A. COVER PAGE

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hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: Examine the exposure-response between straight, soluble, and synthetic MWF, as well as biocides and nitrosamines, and updated incidence of selected cancers, allowing for latency, adjusted for confounding by cigarette smoking, and stratified by sex.

1a. Examine female breast cancer, in relation to age windows of exposure defined to capture temporal hormonal variation in susceptibility, accounting for tumor hormone receptor status.

Aim 2: Apply the parametric g-formula to estimate the exposure-response adjusted for the Healthy Worker Survivor Effect (HWSE), and assess a series of binary MWF exposure cut-points (mg/m3) as potential exposure limits to identify the most sensitive of cancer endpoints for men and for women.

Aim 3: Address HWSE bias in the left truncated cohort by using data on subjects who died prior to start of incidence follow-up to compute left censoring weights, based on probability of being alive.

Aim 4: Apply a novel risk assessment framework, based on the g-formula, to identify the concentration of each type of MWF needed to achieve a total cancer incidence risk of less than 1/1000 workers exposed for a working life.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

B.2 (Accomplishments .pdf)

1. Major activities

We extended vital status follow-up to 2015 and linked with the Michigan Cancer Registry to update incident cancers diagnosed over the past 30 years.

We conducted exposure-response analysis for each of 14 cancers in relation to each of the three types of metalworking fluids (straight, soluble and synthetic). Cox proportional hazards models for cancer incidence were fit to estimate adjusted hazard ratios (HR) with categorical variables for cumulative exposure to each type of MWF (straight, soluble, synthetic). We lagged exposure by 21 years because follow-up extends 21 years beyond the end of work history records and also to account for cancer latency. Cox models were also fit to explore the potential for healthy worker survivor effect (HWSE) bias due to the more susceptible workers leaving work by estimating the following pathway-specific adjusted HRs: (1) cumulative exposure predicts leaving work; and (2) leaving work predicts cancer incidence.

We applied g-methods (parametric G-formula or TMLE) to analyze exposure-response for specific cancers when the pathway analysis indicated HWSE was operating. We developed an approach to reduce bias due to the healthy worker survivor effect exacerbated by the left truncated cohort available for cancer incidence follow-up that starts decades after mortality follow-up. The novel approach was based on applying censoring weights to each subject in the cohort. Finally, we developed a novel method for risk assessment based on g-methods and present an example for total MWF and lung cancer.

2. Specific Objectives

Aim 1: Examine the exposure-response between straight, soluble, and synthetic MWF, as well as biocides and nitrosamines, and updated incidence of selected cancers, allowing for latency, adjusted for confounding by cigarette smoking, and stratified by sex.

Aim 2: Apply the parametric g-formula to estimate the exposure-response adjusted for the Healthy Worker Survivor Effect (HWSE), and assess a series of binary MWF exposure cut-points (mg/m^3) as potential exposure limits to identify the most sensitive of cancer endpoints for men and for women.

Aim 3: Address HWSE bias in the left truncated cohort by using data on subjects who died prior to start of incidence follow-up to compute left censoring weights, based on probability of being alive.

Aim 4: Apply a novel risk assessment framework, based on the g-formula, to identify the concentration of each type of MWF needed to achieve a total cancer incidence risk of less than 1/1000 workers exposed for a working life.

3. Significant results, major findings, developments, or conclusions

Aim 1: Examine the exposure-response between straight, soluble, and synthetic MWF, as well as biocides and nitrosamines, and updated incidence of selected cancers, allowing for latency, adjusted for confounding by cigarette smoking, and stratified by sex.

We examined 14 cancers, including colon, rectal, pancreatic, esophageal, stomach, laryngeal, lung and bronchial, breast, prostate, kidney and renal pelvic, and bladder; melanoma, leukemia, and non-Hodgkin lymphoma, in the United Auto Workers-General Motors (UAW-GM) cohort exposed to MWFs (Colbeth et al 2022). The cohort included 39,132 workers followed for cancer incidence from 1973 to 2015.

There were 7,809 incident cancer cases of interest. Exposure–response patterns were consistent with prior reports on this cohort. We found significantly increased incidence of stomach and kidney cancer, and also bladder cancer, with higher levels of straight fluid exposure and increased rectal and esophageal cancer with increasing synthetic fluid exposure. Non-Hodgkin lymphoma was associated with soluble MWF. Results for each of the 14 cancers with the three types of MWF are presented graphically in our 2022 paper (Colbeth et al). These results are described in more detail below.

