Metalworking Fluids and Malignant Melanoma in Autoworkers

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Background: Occupational exposure to mineral oil-based metalworking fluids has been consistently linked with skin conditions such as contact dermatitis and squamous cell skin cancer, especially of the scrotum. We examined the incidence of malignant melanoma in a study of autoworkers.

Methods: We followed a cohort of autoworkers from 1985 through 2004 for cancer incidence. Hazard ratios (HRs) were estimated in Cox models for cumulative exposure to total particulate of straight fluid (neat oil), soluble fluid (oil emulsified in water), and synthetic fluid (no oil). Exposure was partitioned into time windows by latency and by calendar periods defined by changes in the content of polycyclic aromatic hydrocarbon in the refined oils. The population was restricted to workers born after 1935. We examined the date-of-birth restriction in a sensitivity analysis.

Results: On the basis of 76 incident cases of malignant melanoma in the cohort of 14,139 white males, the HR was 1.99 (95% confidence interval = 1.00–3.96) for the highest category of straight fluid. Risk was greatest in the most recent time window. Penalized splines suggested a linear exposure-response over the full range of exposure. The change in HR for malignant melanoma per mg/m^3-year of straight fluid increased monotonically from 1.01 to 1.04, when the date-of-birth restriction increased from 1925 to 1945 in 5-year intervals. Results for soluble fluid were more modest. There was no association with synthetic fluid.

Conclusions: Results provide evidence, based on quantitative measures of metalworking fluid, that oil-based fluid, particularly straight mineral oils, are associated with the incidence of malignant melanoma.

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Occupational exposure to metalworking fluids has been consistently linked with squamous cell skin cancer,[1–3] especially cancer of the scrotum.[3–7] Metalworking fluids are widely used in machining operations as coolants and lubricants during cutting or grinding operations. The National Institute of Occupational Safety and Health (NIOSH) estimates that 1.2 million US workers are exposed to metalworking fluid.[8] Occupational exposure can occur from inhalation of metalworking fluid aerosols or dermal exposure from splashes, dipping hands into fluids, or handling parts covered in fluids.[9] Although the composition of metalworking fluid can vary, these complex mixtures are generally grouped into 3 broad classes: straight (neat mineral oils), soluble (oils emulsified in water), and synthetic fluids (no oils). Straight and soluble fluids may contain polycyclic aromatic hydrocarbons (PAH); the PAH content depends on how severely the base oils have been refined. Soluble and synthetic fluids are water-based, and contain biocides that have been added to control microbial contamination, as well as other chemical additives known to be skin irritants.[10]

Reports linking machining fluids and skin cancer first began to appear in the 1950s. In 1984, the International Agency on Cancer Research (IARC)[11] concluded that petroleum-based mineral oils cause skin cancers in humans. NIOSH reached a similar conclusion a few years later.[12] Both the IARC and NIOSH reports were based largely on evidence for squamous cell carcinoma of the skin. Malignant melanoma, a less common but more lethal skin cancer, was not addressed directly in either of these reviews, despite the fact that it comprises most skin cancer mortality. Melanoma originates in the melanocytes, the cells that provide skin pigmentation. The incidence of melanoma has been rising in the US[13] over the past 30 years, and this increase has been explained primarily by increasing ultraviolet radiation from environmental exposure to sunlight or tanning beds.[14] Although the risk of melanoma increases with age, it is one of the few cancers that affect younger adults. It has an excellent 5-year survival rate (91%), even though it is the most dangerous skin cancer—making incidence a more appropriate outcome than mortality for epidemiologic studies.[15]

Only one study to date has estimated the risk of incident melanoma in relation to mineral oils. In a retrospective occupational cohort of 55,000 aerospace workers, a rate ratio of 3.3 (95% confidence interval [CI] = 1.2–9.2) was reported at the highest level of a semiquantitative exposure metric.[16] The only cohort with a fully quantitative exposure assessment for mineral oils and other metalworking fluids is our cohort of

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more than 46,000 Michigan autoworkers.[17] Originally designed as a cancer mortality study, several cancers have been associated with lifetime exposure to oil-based fluids based on follow-up from 1941 to 1985[18,19] and later extended to 1995.[20] In the most recent extended follow-up to 2005—the current study—we were able to add cancer incidence as an outcome. The Michigan Cancer Registry was established in 1985, allowing 20 years of follow-up for cancer incidence. The quantitative exposure assessment of metalworking fluid, our updated vital status, and the new follow-up for incident cancer in this cohort provided an excellent opportunity to explore the association between exposure to metalworking fluid and the risk of melanoma—both mortality and incidence.

METHODS

Study Population

Mortality Cohort

The cohort used for the mortality analysis is a subset of the population of the original study. The original study included all 46,316 hourly workers from 3 Michigan automobile manufacturing plants who worked for at least 3 years and had been hired by 31 December 1981 (Fig. 1). The subset used in this analysis includes white men hired between 1 January 1938 and 31 December 1981. Cohort eligibility was determined from company records that included birth date, sex, and race. Vital status follow-up started on 1 January 1941[17,20] and has recently been extended to 2005.

