases with pathological constrictive bronchiolitis on thoracoscopic lung biopsy, 28 of whom had been exposed to ambient sulfur dioxide from a sulfur mine fire near their barracks (231). None of the 38 had reported symptomatic overexposure or had acute onset of symptoms; 13 had normal spirometry, lung volumes, and carbon monoxide diffusing capacity; and 19 had an isolated low carbon monoxide diffusing capacity. Three had restriction, two had obstruction, and one had mixed obstruction and restriction. Sixty-eight percent had normal HRCT. The finding of pathological abnormalities that explained their exercise intolerance suggests that constrictive bronchiolitis is likely missed in many persons, given the insensitivity of HRCT and spirometry. These findings call into question much of what we know about inhalation-induced BO, which in the historical overexposure setting was likely diagnosed only in disabling cases. The insensitivity of spirometry and chest HRCT in biopsy-documented constrictive bronchiolitis has also been confirmed in long-term follow-up of Iranian victims of mustard gas who were exposed on a single occasion (232). Previous reports of absence of long-term sequelae of acute toxic inhalation may have dismissed symptoms of dyspnea when radiology and pulmonary function studies were normal (233). In workforces with indolent BO, pathological abnormalities may exist in the many symptomatic persons whose pulmonary function tests are normal (216,224).

## FUTURE RESEARCH NEEDS

Many aspects of the relationship between COPD and occupational exposures await further investigation. For example, the relationship between occupational factors and COPD disease severity remains to be explored more fully. Further, the role of occupational factors in emphysema (as opposed to airflow obstruction) is also not well delineated. The detrimental impact of dusty work in A1AT deficiency, as highlighted in the case scenario presented at the outset, underscores the biological plausibility of this association, which has been further supported by miner autopsy studies. Beyond coal dust, silica, and asbestos, exposure-specific epidemiological studies in other cohorts, linked to experimental models, are needed to further clarify the pathophysiology of occupationally related COPD and chronic bronchitis. This is also certainly true for organic dusts, as addressed elsewhere in this text. In terms of bronchiolitis, the research agenda is rapidly evolving. For example, a possible new cause of BO ripe for investigation is the fiberglass boat-building industry. Occupational physicians and pulmonologists have assembled five cases in four boat yards, which occurred in Britain over a 20-year period (234), and this report stimulated recognition of a case in fiberglass water tower manufacture in Taiwan (235). Clearly, much remains to be investigated regarding prevention. For secondary prevention, this includes whether interventions can be based on excessive $FEV_1$ declines (yet within the normal range) in workforces with indolent bronchiolitis; for tertiary prevention, the applicability of approaches borrowed from transplant-associated BO to work-related disease remains to be assessed. For the entire range of occupationally related obstructive lung disease, further elucidation of the mechanisms of injury arising from diverse agents that can lead to such a heterogeneous group of responses remains a research priority.

## SUMMARY

Occupational exposures are relevant to obstructive airway diseases across a wide spectrum of diagnostic entities. For COPD and chronic bronchitis, the consistency of findings from multiple studies worldwide, using a variety of analytic approaches in heterogeneous populations and over a wide range of working conditions, strongly supports a causal association between occupational exposures and disease. Thus, it is reasonable to assume that 15% of COPD (3 in 20 cases) is attributable to work factors. Furthermore, as cigarette smoking declines, nonsmoking causes of COPD, including salaried and unsalaried working conditions (which can include biomass fuel cooking), will become even more prominent, an emerging importance underscored by an ATS Statement on this topic (236).

For selected mineral dusts and fumes, multiple epidemiological studies have shown an association between occupational exposure lung function impairment in both never-smokers and smokers, the latter after adjustment for smoking. There are likely to be various mechanisms by which such exposures can cause lung function impairment or chronic bronchitis. Whatever the underlying pathway, multiple epidemiological studies of large coal and hard rock mining cohorts have clearly established that both coal and silica dust are associated with obstructive impairment due to the effect of dust itself, independent of the presence of pneumoconiosis radiographically or a restrictive deficit physiologically. Data for other occupational factors are more limited due to smaller cohorts and more heterogeneous exposures.

Beyond COPD, diseases specific to the terminal airways are associated with many toxic occupational exposures. In settings of toxic inhalation, obstructive, restrictive, and mixed obstructive and restrictive spirometry have all been described. Characterization of these processes can be limited because of underrecognition of disease, lack of pathological confirmation, or even, when aggressively studied, the potential insensitivity of lung biopsy sampling in the presence of patchy terminal bronchiolar involvement in a disease process. While the causal association between BO and acute lung injury following a high-level exposure scenario is usually straightforward, the emerging recognition of indolent bronchiolitis even without an acute overexposure raises the specter that the occupational contribution to the burden of such disease may be underappreciated.

Clinicians should be alert to the possibility that COPD, chronic bronchitis, or bronchiolitis may be related to past or current occupational exposures. A history of smoking, in and of itself, does not preclude a link between work and obstructive lung disease. For fibrogenic dusts, the presence of interstitial disease radiographically or a restrictive ventilatory deficit by lung function testing does not exclude the presence of concomitant dust-related obstruction. Similarly, mixed obstructive and restrictive deficits may be seen with other scenarios as well, in particular in association with exposures suspected of causing bronchiolitis potentially within a spectrum of pathological responses. When a clinical suspicion arises that a patient may have disease that is related to a novel exposure or may be part of a larger disease outbreak of occupationally related obstructive disease from an established risk factor, reporting to public health authorities may facilitate the recognition of a case cluster in a workplace and the prevention of further disease in coworkers. In the USA, clinicians may contact the Division of Respiratory Disease Studies of the National Institute for Occupational Safety and Health (NIOSH) at 800-232-2114.

