CHAPTER 5

Occupational Health Risks for Workers Exposed to MWFs

5.1 Nonmalignant Respiratory Effects

Occupational exposure to MWF aerosols is associated with a variety of nonmalignant respiratory conditions, including lipid pneumonia, HP, asthma, acute airways irritation, chronic bronchitis, and impaired pulmonary function. This chapter reviews relevant clinical case reports, surveillance data, and epidemiologic studies of nonmalignant respiratory conditions and their association with exposure to MWF aerosols.

5.1.1 Diseases of the Lung Parenchyma

5.1.1.1 Lipid Pneumonia

Lipid ("lipoid") pneumonia (characterized by lipid deposits within pulmonary macrophages) involves an inflammatory and sometimes fibrotic response of lung tissue to exogenous lipid. In equivalent doses, mineral oils deposited in the lungs are more likely than vegetable oils to be associated with lipid pneumonia; pure synthetic MWF cannot cause lipid pneumonia because it contains no oil. Case reports of lipid pneumonia resulting specifically from occupational exposure to aerosolized oil in metalworking environments have appeared rarely in the published literature. In recent decades, Penes et al. [1990] reported lipid pneumonia in a person who worked for 16 years as a machinist, and Cullen et al. [1981] reported lipid pneumonia in a steel rolling mill worker exposed for 3 years to both straight and soluble oil MWFs. Systematic epidemiologic studies have not assessed the incidence or prevalence of lipid pneumonia among workers exposed to MWFs. However, the apparent rarity of lipid pneumonia associated with occupational exposure to oil mists in metalworking operations suggests that current exposure concentrations are generally insufficient to cause clinical cases of the disease. Clinically diagnosed lipid pneumonia is more frequently associated with nonoccupational aspiration of oily products into the lungs than with inhalation of oil aerosols in occupational settings [Proudfit et al. 1950; Foe and Bigham 1954; Sprince et al. 1994].

5.1.1.2 Hard Metal Disease

Hard metal disease of the lung (caused by inhaled tungsten carbide/cobalt) is characterized by pneumonitis and interstitial pulmonary fibrosis. Metalworkers exposed to MWF

aerosols contaminated with cobalt from tungsten carbide/cobalt tool pieces (primarily in operations involving the grinding of hard metal parts such as cutting tools) are at risk for this disease. Cobalt concentrations averaged 664 mg/L in bulk samples of MWF taken from sumps in some grinding operations [Kennedy et al. 1995a]. Hard metal disease may develop within 2 years of initial exposure and may have a rapid progression; or it may become clinically apparent only after 30 years of occupational exposure [Sprince 1992]. Cobalt toxicity may be enhanced when it is in the ionized form in MWFs used for grinding operations [Sprince 1992].

5.1.1.3 Legionellosis

A large outbreak of Pontiac fever (a self-limited, nonpneumonic form of legionellosis with influenza-like symptoms) was shown to be caused by exposure to contaminated MWF aerosol in an engine manufacturing plant [Herwaldt et al. 1984]. The outbreak occurred on startup following an 8-day shutdown that had allowed bacterial growth in the MWF reservoir. A newly identified species of *Legionella* was isolated from this soluble MWF. Compared with controls, workers with symptoms meeting the case definition criteria had significantly elevated antibody titer to this organism ($P<0.0001$). To date, no cases of legionnaires' disease (the sometimes fatal pneumonic form of legionellosis) have been documented to be associated with exposure to contaminated MWF, and no other outbreaks of MWF-associated nonpneumonic legionellosis have been reported in the scientific literature.

5.1.1.4 HP

HP, also known as allergic alveolitis, involves an immunologic reaction to inhaled antigen and is believed to require prior sensitization to the antigen. This disease is characterized in its acute phase by alveolar inflammation and influenza-like symptoms; in its chronic phase (following repeated exposures), it is characterized by pulmonary fibrosis associated with respiratory impairment. Common antigens associated with HP in nonmetalworking occupational settings include airborne microbes (especially bacterial spores of *Saccharopolyspora* spp., spores of *Thermoactinomyces spp.*, fungal spores of *Alternaria* and *Aspergillus spp.*, and various large-molecular-weight compounds, including proteins). Two cases of HP associated with MWFs were reported during a 3-year period to an occupational respiratory disease surveillance program operating in the United Kingdom [Merideth and McDonald 1994]. Many more cases at a number of facilities in North America have been recently recognized [Rosenman et al. 1994; Bernstein et al. 1995; Rose et al. 1996; Kreiss and Cox-Ganser 1997].

Bernstein et al. [1995] published the first detailed case reports of HP associated with occupational exposure to MWF. A small metalworking shop introduced a synthetic MWF in 1991; 6 to 11 months later, 6 workers developed HP symptoms. Symptoms and other clinical abnormalities resolved in all six workers after they were removed from the

workplace (and after additional corticosteroid treatment in two of the workers). MWF sump samples were found to be contaminated with bacteria, and all six affected workers had precipitating antibodies to one of the bacterial contaminants, *Pseudomonas fluorescens*. Serum-precipitating antibodies to other organisms isolated from the MWF were also present in some of the affected workers. The available data do not permit a definitive conclusion regarding *Pseudomonas* as a cause of the outbreak, particularly since precipitating antibodies to *Pseudomonas* have been found in apparently healthy workers exposed to contaminated MWF [Mattsby-Baltzer et al. 1989a, 1990]. Nevertheless, on the basis of this investigation and by analogy to other occupational settings in which HP is known to occur, microbes that contaminate MWF would be likely etiologic suspects.

Rose et al. [1996] recently reported an additional six cases of biopsy-confirmed cases of HP among MWF-exposed automobile production workers in three different plants. In all cases, episodic respiratory and systemic symptoms were temporally related to the presence of affected workers in work areas where soluble MWFs were in use. One affected worker (a 57-year-old who had not smoked for the preceding 28 years) had been a toolmaker at the same plant for 28 years. Progressive illness resulted in hospitalization for respiratory failure. Physical examination revealed inspiratory crackles; a chest radiograph revealed diffuse interstitial infiltrates; arterial oxygenation was markedly reduced; and pulmonary function tests showed restriction and reduced diffusing capacity. Treatment included corticosteroids and removal from work. Repeat pulmonary function tests 1 year later revealed substantial improvement. At the time of the report, exposures had not been well characterized and no specific agent(s) had been identified as the likely cause.

These and several other recent outbreaks of MWF-associated HP led to a topical workshop sponsored by the International Union, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW)-Chrysler National Joint Committee on Health and Safety [Kreiss and Cox-Ganser 1997]. Participants discussed eight different outbreaks at eight plants involving a total of 98 physician-diagnosed cases of HP. Major conclusions of that workshop included the following:

- A risk of HP is associated with use of microbially contaminated, water-based MWFs characterized by a predominance of "unusual" flora (e.g., *Mycobacteria chelonae* was found in MWF in 4 of the 6 outbreaks in which investigators attempted to isolate *Mycobacteria*).
- Most reported cases occurred despite apparent MWF aerosol exposure concentrations below 0.5 mg/m^3 (TWA).

In the absence of more definitive information on which to base primary prevention, workshop participants identified research needs and outlined secondary prevention strategies aimed at early case identification and removal [Kreiss and Cox-Ganser 1997].

5.1.1.5 Summary

Until recently, all four of these diseases of the lung parenchyma (lipid pneumonia, hard metal disease, legionellosis, and HP) appeared to have been relatively unusual in workers exposed to MWF aerosols. However, these diseases have generally not been systematically studied among workers exposed to MWF aerosol, and the recent emergence of HP-like disease associated with MWF aerosol and the large numbers of workers exposed justify considerable concern [Blanc 1995; Kreiss and Cox-Ganser 1997]. It is possible that HP has been occurring in MWF-exposed workers for many years but has not been detected because HP is sometimes difficult to diagnosis and has only recently been targeted for study among workers exposed to MWF; however, it is also possible that recent changes in the work environment, fluid composition, or biocide use have increased the risk of HP among these workers [Kreiss and Cox-Ganser 1997].

Prevention depends on reducing and eliminating worker exposures to the causative agents. In the case of lipid pneumonia, no reliable quantitative exposure-response data are available, but the apparent rarity of the disorder among MWF-exposed workers suggests that current exposure concentrations are not generally associated with the disease. Prevention of hard metal disease depends largely on keeping exposures associated with operations involving tungsten carbide tools below the current NIOSH REL of 50 $\mu g/m^3$ for cobalt [NIOSH 1988a] (and perhaps limiting them to a concentration considerably lower than that REL) [Kennedy et al. 1995a]. The prevention of contamination of MWFs by *Legionella* spp. would eliminate legionellosis associated with occupational exposure to MWF aerosol. The specific etiologic agent(s) for HP among workers exposed to MWF aerosol remain(s) unknown. However, possible preventive approaches are the control of microbial growth, reformulation of MWFs to eliminate specific components (if any are identified as causative agents), and perhaps the general reduction of MWF aerosol exposures. Caution is warranted with regard to the use of biocide additives to control microbial growth in MWFs: Not only might the biocides be associated with toxic effects on workers who inhale MWF aerosol, but they might suppress the microorganisms that are more susceptible to biocide thereby allowing the overgrowth of less susceptible organisms that may cause HP [Kreiss and Cox-Ganser 1997].

5.1.2 Asthma and Other Disorders of the Pulmonary Airways

5.1.2.1 Background

Recent concerns about the respiratory hazards of occupational exposure to MWF aerosols have focused on airways disorders even more than on HP. A variety of components, additives, and contaminants of MWFs are sensitizers or irritants known to induce new-onset asthma, aggravate pre-existing asthma, and irritate the airways of nonasthmatic workers. These sensitizers, irritants, or toxicants include ethanolamine and other amines, colophony, pine oil, tall oil, metals and metallic salts (e.g., chromium, nickel, cobalt, and tungsten carbide), castor oil, formaldehyde, chlorine, various acids, and

fungal and other microbial contaminants (including gram-negative bacterial endotoxin) [Chan-Yeung and Malo 1993b; Hendy et al. 1985; Kennedy 1992; Michel et al. 1992]. However, only a few of these agents have been documented as causes of MWF-associated asthma.

Symptoms of airways irritation (e.g., cough) occur with sufficient exposure to airborne irritants. In addition to symptoms, the acute airways response to an inhaled irritant often involves short-term, apparently reversible decrements in measured pulmonary function. Repeated exposure to an irritant can evolve into chronic bronchitis, a condition characterized by chronic production of phlegm. Inflammation associated with chronic airways irritation may also cause accelerated decline in lung function, which can ultimately result in symptomatic functional impairment and pulmonary disability.

Asthma is an airways disease with a marked variability in airflow limitation. It can be induced by exposure to an immune sensitizer (classic immunologic asthma) or an irritant agent (irritant-induced asthma). Whether initially induced by a sensitizer or an irritant, symptomatic episodes of immunologic or irritant asthma can be triggered by subsequent exposure to the specific causative agent or any irritant, even at concentrations substantially lower than those tolerated by nonasthmatic persons. Clinical asthma spans a broad range of severity—from occasional mild symptoms to frequent, severe episodes requiring immediate medical attention and sometimes (though rarely) resulting in death. Increasing evidence suggests that worker's occupational asthma is more likely to become chronic (i.e., with irreversible airflow limitation and continuing airways hyperresponsiveness even after removal from exposure) the longer that worker continues to be exposed after onset of the asthma [Chan-Yeung and Malo 1995].

The remainder of this section on asthma and airways disorders reviews evidence relating MWF aerosol exposure to asthma, airways irritation and other respiratory symptoms, chronic obstructive pulmonary disease, and acute reductions in lung function.

5.1.2.2 Asthma

Case reports and observations from surveillance programs

Forbes and Markham [1967] reported two cases of work-related asthmatic illness in workers exposed to MWFs. Both workers (one a machinist using straight oil MWF and the other a hard-metal tool grinder using soluble oil MWF) experienced the onset of asthmatic symptoms while employed, and both experienced increased symptoms on exposure to MWF aerosol. No information was provided on levels of exposure.

Savonius et al. [1994] reported two metalworkers who, after several years of exposure, developed asthma attributed to TEA in the MWF they used. Exposure concentrations were not reported. Neither worker reacted to laboratory inhalation challenge with a MWF containing no TEA. But when challenged with stirred MWF containing TEA,

both workers showed substantial reductions in peak expiratory flow. Two other patients with hyperreactive airways did not respond to a similar inhalation challenge. On the basis of these findings, Savonius et al. [1994] concluded that exposure to TEA vapor may induce asthma. Note that the triggering of asthmatic reactions in these workers did not require exposure to the MWF in aerosol form.

Robertson et al. [1988] reported on 25 workers who were exposed to MWF aerosols and were referred to an occupational health clinic for evaluation of symptoms suggestive of occupational asthma. On the basis of serial peak flow monitoring, 20 of these workers were found to have either definite occupational asthma (i.e., work-related variation in peak flow of at least 20% in more than 75% of monitored workweeks) or equivocal occupational asthma (i.e., work-related variation in peak flow of at least 20% in 25% to 75% of monitored workweeks). The median latent period (i.e., from initial hire to first symptoms) among the 13 definite cases was 12 years (range was <1 to 41 years). One had worked only with straight oil MWF, nine had worked only with soluble oil MWF, two had worked with both straight and soluble oil MWFs, and one had worked with "various" MWFs. MWF aerosol exposure concentrations were not reported. Inhalation challenge testing carried out in 6 of these 13 definite cases resulted in clear-cut asthmatic reactions (maximum immediate or late FEV_1 [forced expiratory volume in 1 sec] reductions ranged from 17% to 42%) in four, and inconclusive reactions in the other two. One of the four with clear-cut reactions reacted to nebulized, used soluble oil MWF (which was microbially contaminated) but not to nebulized, unused (and therefore uncontaminated) soluble oil MWF. The other three reacted to challenge with fresh soluble oil MWF. Interestingly, one of these latter three cases (described in detail by Hendy et al. [1985]), reacted to volatiles from stirred (not nebulized) soluble oil MWFs, to volatiles from the pine oil reodorant contained in the soluble MWF, and to colophony (a related agent known to induce occupational asthma), which was a component of the emulsifier used in the soluble MWF. Further challenges with other constituents of the soluble oil MWF failed to identify any other specific agent(s) responsible for the asthmatic reaction in this individual.

