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Lung cancer mortality and exposure to synthetic metalworking fluid and biocides; controlling for the healthy worker survivor effect

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Abstract

Objectives: Synthetic metalworking fluids (MWF), widely used to cool and lubricate industrial machining and grinding operations, have been linked with increased risk of several cancers. Estimates of their relation with lung cancer, however, are inconsistent. Controlling for the healthy worker survivor effect, we examined the relations between lung cancer mortality and exposure to synthetic MWF, as well as to biocides added to water-based fluids to control microbial growth, in a cohort of autoworkers. Biocides served as a marker for endotoxin, which has reported antitumor effects, and were hypothesized to be the reason prior studies found reduced lung cancer risk associated with exposure to synthetic fluids.

Methods: Using the parametric g-formula, we estimated risk ratios (RR) comparing cumulative lung cancer mortality under no intervention to what would have occurred under hypothetical interventions reducing exposure to zero (i.e., 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.

Results: 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

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CONTRIBUTORS

EG and EE conceived and designed the study. EG conducted data analyses, interpreted results, and wrote and revised the manuscript. SP, AN, and PB advised on analytic approach and reviewed and revised the manuscript. JB reviewed and revised the manuscript. EE contributed to the design of the analysis, interpretation of results, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

None declared

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(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.

Conclusions: Findings suggest a modest positive association for synthetic MWF with lung cancer mortality, contrary to the negative associations reported in earlier studies. Biocide exposure, however, was inversely associated with risk of lung cancer mortality.

Keywords

Lung cancer; Metalworking fluids; Healthy worker survivor effect; Occupational exposure; Parametric g-formula

INTRODUCTION

Lung cancer has the largest global burden of disease among all neoplasms. In 2015, tracheal, bronchus, and lung cancer caused the loss of 36.4 million disability-adjusted life years (DALYs), and 1.7 million deaths, worldwide.[1] Occupational exposures are a large contributor to this disease burden, with 25% of tracheal, bronchial, and lung cancer DALYs lost estimated to be attributable to occupational carcinogens.[2] We set out to examine lung cancer mortality risk associated with a particular type of airborne occupational exposure: metalworking fluids (MWF). MWF are classified into three categories based on composition: straight, soluble, and synthetic. Straight fluids are complex mixtures of paraffinic, naphthenic, and aromatic compounds refined from mineral oil.[3] Soluble fluids are composed of oils emulsified in water. Synthetic fluids are water-soluble chemical lubricants without oil. Straight fluids have been widely used since the 19th century, while soluble and synthetic fluids were introduced more recently in the 1940s. In the United States, 4.4 million workers are potentially exposed to MWF, which are coolants and lubricants used in industrial machining and grinding operations.[4] Additionally, there is a growing workforce employed in metal manufacturing worldwide as evident by the increasing global market volume of MWF: an annual growth rate of 2.5% is forecasted for volume shipments in 2010–2020.[5] Much of the MWF use occurs outside of North America and Europe: in 2013, Asia had the largest share of volume shipments, 42%, compared to North America, 28%, and Europe, 23%.[5]

Our primary focus was on synthetic MWF, the most recently introduced fluid type that contains no oil. Although synthetic MWF have been modestly linked with increased risk of several cancers, including esophageal,[6] liver,[6] prostate,[6] and rectal,[7] results for lung cancer have been inconsistent. Several studies have reported decreased lung cancer risk associated with the water-based synthetic fluids.[8–10] These protective results were suggested to be due to endotoxins, also known as lipopolysaccharides, in the synthetic MWF. Endotoxins are components of the outer membrane of gram-negative bacteria cell walls that are released when bacteria lyse.[11] They have reported antitumor activity, possibly through release of tumor necrosis factor-α in response to exposure, and are thought to be responsible for reduced lung cancer rates in cotton textile and agricultural workers.[8 11] This is consistent with the recent extension of the hygiene hypothesis—the hypothesis that reduced exposure to certain microorganisms causes immunoregulatory defects resulting in increased susceptibility to chronic inflammatory disorders and possibly cancer.[12 13] Chronic

infection causes chronic inflammation that may drive oncogenesis; however, transient exposure to microbial components, such as endotoxin, or transient infections would be expected to enhance immune responses and have adjuvant effects.[12] Bacterial contamination of water-based MWF, particular by gram-negative species, can be considerable and lead to fluid deterioration and foul odors.[14] Workers are potentially exposed to endotoxins when working with these water-based MWF. Biocides are routinely added to the fluids to counteract microbial growth in the short term, and thus serve as a temporal indicator of exposure to bacterial and endotoxin contamination.[8 9 14–16] We hypothesized that endotoxin contamination of the synthetic MWF, rather than the fluid itself, caused the apparent protective effect on lung cancer risk.

