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Chronic Airway Disease Due to Occupational Exposure

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INTRODUCTION

Long before personal cigarette smoking was widespread, medical writers recognized that dusty trades were associated with various lung diseases. Much of this, often termed "miner's phthisis," was due to inorganic dusts and is best understood by today's nosology as one of the pneumoconioses (with or without superimposed tubercular disease). Nonetheless, clinical syndromes consistent with chronic

[a] The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

bronchitis or airway obstruction, in particular among persons experiencing heavy organic dust inhalation, were also well described throughout the 19th century (1,2).

By the mid-20th century, occupational exposures, characterized by dusty trades, were generally presumed to be contributors to chronic bronchitis specifically and, by extension, the airway disease generally. 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 (3). In 1958, Fletcher himself noted that, "men who work in dusty trades, especially coal miners, have a higher prevalence of symptoms of bronchitis and emphysema..." (4). When Fletcher's landmark studies downplayed the role of chronic bronchitis in the progression of airway obstruction, the ascendancy of cigarette smoking as a major independent risk factor for the latter tended to eclipse all other potential associations. This was most especially true of possible links between occupational exposures and chronic obstructive pulmonary disease (COPD), with or without concomitant chronic bronchitis.

Over the ensuing 30 years since 1960, many epidemiological studies investigated the question of COPD in relation to occupational exposures. During this time, a number of industry-based and population-based studies did publish interesting and surprisingly consistent findings indicating that work-related exposures were linked to symptoms of bronchitis or COPD/emphysema, or to airway obstruction by lung function testing. In many of these investigations, occupational risk was not a study focus and often the occupational findings were published as little more than a controlling cofactor in multivariate modeling. At the same time, exposure-specific studies were providing new insights relevant to the biological plausibility of industrial toxins and airway obstruction. For example, research linked occupational cadmium exposure to emphysema in a dose-dependent manner, while other studies delineated the pulmonary function characteristics of fixed obstruction in byssinosis (5,6).

The revival of general biomedical interest in occupational exposures in the causation of chronic bronchitis, COPD, and emphysema has been revived through the seminal work of Dr. Becklake (7). Early on, she had observed the airway obstruction of irritant gas inhalation among miners exposed to explosive blast fumes (7) and had also shown that lung function decline among gold miners need not be linked to the extent of radiographic disease (8,9). Beginning in 1989, she authored a series of reviews and informal meta-analyses systematically compiling together the scattered epidemiological reports that had been appearing in the medical literature. The key analysis from this series included five large population-based studies (two from the United States and one each from Italy, France, and Poland), all showing longitudinal decline in airflow or a greater prevalence of airflow obstruction associated with work-related inhalation of gases and vapors or fumes and dust or both categories of exposure. In the same analysis, Becklake also summarized data from nine industry-specific studies (almost all inorganic dust) indicating an accelerated lung function decline (10–12). Becklake's work was followed by a series of other reviews and commentaries addressing this question anew (13–17).

The spectrum of occupational COPD also encompasses exposure to toxic agents which cause irreversible inflammatory disease in the terminal bronchioles, respiratory bronchioles, and alveolar ducts. The unique histopathology features of bronchiolitis (B) and bronchiolitis obliterans (BO) clearly distinguish these airway diseases from other COPD entities. In recent years, workplace exposure to a variety of toxic agents has been directly associated with these outcomes. Although the total number of reported cases has been modest, future industry-specific epidemiologic studies may be warranted. Because workplace experience with B or BO is limited, relevant clinical data will be discussed in the context of specific causal agents.

In this chapter, we first present the epidemiological evidence of chronic airflow obstruction based on specific occupational or industrial groups relevant to cohorts with specific exposures. Second, after summarizing findings relevant to specific exposures, we will review the population attributable risk percent (PAR%) or attributable fraction of COPD and chronic bronchitis related to workplace exposures across all occupational groups rather than limited to a single industrial cohort.

EXPOSURE TO MINERAL DUST

Occupational exposure to mineral dust occurs in many industrial operations worldwide. Occupational mineral dust exposures can be broadly categorized as strongly fibrogenic dusts (silica, asbestos, and coal) and other mineral dusts (emery, graphite, gypsum, marble, mica, perlite, plaster of Paris, Portland cement, silicon, silicon carbide, soapstone, and talc) that may also be associated with adverse lung effects (18). Mineral dust-induced pneumoconioses [silicosis, asbestosis, and coal workers' pneumoconiosis (CWP)] and associated tuberculosis have been the main causes of morbidity and mortality directly attributable to mineral dust exposure at workplace. Many epidemiological studies of specific industry cohorts, however, have demonstrated that exposure to mineral dusts, primarily the more highly fibrogenic types of dusts, is associated with increased levels of obstructive lung function impairment and increased prevalence of chronic bronchitis (11,13,19–21). Extending this association from highly dust-exposed groups to those with lower mineral dust exposure in the absence of radiological signs of pneumoconiosis is an area of ongoing research (21,22).

In addition to the classic features of COPD whose predominant pathological features are emphysema, small airway disease, and chronic bronchitis (23) in mineral dust–exposed workers, lung fibrosis and pulmonary tuberculosis can also cause airflow limitation (24–26). Epidemiologic investigations of exposure–response relationships between indices of occupational dust exposure and lung function impairment, symptoms of chronic bronchitis, and mortality from COPD, adjusted for the confounding effect of age and tobacco smoking, can provide an evidence on whether a particular occupational exposure has a potential of increasing the risk of COPD in the exposed workers. Given the complexity of COPD etiology, however, to obtain reliable estimates of the exposure–response relationships, a relatively large sample size of exposed workers, and if possible a comparable control group, may be required. In many workplace cohorts the number of exposed workers may be relatively small, causing the estimated effect to have a large error leading to poor study power to detect a relationship. For this reason, epidemiological studies conducted on large mining populations often provide the most reliable estimates of the exposure–response relation between mineral dust exposure and lung function impairment (13). Another generalizable problem is the parallel relationships (collinearity) among age, exposure measured in dust-years, and cigarette exposure measured in pack years. This can also increase error terms in estimating equations or lead to overadjustment that masks a true exposure–effect relationship.

