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Respiratory exposures to solvents and metalworking fluids in relation to chronic health outcomes: strategies for reducing bias within conditional modeling approaches

by

Stella Fay Beckman

A dissertation submitted in partial satisfaction of the

requirements for the degree of

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in

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of the

University of California, Berkeley

Committee in charge:

Professor Ellen A. Eisen, Chair
Professor John R. Balmes
Professor S. Katharine Hammond
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Spring 2016

Respiratory exposures to solvents and metalworking fluids in relation to chronic health outcomes: strategies for reducing bias within conditional modeling approaches

Stella Fay Beckman

Abstract

Respiratory exposures to solvents and metalworking fluids in relation to chronic health outcomes: strategies for reducing bias within conditional modeling approaches

by

Stella Fay Beckman

Doctor of Philosophy in Epidemiology

University of California, Berkeley

Professor Ellen A. Eisen, Chair


**Background**
Occupational injury and illness are significant contributors to the global burden of disease, with more than 2 million deaths caused by work-related hazards estimated to occur worldwide each year. The goal of occupational epidemiology is to identify and characterize the causes of work-related injury and illness in order to inform workplace health and safety interventions. While occupational groups provide opportunities to study exposures at higher levels than those seen in the general population and with well-characterized exposures, studies of chronic diseases among workers are subject to a unique form of bias: the healthy worker effect. This results in downward bias, which can even make a truly hazardous exposure appear protective, under two circumstances: 1) when workers, who are overall healthier, are compared to the general population and 2) when workers with more robust health (survivors) remain in highly exposed jobs and accrue more exposure than those who leave work. While causal inference techniques are required to fully address this effect, there are approaches that may mitigate the bias within a standard conditional model.

**Methods**
In this dissertation, I explore the associations between occupational exposures and health outcomes with particular attention to bias caused by the healthy worker effect. In the second chapter, I estimate the association between acquired color vision defects and past exposure to *n*-hexane in a cross-sectional study of active and retired automobile repair workers in the San Francisco Bay Area, California. Color vision defects are hypothesized to be an early indicator of neurotoxicity caused by *n*-hexane. In the third and fourth chapters, I consider exposure to metalworking fluid (MWF) in a large cohort of machinists. I investigate the association between MWF and chronic obstructive pulmonary disease mortality in chapter three, using indirect adjustment for confounding by cigarette smoking status as well adjustment for cardiovascular disease mortality as a potential competing risk. In chapter four, I estimate the association between mineral oil-based MWF and mortality due to natural causes and cardiopulmonary disease in weighted Cox proportional hazards models, using inverse probability weights to address informative censoring and selection bias in a cross-sectional sample of the cohort. I contextualize all findings in within subject matter literature and discuss limitations of the methods chosen to address bias due to the healthy worker effect.

**Conclusion**

The chapters of this dissertation explore the associations between common industrial exposures (solvents and metalworking fluid) and health outcomes occurring many years after exposure. I find an elevated, though not statistically significant, association between *n*-hexane exposure and acquired color vision defects among automobile repair mechanics exposed to levels of *n*-hexane below current regulatory limits. For exposure to MWF, I find elevated risk of chronic obstructive pulmonary disease with 95% confidence intervals excluding 1 when adjusted for cardiovascular disease as a competing risk in Cox proportional hazards models. I report modestly but inconsistently elevated risks of natural cause and cardiopulmonary disease mortality with exposure to mineral oil-based MWF in models weighted to adjust for informative censoring and sample selection. Given the evidence of residual downward bias due to elements of the healthy worker survivor effect that can only be addressed with causal inference methods, these results taken as a whole suggest that current occupational safety and health regulations are not sufficiently protective of worker health, and should be reconsidered in light of this evidence.

For my parents, Swiss and Alan Beckman: your love and support made this journey possible.

