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A Field Investigation of the Acute Respiratory Effects of Metal Working Fluids. II. Effects of Airborne Sulfur Exposures

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An investigation of the acute respiratory effects of workers exposed to metal working fluids (MWF) was conducted in an automobile parts manufacturing facility. After observing an association between cross-shift decline in forced expiratory volume in the first second (FEV_1) and aerosol mass concentration, improved characterization of the exposure was sought through investigation of four elements of a priori interest (Cl, Cr, Ni, S). Of these, only sulfur showed an association with cross-shift FEV_1 decrement. The relative risk of 5% cross-shift FEV_1 decrement was 2.7 (95% confidence interval = 1.0–6.0) comparing those with >4.4 $\mu g/m^3$ to those with <2.5 $\mu g/m^3$ sulfur exposure. Because the concentrations of sulfur in this environment were relatively low and other respiratory irritants were present, sulfur is more likely to be an indicator of more irritating conditions than the sole agent responsible for the observed acute respiratory effects. Am. J. Ind. Med. 31:767–776, 1997.

KEY WORDS: metalworking; spirometry; peak expiratory flow rate; sulfur; oil mist; bronchoconstriction; epidemiology; occupational exposure

INTRODUCTION

Metal working fluids (MWFs) have been associated with several adverse respiratory health effects, including asthma [Hendy et al., 1985; Robertson et al., 1988; Gannon and Burge, 1991; Rosenman et al., 1994] and chronic decrements in pulmonary function [Jarvholm et al., 1982; Kriebel et al., 1997], as well as acute changes in pulmonary function over the course of a working day [Kennedy et al., 1989; Kriebel et al., 1997; Robins et al., 1995].

This paper and the companion paper [Kriebel et al., 1997] report results from an investigation of acute respiratory responses (cross-shift declines in FEV_1) in relation to machining fluid exposure in an American automobile parts manufacturing facility. That paper examined the relationships observed in a cross-sectional study of 386 workers (216 machinists and 170 nonmachinists) between cross-shift decrement in FEV_1 and airborne exposure to inhalable aerosol mass concentration, as well as to airborne endotoxin and culturable bacteria [Kriebel et al., 1997]. Elemental analyses of the inhalable aerosol exposures were also performed for a subset of the participants, and in this paper we present the results of investigations of several elements hypothesized a priori to be respiratory irritants or sensitizers and their relationships to cross-shift changes in pulmonary function in these workers.

The study methods, protocol, and population were described in detail in the first paper. Briefly, the study consisted of two phases. In the first, 386 participants in the same plant were tested with spirometry and symptom questionnaires on a single day, both pre- and post-shift. Machinists were exposed to either straight MWF (mineral oil with various additives) or soluble MWF (water-based emulsions of mineral oil and additives), but not to synthetic or semisynthetic MWF. Each participant wore a personal air

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sampler that collected a full-shift inhalable aerosol mass sample. In the second phase of the study, 48 MWF exposed machinists were followed for 6 consecutive days, measuring their peak expiratory flow rate (PEF) five times each day. Full-shift inhalable personal particulate mass samples were also collected on each work day for these participants.

One objective of the study was to identify likely causal agents for the acute irritant effects of MWF by testing hypotheses concerning various additives and components of MWF. Because of the expense of the numerous chemical analyses, a nested case-control analysis of a subset of the cross-sectional study was designed and incorporated into the study to investigate some of these hypotheses concerning additives and components.

This paper presents the results of the nested case-control analyses for the following respiratory irritants and sensitizers chosen a priori for investigation: sulfur, chlorine, chromium, and nickel. Cobalt was also of initial concern, but because more than 40% of all the air samples collected were found to have cobalt concentrations below the limit of detection, this element was not investigated further. When the pulmonary function data revealed an association only with sulfur, we investigated this compound further. Inhalable aerosol exposure to elemental sulfur was estimated for the rest of the machinists not included in the case-control study, so that the association could be estimated in the full cohort. Elemental sulfur was also measured for each person-day of observation in the second phase of the study, and so the relationship between sulfur exposure and cross-shift change in PEF was also studied in these data.

MATERIALS AND METHODS

Study Site

The study was conducted in a large automotive vehicle parts manufacturing facility in a midwestern state. The plant has been in existence since before World War II and employed approximately 3,200 hourly employees running production on three shifts in addition to 1,700 salaried employees. Participants were drawn from among the day-shift hourly employees of the facility. The study methods were approved by the Human Use Committee of the University of Massachusetts Lowell. Each participant signed a consent form after having the study objectives explained to them. There were many machining operations performed at the facility; in this investigation, they were collapsed into seven categories based on the tool or part movement, severity of the operation (amount of metal removed), presence of abrasives, presence of multiple spindles, and the location of the cut (inside part or outside part). The seven operation types were turn, drill, grind, broach, chuck, multiple drill, and a mixed category for the few participants whose machining could not be classified into one of these six.

