



## Original Contribution

# Quantitative Exposure to Metalworking Fluids and Bladder Cancer Incidence in a Cohort of Autoworkers

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*Initially submitted January 18, 2009; accepted for publication March 10, 2009.*

Occupations with mineral oil exposure have been associated with bladder cancer in population-based case-control studies. The authors report results from the first cohort study to examine bladder cancer incidence in relation to quantitative exposures to metalworking fluids (MWFs), based on 21,999 male Michigan automotive workers, followed from 1985 through 2004. Cox regression was used to estimate hazard ratios based on categorical exposure variables for straight, soluble, and synthetic MWFs, as well as duration of exposure to ethanolamines and nitrosamines. Penalized splines were also fit to estimate the functional form of the exposure-response relation. Increased bladder cancer risk was associated with straight MWFs but not with any other exposure. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mg/m<sup>3</sup>-year straight MWF exposure (lagged 20 years). Calendar time windows relevant to polycyclic aromatic hydrocarbon exposure were examined but could not be distinguished from the lagged (10-, 20-year) metrics. No association was observed between any exposure and incident lung cancer, suggesting that smoking is unlikely to confound the associations observed here. The quantitative relation with straight MWFs strengthens the evidence for mineral oils as a bladder carcinogen.

cohort studies; Cox model; ethanolamines; lung neoplasms; mineral oil; nitrosamines; polycyclic hydrocarbons, aromatic; urinary bladder neoplasms

Abbreviations: CI, confidence interval; MWF, metalworking fluid; PAH, polycyclic aromatic hydrocarbon.

Metal machining and other mineral oil-exposed occupations have been consistently associated with excess risk of bladder cancer in population-based case-control studies. Increased bladder cancer risk has been reported for jobs in metal machining (1–3), machinists in the automotive industry (4, 5), and those having ever worked in a job with exposure to oil mist (6). Components of metalworking fluids (MWFs), which are used to cool and lubricate metal during cutting or grinding operations, are suspected to have caused the excess bladder cancer risk. However, there have been no quantitative estimates of risk. One previous cohort study examined the risk of bladder cancer with semiquantitative categories of mineral oil exposure. In that retrospective cohort study of 55,000 aerospace workers, a suggestive, but not strong, increased risk of incident bladder cancer with mineral oil exposure was found, with incidence rate ratios of

1.8 (95% confidence interval (CI): 0.9, 3.5) and 1.4 (95% CI: 0.5, 3.9) for those with medium and high cumulative mineral oil exposure, respectively (7).

The composition of MWF formulations varies but is generally grouped into 3 main classes according to the base composition: straight, soluble, and synthetic MWFs. Straight and soluble MWFs contain petroleum (mineral) oils that may contain polycyclic aromatic hydrocarbons (PAHs), depending on how the base oil stock has been refined. Soluble and synthetic MWFs can contain biocides and ethanolamines, among other additives. In 1984, mineral oil was classified as a human carcinogen by the International Agency for Research on Cancer, largely because of its PAH content and increased risk of skin and scrotal cancers (8, 9). PAH exposure has also been associated with bladder cancer risk in industries using PAH-containing coal tar

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**Table 1.** Demographic Characteristics of the Subcohort of Male Michigan Autoworkers and Incident Cases of Bladder Cancer and Lung Cancer From 1985 Through 2004

	Cohort ( <i>n</i> = 21,999)		Bladder Cancer Cases ( <i>n</i> = 153)		Lung Cancer Cases ( <i>n</i> = 480)	
	No.	%	No.	%	No.	%
Race						
White	15,069	68	107	70	264	55
Black	3,796	17	15	10	112	23
Unknown	3,134	14	31	20	104	22
Plant						
1	4,723	21	28	18	153	32
2	8,454	38	54	35	164	34
3	8,801	40	71	46	161	34
>1	21	0.1			2	0.4
Vital status, December 31, 2004						
Dead	4,042	18	57	37	435	91
Alive	17,917	81	96	63	45	9
Unknown	40	0.2				
	Mean	Range	Mean	Range	Mean	Range
Year hired	1968	1942–1981	1963	1943–1979	1962	1943–1979
Birth year	1944	1925–1961	1937	1925–1959	1935	1925–1958
	Mean (SD)		Mean (SD)		Mean (SD)	
Age at diagnosis, years			61.2 (9.0)		61.4 (8.3)	