## Table of contents

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## Chapter 1: Background

Occupational factors contribute significantly to the global burden of injury, illness, and death. Recent research has estimated that there are approximately 310,000 fatal injuries and 2.02 million deaths from illness related to occupational hazards each year worldwide (1). In the United States a conservative estimate of 55,200 deaths due to occupational disease or injuries occurred annually, makes work-related mortality the 8th leading cause of death nationally (2). An estimated 4% of annual global GDP ($2.8 trillion US dollars) is lost due to occupational injuries and illness (1), with losses of $250 billion in direct and indirect costs lost the US in the year 2007 alone (3). Due to data limitations and consistent under-reporting of occupational injury and illness even in countries with well-established and regulated occupational health infrastructures, these measures are very likely to undercount of the true burden of injury and illness caused by work. Rates of occupational illness and injury are substantially higher in developing regions of the world, and some of the improvement in occupational health in industrialized economies results from the shifting of hazardous jobs from industrialized to developing regions (1,4). As of 2004, 80% of the 3.2 billion working people in the world lived in developing countries; multinational corporations take advantage of lower pay and weak regulations to locate manufacturing operations in developing regions, where only an estimated 10% of workers are protected by occupational safety and health laws (5). The United States' global share of manufacturing activity has declined from 30% in the 1980s to 17-18% in 2015, while China became the world leader in manufacturing (6). Brazil, India, and Mexico are also world leaders in manufacturing and along with China are described by the International Monetary Fund as developing economies (7). Occupational safety and health issues that were formerly of most concern in industrialized nations have spread to vulnerable workers worldwide.

The goal of occupational epidemiology is to identify causes of ill-health and characterize the relationships between exposures and outcomes in order to inform interventions designed to reduce or eliminate hazardous workplace exposures. Work-related diseases have been recognized since antiquity - Hippocrates instructed physicians to take patients' vocation into account when diagnosing and treating disease. Many chronic occupational diseases were characterized during the 19th and early 20th centuries using case series, and the development of the retrospective cohort study design in the 1950s provided occupational epidemiologists with methods for studying less common diseases with long latency periods (8). Moreover, occupational settings provide the opportunity to study large populations well defined by employment records, with well documented exposures occurring at higher levels than in the general population. Studies of chronic disease in worker populations, however, pose a unique challenge: people who obtain employment and remain employed are healthier than the general population, resulting in what is known as the healthy worker effect (9).

The healthy worker effect can be described as confounding or selection bias and has two components. The first, termed the healthy hire effect, occurs when people are selected into the workforce; people who are able to work are in better health than those who, due to age or ill health, are unable to seek employment. When the general population is used as a reference group for the more robust workers, the groups are unexchangeable and an adverse effect of the exposure of interest may be masked. The healthy hire effect can be ameliorated by selecting an appropriate reference group, frequently an internal reference – comparing exposed subjects to unexposed or less exposed workers (9). The second component, the healthy worker survivor effect (HWSE) is more complex. It occurs when workers who are in worse health systematically

leave the workforce or transfer to jobs with lower exposure and accrue less exposure than healthier workers (9,10). In a cross-sectional study design recruiting actively employed workers, those with longer tenure will be more likely to be selected than short term workers, a form of length-based sampling bias. This results in a sample enriched with "survivors" who are in better health than those who leave earlier due to adverse health effects. One method for addressing this source of bias in cross-sectional studies is to lag exposures, that is, consider only exposures that occurred before the onset of disease in cases and ignoring exposures that occurred after; while the experience of individuals who left work before they could become study subjects cannot be captured, this method ignores the additional exposure accrued by subjects who, due to better health, remained in jobs with higher exposures (11). In longitudinal studies, if health status is both influenced by past exposure and a cause of future exposure as well as the outcome, the result is time-varying confounding by health status which results in bias downwards in estimates of the exposure-response relationship as healthier workers accrue more cumulative exposure than workers in poorer health. Causal inference methods such as marginal structural models and g-estimation can be used to adjust for this time-varying confounding without introducing bias by conditioning on a covariate that is also on the causal pathway (12). Several methods have been suggested to reduce bias using standard methods, including conditioning on indicator of active work status at the time of death (leaving work is associated with mortality and exposure ceases when a subject leaves work) and adjusting for time since hire, longer time since hire being a cause of both higher exposure and elevated mortality risk (9).While these methods do not eliminate the bias created by conditioning on a causal intermediate, they may reduce healthy worker bias.

In the second chapter of this dissertation, I investigate the association between exposure to *n*-hexane and other solvents and acquired color vision defects using data from a study of exposure to *n*-hexane in cleaning solvents used by automotive mechanics. Exposure to *n*-hexane has been associated with neurotoxicity in workers, with case reports of neuropathy dating back to 1964 (13); acquired color vision defects may be a preclinical marker of neurotoxicity (14). The Bay Area Solvent Study (BASS) was designed to investigate associations with neurologic and reproductive outcomes in a group of workers exposed to solvent-based cleaning products that were formulated with *n*-hexane during 1989-2002. Using quantitative measures of solvent exposure and color vision acuity, I estimate the prevalence ratio for color vision defects among workers exposed *n*-hexane and other solvents. Although both retired and active workers were recruited to avoid healthy worker survivor bias due to over-representation of long-term workers, I consider other limitations related to the cross-sectional study design. This is the largest epidemiologic study of the association between hexane exposure and color vision defects to date.