Population

Each of the machinists was studied for at least 1 day. Some were recruited for further study (see ‘‘6-day longitudinal study data’’). The nonmachinists in the original study were not included in the analyses presented here, because the investigation of specific MWF components could only be meaningfully carried out among exposed participants.

Cross-sectional Study

Pre- and post-shift pulmonary function tests were conducted by technicians who successfully completed a NIOSH-certified training course. An eight liter water seal survey spirometer (W.E. Collins Co., Braintree, MA) was used in conjunction with O.M.I. spirometric software (O.M.I., Houston TX), which gathered and stored electronic flow-volume data from the spirometer and passed it to a portable computer. Spirometers were calibrated with a 3-L syringe twice a day—before each morning and afternoon testing session, and spirometric data were corrected to BTPS. The American Thoracic Society criteria for standardization of spirometric measures of pulmonary function were employed for all spirometric tests [Ferris, 1978; ATS, 1987, 1991]. The forced expiratory volume in the first second (FEV_1) from the acceptable blow with the highest FEV_1 was used in all analyses presented here. Cross-shift change in FEV_1 was calculated as post-shift FEV_1 minus pre-shift FEV_1 expressed as a fraction of pre-shift FEV_1. To identify the most sensitive fraction of the population in terms of cross-shift declines, and to increase the ability to detect these small cross-shift decrements, cross-shift change in FEV_1 was dichotomized as greater or less than 5% of the pre-shift FEV_1.

Respiratory health questionnaires were administered by technicians and included the American Thoracic Society (ATS) standard questionnaire [Ferris, 1978] augmented with an irritant symptom matrix designed for use in studies of organic dusts [Rylander et al., 1990]. This matrix identified the presence of ‘‘regular’’ symptoms (apart from colds) of sinus trouble and eye, nose, and throat irritation.

Nested Case-Control Sampling

Case-control sampling was used in several ways in the design, to minimize costs. At the end of the day’s pulmonary function test, the computerized spirometry software determined immediately whether a participant had experienced a cross-shift decrement in FEV_1 of four percent or greater. These participants (‘‘responders’’) were recruited for additional testing, which is described below.

Two kinds of comparison or control participants were also selected at the end of their day of participation, and were recruited for the same additional testing. Following identification of a responder, the next consecutive machining ‘‘nonresponder’’ (FEV_1 cross-shift decrement of less than 4%) was selected, as was the next nonmachinist tested. These three groups were recruited to receive a skin-prick test for atopy and to give a sputum sample. In addition, the filters from these participants’ air samples were analyzed for endotoxin concentration.

The initial plan had been to use 5% FEV_1 decrement as the trigger for defining responders, following Kennedy et al. [1989]. However, after the first few weeks of testing, it became clear that the incidence of 5% response was lower than we had expected, and so the definition was changed to 4%. As noted below however, we subsequently became concerned that the 4% definition was nonstandard and confusing, and so we present all statistical analyses using the 5% FEV_1 response definition. That is, participants experiencing FEV_1 cross-shift decrements of greater than or equal to 4%, but less than 5%, are not included in any analyses, despite the fact that we gathered some additional data on them.

Six-Day Longitudinal Study Data

Each of 48 machinists participated in an intensive serial peak expiratory flow study for 6 consecutive days. Invited to participate were machinists in the full cross-sectional study who experienced a cross-shift decline in FEV_1 greater than or equal to 4%, as well as other participants who did not experience a cross-shift FEV_1 decrement, but who reported a specific constellation of chronic respiratory symptoms, which as a group, were strong predictors of cross-shift FEV_1 decrement. This latter group was added to increase the size of the cohort for the longitudinal study. The symptoms were usual cough, usual phlegm, wheeze without cold, and throat irritation.

Each participant was trained in the use of the Mini-Wright Peak Flow meter (Clement Clarke, Columbus, OH) and was given an individual meter with a diary in which to record the serial PEF measurements. The 6-day period most often began on Thursday and ended on Tuesday, including the weekend. Participants recorded the time of each session, as well as the PEFs in the order of their maneuvers in addition to their responses to daily questions regarding the presence of a cold, the flu, asthma, or allergy symptoms. Participants were instructed to measure their PEF five times daily: upon arising, starting work, lunch, leaving work, and at bedtime. They were asked to perform three to five blows with a goal of producing three blows within 20 L/min of their highest effort. It was stressed that the measurements would be more accurate if performed at the same time each day. The maximum blow of each session was used for analyses.