The cohort for this analysis of melanoma mortality was restricted to white men because there were so few deaths among African-Americans or women (2 African-American men and 3 white women). To reduce bias due to left truncation, we also restricted the original population to the 84% who became eligible after the start of follow-up in 1941, thus including only workers hired after 1 January 1938 to account for the 3 years of employment criteria. Malignant melanoma was identified as the underlying cause of death as coded on the death certificate (International Classification of Disease [ICD] Ninth Edition 172.0–172.9 and 10th Edition C43.0–C43.9: earlier ICD codes updated to ICD9). Unknown race was classified as white race for all analyses.

Incidence Cohort

The incidence cohort includes a subset of the white men in the mortality cohort who were alive on 1 January 1985, based on information from the National Death Index. We did not impose any further hire date restrictions on the incidence cohort; thus as in the mortality cohort, subjects had been hired between 1 January 1938 and 31 December 1981. Living subjects were linked with the Michigan Cancer Registry to obtain cases of incident melanoma diagnosed between 1 January 1985 and 31 December 2004 (Fig. 1).Only first diagnoses of malignant melanoma were included in the analysis (International Classification of Disease for Oncology

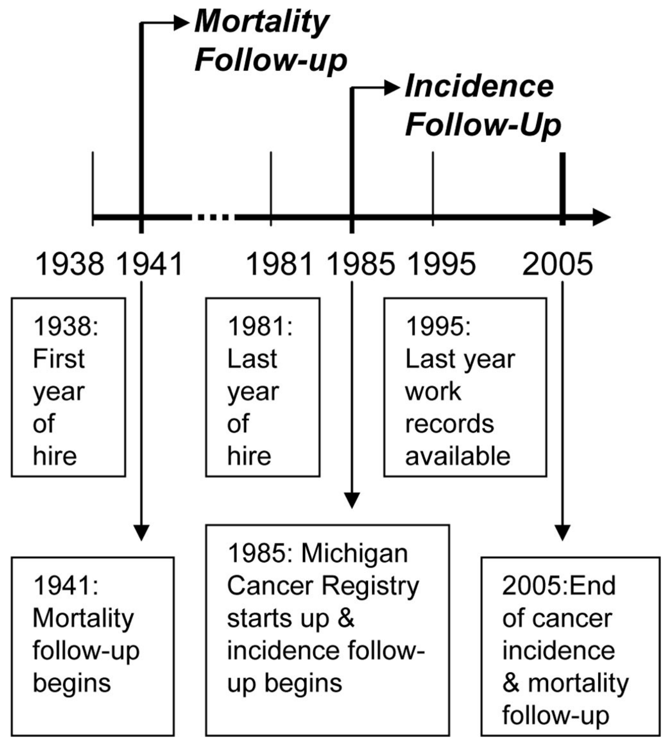

FIGURE 1. Timeline for autoworkers mortality and cancer incidence studies. Follow-up started in 1941 for the mortality cohort and in 1985 for the incidence cohort. Eligibility for the dynamic mortality cohort required a minimum of 3 years employment; therefore, subjects hired in 1938 were enrolled in 1941 and subjects hired in 1981 were enrolled in 1984. All subjects were hired by the start of follow-up for the incidence study in 1985.

Third Edition codes C44.0–C44.9, histologic types 8720–8790). The cohort for melanoma incidence was similarly restricted to white men because there were few incident cases among African-Americans (1 man and 1 woman). Although 6 white women were diagnosed with melanoma during follow-up, all of them were unexposed to straight fluid, preventing meaningful analysis in this group.

By original design, the entire incidence cohort was hired by 1981, which was before the start of Michigan cancer registry (and incidence follow-up) in 1985. Therefore, unlike the approach we took with the mortality cohort, we could not avoid left truncation bias by restricting the incidence cohort to those enrolled after the start of follow-up. In addition, we were concerned about 2 sources of outcome misclassification: (1) unknown prevalent cancers at the start-up of incidence follow-up and (2) missing incident cases diagnosed out-of-state. To reduce both selection and outcome misclassification bias, we therefore restricted the incidence cohort by year of birth. We selected a year of birth considering both the age distribution of melanoma diagnosis among US white men[21] and the length of follow-up in this study. We examined the cohort born after 1 January 1935, so that the oldest would reach 62, the median age of diagnosis, approximately halfway through follow-up. In a sensitivity analysis, we also examined subcohorts born after 1 January 1920, 1925, and so on, up to 1950, in 5-year increments.

