Distinguishing the Common Components of Oil- and Water-Based Metalworking Fluids for Assessment of Cancer Incidence Risk in Autoworkers

Melissa C. Friesen, PhD,[1] Sadie Costello, PhD,[1] Sally W. Thurston, PhD,[2] and Ellen A. Eisen, ScD[1]*

Background *Metalworking fluids (MWF)—straight, soluble, and synthetic—have over-lapping components. We derived constituent-based metrics of polycyclic aromatic hydro-carbons (PAHs), water-based MWF, biocides, and nitrosamines to account for this overlap and examined their relations with cancer incidence.*
Methods *An autoworkers cohort of 30,000 was followed for cancer incidence. Hazard ratios were estimated for each cancer and cumulative exposure (lagged) to each new metric; soluble MWF contributed variably to several metrics with weight k = 0–1.*
Results *For most cancer sites, the constituent-based metrics resulted in stronger exposure-disease associations than the MWF classes alone. Laryngeal and bladder cancer were most strongly associated with PAH (k = 0). Protective effects for stomach and lung cancer were observed with biocide, a component that may be a surrogate for endotoxin.*
Conclusions *Our findings provide support and clarification of possible etiologies for previous positive associations and provide support for distinguishing exposure from oil- and water-based MWF in epidemiologic studies.* Am. J. Ind. Med. 54:450–460, 2011. © 2011 Wiley-Liss, Inc.

KEY WORDS: *metalworking fluids; polycyclic aromatic hydrocarbons; cancer incidence; cohort study; endotoxin; biocides; nitrosamines*

INTRODUCTION

Metalworking fluids (MWFs) are widely used as lubri-cants and coolants in a variety of industries, including motor vehicle manufacturing and aerospace. MWFs are broadly grouped into three classes—straight (also referred to as mineral oils), soluble, and synthetic—based on their com-position, but these groups have substantial overlap in their components, as we show in Figure 1 [Mirer, 2003]. Several components are suspected or known carcinogens, including polycyclic aromatic hydrocarbons (PAHs) in straight and soluble MWFs and nitrosamines (formed by the reaction of ethanolamines and N-nitrosating agents) in synthetic and soluble MWFs [IARC, 1984, 1987, 2000].

In most epidemiologic studies of cancer, MWFs have been treated as a single exposure agent, without regard to type, constituents, or concentration. There are two
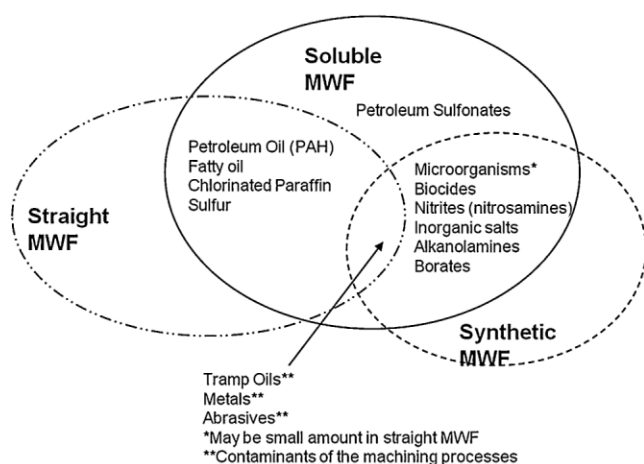
FIGURE 1. Common components of oil- and water-based MWF. Adapted from Mirer [2003].

exceptions. One is a large aerospace cohort study that assessed semi-quantitative exposure categories of mineral oils [Zhao et al., 2005]. The other is the United Autoworkers-General Motors (UAW-GM) cohort, which has differentiated quantitative exposures separately for straight, soluble, and synthetic MWFs [Eisen et al., 1992, 2001; Tolbert et al., 1992]. These three MWF classes have been used as surrogates for the underlying, but unknown or unquantifiable, carcinogenic components. Although the three fluid classes are not statistically collinear [Schroeder et al., 1997; Eisen et al., 2001], the standard approach of examining each adjusted for the others does not address the issue of common components among fluid types.

In his review of the MWF and cancer literature, Savitz [2003] emphasized the need to separate the effects of the fluids' constituents. In this paper, we derive four constituent-based metrics for the UAW-GM autoworkers cohort to account for the common components of the overlapping mixtures. First, we derived metrics to represent the oil-(PAH-containing) and water-based MWF components. Then, we derived metrics to represent the biocides- and nitrosamines-containing water-based MWF. In this study, we examined cancer incidence from 1985 through 2004 in relation to the new constituent-based metrics alongside the original three MWF classes for the subset of the original UAW-GM cohort still alive at the beginning of the cancer incidence follow-up. Our aim was to determine whether the constituent-based metrics provided insight into the possible etiologic components of metalworking fluids; thus, we included only cancer sites previously associated with metalworking fluids. We did not focus on statistical significance at this time, because the strongest associations observed here warrant more detailed analyses, including examining the shape of the dose–response curves and time windows of exposure.

