

MEETING REPORT

Metalworking Fluid-Associated Hypersensitivity Pneumonitis: A Workshop Summary

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A workshop discussing eight clusters of hypersensitivity pneumonitis in the automotive industry among metalworking fluid-exposed workers concluded that a risk exists for this granulomatous lung disease where water-based fluids are used and unusual microbial contaminants predominate. Strong candidates for microbial etiology are nontuberculous mycobacteria and fungi. Cases of hypersensitivity pneumonitis occur among cases with other work-related respiratory symptoms and chest diseases. Reversibility of disease has occurred in many cases with exposure cessation, allowing return to work to jobs without metalworking fluid exposures or, in some situations, to jobs without the same metalworking fluid exposures. Cases have been recognized with metalworking fluid exposures generally less than 0.5 mg/m³. The workshop participants identified knowledge gaps regarding risk factors, exposure-response relationships, intervention efficacy, and natural history, as well as surveillance needs to define the extent of the problem in this industry. In the absence of answers to these questions, guidance for prevention is necessarily limited. Am. J. Ind. Med. 32:423-432, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: *metalworking fluid; machining fluid; hypersensitivity pneumonitis; mycobacteria; occupational respiratory disease; granulomatous disease*

BACKGROUND

In the fall of 1996, the health and safety director of the United Auto Workers (UAW) asked the National Institute for Occupational Safety and Health (NIOSH) to facilitate a workshop on the prevention of hypersensitivity pneumonitis (HP), clusters of which had occurred in several plants with metal machining operations in the automotive industry and its component suppliers [Muilenberg et al., 1993; Bernstein et al., 1995; CDC, 1996]. With the sponsorship of the UAW-Chrysler National Joint Committee on Health and Safety, NIOSH invited participation of corporate and plant health and industrial hygiene personnel, union health and

safety representatives from the implicated plants, and independent investigators to a workshop on January 28-29, 1997. The goals of the workshop were to identify gaps in knowledge regarding cause, exposures, control, and prevention of this occupational lung disease; tools for addressing these knowledge gaps; and best practices for control and prevention, where consensus existed.

In preparation for the workshop, NIOSH staff compiled available information on the existing investigations of this problem in eight plants with cases of HP. These findings were presented and amplified both at the workshop and after by additional submitted material.

FINDINGS

Plant Outbreaks

The eight plants with physician-documented cases of HP manufactured engines, transmissions, electronics, refrigeration, and other components. Three major

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TABLE I. Hypersensitivity Pneumonitis Associated With Metalworking Fluid Exposures: Cases and Attack Rates, by Plant

Plant	Symptoms onset dates (diagnosis dates)	Cases HP	Cases with abnormal lung biopsy	Cases with abnormal CXR or CT	Attack rates (%)
1	04/1992–09/1992	9	0	4	In one area 9/12 (75.0%)
2	09/1994–06/1995	3	0	3	?
3	(1994–1995)	2	2	2	?
4	08/1995–03/1996	34	4	17	By department 5/130 (3.9%) 4/146 (2.7%) 1/27 (2.7%) 6/352 (1.7%) 2/191 (1.1%) 1/164 (0.6%)
5	(1993–1997)	13*	5	9	By year 3/265 (1.1%) 4/265 (1.5%) 3/265 (1.1%) 2/265 (0.8%) 1/265 (0.4%)
6	(1994–1997)	10*	3	4	In one department 6/129 (4.7%)
7	(1991–1995)**	13	3	2	In one department 5/98 (5.1%)
8	(1992–1997)**	14*	5	?	?

*Includes cases diagnosed with interstitial lung disease.

**Includes cases reported to the state.

automobile manufacturers and two smaller companies had two or more HP cases, prompting a consideration of occupational etiology (Table I). The first case was reported in 1991. In three plants, cases have been diagnosed in 1997, with presumptive cases awaiting clinical evaluation in a fourth plant. HP clusters within plants developed over time periods ranging from six months to several years, reflecting both epidemic and endemic patterns of disease occurrence.

A total of 98 cases of physician-diagnosed HP have occurred in the eight plants. At least 22 of these cases had lung biopsy, and at least 41 had abnormal chest radiographs or computerized tomography scans. In most plants, there were reports of other employees with work-related respiratory symptoms. Some of these other workers were diagnosed with asthma, pneumonia, or bronchitis. In no outbreak were symptomatic workers systematically evaluated for X-ray abnormality or bronchoalveolar lavage lymphocytosis.