Abbreviation: SD, standard deviation.

pitch, including aluminum smelting and asphalt paving (10, 11). The carcinogenicity of other additives to MWFs has also raised concerns. Diethanolamine and triethanolamine, added to adjust pH and inhibit corrosion in soluble and synthetic MWFs, have shown some evidence of carcinogenicity in animals (12–14) but were not classifiable as to their carcinogenicity to humans (15). Ethanolamines in the presence of *N*-nitrosating agents can react to form *N*-nitrosodiethanolamine and other nitrosamines, which are also possible human carcinogens (16).

In most epidemiologic studies of cancer, MWFs have been treated as a single exposure agent, without regard to type, constituents, or level. Only the United Auto Workers–General Motors automotive cohort of 46,400 workers at 3 Michigan automotive plants has differentiated quantitative exposure levels separately for straight, soluble, and synthetic fluids (17–19). The presence/absence of MWF additives, such as ethanolamines and nitrites, has also been identified for each MWF formulation used in the 3 plants. This cohort has been examined primarily for cancer mortality outcomes and some incident cancers, but the association between MWF exposure and bladder cancer risk has never been reported. Bladder cancer's excellent 5-year survival rate of 80% (20) makes incidence a far better outcome for study of bladder cancer than mortality. This cohort has now been followed for cancer incidence from 1985 through 2004 for all subjects still alive in 1985, providing

the first opportunity to examine the risk of incident bladder cancers with quantitative exposure measures for the 3 MWF classes and duration of exposure to ethanolamines and nitrosamines.

## MATERIALS AND METHODS

### Study population

The enumeration of this autoworkers' cohort and their death and vital status ascertainment from 1941 through 1994 are described in previous reports (18, 19). The original study population included 46,399 hourly workers at 3 Michigan automobile manufacturing plants employed a minimum of 3 years before January 1, 1985, and who were alive on January 1, 1941. Birth date, race, and work history records through 1994 were abstracted from company records. A subset of the original cohort was linked to the Michigan Cancer Registry to obtain all incident cancers from January 1, 1985, to December 31, 2004. This subset included all workers who were alive on January 1, 1985, and whose work histories were at least 50% complete (2.4% excluded) and captured employment history at the plants from 1942 through 2004. Vital status follow-up was extended from 1994 through 2004 on the basis of linkage with the National Death Index. This subset was further restricted to include only subjects who were 60 years of age or younger in 1985

**Table 2.** Mean, Interquartile Range, 95th Percentile, and Maximum Cumulative Exposure Metrics for Exposed Michigan Autoworkers (1942–2004) for Each Metalworking Fluid Class (mg/m<sup>3</sup>-years) and for Duration of Nitrosamine Exposure (Years)

Metric	Exposed Workers				
	Proportion (%)	Mean	IQR	95th Percentile	Maximum
Straight, 10-year lag	58	3.69	2.12	34.6	197
Straight, 20-year lag	54	3.57	2.21	20.3	193
Soluble, 10-year lag	89	8.39	7.50	39.8	168
Soluble, 20-year lag	85	7.54	7.10	30.0	168
Synthetic, 10-year lag	38	1.56	1.20	5.8	102
Synthetic, 20-year lag	33	1.41	0.88	5.0	102
Ethanolamine duration, no lag	41	2.22	2.25	11.3	38.3
Nitrosamine duration, no lag	28	0.65	0.47	2.4	26.5

Abbreviation: IQR, interquartile range.

to minimize disease misclassification from cancers diagnosed before the 1985 cancer registry start date.