In this section, an overview of the evidence on the effect of mineral dust exposure on airflow obstruction is provided, focusing on the issue of whether the risk of airflow obstruction is increased due to mineral dust exposure independent of radiological signs of pneumoconiosis. The following are discussed in sequence: the potential mechanisms by which mineral dusts can cause airflow obstruction, the epidemiological evidence from mining cohorts, focusing on the exposure–response relation, and the evidence from other mineral dust exposure studies.

Pathophysiology of Chronic Obstructive Lung Disease Due to Mineral Dusts

There are multiple pathophysiological mechanisms by which mineral dusts may potentially initiate lung injury leading to airflow obstruction, chronic bronchitis, and emphysema, all independent of fibrosis. Upon deposition, mineral dust particles reach two critical target cells in the lung: macrophages and epithelial cells (27,28). Ingestion of various mineral dust particles by the macrophage (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 (28–31) leading to generation of reactive oxygen/nitrogen species (31) and secretion of proinflammatory factors (32), cytokines, chemokines, elastase (31,32) and fibrogenic factors (33,34). Mineral dusts analyzed in terms of these mechanisms and found to be toxic include crystalline silica, coal dust, 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 (28,35) and emphysema (31,32,35–39). Dust particles can also cause epithelial cell injury that facilitates penetration of the particles through the walls of small airways and can cause localized fibrosis (33,34,40).

Mineral dust airway disease 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 (41–44). Nonetheless the association between small airways impairment and silica dust has been reported in only one study (45) and was not found in another when specifically assessed (46). 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 coalminers' lungs, typical centrilobular emphysema is caused by coal dust deposition forming the coal macula (47). In silicosis, 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 forced expiratory volume in one second (FEV_1) and D_{LCO} (48–53). Silica dust exposure appears to be associated with more emphysema than asbestos dust (49). In addition, there is an exposure-response relationship between silica dust exposure and emphysema assessed on paper-mounted whole-lung sections at autopsy (54–56). Nonetheless, the degree of emphysema found in silica dust–exposed miners who were never smokers was not correlated with lung function measured five years prior to death (57). Among gold miners, however, emphysema found at autopsy was found to be the most important predictor of lung function measured five years prior to death (58).

Coal Mining Dust—Epidemiological Evidence

Epidemiological studies of British, U.S., and Italian coal miners have established the existence of an exposure–response relationship between cumulative coal dust exposure and decreased lung function. The association was found in smokers, ex-smokers, and never-smokers, and across all age groups. The studies demonstrated that the severity of the impairment associated with coal mining dust exposure puts

coal miners at an increased risk of COPD. Because of this evidence, COPD (i.e., chronic bronchitis and emphysema) are now compensable occupational diseases among coal miners in many countries (e.g., Britain, Germany, South Africa). The issues that are currently debated in scientific literature are whether current permissible concentrations of coal mining dust (2 mg/m^3 in the United States) can increase the risk of COPD, especially in the absence of CWP (21).

Several large studies based on a large industry-wide survey of more than 30,000 British coal miners, initiated during 1953–1958 with follow-up studies up to 1991, have shown excessive losses of FEV_1 with cumulative dust exposure with dose-dependent relationship and independent of the presence of CWP; the loss was found to be greatest in younger men and in men with respiratory symptoms (Table 1)

Table 1 Epidemiological Studies of the Effect of Coal Mining Dust Exposure on Airflow Limitation

Country (Reference)	*N*	Design	Reduction of FEV_1 (mL/ghm^{-3}) [$mL/(mg/m^3-yrs)$][a]	Cumulative exposure mean ghm^{-3} (mg/m^3-yrs)[a]	Comment
United Kingdom (59)	3581	Cross-sectional	0.6	175	Current miners
United Kingdom (60)	4059	Cross-sectional	0.76	174	The effect observed across all ages
United Kingdom (61)	2757	Cross-sectional	1.04	204	South Wales miners
			0.08	148	Yorkshire miners, no effect was observed in N.E. England miners ($ghm^{-3} = 103$)
United States (62)	7139	Cross-sectional	0.69		
United States (63)	977	Cross-sectional	5.9[a]	15.4[a]	Miners who started work from 1970
United Kingdom (64)	1677	Longitudinal	0.42	117	Loss over 11 yrs in relation to previous exposure
United States (65)	1161	Longitudinal	1.6		Loss over 11 yrs in relation to current exposure
Italy (66)	909	Longitudinal	10.9[a]	1.8–6.1[a]	Sardinian coal miners follow-up 1983–1993

[a]Applies to studied done in U.S. (62) and Italy (66).
Abbreviation: FEV_1, forced expiratory volume in one second.

(59,60,64,67). Investigating the severity of the impairment associated with coal dust exposure, one study reported that the risks of having symptoms of chronic bronchitis and FEV_1 less than 80% predicted and FEV_1 less than 65% predicted were almost doubled in men with the highest exposure category of 348 ghm^{-3} (61). The excess loss of FEV_1 persisted even after dust levels were substantially reduced in coal miners employed after 1970 (68,69). Another study found that adjusted FEV_1 was on average 155 mL (95% CI, 74–236 mL) lower in miners than in the controls, the difference being greatest in younger men (62).

The findings of the National Study of CWP in the United States of coal miners were essentially similar (Table 1) (62,63). Coal mining dust was also associated with higher rate of decline in lung function (65). Other important occupational risk factors that were reported to contribute to increased rate of decline in lung function in the U.S. coal miners 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 (70). Furthermore, a rapid 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 (NMRD) (71). Relationships between exposure to coal mining dust and increased mortality from COPD have also been found in British, U.S., and Dutch studies (72–74).