Gannon and Burge [1991] examined data from a physician reporting system for occupational asthma in the West Midlands Region of England. They reported that MWF aerosols and machine tool operators were among the four most frequently implicated agents and occupations, respectively. They also estimated an annual incidence for occupational asthma of 36 per million among metal and electrical manufacturing and repair workers—compared with a rate of less than 12 per million in professional and clerical workers (suggesting a threefold relative risk [RR]). Gannon and Burge [1991] provided no estimates of exposure concentrations for identified cases.

An occupational respiratory disease surveillance program operating in the United Kingdom has provided additional evidence regarding the incidence of work-related asthma associated with MWF aerosols. In 1989, 7 reported cases of occupational asthma were

attributed to MWF exposure, and the estimated annual incidence of reported occupational asthma was approximately 250/million in the *metal making and treating* occupational group—25 times higher than the estimated annual incidence of less than 10/million for the *professional, managerial, clerical, and selling* occupational group [Meredith et al. 1991]. By the end of 1991, a total of 22 cases of MWF-associated occupational asthma were reported in that program [Merideth and McDonald 1994]. A total of 119 cases of occupational asthma—nearly 2% of the estimated cases for the 1989–1996 period in the United Kingdom—were attributed to "cutting oils" [Ross et al. 1997]. No exposure concentrations were provided in any of these surveillance reports.

An occupational asthma surveillance program in Michigan (Sentinel Event Notification System for Occupational Risks [SENSOR]) also provides evidence regarding asthma associated with exposure to MWF aerosol [Rosenman et al. 1995; 1997a,b]. MWFs are reported as the second most common cause of work-related asthma in Michigan, accounting for 13% (137 of 1,047) of the cases of occupational asthma reported during the period 1988–96 [Rosenman et al. 1997a]. Workers identified as cases worked at 54 different facilities, and the majority were employed in metal parts manufacturing. Seventy-five of the cases were employed in the automobile parts manufacturing industry [Rosenman et al. 1995]. Of 773 interviewed coworkers of the reported cases, 21% had developed (since hire) new asthma or new work-related symptoms consistent with occupational asthma (i.e., work-associated daily or weekly shortness of breath, wheezing, or chest tightness) [Rosenman et al. 1997b]. Of 113 coworkers interviewed at 6 facilities with measured MWF aerosol concentrations below 0.5 mg/m^3, 13 (11.5%) reported new onset asthma or symptoms consistent with asthma, compared with 34 of 145 (23.4%) at 7 facilities where measured MWF aerosol ranged from 0.5 to 1.0 mg/m^3, and 30 of 179 (16.8%) at 6 facilities where exposure concentrations were 1.0 mg/m^3 or higher [Rosenman et al. 1997b]. Limitations of these findings include (1) lack of information to enable any assessment of potential for participation bias, and (2) lack of exposure measurements for 13 other facilities where no air sampling was conducted because the industrial hygienist felt that the MWF aerosol concentration was well below the current PEL of 5 mg/m^3 for oil mist (but where 25% of 306 coworkers reported new-onset asthma and/or symptoms suggestive of work-related asthma).

Rosenman et al. [1997b] also found that new-onset asthma or symptoms suggestive of work-related asthma were reported by 10% (18 of 183) of coworkers in 10 facilities using only straight oil MWFs, 23% (27 of 115) of those in 7 facilities using soluble (and no synthetic or semisynthetic) MWFs, 28.6% (4 of 14) of those in 2 facilities using semisynthetic (and no synthetic) MWFs, and 25% (105/420) of those in 12 facilities using synthetic MWFs. Measures of association calculated from these data with this method of categorizing exposure by type of MWF include odds ratios (ORs) of 2.8 (95% confidence interval [CI] =1.4–5.7) for soluble MWFs, 2.9 (95% CI=0.8–14.5) for

semisynthetic MWFs, and 3.1 (95% CI=1.8–5.5) for synthetic MWFs relative to straight MWFs.

An additional eight cases of occupational asthma associated with exposure to MWFs have been reported in New Jersey and Massachusetts, the only other States that have had similar occupational asthma surveillance programs under development over the same period [SENSOR 1996; Reilly et al. 1994]. Also, six newly diagnosed cases of occupational asthma attributed to "cutting oils" were reported by several occupational medicine clinics to the AOEC Occupational and Environmental Disease Surveillance Data-base between 1991 and 1993 [Hunting et al. 1995].

The case reports and surveillance data summarized above provide minimal, if any, information about concentrations of MWF aerosol exposure and therefore cannot be used to define an exposure limit. But they do provide considerable evidence that MWF exposures are associated with the development of work-related asthma. They also provide limited evidence suggesting that risk is higher for soluble oil, semisynthetic, and synthetic MWFs compared with straight oil MWFs.

Research findings

In reevaluating a major cross-sectional respiratory morbidity study, Eisen [1995] described an inverse exposure-response relationship between the synthetic MWF aerosol exposure concentration and the prevalence of self-reported, physician-diagnosed asthma. Excluding those who had developed asthma before employment as a machinist, and using an analysis designed to control for transfer bias, Eisen demonstrated that the incident asthma cases were more than twice as likely as the nonasthmatic machinists to have been exposed to synthetic MWF aerosol in the year of asthma onset. She and her colleagues also observed indications of selective transfer of incident asthma cases away from jobs with exposure to synthetic MWFs ($P<0.10$) [Eisen 1995; Eisen and Greaves 1995]. More definitive analysis of this data by Eisen et al. [1997] is described in more detail below.

Greaves et al. [1995b, 1997] reported a comprehensive analysis of the data previously reported on by Eisen [1995]. Although there was no clear relationship between self-reported, physician-diagnosed asthma and current aerosol exposure concentrations of straight oil, soluble oil, or synthetic MWFs, the results of this analysis did suggest that cumulative exposure to soluble fluids was related to asthma among these workers. Controlling for age, race, smoking, plant, and grinding, past (cumulative) exposure to soluble MWF aerosol (thoracic fraction) was significantly associated with asthma (OR=1.02 per mg/m^3-year; $P<0.05$) despite a low OR for asthma among workers with current exposure to soluble MWFs (OR=0.6). These and related findings again suggest possible selective transfer of affected workers away from jobs with more intense exposure. Note that an OR of 1.02 per mg/m^3-year of exposure suggests a greater than two-fold risk of developing occupational asthma over a 45-year working lifetime of

exposure to MWF aerosol at 1 mg/m^3 (thoracic fraction). This may be an underestimate of effect, as only current workers were included in the study; workers who may have left these three plants as a result of their asthma would not have been included in the study.

Basing an analysis on the same population reported on previously by Greaves et al. [1995b], Eisen et al. [1997] used a cohort approach and proportional hazards model to evaluate the association of post-hire asthma to MWF aerosol exposures. Among 1,788 active workers (including assembly workers) in the analysis, 29 reported asthma initially diagnosed after hire. Based on MWF exposures during the 2-year period preceding diagnosis (to correlate with likely time of asthma onset), incidence rate ratios (RRs) were calculated. With adjustment for age and period of hire (before or after 1970), RRs were as follows: 2.0 (95% CI=0.9–4.6) for straight MWF; 0.5 (95% CI=0.2–1.1) for soluble MWF; and 3.2 (95% CI=1.2–8.3) for synthetic MWF. Aerosol exposures for the six asthmatics who worked with synthetic MWFs during the 2 years before diagnosis averaged 0.6 mg/m^3 (inhalable fraction); the range was 0.36 to 0.91 mg/m^3, and the median was 0.58 mg/m^3.

Kriebel et al. [1994, 1997] studied workers exposed to soluble oil MWFs (142 workers) and straight oil MWFs (74 workers) along with less exposed assembly workers in a major machine shop complex manufacturing automobile transmissions. These investigators found evidence for an association between self-reported physician-diagnosed asthma and work as a machinist. After controlling for age, race, gender, and smoking, machinists exposed to soluble oil MWF reported asthma twice as often as nonmachinists (OR=2.1; 95% CI=0.9–4.6; $P<0.10$); those exposed to straight MWF also reported more asthma (OR=1.4), but this latter finding was more likely than the former to be due to chance ($P>0.10$). In an analysis stratified by whether the asthma diagnosis predated employment as a machinist, Kriebel et al. [1994, 1997] found that the association was stronger for asthma with onset following employment than for asthma predating employment as a machinist. Aerosol exposure measurements were made using samplers with a seven-hole cassette inlet face selected to approximate collection efficiencies of the American Conference of Governmental Industrial Hygienists/International Standards Organization (ACGIH/ISO) size-selective criteria for inhalable mass [Kriebel et al. 1994]. At the time of the questionnaire survey, machinists at this facility who worked with straight oil MWF had a mean aerosol exposure of 0.24 mg/m^3 (inhalable fraction), and those who worked with soluble oil MWF had a mean exposure of 0.22 mg/m^3 (inhalable fraction).

Robins et al. [1997] provided relevant data from a study of machinists exposed to aerosols of soluble MWF and relatively unexposed assembly workers at an automotive transmission manufacturing plant. Among workers who reported not having pre-existing asthma, current asthma was reported and/or a clinically significant cross-shift FEV_1 decrement (of at least 12%) was experienced by 11 of 83 machinists compared with 3 of 44 assembly workers (calculated unadjusted OR=2.1; 95% CI=0.5–12.3).

Personal exposure measurements for the machinists observed to have cross-shift FEV_1 decrements of at least 12% ranged from 0.17 mg/m^3 to 0.82 mg/m^3, with a median just above 0.5 mg/m^3 (thoracic fraction).

Ameille et al. [1995] evaluated self-reported responses to the question "Have you ever had asthma?" from workers employed at a gear-box machining shop with at least 1 year of MWF exposure. Three currently exposed groups and one unexposed group were identified: 40 workers with exposure only to straight oil MWFs; 51 with exposure only to soluble oil MWFs; 139 with mixed exposure to both soluble and straight oil MWFs; and the unexposed group of 78 assembly workers. The four groups were similar with respect to smoking habits. The arithmetic mean exposure (measured as oil mist using a solvent extraction procedure) was 2.6 mg/m^3 (SD=1.8; geometric mean=2.2, geometric SD=1.9) in areas using straight oil MWFs. No sampling was done in areas using soluble MWFs. Currently exposed workers tended to be less likely to report asthma than assembly workers. Based on data provided by Ameille et al. [1995], calculated asthma ORs were 0.9 (0.26–3.34) for current exposure to straight oil MWFs and 0.8 (0.24–3.13) for current exposure to soluble oil MWFs compared with the unexposed assembly workers. Although these findings may indicate that there was no significant effect of exposure to MWF aerosol in this population, the authors presented evidence suggesting that affected workers (particularly from the subgroup currently exposed to soluble MWFs) may have left employment before the study was initiated (see next paragraph). Such selection, if it occurred, would likely have biased the measurement of any association between asthma and MWF aerosol exposure toward the null.

Ameille et al. [1995] found no significant differences in bronchial responsiveness between workers exposed to MWFs and comparison workers, or among subgroups of workers exposed to straight oil and/or soluble oil MWFs. However, the authors noted that prior self-selection away from exposure may have biased their findings: only 2 of 51 workers (4%) exposed to soluble oil MWFs alone over the previous 5 years had been excluded from methacholine testing because of impairment of baseline lung function—compared with 33 of 257 other study participants (13%) (P=0.07). Also, certain aspects of the methods used by Ameille et al. [1995] but not described in their published report may have influenced their findings (see below).

Massin et al. [1996] studied 114 male employees exposed to aerosol from soluble oil MWF in a ball-bearing plant and 55 unexposed workers in other plants in the same region of France. Geometric mean total aerosol concentrations in the machining areas of the ball-bearing plant (measured as dichloromethane-extractable oil) ranged from 65 mg/m^3 in more recent years to 2.20 mg/m^3 before 1990. Five of 113 exposed workers without prior asthma (compared with none of 53 unexposed workers without prior asthma) reported developing physician-diagnosed asthma after being hired at the ball-bearing plant (OR undefined).

Massin et al. [1996] also studied nonspecific airways responsiveness of these exposed and unexposed workers. Although methacholine challenge tests were positive in similar proportions of exposed (10 of 114) and unexposed (4 of 55) workers ($P>0.05$), the mean methacholine dose-response slope was significantly steeper among the exposed workers ($P=0.03$) after adjusting for age and baseline FEV_1. Furthermore, after adjustment for age and baseline FEV_1, slope was significantly related to cumulative exposure to MWF aerosol ($P=0.004$). Citing a personal communication from one of the coauthors of the Ameille et al. [1995] report, Massin et al. [1996] pointed out that similar results were found using the same methods applied to data for workers exposed to aerosol from soluble oil MWF in the study by Ameille et al. [1995]. This has been confirmed by authors of the Ameille et al. [1995] study [Wild and Ameille 1997].

In a prospective study of nonspecific bronchial responsiveness, Kennedy et al. [1995b] followed apprentices in metalworking and other trades over 2 years. Study subjects were nonasthmatic at the beginning of the study, and MWF exposures (total aerosol) in machine shops ranged from nondetectable to 3.65 mg/m^3 (mean 0.46 mg/m^3). Although no clinically obvious cases of asthma occurred in this group over the 2-year period of study, apprentices with at least 1,800 hr of exposure to MWFs were more likely to develop a marked increase in methacholine responsiveness over the period of observation compared with others with less exposure ($P<0.05$). In an analysis of all study subjects, increased bronchial responsiveness was positively associated with exposure to MWF [Kennedy et al. 1995b] and with development of work-related asthma symptoms (wheezing and chest tightness). Increased responsiveness was negatively associated with wearing respiratory protection at least some of the time ($P<0.05$) [Kennedy et al. 1995b]. Further followup of these study subjects is planned.