Straight fluid exposure
We first considered all-cancers-combined as the outcome of interest (n= 7,809 first primary incident cancer cases diagnosed at any site) during follow-up. In the highest category of cumulative exposure to straight MWF, the adjusted hazard ratio (HR) was 1.13 (95% CI: 1.06-1.21). The estimated exposure-response for cumulative straight fluid exhibited a monotonic pattern for colon and rectal cancers. In the highest cumulative straight fluid exposure category, stomach cancer rose to a HR of 1.54 (1.01-2.35), kidney and renal pelvic cancer to 1.59 (1.09-2.31), and bladder cancer to 1.28 (0.99-1.65). Modestly elevated HRs were found for rectal, esophageal and breast cancers and melanoma in response to straight fluid exposure. Results were generally below or closely surrounding the null for colon, pancreatic, prostate, and lung and bronchial cancers, leukemia, and non-Hodgkin lymphoma.

Soluble fluid exposure
In association with all cancers combined, exposure to cumulative soluble MWFs exhibited a slight dose-response gradient with a significantly elevated HR in the highest exposure category (HR: 1.14; 95% CI: 1.05-1.24). Melanoma and non-Hodgkin lymphoma HRs increased with increasing exposure; by contrast, a negative dose-response gradient was found for kidney and renal pelvic cancers. All other cancers demonstrate non-monotonic exposure-response patterns. A significantly elevated HR was found in the highest exposure category for prostate cancer (HR: 1.28; 1.10-1.49).

Non-Hodgkin lymphoma HRs were significantly elevated in categories with the greatest exposures, with the highest exposure category rising to 1.70 (1.13-2.54).

Synthetic exposure
The association of all-cancer combined with cumulative exposure to synthetic fluids hovered close to the null. A negative exposure-response gradient with increasing cumulative synthetic MWF exposure was found for breast cancer, kidney and renal pelvic cancer, and melanoma; positive monotonic exposure-response patterns were found for rectal cancer, lung and bronchial cancer, esophageal, and for non-Hodgkin lymphoma excluding the referent group. The HR in the highest exposure category was 1.52 (1.01-2.29) for rectal cancer, 1.47 (0.90-2.40) for esophageal cancer, and 1.16 (1.00-1.35) for prostate cancer. HRs were close to or below the null for the other cancers at any level of exposure.

Pathway Analysis
Results for the assessment of condition (2), cancer incidence and leaving work, were not entirely consistent across the fourteen incident cancer outcomes examined (Figure 4). Based on the main model adjusted for covariates, we found that the hazard of lung and bronchial (HR: 1.91; 95% CI: 1.47-2.48) and pancreatic (HR: 2.02; 95% CI: 0.94-4.35) cancers among those who left work were approximately twofold the hazard of those who were still at work at the time of cancer incidence. The association between leaving work and cancer incidence was slightly elevated for rectal cancer and non-Hodgkin lymphoma. Cancers with results below the null were kidney and renal pelvic, melanoma, stomach, and leukemia and statistical significance below the null was found for prostate, and bladder cancers.

With respect to condition (3), prior exposure in association with probability of leaving work, MWF exposure was associated with leaving work in at least one category of MWF exposure. Those in the second quartile of cumulative exposure to oil-based straight fluid were at a slightly higher risk for leaving work. In contrast, all MWF exposure levels for cumulative soluble and synthetic fluids had a statistically significant lower risk of leaving work compared with those with the lowest level of the respective fluid exposure.

Pathway-specific analyses suggested that HWSE bias may impact only the cancers with the poorest 5-year survival rates, reducing concern about attenuation for most of the other cancers. Our results provide further evidence for associations between MWF exposure and several types of cancer. Targeted analyses applying g-methods are needed to account for HWSE for those rapidly fatal cancers.

1a. Examine female breast cancer, in relation to age windows of exposure defined to capture temporal hormonal variation in susceptibility, accounting for tumor hormone receptor status.

In the prospective cohort of 4,503 female autoworkers, we examined MWF exposure and its association with incident breast cancer based on follow-up from 1985 to 2013 (Garcia et al 2017). Exposure to straight MWF, but neither soluble nor synthetic, was

positively associated with breast cancer. This was evident in the analyses using sub-cohorts restricted by year of hire. When restricted to subjects hired 1959 or later, the hazard ratio (HR) for straight MWF exposure was elevated in both models with continuous and categorical exposure variables. Results became stronger when we examined the sub-cohort restricted to subjects hired 1969 or later. Restriction to the later sub-cohort was intended to reduce attenuation due to left truncation, and may explain the stronger results observed in these analyses.