Exposure–response relationship for airflow obstruction and coal mining dust was also found in a longitudinal study of Italian coal miners (66).

In summary, the epidemiological evidence from coal mining studies shows an exposure–response between various outcomes of COPD and indices of coal mining dust exposure. It has been estimated that 8.0% (95% CI, 3.4% to 13.7%) of nonsmoking coal miners with a cumulative respirable 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 (13). Among smoking miners, the estimate attributable to dust was 6.6% (95% CI, 4.9% to 8.4%), (13) but 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 (75).

Silica Dust—Epidemiological Evidence

Despite the dramatic reduction of silica dust exposure levels in most developed countries during the last century (76), airflow limitation and associated COPD remain health issues in workers exposed to silica dust (22). Recent epidemiologic studies show that silica dust exposure can lead to airflow limitation in the absence of radiological signs of silicosis and that airflow limitation associated with silica dust exposure occurs in many different types of industrial operations (77–99).

Epidemiological 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 both in smokers and nonsmokers (77,78). The average loss in lung function attributable to silica dust exposure, estimated for a 50-year-old white South African gold miner exposed for 24 years to standard exposure levels, was equivalent to an average excess loss of 9.8 mL/yr of FEV_1 and 9.0 mL/yr of FVC (22). Similar results were also observed among black South African gold miners (79), Canadian hard rock miners (80), Western Australian miners (81), and U.S. molybdenum miners (82) (Table 2).

Table 2 Epidemiological Studies of the Effect of Mineral Dust (Silica and Mixed) on Lung Function Loss in Selected Studies

			Mean exposure to silica dust			Loss of lung function associated with mean cumulative dust exposure or duration of exposure		
Silica dust exposure (Reference)	*N*	Age	Years	Respirable dust (mg/m^3); % silica	Cum. respirable dust (mg/m^3–yr)	FEV_1 (mL) loss/yr of exposure	FEV_1 %	FVC (mL)
South African gold (77,78)	2260	50	24	0.6[a]; 15	13.4	236; 9.8	2.3	217
South African gold miners (79)	1197	46	25	0.6[a]; 15	NA	200; 8; 447[b]	3.3	NS 351[b]
Canadian hard rock miners (80)	95	39	13	0.5; 8	NA	325	NS	364
U.S. hard rock miners (82)	281	44	9	NA;19	8.3	155	NS	NS
Silica dust exposed subjects (83)	3445	38	7	<0.2[c]; NA	NA	31;4.3	4.5	NS
Swedish granite crushers (84)	45	52	22	0.16[c]; NA	7.2	150	3.2	NS
Norwegian tunnel workers (85)	345	40	19	2; 24	15.3	162	NA	NA
Dutch construction workers (88)	1335	42	19	NA; NA	NA	117	NS	126
Dutch construction workers (87)	144	36	11	0.8; 9	7.0	NS	2.2	NS
Brick-manufacturing workers (88)	382	35	16	2	NA	NS	NS	18.5
Italian ceramic workers (93)	380	35	5	NA	NA	NA; 5.7	NA; 9.2	NA
Stone carvers (94)	97	33	11	0.2–0.9[c]; NA	19.6	195; 18	NS	207
Potato sorters (98)	172	45	12	2.2; 12	NA	124; 11	3.8	NS

[a]Respirable dust measured before hydrochloric acid treatment.
[b]Additional loss associated with silicosis ILO category 3/3.
[c]Respirable silica.
Abbreviations: FEV_1, forced expiratory volume in one second; NS, not significant; NA, not available.

Several recent epidemiological studies have shown that silica dust exposure constitutes a hazard for airflow limitation in many nonmining industries (granite crushers, tunnel workers, construction workers, brick-manufacturing workers, slate workers, stone carvers, ceramic workers, refractory ceramic fiber industry, etc.) (Table 2). A dose-dependent relationship between exposure, either in the duration of employment or in the dust level, 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 to 46 years of age (83). Workers with 15 or more years of silica dust exposure had a statistically significant excess loss of FEV_1 of 4.3 mL (95% CI, 1.1–7.5) with each year of exposure; the exposure–response relationship was similar among nonsmokers, ex-smokers, and smokers. This study is also addressed in the later section on PAR% estimates.

Several mortality studies of cohorts of silica dust–exposed workers reported increased mortality from NMRD (100,101) and from COPD (102,103). Generally, NMRD combines deaths from pneumoconioses and COPD.

In summary, the epidemiological evidence from large studies of hard rock miners demonstrates an exposure–response relation for airflow limitation and silica dust exposure that is not dependent on the presence of silicosis. In addition, several recent industry-based studies show that the silica dust–associated airflow limitation can occur in a variety of industrial settings.

Asbestos Dust—Epidemiological Evidence

Occupational exposure to asbestos dust occurred mainly in the past in mining, in asbestos product manufacturing, and in workplaces where asbestos was used for its heat insulation properties. In the presence of asbestosis, lung function impairment associated with asbestos dust exposure is primarily of restrictive nature (20,104,105). Nonetheless, several epidemiologic studies have shown that exposure to asbestos dust can be associated with obstructive as well as restrictive lung function impairment (106–113). This suggests that asbestosis-related functional changes can be coexistent with dust-related airway disease (20). 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 (112). Other occupational groups potentially exposed to asbestos and investigated for asbestos-related lung function impairment were electricians (114), boilermakers (115), and plumbers and pipe fitters (116) from the construction industry in Edmonton, Canada. All three groups of workers had significantly higher prevalence of respiratory symptoms in comparison with telephone workers, but only the pipe fitters and plumbers combined together had significantly lower FVC in comparison with the telephone workers (115,116).

Portland Cement

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 (117–120). One of these studies also reported very high respirable dust exposure ($> 40\ mg/m^3$). However, in two recent studies, no relation between exposure to Portland cement dust and airflow limitation was found (121,122). 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 this particular exposure may be as relevant to the epidemiology of irritant gas as mineral dust exposure.