Exposure Assessment

Quantitative levels of exposure to each metalworking fluid class (straight, soluble, and synthetic) for plant, department, and job were estimated over time, based on airborne exposure measurements for total particulate matter (mg/m^3) as collected by the company and researchers.[22,23] Estimates of cumulative exposure to each type of fluid were computed at the individual level by combining work histories available up to 1995 with the estimated exposure concentrations. Subjects missing more than 50% of their work histories were excluded (less than 3%). Gaps in work-history information for individual subjects were interpolated by averaging the exposures from the previous and subsequent jobs. Cumulative exposure to each type of fluid was calculated for each subject and lagged by 10 years to allow for a minimum latency period for malignant melanoma.

We also partitioned unlagged cumulative exposure into 2 sets of time windows designed to explore (1) latency and (2) unmeasured constituents of exposure related to calendar period. To examine latency, we constructed exposure windows for the 10–19 years and >20 years prior to risk year. To capture industry-wide changes in PAH content, we constructed time windows of exposure that occurred pre-1970, 1970–1984, and 1985–1995.[24] The 1970s marked a transition to more highly refined base oils with lower PAH content, and regulatory pressure in the mid-1980s caused further changes in the formulation of metalworking fluid to reduce PAH content.[25]

Statistical Analysis

Cox proportional hazard models were fit to estimate the effect of exposure to straight, soluble, and synthetic fluids (10-year lag) on melanoma mortality and melanoma incidence. Models were fit for cumulative exposure to each fluid type (mg/m^3-years) defined as categorical and continuous variables. To maximize statistical efficiency, category cutpoints were based on the distribution of exposure among the cases. Penalized splines were incorporated into the Cox models to assess linearity of exposure-response relationships. We selected degrees of freedom based on minimum Akaike's Information Criterion (AIC) and biologic plausibility.

In all Cox models, age was the time metric. In addition to the exposure variables, calendar year (continuous) was treated as a time-varying covariate to adjust for secular trends in diagnosis of melanoma. Year of hire (continuous) was included to adjust for unmeasured secular trends in exposure, including PAH content, personal protective equipment use, and plant ventilation. Separate terms for each type of fluid were included in all models. Manufacturing plant was considered as a confounder and effect-measure modifier, but due to lack of evidence for either, plant was not included in the final models. The same covariates were used for both the mortality and incidence analyses. R software (version 2.7.2, R Development core team, Vienna, Austria) was used for all analyses.

All research protocols were approved by the Office for the Protection of Human Subjects at the University of California at Berkeley.

RESULTS

Characteristics of both the mortality and incidence cohorts are presented in Table 1. There were 39 deaths due to melanoma in the mortality cohort of 28,120 white, male automobile workers who were followed from 1941 through 2004. In the full incidence cohort, we identified 121 melanoma cases among the 23,075 still alive in 1985. In the 14,139 individuals born after 1935, there were 76 incident cases. On average, the mortal cases were 58 years of age and the incident cases were 59 years of age in the full incidence cohort. In the cohort restricted to those born after 1935, cases were 51 years of age at the date of diagnosis. The mortality cohort was older and had higher median exposures than both incidence cohorts. The restricted incidence cohort was born later, was hired later, and had lower median metalworking fluid exposures.

Mortality

There was a modestly elevated hazard ratio (HR) of 1.34 (95% confidence interval [CI] = 0.61–2.94) for malignant melanoma mortality in the highest category of straight fluid (Table 2). The exposure-response trend plateaued over increasing categories and all confidence intervals were wide. There was no elevated HR for either soluble or synthetic fluid.

Incidence

For the exposure-response results in the full incidence cohort (not presented in tabular form), we were able to define exposure by quartiles rather than by the median. In the highest 2 categories of straight fluid, with cut-offs of 0.97 and 3.69 mg/m^3-years, the HR was 1.45 (95% CI = 0.86–2.45; n = 19 cases) and 1.58 (95% CI = 0.98–2.72; n = 20 cases), respectively. Results for soluble and synthetic fluid were null (data not shown).

When the incidence cohort was restricted to younger workers by year of birth (born after 1935), the HR was 2-fold (1.99 [1.00–3.96]) among those for whom cumulative exposure to straight fluid exceeded 4.62 mg/m^3-years (Table 3). We also observed an increase in HR with increasing exposure to soluble fluid, although the HR of 1.72 in the highest category had wide confidence intervals. Results for synthetic fluid were inconclusive. Penalized spline plots, based on Cox models with a smoothed function of exposure, were approximately linear for

TABLE 1. Tabulations of Study Subjects, Demographic Characteristics, and Exposure to Metalworking Fluids in Study of White Male Autoworkers: Mortality Cohort and Incidence Subcohorts