In addition to bladder cancer, we also examined associations with lung cancer (*International Classification of Diseases for Oncology*, Third Edition, codes C670–679 and C340–349, respectively) to evaluate confounding by smoking. For both cancers, histologic types 9590–9989 were excluded. The analyses here include only males ( $n = 21,999$ ), as there were only 7 female bladder cancers. All procedures were performed in accordance with a protocol approved by the Office for the Protection of Human Subjects at the University of California at Berkeley.

### Exposure assessment

The 3 plants in this study represented exposure to 3 broad MWF classes: straight mineral oil, soluble oil (includes semisynthetic oils), and synthetic fluids. Quantitative exposure levels for each class of fluids had been previously developed for each time period-, plant-, department-, and job-specific exposure category (17, 21). Scale factors for each fluid, operation, and time period were developed from a statistical model based on 394 air measurements collected by the company between 1958 and 1987 and determinants of exposure. As the company monitoring strategy was targeted to problem areas, their measurements were used to derive relative scale factors rather than absolute concentrations. The scale factors were then applied to plant-, operation-, and fluid-specific exposure levels from measurements collected by the original research study team in 1986–1987 (21). An industrial hygienist revisited the plants in 1995 to update the scale factors for the 1985–1995 time period on the basis of company measurements collected since the study team's field visits (18). The airborne measurements had been collected by using 37-mm filters and analyzed either gravimetrically for total particulate or by infrared spectroscopy for oil content; the difference between the 2 methods of analysis was small (17).

Twenty-two percent of the subcohort were missing some of their work history records (median, 1.9 years missing);

subjects missing more than 50% were excluded (2.4%). Missing work history information was interpolated by averaging the exposures from the previous and subsequent job for each subject, through 1994. Cumulative exposure to the 3 fluid classes was calculated for each subject, with a lag of 10 or 20 years to account for the latency period of bladder and lung cancer. Thus, exposures during the last 10 years of follow-up, 1995–2004, were not necessary for the analyses.

Two PAH-relevant time windows were identified. The first time window was pre-1986. In the mid-1980s, most oil-containing MWFs were reformulated to use highly treated base oils to remove or minimize PAH exposure, thus avoiding the carcinogen label on the Material Safety Data Sheets (22). The earlier time window was further restricted to exposures pre-1970, before the transition to more highly refined base oils with lower PAH content began.

Exposures to ethanolamines and nitrites were identified from the MWF formulations' Material Data Safety Sheets. Ethanolamines and nitrites were first added to the machining fluids used in these plants in the early 1950s. In these plants, the use of nitrites decreased in the mid-1980s until their exclusion by the early 1990s. Exposure to nitrosamines was defined as the co-presence of ethanolamines and nitrites. For ethanolamines and nitrosamines, we evaluated exposure–response associations based on duration of exposure.

### Statistical analysis

Adjusted hazard ratios for bladder cancer and exposure to straight, soluble, and synthetic fluids were estimated, on the basis of internal comparisons, by using Cox regression models (Stata/SE, version 9.2, software; StataCorp LP, College Station, Texas). Analysis time was based on age, and the model included covariates for race, calendar year (linear), and year hired (linear). Follow-up ended at the minimum age at diagnosis of the cancer of interest, loss to follow-up, death, or study end. A robust variance (sandwich) estimator was specified by using the “cluster(id)” option to be robust to possible model misspecifications, such as the lack of

proportional hazards, incorrect functional form of the covariates, and omitted covariates (23). All 95th percentile confidence intervals are 2 sided.

Cumulative exposure to each of the 3 MWF classes was first examined in a separate Cox model and treated as a categorical variable defined by the exposure distribution of the cases (20th, 40th, 60th, and 80th percentiles of exposed cases), with the other 2 fluid classes included as linear covariates. Cases were used to select cutpoints rather than all subjects, because they are likely to be the limiting factor in cohort analyses with far fewer cases than noncases (24). For ethanolamines and nitrosamines, exposure duration was categorized as no exposure, less than 1 year of exposure, and 1 year or more of exposure because of the small number of exposed cases. The trend across categories was tested by treating the ordinal rank of each category as a continuous variable.