Mineral Dust—Summary Comments

Many epidemiological studies show association between occupational mineral dusts and increased lung function impairment in nonsmokers and in smokers after adjustment for smoking. There can be several mechanisms by which mineral dust exposure causes lung function impairment even in the absence of radiological signs of pneumoconiosis or a restrictive pattern of impairment. Depending on the type of dust, exposure pattern, and individual susceptibility, there can be pathologic states with various effects on pulmonary function: chronic bronchitis, bronchiolitis, and emphysema, which cause airflow obstruction. The large epidemiological studies on coal and gold miners show that both coal and silica dust are associated with obstructive impairment due to the effect of dust itself and are independent of the presence of pneumoconiosis radiographically or restriction physiologically. The variability between the smaller studies in the estimated excess loss in lung function and the pattern of impairment may be due to differences in exposure levels, dust toxicity, the prevalence of pneumoconiosis, sample size, and the prevalence of smoking, because smoking usually potentiates the effect of dust on morbidity and mortality from COPD (75). Because of the complexity of the various mechanisms involved in airflow limitation in mineral dust–exposed workers, it is difficult in smaller studies to discern the individual risk factors in the absence of good data on occupational exposure, radiological changes, and smoking history.

EXPOSURE TO ORGANIC DUSTS

There is considerable evidence that agricultural exposures are associated with the development of chronic airway disease. These exposures included dusts from cereal grain, animal feed, soil, and components of microorganisms such as endotoxin and fungi which initiate an inflammatory process in the airways and may ultimately lead to chronic airway disease. We have already presented evidence of development of chronic airflow obstruction due to chronic exposure to cotton dust (Stage IV byssinosis) and grain dust in Chapter 27 and wood dust in Chapter 22. In this section, the effects of chronic exposure to organic dust in crop and dairy farming are discussed. It should be noted that fewer studies have been conducted among crop and dairy farmers compared with other types of organic dust.

Crop Farmers

The prevalence of chronic bronchitis from mailed questionnaire surveys was 7.5% among Finnish farmers (123) and 23% among cattle farmers in Manitoba (124). Dosman et al. (125) reported significantly lower lung function in farmers in Saskatchewan compared with controls. A questionnaire study of crop farmers in Europe found that 12.4% had chronic phlegm, 3.3% asthma, 14.9% wheeze, and 15.2% organic toxic syndrome (126). Another cross-sectional study of European and Californian crop farmers (127) found that rhinitis and asthma were less prevalent in European farmers

than in Californian farmers (12.7% vs. 23.9% and 2.8% vs. 4.7%), but chronic bronchitis and toxic pneumonitis were more prevalent in Europe than in California (10% vs. 4.4% and 12.2% vs. 2.7%). The high prevalence of chronic bronchitis and toxic pneumonitis in European farmers was attributable to indoor work (Table 3).

On the other hand, some studies failed to detect differences in the prevalence of symptoms or lung function abnormalities in grain farmers compared with controls as in Manitoba (128) and in England and Wales (131). In addition, low prevalence of symptoms has been reported among Hispanic farm workers in the citrus, tomato, and grape industries (132).

Dairy Farmers

In general, farming involving animals tended to have a higher prevalence of symptoms than farming involving grain or crops (Table 3). Babbott et al. (129) reported chronic bronchitis in 30% of smoking and 16% of nonsmoking dairy farmers in Vermont compared with 21% and 10% in respective controls. Lung function was significantly lower in nonsmokers only. In France, higher prevalence of chronic bronchitis and lower lung function were found among nonsmoking dairy farmers than in nonsmoking controls (130,133). Higher rates of chronic bronchitis were also reported among Yugoslavian cattle breeders compared with other farm workers (134). A study of agricultural workers in a rural area in Tuscany showed that the prevalence of chronic bronchitis was related to jobs in the cowshed (135). Measurements of organic dust were carried out on six different farms in Switzerland by Catbomas et al. (136). The concentration of PM_{10} was found to be 109 to 2207 $\mu g/m^3$ of daily barn activities in winter months and from 76 to 4862 $\mu g/m^3$ for hay storage in summer time; these levels were similar to those found in other dairy farms in Finland and in the United States. Although levels of dust were not measured in other farming facilities, the authors considered that these levels were moderate to high and suggested that long-term exposure to these levels may lead to the development of chronic obstructive lung disease (COLD). Chaudemanche et al. (137) conducted a follow-up study on the cohort of French dairy farmers in Doubs. They demonstrated an accelerated decline in FEV_1/FVC among farmers compared to controls after adjustment for other covariates, again suggesting that farmers were at a higher risk for developing COLD (Table 3).

Organic Dust—Summary Comments

There is considerable evidence that chronic exposure to organic dusts is associated with development of chronic airflow obstruction, especially for cotton and grain dust exposure when studies of relatively large numbers of workers were found to have excessive decline in lung function with a dose–response relationship irrespective of smoking. In cotton dust exposure, there is pathological evidence of airway disease from autopsy findings; in grain workers, pathological findings were scarce. In a study of retired grain workers, significant airflow obstruction was found even in nonsmokers. While endotoxin present in organic dust is likely to be responsible for acute or chronic airflow obstruction, other contaminants such as beta-glucan in molds may also be responsible. Further studies are required to identify the pathogenesis of airflow obstruction arising from exposure to these organic dusts.