Exposure Assessment

Both personal samples and descriptive environmental data were collected for each participant. Personal inhalable particulate samples were collected for each exposed individual on each day of study. Each subject was fitted with a personal sampling pump (2 L/min) that was in line with a filter cassette that collected a full shift sample of inhalable aerosol (particulate matter) in the breathing zone of the participant (Gillian Instrument Co., West Caldwell, NJ). A seven- hole sampler was used to collect inhalable airborne particulate [Health and Safety Executive, 1986]. Filters were analyzed gravimetrically, as well as elementally, using Proton Induced X-ray Emission Spectroscopy (PIXE). The PIXE analyses used a General Ionex 4-MeV accelerator to produce a beam with a proton current of 400 nA (Elemental Analysis Corporation, Tallahassee, FL). The irradiation time was 360 sec and the beam size was 5/8 inch, targeted to one quadrant of the filter. Elements that had more than 40% of values at or below the limit of detection (LOD) were not included in the statistical analyses of these data. Descriptive data concerning the specific details of individual work stations/machines were also collected for each participant, including information such as metal working operation, type of base metal being machined, metal working fluid type, temperature, and humidity [Woskie et al., 1996].

Elemental Exposure–Respiratory Response Methods

An exposure–response model was constructed for each of the irritants and sensitizers (sulfur, chlorine, chromium, and nickel) in a nested case-control analysis. Because of the small size of this case-control study, odds ratios were calculated comparing those above and below the median concentration for each element.

As noted above, the association between sulfur exposure and cross-shift decrement in FEV_1 was further investigated by estimating sulfur exposures for those in the cross-sectional cohort who were missing these exposure data. We then evaluated the sulfur–respiratory response relationship further in the full cross-section. Initially, simple stratified analyses were conducted, calculating risk ratios for medium and high sulfur exposure, using those with ‘‘low’’ sulfur exposure as the reference group. Potential confounders and effect modifiers were assessed by comparing incidence of 5% decrement in cross-shift FEV_1 in various strata. Data were stratified by age, gender, race, duration of exposure, smoking status, coolant type, sump refill time, asthma, and the presence of selected symptoms.

Multivariate models were also constructed to further investigate the exposure–FEV_1 decrement association. The Breslow–Cox model was used for regression modeling. The Breslow–Cox method of estimating the incidence ratio is more appropriate than logistic regression in these data as the condition being studied is not rare [Axelson, 1994]. Reports by Lee and Axelson have demonstrated that with a common outcome, the odds ratio tends to overestimate the risk ratio [Axelson, 1994; Lee and Chia, 1993; Lee and Chia, 1994]. Because this approach is somewhat new, logistic models were also fit, and in all cases were found to give broadly similar results, while generally providing odds ratios that were, as expected, higher than the risk ratio estimates (data not shown).

Sulfur exposure was included as an explanatory variable in continuous (logged) form, as well as in trichotomized form. Cutpoints were determined a priori to divide the data approximately into the highest quartile, the middle two quartiles and the lowest quartile. These cutpoints were 2.5 and 4.4 $\mu g/m^3$ of elemental sulfur. Potential confounders and effect modifiers evaluated in the models included age, race, gender, smoking status, asthmatic status, and MWF type.

Peak expiratory flow data collected in the 6-day longitudinal study were analyzed as the change in PEF from start to end of shift (cross-shift PEF). Results were similar whether cross-shift change in PEF was expressed in liters/minute or as a percent of pre-shift value. (Only results using the former value shown.)

It was necessary to analyze the PEF data with methods that took account of the nonindependence of the repeated observations of each participant. Models were constructed that estimated the strength of the association between the cross-shift PEF and one or more exposures or covariates. The SAS MIXED [SAS Institute Inc., 1992] procedure allows great flexibility in the specification of such models. Various forms were tested, but here we present results of models that specified a ‘‘simple’’ or ‘‘exchangeable’’ working correlation structure (i.e., the model assumed that the correlation between any pair of PEF measurements for a person was the same as that for any other pair of measurements regardless of the time between tests) because day-to-day correlations between individual PEF measurements were low and relatively constant in these data.

Methods of Sulfur Exposure Prediction

Sulfur measurements and descriptive industrial hygiene data were available for 105 participants from the nested case-control subset of the full cross-sectional study, and for the 48 participants in the longitudinal substudy on an average of 3.6 days each (172 person-days). With these data, a prediction model was developed so that sulfur estimates could be made for the remaining 104 exposed subjects in the cross-sectional cohort. We elected not to divide the data into a prediction and a validation subset because, with so few observations, it was felt that this would further reduce the predictive power of the data to an unacceptable degree.

