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**Manuscript title:** Hypothetical limits on workplace exposure for reducing non-Hodgkin lymphoma: An application of the hazard-extended iterative conditional expectation parametric g-formula

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**Keywords:** Metalworking fluid, occupational exposure, non-Hodgkin lymphoma, cancer, causal inference, g-formula, healthy-worker effect, United States

# Abstract

(Limit: 250 words)

**Background:** Non-Hodgkin lymphoma (NHL) incidence has increased substantially in the US since 1960 and was recently linked to workplace exposure to soluble metalworking fluids (MWF) in a standard survival analysis of the United Auto Workers-General Motors (UAW-GM) cohort. To further explore this association, we estimate the effects of hypothetical limits on soluble MWF exposure in relation to NHL risk in the same cohort of autoworkers.

**Methods:** We estimated counterfactual risk of NHL between 1985 and 2015 in the UAW-GM cohort of autoworkers at three Michigan plants (n = 33,134) under hypothetical limits on annual average daily exposure to soluble MWF. We applied the hazard-extended ICE parametric g-formula, an estimator capable of adjusting for time-varying confounding affected by past exposure.

**Results:** 339 NHL cases occurred over the 30-year follow-up period. Stronger hypothetical limits on soluble MWF exposure resulted in monotonic reductions in NHL risk. Capping annual average daily exposure at 2 mg/m3 would have prevented 98 (95% CI: 45, 161) cases of NHL. Capping at 0.5 mg/m3, the NIOSH recommended exposure limit, would have prevented 112 (95% CI: 57, 181) cases. Finally, capping at 0.05 mg/m3 would have prevented 129 (95% CI: 66, 214) cases.

**Conclusion:** Limits on soluble MWF exposure would have prevented cases of NHL in the UAW-GM cohort. Although MWF use is expected to decline as the automotive industry turns to electric vehicles, a boom in electric vehicle manufacturing could nonetheless lead to global increases in worker exposure to MWF. Maintaining limits on exposure to MWF may protect workers against risk of NHL.

# Introduction

Non-Hodgkin Lymphoma (NHL) incidence in the United States doubled between 1973 and 1994, before plateauing at around 19 per 100,000 persons per year, making it the seventh most common cancer in the country.1,2 The strongest known risk factor of NHL is immunosuppression, both congenital and acquired.3,4 Modulation of immune function contributes to the pathogenesis of NHL directly by perturbing lymphocyte function or indirectly by reducing immunosurveillance against neoplasms. Immunodeficiency may also interact with infection with Epstein-Barr Virus, resulting in uncontrolled B-cell proliferation.5 Acquired immunodeficiency through infection with human immunodeficiency virus (HIV) can lead to genetic lesions and dysregulation while increasing vulnerability to infection by other oncogenic agents.6,7 However, since immunodeficiency and infection with HIV are rare, they cannot fully explain the historic rise or present burden of NHL.8 The rise in NHL incidence coincided with a period of rapid and extensive chemicalization in industry, agriculture and warfare, suggesting that environmental and occupational exposures may have an important explanatory role in the epidemiology of NHL.9,10

Pesticide exposure in agricultural occupational settings was a common target of NHL research in recent decades. A meta-analysis of 44 articles published between 1980 and 2014 found statistically significant associations between NHL and exposure to several classes of pesticides including carbamate, organophosporus, triazine, and organochlorine.11 Occupations associated with NHL are not limited to the agricultural sector, however. Metal processors, health workers, salespeople, machinists, and electricians have all been identified as occupational groups with higher risk of NHL.2,12,13 Workers in these occupational groups often come into contact with industrial chemicals such as gasoline, solvents, coolants, and lubricants such as metalworking fluids.

Metalworking fluids (MWF) are complex mixtures of oil, water, and chemical additives that optimize metal machining operations. During shaping, grinding, and cutting operations, MWF are misted, poured, or blasted at high pressure onto work surfaces to remove debris, cool metal, improve efficiency, and prevent deterioration of tools. Although MWFs provide essential engineering benefits to manufacturing processes, they may also present a potential health hazard to exposed workers, who may inhale or ingest aerosolized MWFs. There are three general types of MWF: straight, soluble, and synthetic. The type of MWF applied has changed over the decades in response to engineering, economic, and health considerations.