MATERIALS AND METHODS

Study Population

This cohort was originally enumerated to examine cancer mortality outcomes from 1 January 1941 through 31 December 1984, with a subsequent study extending follow-up to 31 December 1994 [Eisen et al., 1992, 2001; Tolbert et al., 1992]. The cohort included all hourly workers (n = 46,316) at three Michigan automotive plants who were employed $\geq$3 years prior to 1985. Identifying information, including race and work history records were abstracted from company records. We linked the sub-cohort of subjects who were alive on 1 January 1985 to the Michigan cancer registry (full incidence cohort) to obtain all cancers diagnosed between 1 January 1985 and 31 December 2004. The diagnoses were classified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). 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

Quantitative exposure metrics for three MWF classes (straight, soluble, and synthetic fluids) were previously developed for the three plants in this study [Hallock et al., 1994; Woskie et al., 1994]. Research industrial hygienists extracted MWF type used in each operation (e.g., machining, grinding, assembly), plant, and time period from company records. The research study team collected exposure measurements in 1986/87. The arithmetic means of these baseline measurements were then modified by scale factors for each time period pre-1986, plant, operation, and fluid type. The scale factors were determined empirically from statistical models of 394 company air measurements collected between 1958 and 1987. An industrial hygienist revisited the plants in the late 1990s to update the scale factors for 1985–1995. The exposure levels were not updated for 1995–2005, because of the expected long latency of the cancers examined here.

Exposures to biocides and nitrosamines were identified from the MWF formulations' material safety data sheets (MSDS). Biocides were added to synthetic and soluble MWFs to control contamination by bacteria and other microorganisms. The prevalence of biocides in the formulations was constant in synthetic fluids from the 1950s, when synthetics were first introduced in these plants. Over 80% of the synthetic MWF-exposed workers were exposed to biocides. Biocides were not a common additive to soluble MWFs in these plants until the late 1970s. Biocides were gradually introduced: 30% of the soluble MWF-exposed workers were exposed to biocide-containing formulations by 1985 and 60% were exposed by 1995.

We defined nitrosamine exposure as the co-presence of ethanolamines and nitrites in the MWF formulations. The prevalence of nitrosamine gradually decreased from 80% of the synthetic-exposed workers in the 1950s to 40% in the mid 1970s. Nitrites were eliminated in the formulations used in these plants by the late 1980s. Nitrites and ethanolamines were not found within the same soluble MWF formulations in these plants. Neither biocides nor ethanolamines were present in straight MWFs.

Exposure Metrics for MWF Components

Cumulative exposure levels for the three MWF classes were calculated for each subject by combining work history information with exposure estimates based on job, time period, operation, and plant. Workers with more than 50% of their work histories missing were excluded (2.4%), but some gaps remained for 20% of the cohort (median 1.9 years missing). We interpolated these gaps by averaging the exposures from the previous and subsequent job.

We derived exposure metrics for the PAH, water-based MWF, biocide, and nitrosamine components (Z_{PAH}, Z_{Water}, Z_{Bio}, and Z_{Nitro}, respectively). For each component, we calculated the cumulative exposure, Z, as the sum of annual exposures each subject accrued from his or her year of hire to study year t for each year of cancer incidence follow-up (1985–2004), with a 10- or 20-year lag applied, using Equations (1)–(4):

$$Z_{PAH,t} = \sum_{i = \text{Yr Hired}}^{t-\text{lag}} \left[X_{Str, \leq 1985} + k \times X_{Sol, \leq 1985} \right] \quad (1)$$

$$Z_{Water,t} = \sum_{i = \text{Yr Hired}}^{t-\text{lag}} \left[X_{Syn} + k \times X_{Sol} \right] \quad (2)$$

$$Z_{Bio,t} = \sum_{i = \text{Yr Hired}}^{t-\text{lag}} \left[X_{Syn} \times E_{Bio} + k \times X_{Sol} \times E_{Bio} \right] \quad (3)$$

$$Z_{Nitro,t} = \sum_{i = \text{Yr Hired}}^{t-\text{lag}} \left[X_{Syn} \times E_{Nitro} \right] \quad (4)$$

where X_{Str}, X_{Sol}, and X_{Syn} were the annual exposure level for straight, soluble, and synthetic MWFs; E_{Bio} and E_{Nit} represented the absence (0) or presence (1) of biocides or nitrosamines in the synthetic or soluble fluid; and k was a weight to account for the relative contribution of soluble MWF to each of the constituent-based metrics (described below).

Soluble MWF contributed to the Z_{PAH}, Z_{Water}, and Z_{Bio} metrics. Z_{PAH} was the sum of the straight and soluble MWFs, weighted by k, prior to 1986 (Eq. (1)). We assumed that there were negligible amounts of PAHs from 1986 onwards, because the oil-containing MWFs were reformulated to use highly treated base oils to minimize PAH exposure [Woskie et al., 2003]. Z_{Water} was the sum of the soluble MWF, weighted by k, and synthetic MWF (Eq. (2)); this metric represented the group of components in common between the two fluid types, rather than a specific constituent. Z_{Bio} was the sum of biocide-containing synthetic and soluble MWFs, weighted by k (Eq. (3)). Z_{Nitro} was the sum of nitrite- and ethanolamine-containing synthetic MWFs (Eq. (4)). These metrics assume that the exposure to the component is proportional to the MWF exposure and does not vary. Since the fraction of the components within the three MWF types is unknown, the units of these new metrics relate to the original MWF class in mg/m^3-years, rather than the specific component. For example, 1 mg/m^3-year synthetic biocide exposure relates to 1 mg/m^3-year synthetic MWF exposure level when biocides are present, rather than the concentration of biocides.