REFERENCES


1. Zutler M, Quinlan PJ, Blanc PD. Alpha-1-antitrypsin deficient man presenting with lung function decline associated with dust exposure: a case report. J Med Case Rep 2011; 5: 154.
2. Thackrah CT. The Effects of Arts, Trades, and Professions, and of Civic States and Habits of Living, on Health and Longevity, 2nd edn. London: Longman, 1832.
3. Greenhow EH. Chronic Bronchitis. Philadelphia, Pennsylvania: Blakston Son & Co, 1868.
4. Goodman N, Lane RE, Rampling SB. Chronic bronchitis: an introductory examination of existing data. BMJ 1953; 2: 237–43.
5. Fletcher CM. Disability and mortality from chronic bronchitis in relation to dust exposure. AMA Arch Ind Health 1958; 18: 368–73.
6. Vestbo J, Prescott E. Update on the "Dutch hypothesis" for chronic respiratory disease. Thorax 1998; 53: S15–19.
7. Elias J. The relationship between asthma and COPD. Lessons from transgenic mice. Chest 2004; 126: 111S–6S.
8. Honeybourne D, Pickering CA. Physiological evidence that emphysema is not a feature of byssinosis. Thorax 1986; 41: 6–11.
9. Davison AG, Newman Taylor AJ, Darbyshire J, et al. Cadmium fume inhalation and emphysema. Lancet 1988; 1: 663–7.
10. Becklake MR, Goldman HI, Bosman AR, Freed CC. The long-term effects of exposure of nitrous fumes. Am Rev Tuberc 1957; 76: 398–409.
11. Becklake MR, Du Preez L, Lutz W. Lung function in silicosis of the Witwatersrand gold miner. Am Rev Tuber Lung Dis 1958; 77: 400–12.
12. Becklake M. Chronic airflow limitation: its relationship to work in dusty occupations. Chest 1985; 88: 608–17.
13. Becklake MR. Occupational pollution. Chest 1989; 96:S372–8.
14. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 1989; 140: S85–91.
15. Becklake MR. The work relatedness of airways dysfunction. In: Proceedings of the 9th International Symposium on Epidemiology in Occupational Health. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health,[DHHS (NIOSH) Publication No. 94-112], 1992: 1–28.
16. Becklake MR. When the chest x-ray does not tell the whole story. Am J Respir Crit Care Med 2001; 164: 1761–2.
17. Oxman AD, Muir DCF, Shannon HS, et al. Occupational dust exposure and chronic obstructive pulmonary disease. Am Rev Respir Dis 1993; 148: 38–48.
18. Hendrick DJ. Occupation and chronic obstructive pulmonary disease (COPD). Eur Respir J 1994; 7: 1032–4.
19. Walter R, Gottlieb DJ, O'Connor GT. Environmental and genetic risk factors and gene-environment interactions in the pathogenesis of chronic obstructive lung disease. Environ Health Perspect 2000; 108: 733–42.
20. Burge PS. Occupation and COPD. Eur Respir Rev 2002; 12: 293–4.
21. Viegi G, Di Pede C. Chronic obstructive lung diseases and occupational exposure. Curr Opin Clin Immunol 2002; 2: 115–21.
22. Balmes J, Becklake M, Blanc P, et al. American Thoracic Society statement: occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003; 167: 787–97.
23. Eden E. Asthma and COPD in alpha-1 antitrypsin deficiency. Evidence for the Dutch hypothesis. COPD 2010; 7: 366–74.
24. Hnizdo E, Kennedy SM, Blanc PD, et al. Chronic airways disease due to occupational exposure In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Occupational Asthma, 3rd edn. New York: Marcel Dekker, 2006: 683–712.

25. Meldrum M, Rawbone R, Curran AD, Fishwick D. The role of occupation in the development of chronic obstructive pulmonary disease (COPD). Occup Environ Med 2005; 62: 212–14.
26. Balmes JR. Occupational contribution to the burden of chronic obstructive pulmonary disease. J Occup Environ Med 2005; 47: 154–60.
27. Boschetto P, Quintavalle S, Miotto D, et al. Chronic obstructive pulmonary disease (COPD) and occupational exposure. J Occup Med Toxicol 2006; 1: 11.
28. Fishwick D, Barber CM, Darby AC. Chronic Obstructive Pulmonary Disease and the workplace. Chron Respir Dis 2010; 7: 113–22.
29. Blanc PD. COPD and occupation: a brief review. J Asthma 2012; 49: 2–4.
30. Naidoo RN. Occupational exposures and chronic obstructive pulmonary disease: incontrovertible evidence for causality? Am J Respir Crit Care Med 2012; 185: 1252–4.
31. Diaz-Guzman E, Aryal S, Mannino DM. Occupational COPD: an update. Clin Chest Med 2012; 33: 625–36.
32. Blanc PD, Torén K. Occupation in COPD and chronic bronchitis: an update. Int J Tuberc Lung Dis 2007; 11: 1–7.
33. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the U.S. population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2002; 156: 738–46.
34. Mak GK, Gould MK, Kuschner WG. Occupational inhalant exposure and respiratory disorders among never-smokers referred to a hospital pulmonary function laboratory. Am J Med Sci 2001; 322: 121–6.
35. Bergdahl IA, Torén K, Erikkson K, et al. Increased mortality in COPD among construction workers exposed to inorganic dust. Eur Respir J 2004; 23: 402–6.
36. Weinmann S, Vollmer WM, Breen V, et al. COPD and occupational exposures: a case-control study. J Occup Environ Med 2008; 50: 561–9.
37. Mehta AJ, Miedinger D, Keidel D, et al. Occupational exposure to dusts, gases and fumes and incidence of COPD in the Swiss Cohort Study on Air Pollution and Kung and Heart Disease in Adults (SAPALDIA). Am J Respir Crit Care Med 2012; 185: 1292–300.
38. Trupin L, Earnest G, San Pedro M, et al. The occupational burden of chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 1–9.
39. Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: dusty trades revisited. Thorax 2009; 64: 6–12.
40. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. J Occup Environ Med 2008; 50: 366–70.
41. Blanc PD, Eisner MD, Earnest G, et al. Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. J Occup Environ Med 2009; 51: 804–10.
42. Blanc PD, Menezes A-M B, Plana E, et al. Occupational exposures and COPD: An ecological analysis of international data. Eur Respir J 2009; 33: 298–304.
43. Melville AM, Pless-Mulloli T, Afolabi OA, et al. COPD prevalence and its association with occupational exposures in a general population. Eur Respir J 2010; 36: 488–93.
44. Govender N, Lalloo UG, Naidoo RN. Occupational exposures and chronic obstructive pulmonary disease: a hospital based case-control study. Thorax 2011; 66: 597–601.
45. Darby AC, Waterhouse JC, Stevens V, et al. Chronic obstructive pulmonary disease among residents of an historically industrialised area. Thorax 2012; 67: 901–7.
46. Blanc PD, Eisner MD, Trupin L, et al. The association between occupational factors and adverse health outcomes in chronic obstructive pulmonary disease. Occup Environ Med 2004; 61: 661–7.
47. Rodríguez E, Ferrer J, Martí S, et al. Impact of occupational exposure on severity of COPD. Chest 2008; 134: 1237–43.
48. Lange AM. Characterization and measurements of the industrial environment. In: Merchant JA, ed. Mineralogy. Occupational Respiratory Disease. U.S. Dept of Health and Human Services (NIOSH) Publication No. 86-102, 1986.
49. Higgins ITT. The epidemiology of chronic respiratory disease. Prev Med 1973; 2: 14–33.
50. Coggon D, Taylor AN. Coal mining and chronic obstructive pulmonary disease: a review of the evidence. Thorax 1998; 53: 398–407.
51. Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup Environ Med 2003; 60: 237–43.
52. Schins RPF, Borm PJA. Mechanisms and mediators in coal dust induced toxicity: A review. Ann Occup Hyg 1999; 43: 7–33.
53. Castranova V. From coal mine dust to quartz: Mechanisms of pulmonary pathogenicity. Inhal Toxicol 2000; 12: 7–14.
54. Hunter DD, Castranova V, Stanley C, Dey RD. Effects of silica exposure on substance P immunoreactivity and preprotachykinin mRNA expression in trigeminal sensory neurons in Fischer 344 rats. J Toxicol Environ Health 1998; 24: 593–605.
55. Bernard AM, Gonzales-Lorenzo JM, Siles E, et al. Early decrease of serum Clara cell protein in silica-exposed workers. Eur Respir J 1994; 7: 1932–7.
56. Vallyathan V. Generation of oxygen radicals by minerals and its correlation to cytotoxicity. Environ Health Perspect 1994; 102: 111–15.
57. Zay K, Loo S, Xie C, et al. Role of neutrophils and alpha1-antitrypsin in coal- and silica-induced connective tissue breakdown. Am J Physiol 1999; 276: L269–79.