Straight MWF, the oldest class of MWF, is comprised mostly of mineral oils, which were classified as carcinogenic by the International Agency for Research on Cancer (IARC) in 1973, citing studies of occupational exposures among workers in oil, textile, and metal industries.14 In the same decade, additional factors including the high cost of oil and the introduction of performance-enhancing water-soluble chemical additives spurred the gradual replacement of straight MWF with water-based soluble and synthetic MWFs for many, but not all metalworking operations.15 Although water-based MWF contain little to no mineral oil, they contain a richer cocktail of additives including chromates, cycloalkanes, phenols, organochlorines, nitrites, sulfonates, and triazines: classes of chemicals with known or plausible carcinogenicity.16–18 With policy makers and companies anticipating a boom in domestic manufacturing, occupational exposure to MWFs will remain an important concern for worker health in the US.19–21

Here, we assess the effect of hypothetical MWF exposure limits on cumulative incidence of NHL from 1985 to 2014 in the United Auto Workers-General Motors (UAW-GM) occupational cohort study. A recent study of cancer incidence in this cohort linked NHL with exposure to soluble MWF in a Cox proportional hazards regression.22 Standard regression methods are vulnerable to downward bias due to the healthy worker survivor effect (HWSE), the process by which healthier individuals remain at work where they accumulate more occupational exposure. Therefore, we further explored this association using an estimator capable of adjusting for the HWSE and other sources of time-varying confounding and censoring affected by past exposure: the hazard-extended iterative conditional expectation (ICE) parametric g-formula.23,24 Like other causal estimators in statistics, the hazard-extended ICE g-formula yields marginal effect estimates of hypothetical interventions, which may be more interpretable under a population health framework than conditional measures.

# Methods

We estimated NHL cumulative incidence from 1985 to 2014 under hypothetical limits on annual average daily exposure to soluble MWF by applying the hazard-extended ICE parametric g-formula estimator.25 First, we estimated the expected number of NHL cases that we would observe if there were no censoring by competing risks. Then, we contrasted this counterfactual cumulative incidence to that under interventions enforcing one of five hypothetical exposure limits in addition to no censoring, when positivity allows. The five limits we evaluated were (1) 2.0 mg/m3, (2) 1.0 mg/m3, (3) 0.5 mg/m3, (4) 0.25 mg/m3, and (5) 0.05 mg/m3. The National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) for total particulate mass (PM) composed of MWFs is 0.5 mg/m3.26 These interventions reduce exposures above the hypothetical limit, but allow exposures below the limit to vary according to their natural distribution. To prevent extrapolation, interventions considered reduce above-limit exposures to the highest limit-abiding exposure observed among other workers in the study population with the same confounder and exposure history at that time. If no such peers existed, the above-limit exposures among those workers would retain their natural distribution.

## Study population

We used data from the UAW-GM cohort, which included all hourly workers at three automobile manufacturing plants in Michigan who had worked at least three years by 1985. Past papers provide detailed descriptions of the cohort.27,28 The large size of the study population and rich time-varying, quantitative MWF exposure data provide an opportunity to study a relatively rare cancer and evaluate realistic interventions on MWF exposure in a longitudinal cohort setting. The present study population (N = 33,134) was restricted to the autoworkers who were at work in 1941 or not yet hired, missing no more than half of their employment history, and still alive at the start of follow-up. Autoworkers in the study population were followed for NHL incidence from January 1, 1985 until NHL diagnosis, death, December 31, 2014 (20 years after the end of employment record availability), or the oldest observed age at death (108 years), whichever came earlier.

