**Metalworking Fluids and Cancer Mortality from 1941 to 2015 in a US Autoworker Cohort**

**Abstract**

This report describes the extended follow-up (1941-2015) of a cohort of 38,649 automobile manufacturing workers with potential exposure to metalworking fluids (MWF). The outcomes of interest were mortality from cancers of the esophagus, stomach, intestine, rectum, bladder, liver, pancreas, larynx, lung, skin, prostate, brain, and female breast, as well as leukemia. This report includes 5,472 deaths from cancer, more than 10 times the numbers of deaths in our last summary report published 20 years ago. Standardized mortality ratios were computed for the entire study period. Adjusted hazard ratios (HR) were estimated in Cox proportional hazard models with categorical variables for cumulative exposure to each type of MWF. Exposure response patterns are consistent with prior mortality reports from this cohort. We found increased risk of skin and breast cancer with straight fluid. For the first time, we found elevated risk of stomach cancer mortality. Overall, many of the exposure-response results did not suggest an association with MWF. These results may be attenuated due to using mortality as an outcome and healthy worker survivor effect. Mortality is a poor proxy for cancer diagnosis for treatable cancers, and may not be the optimal outcome measure in etiological studies. Although the HR presented here handle bias from the healthy worker hire effect and left truncation, they do not handle bias from healthy worker survivor effect which likely results in underestimates of the health impacts of MWF. Although this updated summary helps shine the light on the risk of cancer from MWF, targeted future analyses will help clarify associations.

**Introduction**

Metalworking fluids (MWFs) are complex mixtures of oils and chemical additives widely used to cool and lubricate metal machining operations. MWFs are aerosolized when sprayed, generating airborne particulate matter (PM) at concentrations up to two orders of magnitude higher than allowable by the U.S. ambient air pollution standards.1 Classified as straight (mineral oils), soluble (oils emulsified in water), or synthetic (without oils), MWFs continue to pose a potential hazard to millions of workers in automobile manufacturing and other metal machining jobs related to electronics manufacturing, new technologies, and alternative energy. Some MWF constituents are carcinogenic in animals, including N-nitrosamines2 found in water-based synthetic fluids and some polyaromatic hydrocarbons (PAHs)3 found in the oil-based fluids. Efforts to reduce exposures to these potentially carcinogenic MWFs have been ongoing for decades. Removal of PAHs from MWFs began in the 1950s when large industrial users began shifting to more refined oils and U.S. Environmental Protection Agency (EPA) regulations during the 1980s were directed at reducing nitrosamine exposures4. In 1998, the National Institute of Occupational Safety and Health (NIOSH) released a Criteria Document with a Recommended Exposure Limit (REL) for occupational exposure to MWFs of 0.5 mg/m3 for total PM (TPM) and 0.4 for respirable PM.5

Several reviews of the evidence on MWFs and cancer followed the NIOSH Criteria Document.4,6–9 Calvert et al summarized the evidence basis of the NIOSH report on cancer risk among workers exposed to MWF, concluding that there was substantial evidence for increased risk at several sites, including larynx, rectum, pancreas, skin, scrotum, and bladder, associated with at least some MWFs.4 Savitz concluded that evidence was strongest for associations between cancers of the larynx and rectum in relation to the oil-based fluids, and Mirer noted positive results for stomach cancer in older studies and internal UAW analyses without quantitative exposure information, as well as for lung, liver, pancreatic, and laryngeal cancer, as well as leukemia.6–8 In all reviews, attention was focused on air and skin exposure to the oil-based MWFs in use before the oils became more highly refined in the mid-1970s. Most of the quantitative evidence cited in all the reviews came from the ongoing United Autoworkers-General Motors (UAW-GM) cohort study.10

The UAW-GM study was jointly funded by labor and management as a cancer mortality study with an extensive exposure assessment component, motivated by worker concerns about digestive and respiratory cancers in relation to metalworking fluid (MWF) exposure. Standardized Mortality ratios (SMRs) have been reported twice for this cohort, the first based on the original end of follow-up in 1985 and the second based on extended follow-up to 1995.10,11 SMRs for the two outcomes of original interest, stomach and lung cancer, were not elevated in either report. A series of results from exposure-response analyses have also been reported based on the extensive historical exposure assessment for straight, soluble and synthetic MWFs. Results based on Cox proportional hazard models for digestive and respiratory cancer mortality in relation to MWF exposures have been largely null.11–15However, results based on cancer incidence in this cohort have been more mixed. There is modest evidence that exposure to straight oil-based MWF increases the risk of laryngeal,14,16 bladder,17 melanoma,18 breast,19 and colon20 cancer incidence. Limited evidence was also reported for increased risk of cervical cancer21 and breast cancer in younger women19.