The United Autoworkers-General Motors (UAW-GM) study is an occupational cohort of 46,316 hourly workers in automotive manufacturing and is considered to be the most comprehensive cohort study of MWF-exposed workers.[17–19] We took advantage of the cohort's long follow-up and extensive quantitative exposure assessment to examine the relationship between lung cancer mortality and exposure to synthetic MWF and biocides. Prior analyses demonstrated the presence of the healthy worker survivor effect (HWSE)[20] for lung cancer in the UAW-GM cohort,[21] indicating the need to employ a method that can adjust for time-varying confounding affected by prior exposure.[22 23] Therefore, we employed the parametric g-formula,[24] which generalizes standardization to control time-varying confounders affected by prior exposure,[25] to evaluate lung cancer mortality under hypothetical interventions on synthetic fluids. Biocide exposure was considered as a proxy for endotoxin contamination and was additionally "intervened" upon in order to observe the independent effect of synthetic fluids on lung cancer mortality.

METHODS

Study Population

The UAW-GM cohort has been described in detail previously.[6 17] Briefly, the original study included all hourly workers hired between 1938 and 1982 who worked at least three years at any of three automobile manufacturing plants in Michigan, USA.[17] The manufacturing facilities were selected to produce a pool of workers exposed almost exclusively to MWFs and to reduce likelihood of exposure to a variety of known toxic and carcinogenic agents.[17] We restricted the cohort to those missing less than half of their employment history and hired no younger than age 16. The final study population comprised 38,560 workers. Information on date of birth, year of hire, race, sex, and plant was ascertained from employment records. For our analysis, follow-up began three years after hire and ended at death, age 86 (age of oldest case), or the end of 1994, whichever occurred first.

Outcome ascertainment

Data on vital status were obtained through linkage with the Social Security Administration, the National Death Index, plant records, and state mortality files. Death certificates, state vital records, and the National Death Index were used to determine cause of death. The outcome of interest was lung cancer mortality (ICD-9 162; ICD-10 C34). We identified 873 lung cancer deaths during follow-up from 1941 through 1994.

Exposure Assessment

Exposure estimates for each MWF fluid were calculated for each subject based on detailed employment records and a time-varying job-exposure-matrix (JEM). The JEM was based on an extensive retrospective exposure assessment.[26 27] MWF concentrations characterized by particle-size fraction were estimated for homogenous exposure groups as an 8-hour time-weighted average (mg/m^3) based on measurements collected during the mid-1980s. Scale factors were developed to adjust MWF concentrations for temporal trends. This study uses the thoracic size fraction (<9.8 μm) of the exposure estimates, which deposit mostly in the tracheobronchial and alveolar regions of the lung. The presence of biocide was determined for each homogenous exposure group over time by reviewing Material Safety Data Sheets and historical records of lubricant specification. The JEM was combined with employment records to estimate time-varying annual average daily and cumulative exposure to straight, soluble, and synthetic MWF (mg/m^3 and mg/m^3-years, respectively) and to categorize subjects into a time-varying indicator of past biocide exposure (never or ever exposed). Gaps in employment history information were interpolated by averaging exposures from previous and subsequent jobs. To account for lung cancer latency, cumulative MWF exposures were lagged by 15 years.