Though power was adequate for a pooled analysis of pre and post-menopausal cases, when we restricted to cases presumed to be premenopausal, the exposed categories were sparse. Results however, were modestly suggestive of an increased risk associated with higher synthetic MWF exposure. Because of a lack of menopausal status data, age at diagnosis was instead used to define premenopausal breast cancer cases. A discernibly positive exposure-response, however, was found for all four case definitions examined. More pronounced associations were observed when we used a younger age cut point to define cases. Case definitions with these younger cut points were more specific for premenopausal breast cancer, which, when the outcome is rare, is more important than sensitivity and will reduce bias. Among this younger subset we observed the strongest results for an association between synthetic MWF exposure and incident breast cancer. Our interpretation of these analyses, however, was constrained by the small number of cases.

We included cancer cases identified in the SEER registry (1973-1985) in our all cancer incidence paper described above. There were few additional breast cancer cases in the SEER registry and the results for breast cancer and straight MWF (Colbeth et al 2022) were similar to these earlier results (Garcia et al 2017).

Aim 2: Apply the parametric g-formula to estimate the exposure-response adjusted for the Healthy Worker Survivor Effect (HWSE), and assess a series of binary MWF exposure cut-points (mg/m^3) as potential exposure limits to identify the most sensitive of cancer endpoints for men and for women.

Based on the pathway analysis, leaving work was a time varying confounder on the causal pathway from past MWF exposure to **lung cancer**. Cox models cannot handle such a data structure so we applied the parametric g-formula to account for HWSE. Results provided evidence that synthetic MWF exposure causes lung cancer (Garcia et al 2018). We compared the risk of lung cancer under no intervention with what would have occurred under hypothetical interventions reducing exposure to zero (ie, a ban) separately for two exposures: synthetic fluids and biocides. We also specified an intervention on synthetic MWF and biocides simultaneously to estimate joint effects. Under a synthetic MWF ban, we observed decreased lung cancer mortality risk at age 86, RR=0.96 (0.91–1.01), but when we also intervened to ban biocides, the RR increased to 1.03 (0.95–1.11). A biocide-only ban increased lung cancer mortality (RR=1.07 (1.00–1.16)), with slightly larger RR in younger ages. One possible explanation for this finding involves the endotoxin growing in the water-based fluid sumps; endotoxins have been found to be protective for lung and stomach cancer in

other occupational settings, such as cotton textile mills. Perhaps biocides are a marker for endotoxin exposure.

Just prior to receiving funding for this grant, we examined the exposure-response between straight, soluble and synthetic MWF and **colon cancer** incidence based on the existing cancer incidence data (follow-up through 2009). We applied longitudinal targeted minimum loss-based estimation (TMLE) to estimate the difference in the cumulative incidence of colon cancer comparing counterfactual outcomes if always exposed above to always exposed below an exposure cutoff while at work (Izano et al 2019). TMLE is a nonparametric G-method designed to control for time-varying confounding affected by prior exposure, a key feature of the healthy worker survivor effect in occupational cohorts.

Cohort members alive on January 1, 1985 (N=33,063), the year in which the Michigan Cancer Registry was established, constitute the cancer incidence sub-cohort, the study population for this analysis. During the 25-year follow-up, from 1985 through 2009, we identified 466 incident colon cancers. Colon cancer cases were more likely to be women, black, and older at the time of their hire than non-cases. In addition, cases had higher lagged cumulative exposure to all three fluid types, and were more likely to have ever been exposed (assuming a lag) to each of the three fluids at baseline (1985).

Results are presented as estimates of the 25-year cumulative incidence (i.e. risk) of colon cancer under hypothetical interventions in which workers were (1) always exposed above the 90th percentile cutoff (“exposed”), (2) and always exposed at or below the 90th percentile (“unexposed”) of each fluid type, while at work. The estimated 25-year risk differences were 3.8% (95% confidence interval [CI]: 0.7 - 7.0) for straight, 1.3% (95% CI: -2.3 - 4.8) for soluble, and 0.2% (95% CI: -3.3 - 3.7) for synthetic MWFs, respectively. The corresponding risk ratios were 2.39 (1.12 – 5.08), 1.43 (0.67 – 3.05), and 1.08 (0.51-2.30) for straight, soluble, and synthetic MWFs, respectively. Applying this approach allowed us to provide evidence for a causal effect of straight MWF exposure on colon cancer risk that was not found using standard analytical techniques in previous reports.