We applied a weight, k, to soluble MWF's contribution to Z_{PAH}, Z_{Water}, and Z_{Bio} since 1 unit of soluble MWF is not likely to be toxicologically equivalent to 1 unit of straight or synthetic MWF. Soluble fluids are likely to have lower percentages of the possible carcinogenic agent(s) because they contain components of both straight and synthetic fluids. For example, soluble MWFs consist of approximately 10% petroleum oils in the bulk mixture. The analytical method for measuring airborne MWF exposure does not capture the water and volatile components of the fluid, which evaporate before the filters are weighed [Woskie et al., 2003]. Thus, the concentration represents the oil component, the non-volatile additives, and process contaminants (e.g., tramp oil, metal particulate), with the proportions varying by fluid type. In the absence of any guiding information on what weights to use, we examined the sensitivity of the exposure-response associations to weights ranging from 0 to 1.

Statistical Analysis

We focused our examinations on cancer sites previously associated with MWFs in reviews of the MWFs and cancer literature [Tolbert, 1997; NIOSH, 1998; Savitz, 2003] or that were linked to MWFs in more recent studies [Bardin et al., 1997; Thurston et al., 2002; Agalliu et al., 2005, 2007; Thompson et al., 2005; Zhao et al., 2005; Malloy et al., 2007; Friesen et al., 2009; Mehta et al., 2010; Costello et al., 2011]. The tumor sites examined were the esophagus, stomach, rectum, pancreas, larynx, lung, skin (malignant melanoma), breast (females), prostate, and bladder. Although there is no prior evidence, colon cancer was also included because colon cancer's excellent survival rate makes incidence a better outcome for study than mortality.

Exposure–disease associations were examined in internal comparisons within the cohort using Cox regression models (Stata/SE v. 9.2, StataCorp LP, College Station, TX). Analysis time was based on age, with covariates included for calendar year (linear), race, sex, and year hired (linear). The

exposure metrics and calendar year were time-varying variables. Follow-up began for all subjects on 1 January 1985 and ended at the minimum of first diagnosis of the cancer of interest, death, or study end date. Confidence intervals (CI) were calculated using a variance estimator robust to possible model misspecifications [Therneau and Grambsch, 2000].

We treated all exposure metrics as continuous variables and estimated the linear relationship between the log hazard ratio (HR) and exposure. Cumulative exposures to straight, soluble, and synthetic MWFs were first examined as separate variables in a single model. The constituent-based metrics were examined in separate models; analyses of Z_{PAH} were adjusted for cumulative synthetic exposure and the analyses of Z_{Water}, Z_{Bio}, and Z_{Nitro} were each adjusted for cumulative straight exposure. For each cancer site and the Z_{PAH}, Z_{Water}, and Z_{Bio} metrics, the exposure-response relations were examined in 11 separate analyses per metric, with the weight k for soluble MWF varying from 0 to 1 in increments of 0.1. We evaluated the contribution of soluble MWF to each component by calculating the standardized slope of the exposure–response relationship based on the Wald statistic (parameter estimate/standard error, β/SE) for each value of k [Kromhout et al., 1997; Friesen et al., 2007]. Wald statistic values ≥ 1.96 and ≤ -1.96 represent associations that were statistically significant at P-value <0.05. We plotted the HR and Wald statistic by k for each cancer site and metric to determine what range of k maximized the Wald statistic.

All of the subjects in this cohort were hired before the start of incidence follow-up, introducing potential survivor bias due to left truncation [Applebaum et al., 2007]. We were also concerned about potential outcome misclassification due to cancers diagnosed before the Michigan cancer registry start date. To address these potential biases, we examined exposure–response models in younger subsets of the cohort restricted by age at start of follow-up, as explained in more detail elsewhere [Costello et al., 2011]. For each cancer, we restricted the analysis to a sub-cohort of all subjects who were ten or more years younger than the median age of diagnosis [based on SEER, 2009] for that cancer site on 1 January 1985, such that the oldest worker reached the median age of each disease half-way through follow-up. For example, the median age of diagnosis for bladder cancer is 73; thus, we restricted the bladder cancer analysis to subjects age 63 years or younger on 1 January 1985.

RESULTS

There were 33,840 automotive workers (13% female, 18% African-American) in the incident cancer cohort (Table I). Race was unspecified for 15% of the cohort. Based on the demographics at the time, we determined that these subjects were most likely to be Caucasian [Eisen et al., 1992]; these subjects were grouped with Caucasians in all analyses.

TABLE I. Characteristics of the Autoworkers in the Original UAW-GM Cohort Still Alive on 1 January 1985 and Included in the Cancer Incidence Follow-Up (1985–2005)

Characteristic	
Size of cohort (%)	
All	33,840 (100)
Males	29,270 (87)
Females	4,570 (13)
Race (%)	
Caucasian	22,516 (67)
African-American	6,113 (18)
Unspecified	5,211 (15)
Vital status 12.31.2004 (%)	
Dead	11,025 (33)
Alive	22,718 (67)
Unknown	97 (0.3)
Year hired, mean (range)	1963 (1920–1981)
Birth year, mean (range)	1937 (1883–1961)

UAW-GM, United autoworkers-General Motors.