58. Dai J, Gilks B, Price K, Churg A. Mineral dust directly induces epithelial and interstitial fibrogenic mediators and matrix components in the airway wall. Am J Respir Crit Care Med 1998; 158: 1907–13.
59. Rom WN. Relationship of inflammatory cell cytokines to disease severity in individuals with occupational inorganic dust exposure. Am J Ind Med 1991; 19: 15–27.
60. Vallyathan V, Shi X. The role of oxygen free radicals in occupational and environmental lung disease. Environ Health Perspect 1997; 105: 165–77.
61. Becher R, Hetland RB, Refsnes M, et al. Rat lung inflammatory responses after in vovo and in vitro exposure to various stone particles. Inhal Toxicol 2002; 13: 789–805.
62. Li K, Keeling B, Churg A. Mineral dusts cause collagen and elastin breakdown in the rut lung: a potential mechanism of dust induced emphysema. Am J Respir Crit Care Med 1996; 153: 644–9.
63. Li K, Zay K, Churg A. Mineral dusts oxidize methionine residue. Possible mechanism of dust-induced inactivation of α-1-antitrypsin. Ann Occup Hyg 1997; 41: 379–83.
64. Churg A, Zay K, Li K. Mechanisms of mineral dust-induced emphysema. Environ Health Perspect 1997; 1215–18.
65. Churg A. The uptake of mineral particles by pulmonary epithelial cells. State of the Art. Am J Respir Crit Care Med 1996; 154: 1124–40.
66. Wright JL, Harrison N, Wiggs B, Churg A. Quartz but not iron oxide cause air-flow obstruction, emphysema, and small airways lesions in the rat. Am Rev Respir Dis 1988; 138: 129–35.
67. Churg A, Wright JL, Wiggs B, Pare PD, Lazar N. Small airways disease and mineral dust exposure. Prevalence, structure, and function. Am Rev Respir Dis 1985; 131: 139–43.
68. Wright JL, Cagle P, Churg A, et al. Diseases of the small airways. Am Rev Respir Dis 1992; 146: 240–62.
69. American Thoracic Society. Adverse effects of crystalline silica exposure. Am J Respir Crit Care Med 1997; 155: 761–5.
70. Wiles FJ, Faure MH. Chronic obstructive lung disease in gold miners. In: Walton WH, ed. Inhaled Particles IV. Part 2. Oxford: Pergamon Press, 1977: 727–35.
71. Hnizdo E. Loss of lung function associated with exposure to silica dust and with smoking and its relation to disability and mortality in South African gold miners. Br J Ind Med 1992; 49: 472–9.
72. Ehrlich RI, Myers JE, te Water Naude JM, et al. Lung function loss in relation to silica dust exposure in South African gold miners. Occup Environ Med 2011; 68: 96–101.
73. Cowie RL, Mabena SK. Silicosis, chronic airflow limitation, and chronic bronchitis in South African gold miners. Am Rev Respir Dis 1991; 143: 80–4.
74. Manfreda J, Sidwall G, Maini K, et al. Respiratory abnormalities in employees of the hard rock mining industry. Am Rev Respir Dis 1982; 126: 629–34.
75. Holman CD, Psaila-Savona P, Roberts M, McNulty JC. Determinants of chronic bronchitis and lung dysfunction in Western Australian gold miners. Br J Ind Med 1987; 44: 810–18.
76. Kreiss K, Greenberg LM, Kogut SJH, et al. Hard-rock mining exposure affects smokers and non-smokers differently. Am Rev Respir Dis 1989; 139: 1487–93.
77. Humerfelt S, Eide GE, Gulsvik A. Association of years of occupational quartz exposure with spirometric airflow limitation in Norwegian men aged 30-46 years. Thorax 1998; 53: 649–55.
78. Ng TP, Tsin TW, O'Kelly FJ, Chan SL. A survey of the respiratory health of silica-exposed workers in Hong Kong. Am Rev Respir Dis 1987; 135: 1249–54.
79. Malmberg P, Hedenstrom H, Sundblad B-M. Changes in lung function of granite cruschers exposed to moderate highly silica concentrations: a 12 year follow up. Br J Ind Med 1993; 50: 726–31.
80. Ulvestad B, Bakke B, Melbostad E, et al. Increased risk of obstructive pulmonary disease in tunnel workers. Thorax 2000; 55: 277–82.
81. Ulvestad B, Bakke B, Eduard W, et al. Cumulative exposure to dust causes accelerated decline in lung function in tunnel workers. Occup Environ Med 2001; 58: 663–9.
82. Meijer E, Kromhout H, Heederik A. Respiratory effects of exposure to low levels of concrete dust containing crystalline silica. Am J Ind Med 2001; 40: 133–40.
83. Tjoe-Nij E, de Meer G, Smit J, Heederik D. Lung function decrease in relation to pneumoconiosis and exposure to quartz-containing dust in construction workers. Am J Ind Med 2003; 43: 574–83.
84. Zuskin E, Mustajbegovic J, Schachter EN, et al. Respiratory findings in workers employed in brick-manufacturing industry. J Occup Environ Med 1998; 40: 814–20.
85. Chen YH, Wu TN, Liou SH. Obstructive pulmonary function defects among Taiwanese firebrick workers in a 2-year follow-up study. J Occup Environ Med 2001; 43: 969–75.
86. Liou SH, Chen YP, Shih WY, Lee CC. Pneumoconiosis and pulmonary function defects in silica-exposed fire brick workers. Arch Environ Health 1996; 51: 227–33.
87. Cowie HA, Wild P, Beck J, et al. An epidemiological study of the respiratory health of workers in the European refractory ceramic fiber industry. Occup Environ Med 2001; 58: 800–10.
88. Forastiere F, Goldsmith DF, Sperati A, et al. Silicosis and lung function decrements among female ceramic workers in Italy. Am J Epidemiol 2002; 156: 851–6.
89. Yingratanasuk T, Seixas N, Barnhart S, Brodkin D. Respiratory health and silica exposure of stone carvers in Thailand. In J Occup Environ Health 2002; 8: 301–8.
90. Ahman M, Alexandersson R, Ekholm U, et al. Impeded lung function in moulders and coremakers handling furan resin sand. Int Arch Occup Environ Health 1991; 63: 175–80.
91. Gomes J, Lloyd OL, Norman NJ, Pahwa P. Dust exposure and impairment of lung function at a small iron foundry