Table 3 Studies of Farmers and Farm Workers

References	Type/method	Place/population	N	Prevalence of symptoms (%)		Lung function	
(123)	All farmers/postal survey	Finland		Chronic cough		NA	
		Farmers	9699	2			
		Nonfarmers	NA	0.7			
(124)	All farmers/mailed questionnaire	Manitoba		Chronic bronchitis	Dyspnea	NA	
		Farmers	833	23	14		
(128)	All farmers/ questionnaire	United Kingdom		Chronic bronchitis: no difference between groups		Dairy farmers and silage workers more likely to have reduced FEV	
		Farm workers	428				
		Controls	356				
(125)	All farmers/ questionnaire and spirometry	Saskatchewan		Chronic bronchitis	Dyspnea	FEV_1% p	FVC% p
		Farmers	1824	11	33	96.1	97.7
		Nonfarmers	556	7.7	18.2	102.8	106.1
(129)	Dairy farmers/ questionnaire and spirometry	Vermont		Chronic sputum		$FEV_1/FVC < 70\%$	
				Smokers	Nonsmokers	Smokers	Nonsmokers
		Dairy farmers	198	30	16	20%	14%
		Controls	516	21	10	18%	7%
(130)	Dairy farmers/ questionnaire and spirometry	France		Chronic bronchitis		FEF% p	VC% p
				Men	Women		
		Dairy farmers	250	17.7	5.8	78.8	95.2
		Controls	250	9.2	2.5	90.1	98.6

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEF, forced expiratory flow; p, predicted; NA, not available.

EXPOSURE TO IRRITANT GASES AND FUMES

Studying the pulmonary effects of exposure to irritant gases and fumes alone is complicated by the fact that most workplaces are complex environments where gases and fumes are comingled with dust particles larger than the submicron particles that comprise fumes. For example, in many workplaces, welders are exposed not only to metal fumes and gases, but also to larger inorganic particles (or dusts) generated by other industrial operations nearby in the workplace (138). This is also true of many metal industry and construction workplaces (139,140). Intensive animal confinement (141) and pulp and paper manufacturing (142) operations also expose employees to complex mixtures of irritant gases in addition to organic particulate matter and bioaerosols. Furthermore, in many of these environments there are concomitant exposures to agents that provoke asthma and acute nonspecific airway hyperresponsiveness that may or may not progress to chronic bronchitis symptoms and chronic airflow obstruction (143,144).

Nevertheless, there is a growing body of evidence that exposure to irritant gases and fumes can lead to both acute and chronic airflow limitations. Some evidence also suggests that these exposures in combination with inorganic and organic particulate matter may augment the effect of exposure to dust alone. This has been seen in mining and smelter workers (80,145), workers in rubber manufacturing (146,147), welders (148–150), tunnel and road workers (85,151,152), firefighters (153–155), and, recently, in a general population-based case–control study of risk factors for COPD (156). The remainder of this section will review evidence from occupational groups where exposure to irritant gases and fumes predominate over inorganic and organic particulate matter, and examine population-based studies in which investigators have attempted to separate the effect of gases and fumes from dust.

Welding

Airborne exposures associated with welding include volatilized metal and submicron particles from both the welding rod and the base metal being welded; smoke or fume from burning of metal coatings, shielding gases, fluxes; and, often, dust or other airborne contaminants present in the surrounding workplace. The nature and extent of exposures experienced by welders have been reviewed by many authors (157–160) and, although they have been shown to vary widely, exposure levels are often in excess of regulated occupational exposure limits or guidelines (138–141).

Some welders experience acute airflow obstruction demonstrated by changes in airflow rates over a work shift (161,162) or changes in nonspecific bronchial responsiveness in response to welding exposures (143). 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 (163–165). Epidemiologic studies have shown welders to experience increased cough and phlegm in association with measures of increased cumulative exposure to welding (150,166); however, one study found that bronchitis symptoms were reversible and not associated with lung function decline over a subsequent three-year period (161). The possibility that the inflammatory response to welding fume components may be lessened by the development of "tolerance" has been suggested (167).

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 (148,149,168); one study also reported functional changes in small airways among nonsmoking welders (169), 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 et al. 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 who were consistently using local exhaust ventilation (148). 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 nonwelders, but no differences were seen when comparing nonsmoking welders and nonwelders (170).

Industries at High Risk for "Gas and Fume" Exposure in Addition to Dust

Other environments in which irritant gases and fumes are commonly encountered include foundries and smelters, rubber production, pulp and paper production, and animal confinement operations. Few studies of foundry and smelter workers report pulmonary effects of gases or fumes separately from the effects of dust (particularly silica and asbestos) or polycyclic aromatic hydrocarbons. In a study of workers at a small iron foundry, Gomes et al. (97) found reduction in measures of airflow among workers in high dust exposure jobs, and in one job with high exposure to gases and fumes but low dust exposure. Similarly, in a study that included underground miners and smelter workers, Manfreda et al. (80) found abnormal airflow rates (compared to expected values) only in smoking smelter workers but not in miners. The main exposure difference between the two work groups was exposure to sulfur dioxide and metal fumes among smelter workers. Among tunnel construction workers, exposure to nitrogen dioxide (from blasting gases and diesel fumes) was associated with increased longitudinal decline in airflow rates (151).

Rubber production workers exposed to high levels of rubber curing fumes have been shown to have increased prevalence of chronic bronchitis symptoms, significantly reduced airflow rates, and a greater longitudinal decline in lung function, compared to internal control groups (147,171,172). A recent study of Dutch rubber workers found no exposure-related symptom differences or acute changes in lung function, but did find an association between cumulative exposure and airflow obstruction (173). Finally, another recent study of Norwegian asphalt workers found a significantly higher prevalence of COPD (defined as FEV_1/FVC ratio less than 0.7 plus chronic bronchitis symptoms) compared to outdoor construction workers (152). None of these studies were able to differentiate the effects of dust from those of "fume" in the populations studied. Rubber "fume" includes a wide variety of cyclohexane soluble chemicals, whose concentrations vary greatly with production associated factors (174).