		Incidence Subcohorts	
	Mortality Cohort	Alive in 1985	Alive in 1985 and Born ≥1935
No. subjects	28,120	23,075	14,139
No. cases	39[a]	121[b]	76[b]
No. person-years	893,444	396,888	271,114
Follow-up period	1941–2004	1985–2004	1985–2004
Demographic characteristics; mean (range)			
Year of birth	1934 (1873–1961)	1940 (1890–1961)	1947 (1935–1961)
Year of hire	1962 (1938–1981)	1965 (1938–1981)	1970 (1951–1981)
Case age (years)	58.3 (38.2–88.2)	59.0 (30.0–92.8)	50.8 (29.5–69.8)
Type of metalworking fluid (mg/m^3-years)[c]; median (IQR)			
Straight	0.72 (2.52)	0.69 (2.36)	0.52 (1.61)
Soluble	4.37 (9.21)	3.91 (8.76)	2.81 (5.41)
Synthetic	0.50 (1.61)	0.40 (1.46)	0.27 (0.81)
Years employed; median (IQR)	18.06 (16.91)	17.50 (16.58)	17.07 (13.18)

[a]Death due to malignant melanoma.
[b]Diagnosis of malignant melanoma.
[c]Lagged 10 years.

straight and soluble fluid up to the 99th percentile (Fig. 2). When cumulative exposures were treated as continuous variables in a single model, the HR was 1.023 (95% CI = 1.012–1.036), 1.015 (95% CI = 0.995–1.035), and 0.995 (95% CI = 0.932–1.063) per mg/m^3-year of exposure to straight, soluble, and synthetic fluids, respectively.

To examine the impact of the specific year of birth used to restrict the incidence cohort we conducted a sensitivity analysis. Subcohorts were defined to include workers born after 1920, after 1925, and so on, up to 1950 by 5-year increments. The same form of the Cox model for malignant melanoma and straight (or soluble) fluid was fit to data from each cohort, adjusted for calendar year as a time-varying covariate and year of hire. The number of cases decreased from 121 in the full incidence cohort, to 100, then 76, and then 40 in the subcohorts born after 1925, 1935, and 1945, respectively. For straight fluid, the HR increased from 1.009 per mg/m^3-year (1.000–1.018) in the full cohort, to 1.014 (1.003–1.025), to 1.023 (1.012–1.036), and up to 1.04 (1.001–1.079) in subcohorts born after 1925, 1935, and 1945, respectively (Fig. 3). In the youngest subcohort born after 1950, there were only 22 cases, and the HR was just less than 1.00 with wide confidence intervals. For soluble fluid, the HRs were weaker. The HR increased from 1.003 (0.991–1.015) in the full cohort, to 1.008 (0.994–1.022), to 1.015 (0.995–1.035), and up to 1.027 (0.998–1.058) in subcohorts born after 1925, 1935, and 1945, respectively (data not shown).

When we used calendar-time windows to explore changes in unmeasured PAH content in straight fluid (unlagged), we found elevated HRs of 1.54 and 1.02 for the most recent and earliest periods, respectively (Table 4). The nonparametric correlation coefficient between these 2 time windows was low (r = 0.10). Results for soluble fluids were inconclusive. In the latency analysis, the HR for straight fluid was the same for both exposure windows. For soluble fluid, the HR was higher for exposure in the 10–19 years prior to diagnosis than for exposure more than 20 years ago. The latency windows were moderately correlated (straight fluid: r = 0.31; soluble fluid: r = 0.26).

DISCUSSION

To our knowledge, this is the first study to report evidence, based on quantitative metrics of exposure to metalworking fluids, that the incidence of malignant melanoma is associated with mineral oil-based fluid. In this study of automobile manufacturing workers, the association was strongest for straight fluids and more modest for soluble fluids, which have lower oil content. There was no association found with water-based synthetic fluids, which contain no oil.

This was primarily a study of incident malignant melanoma, but we also present results for mortality. A modestly elevated relative risk with a wide confidence interval was found for straight fluid, with no elevation for soluble or synthetic fluid. By contrast, in our previous mortality follow-up to 1995, malignant melanoma was associated with both types of oil-based fluids, with a higher rate ratio for soluble than straight fluid.[20] Unlike the previous report, we restricted the current analysis to a homogeneous population of white males. We also excluded subjects hired before 1938 to avoid left truncation (a form of

TABLE 2. Association of Exposure to Metalworking Fluids With Malignant Melanoma Mortality in White Male Autoworkers Hired After 1938

Metalworking Fluid Exposure Type and Amount (mg/m^3-years)	No. Cases	No. Person-years	HR[a] (95% CI)
Straight			
0[b]	14	503,787	1.00
>0–0.97	13	222,550	1.44 (0.68–3.07)
>0.97	12	167,107	1.34 (0.61–2.94)
Test for trend			$P = 0.42$
Soluble			
0[b]	7	281,701	1.00
>0–7.31	16	397,927	0.83 (0.34–1.98)
>7.31	16	213,816	0.91 (0.38–2.22)
Test for trend			$P = 0.94$
Synthetic			
0[b]	31	675,234	1.00
>0	8	218,210	0.59 (0.27–1.30)

[a]Estimated in separate Cox models, each adjusted for year of hire, calendar year, and each of the other fluid types as continuous variable.
[b]Reference category.