In the third and fourth chapters I address exposure to airborne particulate matter (PM) among workers in three US automobile manufacturing facilities. Machinists are exposed to PM created by aerosolization of metalworking fluid (MWF) when it is sprayed over tools and parts being worked as a coolant and lubricant. In order to assess the association of MWF with cancer and mortality, the trade union United Auto Workers and manufacturer General Motors jointly funded the GM-UAW cohort study of almost 40,000 workers with quantitative PM exposure assessment throughout their work history who were followed for mortality outcomes from 1941 to 2009. In chapter three, I use these data to explore the association between exposure to respirable MWF PM and mortality due to chronic obstructive pulmonary disease (COPD). Although this analysis does not address bias due to the healthy worker effect, I adjust indirectly for potential

confounding by cigarette smoking using smoking rates from a cross-sectional sample of the GM-UAW cohort performed in 1985; because most occupational cohorts lack data on cigarette smoking habits, this is one of a very few analyses of MWF exposure and COPD that address confounding by smoking. Exposure to PM can cause non-malignant respiratory disease including COPD; although much research focuses on ambient air pollution, occupational exposures are estimated to be responsible for 15-20% of COPD cases (15), with an estimated 318,000 deaths in the year 2000 (16). I discuss limitations of the analysis including bias created by the healthy worker survivor effect, and interpret the results of the analysis in the context of existing literature regarding MWF exposure and COPD.

The fourth chapter describes an analysis of the association between mineral oil-based MWF and mortality in subjects of the cross-sectional study who have detailed data on respiratory health, demographics, and cigarette smoking. In order to be eligible for the cross-section, workers had to be actively employed in 1985, which induces healthy worker survivor bias by excluding workers who left work or died before this date. I address this bias by estimating inverse probability weights (IPW) to apply to models of the exposure-response relationship in the cross-sectional data with the goal of creating a pseudo-population that reflects the full cohort unaffected by differential loss to follow-up (12). By using follow-up of the cross-sectional study population to estimate the exposure-response relationship I am able address confounding by cigarette smoking and socioeconomic factors that were measured only in the cross-section, while attempting to alleviate some of the selection bias with IPW. I discuss the results of the analysis, which uses a relatively novel method to address selection bias, in the context of other studies of MWF exposure and mortality.

The overall objective of this dissertation is to contribute to the body of knowledge about the effects of solvents and metalworking fluid exposure on worker health. In light of the fact that it is rarely possible to obtain unbiased estimates of the exposure-response relationship in studies of chronic work-related diseases without causal inference methods, I pay particular attention to discussing approaches to reduce this bias within standard conditional modeling schemes. Understanding the associations between occupational exposures and health outcomes is critical to informing efforts to reduce exposures and protect worker health.

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**Chapter 2: Acquired color vision defects and hexane exposure; a study of Bay Area automotive mechanics**

**Introduction**

Solvent-based cleaning products are used in the automobile repair industry to remove oil and grease from auto parts. Aerosol spray cans are the most commonly used application, with over 12,000 metric tons of automotive cleaning aerosol solvent products sold in California in 1997 (1). During 1989-2002, some products were formulated with 25-90% commercial hexane, and some contained both hexane and acetone (1). By 2002, hexane had been phased out of all commercial products (2). Other solvents commonly included were toluene, methyl ethyl ketone, and xylenes. The *n*-hexane isomer is not quantified in individual commercial products, although commercial hexane typically contains 20-80% *n*-hexane (1). Exposure to *n*-hexane has been shown to cause neurotoxicity in occupational settings, with case reports of neuropathy appearing in the medical literature as early as 1964 (3). Toxicity is believed to occur via the metabolite 2,5-hexanedione, which binds with proteins to form crosslinks between neurofilaments in both the central and peripheral nervous systems (4–7). Animal studies indicate that the neurotoxic action of *n*-hexane may be potentiated by co-exposure to acetone, possibly by slowing the elimination of 2,5-hexandedione from the body (8–10). A study of hexane and acetone-exposed workers had increased urinary 2,5-hexanedione compared to those exposed to hexane alone (11). Several studies have found associations between exposure to hexane and acquired color vision defects, although cumulative exposure was not well characterized (6,12,13).