Predictions were based on the hypothesis that personal airborne sulfur concentration would be associated with the inhalable airborne particulate concentration (available for all participants) as well as with various aspects of the machining operations that produced the aerosols, and with variables describing the work environment. The data available for development of sulfur prediction models included: MWF type (straight or soluble), pH of the MWF, number of days since the MWF in the machine sump (the coolant storage and circulation system) had been changed, whether the sump had been circulating during the previous night, the number of machines within 9 feet that were operating with MWF, metal working operation type, type of base metal of part being machined, indoor and outdoor temperature and humidity, presence of local exhaust ventilation on the machine, presence of separate area ventilation, use of a personal cooling fan, degree of machine enclosure, whether compressed air was used to blow off parts, distance from machine to worker, and percentage of workday spent machining.

Linear regression models were constructed with sulfur concentration as an outcome variable in untransformed, as well as in log-transformed format to investigate potential environmental, process or individual variables as determinants of sulfur level. Models using the log transformed sulfur concentration fit the data better, and are reported here. Prediction models were nested in order to compare goodness of fit statistics. Interaction terms were included in some models to assess possible effect modification. Final model selection was based on goodness of fit and parsimony.

The best prediction model was used to estimate sulfur for the remainder of the cross-sectional cohort. Finally, relative risks for 5% cross-shift decline in FEV_1 and sulfur exposure were estimated in the full cohort of machinists as described.

RESULTS

The participating machinists represented approximately 87% of the day-shift workers with consistent exposure to either straight or soluble MWF, and without exposure to synthetic MWF. The population had a mean age of 41 years and was primarily white (87%) and male (91%). There were 21 asthmatics. Smoking status was as follows: 30% current smokers, 35% ex-smokers, and 35% never smokers. The participation rate in the 6-day longitudinal substudy, was approximately 88% of those eligible to participate. Of the 48 participants in this phase, only one diary could not be included in the analyses. Two others submitted data for 3 days or less.

TABLE I. Elemental Aerosol Exposure ($\mu g/m^3$) by Current MWF Exposure Category in Automobile Part Workers

Element[a]	Mean	SD	Geometric mean	Geometric SD
Straight MWF (n = 47)				
Cl	1.90	1.08	1.65	1.73
Cr	0.16	0.09	0.15	1.63
Ni	0.03	0.04	0.02	2.08
S	4.21	3.61	3.52	1.72
Soluble MWF (n = 57)				
Cl	3.13	2.52	2.55	1.85
Cr	0.15	0.05	0.14	1.44
Ni	0.02	0.01	0.02	1.75
S	3.52	1.42	3.25	1.51

[a] None of the samples was at or below the limit of detection.
MWF, metal working fluid; SD, standard deviation.

TABLE II. Odds Ratios of 5% or Greater Decrement in FEV_1 for Elemental Aerosol Exposure by Current MWF Exposure Category, Comparing those Above and Below the Median Exposure

	Straight MWF		Soluble MWF		Total	
Element	OR	95% CI	OR	95% CI	OR	95% CI
Cl	3.8	0.4–31.5	0.9	0.2–3.9	1.2	0.4–3.7
Cr	2.5	0.3–18.9	2.1	0.6–8.2	2.3	0.8–6.9
Ni	1.1	0.2–7.3	2.5	0.6–9.5	1.9	0.6–5.6
S	5	0.7–37.7	2.9	0.7–12.6	3.3	1.0–10.7

CI, confidence interval; MWF, metal working fluid; OR, odds ratio.

On average, aerosol exposures to MWF (GM = 0.18 mg/m^3) were lower than in previously studied machining environments [Kennedy et al., 1989; Milton et al., 1996; Robins et al., 1995]. There were, however, clear differences between the machining and nonmachining exposures; for example, machinists had higher average inhalable aerosol mass concentrations (GM = 0.18 mg/m^3) than those of nonmachinists (GM = 0.05 mg/m^3). Sulfur was present in the highest concentration of all the elements that were measured for the study both overall and in those with straight or soluble MWF exposure separately (Table I). Chlorine exposure concentrations were also moderately high in these two exposure groups, whereas chromium and nickel were present in very small quantities.

The nested case-control analyses for each element demonstrated weak positive associations for chlorine, chromium and nickel, and a stronger association for sulfur (Table II). There was more than a threefold relative risk of cross-shift decrement in FEV_1 in those with sulfur exposure above the median compared to those with exposures below the median. This association was observed in those exposed to both straight and soluble fluids, although the confidence intervals were somewhat wider in the stratified data. Chromium showed some evidence of an association in all machinists combined, but because the levels of exposure were so low and the 95% confidence intervals included the null, this potential association was not pursued further. Chlorine and nickel showed essentially no evidence of association.

Prediction of Sulfur

Because of missing exposure data, only 209 of the 216 machinists from the original cross section were included in these sulfur analyses. Actual sulfur concentrations were available for 105 workers (the nested case-control subset), and concentrations were predicted for 104 workers. (Because of missing industrial hygiene data needed for sulfur prediction, personal exposure concentrations could not be estimated for 7 workers in the cohort.)