TABLE 3. Association of Exposure to Metalworking Fluids With Malignant Melanoma Incidence in White Male Autoworkers Alive in 1985 and Born After 1935

Metalworking Fluid Exposure Type and Amount (mg/m^3-years)	No. Cases	No. Person-years	HR[a] (95% CI)
Straight			
0[b]	29	128,608	1.00
>0–0.21	11	39,489	1.26 (0.62–2.58)
>0.21–0.79	12	44,886	1.07 (0.54–2.10)
>0.79–4.62	12	38,981	1.14 (0.59–2.20)
>4.62	12	19,151	1.99 (1.00–3.96)
Test for trend			$P = 0.15$
Soluble			
0[b]	9	48,020	1.00
>0–1.75	17	82,041	1.02 (0.46–2.26)
>1.75–3.84	17	52,085	1.39 (0.62–3.11)
>3.84–10.41	17	58,058	1.17 (0.53–2.61)
>10.41	16	30,909	1.72 (0.69–4.27)
Test for trend			$P = 0.24$
Synthetic			
0[b]	47	179,228	1.00
>0–0.27	15	46,121	1.41 (0.77–2.59)
>0.27	14	45,765	1.02 (0.56–1.85)
Test for trend			$P = 0.72$

[a]Four separate Cox regression models adjusted for year of hire, calendar year of follow-up, and the other metalworking fluid exposures (as continuous terms).
[b]Reference category.

selection bias that arises when follow-up time is truncated for otherwise eligible individuals, excluding them from entering the cohort[26]). In occupational studies that condition on employment

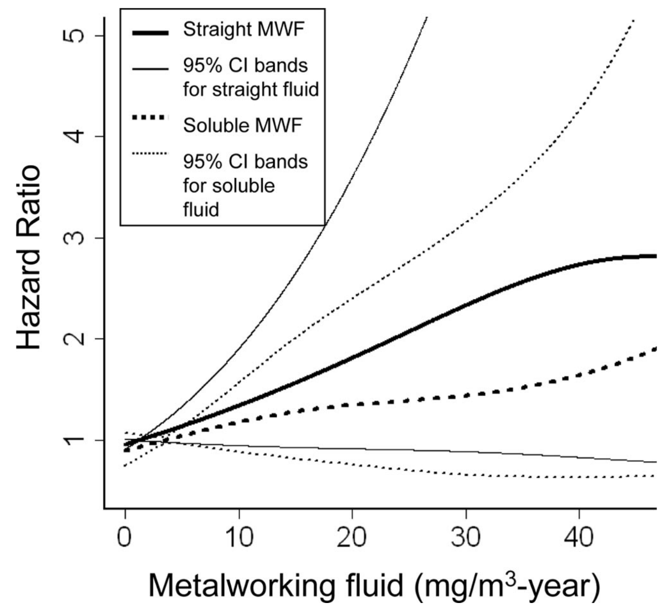

FIGURE 2. Adjusted HR for malignant melanoma incidence as a smoothed function of cumulative exposure to straight and soluble metalworking fluids (MWF) as estimated in 2 Cox regression models using penalized splines, based on a cohort of white male autoworkers restricted by year of birth 1935. Each model included a penalized spline for straight metalworking fluid or soluble fluid (degrees of freedom = 3), and linear terms for the other fluids, calendar-year of follow-up, and year of hire. Graph truncated at 99.5th percentile of straight fluid (40.8 mg/m^3-year) and 99th percentile of soluble fluid (40.6 mg/m^3-year).

status, the inclusion of subjects hired before the start of follow-up can cause such bias if subjects who leave work prior to the start of follow-up are not comparable to those who stay.[27] Another explanation contributing to the inconsistent mortality results is the excellent survival rate for malignant melanoma, which makes mortality a poor outcome by which to study this disease.

Incidence of malignant melanoma provides a more valid measure of the disease as well as more power. Within the context of this original study design, however, we identified 3 potential biases at the outset that were inherent in the design of the incident study. First, there was a similar problem with left truncation whereby otherwise eligible subjects in the mortality cohort had died prior to the start of incidence follow-up in 1985, resulting in potential selection bias. Second, prevalent cancers were not identified and excluded at baseline, leading to misclassification if subjects with malignant melanoma diagnosed prior to 1985 were treated as healthy and at risk for a first diagnosis. Third, potential misclassification might result from the incomplete ascertainment of cases that were diagnosed outside the state of Michigan.

The full incidence cohort was restricted by year of birth to reduce these 3 biases. First, younger cohorts include fewer

FIGURE 3. Adjusted HR and confidence interval bars for malignant melanoma incidence as a function of cumulative exposure to straight metalworking fluid, as estimated in Cox regression analysis based on the full incidence cohort and on subcohorts defined by year of birth. All models adjusted for cumulative exposure to soluble and synthetic fluids, calendar-year of follow-up, and year of hire as continuous terms.