Summary

Considered in aggregate, the studies summarized above provide evidence indicative of an elevated risk of asthma among workers exposed to MWF aerosol exposure concentrations currently found in large metalworking shops. As suggested by published clinical case reports, asthma induced by MWFs appears to involve known sensitizers in some cases; but various other agents, possibly acting through irritant or inflammatory mechanisms, may be responsible for a high proportion of MWF-associated asthma cases. Table 5–1 presents selected risk estimates for asthma morbidity derived from these studies. Some evidence from cross-sectional studies strongly suggests a tendency for affected workers to transfer away from jobs with exposure to MWF.

With respect to MWF type, exposure to MWF aerosol in operations using synthetic MWFs has been associated with asthma. A State-based surveillance program received 44 reports of occupational asthma attributed to synthetic MWFs during the period 1988–94 [Rosenman et al. 1997b]; however, some of the plants where these cases were identified may also have been using other types of MWF. Also, occupational asthma has

been shown to be related to alkanolamine components commonly found in synthetic MWFs [Savonius et al. 1994]. The overall evidence from the recent research studies suggests an approximate twofold to threefold asthma risk among groups of machinists working with synthetic MWFs exposed to aerosol concentrations averaging from about 0.2 (inhalable fraction) to about 1 mg/m^3 (total oil mist). Elevated risk estimates were found in all three epidemiologic studies relevant to the association of asthma with exposure to synthetic MWF aerosol [Greaves et al. 1995b, 1997; Eisen et al. 1997; Rosenman et al. 1997b] (Table 5–1). One of these three studies had "mixed" results with respect to synthetic MWF aerosol exposure, but the findings were consistent with selection of affected workers away from the most hazardous exposure [Greaves et al. 1995b, 1997]. Findings consistent with a statistically significant, approximately threefold risk resulted from the other two studies—including the study by Eisen et al. [1997], which reanalyzed data from Greaves et al. [1995b] and took transfer bias into account. Estimated MWF aerosol exposures in the 2 years before asthma diagnosis ranged from about 0.4 to 0.9 mg/m^3 (inhalable fraction), with a mean of 0.6 mg/m^3 [Eisen et al. 1997].

Although the evidence suggesting a causal association between asthma and exposure to soluble MWF aerosol is in some ways less consistent than that for synthetic MWF exposures, there have been more studies about the relationship between asthma and exposure to soluble oil MWF aerosol. Case reports have documented asthma caused by exposure to soluble oil MWF [Hendy et al. 1985; Robertson et al. 1988] or to common components of soluble oil MWFs [Savonius 1994]. A surveillance program in Michigan received 13 case reports of occupational asthma attributed to soluble oil MWFs during 1988–94 [Rosenman et al. 1997b], although some of the plants in which these cases worked may have also been using straight oil MWF. Of the seven relevant epidemiologic studies, results consistent with statistically significant elevated risk estimates were presented only by Greaves et al. [1995b, 1997] (for cumulative exposure) and Rosenman et al. [1997b]. Findings of three of the other five studies indicated elevated, though not statistically significant, risk estimates for asthma, with point estimates ranging upward from 2.1 [Kriebel et al. 1994, 1997; Robins et al. 1994, 1997; Massin et al. 1996]. In two studies [Ameille et al. 1995; Eisen et al. 1997], the risk estimates associated with soluble MWF aerosol were less than 1. However, Ameille et al. [1995] found evidence suggesting that affected workers had transferred out of jobs with exposure to soluble MWF aerosol. Such job transfer may have biased findings from that study, and the apparently negative finding of Eisen et al. [1997] must be tempered by a statistically significant positive association between asthma and cumulative exposure to soluble MWF aerosol in the same study group [Greaves et al. 1995b, 1997]. In addition, data from both the Ameille et al. [1995] and the Massin et al. [1996] studies indicated a positive association between increased bronchial responsiveness and cumulative exposure to soluble MWF aerosol [Massin et al. 1996]. Overall, the preponderance of evidence from all these studies indicates that both airways hyperresponsiveness and asthma are associated with exposure to soluble MWF aerosol. The two European

Table 5–1. Estimated risk of asthma associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value*
Surveillance studies:					
Gannon and Burge 1991	Metal and electrical workers	—	—	—	>3-fold incidence rate (relative to professional/clerical workers [i.e., 36/million versus <10/million])
Meredith et al. 1991	Metal making and treating	—	—	14/56,270	25-fold annual incidence rate (relative to professional/clerical/ selling workers)
Cross-sectional studies:					
Ameille et al. 1995	Automobile parts manufacture	Straight Soluble	Current mean: 2.6 mg/m^3 (SD=1.8) (extractable oil mist)	10/179 (6%) 10/190 (5%) (groups overlap)	OR=0.9 (0.3–3.3) OR=0.8 (0.2–3.1) (relative to assembly) (evidence suggests transfer bias)
Eisen et al. 1997†	Automobile parts manufacture	Straight Soluble Synthetic	See text.	See text.	Incidence RR=2.0 (0.9–4.6) Incidence RR=0.5 (0.2–1.1) Incidence RR=3.2 (1.2–8.3) (relative to assembly or otherwise unexposed for 2-year period before onset, adjusted for period of hire)

See footnotes at end of table.

(Continued)

Table 5–1 (Continued). Estimated risk of asthma associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value
Cross-sectional studies (continued):					
Greaves et al. 1995b, 1997	Automobile parts manufacture	Straight Soluble Synthetic	Current mean: 0.43 mg/m^3 (SD=0.3) 0.55 mg/m^3 (SD=0.2) 0.41 mg/m^3 (SD=0.1) (thoracic fraction)	 21/364 (6%) 25/452 (6%) 13/226 (6%)	 OR=1.0 (*P*>0.10) OR=0.8 (*P*>0.10) OR=0.8 (*P*>0.10) (evidence of transfer)
			Cumulative: Straight Soluble Synthetic		At 1 mg/m^3 (thoracic fraction) for 45 years: OR=0.6 (*P*>0.10) OR=2.4 (*P*<0.05) OR=2.4 (*P*>0.10)
Kriebel et al. 1994	Automobile parts manufacture	Straight Soluble	Current mean: 0.24 mg/m^3 (SD=0.3) 0.22 mg/m^3 (SD=0.3) (inhalable fraction)	 6/74 (8%) 17/142 (12%)	 OR=1.4 (*P*>0.10) OR=2.1 (0.9–4.6) (relative to assembly)
Massin et al. 1996	Ball-bearing manufacture	Soluble	Current mean (geometric): 1.49 mg/m^3 in cutting area 0.65 mg/m^3 in machining area Past means (geometric): 1.49 mg/m^3 in cutting area 2.20 mg/m^3 in machining area (total extractable-oil aerosol)	 0/53 (0%) (unexposed) 5/113 (4%) (exposed) (post-hire onset among workers without prior asthma)	 OR undefined (exposed relative to unexposed)

See footnotes at end of table.

(Continued)

Table 5–1 (Continued). Estimated risk of asthma associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value
Cross-sectional studies (continued):					
Robins et al. 1997	Automobile parts manufacture	Soluble	Current mean: 0.44 mg/m^3 (thoracic fraction)	11/83 (13%) (suspect OA)	OR=2.1 (0.5–12.3) (relative to assembly)
Rosenman et al. 1997b	Automobile parts manufacture	Straight	Generally <1.0 mg/m^3	18/183 (10%)	OR=2.8 (1.4–5.7)
		Soluble	Generally <1.0 mg/m^3	27/115 (23%)	OR=2.9 (0.8–14.3)
		Semisynthetic	Generally <1.0 mg/m^3	4/14 (29%)	OR=3.1 (1.8–5.5)
		Synthetic	Generally <1.0 mg/m^3 (oil mist)	105/420 (25%) (suspect OA)	(relative to straight MWF exposure)

*Abbreviations: CI = confidence interval, OA=occupational asthma, OR=odds ratio, RR= rate ratio, SD=standard deviation.

†Analyzed using a cohort approach and proportional hazards model.

studies [Ameille et al. 1995; Massin et al. 1996] reported current mean soluble MWF aerosol exposures ranging from about 0.7 to 2.5 mg/m^3 (total *extractable* oil mist); the U.S. studies reported mean soluble MWF aerosol ranging from about 0.2 (inhalable fraction) [Kriebel et al. 1994, 1997] to about 0.6 mg/m^3 (thoracic fraction) [Greaves et al. 1995b, 1997]. In the other study (for which mean exposures were not reported), most of the air samples taken yielded measurements of less than 1.0 mg/m^3 oil mist [Rosenman et al. 1997b].

The overall evidence also suggests an association between asthma and exposure to straight oil MWF aerosol. A State-based surveillance program received 17 reports of occupational asthma attributed to exposure to straight oil MWFs from the period 1988–94 [Rosenman 1997b]. Furthermore, Rosenman [1997b] found that workers exposed to straight oil MWF aerosol (at plants from which occupational asthma cases had been reported) had a 10% prevalence of new asthma since hire or new work-related symptoms consistent with work-related asthma. For two other studies, the point estimate for risk was elevated (though not statistically significant) [Eisen et al. 1997; Kriebel et al. 1994]. Also, clinical case reports suggest that asthma may be associated with exposure to straight oil MWF aerosol [Forbes and Markham 1967; Robertson et al. 1988] or to compounds commonly found in straight oil MWFs (e.g., TEAs) [Savonius 1994].

Available exposure data have been measured as TWAs over several hours, approximating the duration of a work shift. These measurements do not permit analyses to evaluate the possibility that occasional peak exposures (of relatively high concentration but lasting only a few minutes) may be required to induce MWF-associated airways hyperresponsiveness or clinical asthma. Clinical inhalation challenge studies indicate that in some affected workers, vapor (of MWF components) can trigger asthmatic reactions, even in the absence of aerosol exposure.

5.1.2.3 Symptoms of Airways Disorders

Study findings

Ely et al. [1970] investigated prevalences of cough, phlegm, dyspnea, and wheeze in a cross-sectional study of more than 1,700 plant workers, including 242 "machine hands" primarily exposed to mists from straight oil MWF. Oil mist concentrations were measured with a high-volume air sampler during the period 1955–70. Concentrations ranged from 0.07 to 110.0 mg/m^3 (median=1.0; mean=5.2 mg/m^3). In a multiple regression analysis involving only the exposed group of workers and employing variables such as age and smoking history correlated with job tenure, Ely et al. [1970] found no significant associations between years on the job and symptoms. The investigators did not comment on their finding that none of 49 exposed nonsmokers reported wheezing, versus 6.5% (26/400) of unexposed nonsmokers. One possible explanation for this

observation would be that workers adversely affected by exposure to MWFs may have tended to transfer away from jobs with exposure.

Krzesniak et al. [1981] used a cross-sectional design to compare 531 workers exposed to oil mist in machining operations in a tractor factory with 245 office workers in the same factory. Twenty-four percent of the exposed group and 42% of the comparison group were female, though the two groups did not significantly differ with respect to smoking prevalence. Duration of exposure ranged from 1 to 20 years. The concentration of oil mist exposure ranged between 5 and 99.5 mg/m^3, although MWF classes were not identified, nor were details provided on exposure measurement methods. Compared with unexposed workers, exposed workers reported significantly increased prevalences of cough and phlegm (38.8% versus 17.9%; $P<0.05$) and dyspnea (27.8% versus 9.4%; $P<0.01$). Approximate unadjusted ORs for exposure to oil mist calculated from the data are 2.9 (95% CI=1.98–4.29) for cough and phlegm and 3.7 (2.31–6.25) for dyspnea.

Järvholm et al. [1982] used a cross-sectional design to compare symptoms reported by 164 metal workers exposed for at least 3 years to straight and soluble oil MWFs with those reported by 159 office workers. MWF aerosol exposure concentrations ranged from 0.3 to 18.0 mg/m^3, with median exposures in the five departments studied ranging from 1.1 to 4.5 mg/m^3. The four symptoms that questions assessed were the following: usual cough; usual cough for at least 3 months each year; usual phlegm; and usual phlegm for at least 3 months each year. After controlling for age and smoking, a statistically significant relationship was observed between exposure and reporting of at least one respiratory symptom ($P<0.0001$). Adjusted for age and smoking, the 30-to 65-year-old metalworkers reported more chronic cough (RR=2.8; 95% CI=1.3–6.2) and chronic phlegm (RR= 2.2; 95% CI=1.2–3.9) than the comparison group of office workers. In a related 3-year followup survey of workers who had been asymptomatic at the time of this initial survey, Järvholm [1982] found that exposed workers tended to be more likely than controls to have developed new respiratory symptoms ($P<0.10$). The data provided allow calculation of an unadjusted relative risk of 4.9 (95% CI=0.7–34.2) associated with exposure.

Oxhoj et al. [1982] studied 385 machine shop workers exposed to straight, soluble, semisynthetic, or synthetic MWFs in 27 different facilities. Measured oil aerosol concentrations in these facilities ranged from 0.1 to 2.0 mg/m^3 (median 0.35 mg/m^3). Among smokers, workers with oil aerosol exposures exceeding 0.1 mg/m^3 had significantly higher prevalences of chronic cough (32% versus 18%; $P<0.05$) and chronic phlegm (25% versus 11%; $P<0.05$) than workers with lower exposure to oil aerosol. No symptom differences were reported for various MWF classes. No significant differences in symptom prevalences associated with differences in aerosol concentration were identified among nonsmokers. Likewise, no prevalence differences associated with oil vapor, nitrites, or amines were identified.