Where categorical analyses suggested a possible exposure-response relation, we then examined the shape of the exposure-response curve using penalized splines (R, version 2.7.2; R Development Core Team, Vienna, Austria) (25). This flexible semiparametric smoother does not assume a shape for the function form of the relation and can be incorporated into the Cox model described above (26). The optimal degree of smoothing was chosen in the model estimation procedure on the basis of the Akaike Information Criterion.

## RESULTS

### Study population

The basic demographic characteristics of the cohort and of the bladder and lung cancer cases are presented in Table 1. This cohort included 21,999 males, consisting of 68% Caucasian, 17% African American, and 14% unknown race, with 407,660 person-years of follow-up. On average, the cases were hired earlier and born earlier than the average worker. The mean age at diagnosis was similar for the 2 cancers. Bladder cancer has a higher survival rate than lung cancer does, which is reflected in the proportions of the cases alive at the end of the study, 63% and 9%, respectively.

### Exposure metrics

The cumulative MWF exposure metrics were highly skewed, as exhibited by the narrow interquartile range and the high maximum exposures (Table 2). The correlations between MWF exposure metrics were estimated by the nonparametric Spearman rho correlation statistic. All Spearman correlation coefficients reported below were significant at  $P < 0.001$ . The 3 MWFs had low-to-moderate correlation (straight/soluble:  $\rho = 0.3$ ; straight/synthetic:  $\rho = 0.3$ ; soluble/synthetic:  $\rho = 0.2$ ). Within each MWF type, the metrics using a 10-year lag versus a 20-year lag were strongly correlated (all MWF classes:  $\rho = 0.8$ ). The pre-1970 exposure metric was correlated with the pre-1986 exposure metric (straight MWF:  $\rho = 0.6$ ; soluble MWF:  $\rho = 0.8$ ); the 10-year lag metric (straight MWF:  $\rho = 0.6$ ; soluble MWF:  $\rho = 0.7$ ); and the 20-year lag metric (both straight and soluble MWFs:  $\rho = 0.8$ ). The 1970–1985

**Table 3.** Categorical Exposure-Response Relations of Bladder Cancer and Lung Cancer Incidence in Male Michigan Autoworkers (1985–2004) and Cumulative Metalworking Fluid Exposure ( $\text{mg}/\text{m}^3\text{-years}$ , 20-Year Lag) Using Cox Regression Models With Covariates for Race, Hire Date, Calendar Year, and the Other Metalworking Fluid Exposures (as Linear Terms)

Straight Metalworking Fluid, 20-Year Lag					Soluble Metalworking Fluid, 20-Year Lag					Synthetic Metalworking Fluid, 20-Year Lag				
Category <sup>a</sup>	No. of Cases	Person-Years, no.	Hazard Ratio	95% Confidence Interval	Category <sup>a</sup>	No. of Cases	Person-Years, no.	Hazard Ratio	95% Confidence Interval	Category <sup>a</sup>	No. of Cases	Person-Years, no.	Hazard Ratio	95% Confidence Interval
Bladder cancer														
0	65	263,815	1		0	29	161,554	1		0	113	329,692	1	
>0<-<0.15	17	32,200	1.40	0.82, 2.38	>0<-<1.04	25	63,267	1.20	0.69, 2.08	>0<-<0.07	8	17,126	1.14	0.56, 2.31
0.15<-<0.52	18	34,691	1.22	0.71, 2.09	1.04<-<2.84	24	51,660	1.08	0.61, 1.89	0.07<-<0.19	8	14,502	1.08	0.52, 2.23
0.52<-<1.86	18	36,073	1.13	0.67, 1.90	2.84<-<6.69	25	52,609	0.90	0.52, 1.57	0.19<-<0.45	8	11,996	1.18	0.57, 2.42
1.86<-<8.98	18	25,421	1.51	0.88, 2.61	6.69<-<17.1	26	47,925	0.89	0.50, 1.60	0.45<-<2.08	8	19,846	0.61	0.29, 1.26
≥8.98	17	15,459	2.07	1.19, 3.62	≥17.1	24	30,643	1.02	0.56, 1.88	≥2.08	8	14,496	0.78	0.38, 1.61
<i>P</i> <sub>trend</sub>				0.02					0.65					0.30
Lung cancer														
0	260	263,802	1		0	98	161,560	1		0	358	329,777	1	
>0<-<0.18	44	36,721	0.82	0.59, 1.13	>0<-<1.34	76	74,531	0.94	0.69, 1.27	>0<-<0.11	24	23,220	0.90	0.59, 1.36
0.18<-<0.49	44	28,684	0.95	0.69, 1.30	1.34<-<4.00	77	61,591	0.80	0.59, 1.09	0.11<-<0.38	25	18,214	0.95	0.63, 1.43
0.49<-<1.34	44	30,103	0.80	0.58, 1.11	4.00<-<9.13	76	50,490	0.76	0.55, 1.04	0.38<-<0.88	24	12,074	1.11	0.73, 1.70
1.34<-<5.15	44	25,331	0.86	0.62, 1.20	9.13<-<20.0	77	35,083	0.91	0.66, 1.26	0.88<-<2.27	25	11,152	1.08	0.72, 1.63
≥5.15	44	23,149	0.88	0.64, 1.21	≥20.0	76	25,535	1.08	0.76, 1.51	≥2.27	24	13,354	0.89	0.58, 1.36
<i>P</i> <sub>trend</sub>				0.20					0.99					0.93