All plants used water-based metalworking fluids (Table II). The metalworking fluid microbial exposures in these outbreaks were complex (Table III), but it is noteworthy that *Mycobacterium chelonae* was found in four of the eight plants. In two plants (plants 6 and 7), mycobacterial

cultures were performed and none were detected, suggesting that other microbial flora may be implicated. In the four plants without documented mycobacteria and in at least two plants with mycobacteria, Gram-positive bacteria and/or fungi were also found. Gram-positive bacteria are not usually present in microbially contaminated metalworking fluids, but fungal species may be found in systems following a permanent or temporary die-off of pioneering bacterial species [Rossmore, 1985]. Endotoxin was detected in the fluid where sought, and levels ranged from less than 10 to 2.9×10^5 EU/ml, consistent with the Gram-negative flora usually characteristic of in-use metalworking fluids. Total particulate exposures were often 0.5 mg/m^3 or less.

Efforts at control included improvements in local exhaust and ventilation systems, increased outside air delivery, machine enclosure, replacement of metalworking fluids, substituting type of fluids, improved housekeeping, cleaning of the systems, increased filtration, pasteurization, and biocides. Documentation pertinent to the efficacy of such remediation attempts was virtually nonexistent. Environmental characterization commonly lagged months

TABLE II. Metalworking Fluid Type and Exposure Levels, by Plant

Plant	MWF type in affected areas	Total particulate area samples			Total particulate personal samples		
		Date	Concentration range mg/m ³	Comment	Date	Concentration range mg/m ³	Comment
1	Synthetic, (during out-break switched to Semi-synthetic)	—	—		—	—	
2	Semi-synthetic	—	—		—	0.36–0.43	1. Samples from MWF-systems where HP cases worked 2. Sampling done after the episodes of respiratory problems
3	Semi-synthetic	—	—		—	—	
4	Synthetic	01/92–03/96	0.0–3.6	39 samples, 15 ≤ 0.5 mg/m ³	11/96	0.01–0.77	35 samples taken on both HP cases and controls
5	Soluble and semi-synthetic	07/96 & 08/96	0.24–1.08	5 samples, average = 0.6 mg/m ³	07/96 & 08/96	0.08–1.17	21 samples, average = 0.4 mg/m ³
6	Semi-synthetic	—	≤0.5	Data from review of plant records	—	—	
7	Soluble	—	≤0.5	Data from review of plant records	—	—	
8	Semi-synthetic and synthetic	09/92	0.4–1.9	Locations close to visible aerosol releases from machines	10/92 & 11/92	0.1–2.0	25 samples, only one >0.6 mg/m ³
		—	—		11/96	0.3–0.8	3 samples taken by state division of occupational health

to years after the onset of symptoms of those who were eventually diagnosed as cases and frequently occurred only after changes in biocide management, replacement of metalworking fluids, or system cleanup. Ongoing environmental surveillance, when it occurred, could not be linked with health outcomes. No plant was known to have instituted systematic medical screening or health surveillance of metalworking fluid-exposed workforces.

Synopses of Plant Outbreaks

Plant 1

As reported at the workshop, 9 of 12 (75%) machinists working on one machining line served by one metalworking fluid sump had physician-diagnosed HP with symptom onset over a six-month period, from April to September, 1992. A second line supplied by a different sump in the same building had no cases, nor did a second plant operated by the manufacturing facility. Serological testing on six of the cases showed precipitin bands to *Pseudomonas* species in all; to *Rhodococcus* species (an acid-fast organism) in three; and to *Aspergillus niger*,

Staphylococcus capitis, or *Bacillus pumilus* in two cases. A sputum culture from one of these six cases grew *M. chelonae* [Bernstein et al., 1995]. This same case had strong serum precipitin bands against the implicated metalworking fluid [Muilenberg et al., 1993]. Eight of the cases were relocated to the second plant with apparent recovery; the ninth was placed on disability. In 1992, three cases of work-related asthma among workers at this plant were reported to the state health department. Microbiological consultants demonstrated *M. chelonae* as the predominant microorganism in the metalworking fluid from the implicated sump, in contrast to the Gram-negative bacterial flora (e.g., *Pseudomonas* and *Acinetobacter*) in the other sump and other plant. Fungi were present along with the Gram-negative flora, but not with the acid-fast mycobacterium [Muilenberg et al., 1993]. Monthly surveillance of metalworking fluid cultures documented an initial decrease of these organisms in response to biocides and then the emergence of apparently resistant mycobacteria at the previous concentrations. The investigators were unaware of continuing health surveillance, if any, in the plant but had been assured by the plant management that no continuing health problem existed.