TABLE 4. Association of Time Windows of Cumulative Exposure to Metalworking Fluids With Melanoma Incidence in a Subcohort of White, Male Autoworkers Alive in 1985 and Born After 1935

Exposure Window	HR[a] (95% CI)
Calendar Time Windows of Exposure to Cumulative Exposure to Straight and Soluble Metalworking Fluids[b]	
Straight fluids	
1985–1994	1.54 (1.21–1.95)
1970–1984	0.95 (0.87–1.04)
Pre-1970	1.02 (1.01–1.05)
Soluble fluids	
1985–1994	1.06 (0.96–1.17)
1970–1984	1.02 (0.97–1.07)
Pre-1970	1.00 (0.97–1.04)
Latency Time Windows of Exposure to Cumulative Exposure to Straight and Soluble Metalworking Fluids[c]	
Straight fluids	
10–19 years ago	1.02 (0.96–1.10)
≥20 years ago	1.02 (1.01–1.04)
Soluble fluids	
10–19 years ago	1.05 (0.99–1.10)
≥20 years ago	1.01 (0.98–1.04)

[a]Cumulative exposure was used as a continuous variable and the hazard ratios are expressed as change in HR per 1 mg/m^3-year.
[b]Adjusted for year hired, calendar year, and the other straight metalworking-fluid PAH time windows and soluble metalworking-fluid PAH windows.
[c]Adjusted for year hired, calendar year, and all other metalworking-fluid time windows.

otherwise-eligible subjects who died prior to start of follow-up. There were 5045 (18%) workers from the mortality cohort who would have been eligible for the full incidence cohort had they not died prior to 1985. By contrast, 713 (5%) workers from the mortality cohort born in or after 1935 would have been eligible for the younger cohort had they not died. Second, the younger cohorts also include fewer expected prevalent cases because melanoma incidence increases with age. Third, extrapolating from the state in which deceased subjects lived at the time of their death, members of the younger cohorts were less likely to leave the state during follow-up (947 [27%] deaths occurred out of state in the full incidence cohort vs. 144 [16%] in the cohort restricted by year of birth 1935). We found no suggestion of differential misclassification when we examined the proportion of deaths outside Michigan by quartiles of exposure to cumulative straight fluid. However, we conducted a sensitivity analysis assuming that we missed 15% or 20% of the melanomas and that all missed cases were unexposed (an extreme situation). We found that differential misclassification of disease by incomplete catchment area was unlikely to explain the positive association observed between straight fluid and melanoma incidence (data not shown).

The decreasing bias achieved by restricting the full incidence cohort by year of birth was reflected in the increasing HR for malignant melanoma and straight fluid across a series of increasingly younger cohorts (born after 1920–1945). The downside to restricting the cohort by age was fewer incident cases in the smaller subcohorts; in the youngest cohort considered (born after 1950), there were too few cases for meaningful analysis.

Mineral oils are complex mixtures of aliphatic hydrocarbons, naphthenics, and aromatics. The carcinogenicity of oil-based fluid depends on the treatment of the base oils and the chemicals added to improve their performance as coolants and lubricants. Both straight and soluble fluids contain PAH, chlorinated paraffins, and sulfur. Soluble fluid also contains nitrosamines, long-chain aliphatics, N-phenyl-2-naphthylamine, and formaldehyde. The evidence here points to one of the common constituents of straight and soluble fluid as the causal agent for melanoma. However, the analysis of exposure windows was inconclusive for PAH as the etiologic agent, as increased risks were observed in both the pre-1970 and 1985–1994 calendar time windows. Contrary to our initial hypothesis, the HR of 1.54 in the 1985–1994 calendar time window was higher than the HR of 1.02 in the pre-1970 time window.

There are 3 explanations that might contribute to the elevated HR in the most recent time period, when the PAH content was presumed to be lowest. First, in all other models we lagged cumulative exposure, in part to address the lack of work histories over the last 10 years of the follow-up period. Therefore, the higher HR in the most recent time period might reflect a shorter latency period for malignant melanoma. The inability to distinguish latency from secular changes in the composition of the fluids is a limitation of the study. Second, the exposure metric is more accurate in the most recent time window because we collected our own air samples during that period.[22,23] Therefore, part of the difference in HRs between exposure windows may be because of more attenuation in the older time window. Finally, it is possible that PAH is not the primary causal agent. Although the time windows were constructed as surrogates of PAH exposure, changes in the refining process designed to reduce PAH content must also have caused other changes in the hydrocarbon mix. Although we cannot identify any particular carcinogenic agent that increased, the possibility surely exists.