## Outcome and covariates

We identified incident cancers in the UAW-GM cohort that occurred between 1985 and 2014 by linkage to the Michigan Cancer Registry (MCR). Workers at Plants 1 and 2, located in the greater Detroit metropolitan area, were also linked to the Detroit Regional Registry of the Surveillance, Epidemiology, and End Results (SEER) Program. Cancer types were distinguished using site and histology codes conforming to the International classification of Diseases for Oncology, 3rd edition (ICD-O-3). Non-Hodgkin lymphoma was defined by cancers with any of the following ICD-O-3 Histology codes: 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687-9691, 9695, 9698-9702, 9705, 9708-9709, 9712, 9714-9719, 9724-9729, 9735, 9737-9738, 9811-9818, 9823, 9827, 9837. Details regarding cancer incidence follow-up are described elsewhere.22 Vital status was ascertained from company records and by linkage to Social Security Administration, National Death Index, and state mortality files.

Covariates including year of hire, sex, race, and plant location were obtained from company records. Race was missing for about 16% of the cohort, most commonly among workers hired before 1960 in Plant 2. In analyses, missing race was considered a distinct category. All covariates were coded as categorical variables. Cut-points for categorizing continuous covariates were determined according to the quantiles among cases.

## Exposure

Quantitative measurement of time-varying MWF exposure is a distinguishing strength of the UAW-GM cohort study relative to other occupational cohort studies. Exposure assessment was based on direct air sampling as well as company records. Company industrial hygienists collected several hundred personal and area samples for total particulate matter (mg/m3) composed of MWF over many decades. Research industrial hygienists collected additional air sampling data when the cohort study was launched in the mid 1980s. These additional data were combined with the historical data and company records to construct a job-exposure matrix of quantitative 8-hour time-weighted average daily exposure estimates to soluble, straight, and synthetic MWFs for each combination of job, department, and plant over time. Workers’ time-weighted annual average daily exposure to each MWF type was determined by combining this job-exposure matrix with employment records, which recorded time-varying job type, department, and plant for each employee from hire to termination or 1994, whichever came sooner. For employment records that were at least half complete, gaps in the record were interpolated by carrying forward the last known job type. The exposure assessment is described in detail elsewhere.29–31

Previous analyses of NHL applied exposure lags of 1 to 20 years to account for disease latency; we lagged cumulative MWF exposures by 20 years and therefore ended follow-up on January 1, 2015.32–34 In analyses, MWF exposure at start of follow-up was summarized as the cumulative sum of annual exposure intensities. Exposure was coded as categorical variables with cut-points at zero and the quintiles of exposure among cases. In analyses, we estimated the effects of interventions on soluble MWF while treating exposure to straight and synthetic MWFs as potential confounders.

## Hazard-extended ICE parametric g-formula

We split the 30-year follow-up period into ten time periods based on the deciles of the dates of diagnosis of NHL. The number of years per period range from two to four years. The hazard-extended ICE parametric g-formula involves two stages. In the first, we estimate counterfactual discrete hazards over the person-periods. In the second, we pool those estimates to estimate counterfactual risk over the entire follow-up period. During pooling, we iteratively combine estimates of the counterfactual hazard starting with the last two periods, then the last three, then the last four, and so forth. In each iteration, we perform model-based standardization over exposure and covariate histories before combining the counterfactual discrete hazard with that pooled over subsequent periods. This iterative process results in a sequentially standardized estimate of NHL cumulative incidence over the entire follow-up period under the post-intervention distribution of exposure.

At the start of follow-up and in the first stage of estimation, we summarized history of exposure to soluble MWF as the cumulative sum of average daily exposure. In the first stage, we fitted a pooled logistic regression for NHL over at-risk person-periods given cumulative exposure to straight, soluble, and synthetic MWFs, employment status, cumulative time off, age, duration of employment, sex (male/female), race (Black/white/unknown), and plant (Plant 1/Plant 2/Plant 3). Exposure to MWFs, employment status, time off, and duration of employment were lagged 20 years. All continuous variables were represented as categorical variables with cut points determined by the quantiles of nonzero values among NHL cases. In the second stage, we conducted model-based standardization using logistic regression on the entire set of exposure and covariate histories. An overview of the general steps of the estimation procedure are presented below. Note that we refer to discrete hazards simply as hazards.