Exposure Metrics

Descriptive statistics of the cumulative exposure metrics are reported in Supplementary Table A. The original three MWF metrics were not correlated with each other (Pearson r, all <0.12, not shown). The magnitude of the correlation between the original metrics and the constituent-based metrics varied by weight k; the correlations for selected values of k are shown in Table II. Z_{Bio} and Z_{Nitro} were moderately correlated (for all values of k, r = 0.55–0.58).

Cancer in Relation to MWF

The Wald Statistics and the k that maximized the Wald statistic for the straight, soluble, synthetic, Z_{PAH} and Z_{Water} metrics are reported for all cancer sites for the age-restricted cohorts in Table III. The associations were generally stronger in the age-restricted sub-cohorts for almost all cancers, despite the smaller number of cases. The results below refer to the age-restricted sub-cohorts except when specified. For each of the cancer sites, we mention only the component that had the largest Wald statistic within each cancer site and do not focus on statistical significance. We show plots of HR and the Wald statistic by weight k for the contribution of soluble MWF only for cancers whose strongest association was observed with a constituent-based metric, with a k $>$ 0.

Components of mineral oils, represented by straight MWF and Z_{PAH}, were associated with elevated risks of malignant melanoma and cancers of the larynx, breast, prostate (full incidence cohort), and bladder cancer (Table III). For laryngeal and bladder cancer, the strongest (but not

TABLE II. Pearson Correlation Coefficients Between the Three Original and Constituent-Based Cumulative Metrics for Selected Values of k for the Contribution of Soluble MWF (All Lagged 10 Years)

Constituent-based metric	Pearson correlation coefficients		
	Straight	Soluble	Synthetic
PAH[a]			
When $k = 0.2$	0.95	0.42	0.02
When $k = 0.5$	0.79	0.70	0.03
When $k = 1.0$	0.58	0.88	0.04
Water-based MWF[b]			
When $k = 0.2$	0.09	0.73	0.72
When $k = 0.5$	0.11	0.93	0.40
When $k = 1.0$	0.12	0.98	0.24
Biocides[c]			
When $k = 0.2$	−0.02	0.02	0.54
When $k = 0.5$	−0.02	0.03	0.53
When $k = 1.0$	−0.03	0.03	0.51
Nitrosamines[d]	−0.00	0.00	0.81

MWF, metalworking fluids; PAH, polycyclic aromatic hydrocarbons.
[a]PAH, $Z_{PAH} =$ straight $+ k \times$ soluble.
[b]Water-based MWF, $Z_{Water} =$ synthetic $+ k \times$ soluble.
[c]Biocide, $Z_{Bio} =$ biocide present $\times$ synthetic $+ k \times$ biocide present $\times$ soluble.
[d]Nitrosamines, $Z_{Nitro} =$ (co-presence of ethanolamines and nitrites) $\times$ synthetic.

statistically significant) associations were observed with Z_{PAH} when $k = 0$, suggesting that the association may be limited to straight MWF exposure pre-1986, rather than the unrestricted straight MWF metric. The Wald statistic was maximized for Z_{PAH} when $k = 0.3$ for malignant melanoma, $k = 0.5$ for breast cancer and $k = 1.0$ for prostate cancer (Fig. 2).

Components of water-based MWF, evaluated using the soluble and synthetic MWF metrics and Z_{Water}, were associated with elevated risks of cancers of the esophagus, colon, rectum, larynx, and lung (Table III). For esophageal and pancreas cancers, the strongest associations occurred with synthetic MWF ($k = 0$ in the water-based metric), suggesting that soluble MWF adds nothing to the water-based MWF risk for these cancer sites. Z_{Water} was associated with statistically significant elevated risks for colon, rectal, and lung (full incidence cohort) cancer that was maximized when $k = 0.1$–0.2 (Fig. 3A–C). Z_{Water} was also associated with a statistically significant decreased risk for stomach cancer; the Wald statistic was maximized when $k = 0.1$–0.2 (Fig. 3D).

The associations with Z_{Bio} and Z_{Nitro} are reported only for those cancer sites which showed a potential association with the soluble, synthetic, or Z_{Water} metrics (Table IV). For colon and rectal cancers, the strongest associations were observed with these more specific components. For colon cancer, a statistically significant association was observed

with Z_{Bio} that was similar across all values of k (not shown). For rectal cancer, the statistically significant association with Z_{Nitro} was stronger than for Z_{Water} ($\beta/SE = 2.92$ vs. 2.50, respectively).

The HRs for the three original MWF classes (10 year lag) are shown in Supplementary Table B for both the full incidence cohort and the age restricted sub-cohorts. The HRs for the cancer sites whose strongest association was with the Z_{PAH} and Z_{Water} metrics are shown in Supplementary Table C.

DISCUSSION

This study accounted for the overlapping fractions of oil- and water-based MWFs in the assessment of cancer risk. The results of this cancer incidence study generally support previous findings in this cohort, identify MWF-related risk for colon cancer and a decreased risk of stomach cancer in this cohort for the first time, and provide new insights into possible etiologic agents. For eight of the eleven cancer sites examined, the new constituent-based metrics provided additional information regarding exposure-disease associations beyond that offered by any of the three MWF classes alone, although in some cases the differences were small.