In 2003, the UAW petitioned the Occupational Safety and Health Administration (OSHA) for a temporary standard for MWF with an exposure limit of 0.5 mg/m3 total PM. The petition was based on the evidence for nonmalignant respiratory health effects of MWFs, asthma and hypersensitivity pneumonitis, rather than for cancer. OSHA ultimately denied the petition.6 The UAW’s decision to petition for regulatory efforts based on nonmalignant health effects suggests that in 2003, there was insufficient evidence that MWFs are carcinogenic at concentrations found in the workplace. Yet, a recent risk assessment for cancer and MWFs based entirely on published results from the UAW-GM cohort study, concluded that substantial risk exists at 0.1mg/m3respirable PM, one quarter of the current NIOSH REL (and the GM internal limit).9 The cancer sites contributing the most attributable cases were larynx, esophagus, brain, breast and cervix.

In summary, the literature to date suggests that oil- and water-based MWFs may indeed cause increased risk of several specific cancers, although none of the evidence is conclusive. In this context, we report results from an extended vital status follow-up, from 1941 to 2015 – twenty years beyond the last reported mortality follow-up of the UAW-GM cohort. Results are presented as SMRs as well as adjusted hazard ratios, estimated in Cox models based on quantitative exposure estimates for each fluid type.

**Methods**

Details regarding the UAW-GM cohort mortality study have been described extensively in previous publications.10,11,22–24 Here we describe the methods in brief.

**Study Population**: The present study of the UAW-GM cohort includes all hourly workers identified through company records at three automobile manufacturing plants in Michigan who worked for at least three years and were hired between Jan 1 1938 and Dec 31 1981. After excluding the 4% of subjects missing more than half of their employment record, 38 549 were included in this analysis. Follow-up for mortality now extends from 1941 to 2015, 21 years longer than the previous update11 and includes more than 1.5 million person-years. Over the 74 years of follow-up, 53% of the study population has died. Subjects were considered lost to follow-up upon reaching the oldest observed age at death (106 years). By this definition, less than 0.5% of the participants were lost to follow-up.

**Covariates**: Subject characteristics, including year of birth, sex (male or female), race (white, Black, or unknown), and work-site (Plant 1, 2, or 3) were obtained from company records. Subjects with missing race data (22%) were assumed to be white based on available demographics.10 In a sensitivity analysis, subjects at Plant 1 with missing race were assumed to be Black.

**Exposure:** Exposure assessment has been described in previous publications.23,25,26 Quantitative exposure to MWF was based on several hundred personal and area size-selective samples for particulate matter (mg/m3) collected across jobs and departments by the research team, in combination with historical industrial hygiene records. Scale factors were applied to estimate historical levels of exposure relative to baseline measurements made by the research industrial hygienists (mid 1980s).23 These scale factors reflect the dramatic decreases in exposure concentrations over the second half of the 20th century, particularly in the early 1970s with the passage of the Occupational Safety and Health Act (OSHA).

MWF exposures were assigned to individuals according to job and department and calendar time, weighted by work time. Missing exposure data were interpolated for those missing less than half of their work history. The exposure-response models considered exposure to straight, soluble, and synthetic metalworking fluids as measured as cumulative exposure to total PM (TPM). The work history records were initially collected in 1985 and extended up to 1995. Exposure-response models for this analysis are based on cumulative MWF exposure (mg/m3-years) lagged by 21 years; lagging accounts for disease latency and is necessitated by the available data.