The exposure metrics developed for this study were based on airborne levels and did not take into account the dermal route of exposure. It is likely that the 2 routes of exposure are positively correlated because jobs with the highest airborne levels are also likely to have the greatest splash potential. Some of the material handling jobs, however, may have low airborne levels but high dermal exposure. If the dermal and inhalation routes are not highly correlated and if the dermal route is an important contributor to the carcinogenic effects, our metrics may introduce nondifferential exposure misclassification that would probably attenuate exposure-response associations.

Dermal exposure to mineral oils is known to cause other skin diseases such as contact dermatitis[28–30] and oil folliculitis.[31] In the more recent epidemiologic literature, water-based fluids have been associated with both irritant and allergic dermatitis.[32] Recent research indicated that chemicals in synthetic fluid have greater dermal permeability, and therefore greater potential to cause dermatitis, compared with chemicals in soluble fluid.[33] The higher irritancy of soluble fluid compared with straight fluids has been attributed to the emulsifying component, either a detergent or surfactant.[34] There is some speculation that the local inflammation associated with irritant dermatitis may increase the risk of melanoma, although recent evidence consistent with our results suggests this is not the case in mice.[35] Therefore, although mineral oils are known to cause skin diseases, these diseases do not appear to be on the causal pathway to melanoma, and may, in fact, be caused by noncarcinogenic components of metalworking fluid.

The only established environmental causes of malignant melanoma are sun exposure and use of tanning beds. We have no information about either of these exposures in this retrospective cohort study. It is unlikely that sun exposure varied by exposure to metalworking fluid, hence causing confounding. Effect measure modification may be plausible if exposure to sun exacerbates the effect of metalworking fluid on risk of melanoma. There is some recent evidence of a biologic interaction between sunlight and PAH exposure.[36,37]

The association reported here between increased risk of incidence of malignant melanoma and higher exposure to airborne metalworking fluid is consistent with 2 biologic mechanisms. One possible mechanism is that malignant melanoma is caused by direct dermal contact, and the inhaled metalworking fluid is serving as a surrogate measure of that exposure. Alternatively, malignant melanoma might be caused by inhalation of metalworking fluid particulate, although we are not aware of any evidence of affinity of PAH metabolites to the skin from systemic exposure. If splashes or other acute dermal exposures are the most relevant exposure route, we would expect to see more melanoma on the hands, forearms, face, and neck of exposed workers. The anatomic distribution, however, was typical of the US white male population. Almost half of the malignant melanomas in this study were on the trunk, one-third on the upper limbs or shoulders, and the remainder distributed across the face, scalp and neck, and lower limbs. Although we cannot differentiate covered shoulders from uncovered forearms and hands, it appears most likely that contaminated clothing caused direct and prolonged contact of oil-based fluid with the trunk and limbs resulting in increased risk of melanoma.

These findings build on the existing body of literature on the association of mineral oils with cancer of the skin. Results provide evidence, based on quantitative measures of metalworking fluid, that oil-based fluids, particularly straight oils, are associated with incident cases of malignant melanoma.

REFERENCES

1. Cruickshank CN, Gourevitch A. Skin cancer of the hand and forearm. *Br J Ind Med*. 1952;9:74–79.
2. Järvholm B, Easton D. Models for skin tumour risks in workers exposed to mineral oils. *Br J Cancer*. 1990;62:1039–1041.
3. Järvholm B, Fast K, Lavenius B, Tomsic P. Exposure to cutting oils and its relation to skin tumors and premalignant skin lesions on the hands and forearms. *Scand J Work Environ Health*. 1985;11:365–369.
4. Cancer from mineral oil. *BMJ*. 1969;4;443.
5. Cruickshank CN, Squire JR. Skin cancer in the engineering industry from the use of mineral oil. *Br J Ind Med*. 1950;7:1–11.
6. Roush GC, Kelly JA, Meigs JW, Flannery JT. Scrotal carcinoma in Connecticut metalworkers: sequel to a study of sinonasal cancer. *Am J Epidemiol*. 1982;116:76–85.
7. Järvholm B, Lavenius B. Mortality and cancer morbidity in workers exposed to cutting fluids. *Arch Environ Health*. 1987;42:361–366.
8. National Institute for Occupational Safety and Health, Prevention CfDCa. Metalworking Fluids, 2009. Available at: http://www.cdc.gov/niosh/topics/metalworking/. Accessed January 4, 2010.
9. Cherrie JW, Semple S. Dermal exposure to metalworking fluids and medium-chain chlorinated paraffin (MCCP). *Ann Occup Hyg*. 2010;54:228–235.
10. Anderson SE, Brown KK, Butterworth LF, et al. Evaluation of irritancy and sensitization potential of metalworking fluid mixtures and components. *J Immunotoxicol*. 2009;6:19–29.
11. International Agency for Research on Cancer. Polynuclear aromatic hydrocarbons, part 2: carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. *IARC Monogr Eval Carcinog Risk Chem Hum*. 1987;33:1–245.

12. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. *What You Need to Know About Occupational Exposure to Metalworking Fluids*. Cincinnati, OH: US Department of Health and Human Services; 1998. Publication No. 98–116.
13. American Cancer Society. *Cancer Facts and Figures 2009* Atlanta, GA:American Cancer Society; 2009.
14. Berwick M, Erdei E, Hay J. Melanoma epidemiology and public health. *Dermatol Clin*. 2009;27:205–214.
15. Surveillance Epidemiology and End Results, National Cancer Institute. Cancer Stat Fact Sheets: Melanoma of the Skin, 2008. Available at: http://seer.cancer.gov/statfacts/html/melan.html. Accessed January 4, 2009.
16. Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, Ritz B. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. *Am J Ind Med*. 2005;48:249–258.
17. Eisen EA, Tolbert PE, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry. Part I: a standardized mortality ratio analysis. *Am J Ind Med*. 1992;22:809–824.
18. Eisen EA, Tolbert PE, Hallock MF, Monson RR, Smith TJ, Woskie SR. Mortality studies of machining fluid exposure in the automobile industry. Part III: a case-control study of larynx cancer. *Am J Ind Med*. 1994;26:185–202.
19. Tolbert PE, Eisen EA, Pothier LJ, Monson RR, Hallock MF, Smith TJ. Mortality studies of machining-fluid exposure in the automobile industry. Part II: risks associated with specific fluid types. *Scand J Work Environ Health*. 1992;18:351–360.
20. Eisen EA, Bardin J, Gore R, Woskie SR, Hallock MF, Monson RR. Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. *Scand J Work Environ Health*. 2001;27:240–249.
21. Surveillance Epidemiology and End Results, National Cancer Institute. Median Age of Cancer Patients at Diagnosis, 2001–2005, 2005. Availableat:http://seer.cancer.gov/csr/1975_2005/results_merged/topic_med_age.pdf. Accessed April 14, 2009.
22. Hallock MF, Smith TJ, Woskie SR, Hammond SK. Estimation of historical exposures to machining fluids in the automotive industry. *Am J Ind Med*. 1994;26:621–634.
23. Woskie SR, Smith TJ, Hallock MF, et al. Size-selective pulmonary dose indices for metal-working fluid aerosols in machining and grinding operations in the automobile manufacturing industry. *Am Ind Hyg Assoc J*. 1994;55:20–29.
24. Friesen MC, Costello S, Eisen EA. Quantitative exposure to metalworking fluids and bladder cancer incidence in an autoworkers cohort. *Am J Epidemiol*. 2009;169:1471–1478.
25. Woskie SR, Virji MA, Hallock M, Smith TJ, Hammond SK. Summary of the findings from the exposure assessments for metalworking fluid mortality and morbidity studies. *Appl Occup Environ Hyg*. 2003;18:855–864.
26. Szklo M. Design and conduct of epidemiologic studies. *Prev Med*. 1987;16:142–149.
27. Applebaum KM, Malloy EJ, Eisen EA. Reducing healthy worker survivor bias by restricting date of hire in a cohort study of Vermont granite workers. *Occup Environ Med*. 2007;64:681–687.
28. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH). *Health Hazard Evaluation Report: Evaluation of Contact Dermatitis Among Machinists at an Automotive Parts Manufacturer, Bristol, VA*. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH. HETA No. 2006-0155-3072.
29. Sprince NL, Palmer JA, Popendorf W, et al. Dermatitis among automobile production machine operators exposed to metal-working fluids. *Am J Ind Med*. 1996;30:421–429.
30. Alomar A, Conde-Salazar L, Romaguera C. Occupational dermatoses from cutting oils. *Contact Dermatitis*. 1985;12:129–138.
31. Kokelj F. Occupational acne. *Clin Dermatol*. 1992;10:213–217.
32. Pryce DW, White J, English JS, Rycroft RJ. Soluble oil dermatitis: a review. *J Soc Occup Med*. 1989;39:93–98.
33. Vijay V, White EM, Kaminski MDJr, Riviere JE, Baynes RE. Dermal permeation of biocides and aromatic chemicals in three generic formulations of metalworking fluids. *J Toxicol Environ Health A*. 2009;72:832–841.
34. Scheuplein RJ, Blank IH. Permeability of the skin. *Physiol Rev*. 1971;51:702–747.
35. Donawho CK, Wolf P, Kripke ML. Enhanced development of murine melanoma in UV-irradiated skin: UV dose response, waveband dependence, and relation to inflammation. *Melanoma Res*. 1994;4:93–100.
36. Nair S, Kekatpure VD, Judson BL, et al. UVR exposure sensitizes keratinocytes to DNA adduct formation. *Cancer Prev Res*. 2009;2:895–902.
37. Toyooka T, Ibuki Y. DNA damage induced by coexposure to PAHs and light. *Environ Toxicol Pharmacol*. 2007;23:256–263.