Statistical Methods

We applied the parametric g-formula to estimate the cumulative risk ratio of three hypothetical exposure interventions on lung cancer mortality. In addition to the simulated natural course of exposure (no intervention), we evaluated interventions reducing exposure to zero (i.e., a ban) separately for synthetic fluids and for biocides, as well as a joint intervention on both. The interventions are:

1. Reducing synthetic MWF exposure to 0 mg/m^3
2. Reducing synthetic MWF exposure to 0 mg/m^3 and setting biocides to unexposed
3. Setting biocides to unexposed (but leaving synthetic MWF exposure unchanged)

The parametric g-formula is a generalization of standardization that can be applied to estimation of measures of association in the presence of time-varying exposures and covariates under the following three assumptions: 1) no unmeasured confounders (conditional exchangeability), 2) counterfactual consistency, and 3) correct model specification.[22 28 29] It has been applied in several epidemiologic studies, including a number of pedagogic articles.[28 30–32] We describe it briefly. This method estimates the risk of lung cancer mortality under each intervention as a weighted sum of the probability of lung cancer death, conditional on past exposure and covariate histories. We first developed parametric models for the outcome (lung cancer mortality), competing risk (non-lung cancer death), the three separate MWF exposures (annual average daily exposure to straight, soluble, and synthetic fluids lagged 15 years), and the time-varying covariate employment status (lagged 15 years), based on the observed data. These models were all conditional on calendar year, age, prior covariate and exposure histories and baseline covariates (sex, race, plant, and year of hire). MWF exposures and employment status were both predicted with a 15-year lag and used in subsequent predictions with the lag. Cumulative MWF

exposures (lagged 15 years) for each of the three fluid types were calculated based on the annual exposure histories. A model was fit for biocide exposure, conditional on calendar year, age, prior covariate and exposure histories and baseline covariates as well as prior biocide exposure and the current year's MWF exposure level for each fluid type. Cumulative MWF exposures and the biocide covariate were used only in the prediction of the outcome and competing risk, not in the prediction of MWF exposures or employment status. Model specifications were selected with the goal of minimizing the difference between the observed and simulated natural course cumulative lung cancer mortality, a strategy for reducing model misspecification. This evaluation of risk prediction was done by comparing 1) the overlap between the cumulative incidence in the observed data and the simulated natural course, and 2) the cumulative risk of lung cancer mortality through the end of follow-up in the observed data to that simulated in the natural course. See appendix for additional details. Next, pseudo-samples based on the observed sample population were used in Monte Carlo simulations along with the estimates from the parametric models to generate covariate and exposure histories. Lastly, cumulative risk of lung cancer mortality under each hypothetical intervention was quantified, and interventions were compared using risk ratios.

Workers in the pseudo-sample, drawn to be of the same size as the cohort (n=38,560), were followed from their age at the beginning of follow-up through age 86. Parameters from the models for exposures and covariates described above were used to simulate exposure and covariate levels at each age. After employment termination, all exposures were set to 0. For each of the three interventions, the value of the exposure(s) of interest was intervened upon for all workers in the pseudo-sample by changing it from the predicted value to 0 mg/m^3 for synthetic MWF and/or unexposed for biocide. Subsequent values of exposure, covariates, and risk of non-lung cancer and lung cancer mortality were then similarly simulated, and exposures intervened upon, at each age through the end of follow-up. For the simulated natural course, no variables were intervened upon and the simulation predicted risk under the natural course of events. For each intervention, lung cancer mortality was evaluated using a cumulative mortality estimator for the sub-distribution of the event of interest in the presence of competing risks.[33] We then calculated cumulative incidence ratios for lung cancer mortality by ages 86, 75, 65, and 55 years, comparing each intervention to the simulated natural course. We ascertained 95% confidence intervals from 500 bootstraps each the same size as the cohort (n=38,560).

The analysis was performed in SAS software version 9.4 (SAS Institute, Cary, NC) based on the GFORMULA macro available at https://www.hsph.harvard.edu/causal/software/. Use of human subjects data in this study was reviewed and approved by the Office for the Protection of Human Subjects at the University of California, Berkeley.

RESULTS

Table 1 presents descriptive characteristics of the 38,560 autoworkers included in the study population. Online supplementary figure S1 shows the number of workers being followed, indicating person-time, and the number of lung cancer deaths by age.