Pulp and paper workers are also exposed to organic dusts (e.g., wood and paper) and highly irritating gases (such as chlorine, chlorine dioxide, and ozone) especially in bleaching operations. Numerous studies have shown that high exposure peaks to these irritant gases are linked to increased acute airflow obstruction and increased asthma in pulp workers (144,175–177). The relationship of exposures in

this industry to chronic airflow obstruction has also been investigated. Increased mortality for obstructive lung disorders was seen among Swedish pulp and paper workers (178), but not in U.S. workers (179). Among the U.S. pulp and paper population, episodes of high exposure to chlorine or sulfur dioxide were associated with chronic changes in spirometric measures of airflow (180). Similar findings have been seen in populations of workers exposed to organic dusts in combination with highly irritating gases such as ammonia, especially in animal confinement agriculture (181–184). An exposure–response relationship between chronic airflow obstruction and duration of exposure in hog barns was even observed recently among swine veterinarians (185), and Donham et al. (183) found a significant synergistic effect of dust and ammonia combined on airflow rates among poultry workers.

Irritants—Summary Comments

A number of studies show that exposures to irritant gases and fumes can work additively or synergistically with exposure to airborne particulate matter (both organic and mineral dust) to enhance the risk of COPD across a broad range of industries and settings. These studies are supported by laboratory evidence of airway inflammation in response to specific metals and metal fume mixtures and irritant gases.

EXPOSURE TO TOXIC AGENTS THAT CAUSE BRONCHITIS AND BRONCHIOLITIS OBLITERANS (BO)

Nature of Obstructive Disease in the Terminal Airways

In recent years, workplace exposure to several toxic agents has been associated with acute bronchiolitis, which often evolves into a chronic bronchiolar inflammatory process termed BO. If the toxic exposure is of specific type and/or of sufficient magnitude, there can be rapid progression to obliterative bronchiolitis (BO), a small airway inflammatory disease involving the terminal bronchioles, respiratory bronchioles, and alveolar ducts to various degrees. Although formerly considered to be rare, it is now more frequently diagnosed in adults as a complication of chronic graft versus host as well as in other conditions, such as in association with connective tissue diseases over and above sporadic toxin-related cases. In addition, the condition is often idiopathic in form. When BO occurs together with an organizing pneumonia, the designation bronchiolitis organizing pneumonia (BOOP) or cryptogenic organizing pneumonia (COP) is used. As opposed to BO, associated with a poorly reversible, obstructive ventilatory deficit, BOOP is associated with restrictive finding on lung function and a decreased D_{LCO}. Although BOOP has also been reported in association with certain occupational triggers, it will not be considered further here.

Occupational Agents Associated with BO

Both acute and chronic exposure to occupational agents may induce BO. Acute exposure to a number of toxic agents may cause acute respiratory distress which initially might resemble irritant-induced asthma. As the disease process evolves, however, the clinical-physiologic-radiologic changes of BO become evident.

Acute injury by toxic gases is a common cause of BO and has been reported after inhalation of high concentrations of nitrogen dioxide, sulfur dioxide, ammonia, hydrogen fluoride, phosgene, hydrogen bromide, and hydrogen chloride (187–194).

It is important to remember that these outcomes appear to be quite uncommon, even in larger series of irritant gas exposed persons. The typical scenario among these affected workers is that they initially develop chemical pneumonitis followed by a silent interval with subsequent development of the severe, irreversible BO syndrome. In 1984, a massive leak of methyl isocyanate in an Indian pesticide plant caused many lethal and sublethal respiratory injuries (195). Long-term chronic lung disability in many exposed workers suggested fibrosing constrictive BO but pathological confirmation is scarce. The chronic nature of some cases of BO was further confirmed by an investigation of 77 Iranian war veterans who were exposed to very low levels of a chemical warfare agent, sulfur mustard, and initially suffered no acute respiratory effects. Serial lung high resolution CAT scans, questionnaire data, and pulmonary function tests in these subjects later revealed significant air trapping in over one-third of them. Septal wall thickening and bronchiectasis were also demonstrated in five and three cases, respectively.

Man-Made Organic Fibers

The role of man-made organic fibers, as a potential cause of BO has received considerable attention in recent years (197). This may have coincided with new industrial developments of producing respirable fine-diameter fibers. In 1998, symptomatic workers with unexplained radiographic and physiologic abnormalities in a nylon flocking plant had open lung biopsies which revealed interstitial pneumonia in six cases and BOOP in one case, respectively (198). All seven biopsies also showed peribronchiolar, vascular, interstitial lymphoid nodules with germinal centers, and most had lymphocytic bronchiolitis and interstitial fibrosis. Review of tissue specimens from workers at a different nylon flock plant demonstrated similar findings. This investigation caused a wild flurry of accusations and counter-accusations between management in the nylon flock company and the investigational team (196). This culminated in a Centers for Disease Control consensus clinical-pathologic workshop which concluded that nylon flock had caused a heretofore undescribed form of lymphocytic bronchiolitis and peribronchiolitis (199,200). Of interest was the fact that six of these cases improved after removal from the workplace, and six others who had improved and decided to return to their original jobs had relapses (200).

Food Flavorings

The most recent outbreak of toxin-related BO occurred in eight workers in a microwave-popcorn production plant (201). These workers developed severe BO and had to be removed from the workplace. This experience led to an expanded study involving the remaining workers in the plant. This was a combined questionnaire and spirometric epidemiologic survey in which 87% of the current workforce participated. Analysis of these results revealed that workers at this plant had 3.3 times the expected rate of clinical obstructive symptoms and twice the expected rate of physician-diagnosed asthmatic/chronic bronchitis. There was also a strong association between the highest exposure quartile of diacetyl, a volatile butter-flavor ingredient, and the extent of airway obstruction found in these workers.

Miscellaneous Causes

Individual instances of BO have occurred after exposure to incinerator fly ash, animal feed, spices, and benzalkonium (202–205).

BO—Summary Comments

Acute and chronic irreversible injury to terminal small airways may at times be confused with asthma or other COPD diseases. For the most part B and BO are caused by known toxic agents, but several epidemics of BO have occurred after previously unrecognized toxic substances. Bronchiolitis and BO should be considered as a possible cause in the differential diagnosis of workplace obstructive syndromes.