in a rapidly developing country. Occup Environ Med 2001; 58: 656–62.
92. Jorna THJM, Borm PJA, Koiter KD, et al. Respiratory effects and serum type II procollagen in potato sorters exposed to diatomaceous earth. Int Arch Occup Environ Health 1994; 66: 217–22.
93. Neukirch F, Cooreman J, Korobaeff M, Periente R. Silica exposure and chronic airflow limitation in pottery workers. Arch Environ Health 1994; 49: 459–64.
94. Oliver LC, Miracle-McMahill H. Airway disease in highway and tunnel construction workers exposed to silica. Am J Ind Med 2006; 49: 983–96.
95. Tiwari RR, Sharma YK. Respiratory health of female stone grinders with free silica dust exposure in Gujarat, India. Int J Occup Environ Health 2008; 14: 280–2.
96. Johnsen H, Hetland SM, Benth JS, et al. Exposure assessed by a Job Exposure Matrix is associated with increased annual decline in $FEV_1$. A 5-year prospective study of employees in Norwegian smelters. Am J Respir Crit Care Med 2010; 181: 1234–40.
97. Dement JM, Welch L, Ringen K, et al. Airways obstruction among older construction and trade workers at Department of Energy nuclear sites. Am J Ind Med 2010; 53: 224–40.
98. Søyseth V, Johnsen HL, Bugge MD, et al. Prevalence of airflow limitation among employees in Norwegian smelters: a longitudinal study. Occup Environ Med 2011; 68: 24–9.
99. Steenland K, Brown D. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of follow-up. Am J Ind Med 1995; 27: 217–29.
100. Costello J, Castellan RM, Swecker GS, Kullman GJ. Mortality of a cohort of US Workers employed in crushed stone industry, 1940-1980. Am J Ind Med 1995; 27: 625–40.
101. Hnizdo E. Combined effect of silica dust and tobacco smoking on mortality from chronic obstructive lung disease in gold miners. Br J Ind Med 1990; 47: 656–64.
102. Reid PJ, Sluis-Cremer GK. Mortality of white South African gold miners. Occup Environ Med 1996; 53: 11–16.
103. Tse LA, Yu ITS, Leung CC, et al. Mortality from non-malignant respiratory diseases among people with silicosis in Hong Kong: exposure–response analyses for exposure to silica dust. Occup Environ Med 2007; 64: 87–92.
104. Bugge MD, Føreland S, Kjærheim K, et al. Mortality from non-malignant respiratory diseases among workers in the Norwegian silicon carbide industry: associations with dust exposure. Occup Environ Med 2011; 68: 863–9.
105. Vacek PM, Verma DK, Graham WG, et al. Mortality in Vermont granite workers and its association with silica exposure. Occup Environ Med 2011; 68: 312–18.
106. Bergin CJ, Muller NL, Vedal S, Chan-Yeung M. CT in silicosis: correlation with plain films and pulmonary function tests. Am J Roentgenol 1986; 146: 477–83.
107. Begin R, Filion R, Ostiguy G. Emphysema in silica- and asbestos-exposed workers seeking compensation. A CT scan study. Chest 1995; 108: 647–55.
108. Cowie RL, Hay M, Glyn- Thomas R. Association of silicosis, lung dysfunction, and emphysema in gold miners. Thorax 1993; 48: 746–9.
109. Wang X, Yano E. Pulmonary dysfunction in silica-exposed workers: a relationship to radiographic signs of silicosis and emphysema. Am J Ind Med 1999; 36: 299–306.
110. Becklake MR, Irwig L, Kielkowski D, et al. The predictors of emphysema in South African gold miners. Am Rev Respir Dis 1987; 135: 1234–41.
111. de Beer M, Kielkowski D, Yach D, Steinberg M. Selection bias in a case-control study of emphysema. S Afr J Epidemiol Infect 1992; 7: 9–13.
112. Hnizdo E, Sluis-Cremer GK, Abramowitz JA. Emphysema type in relation to silica dust exposure in South African gold miners. Am Rev Respir Dis 1991; 143: 1241–7.
113. Kinsella M, Muller N, Vedal S, et al. Emphysema in silicosis. A comparison of smokers with nonsmokers using pulmonary function testing and computed tomography. Am Rev Respir Dis 1990; 141: 1497–500.
114. Hnizdo E, Sluis-Cremer GK, et al. Emphysema and airway obstruction in non-smoking South African gold miners with long exposure to silica dust. Occup Environ Med 1994; 51: 557–63.
115. Hnizdo E, Murray J, Davison A. Correlation between autopsy findings for chronic obstructive lung disease and in-life disability in South African gold miners. Int Arch Occup Environ Health 2000; 73: 235–44.
116. Meijer E, Tjoe Nij E, Kraus T, et al. Pneumoconiosis and emphysema in construction workers: results of HRCT and lung function findings. Occup Environ Med 2011; 68: 542–6.
117. Rogan JM, Attfield MD, Jacobsen M, et al. Role of dust in the working environments in development of chronic bronchitis in British coal miners. Brit J Ind Med 1973; 30: 217–26.
118. Love RG, Miller BG. Longitudinal study of lung function in coal-miners. Thorax 1982; 37: 193–7.
119. Miller BG, Jacobsen M. Dust exposure, pneumoconiosis, and mortality of coal miners. Br J Ind Med 1985; 42: 723–33.
120. Soutar CA, Hurley JF. Relation between dust exposure and lung function in miners and ex-miners. Br J Ind Med 1986; 43: 307–20.
121. Hurley JF, Soutar CA. Can exposure to coalmine dust cause a severe impairment of lung function? Br J Ind Med 1986; 43: 150–7.
122. Marine WM, Gurr D, Jacobsen M. Clinically important respiratory effects of dust exposure and smoking in British coal miners. Am Rev Respir Dis 1988; 137: 106–12.
123. Soutar C, Campbell S, Gurr D, et al. Important deficits of lung function in three modern colliery populations. Am Rev Respir Dis 1993; 147: 797–803.
124. Soutar CA, Hurley JF, Miller BG, et al. Dust concentration and respiratory risks in coalminers: key risk estimates from British Pneumoconiosis Field Research. Occup Environ Med 2004; 61: 477–81.

