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Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry

by Ellen A Eisen, ScD,^{1,3} Judith Bardin, ScD,¹ Rebecca Gore, PhD,¹ Susan R Woskie, PhD,¹ Marilyn F Hallock, MS,² Richard R Monson, ScD³

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Objectives This report describes the extended follow-up of a cohort of 46 399 automobile manufacturing workers with potential exposure to metalworking fluids (MWF). The outcomes of interest were cancers of the esophagus, stomach, colon, rectum, liver, pancreas, larynx, skin, prostate, and brain, as well as leukemia. Additional follow-up increased the power to detect modest elevations in mortality rates in association with specific types of MWF, including synthetic fluids not in widespread use until the 1970s.

Methods Standardized mortality ratios (SMR) were computed for the most recent 10 years of follow-up, as well as for the entire study period. Adjusted relative risks (RR) were estimated in Poisson regression models with categorical variables for cumulative exposure to each type of MWF and in proportional hazards models with continuous exposure variables.

Results Associations were found between straight MWF and esophageal, laryngeal and rectal cancer; soluble MWF and cancer of the esophagus, larynx, skin, and brain; synthetic MWF and cancer of the esophagus, liver, and prostate. The elevated RR values were modest in magnitude (1.5 to 2.0). SMR values were increased for stomach, liver, and pancreatic cancer and also for leukemia in the last 10 years of follow-up. The SMR values were also elevated for stomach and liver cancer among the persons recently hired.

Conclusions The results provide further evidence that exposure to metalworking fluids causes cancer among workers in automobile manufacturing. Although airborne exposures declined over the study period, this study suggests that modest risk of several digestive cancers, as well as prostatic cancer and leukemia, may persist at current levels of exposure to water-based metalworking fluids.

Key terms cancer, case-cohort, metalworking fluids, proportional hazards model.

Metalworking fluids is a generic term that describes the broad range of complex mixtures used as coolants and lubricants in the manufacture of metal products. Metalworking fluids are widely used in the automobile industry to reduce friction between the tool and metal surface and to remove metal chips and residues during machining operations. They are grouped into the following four major classes: straight mineral oil, soluble oil, semisynthetic fluids and synthetic fluids. A variety of chemicals is added to improve the performance characteristics of all types of metalworking fluids. Typically, the chemical additives are either rust and corrosion inhibitors, biocides to control bacterial and fungal con-

tamination, or extreme pressure additives. The precise formulation of metalworking fluids varies considerably among manufacturers and end-users. Estimates suggest that approximately 1.2 million workers are exposed in the United States to metalworking fluids (1). Exposure occurs via skin absorption and inhalation of the aerosolized fluids.

In response to growing concern in the early 1980s regarding the carcinogenic effects of these fluids, the United Automobile Workers (UAW) union and General Motors (GM) corporation jointly funded a retrospective cancer mortality study. Standardized mortality ratios (SMR) have been reported for this cohort of autoworkers

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(1), as has exposure-response results based on the cohort as a whole (2) and nested case-referent studies (3–7). Associations have been observed for several cancers of a priori interest, including cancer of the larynx (3), esophagus (6), pancreas (5), and rectum (7). Lung cancer was not found to be positively associated with metalworking fluids in this cohort (4).

In its 1997 criteria document recommending a reduced exposure limit for metalworking fluids (8), the National Institute for Occupational Safety and Health (NIOSH) concluded that the metalworking fluids used before the mid-1970s were associated with cancer in several organ sites. Since that time, broad industry-wide changes have occurred in the ways the oils are refined and the fluids are formulated and the types of fluids used. For example, the more severe refining methods that first appeared in the 1950s and gained in popularity in the 1970s have reduced the content of polycyclic aromatic hydrocarbons (PAH) in straight oils (9, 10). At the same time, the use of water-based fluids increased because their superior coolant properties made them better suited for the higher speed grinding operations found in automobile manufacturing today. This expansion of synthetic and semisynthetic fluids has introduced a whole new array of chemical exposures with unknown carcinogenic risk for humans. What impact the totality of these changes has had on carcinogenic risk is unknown.

The results presented in this report are based on 10 more years of follow-up. It has now been more than 25 years since the reduction of PAH in straight oils and the expanded use of synthetic fluids throughout the industry. The additional follow-up has increased the power of the study to detect more modest elevations in risk in association with less common causes of death among more recently employed subjects in the cohort.

Subjects and methods

Details on the sources of data, cohort verification, vital status ascertainment, and exposure assessment can be

found in previous reports on this cohort study (1, 2,11,12). The methods are briefly described in this report.

Cohort

The study population included 46 399 hourly workers at three automobile manufacturing plants in Michigan. All hourly employees who had worked at least 3 years (prior to 1 January 1985) were identified from company records and included in the cohort. Follow-up now extends from 1941 to 1994, 10 years longer than the original study, and it includes more than 1.5 million person-years.

After 53 years, 32.5% of the cohort has died and 4% has been lost-to-follow-up. The cohort was predominantly white and male, although 7751 (16%) subjects were African American and 4372 (9%) were female (table 1). Most of the African American subjects (68%) had worked in plant I, although the cohort as a whole was equally divided between the three plants.