Over the entire study period, the percentage of subjects ever exposed to straight, soluble, and synthetic MWF was 58, 90, and 36, respectively. Estimated annual average daily exposure concentrations were highest for soluble and lowest for synthetic fluids. Patterns of synthetic fluid and biocide exposure over time are shown in figure 1. Among exposed workers, the mean annual daily average exposure concentration was highest in the decades following synthetic MWF's introduction and decreased markedly in 1970 through the early 1990s. The number of workers exposed to synthetic MWF and biocides in each calendar year overlaid on number of active workers indicates that in a given year a sizable fraction of workers were exposed, and most workers who were exposed to synthetic fluids were also exposed to biocides. Over the entire study period, 36% of workers were ever exposed to biocides. Synthetic MWF exposure did not always entail biocide exposure. In our study population, workers were unexposed to biocide 22% of the time they worked with synthetic exposure. Subjects were less often exposed to biocide when working with soluble fluids, however, as synthetic fluid exposure decreased in the early1980s, more biocide exposure occurred through soluble MWF (figure 1). Online supplementary table S1 shows the distributions of employment status and exposure over person-time in the observed data and in the pseudo-populations for the simulated natural course and for the simulated intervention on synthetic MWF.

The natural course simulation was somewhat consistent with the observed data. The simulation under-predicted both *whether* a subject was exposed to straight or soluble fluids in a given year and the exposure *levels* among the exposed for soluble and synthetic fluids. Because biocide exposure was not used in the prediction models for leaving work or MWF exposure, the distributions reported for the synthetic fluid intervention in online supplementary table S1 were essentially the same as those when we also intervened on biocide exposure (data not shown).

Figure 2 shows the cumulative mortality curve for lung cancer in the observed data compared to the simulated natural course. The cumulative lung cancer mortality under the natural course simulation (7.202%) was nearly identical to the observed cumulative risk (7.202%) by the end of follow-up at age 86; though at younger ages the fit was not as close.

Figure 3 shows the cumulative mortality curves for lung cancer under the interventions. The cumulative risk of lung cancer mortality under the natural course and three interventions along with the risk ratios (RR) comparing each intervention to the natural course are presented in Table 2. For synthetic fluid exposure (intervention 1), the RRs for lung cancer mortality at all four ages indicated modestly reduced lung cancer death risk with borderline statistical significance associated with a synthetic fluid ban. When we additionally intervened to also ban biocide exposure (intervention 2), risk of lung cancer death increased compared with the natural course, although confidence intervals included the null. When instead only biocides were banned and synthetics MWFs allowed to follow a natural course (intervention 3), we observed an increased risk of lung cancer mortality with borderline statistical significance and slightly larger effects at younger ages.

DISCUSSION

A previous study in the UAW-GM cohort by Mehta et al. found reduced risk of lung cancer mortality associated with synthetic fluids when biocides were also present.[9] Our hypothesis was that biocide exposure—serving as a proxy for endotoxin contamination—might be causing the protective effect of synthetic fluids on lung cancer. We therefore compared the impact of intervening on synthetic fluid while not intervening on biocide exposure (intervention 1) to intervening on biocide exposure (intervention 2), as well as a biocide-only intervention (intervention 3). The results support our hypothesis. We observed a nominally reduced risk comparing a ban on synthetic MWF to the natural course of exposure, indicating a positive association between synthetic fluid exposure and lung cancer mortality. In contrast, intervening to simulate a ban on biocide exposure increased the risk of lung cancer death compared to the natural course, indicating an inverse association between biocide exposure and lung cancer mortality. Simulating a ban on both synthetic MWF and biocide produced an overall increased lung cancer mortality risk, likely driven by the biocide ban. These results suggest that exposure to synthetic fluid, per se, does not reduce lung cancer mortality, but rather it is the presence of biocide added to the water-based fluid, serving as a surrogate for endotoxins, that reduces the risk, lending evidence in support of the hygiene hypothesis for cancer.

Several occupational studies have supported the link between endotoxin exposure and reduced risk for lung cancer, particularly in the textile and agricultural sectors.[11 34 35] A 2010 meta-analysis reported the summary risk of lung cancer as 0.72 (0.57–0.90) in the cotton textile industry and 0.62 (0.52–0.75) in the agricultural industry.[34] Our results, treating biocide as a surrogate for endotoxin, are consistent with this hypothesized link. Prior lung cancer studies in the UAW-GM cohort are inconsistent regarding this relationship. The most recent UAW-GM study on biocide and synthetic MWF exposure observed a null association for years exposed to biocide.[9] An earlier study, however, found reduced lung cancer odds ratios for workers with longer duration of exposure to biocides.[8] Workers with 8.52 or more years of biocide exposure had an odds ratio of 0.54 (0.34–0.86) compared with unexposed workers. In the present analysis, we dichotomize biocide exposure as ever or never exposed.