<sup>a</sup> Categories are defined by the 20th, 40th, 60th, and 80th exposure percentiles of exposed cases.

exposure time window was highly correlated with the pre-1986 time window (straight MWF:  $\rho = 0.8$ ; soluble MWF:  $\rho = 0.7$ ) but was not correlated with the pre-1970 time window (both straight and soluble MWF:  $\rho = 0.2$ ).

Duration of ethanolamine exposure was moderately to highly correlated with cumulative synthetic MWF exposure ( $\rho = 0.7$ ) but was not correlated with cumulative straight ( $\rho = 0.1$ ) or soluble ( $\rho = 0.04$ ) MWF exposure. Duration of nitrosamine exposure was moderately to highly correlated with duration of ethanolamine exposure ( $\rho = 0.6$ ) and synthetic MWF ( $\rho = 0.8$ ) but had low to moderate correlation with straight MWF ( $\rho = 0.3$ ) and soluble MWF ( $\rho = 0.1$ ).

### Metalworking fluid exposure–response models

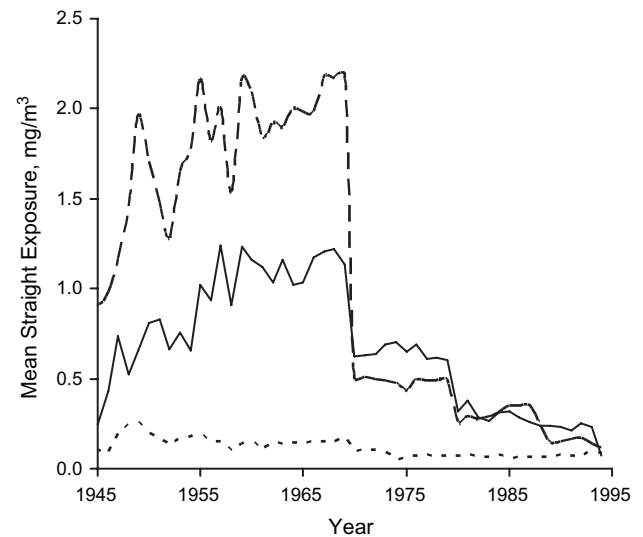
An increased hazard rate ratio for bladder cancer was observed with straight oils but not with soluble or synthetic MWF (Table 3). A 2-fold hazard ratio for bladder cancer was observed in the highest exposure category ( $>9 \text{ mg/m}^3\text{-year}$ ) of straight MWF with a 20-year lag. By use of continuous exposure measures, a stronger relation was observed when cumulative straight exposure was log transformed rather than untransformed ( $P = 0.02$  vs.  $0.08$ , respectively), suggesting a plateau in the hazard ratio at higher concentrations. The plant-specific hazard ratios were similar for plants 1 and 3 (hazard ratio =  $1.05$  and  $1.10$  per  $10 \text{ mg/m}^3\text{-year}$ , respectively) but were not statistically significant in the stratified analysis. Exposure to straight MWF was lower in plant 2 (median straight MWF in exposed workers,  $0.3 \text{ mg/m}^3\text{-year}$ ) and was not examined separately (Figure 1).