Color vision defects may be congenital or acquired, and are commonly classified as red-green, blue-yellow, or nonspecific. Hereditary color vision defects are caused by missing or anomalous photoreceptors, whereas acquired color vision defects are caused by damage to the retina or optic nerve (14). Hereditary red-green color blindness occurs in approximately 10% of males and 0.5% of females; hereditary blue-yellow color blindness is rare, occurring in 0.0001% of the population (14). Acquired color vision defects, especially blue-yellow color confusion, are associated with increasing age, eye diseases such as cataract and glaucoma, alcoholism, and exposure to solvents (14,15).

The Bay Area Solvent Study (BASS) was initiated in 2007 to investigate possible associations between occupational exposure to *n*-hexane and a variety of health outcomes, including acquired color vision defects, among automotive mechanics employed in the San Francisco Bay Area, California, USA. The sentinel event was a 1998 case report of an automotive repair worker diagnosed with peripheral neuropathy at an occupational health clinic in San Francisco, California. He reported using one to nine cans per day of an aerosol solvent product containing hexane (16). A small follow-up study of the exposure and health status of six auto repair workers in a nearby repair shop revealed that five had symptoms of peripheral neuropathy and three had detectable urinary levels of 2,5-hexanedione (16). Two of these workers had sensory or nerve conduction abnormalities, and color vision defects, primarily blue-yellow color confusion, were present in all subjects (16). While color vision defects are not clinically significant outcomes, they may be an early marker of *n*-hexane neurotoxicity (17,18).

The objective of this analysis was to investigate possible associations between past exposure to non-hexane solvents or hexane with or without co-exposure to acetone, and persistent risk of acquired color vision defects, particularly blue-yellow defects, among active and retired San Francisco Bay Area auto mechanics.

**Methods**

Study population

BASS is a cross-sectional study of 835 participants in the San Francisco Bay Area who had worked as an automotive technician (mechanic) at any point during the period that hexane was present in aerosol automotive cleaning products. Eligible workers were identified from the records of a union representing mechanics employed at auto dealerships. Many workers had been employed at more than one automotive repair shop, for a total of 1946 shops. All male workers or retirees who were employed at any time during 1989-2002 (the time period hexane was included in solvent cleaners) who were younger than 60 and still lived in the Bay Area were eligible. Since few women were employed in the industry at the time of hexane use, females were not included. The restriction to current Bay Area residents was necessary due to in-person data collection.

Following telephone contact to recruit and confirm eligibility, appointments were made for participants to attend a clinic staffed by trained study personnel.  For some participants a mobile clinic was used.  All clinic visits occurred between 2008 and 2011. At the clinic, participants responded to a questionnaire that obtained demographic, health and work history information, and participated in clinical assessments, including color vision testing.  The work history component identified frequency and duration of tasks performed that used solvents, and specific products and solvents used. A booklet containing pictures of various products that had been available over the last 2 decades was used as a memory aid.

After identifying 4186 potentially eligible workers from union records based on job title, age and gender, we were able to contact 2848 (68.0%) by telephone or postal mail. Of these, 1765 were eligible, based on residence, age, job duties and active work during 1989-2002. A total of 835 eligible workers participated in the study (47.6% participation rate). The most common reasons for refusal were lack of interest (38.0%) and being too busy (19.9%). Among BASS participants, 18 (2.2%) had missing hexane exposure data and were excluded from the current analysis. Of the remaining 817, 53 (6.5%) with congenital color vision defects and 10 (1.2%) who were unable to complete the full color vision assessment were excluded, resulting in a total of 754 participants. The 81 participants who were excluded were similar to those included in all respects except that they were less likely to be working as a mechanic at the time of the study. For the analysis of blue-yellow color vision defects, participants with acquired nonspecific or red-green defects were excluded, leaving a final total for the analysis of blue-yellow color vision defects of 689.