Ameille et al. [1995] evaluated chronic respiratory symptoms among workers in a French automobile manufacturing plant. All exposed workers in a gear-box machining shop had at least 1 year of exposure to MWFs. On the basis of exposure during the most recent 5 years, three exposed groups and one unexposed group were defined: 40 workers with exposure to straight oil MWFs only; 51 with exposure to soluble MWFs only; 139 with mixed exposure to soluble and straight oil MWFs; and 78 assembly workers. In areas using straight oil MWFs, the arithmetic mean exposure was 2.6 mg/m^3 (SD=1.8; geometric mean=2.2; geometric SD=1.9). No sampling was done in areas using soluble oil MWFs. The four groups were similar with respect to smoking habits. Symptoms assessed were chronic cough, chronic expectoration, and dyspnea. Those currently exposed to straight oil MWFs had a significantly higher prevalence of chronic cough and/or chronic phlegm (25.7% versus 16.3%; $P<0.05$) as well as a higher prevalence of dyspnea (5.0% versus 2.3%). After controlling for smoking, a statistically significant increased risk of chronic cough was observed with increasing duration of exposure to straight oil MWFs ($P=0.03$). Adjusted for smoking, the OR for chronic cough among those with more than 15 years of exposure to straight oil MWFs was 2.2 (95% CI=1.01–4.85) relative to unexposed assembly workers. Although no statistically significant respiratory symptom findings were reported for workers currently exposed to soluble MWF, point estimates for ORs calculated from data presented in the report were elevated for both dyspnea (OR=1.2; 95% CI=0.2–12.8) and for chronic cough and phlegm (OR=1.2; 95% CI=0.6–2.1). Ameille et al. [1995] provided evidence suggesting that affected workers may have self-selected away from jobs with exposure to soluble oil MWF, which would have the effect of biasing these ORs downward.

Greaves et al. [1993, 1995b, 1997] reported results from a cross-sectional respiratory morbidity study of 1,811 automobile parts (transmission, axle, steering gear) manufacturing workers exposed to three classes of MWF (straight oil, soluble oil, and synthetic) in three plants. Prevalences of respiratory symptoms in 1,042 machining and grinding operators were compared with those among 769 assemblers, only 239 of whom had no history of MWF exposures. Mean current exposures to aerosol (thoracic fraction) from straight oil, soluble oil, and synthetic MWFs were 0.43 (SD=0.26), 0.55 (SD=0.17), and 0.41 (SD=0.08) mg/m^3, respectively. Logistic regression analyses were controlled for smoking, race, age, plant, and whether the worker was employed in grinding operations.

Compared with all assembly workers, Greaves et al. [1995b, 1997] found that machinists more frequently reported all previously described respiratory symptoms, including usual cough (OR=1.4; $P<0.05$), usual phlegm (OR=1.6; $P<0.001$), symptoms of chronic bronchitis (OR=1.5, $P<0.05$), and wheezing on most days (OR=1.3, $P<0.05$).

Individual quantitative concentration of current exposure to MWF aerosol was significantly associated in an exposure-related manner with usual cough (OR=2.0 per mg/m^3; $P<0.05$), usual phlegm (OR=3.1 per mg/m^3; $P<0.05$), symptoms of chronic bronchitis (OR=2.6 per mg/m^3; $P<0.05$), and wheezing most days (OR=2.3 per mg/m^3; $P<0.05$).

Machinists *currently* exposed to aerosol from straight oils were more likely than assembly workers to report usual cough (OR=1.5; $P<0.05$), usual phlegm (OR=1.7; $P<0.05$), wheeze on most days (OR=1.5; $P<0.05$), and symptoms of chronic bronchitis (OR=1.6; $P<0.10$) [Greaves et al. 1995b, 1997]. Based on reported symptoms among three subgroups of these machinists (grouped by exposure concentration) and among assembly workers, trend analyses indicated significant exposure-related increases (per mg/m^3 straight oil MWF aerosol) in usual phlegm (OR=2.2 per mg/m^3; $P<0.05$) and wheeze on most days (OR=2.2 per mg/m^3; $P<0.05$), and exposure-related increase in grade 2 dyspnea (OR=2.3 per mg/m^3; $P=0.06$). Individual quantitative concentration of current exposure to straight oil MWF aerosols was associated with usual phlegm (OR=2.8 per mg/m^3; $P<0.05$) and with wheezing most days (OR=2.1 per mg/m^3; $P<0.10$) [Greaves et al. 1995b].

Machinists currently exposed to soluble oil MWFs at aerosol concentrations exceeding 0.65 mg/m^3 (thoracic fraction) had statistically significant excesses in usual cough (OR=2.0; $P<0.05$) [Greaves et al. 1995b] and chest tightness at least once per week (OR=2.1; $P<0.05$). Exposure-related trend ORs exceeded 1.0 but were not statistically significant, and current exposure to soluble oil MWF aerosols below 0.65 mg/m^3 were not significantly associated with respiratory symptoms. Individual quantitative concentration of current exposure to aerosol of soluble oil MWF was not significantly associated with any of the studied symptoms [Greaves et al. 1995b].

The highest prevalences of respiratory symptoms were observed among machinists currently exposed to synthetic MWFs, who were more likely to report usual cough (OR=1.6, $P<0.01$), usual phlegm (OR=2.1, $P<0.001$), symptoms of chronic bronchitis (OR=1.6; $P<0.10$), wheezing on most days (OR=1.7; $P<0.05$), and chest tightness at least once per week (OR=1.7; $P<0.05$) [Greaves et al. 1995b, 1997]. Based on reported symptoms among three subgroups of these machinists (grouped by aerosol exposure concentration) and among assembly workers, trend analyses indicated significant exposure-related increases (per mg/m^3 synthetic MWF aerosol) in usual cough (OR=4.8 per mg/m^3; $P<0.01$), usual phlegm (OR=7.3 per mg/m^3; $P<0.001$), symptoms of chronic bronchitis (OR=3.5 per mg/m^3; $P<0.05$), wheezing on most days (OR=4.9 per mg/m^3; $P<0.01$), and chest tightness at least once per week (OR=3.9 per mg/m^3; $P<0.01$). Increased usual phlegm (OR=3.1; $P<0.001$) and symptoms of chronic bronchitis (OR=1.8; $P<0.05$) were observed even among the subgroup of workers with lowest current synthetic MWF aerosol exposure (below 0.4 mg/m^3) [Greaves et al. 1995b]. Individual quantitative concentration of current exposure to synthetic MWF aerosol was significantly associated with usual phlegm (OR=10.6 per mg/m^3; $P<0.05$), symptoms of chronic bronchitis (OR=4.4; $P<0.05$), and wheezing most days (OR=4.8; $P<0.05$) [Greaves et al. 1995b, 1997].

Many of the ORs reported above by Greaves et al. [1995b, 1997] may underestimate the true association between MWF aerosol exposure and symptoms because the commonly

used reference group of assembly workers included a majority who had past MWF aerosol exposures. In fact, in further analyses that excluded assembly workers who had past MWF aerosol exposure, Greaves et al. [1995b] found generally higher ORs. Greaves et al. [1995b, 1997] also found that a substantial proportion of the machinists reported improvement in symptoms when away from work, regardless of MWF exposure (though this was more common among machinists exposed to synthetic MWF aerosols).

Greaves et al. [1995b] also analyzed reported symptoms based on *ever* having been exposed to MWFs, both overall and by MWF class. Again, machinists ever exposed to any MWFs more frequently reported usual cough (OR=1.6; $P<0.01$) and usual phlegm (OR=1.9; $P<0.001$) [Greaves et al. 1995b].

Machinists ever exposed to aerosols from straight oil MWFs were more likely than assembly workers to report all respiratory symptoms, including usual cough (OR=1.5; $P<0.10$), usual phlegm (OR=2.2; $P<0.001$), and wheeze most days (OR=1.4; $P<0.10$) [Greaves et al. 1995b]. Based on symptoms among three subgroups of these machinists (grouped by cumulative exposure concentration) and among never-exposed assembly workers, trend analyses indicated statistically significant exposure-related increases in grade 2 dyspnea (OR=1.1 per mg/m^3-year; $P<0.05$) [Greaves et al. 1995b, 1997].

Machinists ever exposed to soluble MWF aerosols more frequently reported all respiratory symptoms, including usual cough (OR=1.5; $P<0.05$), usual phlegm (OR=1.8; $P<0.001$), and grade 2 dyspnea (OR=1.7; $P<0.10$). Even those machinists ever exposed to soluble fluids at cumulative aerosol concentrations below 0.71 mg/m^3-years had statistically significant excesses in usual cough (OR=1.6; $P<0.05$), usual phlegm (OR=1.7; $P<0.05$), and grade 2 dyspnea (OR=1.9; $P<0.05$), but ORs for exposure-related trends were not statistically significant [Greaves et al. 1995b].

Machinists ever exposed to synthetic MWF aerosols were similarly more likely than never-exposed assembly workers to report all respiratory symptoms, including usual phlegm (OR=2.2, $P<0.001$) and grade 2 dyspnea (OR=2.2; $P<0.10$) [Greaves et al. 1995b]. Interestingly, based on reported symptoms among three subgroups of these machinists (grouped by cumulative exposure level) and among assembly workers, trend analyses indicated exposure-related declines in usual phlegm (OR=0.9 per mg/m^3-year; $P<0.05$) and symptoms of chronic bronchitis (OR=0.9 per mg/m^3-year; $P<0.10$), per mg/m^3 synthetic MWF aerosol [Greaves et al. 1995b, 1997]. The investigators suggested that these findings of inverse exposure-response relationship could be explained by selective transfer bias, discussed above with respect to physician-diagnosed asthma in this same population [Eisen 1995; Eisen and Greaves 1995; Eisen et al. 1997].

Based on an analysis of each worker's individual quantitative concentrations of both current and past exposures to each MWF class (straight oil, soluble oil, and synthetic), Greaves et al. [1995b] concluded that past and current exposures to straight oil, soluble

oil, and synthetic MWFs are all related to respiratory symptom prevalence, and that current exposure concentrations appear to be the major determinants of respiratory symptoms. Greaves et al. [1995b, 1997] represents the most comprehensive assessment to date of respiratory symptoms among workers exposed to MWF aerosols. Nevertheless, findings from the study remain somewhat limited by the cross-sectional nature of the study, primarily because it is subject to selection effects.

In another cross-sectional study, Kriebel et al. [1994] studied 216 automotive parts manufacturing workers exposed to straight and soluble oil MWFs in one machine shop compared with 170 assembly workers. The studied shop manufactured specialty transmissions using machine tools, most of which had individual MWF sumps. Average aerosol exposures (inhalable fraction) were 0.24 mg/m^3 (SD=0.27) among workers exposed to straight MWFs, 0.22 mg/m^3 (SD=0.26) among workers exposed to soluble MWFs, 0.08 mg/m^3 (SD=0.05) among assembly workers, and 0.03 mg/m^3 (SD=0.03) among classroom/office workers. After controlling for age, race, gender, and smoking, the investigators found that machinists exposed to straight oil MWFs reported cough almost three times more often (OR=2.9; 95% CI=1.2–6.7) and sinus problems almost twice as often (OR=1.7; 95% CI=0.96–3.0) as the comparison workers. Also, machinists exposed to soluble oil MWFs were more likely than those exposed to straight oil MWFs to report an increase in eye, nose, and throat irritation over the course of the workday (P<0.01). In addition, machinists whose MWF sump had not been refilled during the 3 weeks before the symptom survey were more likely to report cough than those whose sump had been changed within the last 3 days (OR=5.6; 95% CI=4.3–6.9).

Robins et al. [1994, 1997] compared respiratory symptoms among machinists exposed to soluble MWF in an automobile transmission manufacturing plant (mean personal aerosol exposure of 0.44 mg/m^3 [thoracic fraction]) and among assemblers working in an area that was physically isolated from the machining operations. In each of three temporally separated rounds of the study, symptoms were reported by a higher proportion of exposed machinists. The differences were statistically significant for phlegm (OR=3.1; P=0.012) and chronic bronchitis (OR=6.8; P=0.04) in Round 1 [Robins et al. 1997] and for wheezing with dyspnea (OR=4.9; P=0.03) in Round 2 [Robins et al. 1994]. In addition, machinists were about 3 times more likely to develop at least one respiratory symptom (dry cough, cough with phlegm, wheezing, chest tightness or dyspnea) during their Monday shift than were assemblers (P=0.012) [Robins et al. 1994, 1997].

In a study of 114 workers exposed to aerosol from soluble MWF in a ball-bearing plant and 55 unexposed workers from other plants in the same region of France, Massin et al. [1996] found that prevalences of chronic bronchitis, chronic phlegm, chronic cough, and bouts of bronchitis were three to nine times higher in the exposed workers than in unexposed. Adjusting for age and smoking, the higher prevalence of chronic cough or chronic phlegm was statistically significant (adjusted OR=4.90; P=0.002). Likewise,

after adjusting for age and smoking, dyspnea was found to be significantly related to cumulative MWF aerosol exposure (P=0.006). Exposures were measured in terms of total extractable oil mist, and work area geometric mean concentrations ranged from 0.65 to 2.20 mg/m^3.

Sprince et al. [1997] studied symptom prevalence among machine operators (n=183) and unexposed assembly workers (n=66) in an automobile transmission parts manufacturing plant. Machine operators were exposed to one of two types of soluble oil MWF or to a semisynthetic MWF. Geometric mean total aerosol exposures were 0.33 mg/m^3 (range 0.04–1.44 mg/m^3) for machine operators and 0.08 mg/m^3 (range 0.02–0.20 mg/m^3) for assembly workers, as measured by MiniRAMs gravimetrically calibrated to Arizona road dust. (Because these instruments work on the principle of real-time light scattering, they indirectly measure all components of the aerosol, including water and other volatile components. In this regard, these aerosol concentrations are not comparable with those measured with standard filter methods, which do not include volatile components of the aerosol.) Exposure concentrations were very similar for each of the three types of MWFs. Adjusted for smoking, sex, race, and age, machine operators reported significantly more usual cough (OR=3.1; 95% CI=1.4–6.9), usual phlegm (OR=3.1; 95% CI=1.6–6.1), and chest-tightness temporally related to work (OR=5.9; 95% CI=1.4–25.7). Total aerosol exposure-response relationships were positive and statistically significant for both usual cough and usual phlegm. In addition, with respect to symptoms developing during the studied work shift, total MWF aerosol exposure-response relationships were observed for cough and throat irritation. Adjusted ORs for these symptoms were 5.3 (95% CI=1.3–21.8) and 5.1 (1.5–17.5), respectively, for the highest exposure quartile [Sprince et al. 1997].