**Outcome:** Data on vital status and cause of death were obtained through the Social Security Administration, the National Death Index, plant records, death certificates, and state mortality files (ref Eisen 1992). Causes of death were selected for exposure-outcome modeling based on the previous report on cancer mortality in this cohort (2001). (See Appendix 1 for ICD codes.)

**Analytic methods:** Person-years were accumulated from three years after hire until death, end of follow-up, or the maximum observed age at death. Causes and dates of death were obtained from company records, the Social Security Administration, state mortality files, and the National Death Index. Underlying causes of death were coded conforming to the International Classification of Diseases, revisions 9 and 10 (ICD-9 and ICD-10, respectively). Where possible, these ICD codes were mapped to cause of death descriptions according to the keys used in the Lifetable Analysis System (LTAS).27–29

Standardized mortality ratios were computed for cancer outcomes, as well as several chronic diseases and external causes of death. Reference rates for deaths prior to 2010 were extracted from LTAS; reference rates for deaths in or after 2010 were obtained through the CDC Underlying Cause of Death database.30,31

We estimated associations between cumulative exposure to straight, soluble, and synthetic MWF and each cancer outcome as adjusted hazard ratios in Cox proportional hazards models with age as the timescale. In addition to age, all models included year of hire, race, sex, and plant, as well as time-varying calendar year and the other MWF exposures to adjust for potential confounding. Cumulative exposures to the three metalworking fluids were categorized with a pre-determined reference group. Zero exposure was the reference group for straight and synthetic fluid. For soluble exposures, the upper bound of the reference group was set to 0.05 mg/m3 to avoid extremely small numbers of cancer cases. This cut-off is approximately 1% of what cumulative exposure would be after 10 years at the NIOSH REL. To maximize statistical efficiency, we used the distribution of exposure to each fluid type among the cases of each cancer to determine the cut points for the exposed categories.

**Results**

A summary of the study population characteristics is presented in Table 1. Over half of this predominantly white and male cohort had died by the end of follow up. While at work, approximately half of the workers had been exposed to straight fluids, a third to synthetics, and a majority (82%) were exposed to soluble fluids. Although the only a quarter of the workforce was employed at plant 1, most of the Black cohort members worked at this urban plant (data not shown).

Standardized mortality ratios: SMRs are presented for specific cancers and other major causes of death in Table 2. The SMR for all causes of death combined was lower than 1.0. This was driven by the low SMR for all heart disease (SMR = 0.75) as well as nonmalignant respiratory diseases (SMR = 0.84) and cerebrovascular disease (SMR = 0.83). The SMR for all cancers was also lower than 1.0. Although the majority of the SMRs for specific cancers were below 1.0, the SMR was elevated for some digestive and respiratory cancers including esophageal (SMR = 1.06), stomach (SMR = 1.10), pancreatic (SMR = 1.05), laryngeal (SMR = 1.17) and lung (SMR = 1.07) cancers.

Proportional hazards models**:** While our primary focus was on cancers of the digestive and respiratory system: esophageal, stomach, rectal cancers, lung and larynx, we also present models for pancreas, prostate, breast and skin cancers as well as leukemia, based on previously elevated SMRs**.** The adjusted hazard ratios (HRs) for these cancers and cumulative exposure to straight, soluble, and synthetic MWFs are presented in Figures 1, 2, and 3, respectively. (See Tables A2.1-A2.3 in Appendix 2.)

The estimated exposure-response pattern for cumulative straight fluid was non-monotonic for all cancers except skin and breast cancer. In the highest exposure categories, skin cancer rose to a HR of 1.32 (95% CI 0.67, 2.58) and breast cancer to 2.13 (95% CI 1.04, 4.39). Notably, the HR for stomach cancer was also highest in the highest category and rose to 1.86 (95% CI 1.17, 2.97). The HR were mostly elevated for esophageal, liver, pancreatic, and prostate cancer in response to straight fluid exposure, but generally below the null for lung, colon, rectal, bladder, and brain cancers and leukemia.

The exposure-response patterns for exposure to cumulative soluble fluid were non-monotonic for all cancers. The HR for rectal cancer rose to 2.18 (95% CI 1.07, 4.48) in the middle category. The HRs were mostly elevated for esophageal, bladder, skin, and brain cancers in relation to soluble fluid, but generally below the null for laryngeal, lung, stomach, colon, liver, pancreatic, prostate, and breast cancers.