Exposure assessment

Exposure to total volatile organic chemicals (VOC) was calculated by combining task-based VOC concentrations with participants' reports of cleaning tasks they performed, daily duration of these tasks, solvent types and brands used, as well as quantities used over their work history. Task-based VOC concentrations were obtained from data collected in San Francisco Bay Area automotive repair shops by Wilson et al. (1). Based on these data, each combination of task and application method (aerosol can, pump spray, solvent tank, etc.) was assigned a concentration of VOC in the breathing zone, which was multiplied by the reported time spent performing that task per day. The 8 hour (shift) time weighted average was calculated in $mg/m^3$ by multiplying the task-based VOC concentration by the minutes per shift spent on a given task, and summing across all tasks performed during the shift. Far-field exposure for shift time not spent on a cleaning task and inhalation equivalent exposure due to dermal contact were added to the task-based exposures.

Exposure to hexane was calculated by applying the percent of hexane in a product, obtained from Material Safety Data Sheets for each product, to the total VOC exposure. Only aerosol products contained hexane, and these products evaporated completely, therefore the fraction of hexane in the product was the same as in the breathing zone. Acetone exposure was not quantified, but was defined as being present or absent in any hexane formulation. Hexane was subtracted from total cumulative solvent exposure to provide a quantitative estimate of non-hexane solvent exposure.

Color vision

Color vision was assessed with the Lanthony desaturated D-15 panel test (19,20). The test is performed by arranging 15 randomly ordered colored caps by color, starting from a fixed reference cap. Incorrect ordering of the caps indicates imperfect color vision. Quantitative scoring systems are used to assess the severity of color confusion, as well as to identify blue-yellow, red-green, or nonspecific color vision defects, based on the participant's arrangement of the caps.

All tests were administered binocularly, with participants wearing their habitual corrective lenses; all participants had sufficient visual acuity and contrast sensitivity to perform the tests. Participants were then screened for congenital color vision defect using Ishihara plates, and those without congenital color vision defects were administered one trial of the Adams desaturated D-15 panel test (similar to the Lanthony test but more saturated and therefore easier to complete) as a demonstration, then two trials of the Lanthony test. Lanthony test results were scored by an optometrist blinded to participants' exposure status using the method described by Adams et al. to calculate continuous color confusion score, a measure of severity, with a higher score indicating worse color vision (21).

Reproducibility between Lanthony trials was measured by the difference between scores on the first and second trials. Participants with the mean color confusion score of the two Lanthony trials greater than 20 were classified as having a color vision defect. For participants with a color confusion score > 20 on the second trial, the Vingrys and King-Smith method was used to classify the color defect type as red-green, blue-yellow, or nonspecific (22). Any color vision defect and blue-yellow defects were considered separately in statistical analyses.

Statistical methods

Cumulative exposures to non-hexane solvents, hexane, and hexane in the presence of acetone were calculated in mg/m$^3$-year for each participant over his work history up to the date of study participation. For participants no longer working as auto mechanics, cumulative exposure was assumed to have remained constant after their last automotive repair exposure. Blue-yellow color vision defects and any color vision defects were treated as binary outcomes. Age was strongly associated with both color confusion and cumulative exposure, and therefore included in all models to adjust for confounding. Analyses were performed using all participants, then repeated in participants age 50 or younger; because blue-yellow color vision deteriorates due to aging beginning at approximately age 50, stratification was performed to reduce bias resulting from inclusion of color vision defects caused by age alone (15,23). Based on an a priori analysis plan informed by acquired color vision defects literature, we considered adjustment for confounding by race, cigarette smoking, alcohol consumption, and history of concussion or head injury; covariates were retained in the model if they resulted in a greater than 10% change in the solvent effect estimate. Eye diseases and diabetes, as intermediate variables rather than confounders, were therefore not included in models.

Prevalence ratios (PRs) for color vision defects by exposure to non-hexane solvents, hexane, and hexane in the presence of acetone were estimated using log-binomial regression (24). Total solvent exposure was divided into quartiles based on the 689 participants in the blue-yellow analysis with the first quartile as the reference group, and hexane with and without acetone co-exposure was divided at the median of the exposed participants, with participants unexposed to hexane as the reference group. Participants exposed to hexane, but not hexane in the presence of acetone, were excluded from analyses of hexane exposure with acetone (85 participants, 11.3%). Effect estimates with a confidence interval excluding one were considered statistically significant.

Statistical analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). The study protocol was approved by the Committee for Protection of Human Subjects at the University of California, Berkeley. Written informed consent was obtained from all participants before participation.