Exposure

The three plants were selected, in part, to represent the full range of metalworking fluids: straight mineral oil, soluble oil (emulsifiable oil), semisynthetic metalworking fluids, which contain a smaller amount of severely refined lubricant-base oil (5–30%), emulsifiers and water, and totally synthetic metalworking fluids, which contain no petroleum oils. As in the previous analyses of this cohort study, semisynthetics were combined with soluble metalworking fluids.

To update the exposure assessment, the industrial hygienist (MH) involved in the original historical reconstruction of the exposures re-visited each of the three plants. On the basis of recent plant records, a type of fluid was assigned to each plant-, department-, and job-specific exposure category. As before, scale factors were estimated to express aerosol exposures relative to the baseline levels (1984). For each unique combination of fluid type and operation, the scale factor was less than 1.0 at the new end of the follow-up, reflecting a continuing downward trend in exposure levels.

Table 1. Distribution by race,^a gender, and plant in the cohort of autoworkers with potential exposure to metalworking fluids, followed from 1941 to 1994.

	Males			Females			Total
	African American	White	Unknown	African American	White	Unknown	
Plant I	4398	9117	2316	455	71	8	16 367
Plant II	1244	8640	4672	529	1545	637	17 267
Plant III	844	9042	1444	281	1057	97	12 765
Total	6486	26799	8432	1265	2673	742	46 399

^a Race as defined at the end of the follow-up.

Cumulative exposure was calculated for each subject as the weighted average of exposures in which the calendar-time-specific estimate of total mass particulate (mg/m^3) in each job was weighted by the time spent in that job. For jobs with mixed exposures, we estimated the percentage of time spent using each particular fluid. Cumulative exposure was estimated for the following four variables: straight fluid, soluble machining fluid, soluble grinding fluid, and synthetic fluid. Virtually all straight oils were used in machining operations, and almost all synthetics were used in high-speed grinding operations. Only solubles could be split by type of operation.

Analytic methods

Person-years were accumulated for each subject from 3 years after hire or 1941 (whichever occurred later) until the date of death, end of follow-up, or the last date known to be alive (for those lost to follow-up). We updated the vital status from the company's current employment records, company and union mortality records, and the National Death Index (NDI). Cause of death was ascertained either from the union or company records or from the death certificate of the deceased subject, as identified by the NDI. The same nosologist as in the original study coded the underlying cause of death from the death certificates using the ninth revision of the International Classification of Diseases (ICD-9).

Handling missing data. For the subjects lost to follow-up, person-years were accumulated until the date of work termination, which was the last date known to be alive. For the small number of subjects who were lost to follow-up and also had missing termination dates, we assumed that they did not live beyond their 85th birthday.

Subjects with more than 25% of their work record missing were excluded from the Poisson exposure-response modeling (less than 5% of the cohort). To impute missing data in the employment records of the subjects included in the analysis, we stretched the most temporally proximate nonmissing exposure data to cover the gaps. For the case-cohort analysis, subjects were included with up to 50% imputed exposure data in order to ensure convergence for all the models.

Standardized mortality ratios. Standardized mortality ratios (SMR) were estimated using software developed by Monson (13) and updated with current United States mortality rates (1990–1994). SMR values are presented for two racial subgroups of men over the entire study period (1941 through 1994) and over the most recent 10-year period (1985–1994). As in the original analysis, the subjects with unknown race were included

together with whites. SMR values were also calculated for the subset hired after 1970.

Poisson regression models. To examine the associations between cumulative exposure to metalworking fluids and specific causes of death, we began by fitting Poisson regression models with categorical variables defined for cumulative exposure to each type of fluid. To establish a common set of exposure categories in all the models, cut points for the categories were based on the *n*-tiles of the case distribution for the combined group of all cancers. Each of the Poisson models included the same set of potential confounders: plant, gender, decade of hire (<1950, 1950s, 1960s, ≥1970), race (white, African American, unknown) at the end of follow-up, age (decade), and calendar year at risk (<1950, 1950–1970, ≥1970). In a person-year analysis, incidence rates were estimated within cells defined by all unique combinations of potential confounders and regression coefficients interpreted as adjusted incidence rate ratios (RR). To increase efficiency, we truncated the person-years for which the subject was less than 40 years of age.

When the rate ratios increased over increasing categories of exposure, we conducted a formal test for linear trend. With the use of an approach described by Rothman (14), the rate ratio was regressed on the midpoint of the exposure category using weighted linear regression. The number of cases in each category determined the weights, and the P-value for the overall F test of the model provided the significance level of the test. We then fit proportional hazards models with continuous exposure variables to examine these associations further.

Proportional hazards models. Because this model is computationally intensive for a cohort of this size, we sampled the cohort using a case-cohort approach (15). A stratified random sampling procedure was used to ensure that the composition of the subcohort would be similar to that observed for all cancer deaths combined with respect to race, gender, and plant. On the basis of power calculations, a subcohort of 3000 subjects was selected from the full cohort. This 6% sample was adequate to provide 80% power to detect risks of 1.5 to 2.0 for the rarer cancers of interest.

To adjust for confounding by age, risk sets (strata) were defined for each case to include all subjects alive at the age of the death (risk age) of the case. For all the subjects in a particular risk set, exposure was cumulated up to the risk age of the index case. Potential confounders of race, gender, calendar year of hire, and calendar year at risk were included in each model. The three exposure variables, one for each type of metalworking fluid, were included together in a single

model for each cancer outcome to adjust for confounding of one type of fluid exposure by another.