We examined the shape of the exposure response further using penalized splines. The hazard ratio increased roughly linearly with exposure up to about  $60 \text{ mg/m}^3\text{-year}$ , after which the steepness of the slope began to decrease until a plateau was reached at about  $100 \text{ mg/m}^3\text{-year}$  (Figure 2). The strongest association (based on model fit) was found with straight MWF lagged by 20 years. The exposure–response curves for the 20-year lag ( $df = 1.56$ ) and the pre-1970 time window ( $df = 1.53$ ) metrics were nearly indistinguishable, but the confidence limits were wider for the pre-1970 time window. The curves for the 10-year lag ( $df = 1.58$ ) and the pre-1986 time window ( $df = 1.59$ ) metrics were also nearly indistinguishable. The hazard ratios and confidence limits estimated by the penalized spline models are presented for selected exposure levels in Table 4.

No MWF class was associated with lung cancer (Table 3), suggesting that the hazard ratio for bladder cancer was not biased by confounding by cigarette smoking. African-American males were half as likely to develop bladder cancer as white males (hazard ratio =  $0.5$ , 95% CI:  $0.3, 0.9$ ).

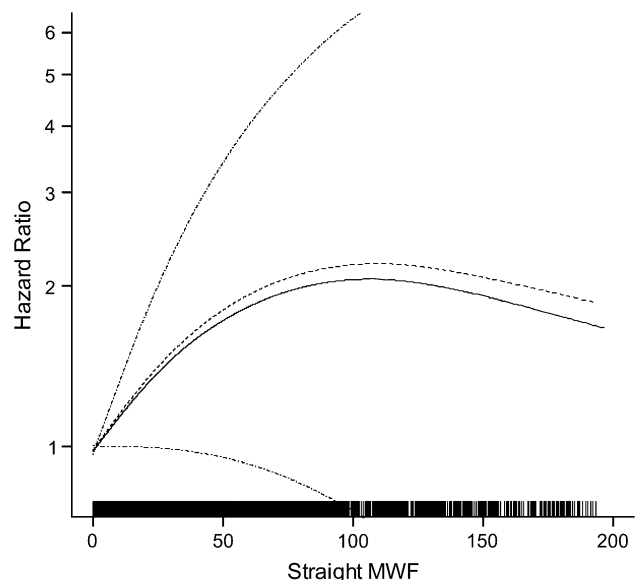
### Ethanolamines' and nitrosamines' exposure–response models

The duration of neither ethanolamine exposure nor nitrosamine exposure was associated with increased risk of bladder cancer or lung cancer in full cohort analyses (Table 5).



**Figure 1.** Mean straight metalworking fluid exposure of exposed male Michigan autoworkers by plant, 1945–1995. Plant 1 (—); plant 2 (---); plant 3 (···).

No association was observed when duration was lagged by 10 or 20 years (not shown). Adjusting for cumulative straight MWF did not change the risk estimates.



**Figure 2.** Hazard ratio of bladder cancer incidence (1985–2004) as a function of cumulative straight metalworking fluid exposure in male Michigan autoworkers, estimated from a Cox proportional hazards model and covariates for hire date, calendar time, race, and cumulative soluble and synthetic metalworking fluid. From top to bottom, the curves represent the following: 1, upper 95% confidence interval for 20-year lag; 2, 20-year lag ( $df = 1.56$ ); 3, 10-year lag ( $df = 1.58$ ); 4, lower 95% confidence interval for 20-year lag.