Both univariate and multivariate models were constructed, using the log-transformed version of sulfur as the outcome variable. Seven operation types (broach, chuck, drill, grind, multiple drill, turn, and mixed operations) and three different part metals (aluminum, cast iron or iron, and steel) were individually evaluated and were eventually collapsed into dichotomous variables. Aerosol mass concentration was the most important predictor of sulfur exposure. It, too, was log normally distributed and so the log transformed aerosol mass concentration was used in the models. In a model for sulfur in continuous form, log-transformed aerosol mass concentration predicted 34.5% of the variability in sulfur concentration.

Nested models were then constructed to enable more direct comparisons of model fit. The explanatory variables that remained important in the final sulfur prediction model were gravimetric concentration (log-transformed), MWF type, outdoor temperature, and operation type (Table III). MWF type was a dichotomous term indicating straight or soluble coolant use. Outdoor temperature was continuous and in units of degrees Fahrenheit. Operation type was dichotomized into those operations associated with higher sulfur exposure: broach, multiple-drill, turn, and mixed operations, compared to those associated with lower sulfur concentrations: grind, chuck, and drill.

Because we intended to use a trichotomous categorization of the exposure variable in estimating the association with pulmonary function, the degree to which this model agreed with the observed data was assessed by a 3-by-3 table comparing the observed and predicted categorizations of ''low,'' ''medium,'' and ''high.'' With cutpoints dividing the data into the upper 25%, the middle 50% and the lowest 25%, 59% of the data used in the prediction model were

TABLE III. Final Sulfur Prediction Model*

Variable	Beta	Standard error	*P*
Intercept	1.780	0.113	$<$0.001
Gravimetric exposure ln (mg/m^3)	0.463	0.043	$<$0.001
MWF type[a]	−0.118	0.054	0.03
Outdoor temp (°F)	0.005	0.001	$<$0.001
Operation type[b]	−0.072	0.050	0.16

*Model predicts sulfur concentration in units of log (µg/m^3). The coefficient of variation (R^2) for this model was 0.39.

[a] Comparing straight (1) to soluble (0).

[b] Comparing drill, grind, and chuck (1) to broach, multiple-drill, turn, and mixed (0).

MWF, metal working fluid.

TABLE IV. Agreement Between Observed and Predicted Categorizations of Sulfur Exposure*

	Observed exposure		
Predicted exposure	Low (2.5 µg/m^3)	Medium (2.5–4.4 µg/m^3)	High ($>$4.4 µg/m^3)
Low ($<$2.5 µg/m^3)	11	7.5	0
Medium (2.5–4.4 µg/m^3)	13	39	16
High ($>$4.4 µg/m^3)	0.5	3.5	9.5

*Percentages of the data set (n = 201) falling into each cell are shown. Those lying on the main diagonal (59%) represent agreement between the observed and predicted exposures.

TABLE V. Relative Risks of 5% or Greater Decrement in FEV$_1$ Among Three Levels of Sulfur Aerosol Exposure*

Elemental sulfur exposure (µg/m^3)	Median exposure (µg/m^3)	RR	95% CI
Low sulfur exposure ($<$2.5)	2.1	1.0	—
Medium sulfur exposure (2.5–4.4)	3.4	1.5	(0.3–6.4)
High sulfur exposure ($>$4.4)	5.6	3.7	(0.9–16.1)

*"Medium" and "high" exposure were compared to "low." Chi-square test for linear trend in proportions = 5.5, *P* = 0.02.

CI, confidence interval; RR, relative risk.

correctly classified (the sum of the percentages lying on the main diagonal in Table IV). Most of the misclassifications were between adjacent categories; only one person was misclassified from low to high or vice versa.

Sulfur Exposure and Acute Respiratory Response in Cross-Sectional Cohort

The sulfur concentration prediction model was used to predict the airborne sulfur exposures for the 104 machinists without actual sulfur measurements. The sulfur exposure–cross-shift FEV$_1$ decrement association was then investigated in 209 machinists from the cross-sectional study. In crude analyses, incidence of cross-shift decline in FEV$_1$ increased with elemental sulfur exposure, although confidence intervals were wide (Table V). A trend test suggested a pattern of increasing incidence with increasing exposure ($P = 0.02$).

Confounding of the association by several factors (age, reporting of wheeze, asthmatic status, smoking status, MWF type, sump refill time, gender, race, and duration of exposure) was assessed first by comparing rates of 5% FEV$_1$ decrement in different strata of these factors and then by including these factors in regression models. None of these factors was found to modify or confound the sulfur exposure–FEV$_1$ decrement association. The risk ratios estimated by the Breslow–Cox model were indistinguishable from those in the categorical analysis (data not shown).