The regression coefficients were interpreted as the change in relative risk per unit increase in exposure. In order to have a more substantial unit of exposure, we redefined a unit as one standard deviation of exposure. The risk estimates presented from these models can therefore be interpreted as the change in relative risk in association with an increase of 13, 30, or 6 mg/m³-years of exposure to straight, soluble, or synthetic metalworking fluids, respectively.

Each subject in the subcohort appears in multiple risk sets. To address the problem of correlated risk sets, a newly available SAS (Statistical Analysis System) macro, called CACO was used to calculate correct confidence intervals (16). The corrected standard errors of the rate ratios estimated in a case-cohort analysis reflect the overlapping nature of the risk sets caused by the limited number of referents available in the subcohort using the method suggested by Barlow (17).

Results

The average exposure to each type of metalworking fluid was estimated annually for all the exposed workers in the cohort (figure 1). The average exposure to soluble metalworking fluids was close to 3 mg/m³ until the 1950s, when it dropped to 2 mg/m³ and then to less than 1 mg/m³ in the early 1970s. Average exposures to straight metalworking fluids were close to 1 mg/m³ until they also declined in the early 1970s. The use of synthetics began later, and the average concentrations have been maintained at <1.0 mg/m³. The maximum daily exposure over the same period was 15 mg/m³ for

soluble metalworking fluids, 10 mg/m³ for straight metalworking fluids, and 5 mg/m³ for synthetic metalworking fluids (data not shown).

Causes of death were selected for exposure-response modeling based on positive findings in the original study or other published studies. Digestive cancers were of primary interest, particularly cancers of the esophagus, stomach, colon, pancreas, liver, and rectum, as well as cancers of the larynx, lung, brain, skin and prostate, and also leukemia.

Standardized mortality ratios

The SMR values over the entire follow-up period were all close to 1.0 when white males from all three plants were combined (table 2). Significantly elevated SMR values were observed only for liver cancer (SMR 1.4) and leukemia (SMR 1.3). These elevations persisted in

Figure 1. Estimated average annual exposure to specific types of metalworking fluids among the exposed workers in the cohort.

Table 2. Standardized mortality ratios (SMR) for white male autoworkers^a according to United States mortality rates. (95% CI = 95% confidence interval)

Cause of death	1940—1994			1985—1994		
	N	SMR	95% CI	N	SMR	95% CI
All causes	13105	1.01	0.99—1.03	4197	1.10	1.07—1.13
All cancers	2983	1.05	1.01—1.09	1134	1.14	1.08—1.21
Esophageal	83	1.22	0.97—1.51	34	1.37	0.95—1.92
Stomach	151	1.16	0.98—1.36	42	1.46	1.05—1.97
Colon	252	0.95	0.84—1.08	98	1.06	0.86—1.30
Rectal	78	1.06	0.84—1.32	17	1.07	0.62—1.71
Liver	78	1.42	1.12—1.77	31	1.82	1.24—2.58
Pancreatic	143	0.99	0.83—1.16	66	1.44	1.11—1.83
Laryngeal	44	1.16	0.85—1.56	11	1.02	0.51—1.83
Lung	1002	1.08	1.02—1.15	401	1.16	1.05—1.28
Skin	35	0.64	0.45—0.89	7	0.32	0.13—0.66
Prostatic	261	1.06	0.94—1.20	114	1.06	0.87—1.27
Brain	84	1.14	0.91—1.41	29	1.24	0.83—1.78
Leukemia	147	1.34	1.14—1.58	51	1.40	1.04—1.84
All nonmalignant respiratory diseases	879	0.94	0.87—1.00	388	1.07	0.96—1.18

^a All three plants combined.

the most recent 10 years. In addition, SMR values for cancer of the stomach, pancreas, and lung were significantly elevated in the more recent time period, while skin cancer mortality was lower than expected.

A stronger healthy worker effect was seen for the African American males, as reflected by a lower SMR for all causes of death combined. Only pancreatic cancer was significantly elevated over the entire period for this group (table 3). The SMR of 1.5 [95% confidence interval (95% CI) 1.1–2.1] decreased to 1.3 in the most recent 10-year period and had a wider confidence interval. The African American males also had elevated risks for both rectal cancer and leukemia during the 1985–1994 period, with an SMR of 2.0.

Among the white males, there were 326 deaths among those hired after 1970. For this subset, the SMR for all causes of death combined was less than 1.0; this value reflects a stronger healthy worker effect with the shorter length of follow-up. The confidence intervals for all the SMR values included 1.0, except for stomach and liver cancer, with SMR values of 2.6 (95% CI 1.0–5.3) and 4.0 (95% CI 1.5–8.9), respectively.

Poisson regression models

Cumulative exposure to straight metalworking fluids. In the model for esophageal cancer and straight metalworking fluids, the pattern of risk was bell-shaped, with the rate ratio increasing to 1.9 (95% CI 1.2–3.2) and then decreasing (table 4). As in the original study, the results suggested significant associations between straight metalworking fluids and cancers of the rectum and larynx. The risk for rectal cancer was 2.0 (95% CI 1.2–3.5) in the highest exposure category, and the linear trend was almost significant. The adjusted rate ratio for laryngeal

cancer increased to a maximum risk of 1.9 (95% CI 0.9–4.0) with a linear trend of borderline significance. There was also some suggestion of an increasing risk of leukemia with a rate ratio of 1.2 for the two highest categories.