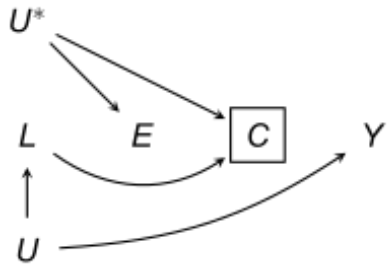
Based on the positive results for **non-Hodgkins lymphoma** and soluble MWF (Colbeth et al 2022) together with results from the path analysis indicating HWSE was operating for this outcome, we applied a g-method in another exposure-response analysis (Chen et al 2022, in preparation). We considered hypothetical interventions based on the NIOSH recommended exposure limit (REL) of 0.5 mg/m^3 for total MWF particulate mass. We then estimated counterfactual risk of NHL from 1985 to 2004 in the UAW-GM cohort of hourly autoworkers at three Michigan plants under hypothetical interventions on exposure. There were 231 NHL cases during the follow-up period. Using the hazard-extended iterative conditional expectation parametric g-formula, we adjusted for time-varying confounding and censoring affected by prior exposure. We contrasted counterfactual risk under no intervention on exposure to static and dynamic stochastic interventions on average annual exposure to soluble MWF. We found that stronger limits on average annual exposure to soluble MWF resulted in monotonically stronger

reductions in NHL risk. Capping soluble exposure at one tenth of the REL resulted in a risk ratio of 0.79 (95% CI: 0.62, 0.97). We considered realistic interventions and showed that stronger limits on average annual exposure may confer stronger protections against NHL risk. Interventions that consider other occupational exposures may be more efficient for preventing NHL.

Aim 3: Address HWSE bias in the left truncated cohort by using data on subjects who died prior to start of incidence follow-up to compute left censoring weights, based on probability of being alive.

The UAW-GM cohort study was designed as a cancer mortality study with mortality follow-up starting in 1941. Cancer incidence was not routinely collected before the local Cancer Registries; the NCI SEER registry was set up for the Detroit metropolitan area in 1973 and the Michigan Cancer Registry was initiated in 1985. We therefore have a left truncated study for cancer incidence because only those autoworkers still alive in when the Registry started are at risk for cancer incidence. This gives rise to two sources of bias, outcome misclassification and selection bias. Outcome misclassification arises because any cancer diagnoses that occurred before the Cancer Registries began is unmeasured and we so treat those individuals as cancer free and at risk. Selection bias may arise because those still alive when the registries started are a survivor subset of the original cohort.

The DAG below represents a causal structure consistent with selection bias. Suppose left censoring C depended on L, which might be underlying health or susceptibility to exposure effects. Conditioning on those not left-censored at start of follow-up opens a backdoor path between E and Y, which would result in a spurious association even if there were no causal effect of E on Y. This would be true even if L had no impact on the exposure of interest E.



Adapted from Figure 6c in Hernán et al. (2004). Take L, E, C, and Y to represent underlying health, occupational exposure, censoring, and cancer incidence, respectively. DAGs do not include the magnitude nor the sign (+/-). But in this case, the unmeasured confounder would result in the observed association underestimating the causal exposure effect.

We know about 14% of the autoworkers were left censored by 1985 due to death. In the presence of the healthy worker survivor effect, we expect the remaining 86% of workers to be healthier and less susceptible to potential adverse effects of occupational

exposure. Hence, we expect naive analyses using data conditional on being alive in 1985 to result in bias toward the null.

To address this form of selection bias we conducted a weighted analysis based on the probability of selection into the analytic dataset for incidence follow-up. This approach is analogous to inverse propensity score weighting, except now, we are considering a counterfactual world where all members of the original study population were selected into the analytic dataset. If we can construct a selection propensity score $g(C = 0 \mid L) = \mathbb{P}(C = 0 \mid L)$ where $C = 1$ indicates left censoring, then we can re-weight each worker by g^{-1} in order to achieve covariate balance in L across those who were selected into the analytic dataset and those who were left censored.

Those with a high risk of cancer incidence should also have a high risk of cancer mortality. Hence, the selection score is the survival function for death due to cancer by 1985. This may be computed for each individual as the product of conditional survival probabilities through 1985: $g_i(C = 0 \mid L) = \prod_t^{1985} \mathbb{P}_i\ (C_t \mid L_t, C_{t-1} = 0)$ for individual *i* at year *t*, conditional on covariates L_t. Now, we can construct stabilized weights:

$$sw_i = \frac{1 - \frac{1}{n}\sum_i^n g_i\ (C = 0 \mid L)}{1 - g_i(C = 0 \mid L)}.$$

The covariates X_t included: years since hire (quartiles or splined), age (quartiles or splined), plant, race (black or white), proportion of year spent in assembly, machining (includes grinding), and off (quartiles), cumulative time spent off (quartiles), year of hire (quartiles), cumulative exposure to straight, soluble, and synthetic MWFs (quartiles), and employment status.