When log sulfur exposure was modeled continuously, the Breslow-Cox model estimated a relative risk of 2.5 (95%CI 1.0–6.0) per log µg/m^3 sulfur exposure. On the linear scale, this means that the risk ratio for FEV$_1$ decrement is 2.7 in those with high sulfur exposure (median exposure = 5.6 µg/m^3) compared to those with low sulfur exposure (median exposure = 2.1 µg/m^3). The same potential confounders and effect modifiers were also evaluated in this log-linear model, and again none were found to be important.

Sulfur and Peak Flow in Repeated Measures Data

On workdays, participants in the 6-day study of PEF showed an overall mean decrement in PEF of 3.1 L/min from start to end of shift, while at home they showed a mean gain in PEF over the day of 1.8 L/min (the null hypothesis that these means are not different is not rejected: $P = 0.25$). There was also a tendency for greater across the day variation in PEF at work than at home. These comparisons are limited however by the tendency of participants to perform their arising measurements approximately three hours later on home days than on workdays. Because the arising blow tends to be the lowest of the day, and because of its use in calculating the cross-shift change, a later arising time will tend to minimize daily amplitude, and may also tend to minimize cross-shift decrements as well.

There is evidence of increasing cross-shift decline in PEF with increasing exposure to sulfur in the raw data, without accounting for the repeated observations (Table VI). When SAS MIXED models were used to account for the nonindependence of repeated observations, this trend was still seen. However, this approach identified a strong difference in the exposure–PEF association between asthmatics (n = 13) and nonasthmatics (n = 35) (Table VII). Asthmat-

TABLE VI. Sulfur and Cross-shift PEF: Crude Relationship, Not Accounting for Repeated Measures

Sulfur exposure ($\mu g/m^3$)	n	Mean PEF[a] (L/min)	SD
<2.5	31	−1.8	39.3
2.5–4.4	69	−2.9	31.9
>4.4	33	−4.4	24.1

PEF, peak expiratory flow rate; SD, standard deviation.

TABLE VII. Association Between Sulfur Exposure and Cross-Shift Change in PEF in Longitudinal Substudy Among Asthmatics and Nonasthmatics in Separate Repeated Measures Models

	Asthmatics			Nonasthmatics		
Variable	Beta	SE	*P*	Beta	SE	*P*
Intercept	−28.19	20.67	0.19	12.98	5.62	0.02
Medium sulfur exposure (2.5–4.4 $\mu g/m^3$)	9.27[a]	13.60	0.51	−15.22[a]	6.05	0.01
High sulfur exposure (>4.4 $\mu g/m^3$)	53.61[a]	33.52	0.13	−18.42[a]	6.93	0.01

[a]Estimated change in PEF (L/min) compared to ''low''-exposure category.
PEF, peak expiratory flow rate; SE, standard error.

TABLE VIII. Final Repeated Measures Model of Association Between Sulfur Exposure and Cross-shift Change in PEF

Variable	Beta	SE	*P*
Intercept	13.34	6.62	0.05
Medium sulfur exposure (2.5–4.4 $\mu g/m^3$)	−16.30	6.69	0.02
High sulfur exposure (>4.4 $\mu g/m^3$)	−19.12	7.73	0.02
Asthma	−42.24	13.29	0.002
Medium exposure × asthma interaction	26.75	12.5	0.04
High exposure × asthma interaction	72.93	27.06	0.01

PEF, peak expiratory flow rate; SE, standard error.

ics had lower baseline PEF than nonasthmatics (as indicated by the intercept terms in the MIXED models), but exposure to sulfur did not result in greater cross-shift decrements among asthmatics. By contrast, the model for nonasthmatics predicted a small mean cross-shift increase in PEF among the nonexposed, but a fairly strong association between sulfur exposure and cross-shift decline in PEF. When an exposure–asthma interaction term was included in a model for all participants, a very similar picture emerged (Table VIII). None of the other covariates (age, gender, race, smoking status, MWF type, duration of exposure) was found to confound or modify.

Again, a similar result was obtained if sulfur exposure was included as a logged continuous variable. In a model based on all the data, the parameter estimate was -3.1 L/min per log($\mu g/m^3$) of sulfur ($P = 0.59$). When stratified on asthma status, the effect estimates were 5.6 L/min per log($\mu g/m^3$) ($P = 0.74$) in asthmatics and -10.3 L/min per log($\mu g/m^3$) ($P = 0.08$) in nonasthmatics.