The exposure-response patters for exposure to cumulative synthetic fluid were only monotonic for esophageal, rectal, and prostate cancers and leukemia. The HR in the highest category for esophageal cancer was 1.39 (95% CI 0.84, 2.30), rectal was 1.64 (0.79, 3.41), prostate was 1.30 (95% CI 0.89, 1.89) and leukemia was 1.37 (95% CI 0.86, 2.19). In addition, the HRs were generally elevated in response to cumulative synthetic fluid for laryngeal, lung, and brain cancers and below the null for colon, pancreatic, bladder, skin, and breast cancers.

Results did not change when we classified people with unknown race as either white or Black in Plant 1 (data not shown).

**Discussion**

This updated report includes almost 5,500 deaths from cancer, more than 10 times the number of cancer deaths in our last summary report published almost 20 years ago. Most of the patterns reported here are consistent with that previous summary, as well as with results of cancer specific papers published from this cohort during the interim. For example, the increased risk of skin and female breast cancers associated with increasing straight fluid exposure. Interestingly, for the first time in this cohort, we report an increase in stomach cancer mortality with increasing straight fluid exposure, which was the original hypothesis motivating this cohort study. Although there are some suggestions of increased risk that we will explore in targeted analyses, many exposure-response results do not suggest any association. It is certainly possible that MWFs simply do not predict many of these cause-specific cancers; however, there are also limitations which can lead to attenuation, including using mortality as a surrogate outcome for cancer diagnosis, a lack of data on potential confounders, such as smoking, and the healthy worker survivor effect.

Mortality may be a reasonable proxy for diagnosis for cancers with a poor 5-year survival rate, for example, lung or pancreatic cancer. However, many cancers have become more highly treatable over the 75 year study period. Thus, cancer mortality is a measure that is bound to 1) be less sensitive for cancers with better 5-year survival and 2) disproportionately include cancers that were diagnosed at later stages, were more aggressive, or were treated less effectively. Given the known social and racial disparities in medical care32 and cancer survival33, we assume that the cause-specific cancer deaths identified in this analysis are a non-random subset of all occurrences of cancer in this cohort. Mortality outcomes can also obfuscate a time-window or lagged analysis since date of death can be years after the first date of diagnosis. For these reasons, incidence is generally preferred to mortality as an outcome measure for cancer etiology studies.

Mortality does, however, offer some advantages as an outcome over incidence. The Michigan Cancer Registry started in 1985, and linkage would identify cancer incidence in the cohort, limited to diagnoses in the state of Michigan that occurred after the initiation of the registry. This data structure can lead to increased potential for misclassified outcomes and survivor bias due to left truncation. Thus, although mortality may not be the best outcome for studying the increased risk of cancer from an occupational exposure, it does allow us to leverage the full cohort of almost 40,000 workers followed for up to 75 years.

There are known risk factors for many of the cancers presented in this paper which were not measured in this cohort, for example, smoking for stomach cancer, sun exposure for skin cancer, diet with rectal cancer, and parity for breast cancer. Clearly, not all risk factors need to be adjusted for; however, those that are also associated with exposure need to be. Given the lack of association between most of the cancers and metalworking fluid, we considered whether we were missing information on a ubiquitous risk factor that might be inversely associated with increased metalworking fluid exposure. That is, is there a risk factor for mortality from several cancers that is more likely to occur among the unexposed? In this cohort, assembly workers were classified as unexposed to each specific type of MWF and comprise a large portion of the reference group for all fluid types, but especially soluble fluid. If the less skilled assembly workers were more likely to smoke or have less favorable socio-economic standing compared to the highly exposed and more skilled machinists, our results could be globally attenuated due to confounding. Unfortunately, we are not able to test this theory since we do not have smoking or socio-economic data for members of our cohort.