Re-weighting by a selection score given L allows us to remove bias arising from the open backdoor path though it, however since underlying health and/or susceptibility are not measured, we can only re-weight by the selection score given X:

$$\widehat{sw}_i = \frac{1 - \frac{1}{n}\sum_i^n \hat{g}_i\ (C = 0 \mid X)}{1 - \hat{g}_i(C = 0 \mid X)}$$

When the observed covariates X are sufficient for representing underlying health/susceptibility L, then the $\widehat{sw}_i$ should do a good job at de-biasing our analysis.

Because the SEER registry was initiated before the statewide registry, we have restricted this analysis to plants 1 and 2 located in the Detroit area. This allows us to correct for the outcome misclassification for all cancers diagnosed between 1973 and 1985.

The three following Tables 1-3 present the exposure-response results between lung cancer and exposure to each type of MWF, for three different models. Model 1 is an unweighted Cox model (naïve). Model 2 is a Cox model weighted by $\widehat{sw}_i$, the inverse

probability of cancer death by 1985, whereby individuals with a higher probability of cancer death by 1985 who have survived are down weighted. Model 3 is a weighted Cox model with censoring weights inversely proportional to the probability of surviving until 1985. Note that Model 3 is the typical left censoring weighted model where the super survivors are *upweighted* to represent all those who have been censored. Model 2, however, is the approach that makes sense in the context of HWSE where we want to recreate a more naïve population by *down weighting* the super survivors.

In Table 1 we see that the HRs for lung cancer and straight MWF are higher in Model 2 than Models 1 or 3 in the two highest exposure categories. This is consistent with our hypothesis. The confidence intervals are wider because we have upweighted most of the population. For all MWF types the left censoring weighted Model 3 and unweighted Model 1 provide similar results. Model 2, with atypical censoring weights yields different results; stronger for straight MWF and weaker for the water-based fluids.

Table 1: Adjusted HR estimates for lung cancer and cumulative exposure to straight metalworking fluids.

		Model 1*	**Model 2****	Model 3***
Level of exposure	n	HR (95% CI)	HR (95% CI)	HR (95% CI)
0	433	1.00	1.00	1.00
>0.01 to 0.36	210	1.09 (0.89, 1.34)	1.01 (0.57, 1.79)	1.09 (0.90, 1.33)
>0.37 to 1.63	203	1.08 (0.88, 1.32)	1.21 (0.69, 2.11)	1.08 (0.89, 1.32)
>1.64	137	1.06 (0.87, 1.31)	1.16 (0.57, 2.35)	1.07 (0.87, 1.31)

*Unweighted Cox model. ** Survivors are down-weighted *** Survivors are up-weighted

Table 2: Adjusted HR estimates for lung cancer and cumulative exposure to soluble metalworking fluids.

		Model 1	Model 2	Model 3
Level of exposure	n	HR (95% CI)	HR (95% CI)	HR (95% CI)
0 to 0.05	141	1.00	1.00	1.00
>0.06 to 3.49	288	1.01 (0.81, 1.27)	0.74 (0.42, 1.31)	1.01 (0.81, 1.27)
>3.50 to 11.90	270	0.96 (0.75, 1.22)	0.78 (0.43, 1.43)	0.96 (0.75, 1.21)
>11.91	284	1.19 (0.92, 1.53)	1.10 (0.59, 2.05)	1.18 (0.92, 1.53)

*Unweighted Cox model. ** Survivors are down-weighted *** Survivors are up-weighted

Table 3: Adjusted HR estimates for lung cancer and cumulative exposure to synthetic metalworking fluids.

Level of exposure	n	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
0	611	1.00	1.00	1.00
>0.01 to 0.28	134	0.97 (0.76, 1.24)	0.92 (0.49, 1.72)	0.98 (0.77, 1.24)
>0.29 to 1.38	125	1.10 (0.86, 1.40)	1.23 (0.63, 2.41)	1.10 (0.86, 1.39)
>1.39	113	1.19 (0.93, 1.51)	0.94 (0.44, 2.02)	1.19 (0.94, 1.51)

*Unweighted Cox model. ** Survivors are down-weighted *** Survivors are up-weighted

Aim 4: Apply a novel risk assessment framework, based on the g-formula, to identify the concentration of each type of MWF needed to achieve a total cancer incidence risk of less than 1/1000 workers exposed for a working life.