**Results**

Study population

Color vision and demographic characteristics of the BASS participants are presented in Tables 1 and 2. Physician-diagnosed eye disease was reported by 6.2% of participants, the most common condition being cataract. Of the 754 participants completing the Lanthony test, 359 (47.6%) were ≤ 50 years of age. The prevalence of any acquired color vision defects among younger participants was 22.6% and 16.7% had blue-yellow defects.

Most participants (53.6%) were no longer working as a mechanic at the time of the study (Table 2).The majority of participants were non-Hispanic whites, drank alcohol in moderation, had never smoked cigarettes, and had at least some college education. All participants were exposed to solvents, and 53.1% were exposed to hexane. Fewer participants were exposed to hexane in the presence of acetone, and among them, cumulative hexane exposures were lower.

On average, Lanthony scores were lower on the second trial (Table 1) indicating improvement. However, although 46.2% of participants improved, 32.0% got worse, suggesting no consistent learning effect. The median difference between trials was 0, with a narrower range among younger participants, (IQR, -4.4 to +8.7) compared to IQR -6.0 to +9.4 among all participants, indicating better reproducibility among younger participants.

Blue-yellow color vision defects

Continuous age in years was the only covariate that contributed to the exposure-response model. We observed elevated PRs for blue-yellow defects for all quartiles of non-hexane solvent exposure, although all 95% confidence intervals (95% CI) included one. When the analysis was restricted to participants younger than 50, a monotonic increase in PRs from 1.75 (95% CI: 0.89, 3.46) in the second quartile to 2.17 (95% CI: 1.03, 4.56) in the fourth quartile was observed (Table 3). There was no association with exposure to hexane at any level. For hexane in the presence of acetone, however, an elevated PR of 1.15 (95% CI: 0.84, 1.57) in the most highly exposed group was seen among all participants, which increased to 1.62 (95% CI: 0.97, 2.72) when restricted to younger participants. A statistically significant protective association was seen in the first exposure quartile for hexane in the presence of acetone. Among all participants, age was associated with statistically significantly increased PRs, but in participants ≤ 50 all PRs for age were null.

Any color vision defect

As with the models for blue-yellow defects, continuous age was the only covariate included in the exposure-response models. Among all participants, a non-significantly elevated PR was observed for any color vision defect in all non-hexane solvent exposure levels, with the highest in the fourth quartile (PR=1.28, 95% CI: 0.93, 1.76) (Table 4). In participants younger than 50, exposure to non-hexane solvents was associated with any color vision defect, with PRs of 1.73 (95% CI: 1.02, 2.94) in the third quartile and 1.72 (95% CI: 0.97, 3.08) in the fourth quartile. For all exposures to hexane, with or without acetone co-exposure, the effect estimates were in a protective direction, with all 95% confidence intervals including the null. In younger participants, hexane exposure with or without acetone was associated with an elevated PR for any color vision defect, although 95% CI included one.

**Discussion**

These analyses are from the first epidemiologic study of hexane exposure and acquired color vision defects with quantitative exposure assessment, and one of few published studies of this exposure-response relationship in humans. Our findings provide evidence of an association between non-hexane solvent exposure and blue-yellow as well as all color vision defects in male automotive workers aged ≤ 50. While no associations with hexane exposure were statistically significant, elevated PRs in the more highly exposed younger participants are suggestive of an association. A 2003 literature review by Gobba and Cavalleri found evidence of associations between color vision defects and exposure to styrene, perchloroethylene, and toluene, with less evidence for hexane and mixtures of solvents (25). While acquired blue-yellow defects are generally associated with damage to the retina (26), there is also evidence that the mechanism of solvent-induced color vision defects could be neurologic (27,28). Color vision defects associated with occupational solvent exposures are most commonly of the blue-yellow type, with blue-yellow mixed with red-green occurring more rarely and with higher exposures (25).

A key reason for carrying out this study was to explore the potential of using acquired color vision defects as a sensitive early marker of *n*-hexane neurotoxicity (17,18). Color vision defects and maculopathy were noted in two of 28 subjects in a polyneuropathy outbreak investigation among hexane-exposed Taiwanese printing press workers, with the defects persisting after four years of follow-up (29). A study of 15 subjects exposed to concentrations in air typically below 1765 mg/m$^3$ with peaks as high as 10,500 mg/m$^3$ found that 12 had a color vision defect (13). A study of 26 workers exposed to hexane and 50 controls published in 2002 showed worse overall color discrimination among the exposed, with blue-yellow and red-green defects present (13). In our study, the presence of acetone in some solvent products provided an opportunity to examine its potential synergistic effect on hexane toxicity (29). While no statistically significant associations were seen in younger participants for blue-yellow defects and hexane exposure, PRs in the more highly exposed participants were elevated, with stronger associations for hexane with co-exposure to acetone despite lower hexane concentrations.