TABLE III. Microbial Characterization of Bulk Metal-Working Fluids, by Plant

Plant	Sampling period	Mycobacteria		Other acid fast or gram-positive bacteria		Fungi		Gram-negative bacteria	Endotoxin in MWF EU/ML
		Y/N	Species & concentration CFU/ML	Y/N	Species & concentration CFU/ML	Y/N	Species & concentration CFU/ML		
1 (Report at workshop)	At time of outbreak	Y	<i>M. chelonae</i> , 10 ⁶ –10 ⁷	N	—	N	—	N	—
1 (Bernstein et al., 1995)	MWF in use during occurrence of illness	?		Y	<i>Rhodococcus sp.</i> <i>Bacillus spp.</i> <i>Staphylococcus capitis</i>	Y	<i>Aspergillus niger</i> , <10	Y	4.0 × 10 ² – 1.7 × 10 ³
2	05/95 (microbial) 01/96 (endotoxin)	?		Y	bacillus branching bacillus	Y	<i>Fusarium solani</i>	?	6.0–1.25 × 10 ⁵ (0.1–10 EU/m ³ in air)
3	1. During time of outbreak 2. Early 1996	Y Y	Atypical mycobacteria, "high" conc. in air <i>M. chelonae- abscessus complex</i> , 10 ⁵ –10 ⁶	? N	—	? N	—	? N	? —
4	12/95–07/96	Y	<i>M. fortuitum/chelonae complex</i> , 1–6.6 × 10 ⁶ <i>M. chelonae</i>	Y	<i>Bacillus spp.</i> <i>Actinomyces sp.</i> <i>Acinetobacter haemolyticus</i> <i>Micrococcus sp.</i> <i>Staphylococcus spp.</i> <i>Propioniacterium sp.</i>	Y	<i>Fusarium sp.</i> <i>Acremonium sp.</i> <i>Candida stelatoidea</i>	Y	?
5	1. Large central sumps 06/96 2. Small local sumps 07, 08/96	Y N	<i>M. chelonae</i> (pre-dominant sp.) 10 ⁶ –10 ⁷ —	Y Y	<i>Bacillus cereus</i> <i>Rhodococcus sp.</i> <i>Corynebacterium nitrophilus</i>	Y N	<i>Fusarium sp.</i> 10 ² – 1.8 × 10 ³	Y Y	ND–4.4 × 10 ⁴
6	04/95	N	—	N	—	Y	Yeasts, 5–10 Fungi, non-sporulating, 25	Y	<2.0 × 10 ² – 1.96 × 10 ⁵
7	04/95	N	—	N	—	Y	<i>Fusarium sp.</i> , 5–9 × 10 ³ Yeasts, 10–1 × 10 ⁵	Y	<2.0 × 10 ² – 2.88 × 10 ⁵
8	09/92	?	—	Y	<i>Bacillus sp.</i> , 10 ⁴ –10 ⁵ <i>Micrococcus sp.</i>	Y	Fungi, non-sporulating, 10 ⁵ <i>Geotrichum</i> , 10 ⁵ <i>Rhinochadiella</i> , 10 ⁵	Y	<10

Plant 2

Three cases of physician-diagnosed HP occurred among approximately 2,000 hourly workers with metalworking fluid exposure in either of two buildings over a 10-month period in 1994–95. All cases had serum precipitins to the thermophilic actinomycete, *Micropolyspora faeni* (which

was not cultured from metalworking fluids in the plant), and two had precipitins to *Fusarium sp.*, a fungus cultured at low levels from in-use metalworking fluid after biocide was added and at a considerable time after the clinical diagnoses were made. Line listings provided by the union showed 124 employees (including the three HP cases) reporting health problems which they attributed to metalworking fluids in

1995-96, of whom 78 had respiratory symptoms. Apart from the three HP cases, 10 of the 78 workers were relocated within the plant and three retired or left work. A respiratory specialist diagnosed four cases of asthma in 12 symptomatic workers referred to him during the same period. Two of the HP cases returned to work at other jobs uneventfully without metalworking fluid exposures, and one case retired for unknown reasons.