1. Fit a pooled logistic regression of NHL on covariates and exposure over all at-risk person-periods.
2. Predict the hazard for each person-period for each possible level of exposure using the model from step 1.
3. Within strata formed by unique combinations of covariates, obtain the post-intervention distribution of exposure by applying the intervention rule to the observed exposure distribution.
4. Within strata, estimate the counterfactual hazard for each person-period by taking a weighted sum of the predicted hazards from step 2.
5. Starting at the penultimate period of follow-up, estimate the pooled counterfactual hazard:
   1. Regress the counterfactual hazard pooled over all subsequent periods on exposure and covariate history at the current period.
   2. Predict the pooled hazard for each person at risk at the start of the period and each possible level of exposure using the model from (a). Retrieve the predicted hazards from step 2. For each person and level of exposure, multiply the predicted pooled hazard by one minus the corresponding predicted hazard and add the predicted hazard to the product.
   3. Within strata formed by exposure and covariate history, obtain the post-intervention distribution of exposure by applying the intervention rule to the observed exposure distribution.
   4. Within strata, estimate the counterfactual hazard pooled over the present and subsequent periods for each person by taking a weighted sum of the predicted pooled hazards from (b).
   5. If the present period is not first period, set the reference period to the preceding period and return to (a).
6. Compute the counterfactual risk by averaging the counterfactual hazard over the entire follow-up period across all persons.

To account for censoring, fit the models in step 1 and step 5a among those who were not censored and obtain predicted hazards for all at-risk person-periods, including those that were censored.

We estimated cumulative incidence under the observed distribution of soluble MWF exposure (natural course) and under the six interventions. We contrasted the cumulative incidence under intervention to that under the natural course by computing the number of cases averted and the cumulative incidence ratios. Confidence intervals were computed using the basic nonparametric bootstrap with 1000 Monte Carlo samples from the population at the start of follow-up. All the necessary script used to reproduce the analyses are available on [GitHub](https://github.com/kvntchn/gm-nhl-ice).

# Results

Table 1 presents summary statistics of exposure and covariates for the full study population and for those diagnosed with NHL between 1985 and 2005. The cohort is predominantly white (66%) and male (87%). The median year of hire among those diagnosed with NHL was 1959 whereas the median year of hire in the full study population was almost a decade later. Age at hire was approximately the same among those with NHL and the full study population. Median lagged cumulative exposure to all three MWF types was higher among NHL cases. Soluble MWFs were the most widely used MWF type, with approximately 90% of workers ever exposed. Median cumulative exposure among the exposed was 6.5 times higher for soluble than for straight MWFs. Figure 1 shows median annual average daily exposure to the three MWF types among exposed workers over calendar time. Exposure to MWF generally followed a downward trend over time.

**Table :** Summary of population characteristics. Statistics shown above the horizontal line are count (%). Those shown below are median (quartile 1, quartile 3).