Cumulative exposure to soluble metalworking fluids.

None of the results for soluble metalworking fluids were remarkable (data not shown). When restricted to the use of these fluids in grinding, a few of the associations became stronger (table 5). The rate ratio for esophageal cancer was close to twofold for all three exposure categories. The risk for rectal cancer rose to 1.4 (95% CI 0.8–2.8) in the highest exposure category. Skin cancer risk reached 2.6 (95% CI 1.0–6.7) and the rate ratios for brain cancer were elevated between 1.6 and 2.1 in all the exposure categories. The linear trend for laryngeal cancer was almost significant, and the risk was 1.8 in the highest category.

Cumulative exposure to synthetic metalworking fluids.

There was limited evidence for several associations with synthetic fluids (table 6). The rate ratio for esophageal cancer was 2.6 (95% CI 1.3–5.3) in the low-exposure category and 1.3 with a wider confidence interval in the higher category. The rate ratios for liver cancer were 2.4 (95% CI 1.1–5.1) and 1.8 (95% CI 0.8–3.9) across increasing categories of exposure. There were also modestly elevated risks of 1.2 and 1.3 for prostatic cancer in the two higher exposure categories.

Most recent hires. Based on parameter estimates for the calendar year at risk in these models, the mortality rates increased over the 50-year period for cancers of the esophagus, larynx, and lung and decreased for cancers

Table 3. Standardized mortality ratios (SMR) for the African American male autoworkers^a based on United States mortality rates. (95% CI = 95% confidence interval)

Cause of death	1940–1994			1985–1994		
	N	SMR	95% CI	N	SMR	95% CI
All causes	1882	0.86	0.82–0.90	883	0.94	0.88–1.01
All cancers	460	0.95	0.86–1.04	224	0.95	0.83–1.09
Esophageal	21	0.76	0.47–1.16	11	0.93	0.46–1.66
Stomach	28	0.96	0.63–1.38	8	0.74	0.32–1.46
Colon	28	0.83	0.55–1.20	18	1.02	0.61–1.62
Rectal	9	1.12	0.51–2.13	6	1.97	0.72–4.30
Liver	16	1.31	0.75–2.13	5	1.05	0.34–2.44
Pancreatic	36	1.50	1.05–2.07	14	1.27	0.69–2.13
Larynx	11	1.26	0.63–2.25	4	0.96	0.26–2.47
Lung	153	0.95	0.80–1.11	74	0.90	0.71–1.13
Skin	3	0.97	0.20–2.85	2	1.27	0.14–4.57
Prostatic	55	0.98	0.74–1.28	29	0.95	0.64–1.36
Brain	4	0.73	0.20–1.86	1	0.41	0.01–2.31
Leukemia	15	1.28	0.71–2.10	11	2.01	1.00–3.61
All nonmalignant respiratory diseases	104	0.78	0.64–0.95	16	0.32	0.19–0.52

^a All three plants combined.

Table 4. Adjusted relative risks of cancer mortality in relation to cumulative exposure (mg/m³-years) to straight metalworking fluids. (RR = risk ratio, 95% CI = 95% confidence interval)

Cause of death ^a	Number of cases	RR ^b	95% CI
Esophageal cancer (150)			
0 mg/m ³ -years	33	1.00	..
0—1 mg/m ³ -years	30	1.90	1.20—3.20
>1—3 mg/m ³ -years	12	1.57	0.79—3.11
>3 mg/m ³ -years	14	1.10	0.57—2.11
Stomach cancer (151)			
0 mg/m ³ -years	80	1.00	..
0—1 mg/m ³ -years	52	1.20	0.82—1.74
>1—3 mg/m ³ -years	14	0.65	0.36—1.16
>3 mg/m ³ -years	30	1.10	0.75—1.70
Colon cancer (153)			
0 mg/m ³ -years	125	1.00	..
0—1 mg/m ³ -years	59	0.95	0.69—1.32
>1—3 mg/m ³ -years	38	1.15	0.73—1.68
>3 mg/m ³ -years	37	0.75	0.51—1.09
Rectal cancer (154)			
0 mg/m ³ -years	30	1.00	..
0—1 mg/m ³ -years	18	1.30	0.71—2.39
>1—3 mg/m ³ -years	13	1.77	0.90—3.48
>3 mg/m ³ -years	24	2.01 ^c	1.15—3.52
Liver cancer (155)			
0 mg/m ³ -years	41	1.00	..
0—1 mg/m ³ -years	28	1.39	0.83—2.32
>1—3 mg/m ³ -years	12	1.18	0.60—2.30
>3 mg/m ³ -years	8	0.45	0.21—0.99
Pancreatic cancer (157)			
0 mg/m ³ -years	77	1.00	..
0—1 mg/m ³ -years	45	1.12	0.72—1.57
>1—3 mg/m ³ -years	21	0.87	0.60—1.63
>3 mg/m ³ -years	26	0.89	0.54—1.37
Laryngeal cancer (161)			
0 mg/m ³ -years	18	1.00	..
0—1 mg/m ³ -years	13	1.37	0.65—2.60
>1—3 mg/m ³ -years	6	1.36	0.53—3.53
>3 mg/m ³ -years	11	1.85 ^c	0.86—3.98
Lung cancer (162)			
0 mg/m ³ -years	526	1.00	..
0—1 mg/m ³ -years	274	0.85	0.73—0.99
>1—3 mg/m ³ -years	132	0.84	0.69—1.03
>3 mg/m ³ -years	191	0.97	0.81—1.15
Skin cancer (172)			
0 mg/m ³ -years	15	1.00	..
0—1 mg/m ³ -years	8	0.75	0.31—1.86
>1—3 mg/m ³ -years	4	0.77	0.24—2.43
>3 mg/m ³ -years	8	1.12	0.44—2.84
Prostatic cancer (185)			
0 mg/m ³ -years	136	1.00	..
0—1 mg/m ³ -years	69	1.10	0.81—1.49
>1—3 mg/m ³ -years	37	1.10	0.74—1.58
>3 mg/m ³ -years	50	1.01	0.72—1.41
Brain cancer (191)			
0 mg/m ³ -years	37	1.00	..
0—1 mg/m ³ -years	19	0.88	0.49—1.59
>1—3 mg/m ³ -years	11	1.12	0.55—2.26
>3 mg/m ³ -years	10	0.71	0.34—1.48
Leukemia (204)			
0 mg/m ³ -years	71	1.00	..
0—1 mg/m ³ -years	31	0.85	0.54—1.32
>1—3 mg/m ³ -years	22	1.22	0.74—2.01
>3 mg/m ³ -years	30	1.23	0.72—1.75