Plant 3

Two cases of physician-diagnosed HP occurred over an 18-month period in 1994-95 among an unknown number of employees exposed to metalworking fluid growing *M. chelonae-abscessus* complex. The cases improved following removal from work, and one case reportedly later returned to work in the metalworking fluid-exposed environment. No details on this return to work experience were available. The other case became symptomatic in the evening after returning to the plant for 20 minutes to remove his personal effects from his locker on his retirement.

Plant 4

As part of a state health department investigation which began in March 1996 (OSHA Consultation Study No. 6114-0 / WI / Health), a three-part respiratory disease surveillance system was developed, using symptom questionnaires, physician contacts, and medical record review. Between August 1995 and May 1996, there were 34 physician-diagnosed cases of HP, 20 of which met an epidemiologic definition for HP. The six departments in which cases occurred had attack rates ranging from 0.6% to 3.9%. Seven departments without metalworking fluid exposures had no cases. In addition to HP cases, three workers had occupational asthma, 20 had bronchitis, and three had chronic obstructive pulmonary disease.

Between December 1995 and August 1996, a contract laboratory cultured over 100 different species of microorganisms from in-use metalworking fluids, including Gram-negative, Gram-positive, and acid-fast bacteria (*M. fortuitum/chelonae* complex) and fungi. Species and counts varied over time and had no evident correlation to earlier occurrence of HP. In-use metalworking fluid samples collected by the state health department in March 1996 and tested at three different laboratories were found to grow *M. chelonae*. Serologic studies with commercial antigens were difficult to interpret, but HP cases were more likely than asymptomatic controls to have a precipitin reaction to in-use metalworking fluid. Cases improved with removal from their work areas. Nine of ten cases successfully returned to work with metalworking fluids with personal respiratory protection, but no follow-up was available.

Plant 5

Eleven cases (ten cases of physician-diagnosed HP and one case of physician-diagnosed interstitial lung disease) occurred over a 40-month period from January 1993 to April 1996 among 265 workers in the area of the plant which used metalworking fluids, with an annual incidence ranging from two to four cases (NIOSH Hazard Evaluations and Technical Assistance (HETA) 96-0156). A twelfth case occurred adjacent to this area. A thirteenth case was diagnosed from the area in early 1997, after the 1996 investigation. All cases improved after removal from their work area, but no return to work details were available. Three other symptomatic workers were diagnosed with asthma. In June 1996, NIOSH investigators sampled central metalworking fluid systems, finding *M. chelonae* to be the predominant organism. Real-time particulate sampling demonstrated that most particles were in the respirable size range.

Serologic studies on metalworking fluid-exposed workers (including six cases of HP) and nonexposed workers used five commercial antigens and an extract of *M. chelonae*. In an ELISA assay, the mycobacterial antigen was significantly associated with both HP and metalworking fluid exposure. In precipitin assays, antigens from *Aspergillus fumigatus*, *Aureobasidium pullulans*, and *Thermoactinomyces vulgaris* were significantly associated with metalworking fluid exposure, while antigens from *A. fumigatus* and *Micropolyspora faeni* were associated with HP.

Plant 6

Nine physician-diagnosed cases (four cases of HP and 5 cases of interstitial lung disease) were diagnosed in 1994-95, with symptoms beginning in late 1993 (NIOSH HETA 95-0172). A tenth case of HP was diagnosed in March 1997 with symptoms beginning in fall 1996. All cases had metalworking fluid exposure, with six of the cases occurring among 129 workers (4.7%) in one department. The one HP case tested had multiple positive precipitin results using a commercial HP antigen panel. All cases improved with removal from work. Two of the HP cases completed a follow-up questionnaire in March 1996. Both were still working at the plant. One case had changed departments, to an area with no metalworking fluid exposure, and was asymptomatic. The other case was still exposed to metalworking fluids and reported current symptoms. In addition to the nine cases, 29 other workers reported recurrent work-related respiratory symptoms which had been evaluated by a physician. Medical record review on 13 of these 29 workers indicated seven diagnoses of asthma and five of bronchitis. In April 1995, microorganisms were cultured from bulk samples of metalworking fluid taken three days after biocides had been added to many systems. The predominant organism was the Gram-negative, *Deleya aesta*.

Plant 7

Eight cases of HP were diagnosed over a 13-month period in 1994–95, with symptom onset occurring from August 1992 to July 1994 (NIOSH HETA 94-0325). Between 1991–93, five additional HP cases were reported to the state health department, along with 14 work-related asthma cases. Additionally, two presumptive cases with symptom onset in February and March 1997 are currently undergoing clinical evaluation.