|  | Study population | |  | NHL cases | |
| --- | --- | --- | --- | --- | --- |
| N (person-years) | 33,134 | (794,733) |  | 339 | (5,809) |
| Race |  |  |  |  |  |
| White | 21,315 | (64%) |  | 250 | (74%) |
| Black | 6,250 | (19%) |  | 40 | (12%) |
| Unknown | 5,569 | (17%) |  | 49 | (14%) |
| Sex |  |  |  |  |  |
| Male | 28,640 | (86%) |  | 297 | (88%) |
| Female | 4,494 | (14%) |  | 42 | (12%) |
| Planta |  |  |  |  |  |
| Plant 1 | 7,273 | (22%) |  | 70 | (21%) |
| Plant 2 | 14,251 | (43%) |  | 137 | (40%) |
| Plant 3 | 11,610 | (35%) |  | 132 | (39%) |
| Ever exposed to MWFsb |  |  |  |  |  |
| Soluble | 29,010 | (88%) |  | 299 | (88%) |
| Straight | 18,710 | (56%) |  | 197 | (58%) |
| Synthetic | 11,824 | (36%) |  | 111 | (33%) |
| Deceased by end of follow-up | 14,434 | (44%) |  | 53 | (16%) |
| Year of birth | 1941 | (1927, 1950) |  | 1935 | (1926, 1945) |
| Year of hire | 1967 | (1953, 1976) |  | 1964 | (1953, 1971) |
| Age at hire (years) | 23.6 | (20.0, 30.3) |  | 25.3 | (20.2, 32.9) |
| Year of leaving workc | 1981 | (1970, 1989) |  | 1981 | (1971, 1989) |
| Age at leaving work (years)c | 45.2 | (31.8, 57.3) |  | 53.0 | (36.4, 60.4) |
| Years at workc | 15.2 | (7.0, 26.6) |  | 21.0 | (7.8, 29.9) |
| Year of death | 2001 | (1994, 2009) |  | 2004 | (1998, 2010) |
| Age at death (years) | 73.4 | (64.4, 81.3) |  | 73.0 | (66.3, 80.8) |
| Cumulative time off (years)b | 1.21 | (0.39, 2.00) |  | 0.93 | (0.23, 1.51) |
| Cumulative exposure to MWFs (mg/m3-years)d | | | | | |
| Soluble | 4.33 | (1.71, 10.69) |  | 5.43 | (2.19, 14.33) |
| Straight | 0.67 | (0.21, 2.38) |  | 0.77 | (0.18, 3.52) |
| Synthetic | 0.44 | (0.15, 1.58) |  | 0.69 | (0.18, 1.91) |
| NHL: non-Hodgkin lymphoma. | | | | | |
| a Plant of longest employment duration among those who worked at multiple plants; b Lagged 10 years; c Among those who left work by December 31, 1994; d Among ever-exposed individuals, lagged 10 years.; | | | | | |

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| --- |
| Figure 1. Median annual average daily exposure to soluble, straight, and synthetic metalworking fluids among exposed workers over time. |

The observed number of NHL cases over the 20-year follow-up period was 231 (corresponding to a 20-year risk of 6.65 per 1000). Table 2 presents the hazard-extended ICE parametric g-formula estimates of the counterfactual number of cases, number of cases averted, and cumulative incidence ratios contrasting hypothetical limits on exposure to soluble MWF to no limit, after elimination of competing risks. Under an intervention eliminating competing risks, the estimated number of cases under no limit on MWF exposure was 332 (285, 380). Stronger limits on annual average daily exposure to soluble MWFs resulted in monotonically stronger reductions in the cumulative incidence of NHL. Capping annual average daily exposure to soluble MWFs at 0.5 mg/m3, 0.25 mg/m3, and 0.05 mg/m3 resulted in 44 (-6, 91), 52 (-5, 106), and 71 (12, 129) fewer NHL cases, respectively. These correspond to cumulative incidence ratios 0.87 (0.73, 1.02), 0.84 (0.68, 1.01), and 0.79 (0.61, 0.97).

**Table :** Counterfactual number of cases, number of cases averted, and cumulative incidence ratio estimates contrasting hypothetical limits on soluble MWF exposure to no intervention on exposure.

| Exposure limit for soluble MWF (mg/m3) | Cases | (95% CI) | Cases averted | (95% CI) | CIR | (95% CI) |
| --- | --- | --- | --- | --- | --- | --- |
| None | 502 | (439, 555) |  |  |  |  |
| 2.0 | 404 | (324, 468) | 98 | (45, 161) | 0.80 | (0.68, 0.91) |
| 1.0 | 396 | (316, 463) | 106 | (51, 173) | 0.79 | (0.66, 0.89) |
| 0.5 | 390 | (311, 459) | 112 | (57, 181) | 0.78 | (0.64, 0.88) |
| 0.25 | 384 | (303, 455) | 118 | (59, 192) | 0.77 | (0.62, 0.87) |
| 0.05 | 373 | (286, 451) | 129 | (66, 214) | 0.74 | (0.58, 0.86) |
| CIR: cumulative incidence ratio. MWF: metalworking fluid | | | | | | |