Elevated PRs for blue-yellow defects as well as for any defect were seen in the two highest exposure quartiles of non-hexane solvent exposure; exposure concentrations for non-hexane solvents were at least an order of magnitude above those for hexane. Evidence in the current literature for the association of color vision defects and exposures to mixed solvents is inconclusive, but generally reflects a positive association (25,30,31). The solvents used by our participants were mixed products, containing toluene, xylenes, and other solvents, in addition to hexane and acetone. Combining data from available publications, Gobba and Cavalleri found a statistically significant correlation between cumulative toluene exposure and color confusion.

Xylene is another component of auto cleaning solvents for which there is evidence of an association with color vision defects: a 2013 study by Lee et al. found an association between the xylene metabolite methylhippuric acid and blue-yellow defects and color confusion in shipyard workers (32).

There are two factors that might have attenuated the observed associations. First, the 5-13 years between cessation of hexane exposure and color vision assessment. No previous studies of hexane exposure and color vision have reported the long-term persistence of color vision defects following exposure cessation, and little has been published on the reversibility of color vision defects associated with other solvents (25). There is evidence, however, that hexane-induced neuropathy is reversible, suggesting that acquired color vision defects might also be reversible following cessation of exposure (8,29). Second, the concentrations of hexane exposure were low relative to the existing regulatory limits – the California Occupational Safety and Health Administration's current permissible exposure limit is 176 mg/m$^3$ as an 8-hour time-weighted average. If a worker were exposed at the permissible exposure limit for the full 13 years that hexane was in use, they would accrue 2,340 mg/m$^3$-years of cumulative exposure; in comparison, the 99$^{th}$ percentile of hexane exposure in BASS is 470 mg/m$^3$-years. Hexane exposures in the presence of acetone were even lower (99$^{th}$ percentile 185 mg/m$^3$-years); a 1997 California regulation capped VOC content of automotive solvents at 50% and manufacturers used acetone as a replacement for hexane and other VOCs (2).

Due to the cross-sectional study design it is not possible to determine whether solvent exposure truly predated the development of a color vision defect; however, analyses restricted to participants age ≤ 50 are less likely to include color vision defects due to age. Furthermore, the participation rate of 48% further raises the possibility of selection bias. However, the most common stated reason for refusal, lack of interest, does not provide evidence that refusals differ systematically with respect to exposure than participants, as would occur if the reason were poor health due to a potential effect of hexane toxicity. Some exposure misclassification is likely since the study relied on self-reported exposure assessment for the types of solvent products used and frequency and duration of tasks performed, sometimes many years in the past.

The associations seen in this analysis suggest a relationship between non-hexane solvent exposure and blue-yellow color vision defects among workers age 50 or younger. For both blue-yellow and any color vision defect, although the confidence intervals largely overlap, PRs are greater for hexane exposure in the presence of acetone than for hexane alone. This suggests that co-exposure to acetone may potentiate the toxic effects of hexane. The consistently elevated PRs for the highest exposures to hexane among younger workers occur at levels far below regulatory limits for hexane, suggesting that these limits may not be sufficiently protective of worker health.

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**Table 1**. Vision Characteristics of 817 Participants with Complete Exposure Data and 388 Participants Aged Less Than 50 at Time of Study Participation, Bay Area Solvent Study, 2007-2013

| Vision Characteristic | All Participants | | Participants Age $\leq$ 50 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Eye disease[a] | | | | |
| Cataracts | 35 | 4.3 | 6 | 1.5 |
| Glaucoma | 8 | 1.0 | 2 | 0.5 |
| Retinal disease | 8 | 1.0 | 3 | 0.8 |
| Exclusions from color vision assay | | | | |
| Congenital color vision defect | 53 | 6.5 | 25 | 6.4 |
| Did not complete test[b] | 10 | 1.2 | 4 | 1.0 |
| Lanthony color vision defect type[c] | | | | |
| Normal | 534 | 70.8 | 278 | 77.4 |
| Blue-yellow | 155 | 20.6 | 60 | 16.7 |
| Nonspecific | 63 | 8.4 | 20 | 5.6 |
| Red-green | 2 | 0.3 | 1 | 0.3 |
| Total - any defect | 220 | 29.2 | 81 | 22.6 |
| | Median | IQR | Median | IQR |
| Lathony color confusion score[c] | | | | |
| Trial 1 | 11.5 | 0, 25.4 | 8.7 | 0, 24.7 |
| Trial 2 | 8.4 | 0, 23.6 | 6 | 0, 17.9 |
| Mean score | 10.4 | 3.4, 24.6 | 8 | 0, 19.4 |
| Score difference (Trial 1 - Trial 2) | 0 | -6.0, 9.4 | 0 | -4.4, 8.7 |