The NIOSH investigation found that of the eight 1994–95 HP cases, three occurred in one department using metalworking fluids and five occurred among 98 trades workers (5.1%) in a plant area with soluble oil use. One of the HP cases had multiple positive precipitin results for a commercial HP test panel, while two other HP cases had negative tests. In addition to the eight cases of HP, seven other workers reported recurrent work-related respiratory symptoms which had been evaluated by a physician. Medical record review on three of these seven workers indicated one with asthma and two with chest pain of uncertain etiology. The HP cases improved upon removal from work. Four of the HP cases completed a follow-up questionnaire in March 1996. Three were still working at the plant in different departments. Two were asymptomatic and were not exposed to metalworking fluids. One worker did not report on metalworking fluid exposure but had current symptoms of chest pain/tightness, shortness of breath, cough, unusual tiredness, sinus congestion, and muscle/body aches. The fourth HP case had taken medical retirement and was still having respiratory and systemic symptoms. The predominant organisms cultured from samples of in-use metalworking fluid in April 1995 were the Gram-negative bacteria *Pseudomonas pseudoalcaligenes* and *Ochrobactrum anthropi*, with lesser concentrations of fungi being found.

Plant 8

From February through September 1992, twelve cases of HP or lung fibrosis occurred among machine operators and skilled trades workers with metalworking fluid exposure. Additionally, one HP case was reported to the state health department in 1995 and a biopsy-documented 1997 case had symptom onset in 1996. Of 80 workers with respiratory symptoms developing in 1992, five had asthma, two had asthma and pneumonia, seven had pneumonia, one had bronchitis and pneumonia, five had bronchitis, and 23 had respiratory irritation. No HP cases had precipitins to antigens tested, but no information was reported on the antigens used.

The microbial sampling on September 3 and 4, 1992, followed biocide addition on September 2. These showed Gram-negative *Pseudomonas*-like species, Gram-positive *Bacillus* species, and fungi. During the same time period,

area samples for alkanolamines taken at locations where visible aerosol was released from machines ranged from none detected to 0.39 ppm. Formaldehyde levels were 0.03–0.08 ppm.

DISCUSSION

Clinical and Epidemiologic Conclusions

The evidence presented and discussed at the workshop left no question that an occupational risk of HP exists in this industry. Moreover, the case series from six of the eight plants show that at least 22 cases had biopsy-proven granulomatous disease, leaving little concern over possible misclassification of diagnosis. No national morbidity data are available for HP in populations unknown to be at occupational risk, in which sporadic cases may be diagnosed as sarcoidosis. Clinically evident granulomatous pneumonitis is a rare disease in the working-age population, with sarcoidosis, for example, having a reported incidence of about 1–4 cases in 10,000 per year, depending on race [Rybecki et al., 1997]. For much smaller workforces, the occurrence of clusters of cases constitutes robust epidemiologic evidence for the association of granulomatous disease with water-based metalworking fluid exposure.

The clinical course of cases and the spectrum of disease have not been systematically studied. Many cases reported on at the workshop appeared to resolve or at least improve with removal from exposure to metalworking fluid aerosols. However, the likelihood of attributing cases of chronic interstitial lung disease to the workplace may have been low in the absence of recognizing an association of HP with this industry. Some cases from recognized outbreaks have had recurrent disease with re-exposure, and some cases had biopsy evidence of fibrosis, which would not be expected to be reversible. The spectrum of disease may be much broader than currently documented. HP is similar to other granulomatous diseases, such as sarcoidosis and beryllium disease, in which a portion of cases is radiologically normal [Lynch et al., 1992; Kreiss et al., 1993; Rybecki et al., 1997]. In several plants, cases of HP occurred against a background of work-related chest symptoms among coworkers, some of whom carried diagnoses of asthma, bronchitis, or pneumonia. It remains unresolved whether this apparent increase in other chest conditions represents undiagnosed granulomatous lung disease, a spectrum of biologic effect from a common cause, or coincidence of exposure to irritants and suspected allergens. Certainly HP is associated with airways hyperreactivity [Freedman and Ault, 1981]. The systematic clinical evaluation of all symptomatic workers needed to address these issues has not been done.