^a Code of the International Classification of Diseases, ninth revision, in parentheses.

^b RR estimated in a separate Poisson regression model for each cancer (including date of hire, calendar time, plant, age, race and gender) based on the full cohort.

^c P = 0.075 in the test for linear trend.

Table 5. Adjusted relative risks of cancer mortality in relation to cumulative exposure (mg/m³-years) to grinding with soluble metalworking fluids. (RR = risk ratio, 95% CI = 95% confidence interval)

Cause of death ^a	Number of cases	RR ^b	95% CI
Esophageal cancer (150)			
0 mg/m ³ -years	14	1.00	..
>0—2 mg/m ³ -years	30	2.09	1.10—3.98
>2—12 mg/m ³ -years	23	1.65	0.85—3.22
>12 mg/m ³ -years	22	1.90	0.95—3.78
Stomach cancer (151)			
0 mg/m ³ -years	44	1.00	..
>0—2 mg/m ³ -years	40	0.88	0.57—1.36
>2—12 mg/m ³ -years	49	1.17	0.78—1.77
>12 mg/m ³ -years	43	1.05	0.68—1.63
Colon cancer (153)			
0 mg/m ³ -years	65	1.00	..
>0—2 mg/m ³ -years	57	0.90	0.62—1.29
>2—12 mg/m ³ -years	78	1.21	0.87—1.69
>12 mg/m ³ -years	59	0.91	0.63—1.30
Rectal cancer (154)			
0 mg/m ³ -years	18	1.00	..
>0—2 mg/m ³ -years	18	1.11	0.56—2.16
>2—12 mg/m ³ -years	23	1.28	0.69—2.39
>12 mg/m ³ -years	26	1.36	0.81—2.76
Liver cancer (155)			
0 mg/m ³ -years	10	1.00	..
>0—2 mg/m ³ -years	10	1.39	0.80—2.42
>2—12 mg/m ³ -years	15	0.75	0.40—1.41
>12 mg/m ³ -years	13	0.84	0.45—1.59
Pancreatic cancer (157)			
0 mg/m ³ -years	40	1.00	..
>0—2 mg/m ³ -years	49	1.13	0.74—1.73
>2—12 mg/m ³ -years	40	1.01	0.65—1.57
>12 mg/m ³ -years	40	1.24	0.78—1.95
Laryngeal cancer (161)			
0 mg/m ³ -years	10	1.00	..
>0—2 mg/m ³ -years	10	0.88	0.36—2.12
>2—12 mg/m ³ -years	15	1.57	0.70—3.50
>12 mg/m ³ -years	13	1.80 ^c	0.76—4.34
Lung cancer (162)			
0 mg/m ³ -years	327	1.00	..
>0—2 mg/m ³ -years	329	0.88	0.76—1.04
>2—12 mg/m ³ -years	263	0.82	0.69—0.96
>12 mg/m ³ -years	204	0.80	0.67—0.96
Skin cancer (172)			
0 mg/m ³ -years	8	1.00	..
>0—2 mg/m ³ -years	8	0.83	0.31—2.25
>2—12 mg/m ³ -years	5	0.63	0.21—1.95
>12 mg/m ³ -years	14	2.64	1.03—6.74
Prostatic cancer (185)			
0 mg/m ³ -years	73	1.00	..
>0—2 mg/m ³ -years	57	0.79	0.55—1.12
>2—12 mg/m ³ -years	74	0.99	0.72—1.37
>12 mg/m ³ -years	88	1.11	0.80—1.53
Brain cancer (191)			
0 mg/m ³ -years	13	1.00	..
>0—2 mg/m ³ -years	24	1.76	0.88—3.49
>2—12 mg/m ³ -years	24	2.08	1.05—4.11
>12 mg/m ³ -years	16	1.58	0.74—3.38
Leukemia (204)			
0 mg/m ³ -years	38	1.00	..
>0—2 mg/m ³ -years	42	1.15	0.73—1.80
>2—12 mg/m ³ -years	38	1.06	0.67—1.66
>12 mg/m ³ -years	36	0.96	0.60—1.55

^a Code of the International Classification of Diseases, ninth revision, in parentheses.