Rosenman et al. [1997b] reported results of symptom questionnaires administered to coworkers of workers reported as cases of MWF-associated occupational asthma in Michigan. Coworkers reported frequent work-related cough, regardless of the MWF type used: 27 (14.8%) of those exposed to straight oil MWFs; 21 (19.3%) of those exposed to soluble oil MWFs; 4 (28.6%) of those exposed to semisynthetic MWFs; and 90 (21.4%) of those exposed to synthetic MWFs.

Summary

With the exception of one early study [Ely 1970], epidemiological studies of respiratory symptoms present generally consistent and (in the case of the more recent studies) compelling epidemiologic evidence indicating that occupational exposure to MWF aerosols causes symptoms consistent with airways irritation, chronic bronchitis, and asthma. The evidence suggests that each class of MWFs (straight oil, soluble oil, and synthetic) is capable of inducing respiratory symptoms at MWF aerosol exposure concentrations that are currently typical of large metalworking shops. To date, there is no convincing evidence that identifies any particular component or components of MWF aerosol as the

predominant cause of these symptoms, although some irritant components of MWF are clearly suspect [Sprince et al. 1997]. Table 5–2 summarizes selected risk estimates, reflecting roughly a twofold to sevenfold increased risk for various respiratory symptoms associated with mean aerosol exposures ranging from 0.22 mg/m^3 (inhalable fraction) to 0.55 mg/m^3 (thoracic fraction) among groups of workers exposed to MWFs. Also, one of these recent U.S. studies (a very large multiplant study with mean exposures for the major types of MWFs ranging from 0.41 to 0.55 mg/m^3 [thoracic fraction], found statistically significant quantitative exposure-response relationships between cumulative concentration of MWF aerosols and respiratory symptoms [Greaves et al. 1995b, 1997]. Likewise, another U.S. study found significant exposure-response relationships between aerosol exposure concentration and chest symptoms [Sprince et al. 1997]. In addition, the onset or worsening of many symptoms over a work shift [Kriebel et al. 1994; Sprince et al. 1997; Rosenman et al. 1997b], and the reported substantial symptomatic improvement experienced by many affected workers when away from work [Greaves et al. 1995b, 1997] suggests that controlling worker exposures can prevent chronic effects induced by MWF aerosol exposure and for reversing early MWF-induced airways effects, through control of worker exposure to MWF aerosol.

5.1.2.4 Cross-Sectional Studies of Lung Function

Study findings

Ely et al. [1970] published the first report regarding pulmonary function among workers occupationally exposed to MWF aerosol, primarily mineral oil aerosol at the following concentrations: median, 1.0 mg/m^3; mean, 5.2 mg/m^3; range, 0.07–110.0 mg/m^3, as measured by a high-volume sampler. Tenure for the 242 exposed workers ranged from less than 1 to 38 years. After adjustment for cigarette smoking (in terms of both cigarette years and smoking years), salary grade, and other factors, the number of years on the job was not a statistically significant independent predictor for either forced vital capacity (FVC) or FEV_1. Beyond issues of possible exposure misclassification resulting from the use of job tenure as a surrogate for exposure, lack of unexposed controls, small numbers, and limitations of cross-sectional studies in general, the authors pointed out that several factors included in the statistical model were correlated with job tenure. They appropriately cautioned that "when predictors are correlated, one is unable to place any interpretation on the coefficients in the regression equation" [Ely et al. 1970]. The negative pulmonary function findings of this study are therefore not compelling as evidence against an adverse effect of occupational exposure to MWF aerosol.

Järvholm et al. [1982] measured spirometry in a cross-sectional study of 164 metal workers exposed for at least 3 years to straight and soluble oil MWFs and in 159 office workers. MWF aerosol exposure concentrations ranged from 0.3 to 18.0 mg/m^3 (oil mist), with median exposures in the five areas studied ranging from 1.1 to 4.5 mg/m^3. A multivariate analysis stratified by smoking status and controlled for age and height

Table 5–2. Estimated risk of respiratory symptoms associated with MWF exposures

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value*
Cross-sectional studies:						
Ameille et al. 1995	Automobile parts manufacture	Straight	2.6 mg/m^3 (SD=1.8) (oil mist)	Chronic cough/phlegm	46/179 (26%)	OR=1.6 (0.8–3.3)
				Dyspnea	9/179 (5%)	OR=2.0 (0.4–19.5) (relative to assembly)
				Chronic cough		OR=2.2 (1.0–4.9) (>15 years of exposure to straight oil MWF, relative to 0 years, adjusted for smoking)
		Soluble	Not measured	Chronic cough/phlegm	43/190 (23%)	OR=1.2 (0.6–2.1)
				Dyspnea	6/190 (3%)	OR=1.2 (0.2–12.8) (relative to assembly)
Greaves et al. 1995b, 1997	Automobile parts manufacture	All types (aggregated)	Current mean (thoracic fraction)	Usual cough	268/1042 (26%)	OR=1.4 (P<0.05)
				Usual phlegm	269/1042 (26%)	OR=1.6 (P<0.001)
				Wheeze most days	246/1042 (24%)	OR=1.3 (P<0.05)
				Chronic bronchitis	138/1042 (13%)	OR=1.5 (P<0.05) (relative to all assembly workers)
		Straight	0.43 mg/m^3 (SD=0.3)	Usual phlegm	89/364 (24%)	OR=2.2 per mg/m^3 (P<0.05)
				Wheeze most days	89/364 (24%)	OR=2.2 per mg/m^3 (P<0.05)
				Dyspnea	49/364 (13%)	OR=2.3 per mg/m^3 (P=0.06)
		Soluble	0.55 mg/m^3 (SD=0.2)	Usual cough	96/452 (21%)	OR=2.0 (P<0.05)
				Chest tightness	72/452 (16%)	OR=2.1 (P<0.05) (>0.65 mg/m^3 relative to assembly)

See footnotes at end of table.

(Continued)

Table 5–2 (Continued). Estimated risk of respiratory symptoms associated with MWF exposures

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value
Cross-sectional studies (continued):						
Greaves et al. 1995b (continued)		Synthetic	0.41 mg/m^3 (SD=0.1)	Usual cough Usual phlegm Chronic bronchitis Wheeze most days Chest tightness	76/226 (34%) 79/226 (35%) 38/226 (17%) 81/226 (36%) 45/226 (20%)	OR=4.8 per mg/m^3 (P<0.01) OR=7.3 per mg/m^3 (P<0.001) OR=3.5 per mg/m^3 (P<0.05) OR=4.9 per mg/m^3 (P<0.01) OR=3.9 per mg/m^3 (P<0.01) (All above ORs are adjusted for age, race, sex, grinding, and plant. See text for additional risk estimates, including quantitative risk estimates for cumulative exposure to MWF aerosols.)
Järvholm et al. 1982	Bearing ring manufacture	Straight plus soluble	Range: 0.3–18.0 mg/m^3 department-specific Medians: ranged from 1.1 to 4.5 mg/m^3 (oil mist)	Chronic cough Chronic phlegm	13/110 (12%) 22/110 (20%)	RR=2.8 (1.3–6.2) RR=2.2 (1.2–3.9) relative to unexposed)

See footnotes at end of table.

(Continued)

Table 5–2 (Continued). Estimated risk of respiratory symptoms associated with MWF exposures

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value
Kriebel et al. 1994	Automobile parts manufacture		Current mean (inhalable fraction):			
		Straight	0.24 mg/m^3 (SD=0.3)	Cough	(19%)	OR=2.9 (1.2–6.7)
				Sinus problems	(51%)	OR=1.7 (1.0–3.0) (relative to assemblers; controlled for age, race, smoking)
		Soluble	0.22 mg/m^3 (SD=0.3)	Acute eye, nose, and throat irritation	(10%–19%)	(*P*<0.01) (compared to straight)
Krzesniak et al. 1981	Tractor parts manufacture	Not specified	Range: 5–99.5 mg/m^3 (oil mist)	Cough and phlegm	206/531 (38.8%)	OR=2.9 (2.0–4.3)
				Dyspnea	44/245 (17.9%)	OR=3.7 (2.3–6.3) (relative to unexposed)
Massin et al. 1996	Ball-bearing manufacture	Soluble	Current mean (geometric): 1.49 mg/m^3 in cutting area 0.65 mg/m^3 in machining area	Chronic bronchitis	9/114 (8%)	
				Chronic cough or phlegm	36/114 (32%)	OR=4.90 (*P* = 0.002)
				Bouts of bronchitis	19/114 (17%)	
				Dyspnea	30/114 (28%)	OR=2.28 (*P*= 0.10) (above ORs relative to unexposed controls, adjusted for age and smoking)
			Past means (geometric): 1.49 mg/m^3 in cutting area 2.20 mg/m^3 in machining area (total extractable oil aerosol)			OR=1.44 (*P*= 0.006) (above OR expressed per 10 mg-yr/m^3, adjusted for age and smoking)

See footnotes at end of table.

(Continued)

Table 5–2 (Continued). Estimated risk of respiratory symptoms associated with MWF exposures

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Number cases/ number exposed	Risk estimate and 95% CI or *P*-value
Oxhoj et al. 1982	27 machine shops	All classes	Range: 0.1–2.0 mg/m^3 Median: 0.35 mg/m^3 (oil mist)	Chronic cough Chronic phlegm	(32%) (25%)	PR=1.8 (X^2 P<0.05) PR=2.3 (X^2 P<0.05) (relative to <0.1 mg/m^3)
Sprince et al. 1997	Automobile parts manufacture	Soluble plus semi-synthetic	Current geometric mean (total aerosol by MiniRAM): 0.33 mg/m^3 (range 0.04–1.44)	Usual cough Usual phlegm Chest tightness Acute chest tightness Acute throat irritation Acute cough		OR=3.1 (1.4–6.9) OR=3.1 (1.6–6.1) OR=5.9 (1.4–25.7) OR=4.5 (1.3–15.2) OR=5.0 (1.7–14.7) OR=4.0 (1.2–14.1) (relative to assemblers; controlled for smoking, etc.)
Cross-sectional study (panel):						
Robins et al. 1994; 1997	Automobile parts manufacture	Soluble	Current mean (thoracic fraction): 0.44 mg/m^3	Phlegm Chronic bronchitis Wheeze and dyspnea Acute eye, nose, and throat irritation		OR=3.1 (P=0.01) OR=6.8 (P=0.04) OR=4.9 (P=0.03) (relative to assemblers) (P=0.01)
Cross-sectional and longi-tudinal study:						
Järvholm 1982	Bearing-ring manufacture	Straight plus soluble	Range: 0.3–18.0 mg/m^3 department-specific Medians: ranged from 1.1 to 4.5 mg/m^3 (oil mist)	Chronic bronchitis New respiratory symptoms among asymptomatic workers	17/164 (10%) 14/49 (29%)	RR=1.8 (1.1–2.9) RR=4.9 (0.7–34.2) (relative to unexposed over a 3-year period and adjusted for age and smoking)

*Abbreviations: CI=confidence interval, OR=odds ratio, PR=prevalence ratio, RR=risk ratio, SD=standard deviation.

revealed no significant differences in FVC or FEV_1 between the exposed metal workers and the office workers. Exposed and office workers who had respiratory symptoms at the initial survey were followed up 3 years later [Järvholm 1982]. Though the difference did not achieve statistical significance, the 58 men exposed to MWFs experienced mean 3-year reductions in FEV_1 and FVC of 30 and 40 ml, respectively, compared with mean increases of 50 and 20 ml for FEV_1 and FVC, respectively, among the 27 office workers. Small numbers of subjects limited the power of this study.

Krzesniak et al. [1981] studied lung function in metal workers exposed to MWF aerosol in a tractor factory in Poland, comparing a group of 531 metal workers (exposed from 1 to 20 years) with a group of 245 office workers. Women comprised 24% of the exposed and 42% of the comparison group. The MWF class was not specified, but the exposure was described as an oil mist with airborne concentrations ranging between 5 and 100 mg/m^3. Though smoking was slightly more prevalent in the exposed group than in the control group (59.7% versus 53.4%), a univariate analysis was conducted. Reduced FEV_1/FVC ratios were more frequent among the exposed workers than among the controls (35.6% versus 11.4%; $P<0.05$), as were reduced forced expiratory flow $_{25-75\%}$ ($FEF_{25-75\%}$) (33.3% versus 18.4%; $P<0.05$) and reduced $FEF_{200-1200}$ (15.8% versus 2.8%; $P<0.05$). Approximate unadjusted ORs for oil mist exposure calculated from the data provided by Krzesniak et al. [1981] are as follows: 4.3 (95% CI=2.75–6.85) for decreased FEV_1/FVC; 2.2 (95% CI=1.52–3.30) for decreased FEF_{25-75}; and 6.39 (95% CI=2.90–16.61) for decreased $FEF_{200-1200}$.

Oxhoj et al. [1982] communicated the results of a Danish study of 385 machine shop workers exposed to straight oil, soluble oil, semisynthetic, or synthetic MWFs in 27 different facilities. Measured oil aerosol concentrations in these facilities ranged from 0.1 to 2.0 mg/m^3 (median 0.35 mg/m^3). Controlling for age, height, and smoking, an analysis of spirometry data from 295 exposed male workers revealed no significant differences between four worker subgroups based on current exposure to straight oil, soluble oil, semisynthetic, or synthetic MWF. The authors summarized their rather limited spirometry findings by concluding that "if the four kinds of exposure influence ventilatory lung function, they do it to approximately the same degree" [Oxhoj et al. 1982].