**Table 4.** Relative Risk Estimates for Bladder Cancer Incidence in Male Michigan Autoworkers (1985–2004) for Given Levels of Cumulative Straight Metalworking Fluids (10- and 20-Year Lags) as Estimated From the Cox Hazards Model by Using Penalized Splines and Covariates for Hire Date, Calendar Time, Race, and Cumulative Soluble and Synthetic Metalworking Fluids

Cumulative Straight Exposure, mg/m <sup>3</sup> -years	Lag 10 Years		Lag 20 Years	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
0	1		1	
5	1.05	1.00, 1.11	1.03	1.00, 1.06
10	1.13	1.00, 1.28	1.10	1.00, 1.21
25	1.37	0.99, 1.91	1.41	0.99, 2.00
50	1.72	0.94, 3.16	1.80	0.95, 3.41
75	1.95	0.85, 4.50	2.07	0.87, 4.92
100	2.06	0.73, 5.81	2.19	0.76, 6.37

## DISCUSSION

This retrospective cohort study is the first to report a statistically significant, quantitative exposure–response relation between exposure to straight MWFs and bladder cancer risk. Our findings strengthen the evidence for an association between mineral oil exposure and increased bladder cancer risk that has been observed in several population-based case-control studies with metal machining and other mineral oil-exposed occupations (1–6). The only other cohort study with semiquantitative exposure measures found weak evidence of an association (7). The association with straight oils, but not with soluble or synthetic fluids, observed here provides additional support for the role of PAHs in the etiology of bladder cancer that has been observed in other PAH-exposed industries (10, 11).

PAHs are hypothesized as the carcinogenic components of the mineral oils that make up straight MWF (8, 9), but we were unable to distinguish between PAH exposure and mineral oil exposure. We are unable to quantify the changes in PAH levels in the various MWF formulations in use over the extensive time period covered by this retrospective study. Measured benzo(a)pyrene levels have ranged from not detectable to 53 µg/g in cutting and quench oils (27). PAHs can also be formed during high temperature operations (28–30), although the dilution effect from topping up fluid levels may mask the PAH generation (27). An unpublished study, briefly described in the report by Woskie et al. (22), demonstrated that the PAH content was associated with MWF exposure intensity within a fluid type and across operations. The PAH content was formulation specific, with wide variability observed within different soluble MWF formulations, but with much less variability within the straight MWF formulations. This variability suggests that the intensity of airborne straight MWF may be an appropriate surrogate for the PAH content of straight MWF, but not of soluble MWF. Thus, an association with PAH-containing soluble MWF formulations cannot be ruled out by the lack of an association between soluble MWF and bladder cancer risk in this study.

The PAH levels in mineral oils decreased substantially in the mid- to late-1980s with the greater use of highly treated base oils (22); however, this decrease coincided with the decrease in airborne MWF exposure concentrations (18). We examined PAH-relevant time windows, but these metrics were not distinguishable from the metrics that used 10- or 20-year latency periods. The stronger associations observed here using a 20-year latency period are consistent with the long latency periods observed with PAH exposure and bladder cancer in the aluminum smelting industry (31, 32). We were unable to examine the risk of bladder cancer associated with exposures within the 10 years of diagnosis because of the lack of continued access to work histories after 1995. This is unlikely to impact our findings, however, because of

**Table 5.** Categorical Exposure-Response Relations of Bladder Cancer and Lung Cancer Incidence in Male Michigan Autoworkers (1985–2004) for Exposure Duration of Ethanolamines and Nitrosamines by Using Cox Regression Models With Covariates for Hire Date, Calendar Time, and Race

	Ethanolamines				Nitrosamines			
	No. of Cases	Person-Years, no.	Hazard Ratio	95% Confidence Interval	No. of Cases	Person-Years, no.	Hazard Ratio	95% Confidence Interval
Bladder cancer								
No exposure	95	237,902	1		103	291,596	1	
<1 year	38	114,749	0.90	0.62, 1.31	42	100,624	1.21	0.84, 1.74
≥1 year	20	55,007	1.13	0.69, 1.87	8	15,439	0.96	0.46, 2.00
<i>P</i> <sub>trend</sub>				0.88				0.55
Lung cancer								
No exposure	326	265,852	1		356	299,783	1	
<1 year	121	109,962	0.94	0.76, 1.16	104	94,837	0.97	0.78, 1.22
≥1 year	33	31,977	0.85	0.59, 1.22	20	13,171	0.79	0.50, 1.24
<i>P</i> <sub>trend</sub>				0.33				0.39

the long latency period observed with bladder cancer in this and other studies and because of the substantial decrease in exposure levels from the 1970s onward (18).