Our final area of concern is attenuation from the healthy worker effect.34 We present both SMRs, using an external reference group, and Cox models, using an internal reference group. The SMR is known to suffer from the healthy worker *hire* effect because people who are hired into physically demanding jobs are healthier at baseline than the general population. Thus, SMRs can mask a harmful effect of occupational exposures. Cox models avoid this well-known bias by using unexposed workers as the reference group. Even internal analyses can be attenuated from the healthy worker *survivor* effect, however, because workers who are the least susceptible to the ill effects of an occupational exposure stay at work the longest and accrue the most exposure. Of note, we avoided a portion of healthy worker survivor effect, known as left truncation bias35, by only including workers who were hired after the start of follow up in 1941. However, eligibility into the study required three years of work prior to entering follow up. We expect that those who survived the first 3 years of work may be different from those that left earlier and therefore note that there is built-in left truncation bias by study design. Other than restricting to those hired after the start of follow up, we did not address the healthy worker survivor effect in this manuscript.

We report elevations in skin, breast and stomach cancer mortality from long term occupational exposure to MWF. Several excess cancer risks previously reported in this cohort have become closer to the null with extended follow-up. Before concluding that MWF exposures are not associated with other cancers, possible attenuation by the healthy worker survivor effect should be excluded. If leaving work is a time dependent confounder of future exposure and the outcome and caused by previous exposure, then the Cox model is not adequate.36 Despite the extensive exposure assessment, large sample size and long follow-up, causal inference methods such as g-methods37 may also be necessary to avoid underestimation.   1. EPA. National Ambient Air Quality Standards (NAAQS). *Federal Register* (2008). Available at: https://19january2017snapshot.epa.gov/criteria-air-pollutants\_.html.

2. IARC. *N-nitrosodiethanolamine. In ‘“IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Some N-Nitroso Compounds.”’* (1978).

3. IARC. Monograph 34: polynuclear aromatic compounds, Part3, industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. Genevia: World Health Organization, 1984.

4. Calvert, G. M., Ward, E., Schnorr, T. M. & Fine, L. J. to Metalworking Fluids : A Systematic Review. *Am. J. Ind. Med.* **292**, 282–292 (1998).

5. NIOSH. *Criteria for a Recommended Standard: Occupational Exposure to metalworking Fluids*. 98–102 (1998).

6. Mirer, F. E. New evidence on the health hazards and control of metalworking fluids since completion of the osha advisory committee report. *Am. J. Ind. Med.* **53**, 792–801 (2010).

7. Mirer, F. Updated epidemiology of workers exposed to metalworking fluids provides sufficient evidence for carcinogenicity. *Appl Occup Env. Hyg* **18**, 902–912 (2003).

8. Savitz, D. A. Epidemiologic evidence on the carcinogenicity of metalworking fluids. *Appl. Occup. Environ. Hyg.* **18**, 913–920 (2003).

9. Park, R. M. Risk assessment for metalworking fluids and cancer outcomes. *Am. J. Ind. Med.* **61**, 198–203 (2018).

10. Eisen, E. A., Tolbert, P. E., Monson, R. R. & Smith, T. J. Mortality studies of machining fluid exposure in the automobile industry I: A standardized mortality ratio analysis. *Am. J. Ind. Med.* **22**, (1992).

11. Eisen, E. A. *et al.* Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. *Scand. J. Work. Environ. Heal.* **27**, (2001).

12. Mehta, A. J. *et al.* Reduced lung cancer mortality and exposure to synthetic fluids and biocide in the auto manufacturing industry. *Scand. J. Work. Environ. Heal.* **36**, (2010).

13. Garcia, E. *et al.* Lung cancer mortality and exposure to synthetic metalworking fluid and biocides: Controlling for the healthy worker survivor effect. *Occup. Environ. Med.* (2018). doi:10.1136/oemed-2017-104812

14. Zeka, A., Eisen, E. A., Kriebel, D., Gore, R. & Wegman, D. H. Risk of upper aerodigestive tract cancers in a case-cohort study of autoworkers exposed to metalworking fluids. *Occup. Environ. Med.* **61**, (2004).

15. Malloy, E. J., Miller, K. L. & Eisen, E. A. Rectal cancer and exposure to metalworking fluids in the automobile manufacturing industry. *Occup. Environ. Med.* **64**, (2007).