In a study based in a French automobile manufacturing plant, Ameille et al. [1995] found no significant differences in baseline percentage of predicted lung function between four exposure groups (straight oil, soluble oil, mixed straight and soluble oil MWF, and unexposed control), which did not differ by smoking habits. Mean spirometry parameters were generally lower for the group of workers exposed to straight oil MWFs (mean total oil mist concentration was 2.6 mg/m^3) compared with the other groups, although the authors concluded that the study size was too small to detect significant differences in mean FEV_1 between exposure groups. After controlling for pack-years, linear regression analysis indicated that current smokers had significantly decreasing trends in FEV_1, $FEF_{25-75\%}$, and maximal flow rates at 50% and 75% of

exhaled with increasing duration of exposure to straight oil MWFs. This finding suggests a synergistic relationship between smoking and straight oil MWF exposure. No similar effects were observed for workers exposed to soluble oil MWF.

Greaves et al. [1993, 1995a] studied pulmonary function of 1,745 automobile parts manufacturing workers employed in machining and grinding operations. Machinists (352 currently exposed to straight MWF, 441 to soluble MWF, and 226 to synthetic MWF) were compared with 726 assembly workers, 239 of whom had never been exposed in metalworking operations. Current exposures to aerosols (thoracic fraction) of straight oil MWFs (mean concentration=0.43 mg/m^3; SD=0.26), soluble MWFs (mean=0.54 mg/m^3; SD=0.17), or synthetic MWFs (mean=0.41 mg/m^3; SD=0.08) were measured. The relationships between pulmonary function and both current and cumulative exposures were evaluated. Previously exposed assemblers were not included in analyses that considered current exposures only. Multivariate analyses controlled for age, height, race, smoking, grinding operation, and plant.

In terms of unadjusted mean lung function, Greaves et al. [1995a] found that approximately 18% of workers ever exposed to any MWFs had abnormal FEV_1 values (i.e., less than 85% of predicted), approximately 25% in excess over the 14% abnormal rate among never-exposed assemblers ($P>0.10$). Mean percentages of predicted and residual (observed minus predicted) FEV_1 values were significantly reduced ($P>0.05$) for the three groups of metalworkers who were ever-exposed to straight oil, soluble oil, or synthetic MWFs, but not for the group of never-exposed assembly workers.

Analyzing the data trichotomized by current aerosol exposure, Greaves et al. [1995a] found trends of declining function with increasing exposure for both straight and soluble oil MWFs. At the highest current exposure categories (>0.54 mg/m^3 for straight oil MWF and >0.65 mg/m^3 for soluble oil MWF), mean percentage of predicted FEV_1 (not adjusted for smoking) was significantly reduced ($P<0.01$). The exposure-related trend was inverted in a similar analysis of current exposure to synthetic MWF, the lowest exposure category (<0.18 mg/m^3) having the lowest mean percentage predicted FEV_1 ($P=0.06$). For both straight oil MWF and soluble oil MWF aerosols, individual quantitative concentration of current aerosol exposures resulted in negative exposure-response coefficients (adjusted for smoking) for percentage of predicted FEV_1 and percentage of predicted FVC ($P<0.05$) and for their residuals (observed value minus predicted value) ($P<0.10$). Adjusted for age, height, race, smoking, plant, and grinding, the coefficients for FEV_1 (-197 ml per mg/m^3) and FVC (-229 ml per mg/m^3) residuals with respect to current straight oil MWF aerosol exposure concentrations were marginally significant ($P=0.06$). Coefficients for soluble and for synthetic MWF aerosol exposures were also negative, although they did not achieve statistical significance.

Analyzing the data trichotomized by cumulative aerosol exposure concentrations, Greaves et al. [1995a] found trends of declining mean percentage of predicted lung

function with increasing exposure to straight and to soluble oil MWFs. At the highest exposure tertile (>1.71 mg/m^3-years for straight oil MWF and >3.41 mg/m^3-years for soluble oil MWF), mean percentage of predicted FEV_1 (unadjusted for smoking) was significantly reduced (P<0.001). Prevalence rates of abnormal FEV_1 among subgroups with highest cumulative aerosol exposures were greater than among never-exposed assembly workers for exposure to straight oil MWF (20.4% versus 14.2%; P=0.06; RR=1.4) and for exposure to soluble MWF (21.9% versus 14.2%; P<0.01; RR=1.5). Also, FEV_1 residuals were negative and statistically significant for the highest exposure categories of both straight MWFs (-117 ml; P<0.001) and soluble MWFs (-139 ml; P<0.001). Similar to the findings in relation to current exposures, there was an inverse trend with increasing exposure category among workers ever exposed to synthetic MWF; prevalences of abnormal FEV_1 were 19.8%, 17.1%, and 13.6% for the lowest to highest cumulative exposure groups, respectively. The lowest exposure group (<0.18 mg/m^3-years) had an abnormality prevalence RR of 1.4 relative to the never-exposed assemblers (P=0.07), representing a 40% excess.

In multiple linear regression analysis considering both current and past exposures simultaneously, Greaves et al. [1995a] found that accelerated decline in FEV_1 was significantly related to past exposures to aerosols from straight oil (FEV_1 residual = -5 ml per mg/m^3-year; P<0.05) and from synthetic MWFs (FEV_1 residual = -7 ml per mg/m^3-year; P<0.10) but not to past exposures to soluble oil MWFs (FEV_1 residual = -1 ml per mg/m^3-year; P>0.10) or to current exposures.

The results of the Greaves et al. [1995a] study show that adverse pulmonary function effects are associated with cumulative exposures to aerosols from straight and synthetic oil MWFs and less consistently with aerosols from soluble oil MWF. In this population, cumulative exposure appeared to be more important than current aerosol exposure concentrations in predicting pulmonary function. Greaves et al. [1995a] suggest that the increased impairment associated with lower current or lower cumulative exposures to synthetic MWF in the categorical exposure analysis may reflect a tendency for selective transfer of affected workers from jobs with higher MWF aerosol exposure to jobs with lower exposures. The investigators expressed caution with respect to the lack of clear evidence of adverse effects of exposure to soluble oil MWFs. Among other reasons for this caution, they pointed out that most of the studied workers exposed to straight oil or synthetic MWFs had at sometime also been exposed to soluble oil MWFs and that very few of the workers exposed to soluble oil MWFs had not also been exposed to straight oil or synthetic MWFs. As a result, inferences about health effects specific to major types of MWFs cannot be made with certainty based on findings of Greaves et al. [1995a].

Kriebel et al. [1994, 1997] studied lung function in transmission manufacturing workers exposed to soluble oil and straight oil MWFs in one machine shop compared with assembly (and office/classroom) workers. Average aerosol exposures (inhalable fraction)

were 0.24 mg/m^3 (SD=0.27) among workers exposed to straight oil MWFs, 0.22 mg/m^3 (SD=0.26) among workers exposed to soluble oil MWFs, 0.08 mg/m^3 (SD=0.05) among assembly workers, and 0.03 mg/m^3 (SD=0.03) among classroom/office workers. After adjustment for age, race, sex, height, and smoking, Kriebel et al. [1994, 1997] observed a statistically significant (P<0.05) deficit in baseline FEV_1 of 115 ml (approximately 3%) associated with exposure to soluble oil MWF. No similar significant difference was associated with exposure to straight oil MWF.

After statistical adjustment for smoking status, Massin et al. [1996] found no significant difference between the mean baseline spirometry of 114 male ball-bearing plant workers exposed to aerosol from soluble oil MWF and that of 55 unexposed male workers from other plants in the same region of France. Also, after adjustment for smoking, baseline FEV_1 was not found to be related to oil mist concentration. This cross-sectional study involved 85% of exposed workers at the studied plant, and these workers had been exposed for a mean duration of 15 years SD=8 years). Exposure concentrations were measured as total extractable oil mist, and work area geometric means ranged from 0.65 mg/m^3 for the machining area in recent years to 2.20 mg/m^3 for that same area before improved exposure controls were installed at the plant in 1990.

Sprince et al. [1997] studied Monday morning spirometry among machine operators (n=183) and unexposed assembly workers (n=66) in an automobile transmission parts manufacturing plant. Machine operators were exposed to one of two types of soluble oil MWF or to a semisynthetic MWF. No information was provided regarding possible previous MWF aerosol exposures among assemblers. After adjusting for smoking, the investigators found no significant differences in percentage of predicted FEV_1 or FVC between machine operators and assembly workers; mean values of FEV_1 unadjusted for smoking were 92% and 93%, respectively. Likewise, no difference was noted in baseline spirometry among machine operators by MWF type, and there was no significant difference associated with current total aerosol exposure concentration. Geometric mean total aerosol exposures, as measured by MiniRAMs gravimetrically calibrated to Arizona road dust, were 0.33 mg/m^3 (range 0.04 to 1.44 mg/m^3) for machine operators and 0.08 mg/m^3 (range 0.02 to 0.20 mg/m^3) for assembly workers. These aerosol concentrations are not comparable with those resulting from standard filter methods. If the exposures in this plant had been measured with a direct gravimetric filter method, the levels would likely have been lower (i.e., equivalent to the nonvolatile proportion of the aerosol entering the sampler). Notably, after adjusting for smoking, Sprince et al. [1997] did find a significant relationship between baseline percentage of predicted FEV_1 and exposure to airborne concentration of viable bacteria (P=0.025).

Summary

Results of these cross-sectional studies of lung function generally parallel those from studies of respiratory symptoms among workers exposed to MWF aerosols. Table 5–3 presents selected risk estimates that generally indicate that occupational exposure to

Table 5–3. Estimated risk of chronic lung function effects associated with MWF aerosol exposure

Study*	Population	Fluid class	Aerosol exposure concentration	Health effect	Risk estimate and 95% CI or *P*-value†
Ameille et al. 1995	Automobile parts manufacture	Straight	Current mean: 2.6 mg/m^3 (oil mist)	FEV_1 in smokers	↓ trend with years of exposure (P=0.004)
				FEF_{25-75} in smokers	↓ trend with years of exposure (P=0.005)
				V_{75} in smokers	↓ trend with years of exposure (P=0.01)
				V_{50} in smokers	↓ trend with years of exposure (P=0.02)
				V_{25} in smokers	↓ trend with years of exposure (P=0.004) (above all adjusted for pack-years of smoking)
Greaves et al. 1995a	Automobile parts manufacture		Current mean (thoracic fraction):		
		Straight	0.43 mg/m^3 (SD 0.3)	FEV_1 (<85% predicted)	PR=1.4 (>0.54 mg/m^3 relative to never exposed)
		Soluble	0.55 mg/m^3 (SD 0.2)	FEV_1 (observed-predicted)	−197 ml per mg/m^3 (P=0.06)‡
		Synthetic	0.41 mg/m^3 (SD 0.1)	FEV_1 (<85% predicted)	PR=1.4 (>0.65 mg/m^3 relative to never exposed)
				FEV_1 (<85% predicted)	PR=1.4 (<0.18 mg/m^3 relative to never exposed) (evidence for transfer)
			Cumulative mean (thoracic fraction):	FEV_1 (<85% predicted)	PR=1.4 (P=0.06) (>1.71 mg/m^3-years relative to never exposed)
		Straight	2.29 mg/m^3-years (SD 7.6)	FEV_1 (observed-predicted)	−5 ml per mg/m^3-year (P<0.05)†
		Soluble	6.40 mg/m^3-years (SD 14.2)	FEV_1 (<85% predicted)	PR=1.5 (P<0.01) (>3.41 mg/m^3-years relative to never exposed)
		Synthetic	0.39 mg/m^3-years (SD 2.9)	FEV_1 (<85% predicted)	PR=1.4 (P=0.07) (<0.18 mg/m^3-years relative to never exposed) (evidence of transfer)
				FEV_1 (observed-predicted)	−7 ml per mg/m^3-year (P<0.10)†

See footnotes at end of table.

(Continued)

Table 5–3 (Continued). Estimated risk of chronic lung function effects associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Risk estimate and 95% CI or *P*-value
Kriebel et al. 1994; 1997	Automobile parts manufacture	Soluble	Current mean: 0.22 mg/m^3 (SD 0.3) (inhalable fraction)	FEV_1	−115 ml ($P<0.05$) (relative to assemblers)
Krzesniak et al. 1981	Tractor parts manufacture	Not specified	Range 5–99.5 mg/m^3	Decreased FEV_1/FVC Decreased $FEF_{25-75\%}$ Decreased $FEF_{200-1200}$	OR=4.3 (2.8–6.9) OR=2.2 (1.5–3.3) OR=6.4 (2.9–16.6) (above ORs all relative to unexposed)
Massin et al. 1996	Ball-bearing manufacture	Soluble	Current mean (geometric): 1.49 mg/m^3 in cutting area 0.65 mg/m^3 in machining area	FVC FEV_1 FEV_1/FVC	$P = 0.14$ $P = 0.06$ $P = 0.30$
			Past means (geometric): 1.49 mg/m^3 in cutting area 2.20 mg/m^3 in machining area (total extractable oil aerosol)	FEF_{25-75} $Vmax_{50}$ $Vmax_{25}$ (all the above indices were expressed as standardized residuals relative to predicted values)	$P = 0.11$ $P = 0.24$ $P = 0.54$ (above P values refer to differences from means of control subjects after adjustment for smoking)
Sprince et al. 1997	Automobile parts manufacture	Soluble/ semi-synthetic	Current geometric mean: 0.33 mg/m^3 (range 0.04–1.44) (total by MiniRAM)	FEV_1	No significant differences (machine operators relative to assemblers; by type of MWF; or by MWF aerosol exposure concentration)

*All are cross-sectional studies.