DEFINING THE PROBLEM OF COPD FROM AN EPIDEMIOLOGICAL PERSPECTIVE

COPD refers to a single clinical condition, but also serves as an umbrella term or category that subsumes several different and only partially overlapping disease entities. Moreover the conditions that are included or separated from the COPD categorization may vary depending on the nature of the epidemiological investigation involved. COPD is characterized by airflow limitation that is not fully reversible. Two main pathological conditions causing COPD are chronic bronchitis and emphysema. Often the two diseases processes overlap and thus their relative contribution is difficult to discern. In epidemiological research the presence of COPD can be ascertained using pulmonary function testing and using ATS/ERS definitions of COPD or doctor diagnosis of COPD, chronic bronchitis, or emphysema. A related, more overarching category of chronic obstructive lung disease (COLD) further includes asthma, but the COLD categorization will not be considered further in this discussion.

Thus, the term COPD has been applied heterogeneously depending on the setting of its use. Some degree of clinical standardization, including severity gradation, has been attempted through international efforts. For example, the recent promotion of "GOLD" criteria attempts to set guidelines based on postbronchodilator spirometry that can be used to categorize or "stage" persons with COPD according to symptoms and lung function (206). Nonetheless, large gaps remain between COPD defined at the level of the individual person, usually a patient in a clinical setting, with the definition based on subjective and objective medical criteria (such as incorporated in the GOLD guidelines), and COPD defined at a population level, based on epidemiological criteria intended to consistently estimate case incidence and prevalence.

Epidemiological analyses of COPD generally rely upon one of two approaches to case definition. Survey research (including secondary analyses of administrative or other data sets) relies upon "report" of one of the underlying COPD conditions. This can be restricted to COPD and emphysema only or also can include chronic bronchitis, as noted above. When chronic bronchitis is included, stratified analyses with and without this condition subset are often presented. The COPD categorization in epidemiological terms can be based on the subject's responses to a questionnaire affirming that the respondent has received a physician's diagnosis of at least one of the target conditions of interest. It can also be based on diagnostic data (for example, International code of death (ICD)-based conditions, prescribed medication, or medical test results) identified through medical records or insurance claims. Some large epidemiological field studies define cases based on primary data collected as part of the study. For COPD, primary definition in these studies depends on spirometry (although cut-off values defining obstruction may vary), whereas chronic bronchitis is typically defined through a standard battery of questionnaire items establishing the presence of productive cough for three months in two consecutive years.

Both of these epidemiological approaches have advantages and disadvantages. Survey approaches allow larger, less costly sampling, but have less precision due to misdiagnosis and potential biases due to recall and access to care. Field studies are limited by case selection effects and, in particular, by limited ability to assess emphysema (given that diffusing capacity measurements and sensitive radiographic assessment are rarely included in such studies). Importantly, despite differences in methodology, epidemiological investigations of COPD provide important measures of association and risk that cannot be gleaned from individual case reports or even large clinical series.

The most familiar epidemiological measure of risk is the relative risk (RR) and the related estimate, the odds ratio. By comparing exposed to unexposed groups, these measures are used commonly to gage the strength of a link between a suspect risk factor and a specific disease outcome. Attributable risk is a different epidemiological measure that can be even more relevant when analyzing factors linked to COPD. Attributable risk, more specifically the "PAR%," integrates the magnitude of the RR together with the general frequency of the exposure in the population. A putative exposure (Exposure I), for example, may carry with it an exceeding high RR, but this exposure may be experienced only by very few people within the population at large. In that case, the actual number of cases induced may be quite small. If another risk factor for the same disease (Exposure II) could have a much lower RR in absolute terms, but may be more ubiquitous, the number of cases it induces may be far greater. Thus, the proportion of all cases of disease attributable to Exposure II will be higher—it will be associated with a larger PAR%. The calculation of the PAR% from an epidemiologic data set can be performed using different algebraic equations. In some cases a published report may not present actual PAR% values but does provide the data (exposure proportion and RR) that allow a post-hoc calculation. The PAR% can also be estimated with corresponding confidence intervals that take into account the variance in cofactors tested in the predictive model.

Regardless of the method of calculation, a key characteristic shared by all PAR% values is that they provide an estimate of the disease caused, at least in part, by the factor in question. This is often described as the burden of disease that would be removed if this factor were eliminated. The PAR%, by definition, recognizes that two factors may act upon each other to magnify risk and that removing either one would reduce disease causation. Indeed, the combined PAR% values calculated for a series of risk factors may very well add to greater than 100% if the effects of these risk factors are multiplicative rather than solely additive.

The epidemiology of occupational asthma has benefited greatly from insights drawn from attributable risk-based approaches (see Chapter 3). The PAR% is no less relevant to the study of occupational COPD. The first reason is because of key diagnostic differences between COPD and asthma, and the second reason is because of the strong link between cigarette smoking and COPD. In asthma, clinical criteria can provide for the diagnosis of occupational disease at the individual patient level, allowing differentiation between work-related and nonwork-related cases. For example, a clinical case series of adults with new-onset asthma could be stratified between those with occupationally related disease based on predefined diagnostic criteria and those who do not meet a clinical definition of occupationally related asthma. On this basis, the incidence of occupational asthma can be estimated and can be compared to general incidence rates. This is not tantamount to a PAR%, and issues of underdiagnosis and underdetection would temper the interpretation of such estimates. Nonetheless, this can provide a basis for population-based inferences of the occupationally

related burden of asthma. Occupational COPD does not lend itself to such an approach. At present, there is no set of generally accepted clinical criteria by which an individual patient is likely to be diagnosed as having "occupational COPD." Furthermore, even the term "chemical bronchitis," which is sometimes used in clinical practice, does not have a standard application; emphysema is rarely, if ever, diagnosed as work related. Occupational disease surveillance programs and registries, although acknowledged to under-report asthma, capture virtually no COPD. In general, workers' compensation insurance schemes have resisted awards for work-related COPD.