125. Attfield MD, Hodous TK. Pulmonary function of U.S. coal miners related to dust exposure estimates. Am Rev Respir Dis 1992; 145: 605–9.
126. Seixas NS, Robins TG, Attfield MD, Moulton LH. Longitudinal and cross sectional analyses of exposure to coal mine dust and pulmonary function in new miners. Brit J Ind Med 1993; 50: 929–37.
127. Attfield MD. Longitudinal decline in FEV1 in the United States coalminers. Thorax 1985; 40: 132–7.
128. Wang ML, Petsonk EL, Beekman LA, Wagner GR. Clinically important $FEV_1$ declines among coal miners: an exploration of previously unrecognized determinants. Occup Environ Med 1999; 56: 837–44.
129. Beeckman LA, Wang ML, Petsonk EL, Wagner GR. Rapid declines in $FEV_1$ and subsequent respiratory symptoms, illnesses, and mortality in coal miners in the United States. Am J Respir Crit Care Med 2001; 163: 633–9.
130. Carta P, Aru G, Barbier MT, et al. Dust exposure, respiratory symptoms, and longitudinal decline of lung function in young coalminers. Occup Environ Med 1996; 53: 312–19.
131. Mamuya SH, Bråtveit M, Mashalla Y, Moen BE. High prevalence of respiratory symptoms among workers in the development section of a manually operated coal mine in a developing country: a cross sectional study. BMC Public Health 2007; 7: 17.
132. Meijers JMM, Swaen GMH, Slangen JJM. Mortality of Dutch coal miners in relation to pneumoconiosis, chronic obstructive pulmonary disease, and lung function. Occup Environ Med 1997; 54: 708–13.
133. Kuempel ED, Stayner LT, Attfield MD, Buncher CR. Exposure-response analysis of mortality among coal miners in the United States. Am J Ind Med 1995; 28: 167–84.
134. Attfield MD, Kuempel ED. Mortality among U.S. underground coal miners: a 23-year follow-up. Am J Ind Med 2008; 51: 231–45.
135. Miller BG, MacCalman L. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. Occup Environ Med 2010; 67: 270–6.
136. Wang ML, Wu ZE, Du QG, et al. Rapid decline in forced expiratory volume in 1 second (FEV1) and the development of bronchitic symptoms among new Chinese coal miners. J Occup Environ Med 2007; 49: 1143–8.
137. Gevenois PA, Sergent G, De Maertelaer V, et al. Micronodules and emphysema in coal mine dust or silica exposure: relation with lung function. Eur Respir J 1998; 12: 1020–4.
138. Ruckley VA, Gauld SJ, Chapman JS, et al. Emphysema and dust exposure in a group of coal workers. Am Rev Respir Dis 1984; 129: 528–32.
139. Kuempel ED, Wheeler MW, Smith RJ, et al. Contributions of dust exposure and cigarette smoking to emphysema severity in U.S. coal miners. Am J Respir Crit Care Med 2009; 180: 257–64.
140. Hnizdo E, Baskind E, Sluis-Cremer GK. Combined effect of silica dust exposure and tobacco smoking on the prevalence of respiratory impairments among gold miners. Scand J Work Environ Health 1990; 16: 411–22.
141. Wang ML, Lu PL. Lung function studies in asbestos workers. Scand J Work Environ Health 1985; 11: 34–42.
142. Becklake MR. Asbestos and other fiber-related diseases of the lungs and pleura: distribution and determinants in populations. Chest 1991; 100: 248–54.
143. Harber P, Dahlgren J, Bunn W, et al. Radiographic and spirometric in diatomaceous earth workers. J Occup Environ Med 1998; 40: 22–8.
144. Kilburn KH, Warshaw RH, Einstein K, Bernstein J. Airway disease in non-smoking asbestos workers. Arch Environ Health 1985; 40: 293–5.
145. Copes R, Thomas D, Becklake MR. Temporal patterns of exposure and non-malignant pulmonary abnormality in Quebec chrysotile workers. Arch Environ Health 1985; 40: 80–7.
146. Demers RY, Neale AV, Robins T, Herman SC. Asbestos-related disease in boilermakers. Am J Ind Med 1990; 17: 327–39.
147. Kennedy SM, Vedal S, Muller N, et al. Lung function and chest radiograph abnormalities among construction insulators. Am J Ind Med 1991; 20: 673–84.
148. Hall SK, Cissi JH. Effects of cigarette smoking on pulmonary function in asymptomatic asbestos workers with normal chest radiographs. Am Ind Hyg Assoc J 1982; 43: 381–6.
149. Siracusa A, Cicioni C, Volpi R, et al. Lung function among asbestos cement factory workers : cross-sectional and longitudinal study. Am J Ind Med 1984; 5: 315–25.
150. Algranti E, Mendonca EMC, DeCapitani EM, et al. Non-malignant asbestos-related diseases in Brazilian asbestos cement workers. Am J Ind Med 2001; 40: 240–54.
151. Hessel PA, Melenka LS, Michaelchuk D, et al. Lung health among electricians in Edmonton, Alberta, Canada. J Occup Environ Med 1998; 40: 1007–12.
152. Hessel PA, Melenka LS, Michaelchuk D, et al. Lung health among boilermakers in Edmonton, Alberta. Am J Ind Med 1998; 34: 381–6.
153. Hessel PA, Melenka LS, Michaelchuk D, et al. Lung health among plumbers and pipefitters in Edmonton, Alberta. Occup Environ Med 1998; 55: 678–83.
154. Kalacic I. Ventilatory lung function in cement workers. Arch Environ Health 1973; 26: 84–5.
155. Saric M, Kalacic I, Holetic A. Follow-up of ventilatory lung function in a group of cement workers. Br J Ind Med 1976; 33: 18–24.
156. Shamssain MH, Thompson J. Effect of cement dust on lung function in Libyans. Ergonomics 1988; 31: 1299–303.
157. Mengesha YA, Bekele A. Relative chronic effects of different occupational dusts on respiratory indices and health of workers in three Ethiopian factories. Am J Ind Med 1998; 34: 373–80.
158. Siracusa A, Forcina A, Volpi R, et al. An 11-year longitudinal study of the occupational dust exposure and lung