†Abbreviations: CI=confidence interval, FEF=forced expiratory flow, FEV=forced expiratory volume, FVC=forced vital capacity OR=odds ratio; PR=prevalence ratio; SD=standard deviation.

‡Adjusted for smoking, grinding, and plant.

MWF aerosols is associated with reduced pulmonary function. Although the observed reductions in pulmonary function may, in part, be acute and reversible, their stronger relationship with past exposures than with current exposures [Greaves et al. 1995a] suggests that they may well be substantially chronic and irreversible. The observed adverse lung function effects are attributable to straight oil, soluble oil, and synthetic MWFs at exposure concentrations recently observed in large metalworking shops. Moreover, evidence from the largest study [Greaves et al. 1995a] involving several different plants using three different major types of MWFs at mean aerosol exposures ranging from 0.41 to 0.55 mg/m^3 (thoracic fraction) suggests that pulmonary function effects associated with cumulative exposure to MWF aerosol occur in a dose-related manner. Some pulmonary function evidence suggests possible interaction between smoking and exposure to MWF aerosol in reducing lung function [Ameille et al. 1995]. Although the actual degree of self-selection away from MWF exposure by affected individuals is not known, such a phenomenon would bias cross-sectional studies toward underestimating the effects of exposure. The lack of association between MWF aerosol exposure and lung function observed in some studies may be attributable to such selection, to statistical power limitations related to study size, to aerosol concentration, to exposure duration, and/or to MWF aerosol composition.

5.1.2.5 Cross-Shift Studies of Acute Effects on Lung Function

Study findings

Kennedy et al. [1989] studied cross-shift changes in lung function in 89 automobile manufacturing workers exposed to MWF aerosols who had worked for at least 5 years, compared with 42 "unexposed" assembly workers. The assembly workers were exposed to aerosol concentrations ranging from 0.07 to 0.44 mg/m^3 (inhalable fraction). The machinists selected for the study had worked with one MWF class (straight oil, soluble oil, or synthetic) for at least the past 6 months at concentrations ranging from 0.16 to 2.03 mg/m^3 (inhalable fraction). Geometric mean exposures for assembly workers and machinists were 0.18 and 0.66 mg/m^3 (inhalable fraction), respectively [Woskie 1996]. These workers were recruited from the same population used in a cross-sectional study reported by Eisen [1995] and Greaves et al. [1995a,b]. The investigators noted that more than 25% of eligible machinists who were invited to participate declined, and that machinists who chose not to participate had significantly lower mean percentage of predicted FEV_1 and FVC at 90% and 92%, respectively (both $P<0.01$). The three other groups (participating machinists, participating assembly workers, and nonparticipating assembly workers) all had comparable lung function, with mean percentage of predicted values ranging from 98% to 100%. This raises the possibility that the study did not include those machinists at greatest risk.

In an analysis stratified by MWF class, Kennedy et al. [1989] found that, regardless of MWF class, more than 20% of exposed machinists experienced a cross-shift FEV_1

decrement of at least 5%, compared with fewer than 10% of assembly workers (RR=2.5; $P<0.05$). In a logistic regression analysis controlling for race, history of childhood asthma, and smoking, acute Monday FEV_1 decrements of at least 5% were associated with straight MWF exposure (OR=5.8; 95% CI=1.1–29.0), soluble MWF exposure (OR=4.4; 95% CI=1.0–20.0), and synthetic MWF exposure (OR=6.9; 95% CI=1.4–35.0). Geometric mean exposures (total inhalable fraction) to MWF aerosol were 0.78 mg/m^3 for those working with straight oil MWF, 0.82 mg/m^3 for those working with soluble oil MWF, and 0.56 mg/m^3 for those working with synthetic oil MWF [Woskie 1996]. A history of childhood asthma was also strongly associated with cross-shift decrement (OR=9.1; 95% CI=1.3–66).

In assessing exposure-response relationships, Kennedy et al. [1989] trichotomized exposure to MWF aerosol (thoracic fraction) and found a significantly increased incidence of cross-shift FEV_1 decrements of at least 5% on each of two separate days of testing for the "high" exposure group (<0.55 mg/m^3) and the "medium" exposure group (0.20–0.55 mg/m^3) compared with the group exposed at lower aerosol concentrations (<0.20 mg/m^3). Even for the "medium" exposure group relative to the lower exposure group, the difference in incidence was statistically significant ($P<0.01$). In a logistic regression analysis controlling for race, smoking, and history of childhood asthma, incremental ORs for increasing exposure category were 1.8 (95% CI=0.9–3.3) for the Monday testing, and 2.0 (95% CI=1.0–3.8) for the Friday testing. Based on their observations, Kennedy et al. [1989] concluded that airways narrowing is a common response to MWF exposure and that the concentration of MWF aerosol at which no such response would be expected would be less than 0.20 mg/m^3 (thoracic fraction). Using a conversion factor of 1.4 derived from Kennedy et al. [1989], Woskie [1996] estimated no effect level is probably less than approximately 0.28 mg/m^3 (inhalable fraction) of MWF aerosol.

Kriebel et al. [1994, 1997] studied cross-shift FEV_1 decrements among 216 machinists exposed to straight and soluble MWF aerosols. The mean aerosol exposure concentration for the exposed machinists was approximately 0.23 mg/m^3 (inhalable fraction), or only about one-fourth the exposure concentrations for the cross-shift study of machinists reported by Kennedy et al. [1989]. The incidence of cross-shift FEV_1 decrements of 5% or greater was substantially lower than that observed by Kennedy et al. [1989], so the investigators initially employed a more sensitive (but less specific) 4% or greater cut-off to categorize FEV_1 decrements. Using inhalable mass exposure cut-points equivalent to the thoracic mass exposure cut-points employed by Kennedy et al. [1989], Kriebel et al. [1994] analyzed data from all study participants and observed a relative risk for 4% or greater FEV_1 decrement of 3.4 (95% CI=1.6–7.2) for the subgroup with "high" exposures (≥0.77 mg/m^3) compared with the group with "low" exposure (≤0.28 mg/m^3). Relative risks for machinists exposed to straight oil MWF aerosols were 2.3 (95% CI=0.6–8.7) for "medium" exposure and 5.3 (95% CI=1.9–14.9) for "high"

exposure compared with "low" exposure; relative risks for machinists exposed to soluble MWF aerosols were 0.6 (95% CI=0.1–2.3) for "medium" exposure and 3.3 (95% CI=0.8–13.9) for "high" exposure.

A further analysis using the more traditional 5% cutoff for FEV_1 response also showed a relationship between categorical MWF aerosol exposure and cross-shift FEV_1 response at lower concentrations [Kriebel et al. 1997]. The adjusted relative risks for cross-shift FEV_1 decrement were 2.3 (95% CI=1.0–5.0) for "medium" exposure (i.e., 0.08 to 0.15 mg/m^3) and 3.2 (95% CI=1.2–8.7) for "high" exposure (i.e., $\geq$0.15 mg/m^3) compared with "low" aerosol exposure (i.e., $\leq$0.08 mg/m^3). This suggests that a no-effect level is probably below 0.15 mg/m^3 (inhalable fraction) for MWF aerosol.

Additional analyses of these same data attempted to identify specific characteristics of MWF aerosol exposures that may cause the observed acute respiratory effects. In an analysis based on a 4% cut-point for cross-shift FEV_1 decrement, and aerosol exposure cut-points equivalent to those of Kennedy et al. [1989], risk of FEV_1 decrement was clearly associated with increasing exposure for those whose sump had not been refilled during the previous 3 days: RR= 1.8 (95% CI=0.6–5.0) for "medium" exposure (0.28–0.77 mg/m^3) and RR=5.9 (95% CI=0.6–5.0) for the "high" exposure ($\geq$0.77 mg/m^3) group, relative to the "low" ($\leq$0.28 mg/m^3) exposure group. Among those with less than 3 days since MWF sump refill, there were no acute FEV_1 decrements in the "medium" and "high" exposure categories, so a similar exposure-response relationship was not observed using the Kennedy cut-points. Using cut-points selected on the basis of the distribution of exposures, an exposure-response relationship was observed among those with more than 3 days since refill but not among those whose sumps had been filled more recently. However, the robustness of these observations relating to time since sump refill is questionable, as Kriebel [1996] reported that results of analogous analyses based on 5% or greater decrements in FEV_1 were inconsistent.

These same investigators [Kriebel et al. 1994; Sama et al. 1997] also evaluated risk associated with specific MWF aerosol components, including endotoxin and sulfur. Endotoxin exposures were low (geometric mean <9 endotoxin units/m^3), and there was no observed statistically significant association of acute ventilatory response with endotoxin exposure. Of four elements (chlorine, chromium, nickel, and sulfur) considered as *a priori* exposure indices, only sulfur was associated with cross-shift FEV_1 decrements. Hydrogen sulfide is a decomposition product of sulfurated hydrocarbons—a known respiratory irritant and a common contaminant of MWFs; petroleum sulfonates, which may decompose to sulfur dioxide, are also known pulmonary irritants commonly used in formulating soluble MWFs [Kriebel et al. 1994; Sama et al. 1997]. Comparing machinists exposed above the median of 3.2 $\mu g/m^3$ sulfur with those exposed to lower concentrations of airborne sulfur, the investigators found an apparent association between exposure to sulfur in MWF aerosols and cross-shift FEV_1 decrement $\geq$5% (OR=3.3;

95% CI=1.0–10.7). In subsequent analyses using exposure cut-points that divided the studied workers into those with exposures in the uppermost quartile, the middle half, and the lowermost quartile, a statistically significant exposure response trend (P=0.02) was observed: RR=1.5 (95% CI=0.3–6.4) for the "medium" exposure group (range, 2.5–4.4 $\mu g/m^3$; median, 3.4 $\mu g/m^3$) and RR=3.7 (95% CI=0.9–16.1) for the "high" exposure group (>4.4 $\mu g/m^3$; median, 5.6 $\mu g/m^3$), relative to the "low" exposure group (<2.5 $\mu g/m^3$; median, 2.1 $\mu g/m^3$) [Sama et al. 1997]. The relationship between sulfur exposure and cross-shift FEV_1 decrement was observed even at sulfur concentrations well below those at which ambient air pollution effects have been observed, leading to speculation that sulfur may not be the causal agent but may serve only as a marker of particularly irritating exposure conditions [Kriebel et al. 1995; Sama et al. 1997].

Robins et al. [1994, 1995a, 1997] studied cross-shift pulmonary function changes experienced by automobile transmission parts manufacturing workers exposed to soluble MWFs in the same concentration ranges as those studied by Kennedy et al. [1989]. By department, average MWF aerosol exposure (thoracic fraction) ranged from approximately 0.1 to 0.6 mg/m^3. For the assembly workers, median aerosol exposure was 0.14 mg/m^3, the 75th percentile was 0.15 mg/m^3, and the maximum exposure was 0.31 mg/m^3. The rate of cross-shift FEV_1 decrement of at least 5% was consistently higher among exposed workers for all three Mondays on which testing was done. Six of 85 exposed workers demonstrated clinically significant (≥19%) cross-shift FEV_1 decrements compared with none of the 46 workers in the assembly group (one tailed P=0.07). Using three exposure categories nearly equivalent to those used by Kennedy et al. [1989], Robins et al. [1994, 1995a, 1997] found evidence of a dose-related risk of cross-shift FEV_1 decrement of 5% or greater on Mondays. Aggregating observations from all three Mondays of the study and assuming independence of observations on the same individual on different Mondays, data from their report [Robins et al. 1994] permit calculations of unadjusted RRs for cross-shift decrements greater than 5% of 1.34 (95% CI=0.76–2.36) for "medium" exposure (0.16–0.47 mg/m^3, thoracic fraction) and 1.98 (95% CI=1.11–3.52) for "high" exposure (>0.47 mg/m^3) relative to "low" exposure (<0.16 mg/m^3). The median personal MWF aerosol exposures of machinists experiencing cross-shift FEV_1 decrements ≥12% ranged from 0.17 to 0.80 mg/m^3 (median, 0.5 mg/m^3) [Robins et al. 1994].

The presence of chronic symptoms and the development of respiratory symptoms on Monday were each associated with larger cross-shift FEV_1 decrements on Monday. Based on multiple regression analyses that excluded all workers who reported that they currently had asthma (and other influential outliers on a model-by-model basis), the magnitude of cross-shift FEV_1 decrement was consistently related to higher airborne bacteria exposure among current smokers with lower baseline FEV_1/FVC ratio. Robins et al. [1995b] reported that 25% of smokers with evidence of pulmonary obstruction at baseline (Monday preshift FEV_1/FVC ratio ≤0.72) experienced a cross-shift decrement

of FEV_1 of at least 10%, compared with only 5% of other study subjects. After controlling for other factors related to pulmonary function decrement, they found an increasing trend in risk of a 10% or greater cross-shift FEV_1 decrement with increasing levels of exposure to both MWF aerosol and airborne bacteria among obstructed smokers, but not among other study subjects. For obstructed smokers, model-derived ORs were 3.1 (95% CI=0.9–10.3), 6.0 (95% CI=2.3–15.8), and 8.8 (95% CI=2.7–28.8) for exposure to MWF aerosol concentrations at 0.14, 0.34, and 0.57 mg/m^3 (thoracic fraction), respectively, compared with other workers exposed at 0.14 mg/m^3 (OR=1, by designation). For other study subjects, corresponding ORs were 1.0 (95% CI=0.6–1.6) and 1.0 (95% CI=0.4–2.2) for exposures of 0.34 and 0.57 mg/m^3, respectively. For obstructed smokers, model-derived ORs were 4.4 (95% CI=1.8–10.7), 6.1 (95% CI=2.4–15.3), and 7.5 (95% CI=2.6–22.1) for exposure to airborne bacteria concentrations at 0.2, 1.0, and 3.0 bacteria/cubic centimeter (cc) (thoracic fraction). For other study subjects, corresponding ORs were 1.0 (by designation), 0.5 (95% CI=0.4–1.1), and 0.5 (95% CI=0.2–1.1). Robins et al. [1997] have also presented model-based comparative ORs for 10% or greater cross-shift FEV_1 decrements for obstructed and nonobstructed workers, regardless of smoking status. The exposure-related trends in ORs closely approximated those summarized in the above paragraph, suggesting an important interaction effect of exposure and baseline airways obstruction (regardless of smoking status) on acute airway response to MWF aerosol.