Based on the totality of our previous studies, we conducted a risk assessment for MWF focused on all digestive cancers combined (stomach, esophagus, and rectal). The four steps are described below are: (1) Hazard identification; (2) Exposure-response; (3) Exposure characterization; and finally (4) Risk characterization.

Hazard Identification: Potential carcinogens in MWFs include hydrocarbons, chlorinated paraffins, aliphatic amines, nitrosamines, PAHs, formaldehyde-releasing agents, diethanolamine, and many other specialty additives. The International Agency for Research on Cancer (IARC) has classified untreated mineral oils as a Group 1 (definite human carcinogen), but considers an assessment of MWFs as complex mixture to be of only medium priority for monographs in the near future. Our own work over the past several decades, summarized here, has provided evidence that metalworking fluids, of all types, both the oil-based straight MWF and the water-based soluble and synthetic MWF, are human carcinogens. Since both the NIOSH REL and the internal GM exposure limit is for total MWF – we have conducted the risk assessment for total MWF, rather than for any specific type.

Exposure-Response: Based on our own work, we focused this risk assessment on lung cancer and all digestive cancers combined. To estimate the exposure-response relationships for MWF and each of these cancer endpoints, we used the parametric g-formula to avoid underestimating risk caused by the HWSE. G-methods account for the fact that less healthy autoworkers are more likely to quit their jobs each year than healthy workers. In addition to avoiding HWSE, there are three other reasons why g-methods are useful for occupational risk assessment:

1. G-methods are designed to figure out how much less cancer would occur if all the miners in the study had been exposed to less metalworking fluids than they actually were.
2. G-methods can tell us whether an exposure actually causes disease or death.
3. G-methods estimate lifetime risk for the whole population of autoworkers exposed to the hazard rather than for specific subgroups of the population.

We applied computer-aided g-methods to the observed data from the UAW-GM study to estimate what the risk of lung cancer death would have been if the autoworkers had all been exposed lower levels. We began by asking how much would the risk of lung cancer have been reduced in the study if the exposure of all active autoworkers had been reduced to 0.50 mg/m^3, the exposure limit for total particulate of MWF recommended by NIOSH and GM's internal limit. We then used g-methods to produce a series of estimates of lung cancer risk for the whole population of miners under several possible lower exposure limits. These estimates of the lifetime risk of lung cancer at different hypothetical interventions are presented below in Table 4.

Exposure Characterization: The next step in risk assessment is to describe the total exposure–*daily intensity* and *exposure duration*–that autoworkers typically have. To do this, we relied on the wide range of exposures observed in the UAW-GM cohort study. We also relied on the observed data to estimate how long autoworkers usually remain employed.

There are several differences between the traditional approach and our approach to exposure characterization using g-methods. The standard approach estimates risk assuming that all workers are exposed at the proposed limit for a working lifetime of 45 years. Using the g-method approach, however, we can base her estimates on a range of daily exposures *below* any new exposure limit – a more realistic assumption. The g-method approach also relies on the observed distribution of how long autoworkers in the research study were actually exposed, which was closer, on average to 20 years. Thus, the g-method approach provides more realistic estimates of exposure in today's world where people are unlikely to remain in the same job for 45 years. However, g-methods also avoid HWSE. Remember, HWSE leads to underestimation of the effect of exposures on disease. By avoiding the healthy worker survivor effect, the g-method approach will be a better reflection of the correct answer. Overall, risk estimates are more realistic if they allow for real world variation in both daily exposure levels and duration of employment, and also account for HWSE.

Risk Characterization**:** In the final step**,** Risk Characterization, we want to estimate the portion of the risk of lung cancer in the autoworker population that was *actually caused* by the exposure to metalworking fluids. There are many different causes of lung cancer that contribute to the risk in autoworkers, and only a portion of that total risk—called "excess risk"—is actually due to MWF. Using g-methods, **excess risk** is simply measured as the difference between the risk in the exposed population under a selected exposure limit compared to what the risk would have been if there had been no exposure to MWF exhaust at all.