^b RR estimated in a separate Poisson regression model for each cancer (including date of hire, calendar time, plant, age, race and gender) based on the full cohort.

^c P = 0.065 in the test for linear trend.

Table 6. Adjusted relative risks of cancer mortality in relation to cumulative exposure (mg/m³-years) to synthetic metalworking fluids. (RR = risk ratio, 95% CI = 95% confidence interval)

Cause of death ^a	Number of cases	RR ^b	95% CI
Esophageal cancer (150)			
0 mg/m ³ -years	65	1.00	..
>0–1.0 mg/m ³ -years	16	2.60	1.28–5.25
>1.0 mg/m ³ -years	8	1.25	0.54–2.89
Stomach cancer (151)			
0 mg/m ³ -years	144	1.00	..
>0–1.0 mg/m ³ -years	22	1.11	0.65–1.90
>1.0 mg/m ³ -years	10	0.56	0.28–1.15
Colon cancer (153)			
0 mg/m ³ -years	213	1.00	..
>0–1.0 mg/m ³ -years	16	0.61	0.34–1.07
>1.0 mg/m ³ -years	30	1.03	0.66–1.62
Rectal cancer (154)			
0 mg/m ³ -years	71	1.00	..
>0–1.0 mg/m ³ -years	4	0.58	0.19–1.75
>1.0 mg/m ³ -years	109	1.35	0.61–2.98
Liver cancer (155)			
0 mg/m ³ -years	65	1.00	..
>0–1.0 mg/m ³ -years	14	2.41	1.14–5.08
>1.0 mg/m ³ -years	10	1.75	0.79–3.86
Pancreatic cancer (157)			
0 mg/m ³ -years	131	1.00	..
>0–1.0 mg/m ³ -years	19	1.09	0.62–1.91
>1.0 mg/m ³ -years	19	1.08	0.62–1.88
Laryngeal cancer (161)			
0 mg/m ³ -years	37	1.00	..
>0–1.0 mg/m ³ -years	7	1.45	0.57–2.79
>1.0 mg/m ³ -years	4	0.90	0.29–2.79
Lung cancer (161)			
0 mg/m ³ -years	863	1.00	..
>0–1.0 mg/m ³ -years	143	0.94	0.77–1.16
>1.0 mg/m ³ -years	117	0.79	0.63–0.98
Skin cancer (172)			
0 mg/m ³ -years	29	1.00	..
>0–1.0 mg/m ³ -years	3	0.48	0.13–1.72
>1.0 mg/m ³ -years	3	0.48	0.13–1.69
Prostatic cancer (185)			
0 mg/m ³ -years	238	1.00	..
>0–1.0 mg/m ³ -years	24	1.20	0.72–1.98
>1.0 mg/m ³ -years	30	1.30	0.82–2.08
Brain cancer (191)			
0 mg/m ³ -years	16	1.00	..
>0–1.0 mg/m ³ -years	4	1.00	0.43–2.27
>1.0 mg/m ³ -years	3	1.28	0.59–2.78
Leukemia (204)			
0 mg/m ³ -years	124	1.00	..
>0–1.0 mg/m ³ -years	15	1.02	0.54–1.91
>1.0 mg/m ³ -years	15	1.02	0.55–1.90

^a Code of the International Classification of Diseases, ninth revision, in parentheses.

^b RR estimated in a separate Poisson regression model for each cancer (including date of hire, calendar time, plant, age, race and gender) based on the full cohort.

of the stomach and rectum (data not shown). The decade of hire was examined in each model for evidence of changes in risk in relation to unmeasured aspects of exposure to metalworking fluids. In a comparison with those hired earlier, the risk was at least as high among those hired after 1970 for cancer of the stomach, liver, and lung and also for leukemia (data not shown) and lower for cancer of the esophagus, rectum, larynx, and skin.

Table 7. Adjusted relative risks of cancer mortality in relation to cumulative exposure to each of three types of metalworking fluids (MWF). (RR = risk ratio, 95% CI = 95% confidence interval)