The direct and powerful link between cigarette smoking and COPD is the second reason why PAR%-based epidemiological assessments of work-related disease are important in COPD. Although theoretical models of COPD induction have always allowed for other causes beyond cigarette smoking, in clinical practice, smoking is typically considered the sole relevant risk factor for such disease. Adopting a PAR% approach to the question of smoking, occupation, and COPD is particularly illuminating precisely because, based on PAR% analyses, "only" 80% of COPD is attributable to smoking. Therefore, a minimum of one in five cases is related to other factors. Moreover, potential interactions between exposures (for example, occupational exposure and cigarette smoking) could mean that the actual PAR% for nonsmoking factors may be even higher. Finally, the epidemiological approach takes into account cigarette smoking exposure on a group level, using appropriate statistical methods to adjust for the impact of this factor, while teasing out occupational risk factors that might otherwise be obscured.

CONTRIBUTION OF OCCUPATION TO THE BURDEN OF COPD

With renewed attention to the question of occupation as a potentially causative factor in COPD, additional studies subsequently appeared that further supplemented the existing literature. In 2001, the American Thoracic Society (ATS) undertook development of a position statement on the "Occupational Contribution of the Burden of Airway Disease." This review was submitted and approved by the ATS in 2002 and published in 2003 (208). The ATS position statement also reviewed the scientific literature in relation to asthma and occupation, but that topic will not be addressed here. The ATS statement findings in relation to COPD and occupation

Table 4 The Occupational Contribution to the Burden of COPD

Disease endpoint	Number of studies	Number of subjects	Countries included	Median PAR%	Range PAR%
Chronic bronchitis	8	> 38,000	8	15	4–24
Breathlessness	6	> 25,000	6	13	6–30
Airflow obstruction	6	> 12,000	5	18	12–55

Note: Based on the analysis presented in the 2002 ATS position statement.
Abbreviations: COPD, chronic obstructive pulmonary disease; PAR%, population attributable risk percent; ATS, American Thoracic Society.
Source: From Ref. 208.

are summarized in Table 4. As with the earlier 1988 review by Becklake, this analysis found a consistent link between occupational exposure and COPD based on PAR% estimates.

It should be noted that although several study endpoints are included in Table 4, many are multiple endpoints derived from the same study (10 independent studies in total). Nonetheless, the consistency and the strength of the associations are impressive. Since the ATS publication, a number of additional analyses have further reinforced the body of evidence linking occupation to COPD. A large study of COPD-related mortality in high and low dust-exposed construction workers in Sweden found a PAR% of 11% overall and 53% among nonsmoking workers (209). A nationwide telephone survey of occupation and COPD in the United States has found a smoking-adjusted occupational PAR% for COPD of 20%, increasing to 28% after excluding those with chronic bronchitis alone without concomitant COPD or emphysema (210). A secondary analysis of the U.S. National Health and Nutrition Examination Survey (NHANES) found that occupationally associated PAR% of airway obstruction was 19% overall and 31% among nonsmokers (211,212). Other reports were also published as the ATS review studies have also indicated the same direction of association between work-related factors and airway obstruction or chronic bronchitis (212–218). Beyond these studies, other analyses of the effects of occupational exposure among persons with alpha-1-antitrypsin deficiency serve to further support the biological plausibility of work-related COPD (219,220). Taken together, these studies support a causal association between occupational exposures to vapor, gas, dust, and fume and COPD.

OVERALL SUMMARY

The body of scientific evidence supports a causal link between occupational exposures broadly defined as gases, vapors, dusts, and fumes and COPD, including airway obstruction, chronic bronchitis, and emphysema. The findings across a number of locations using a variety of analytic methods have been remarkably consistent.

A number of studies have suggested that the strength of the effect of having worked in a "dusty trade" is in a range consistent with the risk associated with light to moderate smoking. We do not yet have strong data delineating the potential interactive effects of noxious workplace exposures combined with smoking, although it is likely that this is more than additive based on the PAR% estimates for both that have been observed.

Even without potential synergism as an issue, on the individual level smoking cessation remains a mainstay for both primary prevention of COPD incidence and secondary prevention of disease progression. This does not mean that ongoing exposure to substantial workplace exposure to gases, dusts, fumes, and vapors should be ignored. To the degree to which nonspecific airway hyperresponsiveness is a comorbid finding in COPD and may be worsened by ongoing workplace exposures, the attribution of this component of disease should parallel the attribution of work-aggravated or work-exacerbated asthma. Retrospective attribution may prove far more challenging, especially in the face of a substantive cigarette smoking history. Each individual case requires a detailed review of all of the salient risk factors. The epidemiological perspective makes clear that simply because a person has been an active smoker does not mean that occupational factors did not play a role in the development of his or her lung disease.

DIRECTIONS FOR FUTURE RESEARCH

- Further studies to determine the pathogenesis of airway disease due to chronic exposure to various dusts, fumes, and vapors in the workplace
- Histopathologic studies on airway disease due to exposure to organic dust such as cotton and grain to determine whether emphysema is a true complication of these exposures
- Studies directed to investigate the independent effects of exposure to various dusts, vapors, and fumes in the workplace and smoking and their interaction
- Studies to determine the effects of exposure to multiple contaminants in the workplace
- Studies to determine the long-term prognosis of persons with airway disease secondary to exposures in the workplace
- Development of animal models with one or more agents that have been shown to induce BO to study the cellular response and various inflammatory indices
- Prospective evaluation of affected workers with BO using physiological tests and proinflammatory markers

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ASTHMA IN THE WORKPLACE

And Related Conditions

THIRD EDITION

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Taylor & Francis
Taylor & Francis Group
New York London

Published in 2006 by
Taylor & Francis Group
270 Madison Avenue
New York, NY 10016

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8247-2977-3 (Hardcover)
International Standard Book Number-13: 978-0-8247-2977-6 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Catalog record is available from the Library of Congress

informa
Taylor & Francis Group
is the Academic Division of Informa plc.

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com