Evaluating associations due to specific components has had limited success in earlier studies of this cohort. For example, metrics for straight and soluble MWFs based on the PAH relevant time period could not be distinguished from the lagged metrics accounting for the long latency period of bladder cancer [Friesen et al., 2009]. Previous metrics for nitrosamines has been limited to ever exposed or duration of exposure [Schroeder et al., 1997; Sullivan et al., 1998; Friesen et al., 2009]. The analyses using the metrics derived here to account for the overlapping components of the MWFs have been more informative. Using the new constituent-based metrics, we show that soluble MWF appears to contribute to the potential carcinogenicity of both the oil- and water-based fractions. The contribution of soluble MWF to risk also appeared to differ for the oil- and water-based metrics. As described below, one unit of soluble MWF was consistently less potent than a unit of either straight or synthetic MWF, with the exception of the biocide metric.

PAH-Containing MWF Metric

The PAH-containing MWF metric provided evidence that both soluble and straight MWF may be associated with the etiology of cancers of the breast and prostate and malignant melanoma, whereas previous analyses have shown strong associations for only one or the other. For these cancers, the strongest associations were observed when each unit of soluble MWF exposure was weighted by $k = 0.3$–0.4, with the exception of prostate cancer where straight and soluble MWF contributed equally. PAHs are the most likely

TABLE III. The Wald Statistic (β/SE) by Cancer Site for the Age-Restricted Sub-Cohorts (Except Where Specified) for the Cumulative Straight, Soluble, Synthetic, PAH-Containing, and Water-Based MWF Metrics

Cancer	Straight β/SE[c]	PAH[a] k[d]	PAH[a] β/SE	Soluble β/SE	Water-based[b] k	Water-based[b] β/SE	Synthetic β/SE	Strongest association	Associations found in previous studies of this cohort
Esophagus	−0.84	0.1	−0.85	−0.15	0.0	1.31	1.31	Synthetic	Synthetic/mortality Sullivan et al. [1998], Eisen et al. [2001], Eisen et al. [1994], Tolbert et al. [1992]
Stomach	0.12	1.0	−1.33	−1.69	0.2	−2.00	−1.78	Water-based (protective)	No association (mortality: Eisen et al. [2001], incidence: Zeka et al. [2004])
Colon	−1.92	0.0	1.43	1.81	0.2	2.72	1.70	Water-based	No association/mortality Eisen et al. [2001]
Rectum	0.83	0.7	1.35	0.75	0.1	2.50	2.31	Water-based	Straight/mortality Eisen et al. [2001]; Malloy et al. [2007]
Pancreas	−0.77	0.2	−0.76	−0.08	0.0	−1.44	−1.78	Synthetic (protective)	Synthetic/mortality Bardin et al. [1998]
Larynx	1.63	0.0	1.82	−1.89	1.0	1.11	1.31	Straight <1986[f]	Straight/mortality Eisen et al. [2001], straight/incidence Eisen et al. [1994], Zeka et al. [2004]
Lung[e]	−0.15	1.0	0.53	0.65	0.1	1.98	1.86	Water-based	No association/mortality Eisen et al. [2001], synthetic (protective/mortality Schroeder et al. [1997]
Malignant melanoma	4.09	0.3	6.12	1.40	1.0	1.00	0.10	PAH	Straight, soluble/incidence Costello et al. [2011], soluble, straight/mortality Eisen et al. [2001]
Breast (females)	0.97	0.3	2.59	0.43	0.1	1.34	1.01	PAH	Soluble/mortality Thompson et al. [2005]
Prostate[e]	1.90	1.0	3.53	2.90	0.4	3.29	1.24	PAH	Straight and soluble/incidence Agalliu et al. [2005, 2007], soluble/mortality Thurston et al. [2002], Eisen et al. [2001]
Bladder	1.33	0.0	1.38	−0.25	0.2	1.02	−1.06	Straight <1986[f]	Straight/incidence Friesen et al. [2009]