Cause of death	Beta	Standard error	RR ^{a, b}	95% CI
Esophageal cancer				
Straight MWF	–0.017	0.012	0.80	0.59–1.09
Soluble MWF	–0.001	0.004	0.97	0.77–1.22
Synthetic MWF	0.022	0.020	1.13	0.90–1.44
Stomach cancer				
Straight MWF	–0.017	0.007	0.80	0.67–0.95
Soluble MWF	0.002	0.002	1.06	0.94–1.19
Synthetic MWF	–0.225	0.101	0.26	0.08–0.84
Rectal cancer				
Straight MWF	0.004	0.005	1.05	0.92–1.20
Soluble MWF	0.001	0.003	1.03	0.86–1.23
Synthetic MWF	–0.116	0.072	0.44	0.21–1.16
Liver cancer				
Straight MWF	–0.005	0.009	0.94	0.75–1.18
Soluble MWF	–0.005	0.004	0.86	0.68–1.09
Synthetic MWF	0.054	0.019	1.38	1.10–1.73
Pancreatic cancer				
Straight MWF	–0.017	0.013	0.80	0.58–1.12
Soluble MWF	0.001	0.003	1.03	0.86–1.23
Synthetic MWF	–0.011	0.033	0.99	0.49–1.06
Laryngeal cancer				
Straight MWF	–0.005	0.010	0.94	0.73–1.21
Soluble MWF	–0.004	0.005	0.89	0.71–1.27
Synthetic MWF	–0.013	0.049	0.92	0.52–1.64
Skin cancer				
Straight MWF	0.015	0.009	1.22	0.97–1.53
Soluble MWF	0.013	0.004	1.48	1.17–1.87
Synthetic MWF	–0.181	0.139	0.34	0.07–1.73
Prostatic cancer				
Straight MWF	–0.005	0.005	0.94	0.83–1.06
Soluble MWF	0.004	0.002	1.13	1.00–1.27
Synthetic MWF	0.026	0.021	1.17	0.91–1.50
Brain cancer				
Straight MWF	–0.007	0.012	0.91	0.81–1.49
Soluble MWF	0.004	0.004	1.13	0.89–1.43
Synthetic MWF	–0.057	0.055	0.71	0.73–2.68
Leukemia				
Straight MWF	–0.002	0.007	0.97	0.86–1.22
Soluble MWF	0.002	0.003	1.05	0.89–1.27
Synthetic MWF	–0.028	0.038	0.85	0.75–1.85

^a RR estimated in a separate proportional hazards model for each cancer (including all three MWF exposures, date of hire, race and gender) based on the case-cohort sample.

^b Change in the rate ratio in association with an increase of one standard deviation in cumulative exposure. Straight: 1 SD = 13 mg/m³-years, soluble: 1 SD = 30 mg/m³-years, synthetic: 1 SD = 6 mg/m³-years.

Proportional hazards models

Proportional hazards models with continuous cumulative exposure variables were fit for the nine cancer outcomes with some evidence of exposure-response trends in the Poisson models. For each outcome, cumulative exposures to the three types of metalworking fluids was included in a single model along with potential confounders. At the end of the follow-up, the correlation between the cumulative exposures was –0.11 for synthetic and soluble metalworking fluids, +0.11 for straight and soluble metalworking fluids, and +0.27 for straight

and synthetic metalworking fluids, and therefore there was little evidence for confounding of one fluid type by another.

Statistically significant positive associations were found between synthetic metalworking fluids and liver cancer and between soluble metalworking fluids and skin and prostatic cancer (table 7). Positive associations with wider confidence intervals were observed for straight fluid and skin cancer and for synthetic fluid and both esophageal and prostatic cancer. Significant negative associations were observed for stomach cancer with both straight and synthetic metalworking fluids.

Discussion

As in the previous follow-up, laryngeal and rectal cancer were associated with straight fluid exposure. There was a dose-response trend; the risk for rectal cancer rose to 2.0 in the highest exposure category, and it was statistically significant. There was no association, however, with rectal cancer when the exposure was modeled as a continuous variable. For laryngeal cancer there was a modest dose-response relationship, with a risk of 1.9 in the highest category. The rate ratio was not quite statistically significant, nor was there any association with the continuous exposure variable. When we examined the risk associated with decade of hire, the risk for both of these cancers was higher for those hired before 1970 than for those hired after this date; this finding suggests that the risk had decreased over time. These observations are consistent with the hypothesis that the reduced PAH content, resulting from changes in the refining of the oils, has reduced the risk associated with straight metalworking fluids.

Our results provide further evidence that the risk of esophageal cancer is associated with exposure to all three types of fluids in this cohort. The highest rate ratios were observed for grinding with soluble or synthetic metalworking fluids, for which the adjusted rate ratio of twofold in both the low and high exposure categories was statistically significant. These findings are consistent with the results of the nested case-referent study of esophageal cancer based on the 1984 follow-up (6), although the risk estimates associated with the water-based fluids in grinding operations in that study were somewhat higher.

Stomach cancer has been associated with metalworking fluids in other cohort studies (18–21). Although the rate ratio was not elevated in the original follow-up of this cohort, additional follow-up has provided new evidence. The most striking findings were the elevated SMR of 1.5 in the last 10 years of follow-up and 2.5

among those hired after 1970. This trend was also corroborated by the decade-of-hire term in the models, which showed a clear increase in risk with later hire. Although there were no exposure-response trends observed, these recent elevations deserve continued surveillance.

In this study, an SMR of 4.0 was found for liver cancer among the subjects hired after 1970. The SMR for liver cancer was also elevated in the last 10 years of follow-up among the white males and associated with cumulative exposure to synthetic fluids in the regression models. Upon closer examination, however, we found that inconsistencies between revisions in the ICD coding had made it necessary to classify cancers of the liver (liver and intrahepatic bile duct) and biliary tract (gallbladder, extrahepatic bile duct, and ampulla of Vater) together as a single entity. To examine these findings further, we have conducted two separate nested case-referent studies using only cases confirmed by a cancer registry (22). The results suggest that biliary cancer, rather than liver cancer, is associated with metalworking fluids.