DISCUSSION

The primary objective of this work was to look for evidence that specific components found in machining fluids might play a role in the MWF-respiratory response relationship, by studying certain elemental irritants and sensitizers that were suspect a priori: chlorine, chromium, nickel, and sulfur. We chose to study only those elements of a priori interest to reduce the risk of false positive associations resulting from multiple comparisons. Sulfur was the only one of these elements that demonstrated a moderate association with 5% cross-shift decline in FEV_1 in the nested case-control subset (odds ratio of 3.3 with a 95% confidence interval of 1.0–10.7). Because this was the first time that this relationship had been observed in an MWF exposed population, we wanted to explore it as thoroughly as possible in these data. In order to evaluate this relationship in the full MWF exposed cross-sectional cohort, sulfur exposures had to be estimated for roughly one-half of the cohort. Prediction equations were developed using the observations in both the cross-sectional cohort and the 6-day longitudinal subcohort for which sulfur measurements were available.

Sulfur prediction models were developed, and the missing cross-sectional sulfur exposure data were estimated for all MWF exposed subjects for whom no direct sulfur measurements were available ($n = 104$). The final prediction model had an R^2 of 0.39, which is comparable to other successfully used exposure prediction equations [Eisen et al., 1984; Woskie et al., 1994; Kromhout et al., 1994]. The predictors of sulfur concentration were: inhalable gravimetric aerosol concentration (logged), MWF type (straight versus soluble), outdoor temperature, and operation type (drill, grind and chuck versus multiple-drill, broach, turn, and mixed operations).

Gravimetric concentration was, as hypothesized a priori, the most significant predictor of sulfur concentration. Both elemental sulfur concentration and gravimetric aerosol level were derived from the same filter, and sulfur concentration is, by definition, a fraction of the total gravimetric concentration. MWF type was also expected to be important in predicting sulfur exposure as sulfur additives in the two types differ. The soluble coolants studied contained 10–30% petroleum sulfonate (by weight), while the straight coolants studied contained smaller amounts of either elemental sulfur (0–1.5% by weight) or sulfurized mineral oil ($<10\%$ by weight). Soluble coolants were supposed to be diluted with water in a 1:5 ratio and according to their material safety data sheets, had higher elemental sulfur concentrations. Although indoor humidity was, as expected, an important predictor of sulfur exposure, outdoor temperature was the climatic variable that performed the best in the model. It is likely that outdoor temperature was a surrogate for indoor humidity, but may have performed better in the models because it had a larger range. Indoor humidity increases with outdoor temperature, and high outdoor temperatures correspond to the hot, humid summer months when this plant was fully air-conditioned, and thus received less outdoor air exchange through open windows and doors.

Misclassification of exposure is one of the issues that must be considered in evaluating the exposure–response models because half of the exposure data in these analyses were estimated by the prediction equation. Based on the half of the cohort with measured sulfur exposures, it does not appear that the prediction equation consistently overestimated or underestimated sulfur concentrations (Table IV). It is therefore likely that the exposure misclassification was nondifferential. It was not possible to assess the sulfur–FEV_1 decrement relationship only in the half of the data with predicted (rather than observed) sulfur values because all of the subjects with 5% FEV_1 decrements were in the half with measured sulfur exposures. This followed from the original study design in which elemental analyses were performed on all ‘‘cases’’ (those demonstrating a cross-shift decrement in FEV_1) and ‘‘controls’’ (a sample of the rest of the cohort).

The sulfur levels in the plant ranged from 1.2 to 24.7 $\mu g/m^3$. Because this analysis identified elemental sulfur only, we do not know to which sulfur compounds workers were actually exposed. The observed concentrations of elemental sulfur will correspond to quite different molecular concentrations of sulfur compounds, depending on the particular molecular species involved. For example, if all of the sulfur that was collected was in the form of sulfur dioxide (SO_2), the mean SO_2 concentration in the high-exposure group would be 12 $\mu g/m^3$, and 4 $\mu g/m^3$ for the low-exposure group. If instead, all the elemental sulfur was present in the form of a much larger molecule such, as a typical petroleum sulfonate (assuming a carbon chain length of 30), we estimate that the mean exposure to this compound in the high-exposure group would be 101 $\mu g/m^3$, and 34 $\mu g/m^3$ for the low-exposure group. For comparison, the OSHA PEL for SO_2 is 5,200 $\mu g/m^3$ and the national primary ambient air quality standard for SO_2 is 80 $\mu g/m^3$. A recent review reports that significant bronchoconstriction occurs in humans exposed to sulfur dioxide at a level of 650 $\mu g/m^3$ [Lippmann, 1992]. Although these calculations certainly represent oversimplifications of the true situation, they provide some orientation to the levels observed.

There is good evidence that machining fluids contain sulfur compounds that are likely to be respiratory irritants. Thermal byproducts of sulfurated hydrocarbons generated at normal operating temperatures may include hydrogen sulfide, a known irritant [NIOSH, 1977] and other sulfur compounds as well. Sulfonates may also act as direct sensory irritants causing reflex bronchoconstriction [Alarie, 1973], and may also thermally decompose at normal machining temperatures, generating sulfur dioxide, a lung irritant [Sax, 1984]. In animal studies evaluating relationships between various components of unused MWF and respiratory irritation in a mouse bioassay, Schaper and colleagues found sodium sulfonate to be the most irritating component tested [Schaper and Detwiler-Okabayashi, 1991, 1995].