There was no evidence of increased bladder cancer risk with nitrosamine exposure in this cohort. The nitrosamine exposure index used here, based on the simultaneous presence of ethanolamines and nitrites as reported on the Material Safety Data Sheets, was a relatively crude indicator of exposure. The Material Safety Data Sheets have been found to provide only a general guideline on the presence or absence of ethanolamines as a class, but they were not reliable for identifying specific ethanolamines (33). The rate of nitrosamine formation is complex and depends upon the specific ethanolamines present and their purity, the pH and temperature of the MWF and process, and the presence of catalysts or the action of bacteria (16). Few bladder cancer cases were exposed to nitrosamines for more than 1 year; additional follow-up time will provide more power to examine this association.

Incident bladder cancer cases are preferred to mortality because of the high 5-year survival of 80% (20). The absence of a national cancer registry, however, limited identification to incident cancers diagnosed in Michigan. To estimate the magnitude of underascertainment of cases, we looked at the state of death recorded in the mortality data and found that approximately 14% of the deceased subjects in the cohort had not died in Michigan. Unidentified incident cancers could lead to overestimates of the relative risk if the lower exposed workers were more likely to leave the state. However, subjects who died out-of-state had approximately the same mean exposure levels as those who died in Michigan, suggesting that migration was nondifferential. Thus, it is unlikely that our results are an overestimate of the true relative risk.

The use of penalized splines provides a flexible approach to exposure–response modeling by not imposing any a priori assumptions on the shape, yet retaining all information in the continuous measure of exposure. Although the hazard ratio increased linearly where data were dense, the curve plateaued at higher exposures where person-years were sparse and decreased at exposure levels greater than the highest exposed bladder cancer case (110 mg/m<sup>3</sup>-year). Occupational cohort studies often report a plateau or decline in risk at the highest exposure levels, which has been attributed to many factors, including exposure misclassification, healthy worker survivor bias, and depletion of the susceptible population (34).

Although both the penalized splines and categorical exposure models predicted a 2-fold excess risk, the categorical models had higher relative risks at lower exposure levels (i.e., >9 vs. 100 mg/m<sup>3</sup>-year). Categorical models are not robust to changes in the cutpoints (35), fail to incorporate information within and between categories, and can introduce differential misclassification if there is measurement error in the continuous exposure metric (36). Although penalized spline models are influenced by outliers in the sparse data tails of the exposure range, they are quite robust in the lower range where data are dense (26). Thus, the lower rate ratios estimated by the smoothed curve are reliable at the lower exposure range and are more appropriate for risk assessment than the categorical analyses.

Smoking is a well-established risk factor for bladder cancer (37). We could not directly adjust for smoking's effects in these analyses. The lack of an association, however, between MWF exposures and either lung cancer incidence in this cohort or lung cancer mortality in earlier analyses of this cohort (38, 39) suggests that smoking is unlikely to confound the associations seen here. Other studies have found that confounding by smoking and other lifestyle habits in internal comparisons of occupational cohorts is generally modest, with changes in the risk estimates of only 20%–30% (40, 41), which would not negate the 2-fold excess risk observed here.

This study was the first cohort study to examine bladder cancer risk with quantitative measures of exposure to 3 metalworking fluid classes and their additives. The strong quantitative exposure–response relation with straight MWF observed here strengthens the evidence for mineral oils as a bladder carcinogen.

## ACKNOWLEDGMENTS

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This work was supported by grant R01 OH008927 from the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

Conflict of interest: none declared.

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