We applied the parametric g-formula to control for the HWSE reported to be operating for lung cancer in a prior analysis of the UAW-GM cohort.[21] A limitation of the parametric g-formula is that it is predicated on the assumption of correctly specified models; in this case the parametric models for employment status, MWF and biocide exposures, death due to a competing risk, and death due to lung cancer (see appendix for details). Models may be biased if there are violations of the assumptions of no unmeasured confounders, no information bias, or correct model specification.[28] Information bias, specifically exposure misclassification, is possible since we rely on a JEM and employment histories to assign exposure; however, any misclassification is unlikely to have been differential with regards to lung cancer mortality. We optimized these models to predict cumulative lung cancer mortality during follow-up, which ends at age 86 for our study; had we selected another age end point the models may have been specified differently. See figure 2 for small deviations in the cumulative mortality curves at ages younger than 86, although the two curves are

relatively aligned. We also assumed the G null paradox is not the reason for our results. The G null paradox states that under the null hypothesis it may be impossible to correctly specify the parametric models for the g-formula, and consequently the parametric g-formula will reject the null when it is in fact true.[22 36] A limitation of the UAW-GM cohort was the lack of smoking data. We were unable to assess whether smoking was associated with exposure, which would make it a potential confounder, nor could we control for it in our analysis. The only data available were limited to a very small number of male subjects selected for a cross-sectional survey mid-way through follow-up (1985–1986). While 1,666 workers in the present study participated in this survey, we did not use the data here because it was too small a subset to be used to impute smoking for the entire study population. Results reported in this study may be affected by this limitation. Additionally, a lack of smoking data may have limited our models for competing risk since it is a major predictor of mortality outside of lung cancer mortality. Lastly, we relied on categories of MWF composition which, while better than combining all MWF exposure, still combines complex, heterogenous mixtures into only three broad classifications. Potential causative agents in the MWF, such as nitrosamines in synthetic fluids, were not uniformly present across processes or time, [26] and thus may not be properly captured by the exposure measures used here, though adjusting for calendar year may have adjusted for any time trends. However, several studies from this cohort, using these same exposure estimates, have reported findings associated with synthetic MWF exposure.[6–10]

This study adds to the literature on MWF exposure and risk of lung cancer. By using the parametric g-formula, we controlled for the HWSE previously observed to be present in this cohort.[21] Results suggest a slightly elevated risk of lung cancer mortality related to synthetic MWF exposure with borderline statistical significance. Our results do not support the protective effect for synthetic fluids reported in earlier studies; instead, biocides added to the fluids, a proxy for endotoxin contamination, were associated with decreased lung cancer risk. This provides additional evidence in support of the hygiene hypothesis for cancer.[11–13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

What is already known about this subject?

- The literature addressing the relationship between occupational exposure to metalworking fluids and risk of lung cancer has been inconsistent.
- Earlier studies may have been biased due to the healthy worker survivor effect.

What are the new findings?

- The results of this study, which controls for this potential source of bias, suggest a modest positive association between synthetic fluid exposure and lung cancer mortality.

How might this impact on policy or clinical practice in the foreseeable future?

- An inverse association was observed for biocide exposure, lending evidence in support of the hygiene hypothesis for cancer.