The cross-sectional study results provide evidence of increasing cross-shift decline in FEV_1 with increasing sulfur exposure. This relationship is consistent when sulfur exposure is considered in categorical and continuous format. There is about a 50% increase in the incidence of 5% FEV_1 decrement in those with medium sulfur exposures in the range from (2.5–4.4 $\mu g/m^3$) (RR = 1.5, 95%CI = 0.3-6.4) and an approximately fourfold increase in risk in those with high sulfur exposure ($>$4.4 $\mu g/m^3$) (RR = 3.7, 95%CI = 0.9–16.1) when compared to those with low exposures (2.5 $\mu g/m^3$). When sulfur is considered in continuous format, there is a two and a half fold increase in incidence of 5% cross-shift decline in FEV_1 per log unit increase in sulfur exposure (RR = 2.5, 95%CI = 1.02-6.04). On the linear scale, this means a relative increase in risk of 5% FEV_1 decrement of 2.7 comparing the low-exposure group to the high-exposure group.

Supportive evidence of this sulfur-respiratory response relationship was observed in the longitudinal substudy peak flow data, although it was found that asthma status strongly modified the relationship between sulfur and PEF response. When the data were stratified based on asthma status, a strong association was observed in nonasthmatics, while there was no exposure–response relationship among asthmatics. Those nonasthmatics with high sulfur exposure ($>$4.4 $\mu g/m^3$) had an average cross-shift decline in PEF of 18 L/min compared to those with low sulfur exposure (2.5 $\mu g/m^3$). This represents approximately 3% of their average peak flow rate. In asthmatics there is no such association. While this lack of association in asthmatics may seem unexpected, it must be remembered that this workforce is probably highly selected. Mean tenure in the plant was approximately 17 years, and there was much movement among jobs in the plant. It is thus possible that the exposed workforce consisted of the less sensitive fraction of the population, and that asthmatics in particular may have selected themselves in such a way that only those who are not responsive to the irritants remain in the machining environment. Since full work histories, including timing and duration of transfers, had not been collected, this possibility could not be directly examined. However, 30% of those with ''low'' sulfur exposure were asthmatic (5 people), while 16% of the ''medium'' sulfur group were asthmatics (7 people), and only 2% of the ''high'' sulfur group (one person) were asthmatic. Thus, self-selection may explain the observation of an association only among nonasthmatics, but we cannot prove this, and other explanations, including chance, are possible. It is interesting to note that this difference between asthmatics and nonasthmatics does not exist in the cross-shift FEV_1 decrements.

Kriebel's earlier report on this same population presented evidence for an association between aerosol mass concentration and cross-shift FEV_1 decrement, using data from both machinists and nonmachinists combined [Kriebel et al., 1997]. The present investigation of exposures to four different elements was confined to the machinists because we constructed a model to predict sulfur exposures based on machining characteristics, and because the 6-day longitudinal study had been restricted to machinists. Among machinists, airborne sulfur concentration appeared to have a clearer dose-response relationship and a stronger association with cross-shift decline in FEV_1 than inhalable aerosol mass concentration. For example, one can compare the trend tests with trichotomous exposure variables constructed in the same way (the lowest 25%, the middle 50%, and the upper 25%) for the two different exposures and their association with cross-shift FEV_1 decrement. For aerosol mass concentration, $P = 0.6$ on the null hypothesis of no trend, while for sulfur concentration, $P = 0.02$. Alternatively, one can compare the linear models with log aerosol mass concentration and log sulfur concentration as the exposure variable. The p-value of the slope parameter was 0.32 for aerosol mass concentration, while for log sulfur concentration it was 0.05. Thus, sulfur exposure appears to be a somewhat stronger predictor of cross-shift decrement in FEV_1 than aerosol mass concentration. However, because of the low sulfur exposures observed, it is not likely to be the sole irritating component. Indeed, other irritants are known to occur in MWF, including endotoxins and high pH. Instead, we suspect that sulfur represents a marker of the MWF exposure conditions at this plant that were particularly irritating.

In conclusion, these analyses provide further evidence consistent with an association between machining fluid exposure and acute changes in pulmonary function. Because this is the first time sulfur has been indicated as a contributor or marker of irritating conditions in the machining environment, it is necessary to pursue it further. The implications for sulfur and respiratory irritation are also more wide-reaching than just MWF exposed individuals. The relationship ought to be considered in other occupational groups that are exposed to inhalable aerosols of sulfur.

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