Attempts to characterize microbial causes of cases with HP have been considerable. Clinical evaluations of cases

have documented serum precipitating antibodies to a puzzling and inconsistent array of known microbial causes of HP, as well as to extracts of microbial organisms cultured from the metalworking fluids found in the plants subsequent to clinical diagnoses. The presence of precipitins documents exposure to organisms for which commercial or prepared antigen extracts are available; it does not document disease. In the setting of diverse potential exposures for which antigen extracts might not be available or characterized, the absence of precipitins should not lead clinicians (or epidemiologists) to exclude the diagnosis of HP. A corollary observation was that precipitin testing could mislead efforts to understand microbial etiology. For example, the precipitin testing results of the only plant case series published to date [Bernstein et al., 1995] did not predict that atypical mycobacteria might be a more likely explanation for the outbreak [Muilenberg et al., 1993]. By analogy to other granulomatous diseases in which the cause is known, cell-mediated immunity may be the predominant pathologic mechanism [Hansen and Penny, 1974; Johnson et al., 1980; Bernstein et al., 1983; Kreiss et al., 1993; Rose, 1994]. Thus, the biomarkers which need development and evaluation in elucidating cause may be antigen-specific lymphocyte proliferation testing on blood or bronchoalveolar lavage cells and delayed hypersensitivity skin tests, rather than serological testing.

Beyond the fact that HP is occurring among metalworkers in some plants, little systematic epidemiologic information is available. The most robust prevalence data came from plant 1, in which the majority of workers in one line had physician-diagnosed HP, with no cases in a comparison line at the plant. In this instance, the two academic groups reporting aspects of the outbreak [Muilenberg et al., 1993; Bernstein et al., 1995] differ in their published or presented numerator and denominator estimates, neither having been involved in epidemiologic investigation. In the four plants with cross-sectional survey data, prevalence rates are limited by lack of systematic case finding, low response rates, or rather crude estimates of the worker population at risk over the period of investigation, which invariably followed the removal of known cases. Prevalence ranged up to about 5% in these investigations and interpretation is limited by confusion about whether the population at risk is all those with exposure to aerosols from metalworking fluid, those with exposure from a particular metalworking fluid sump, or those with exposure limited to time during which aberrations in the fluid may have existed, e.g., from changes in microbial flora. In the absence of a clear cause or causes, confusion is likely to persist regarding the degree of risk. However, now that an association between HP and some aspect of metalworking fluid aerosol exposure is clear, even one case should motivate investigation, surveillance, and preventive action to protect the health of workers.

Because recognition of HP cases in most plants was spread over months or years, efforts to understand the risk factors for these cases have been frustrated. No personal risk factors have been described. No investigation to date could report that cases arose in the context of change in metalworking fluid type, biocide type, pattern of biocide use, or changes in either the ventilation system or engineering controls. Some speculated that onset was related to decreased ventilation with outside air in the winter months. No data were produced to support this hypothesis, which seems unlikely in the presence of a strong aerosol source. Some workshop participants felt that HP was a new problem in the automotive industry and its suppliers, perhaps resulting from changes in microbial contaminants in the setting of more recent aggressive biocide use. On the other hand, other participants expressed skepticism that this emerging problem was really new.

Environmental and Microbiologic Conclusions

Workshop participants did not favor chemical constituents of metalworking fluids or biocides as probable causes of HP, although their likely role in irritant respiratory health effects was readily acknowledged. The limited evidence available from serum precipitin testing to constituents of the unused metalworking fluid did not document immunologic reactivity. A cursory evaluation of biocides and metalworking fluids used in the plants with cases did not document a common product or type, and no information was available to workshop participants about products used across the industry in plants without recognized outbreaks.

Microbial contaminants of in-use metalworking fluids were deemed the likely causes of HP, analogous to the microbial exposures putting farmers, lumber mill workers, and mushroom pickers at risk. This consensus is consistent with the observation that all plants with cases of HP have used synthetic, semi-synthetic, or soluble oil metalworking fluids in the implicated areas, rather than straight oils. The water content of these implicated metalworking fluids supports microbial growth. The usual flora of in-use water-based fluids are Gram-negative bacteria, the cell walls of which contain endotoxin. Endotoxin, while not thought to cause HP, may potentiate immunologic responses as an adjuvant [Ye et al., 1988; Rylander, 1997]. A prominent conclusion of workshop participants was that HP seemed to be associated with unusual flora in metalworking fluid, such as acid-fast bacteria, Gram-positive bacteria, and/or fungi, perhaps resulting from aggressive biocide use to control the usual Gram-negative bacterial flora.