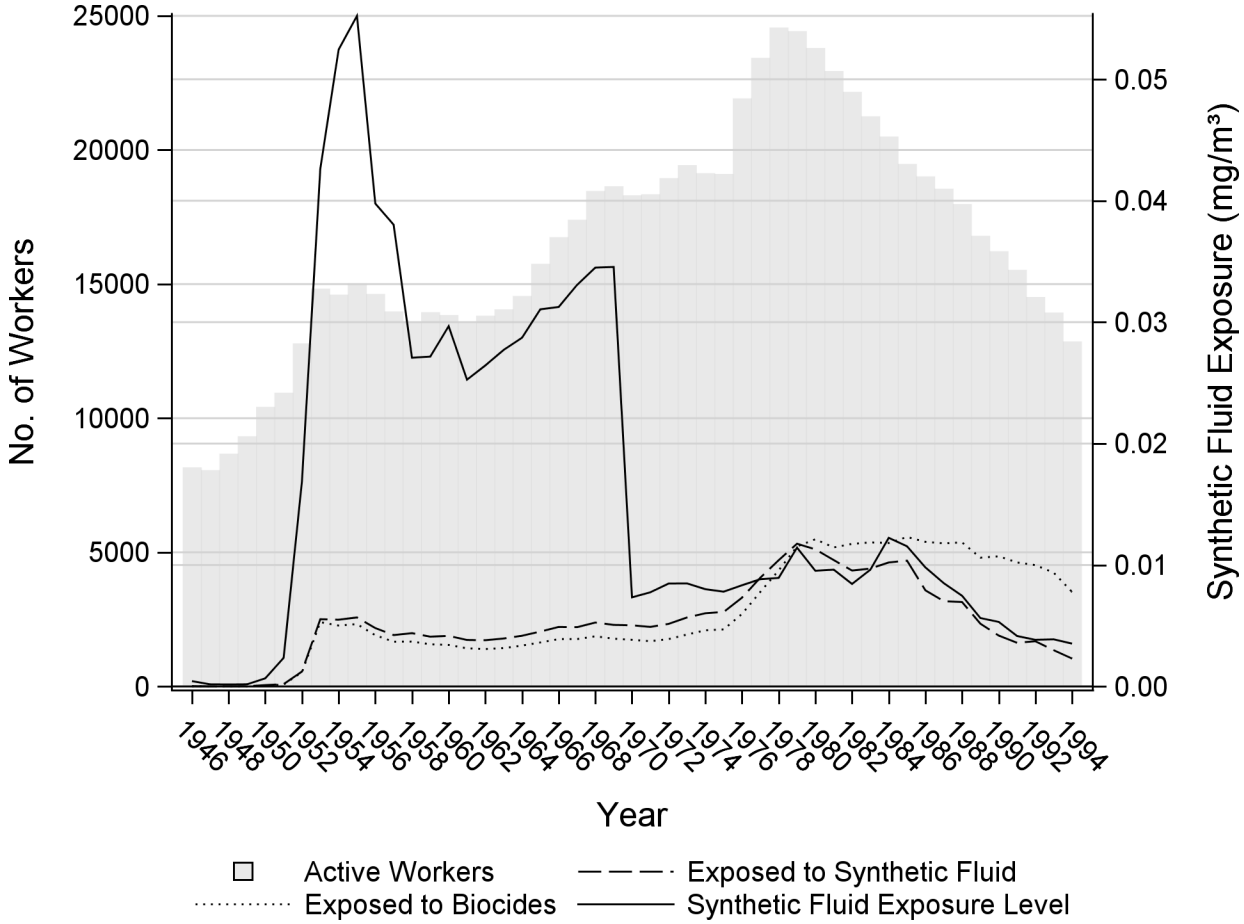

Figure 1.

Number of workers actively employed (grey vertical bars), number exposed to synthetic MWF (dashed line), and number exposed to biocides (dotted line) along with mean annual daily average synthetic fluid exposure concentration among exposed workers (solid line) for each calendar year in the UAW-GM cohort. The x-axis starts with 1946 because exposure prior to this year was nominal.