# Discussion

Although NIOSH concluded that there exists substantial evidence linking MWF exposure to several different cancers, their REL of 0.5 mg/m3 for total particulate matter derived from any type of MWF targeted risk of acute respiratory disorders rather than on cancer.26,35 Hence, they may be inadequate for protecting against cancer risk. Using the hazard-extended ICE parametric g-formula, We estimated the counterfactual expected number of NHL cases from 1985 to 2005 in the UAW-GM cohort if annual average daily exposure to soluble MWF were limited to the NIOSH REL, half the REL, and a tenth of the REL and found a monotonic exposure-dependent relationship with lower cumulative incidence estimates arising from stronger limits.

The g-formula is a well-known approach in causal inference used for the identification of causal effects in the presence of time-varying confounding affected by past exposure.36 Standard representations of the g-formula include (1) a non-iterated expectation over the joint density of covariates, (2) the ICE over time, and (3) an inverse probability weighted expectation. The parametric g-formula is a plug in estimator for the g-formula under its first, non-iterative, representation. It involves the parametric modeling of the full joint distribution of the outcome, exposure, and covariates under study for each time point.37,38 Counterfactual quantities under hypothetical interventions of interest are computed from Monte Carlo samples from distributions implied by the fitted parametric models. In longitudinal settings, this approach often requires specifying and fitting large number of models in order to satisfy the exchangeability assumptions necessary for causal identification.

Parametric estimators using the ICE representation of the g-formula require modeling only the conditional outcome distributions, so they require fewer parametric assumptions than non-iterative parametric g-formula estimators. Counterfactual outcome estimates over the follow-up period are computed from interval-specific conditional estimates by applying the tower rule of expectation. Under the assumptions of conditional exchangeability at all time points, positivity, counterfactual consistency, and correct model specification, the hazard-extended parametric g-formula yields unbiased estimates of counterfactual risk with greater statistical efficiency than both propensity score-based estimators and the classical ICE g-formula.

Under the assumptions of conditional exchangeability, positivity, consistency, and correct model specification, our estimates are unbiased for the true counterfactual risk under the hypothetical interventions. Conditional exchangeability means that for all time points, there is no confounding of the relationship between exposure/censoring and both future exposure/censoring and NHL status given the observed past, including past exposure and covariates.39,40 A major threat to conditional exchangeability in longitudinal occupational studies is the HWSE. We limit potential bias due to the HWSE by conditioning on cumulative exposure, employment status, and cumulative time off history at each time point. Cumulative time off and employment status are reasonable mediators of the causal paths linking past health to future exposure and health, but adjustment for these variables may not be sufficient for eliminating bias due to the HWSE. Declines in a worker’s health may lead to reductions in work-related exposure without affecting employment status or time off work.41 We expect the absence of time-varying measures of worker health over the life course to result in bias toward the null.

Positivity refers to the need for adequate variation in future exposure among strata formed by observed covariate and intervention-compliant exposure histories. Even under conditional exchangeability, where exposures within these strata may be considered the result of experimental assignment, expected counterfactual outcomes under different exposures may not be estimable if there is excessive sparsity in the observed distribution of exposures.42 We investigated static and dynamic stochastic interventions on soluble MWF exposure that intervened only when annual average daily exposure exceeded the hypothetical limit under consideration. Hence, our parameters of interest achieve positivity more easily than those for static deterministic interventions e.g. setting all to a single level of exposure. Nonetheless, violations in positivity were still of concern due to the high dimensionality of covariates, as is common in longitudinal settings. We addressed sparsity by summarizing the 20 years of follow-up over a coarser timescale with only 8 follow-up periods and by representing covariates using fewer categories. Coarsening limits the comprehensiveness of confounding control, but improves positivity. In practice, causal inference using observational data must always balance positivity, covariate adjustment, and model specification.43