Of the unusual flora, the acid-fast *M. chelonae* emerged as a common factor among half of the outbreaks. Immunocompetent hosts would be expected to mount a cell-

mediated immunologic response to nontuberculous mycobacteria. Thus, the high prevalence of HP among mycobacterial-exposed workers in plant 1 is perhaps reflective of normal immunological reactivity to a high level of aerosolized antigen exposure. In plant 1, one of the HP cases had sputum which grew *M. chelonae*. Since the workshop, two published reports document pulmonary disease with characteristics of both hypersensitivity pneumonitis and infection among immunocompetent persons exposed to *Mycobacterium avium* complex in hot-tub aerosols [Embil et al., 1997; Kahana et al., 1997].

Under certain conditions, metalworking fluid environments are a predictable ecologic niche for mycobacteria and organisms with similar characteristics, such as *Rhodococcus*, *Corynebacterium*, *Nocardia*, and *Streptomyces* (the first two of which were also cultured from some metalworking fluids in plants 1 and 5). Inoculation of water-based metalworking fluids with rapid-growing mycobacteria is probable, since they are commonly found in municipal water supplies [Collins et al., 1984; Fischeider et al., 1991]. Mycobacteria are relatively resistant to disinfectants [Carson et al., 1978; Pelletier et al., 1988], form stable biofilms [Collins et al., 1984; Schulze-Robbecke et al., 1992], grow on compounds that other organisms cannot use, such as hydrocarbons and phenols [Falkinham, 1996], and are preferentially aerosolized due to their hydrophobicity [Falkinham, 1996].

The epidemiology of infection with and sensitivity to nontuberculous mycobacteria [Falkinham, 1996] is pertinent to the new recognition of nontuberculous mycobacteria as a possible agent causing HP in the metalworking environment. Early skin-test surveys with purified protein derivative (PPD-B) for *M. avium* complex [Edwards et al., 1969] showed high rates of reactivity in residents of the southeastern U.S. attributed to aerosol exposure from brackish coastal waters, which contain mycobacteria [Falkinham et al., 1980; Gruft et al., 1979]. Current unpublished work shows high skin reactivity to PPD-B in apparently healthy distance swimmers, who may share aerosol exposure to chlorine-resistant mycobacteria found in swimming pools [personal communication, Ford von Reyn, January 1997]. In AIDS patients, use of indoor swimming pools is a risk factor for *M. avium* infection [von Reyn et al., 1996]. Nosocomial *M. avium* infection in HIV-infected patients with impaired immunity has been traced to organisms present in the hospital water supply using molecular epidemiology fingerprinting of mycobacterial DNA [von Reyn et al., 1994]. Purified protein derivatives from the rapid-growing mycobacteria *M. chelonae* and *M. fortuitum* have been prepared and used in skin-test studies [Hoffman et al., 1978; Hansen et al., 1989]. While DNA fingerprinting is only useful if infection is involved, antigen-specific skin testing and lymphocyte proliferation tests warrant evaluation as surveillance and diagnostic biomarkers in occupational settings where immu-

nological reactivity could occur in response to aerosols of both viable and nonviable organisms.

Prevention Conclusions

Guidance for primary prevention of HP is limited in the absence of information regarding cause, risk factors, and intervention effectiveness. With the current state of knowledge, research in all these areas is required to lay the groundwork for primary control of hypersensitivity pneumonitis in the metalworking fluid environment. In the meantime, secondary prevention relies on identification and appropriate management of affected workers before the disease becomes irreversible.

Health and environmental surveillance

When cases of occupational asthma, inhalation fever, or febrile flu-like illness occur in temporal or geographic clusters within a workforce with exposure to metalworking fluid aerosol, most workshop participants agreed that active surveillance for HP is appropriate, recognizing the likely underdiagnosis of granulomatous disease in symptomatic workers, especially when chest X-rays and pulmonary function tests are normal [Lynch et al., 1992]. A single case of physician-diagnosed HP should trigger active surveillance, on the assumption that such a case is a sentinel event for coworkers at risk [Rutstein et al., 1983; Mullan and Murthy, 1991].