function of polyvinyl chloride, cement and asbestos cement factory workers. Scand J Work Environ Health 1988; 14: 181–8.
159. Fell AKM, Thomassen TR, Kristensen P, et al. Respiratory symptoms and ventilatory function in workers exposed to Portland cement dust. J Occup Environ Med 2003; 45: 1008–14.
160. Matczak W, Gromiec J. Evaluation of occupational exposure to toxic metals released in the process of aluminum welding. Appl Occup Environ Hyg 2002; 17: 296–303.
161. Woskie SR, Kalil A, Bello D, Virji MA. Exposures to quartz, diesel, dust, and welding fumes during heavy and highway construction. Am Ind Hyg Assoc J 2002; 63: 447–57.
162. Susi P, Goldberg M, Barnes P, Stafford E. The use of a task-based exposure assessment model (T-BEAM) for assessment of metal fume exposures during welding and thermal cutting. Appl Occup Environ Hyg 2000; 15: 26–38.
163. Dryson EW, Rogers DA. Exposure to fumes in typical New Zealand welding operations. N Z Med J 1991; 104: 365–7.
164. Hewett P. The particle size distribution, density, and specific surface area of welding fumes from SMAW and GMAW mild and stainless steel consumables. Am Ind Hyg Assoc J 1995; 56: 128–35.
165. Antonini JM, Lewis AB, Roberts JR, Whaley DA. Pulmonary effects of welding fumes: review of worker and experimental animal studies. Am J Ind Med 2003; 43: 350–60.
166. Beckett WS, Pace PE, Sferlazza SJ, et al. Airway reactivity in welders: a controlled prospective cohort study. J Occup Environ Med 1996; 38: 1229–38.
167. Fishwick D, Bradshaw LM, Slater T, Pearce N. Respiratory symptoms, across-shift lung function changes and lifetime exposures of welders in New Zealand. Scand J Work Environ Health 1997; 23: 351–8.
168. Contreras GR, Chan-Yeung M. Bronchial reactions to exposure to welding fumes. Occup Environ Med 1997; 54: 836–9.
169. Li GJ, Zhang LL, Lu L, et al. Occupational exposure to welding fume among welders: alterations of manganese, iron, zinc, copper, and lead in body fluids and the oxidative stress status. J Occup Environ Med 2004; 46: 241–8.
170. Antonini JM, Lawryk NJ, Murthy GG, Brain JD. Effect of welding fume solubility on lung macrophage viability and function in vitro. J Toxicol Environ Health A 1994; 58: 343–63.
171. Taylor MD, Roberts JR, Leonard SS, et al. Effects of welding fumes of differing composition and solubility on free radical production and acute lung injury and inflammation in rats. Toxicol Sci 2003; 75: 181–91.
172. Nakadate T, Aizawa Y, Yagami T, et al. Change in obstructive pulmonary function as a result of cumulative exposure to welding fumes as determined by magnetopneumography in Japanese arc welders. Occup Environ Med 1998; 55: 673–7.
173. Bradshaw LM, Fishwick D, Slater T, Pearce N. Chronic bronchitis, work related respiratory symptoms, and pulmonary function in welders in New Zealand. Occup Environ Med 1998; 55: 150–4.
174. Fine JM, Gordon T, Chen LC, et al. Characterization of clinical tolerance to inhaled zinc oxide in naive subjects and sheet metal workers. J Occup Environ Med 2000; 42: 1085–91.
175. Chinn DJ, Stevenson IC, Cotes JE. Longitudinal respiratory survey of shipyard workers: effects of trade and atopic status. Br J Ind Med 1990; 47: 83–90.
176. Cotes JE, Feinmann EL, Male VJ, et al. Respiratory symptoms and impairment in shipyard welders and caulker/burners. Br J Ind Med 1989; 46: 292–301.
177. Chinn DJ, Cotes JE, el Gamal FM, Wollaston JF. Respiratory health of young shipyard welders and other tradesmen studied cross-sectionally and longitudinally. Occup Environ Med 1995; 52: 33–42.
178. Hjortsberg U, Orbaek P, Arborelius M Jr. Small airways dysfunction among non-smoking shipyard arc welders. Br J Ind Med 1992; 49: 441–4.
179. Hayden SP, Pincock AC, Hayden J, et al. Respiratory symptoms and pulmonary function of welders in the engineering industry. Thorax 1984; 39: 442–7.
180. Thaon I, Demange V, Herin F, et al. Increased lung function decline in blue-collar welders exposed to welding fumes. Chest 2012; 142: 192–9.
181. Yu D, Walters DM, Zhu L, et al. Vanadium pentoxide (V(2) O(5)) induced mucin production by airway epithelium. Am J Physiol Lung Cell Mol Physiol 2011; 301: L31–9.
182. Irsigler GB, Visser PJ, Spangenberg PA. Asthma and chemical bronchitis in vanadium plant workers. Am J Ind Med 1999; 35: 366–74.
183. Levy BS, Hoffman L, Gottsegen S. Boilermakers' bronchitis. Respiratory tract irritation associated with vanadium pentoxide exposure during oil-to-coal conversion of a power plant. J Occup Med 1984; 26: 567–70.
184. Kirschvink N, Vincke G, Fiévez L, et al. Repeated cadmium nebulizations induce pulmonary MMP-2 and MMP-9 production and emphysema in rats. Toxicology 2005; 211: 36–48.
185. Leduc D, de Francquen P, Jacobovitz D, et al. Association of cadmium exposure with rapidly progressive emphysema in a smoker. Thorax 1993; 48: 570–1.
186. Mannino DM, Holguin F, Greves HM, et al. Urinary cadmium levels predict lower lung function in current and former smokers: data from the Third National Health and Nutrition Examination Survey. Thorax 2004; 59: 194–8.
187. Katzenstein A-L. Katzenstein and Askin's Surgical Pathology of Non-Neoplastic Lung Disease, 4th edn. Edinburgh: Elsevier Saunders, 2006.
188. Wright JL, Churg A. Diseases caused by gases and fumes. In: Churg A, Green FHY, eds. Pathology of Occupational Lung Disease, 2nd edn. Baltimore: Williams & Wilkins, 1998: 57–76.
189. Moya C, Anto JM, Newman Taylor ASJ. Outbreak of organizing pneumonia in textile printing sprayers. Lancet 1994; 344: 498–502.