The consistency assumption, also known as the no-multiple-versions-of-treatment or stable unit treatment value assumption, is that counterfactual outcomes under each possible exposure value take on a unique value.44,45 This assumption would be violated if there were multiple versions of treatment causally associated with different outcomes. This basic notion of consistency is violated in our analysis because our exposure of interest is a complex mixture of diverse components with substantial variation over time due to changes in formulation as well as the natural physical, chemical, and biological changes in the MWF over the course of its use and reuse.46 However, causal effect estimates under violations in the consistency assumption are still valid and unbiased if there is adequate adjustment for confounders of the exposure-version relationship.45 This may be thought of as conditional consistency within strata, in which there is only one version of treatment. Our analysis indexed time periods over calendar time and adjusted for age, year of hire, and plant. In this way, we limited potential for bias due to variation in MWF composition.

Correct model specification is a standard assumption in all parametric and semi-parametric analyses. The estimator we applied offers greater statistical efficiency than the classical ICE parametric g-formula estimator because it leverages greater parametric smoothing. In causal analyses of longitudinal cohort studies, both the hazard-extended and classical ICE parametric g-formula estimators are less common than the NICE parametric g-formula.47 However, a major limitation of the NICE g-formula is the g-null paradox: the guaranteed misspecification of parametric models resulting in the false rejection of the null hypothesis when the null is true and when there is time-varying confounding affected by past exposure.48,49 As with all ICE g-formula estimators, the estimator we applied is not subject to the g-null paradox. Furthermore, simulation studies show that the variance of the hazard-extended ICE parametric g-formula is similar to that of the NICE parametric g-formula, so we expect the former to be no less conservative than the latter.25

Much of the existing epidemiologic literature linking occupational and environmental exposures to NHL report findings from case-control studies where exposures are measured crudely as binary indicators of exposure or membership in a particular occupational group.50–53 Associations between occupations and NHL risk vary considerably, but one study of working men in Kansas and Nebraska found strong associations between NHL risk and occupations involving metalworking and motor vehicles.54 Both of these occupations may entail exposure to soluble MWFs, which contain a number of additives of concern for human health and for NHL risk in particular. Organic compounds containing phosphorous, chlorine, sulfur, nitrogen, and boron are commonly added to soluble MWF to control microbial growth, improve performance under high heat/pressure, and inhibit corrosion.55 Organophosphorus compounds include organophosphate pesticides, which have been linked to cancer risk in epidemiologic and animal studies. Some were classified as possibly carcinogenic by the IARC.18 Studies of occupational exposure to chlorinated solvents and pesticides have also been linked to NHL risk.56–60 In 2014, the IARC classified trichloroethylene, tetrachloroethylene, and other chlorinated agents as Group 1 carcinogens.17 Chlorinated solvents are commonly used as degreasers in industrial settings, but their use in the plants under study here was rare.61 The structural characteristics shared by MWF additives and known/suspected carcinogens suggest potential similarities in their behavior in biological systems.

This study investigated the effect of hypothetical limits on MWF exposure by comparing the standardized distributions of NHL under various distributions of cumulative exposure induced by applying upper bounds to annual average daily exposure to soluble MWF. We selected these hypothetical limits based on the NIOSH REL of 0.5 mg/m3.26 In the real world, there is no enforcement of the REL, but we nonetheless observed annual average daily exposures below the REL in these GM plants for many years. If the REL were enforced in the real world, we would not expect reductions in exposure for these low-exposure person-years. Hence, contrasting the counterfactual scenario where all workers experienced annual average daily exposure at the REL to one where all workers experienced annual average daily exposure at some higher level would result in an overestimate of the expected real-world benefit of REL enforcement.

# Conclusions

Associations between several occupations and risk of NHL have been reported previously, but none evaluated the potential effect of hypothetical limits on occupational exposures.2,4,53,60 We found evidence that exposure to soluble MWF was associated with NHL incidence after adjustment for time-varying confounding affected by prior exposure using the hazard-extended ICE parametric g-formula. Reducing cumulative exposure to soluble MWF by enforcing hypothetical, but realistic, interventions on annual average daily exposure would reduce NHL incidence.

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