β/SE, parameter estimate/standard error (Wald statistic).
[a]PAH, Z_{PAH} = straight + k × soluble.
[b]Water-based MWF, Z_{Water} = synthetic + k × soluble.
[c]When β/SE > 1.96 and <−1.96, the association is statistically significant at P-value <0.05.
[d]Value of k corresponding to highest absolute value of β/SE. When k = 0, soluble MWF did not contribute to the association.
[e]Full Cohort.
[f]For the PAH metric, we restricted the straight and soluble MWF to the pre-1986 time period by assigning 0 annual exposure for straight and soluble MWF for the years 1986 onwards. Thus, when k = 0 for the PAH metric, the PAH metric is not equivalent to the straight MWF, which has no time window restriction.
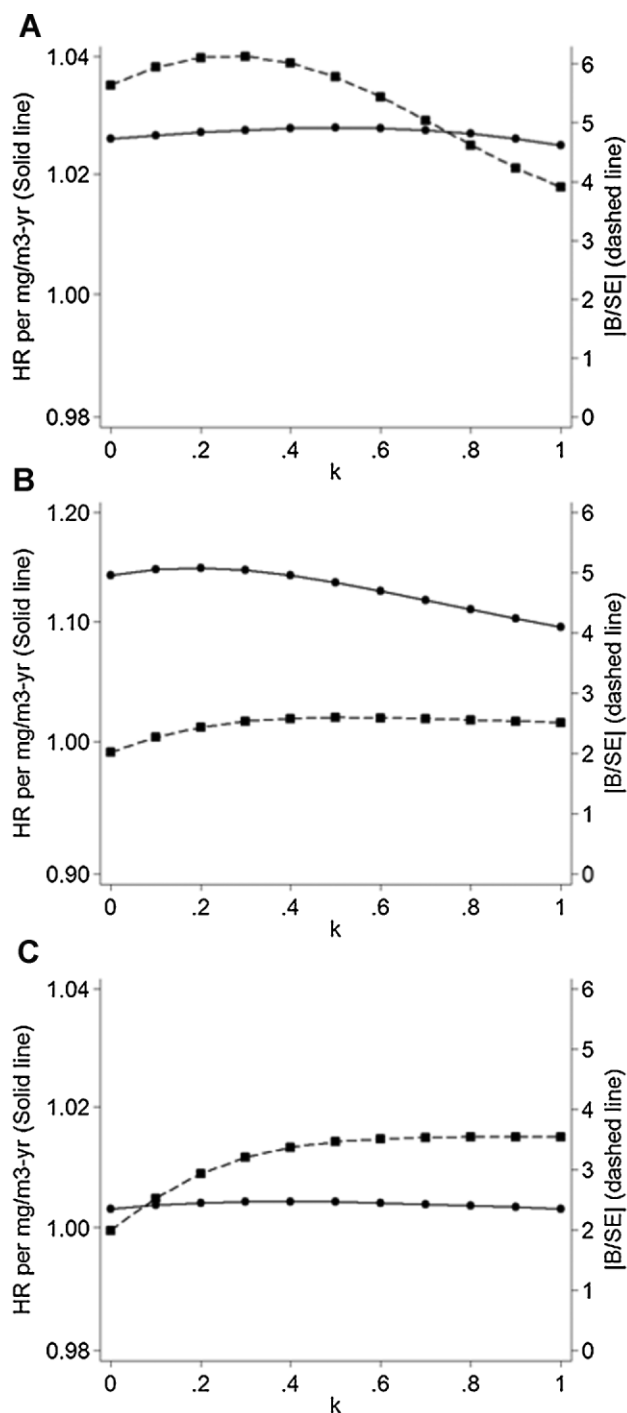
FIGURE 2. The hazard ratios (HR, solid line) and the Wald statistics (β/SE, dashed line, absolute value of slope/standard error) for selected cancer incident sites and the cumulative polycyclic aromatic hydrocarbon metric (straight + k × soluble, 10 year lag) for different values of k. **A**: Malignant melanoma (age at study entry ≤49 years); **B**: Breast (age ≤51 years); **C**: Prostate (full incident cohort).

etiologic agents in the oil-based MWFs; however, the differences between the role of soluble MWF in the PAH component for prostate cancer versus malignant melanoma and breast cancer point to potentially different causal components, although the differences may also result from not examining the relevant time windows (discussed below).

Water-Based MWF Metrics

The water-based MWF metric provided evidence that both soluble and synthetic MWFs may be associated with increased risks of colon, rectal, and lung cancers and with decreased stomach cancer risk in this cohort. Of these cancers, stronger associations were observed with biocides and colon cancer and with nitrosamines and rectal cancers than with the broader water-based MWF metric. For cancers more strongly associated with the water-based metric, the strongest associations were observed when each unit of soluble MWF exposure was weighted by k = 0.1–0.3. For the biocide metric, the associations were similar across all values of k; however, the biocide metrics were highly correlated with each other for all values of k (all Pearson r > 0.95). The potential protective role of endotoxin, found in water-based MWF, for stomach and lung cancer is discussed below. These analyses cannot determine the specific causative agents within the water-based MWF, but do point to the importance of distinguishing between MWF types and their components in epidemiologic analyses.

MWF and Cancer Risk

Our findings were, for the most part, consistent with associations reported in previous incidence and mortality studies of this cohort (Table III). We focus our discussion on the new and the potentially inconsistent findings for stomach, lung, rectal, and colon cancer.