190. Boag AH, Colby TV, Fraire AE, et al. The pathology of interstitial lung disease in nylon flock workers. Am J Surg Pathol 1999; 23: 1539–45.
191. Fraenkel A. Ueber Bronchiolitis fibrosa obliterans nebst Bemerkungen über Lungenhyperämie und indurirende Pneumonie Deutches Arch Klin Med. 1902; 73: 484–510.
192. Wagner JH. Bronchiolitis obliterans following the inhalation of acrid fumes. Am J Med Sci 1917; 154: 511–22.
193. Yockey CC, Eden BM, Byrd RB. The McConnell missile accident: Clinical spectrum of nitrogen dioxide exposure. JAMA 1980; 244: 1221–3.
194. Grayson RR. Silage gas poisoning: nitrogen dioxide pneumonia, a new disease in agricultural workers. Ann Int Med 1956; 45: 393–408.
195. Lowry T, Schuman LM. 'Silo-Filler's Disease'—a syndrome caused by nitrogen dioxide. J Am Med Assoc 1956; 163: 153–60.
196. Horvath EP, doPico GA, Barbee RA, Dickie HA. Nitrogen dioxide-induced pulmonary disease: five new cases and a review of the literature. J Occup Med 1978; 20: 103–10.
197. Zwemer FL, Pratt DS, May JJ. Silo filler's disease in New York State. Am Rev Respir Dis 1992; 146: 650–3.
198. Carke CS, Warrack AJN. Bronchiolitis from nitrous fumes. Thorax 1958; 13: 327–33.
199. Lenci G, Wacker G, Schulz V, et al. Bronchiolitis obliterans nach Stickstoffdioxyd (NO2)–Inhalation: Klinisch-roentgenologisch-histologische beobachung [Bronchiolitis obliterans after inhalation of nitrogen dioxide (NO2): Clinical, radiological, histological observations]. Pneumonologie 1990; 44: 32–6.
200. Woodford DM, Coutu RE, Gaensler EA. Obstructive lung disease from acute sulfur dioxide exposure. Respiration 1979; 38: 238–45.
201. Konichezsky S, Schatter A, Ezri T, et al. Thionyl-chloride-induced lung injury and bronchiolitis obliterans. Chest 1993; 104: 971–3.
202. Kraut A, Lilis R. Chemical pneumonitis due to exposure to bromine compounds. Chest 1988; 94: 208–10.
203. Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin B concentration and distribution in the respiratory tract of lung-transplanted patients. Transplant 2003; 75: 1571–4.
204. Segev JS, Mason UG, Worthen S, et al. Bronchiolitis obliterans: Report of three cases with detailed physiologic studies. Chest 1983; 83: 169–74.
205. Simpson FG, Belfield PW, Cooke NJ. Chronic airflow limitation after inhalation of overheated cooking oil fumes. Postgrad Med J 1985; 61: 1001–2.
206. Tasaka S, Kanazawa M, Mori M, et al. Long-term course of bronchiectasis and bronchiolitis obliterans as late complication of smoke inhalation. Respiration 1995; 62: 40–2.
207. Boswell RT, McCunney RJ. Bronchiolitis obliterans from exposure to incinerator fly ash. J Occup Environ Med 1995; 37: 850–5.
208. Janigan DT, Kiolp T, Michael R, et al. Bronchiolitis obliterans in a man who used his wood-burning stove to burn synthetic construction materials. CMAJ 1997; 156: 1171–3.
209. Mann JM, Sha KK, Kline G, et al. World trade center Dyspnea: bronchiolitis obliterans with functional improvement: a case report. Am J Ind Med 2005; 48: 225–9.
210. Mahut B, Delacourt C, de Blic J. Bronchiectasis in a child after acrolein inhalation. Chest 1993; 104: 1286–7.
211. Kass I, Zamel N, Dobry CA, et al. Bronchiectasis following ammonia burns of the respiratory tract. Chest 1972; 62: 282–5.
212. Emad A, Rezaian GR. The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure: Analysis of 197 cases. Chest 1997; 112: 734–8.
213. Ghanei M, Harandi AA. Long term consequences from exposure to sulfur mustard: a review. Inhal Toxicol 2007; 19: 451–6.
214. Weill H. Disaster at Bhopal: the accident, early findings and respiratory health outlook in those injured. Bull Eur Physiopathol Respir 1987; 23: 587–90.
215. Mishra PK, Samarth RM, Pathak N, et al. Bhopal gas tragedy: review of clinical and experimental findings after 25 years. Int J Occup Med Environ Health 2009; 22: 193–202.
216. Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. N Engl J Med 2002; 347: 330–8.
217. Ger LP, Chiang AA, Lai RS, et al. Association of Sauropus androgynus and bronchiolitis obliterans syndrome: a hospital-based case-control study. Am J Epidemiol 1997; 145: 842–9.
218. Palmer SM, Flake GP, Kelly FL, et al. Severe airway epithelial injury, aberrant repair and bronchiolitis obliterans develops after diacetyl instillation in rats. PLoS ONE 2011; 6: e17644.
219. Kanwal R, Kullman G, Piacitelli C, et al. Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. J Occup Environ Med 2006; 48: 149–57.
220. Kim TJ, Materna BL, Prudhomme JC, et al. Industry-wide medical surveillance of California flavor manufacturing workers: cross-sectional results. Am J Ind Med 2010; 53: 857–65.
221. NIOSH. Health Hazard Evaluation Report: Lung Function (Spirometry) Testing in Employees at a Flavorings Manufacturing Plant – Indiana (NIOSH HETA No. 2008-0155-3131). Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, 2011.
222. Morgan DL, Jokinen MP, Price HC, et al. Bronchial and bronchiolar fibrosis in rats exposed to 2,3-pentanedione vapors: implications for bronchiolitis obliterans in humans. Toxicol Pathol 2012; 40: 448–65.