We found a modest dose-response relationship between prostatic cancer and exposure to synthetic fluid, the adjusted rate ratio increasing from 1.0 to 1.2 to 1.3 across increasing categories of exposure. When exposure was treated as a continuous variable, prostatic cancer risk was modestly associated with both soluble and synthetic metalworking fluids. Although there is no other literature to support these associations, these findings raise the possibility that some of the exogenous chemicals contained in these complex mixtures may interact with the male endocrine system, increasing the risk of prostatic cancer. To pursue these findings we are currently studying recent incident cases of prostatic cancer in the cohort.

Skin cancer was significantly associated with exposure to solubles in grinding operations with a significant risk of 2.6. In the proportional hazards models, the rate ratios were elevated in relation to both straight and soluble metalworking fluids and, therefore, suggested that it is the common oil base or related PAH content of the fluids that causes the increased risk. The adjusted rate ratio was 1.2 per increase of 13 mg/m³-years exposure to straight metalworking fluids and 1.5 per increase of 30 mg/m³-years exposure to soluble metalworking fluids. Case reports first linked skin cancer to occupational exposures to metalworking fluids in the 1940s (23). Since that time, several additional case reports and cancer incidence studies have supported the association as well (20, 24, 25). The risk of skin cancer decreased with increasing decade of hire, similar to the pattern described for laryngeal and rectal cancer. The findings for skin cancer provide further evidence that the lower PAH content in severely refined mineral oils

may be reducing risk among the more recently exposed workers.

The strength of this study lies in the statistical power for relatively rare cancers and the quantitative exposure assessment. Each of the modeling approaches used to analyze the exposure-response data has substantial limitations, however. The Poisson regression model relies on categorical exposure variables with arbitrary cut points. The sensitivity of the observed exposure-response trends to the choice of cut points has been well described (26). Proportional hazards models obviate the need for cut points because they can accommodate continuous exposure variables; however, the assumption of linearity (on the log scale) imposes a strong constraint.

We observed distinctive nonlinear patterns of risk in the Poisson regression models for several cancers. While these patterns may be due to chance, they may also reflect other plausible biological hypotheses. For example, we observed a plateau in risk for esophageal cancer, consistent with a saturation effect. Risk of skin cancer, on the other hand, was flat until the highest category, consistent with a threshold effect. We saw patterns consistent with the healthy worker survivor effect for several outcomes. For example, the risks for laryngeal and esophageal cancer increased with low exposure and then fell in the highest category of synthetic fluid exposure. To address the limitations of conventional modeling approaches, nonparametric regression models that describe risk as a smoothed function of exposure offer a more flexible modeling approach (27). Methods that take account of employment status to control for the healthy worker effect, such as G-estimation, can also be applied (28).

The ultimate objective of this research was to evaluate whether exposure to metalworking fluids poses carcinogenic risk for workers in the cohort. The results could be more easily generalized to currently exposed workers if we could identify specific causal agents in these mixtures. When the carcinogenicity of complex mixtures is assessed, however, it is difficult to assign toxicity to a specific agent or class of agents. The difficulty is compounded in this case by the changes that have occurred in the formulation of these fluids over time. For example, gradual changes in the refining methods for petroleum oils used in mineral oils began in the late 1960s. Severely solvent-refined or hydrotreated oils became more widespread in the 1980s after the Occupational Safety and Health Administration required that mildly refined oils be labeled as carcinogens. More recently the Environmental Protection Agency prohibited the addition of nitrosating agents to metalworking fluids and thus reduced the nitrosamine contamination of water-based fluids (29). Even more recently, a trade association publication reported that both sulfur and chlorine compounds have been reduced or eliminated from

current fluids (Independent Lubricant Manufacturers Association, 1993). In addition to these unmeasured changes in exposure, the exposure assessment for the three plants in our study indicate that airborne concentrations of particulates from metalworking fluids declined substantially over time. This decline is consistent with more general industry trends in sampling data, as seen in health hazard evaluations of metalworking fluids conducted by NIOSH between 1967 and 1997 (8). These data indicate a reduction from 1.2 to 0.6 mg/m³ in the mean concentration of total particulate mass over this time period (8).

While the declining risk patterns observed for some cancers are consistent with the reductions in the concentration of aerosolized fluids, other risks appear to be increasing. The decade-of-hire variable was added to the regression models as a surrogate for unmeasured changes in the fluids over time. With post-1970 as the reference, the relative risk declined with decade of hire for several cancers associated with straight fluids: cancers of the larynx, rectum, and skin. Although risk of rectal cancer was 2.0 (95% CI 1.2–3.5) among those with more than 3 mg/m³-years of exposure to straight metalworking fluids, the totality of our findings suggests that the same level of exposure to more severely refined oil may not pose the same degree of risk. On the other hand, risk was highest for cancer of the stomach and liver, as well as for leukemia, among those hired most recently. Case-referent approaches to the study of incident cases of these cancers in this cohort will provide clearer information for assessing the risk of more recent exposures.

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