The fourth column in the Table below is **the excess risk** of lung cancer for each of the exposure limits considered, based on the research study.[1] Excess risk is the number of lung cancer deaths attributable to MWF for every 1000 workers exposed. It is estimated as the difference between the lifetime risk (%) under each exposure limit and the lifetime risk if autoworkers had not been exposed to MWF at work at all. (Lifetime risk is

converted from a percent, N/100 (%), into N/1000 workers–the standard form for excess risk.)

Table 4: Risk Characterization for All Metalworking fluids (MWF) and Lung Cancer in the UAW-GM Cohort Study of Autoworkers

Exposure Limit	MWF (mg/m3) Total PM	Lifetime risk of Lung Cancer (%)	Excess risk
NIOSH REL	0.5	9.04	12/1000
0.1 X NIOSH REL	0.05	8.24	4/1000
Unexposed	0	7.82	0

The excess lifetime risk attributable to long term daily exposure to any type of MWF capped at the NIOSH REL is 12/1000.

Compared to autoworkers working in assembly with no direct exposure to MWF (not to the general population), as the exposure limit decreases from 0.5 to 0.05 mg/m^3 MWF, the excess risk of lung cancer decreases from 12/1000 to 4/1000. OSHA was instructed by the Supreme Court to try to protect workers so that they would not suffer serious disease or death as a result of their lifetime of exposures at work. The goal of zero risk is not realistic. Instead, the work protection agencies (state and federal OSHA) try to identify an exposure limit that would result in no more than1/1000, or one excess death per 1000 workers. By this criterion, even 0.1 time the NIOSH REL confers too much risk.

Recall that our approach to risk *assessment protects workers exposed for decades at or below the exposure limit*, rather than for *45 years at the exposure limit* as standard risk assessment assumes. Recall also that this g-formula based approach also accounts for HWSE and so in that sense is offers more complete protection, not just to active workers but to all those workers who may not have remained in the workforce.

Aims not met:

In Aim 1 we proposed to examine results stratified by sex and adjust for confounding by cigarette smoking in the Cox models. The number of female cancers would not have produced stable estimates of risk and so we could not justify stratification by sex across the board. Instead, our models were pooled and sex was treated as a confounder in the models (except for female breast cancer and male prostate cancer).

Indirect methods of adjustment for smoking have not been proven an effective approach to control for confounding by smoking. Dr. Aaron Blair (NCI) published an often-cited paper (AJIM, 2007) evaluating the role of confounding by smoking in occupational cohort studies of cancer. Based on several NCI occupational cancer mortality studies where smoking information was collected, he compared results with and without adjustment. Results suggested that there was little confounding by smoking and that exposure misclassification is a larger potential source of bias in occupational cohort studies.

B.2 (Accomplishments .pdf)

4. Key Outcomes or other achievements

Key exposure–response patterns were consistent with prior reports on this cohort, and suggest that exposure to any type of MWF, oil- or water-based, can modestly increase the risk of different types of cancers. Based on the 7,809 incident cancer cases of interest, we found modest evidence of increased incidence of stomach and kidney cancer, colon cancer, bladder cancer, and female breast cancer with higher levels of straight fluid exposure. We found suggestive evidence of increased rectal and esophageal cancer with increasing synthetic fluid exposure. Non-Hodgkin lymphoma was significantly associated with soluble MWF, though exposure-response patterns for other digestive cancers echoed the patterns found with straight MWF.

Beyond the updated evidence on the carcinogenicity of long-term exposure to metalworking fluids, our work on this iconic cohort of autoworkers has also contributed to expanding the tool box of methods used in occupational epidemiology. In order to reduce the potential bias caused by the healthy workers survivor effect, we have applied a series of novel methods in biostatistics and epidemiology. The application of these new causal inference methods was possible because of the richness of our time varying exposure data. The complex longitudinal data that comprise the UAW-GM cohort study provided the basis for our substantial methodologic investigations during the course of this grant period that have broadly contributed to the field of occupational epidemiology.

Peer-reviewed Publications

Garcia E, Bradshaw P, Eisen EA. Breast Cancer Incidence and Metalworking Fluid Exposure in a Cohort of Female Autoworkers. American Journal of Epidemiology. 2017;187(3):539-47.

Garcia E, Picciotto S, Neophytou AM, Bradshaw PT, Balmes JR, Eisen EA. Lung cancer mortality and exposure to synthetic metalworking fluid and biocides: controlling for the healthy worker survivor effect. Occup Environ Med. 2018.

Izano MA, Bradshaw P, Eisen EA. Metalworking Fluids and Colorectal Cancer Risk: Longitudinal Targeted Maximum Likelihood Estimation. Environ Epidem 2019; 2019 Feb 1;3(1).