223. Kern DG, Crausman RS, Durand KT, et al. Flock worker's lung: chronic interstitial lung disease in the nylon flocking industry. Ann Intern Med 1998; 129: 261–72.
224. Washko RM, Day B, Parker JE, et al. Epidemiologic investigation of respiratory morbidity at a nylon flock plant. Am J Ind Med 2000; 38: 628–38.
225. Daroowalla F, Wang ML, Piacitelli C, et al. Flock workers' exposures and respiratory symptoms in five plants. Am J Ind Med 2005; 47: 144–52.
226. Eschenbacher WL, Kreiss K, Lougheed MD, et al. Nylon flock-associated interstitial lung disease. Am J Respir Crit Care Med 1999; 159: 2003–8.
227. Porter DW, Castranova V, Robinson VA, et al. Acute inflammatory reaction in rats after intratracheal instillation of material collected from a nylon flocking plant. J Toxicol Environ Health A 1999; 57: 25–45.
228. Atis S, Tutluoglu B, Levent E, et al. The respiratory effects of occupational polypropylene flock exposure. Eur Respir J 2005; 25: 110–17.
229. Barroso E, Ibanez MD, Aranda FI, Romero S. Polyethylene flock-associated interstitial lung disease in a Spanish female. Eur Respir J 2002; 20: 1610–12.
230. Antao VC, Piacitelli CA, Miller WE, et al. Rayon flock: a new cause of respiratory morbidity in a card processing plant. Am J Ind Med 2007; 50: 274–84.
231. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. N Engl J Med 2011; 365: 222–30.
232. Ghanei M, Tazelaar HD, Chilosi M, et al. An international collaborative pathologic study of surgical lung biopsies from mustard gas-exposed patients. Respir Med 2008; 102: 825–30.
233. Jones RN, Hughes JM, Glindmeyer H, Weill H. Lung function after acute chlorine exposure. Am Rev Respir Dis 1986; 134: 1190–5.
234. Burge PS, Robertson AS, Cullinan P, Howell TJ. Obliterative bronchiolitis in boatbuilders exposed to styrene and isocyanates (Abstract). Am J Respir Crit Care Med 2008; 177: a157.
235. Cullinan P, McGavin CR, Kreiss K, et al. Obliterative bronchiolitis in fiberglass workers: a new occupational disease? Oc Environ Med 2013; (online) 10.1136/oem-2012-101060.
236. Eisner MD, Anthonisen N, Coultas D, et al. 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 2010; 182: 693–718.