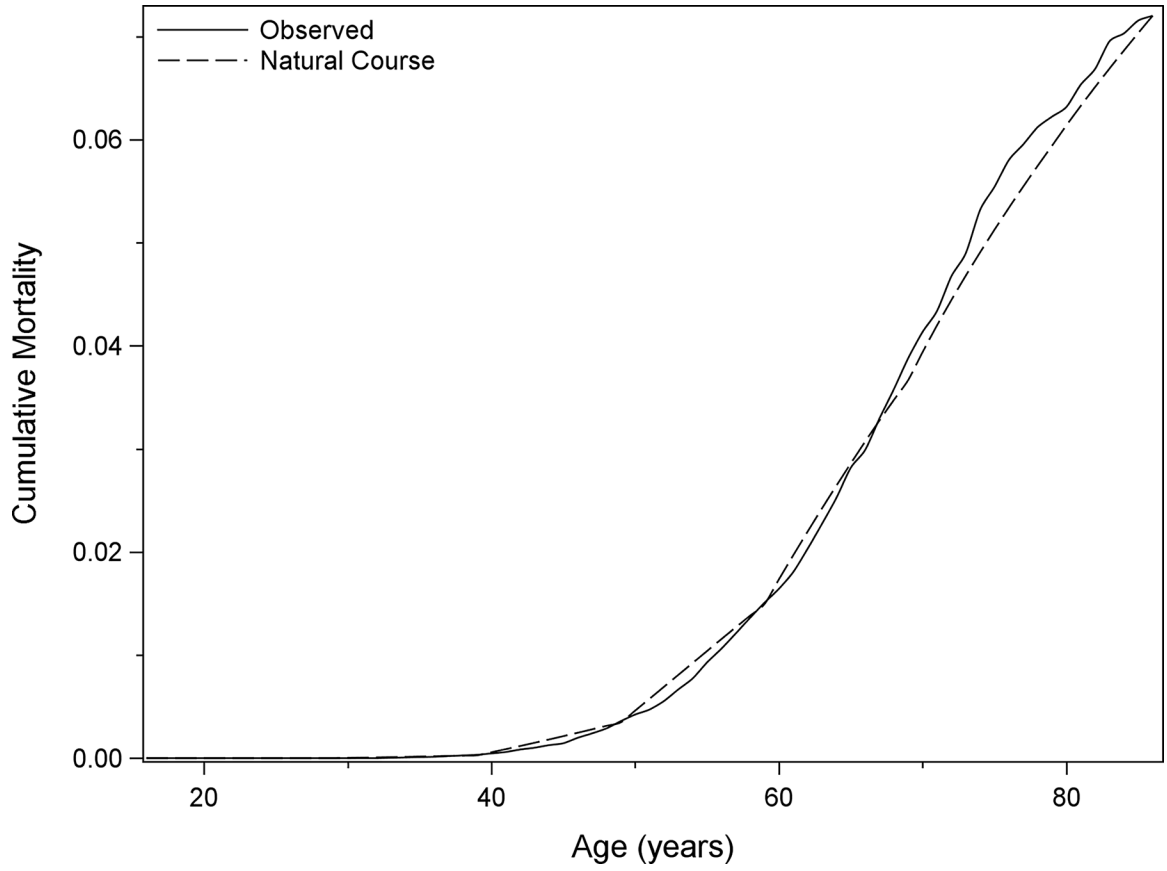

Figure 2.
Observed (solid line) and simulated (dashed line) cumulative lung cancer mortality in the UAW-GM cohort, under the natural course of exposure.