Stomach Cancer

A new finding in this cohort was that water-based MWF might be associated with a statistically significant decreased stomach cancer risk. The association was strongest with the water-based metric, which may represent a protective effect that has been previously observed with endotoxin exposure [Lundin and Checkoway, 2009; Wernli et al., 2006]. Endotoxin exposure can result from the bacteria and other microorganisms can contaminate the water-based fluids. Based on the low k value for soluble MWF in the water-based metric (k = 0.2), our results suggest that 1 mg/m³ exposure synthetic MWF is more protective than 1 mg/m³ soluble MWF. These differences in potencies may represent differences in the formulations and microbial growth rates for the two fluid types. Endotoxin levels have been found to vary by MWF and process characteristics, such as tramp oil contamination,
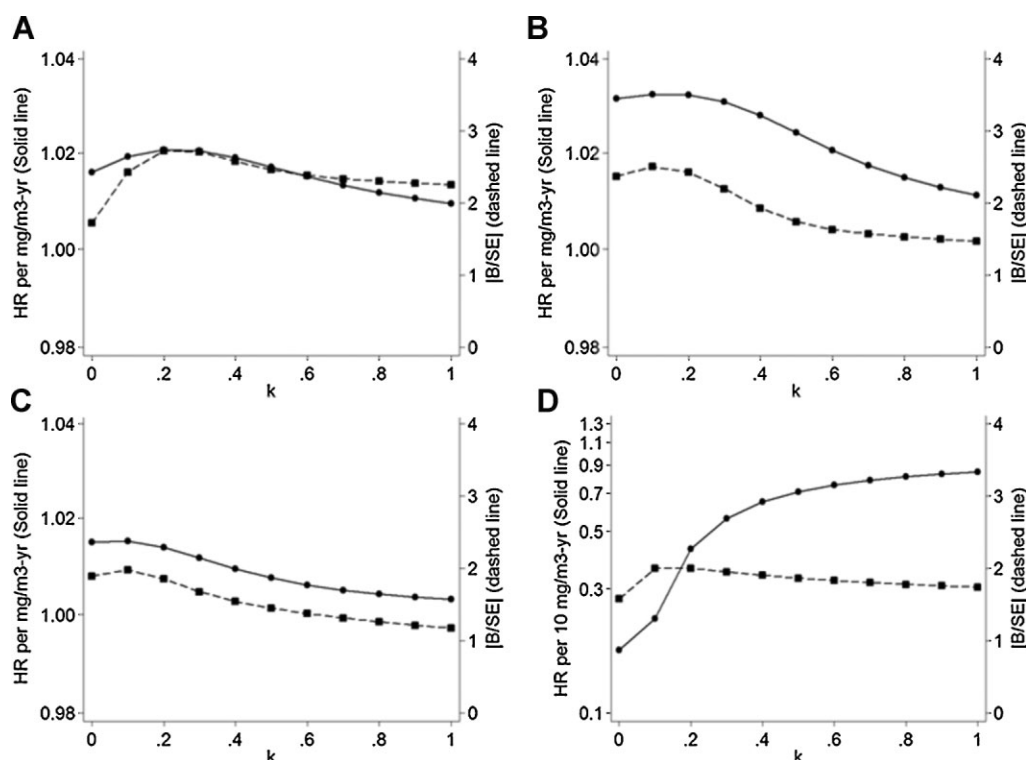
FIGURE 3. The hazard ratios (HR, solid line) and the Wald statistics (β/SE, dashed line, absolute value of slope/standard error) for selected cancer incident sites and the cumulative water-based metalworking fluid metric (synthetic $+$ k $\times$ soluble, 10 year lag) for different values of k in age-restricted sub-cohorts. **A**: Colon (age $\leq$58 years); **B**: Rectum (age $\leq$58 years); **C**: Lung (age $\leq$61 years); **D**: Stomach (age $\leq$61 years).

MWF pH and temperature, and type of MWF [Thorne et al., 1996; Park et al., 2001].

We found no evidence, however, that oil-based MWFs contributed to an increased risk of stomach cancer in the current or previous analyses of this cohort [Eisen et al., 2001; Zeka et al., 2004]. Other studies have reported elevated SMRs for stomach cancer in cohorts of machinists and other occupations with MWF exposure [Park et al., 1988; Silverstein et al., 1988; Park and Mirer, 1996; Kazerouni et al., 2000]. An aerospace cohort also reported a positive association between semi-quantitative measures of mineral oil exposure and combined stomach and esophageal cancer

TABLE IV. Hazards Ratios for the Cumulative Biocide and Nitrosamine Metrics for Cancers Associated With Water-Based MWF (per mg/m^3-year, 10 year lag) in Age-Restricted Sub-Cohorts of the Cancer Incidence Cohort

Cancer	k[c]	Biocide[a] HR (95% CI)	β/SE	Nitrosamine[b] HR (95% CI)	β/SE
Esophagus	0.0	0.04 (0.00, 2.50)	-1.53	0.26 (0.03, 2.20)	1.09
Stomach	1.0	0.77 (0.55, 1.08)	-1.54	0.27 (0.07, 1.13)	-1.79
Colon	0.2	1.04 (1.02, 1.07)	3.05	1.02 (1.00, 1.04)	2.12
Rectum	1.0	1.02 (0.97, 1.08)	0.74	1.04 (1.01, 1.07)	2.92
Pancreas	1.0	0.91 (0.76, 1.09)	-1.07	0.85 (0.54, 1.33)	-0.86
Lung	1.0	0.96 (0.90, 1.03)	-1.17	0.98 (0.95, 1.02)	-0.94

CI, confidence interval; β/SE, parameter estimate/standard error (Wald statistic); HR, hazard ratio; MWF, metalworking fluids.
[a]Biocide, $Z_{Bio} =$ biocide present $\times$ synthetic $+$ k $\times$ biocide present $\times$ soluble.
[b]Nitrosamine, $Z_{Nitro} =$ (co-presence of ethanolamines and nitrites) $\times$ synthetic.
[c]Value of k corresponding to highest absolute value of β/SE.

incidence [Zhao et al., 2005]. The reasons for these inconsistencies between the UAW-GM autoworkers cohort and other studies with mineral oil exposures are not clear, but suggest that there may be important differences in the formulation of different types of MWFs, processes, or work practices that have not yet been identified. Alternatively, co-exposures in other studies may be contributing to their findings of increased stomach cancer risk. The Michigan autoworkers cohort was designed to avoid including workers with other potential toxic or carcinogenic exposures [Eisen et al., 1992].