Among active surveillance tools, participants agreed on the merit of baseline and serial systematic questionnaire surveys seeking chest and systemic symptoms and diagnoses, spirometry testing, and attention to careful maintenance and review of fluid management records. Those workers with positive responses on questionnaire or abnormal spirometry should have more definitive testing, which might include physical examination for rales, chest radiograph or computerized tomography scan, diffusing capacity, and exercise arterial blood gases, as determined by a consulting physician. Some workshop participants felt that bronchoalveolar lavage and transbronchial lung biopsy were necessary to exclude the diagnosis of HP in symptomatic persons with normal chest radiographs and pulmonary function tests. Others felt that biopsy was not necessary for a clinical diagnosis of HP. No one reported experience with specific inhalation challenge testing as a diagnostic procedure for metalworking fluid-exposed workers. Participants felt that X-ray screening had insufficient sensitivity for surveillance use and that routine serological testing for antibodies had little specificity for diagnosis and unclear relation to cause in workers with documented polymicrobial aerosol exposure.

For metalworking fluid-exposed workforces at plants without known cases of occupational lung disease, ongoing

education of workers and their health care providers should be actuated regarding potential disease risk. In addition, passive surveillance of existing data such as sick leave reports, medical clinic visits, work restrictions, and OSHA logs should be carried out. The discussion of case definitions for HP revolved around their potential uses for surveillance, work restriction, workers' compensation, and research. In principle, research case definitions should be more restrictive than surveillance case definitions or criteria used to prompt referral for diagnostic evaluation.

Routine exposure surveillance, in the absence of markers of risk for HP, is impractical at the present time. In specific work settings with one or more cases of HP, microbial species would be more informative than colony counts, and workshop participants advised culture for acid-fast bacteria and other unusual organisms. Careful microbiological evaluation of the metalworking fluid at the time of diagnosis of cases should be done before changes in the system are made. Records of fluid management and characteristics could be correlated with symptom onset of subsequent cases, if they occur. Participants had little confidence that HP could be eliminated by lowering exposures to metalworking fluid aerosols in situations where exposures were already below 0.5 mg/m³.

Return to work

Workshop participants agreed that cases of HP should not be returned to the metalworking environment in which they had become ill until the environmental conditions had been "managed" and were thought to present no further respiratory hazard. Workers whose lung function had not returned to baseline should not be returned to metalworking fluid exposure; they may have irreversible disease or unfavorable prognosis. HP cases who return to machining work should have frequent clinical monitoring for several years, especially in the months immediately following return, as well as the option of personal respiratory protection. Participants did not support the use of respirators in the primary prevention of HP among metalworking fluid-exposed workers. In recovered HP cases returned to metalworking fluid exposures, any evidence of disease recurrence or progression should justify removal from further exposure. Although return to work in a different environment should be considered, participants generally expressed sensitivity to the importance of considering socioeconomic factors before deciding on any such relocations.

Fluid and biocide management

No data were presented at the workshop regarding efficacy of compliance with recommended practices of metalworking fluid maintenance and the use of biocides. Participants offered anecdotal experience regarding reduc-

tion in use of metalworking fluid, research demonstration of using water for cutting (no corrosion inhibition), substitution of vegetable oil (limited use for high-speed tools), fluid changes, enhanced housekeeping and maintenance, increased dilution ventilation, enclosure and exhaust ventilation, and fluid management system changes, with continuous monitoring of critical operating parameters. There is a need for a comprehensive approach incorporating education and "buy-in" of management, line workers, maintenance, and representatives of metalworking fluid suppliers; clear lines of authority regarding fluid management; filtration and aeration; monitoring of tramp oil; and communication between plant management and metalworking fluid managers.

Research Needs

Participants identified several gaps in knowledge which are critical to future prevention of HP in the metalworking environment. Collectively, we need to: 1) identify environmental risk factors for HP by comparing characteristics of plants with and without incident HP (microbial species, biocide usage patterns, aerosol levels, etc.); 2) evaluate hypothesized exposure-response relationships in case plants with longitudinal environmental exposure and health surveillance data (e.g., retrospectively in plant 1); 3) evaluate efficacy of interventions directed at control of microbial growth, aerosol exposure, respiratory protection, work relocation, and education; and 4) describe the natural history of HP and outcome of return to work policies.

Expanded surveillance for HP in the industry was recommended, in order to determine rates of HP and to identify case plants for research intervention. Participants discussed the possible merits of: 1) a registry of outbreaks or cases; 2) common protocols for epidemiologic, environmental, microbiologic, and case investigation and medical follow-up. A pressing need exists for 3) health surveillance tools with known sensitivity and specificity; 4) exposure surveillance tools which are pertinent to health outcome; and 5) education of workers, management, and health personnel, a priority relevant to all research efforts.

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