Costello S, Chen K, Picciotto S, Lutzker L, Eisen EA. Metalworking Fluids and Cancer Mortality from 1941 to 2015 in a US Autoworker Cohort. Scan J Work, Environ and Health. 2020 May 1.

Colbeth HL, Chen K, Picciotto S, Costello S, Eisen EA. Metalworking fluids and cancer incidence in the UAW-GM autoworkers cohort. American Journal of Epidemiology. 2022 Oct 28.

In preparation:

Chen, KT, Eisen EA, Picciotto S. Evaluating hypothetical limits on metalworking fluid exposure for reducing non-Hodgkin lymphoma incidence: An application of the hazard-extended parametric g-formula.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
EEISEN	Y	Eisen, Ellen Aura	BS,MS,SCD	PD/PI	0.0	3.5	0.4			NA
SPICCIOTTO	N	Picciotto, Sally	BS,MA,PHD	Associate Research	3.4	0.0	0.0			NA
SADIE_2012	N	Costello, Sadie	PHD	Assistant Research	0.0	2.4	0.0			NA
LIZA.LUTZKER	N	Lutzker, Elizabeth		Research Data Analyst 2	1.3	0.0	0.0			NA
KEVCHEN	N	Chen, Kevin	BA,MPH,PHD	Research Data Analyst	2.5	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

NOTHING TO REPORT

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT
No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE
Not Applicable
G.11 PROGRAM INCOME
Not Applicable
G.12 F&A COSTS
Not Applicable

I. OUTCOMES

I.1 What were the outcomes of the award?

We report updated evidence for the carcinogenicity of metalworking fluids (MWF) based on cancer incidence, rather than mortality. Although no single type of cancer has been consistently associated with MWF throughout these studies of the UAW-GM cohort, we continue to find evidence for modest increases in risk of many different cancers, despite reductions in exposure to aerosolized metalworking fluids (MWF) over the past 75 years in these automobile manufacturing plants. For this grant, we examined the incidence of each of 14 cancers in relation to each type of MWF; oil-based straight, water-based soluble with a little mineral oil, and water-based synthetic MWF with no oil at all. We applied causal inference methods (e.g.parametric g-formula) when pathway conditions indicate that the healthy worker survivor effect was operating for a specific cancer.

Our results indicate that long term exposure to both straight and soluble MWF is associated with a modest increase in all-cancers-combined. When we look at each cancer separately, we find several positive results. Straight MWF continues to be the most hazardous of the three broad types of MWF. Cumulative straight exposure is modestly associated with increasing the risk of stomach cancer, kidney cancer, colon and possibly bladder cancer, as well female breast cancer. Together with previous results, these findings will potentially impact the workplace by reinforcing existing efforts to reduce exposure to straight MWF via substitution by water-based MWF (soluble or synthetic) in metalworking operations throughout industry.

Today water-based MWF are more common than straight. Although the water-based fluids appear to be less carcinogenic than the oil-based straights, there remains some elevated risk to autoworkers exposed to any type of MWF. Our results suggest that water-based fluids are also associated with increased risk of cancer incidence; soluble MWF was associated with non-Hodgkin's lymphoma and synthetic MWF was linked to lung cancer, as well as esophageal and rectal cancer. These findings suggest that more stringent limits on water-based synthetic and soluble MWF may also be needed. There is currently no OSHA PEL for MWF.

Beyond the updated exposure-response findings for metalworking fluids information, our work on this iconic cohort of autoworkers has promoted the application of novel biostatistics and epidemiologic methods needed to address the healthy worker survivor effect. We propose a novel weighting approach to account for the additional survivor bias that arises because only those workers still alive decades after start of mortality follow-up were eligible for cancer incidence follow-up in the Michigan Cancer Registry (left truncation). NIOSH recommends an exposure limit for all types of MWF combined of 0.5 mg/m3. In a novel approach to risk assessment, we focused on lung cancer because it was modestly associated with both straight MWF in the weighted analysis and with synthetic fluid when g-methods were applied. Our risk assessment was based on g-methods and suggests that an exposure limit of 0.05 mg/m3 for any type of MWF, just 10% of the NIOSH REL, is not low enough to limit lifetime risk of lung cancer to the OSHA goal of 1/1000. The complex longitudinal data that comprise the UAW-GM cohort study have provided the basis for substantial methodologic investigations during the course of this grant period that have broadly contributed to the field of occupational epidemiology.