Lung Cancer

For lung cancer, the picture continues to be complex. Here we found a positive association with the water-based MWF metric as well as a weak, but possibly inverse association with the new biocide metric. In the current and previous analyses of this cohort, the relationship between lung cancer mortality and straight MWF has been consistently null. In a previous analysis of mortality in this cohort, synthetic MWF exposure was associated with a strong inverse association [Schroeder et al., 1997] that was potentially attributed to endotoxin contamination [Lundin and Checkoway, 2009]. In a recent update, the protective effect of synthetic MWF was diminished with extended mortality follow-up; however, effect modification was observed with biocide exposure [Mehta et al., 2010], which is consistent with the weak inverse association observed here with biocides. The decreased risk of both stomach and lung cancer with water-based MWFs seen here in automotive workers provides additional support for the protective role of endotoxin observed previously in cotton textile and agricultural workers [Lundin and Checkoway, 2009].

Rectal and Colon Cancer

Our results support the existing evidence of a MWF-rectal cancer association [Eisen et al., 2001; Savitz, 2003; Malloy et al., 2007] and indicate that the increased risk may not be isolated to straight MWF. In this study, the strongest association was with the water-based metric. Previous analyses of rectal cancer mortality in this cohort found a stronger association with straight MWF than with the other fluid classes; however, elevated risks were also observed in the highest categories of soluble MWF (RR 1.9, 95% CI: 0.6–6.4) and synthetic MWF (RR 1.5, 95% CI: 0.4–6.3) [Malloy et al., 2007]. The causative agents are not known. The three fluid types have few components in common, with the exception of tramp oils, abrasive material, and metal particulate that can contaminate grinding and machining processes.

The increased colon cancer risks with water-based MWF were similar to the risks observed with rectal cancer, but the colon cancer risks had not been observed previously. Earlier

mortality studies of this cohort found no associations with colon cancer mortality and MWF exposure [Eisen et al., 2001] and the aerospace cohort study only examined colon and rectal cancer incidence combined in relation to mineral oil exposure; water-based MWF were not examined [Zhao et al., 2005].

Limitations

The constituent-based metrics have several limitations. First, we assumed that the etiologic components were correlated with the MWF exposure intensity in both the constituent-based and original MWF metrics. In reality, the composition of the fluids varied within and between MWFs over time [Woskie et al., 2003], but there has been insufficient information to quantify those differences in this or other studies. Our assumptions may be particularly weak for the "nitrosamine" metric, which captured solely the co-presence of ethanolamines and nitrites in the fluid based on data from its MSDS and did not capture other circumstances where nitrosamines were present or could be formed. As a result, our findings may be attenuated by exposure misclassification. Second, the assumption of a log-linear relationship between the HR and the exposure metrics may attenuate our findings, as several previous reports have found nonlinear results, with a plateau [Friesen et al., 2009] or decline in risk at the highest exposure levels [Malloy et al., 2007]. Third, the latency period assumed in these analyses may not be the relevant time windows of exposure for all cancers examined here, especially for the hormonally driven cancers such as breast and prostate cancer [Agalliu et al., 2005]. Lastly, we assumed that the most relevant metric would maximize the absolute value of the Wald statistic, as previously assumed by Friesen et al. [2007] and Kromhout et al. [1997]. For many cancer sites, the Wald statistics were similar for the original MWF classes and the constituent-based metrics. Thus, our findings are exploratory and provide insight into possible etiologic agents, but are not sufficient to make conclusive statements about the causative agents.

The large size of this cohort, combined with the use of cancer incidence rather than mortality, and quantitative exposure metrics for each MWF class, provides substantial power to examine MWF-disease associations. To reduce problems related to multiple comparisons, we have focused attention of the constituent-based metrics on outcomes previously shown to be associated with MWFs to provide an indirect validation of the utility of these constituent-based metrics. To reduce potential attenuation due to both survivor bias and undetected prevalent cancers, we applied an age restriction based on the median age at diagnosis for the cohort [Costello et al., 2011]. With the exception of prostate cancer, it was these secondary analyses in the younger sub-cohorts that revealed the associations more clearly. Confounding by personal behaviors, such as smoking and alcohol

consumption, remains a possible explanation for some of the associations. However, previous studies have found that these lifestyle confounders typically impact risk estimates by only 10–20% in occupational cohort studies [Kriebel et al., 2004; Blair et al., 2007]. We focused this study on the utility of the constituent-based metrics; however, further analyses are needed to evaluate the potential effect modification of race or gender and to evaluate the shape of the exposure-response curves for the specific cancer sites.

CONCLUSIONS

The objective of these analyses was to reduce exposure misclassification by capturing the common elements of the different MWF classes. In doing so, we report two new findings—water-based MWFs increased colon cancer risk and decreased stomach cancer risk—and provide support and clarification of possible etiologies for previous positive associations. The results of this study provide additional support for distinguishing exposure from oil- and water-based MWFs in epidemiologic studies. In particular, epidemiologic studies should develop metrics that account for the common components of MWFs and that account for the relative contribution of soluble MWF to each component-based metric. To determine the true causal components with any greater clarity, we would need to isolate and quantify the specific components of the MWF mixtures over time.

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