Robins et al. [1997] also developed predicted fractional cross-shift FEV_1 changes for various levels of baseline obstruction and exposure. These findings indicate a predicted average 10.1% (± 0.03) drop in FEV_1 at a MWF aerosol exposure level of 0.57 mg/m^3 compared with a 3.3 % (± 0.01) drop at 0.14 mg/m^3 for exposed workers with a baseline FEV_1/FVC of 0.6.

Sprince et al. [1997] studied Monday preshift and postshift spirometry among machine operators (n=183) and unexposed assembly workers (n=66) in an automobile transmission parts manufacturing plant. Machine operators were exposed to one of two types of soluble oil MWF or to a semisynthetic MWF. After adjusting for age, race, sex, and smoking, the investigators found no significant differences between machine operators and assemblers in terms of proportions experiencing an FEV_1 decrement ≥5%; unadjusted proportions were 16% for machine operators and 12% for assemblers. Likewise, there was no association between ≥5% FEV_1 decrements and MWF type or exposure concentrations among machine operators. Findings were similar with cross-shift FEV_1 decrement values analyzed as continuous data. Mean FEV_1 decrement was slightly larger among machine operators (−1.5%) compared with assemblers (−0.51%), but this difference was not statistically significant. Nor was magnitude of cross-shift FEV_1 decrement significantly associated with MWF type or exposure concentration among machine operators. Geometric mean total aerosol exposures (as measured by MiniRAMs gravimetrically calibrated to Arizona road dust) were 0.33 mg/m^3 (range

0.04 to 1.44 mg/m^3) for machine operators and 0.08 mg/m^3 (range 0.02–0.20 mg/m^3) for assembly workers. These aerosol concentrations are not comparable with those resulting from standard filter methods. If exposures in this plant had been measured with a direct gravimetric filter method, the concentrations would likely have been lower by a factor equivalent to the nonvolatile proportion of the aerosol entering the sampler.

Summary

Four studies evaluated acute (cross-shift) lung function decrements in workers exposed to MWF aerosols. Table 5–4 presents selected risk estimates from four relevant studies. All but one of these studies found that incidence of cross-shift FEV_1 decrement is associated with occupational exposure to MWF aerosol. The evidence indicates that exposures to aerosols generated during the use of straight oil, soluble oil, or synthetic MWFs all cause acute reductions in ventilatory function at MWF aerosol exposure concentrations currently typical of large metalworking shops. Moreover, in all three studies with affected worker populations, these acute airflow reductions occurred in a dose-related manner and were attributable to MWF aerosol at concentrations in excess of approximately 0.5 mg/m^3 (thoracic fraction). In two of the three studies, they were found to be statistically significant at substantially lower aerosol concentrations. Kennedy et al. [1989] found increasing risk of cross-shift declines occurring at MWF aerosol concentrations above approximately 0.20 mg/m^3 (thoracic fraction), and the results of Kriebel et al. [1997] indicate that a no-effect level for cross-shift FEV_1 decrements may be on the order of 0.10 mg/m^3 (inhalable fraction) or lower.

Previous history of childhood asthma appears to be a predictor of increased risk of acute lung function decrements associated with MWF aerosols [Kennedy et al. 1989], though such decrements occur even in the absence of such history [Robins et al. 1997]. Some evidence suggests that smoking (both active and possibly passive) and/or baseline airways obstruction may increase susceptibility to cross-shift lung function decrement induced by occupational MWF aerosol exposures [Kennedy et al. 1989; Robins et al. 1997]. Consistent with results of toxicological studies that indicate variability in airways effects of various aerosolized MWFs (summarized elsewhere in this document), the specific composition of MWF aerosols is also undoubtedly an important potential predictor of acute airways effect. Specific exposure characteristics evaluated in one or more epidemiological studies include bacterial counts, endotoxin, fungal counts, and various elements including sulfur. Some of these specific characteristics are promising as indicators of MWF aerosol potency in terms of airways effects, but existing data are insufficient to displace the much better documented gravimetric aerosol concentration as the best current indicator of potential potency of MWF aerosol. Given the complexity of MWF aerosol composition, it is questionable whether a single specific exposure index will ever be shown to be better than generic gravimetric measurements of MWF aerosol exposure when used alone to assess potential risk.

Table 5–4. Estimated risk of cross-shift lung function associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Risk estimate (95% CI* or *P*-value)
Kennedy et al. 1989	Workers in automobile parts manufacturing	All classes	Range 0.16–2.03 mg/m^3 (inhalable fraction)	Cross-shift FEV_1 decline (≥5%)	RR=2.5 (P<0.05) (relative to assemblers)
			Current mean: 0.75 mg/m^3 (inhalable fraction)	Cross-shift FEV_1 decline (≥5%): Monday	OR=1.8 (0.9–3.3)
				Cross-shift FEV_1 decline (≥5%): Friday	OR=2.0 (1.0–3.8) (above 2 ORs are for incremental increase in exposure trichotomized at 0.2 mg/m^3 and 0.55 mg/m^3— thoracic fraction)
		Straight	Current mean: 0.81 mg/m^3 (inhalable fraction)	Cross-shift FEV_1 decline (≥5%)	OR=5.8 (1.1–29) (relative to assemblers)
		Soluble	0.88 mg/m^3 (inhalable fraction)	Cross-shift FEV_1 decline (≥5%)	OR=4.4 (1.0–20) (relative to assemblers)
		Synthetic	0.62 mg/m^3 (inhalable fraction) (above exposure data from Woskie [1996])	Cross-shift FEV_1 decline (≥5%)	OR=6.9 (1.4–35) (relative to assemblers)
Kriebel et al. 1994, 1997	Workers in automobile parts manufacturing	Straight	Current mean: 0.24 mg/m^3 (SD=0.3) (inhalable fraction)	Cross-shift FEV_1 decline (≥4%)	RR=2.3 (0.6–8.7) (0.28–0.77 relative to ≤0.28 mg/m^3)
				Cross-shift FEV_1 decline (≥4%)	RR=5.3 (1.9–14.9) (≥0.77 relative to ≤0.28 mg/m^3)
		Soluble	0.22 mg/m^3 (SD=0.3) (inhalable fraction)	Cross-shift FEV_1 decline (≥4%)	RR=3.3 (0.8–13.9) (≥0.77 relative to ≤0.28 mg/m^3)
		Straight/soluble (aggregated data)		Cross-shift FEV_1 decline (≥5%)	RR=2.3 (1.0–5.0) (0.08–0.15 relative to ≤0.08 mg/m^3)
				Cross-shift FEV_1 decline (≥5%)	RR=3.2 (1.2–8.7) (≥0.15 relative to ≤0.08 mg/m^3)

*Abbreviations: CI=confidence interval, FEV_1=forced expiratory volume in 1 sec, OR=odds ratio, RR=risk ratio, SD=standard deviation.

(Continued)

Table 5–4 (Continued). Estimated risk of cross-shift lung function associated with MWF aerosol exposure

Study	Population	Fluid class	Aerosol exposure concentration	Health effect	Risk estimate (95% CI or *P*-value)
Robins et al. 1994; 1997	Workers in automobile parts manufacturing	Soluble	Current mean: 0.44 mg/m^3 (thoracic fraction)	Cross-shift FEV_1 decline (≥20%)	RR=undefined (*P*=0.07) (relative to assemblers)
				Cross-shift FEV_1 decline (≥5%)	RR=1.34 (0.76–2.36) (0.16–0.47 relative to ≤0.16 mg/m^3)
					RR=1.98 (1.11–3.52) (≥0.47 relative to ≤0.16 mg/m^3)
Sprince et al. 1997	Workers in automobile parts manufacturing	Soluble/ semisynthetic	Current mean: 0.33 mg/m^3 (range 0.04–1.44) (total by MiniRAM)	Cross-shift FEV_1 decline	No significant differences (machine operators relative to assemblers, by type of MWF, or by exposure concentration)

5.1.3 Discussion

With the exception of infrequent case reports of lipid pneumonia or asthma, essentially no scientific literature published before the past two decades attributed nonmalignant respiratory disease to MWF aerosol exposures. This lack of early evidence may be at least partly attributable to limited prior research on this issue. Lipid pneumonia (a health risk associated with exposures to airborne concentrations of oil-containing MWF) currently appears to be a much less important occupational health concern than disorders such as HP, acute airways irritation, asthma, chronic bronchitis, and potentially irreversible chronic obstructive impairment of lung function.

Recent studies are not entirely consistent in documenting exposure-response relationships between MWF aerosol exposures and respiratory symptoms and lung function effects (both acute and chronic), including clinically recognized asthma. Nevertheless, for each MWF class, frequent adverse respiratory effects have been clearly attributable to MWF aerosol concentrations in excess of approximately 0.5 mg/m^3 (thoracic fraction) in most recent epidemiological studies, and to even lower aerosol concentrations in some of these studies. Given the complexity of MWF aerosol composition, gravimetric aerosol measurements cannot be considered entirely specific for the hazard potential of MWF aerosol. Various specific characteristics of MWF aerosol exposures have been evaluated in some recent studies, and some have yielded promising findings. However, available data regarding these specific aerosol characteristics is very limited, and nonspecific gravimetric measurement of aerosol exposure remains a reasonably robust indicator of the risk of adverse airways effects. These gravimetric exposure concentrations are expressed in terms of TWAs. The possibility exists that short-term peak exposures are more important determinants of at least some of the airways disorders induced by MWF aerosols (e.g., asthma), but no epidemiologic studies to date have assessed MWF aerosol exposures with respect to short-term peak exposures.

Despite an impressive amount of research recently carried out on the airways effects of exposure to MWF aerosol, the potential importance of various adverse acute airways effects attributed to MWF aerosol is not entirely clear. Particularly in view of the increasing documentation that asthma can be caused by occupational exposure to MWF aerosols, acute symptoms and acute airflow reduction measured across a shift should be considered an important health outcome. In some exposed workers, these acute reactions may be manifestations of attacks of already diagnosed asthma; in others, acute reactions may be manifestations of newly developed but not yet diagnosed asthma. With regard to this latter possibility, it is notable that symptoms of episodic cough, wheeze, and phlegm have been shown to predate (by more than 2 years on average) diagnosis of asthma in the much better studied occupational asthma associated with western red cedar dust [Chan-Yeung et al. 1982]. Although asthma can be mild in many affected individuals, it can be quite debilitating. Moreover, even after removal of affected workers from exposure, occupational asthma frequently persists as a chronic condition

[Chan-Yeung and Malo 1993a]. It is not unreasonable to suggest that the natural history of MWF-associated asthma, although not yet well described, is similar to asthma associated with other better studied occupational agents.

In many exposed workers, acute respiratory symptoms and/or modest functional decrements may never develop into clinical asthma. Nevertheless, they are often quite bothersome to the affected workers, even causing him or her to seek medical treatment [Rosenman et al. 1997b]. They can also serve as biomarkers of potentially hazardous occupational exposure that should be better controlled. Furthermore, repeated modest acute airways effects, though apparently reversible upon removal from exposure, may ultimately lead to irreversible impairment and chronic pulmonary disability. No studies have yet been carried out among exposed metalworkers to relate acute decrements caused by MWF aerosols with chronic airways obstruction. In fact, with the exception of one very limited study [Järvholm 1982] and another study now in progress [Kennedy et al. 1995b], there has been no prospective study of long-term change in lung function among metalworkers exposed to MWF aerosols. For a variety of other occupational respiratory hazards, however, gradually emerging evidence has indicated a link between acute and chronic lung function effects [Peters 1974; Wegman et al. 1982; Weill 1984; Tabona et al. 1984; Becklake et al. 1988; Hankinson and Hodous 1983; Christiani et al. 1994; Glindmeyer et al. 1994; Becklake 1995; Schwartz et al. 1996]. It seems entirely plausible that an analogous phenomenon occurs with regard to adverse pulmonary function effects of occupational exposure to MWF aerosol.

5.2 Tumorigenic Effects in Animals

Few animal data have been published on the tumorigenicity of MWFs. NIOSH is aware of only six animal studies that have examined the tumorigenicity of MWFs [Gilman and Vesselinovitch 1955; Desoille et al. 1973; Jepsen et al. 1977; Wang and John 1988; Gupta and Mehrotra 1989; McKee et al. 1990]. Three of these studies reported only findings related to the skin [Gilman and Vesselinovitch 1955; Jepsen et al. 1977; Gupta and Mehrotra 1989]. Of these three studies, one examined unrefined cutting oil [Gilman and Vesselinovitch 1955], one examined solvent-extracted cutting oil [Jepsen et al. 1977], and the third study did not specify how the cutting oil was refined (although the cutting oil was probably highly refined, as the PAH content was only 5.22%) [Gupta and Mehrotra 1989]. The study by Gilman and Vesselinovitch [1955] found that among mice receiving a skin application of soluble cutting oils formulated from unrefined distillates three times weekly for 310 days, 61% developed skin tumors (of whom 22% had carcinomas) compared with no tumors present in the unexposed control group. Jepsen et al. [1977] found that among mice receiving skin applications of solvent-extracted cutting oils, 80% and 0% of mice developed papillomas after exposure to undiluted and diluted soluble oil, respectively. Jepsen et al. [1977] also studied paraffin-based and naphthalene-based straight oil MWFs. They found that 45% and 0% of mice developed