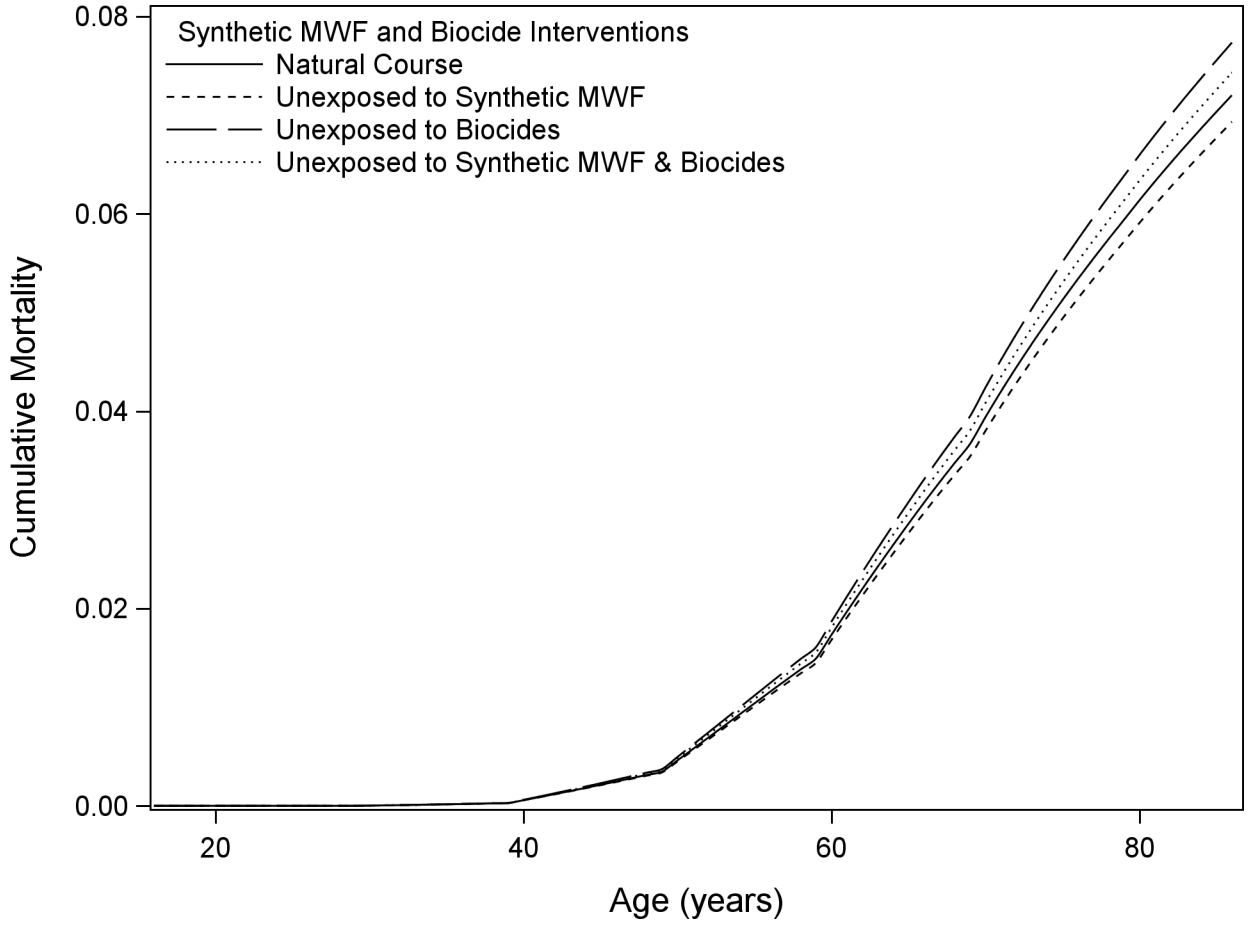

Figure 3.

Simulated cumulative lung cancer mortality in the UAW-GM cohort under three interventions compared with the natural course of exposure (solid line): 1) reduce synthetic MWF exposure to 0 mg/m^3 (short dashed line), 2) always unexposed biocides (long dashed line), and 3) reduce synthetic MWF exposure to 0 mg/m^3 and always unexposed biocides (dotted line).

Table 1.

Demographic characteristics of the UAW-GM cohort at baseline. [IQR=interquartile range]

	N	%	Median	IQR
No. subjects	38,560			
No. person-years	1,122,160			
Characteristic				
Age			24	19–32
Male	33,801	87.7		
Female	4,759	12.3		
White	31,426	81.5		
African American	7,134	18.5		
Plant				
1	9,090	23.6		
2	17,094	44.3		
3	12,376	32.1		
Calendar Year			1965	1952–1973
Number of events				
Lung cancer deaths	873			
Other deaths	8,537			

Table 2.

Cumulative lung cancer mortality by select ages under simulated natural course and three simulated interventions[a] in the UAW-GM cohort. [MWF=metalworking fluid; RR=risk ratio; 95% CI=95% confidence interval]

	55 years-old			65 years-old			75 years-old			86 years-old		
Intervention[a]	**Risk**	**RR**	**95% CI**	**Risk**	**RR**	**95% CI**	**Risk**	**RR**	**95% CI**	**Risk**	**RR**	**95% CI**
Natural course (no intervention)	1.04	Referent		2.86	Referent		5.13	Referent		7.20	Referent	
(1) Synthetic MWF	1.01	0.97	0.92–1.00	2.76	0.97	0.92–1.01	4.94	0.96	0.91–1.01	6.93	0.96	0.91–1.01
(2) Synthetic MWF and biocides	1.08	1.04	0.96–1.11	2.97	1.04	0.95–1.11	5.30	1.03	0.95–1.11	7.43	1.03	0.95–1.11
(4) Biocides	1.12	1.08	1.00–1.16	3.08	1.08	1.00–1.16	5.51	1.08	1.00–1.16	7.73	1.07	1.00–1.16

[a]Interventions intervened on the specified exposure(s) and fixed exposure(s) to always unexposed, i.e., a ban. Contrasts, as RR, were made to the simulated natural course.