16. Eisen, E. A. *et al.* Mortality studies of machining fluid exposure in the automobile industry III: A case‐control study of larynx cancer. *Am. J. Ind. Med.* **26**, (1994).

17. Friesen, M. C., Costello, S. & Eisen, E. A. Quantitative exposure to metalworking fluids and bladder cancer incidence in a cohort of autoworkers. *Am. J. Epidemiol.* **169**, (2009).

18. Costello, S., Friesen, M. C., Christiani, D. C. & Eisen, E. A. Metalworking fluids and malignant melanoma in autoworkers. *Epidemiology* **22**, (2011).

19. Garcia, E., Bradshaw, P. T. & Eisen, E. A. Breast Cancer Incidence and Exposure to Metalworking Fluid in a Cohort of Female Autoworkers. *Am. J. Epidemiol.* **187**, (2018).

20. Izano, M. A., Sofrygin, O. A., Picciotto, S., Bradshaw, P. T. & Eisen, E. A. Metalworking Fluids and Colon Cancer Risk. *Environ. Epidemiol.* **3**, e035 (2019).

21. Betenia, N., Costello, S. & Eisen, E. A. Risk of cervical cancer among female autoworkers exposed to metalworking fluids. *Scand. J. Work. Environ. Heal.* **38**, (2012).

22. Tolbert, P. E. *et al.* Mortality studies of machining-fluid exposure in the automobile industry: II. Risks associated with specific fluid types. *Scand. J. Work. Environ. Heal.* **18**, (1992).

23. Hallock, M. F., Smith, T. J., Woskie, S. R. & Hammond, S. K. Estimation of historical exposures to machining fluids in the automotive industry. *Am J Ind Med* **26**, 621–634 (1994).

24. Woskie, S. R. *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* **55**, 20–29 (1994).

25. Woskie, S. R. *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.* **55**, (1994).

26. Woskie, S. R., Virji, M. A., Hallock, M., Smith, T. J. & Hammond, S. K. Summary of the findings from the exposure assessments for metalworking fluid mortality and morbidity studies. *Appl Occup Env. Hyg* **18**, 855–864 (2003).

27. NIOSH. Lifetable Analysis System (LTAS) Manual 3.0.0. (2014).

28. Schubauer-Berigan, M. K. *et al.* Update of the NIOSH life table analysis system: A person-years analysis program for the windows computing environment. *Am. J. Ind. Med.* **54**, 915–924 (2011).

29. Waxweiler, R. *et al.* A modified life-table analysis system for cohort studies. *JOM* **25**, 115–24 (1983).

30. CDC. Underlying Cause of Death 1999-2017. (2014). Available at: https://wonder.cdc.gov/wonder/help/ucd.html.

31. Friede, A., Reid, J. A. & Ory, H. W. CDC WONDER: A comprehensive on-line public health information system of the Centers for Disease Control and Prevention. *Am. J. Public Health* **83**, 1289–1294 (1993).

32. Nelson, A. Unequal treatment: Confronting Racial and Ethnic Disparities in Health Care. *J. Natl. Med. Assoc.* **94**, 666–9 (2002).

33. Bradley, C. J., Given, C. W. & Roberts, C. Disparities in cancer diagnosis and survival. *Cancer* **91**, 178–188 (2001).

34. Eisen, E., Picciotto, S. & Robins, J. Healthy Worker Effect. *Encyclopedia of Environmetrics* 1–7 (2012). doi:10.1002/9780470057339.vad033

35. Applebaum, K. M., Malloy, E. J. & Eisen, E. A. Left truncation, susceptibility, and bias in occupational cohort studies. *Epidemiology* **In Press**, (2011).

36. Robins, J. & Hernan, M. Estimation of causal effects of time-varying exposures. in *Advances in Longitudinal Data Analysis* (eds. Fitzmaurice, G., Davidian, M., Verbeke, G. & Molenberghs, G.) 553–9 (Chapman & Hall, 2009).

37. Naimi, A. I., Cole, S. R. & Kennedy, E. H. An introduction to g methods. *Int. J. Epidemiol.* **46**, 756–762 (2017).