Abbreviation: IQR, interquartile range

[a] Participant report of physician diagnosis

[b] Unable to perform or test conditions inappropriate

[c] Among 754 participants total and 359 participants age $\leq$ 50 completing Lanthony test

**Table 2**. Demographic Characteristics of 754 Total Participants and 359 Participants Age ≤ 50 Completing the Lanthony Desaturated D-15 Panel Test, Bay Area Solvent Study, 2007-2013

| Characteristic | All Participants | | Participants Age ≤ 50 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Working as mechanic at time of assay | | | | |
| Yes | 350 | 46.4 | 178 | 49.6 |
| No | 404 | 53.6 | 181 | 50.4 |
| Race | | | | |
| White, non-Hispanic | 476 | 63.1 | 215 | 59.9 |
| White, Hispanic | 114 | 15.1 | 67 | 18.7 |
| Asian | 70 | 9.3 | 34 | 9.5 |
| Black | 22 | 2.9 | 7 | 1.9 |
| Other race or multiracial | 72 | 9.5 | 36 | 10.0 |
| Smoking status[a] | | | | |
| Current | 222 | 29.6 | 92 | 25.6 |
| Former | 115 | 15.3 | 1 | 15.6 |
| Never | 414 | 55.1 | 211 | 58.8 |
| Alcohol (drinks per week, typical week)[b] | | | | |
| 0 | 176 | 23.4 | 88 | 24.5 |
| ≤ 7 | 341 | 45.3 | 166 | 46.2 |
| > 7 | 235 | 31.3 | 105 | 29.3 |
| Education | | | | |
| High school or less | 254 | 33.7 | 122 | 34.0 |
| Some college | 326 | 43.2 | 152 | 42.3 |
| College degree | 174 | 23.1 | 85 | 23.7 |
| | Median | IQR | Median | IQR |
| Year of birth | 1960 | 1955, 1965 | 1965 | 1962, 1969 |
| Year of hire | 1982 | 1977, 1988 | 1987 | 1983, 1991 |
| Age in years at interview | 51 | 46, 56 | 45 | 41, 48 |
| Duration of active work (years) | 26 | 19, 31 | 21 | 15, 26 |
| Cumulative solvent exposure (mg/m$^3$-yr) | | | | |
| Non-hexane solvents | 1380.9 | 675.7, 2511.1 | 1042 | 558.2, 1916.3 |
| Hexane[c] | 33.7 | 10.6, 95.3 | 39.6 | 11.3, 113.8 |
| Hexane plus acetone[d] | 17.7 | 5.7, 41.4 | 16.2 | 4.7, 44.8 |

Abbreviation: IQR, interquartile range

[a] 751 participants responded to smoking status question

[b] 752 participants responded to alcohol consumption question

[c] Among 400 total participants and 209 participants age ≤ 50 exposed to hexane

[d] Among 315 total participants and 160 participants age ≤ 50 exposed to hexane in the presence of acetone

**Table 3** Prevalence Ratios for Blue-yellow Color Vision Defect and Cumulative Exposure (mg/m$^3$-year) to Non-hexane Solvents, Hexane, and Hexane in the Presence of Acetone Using Log-binomial Regression Among Participants Completing Lanthony Test, Bay Area Solvent Study, 2007-2013

| Covariate | All Participants | | | Participants Age ≤ 50 | | |
|---|---|---|---|---|---|---|
| | No. of Cases | PR | 95% CI | No. of Cases | PR | 95% CI |
| Non-hexane solvents[a] | | | | | | |
| 0 - 670.9 | 29 | 1.00 | Referent | 12 | 1.00 | Referent |
| > 670.9 - 1364.3 | 39 | 1.25 | 0.81, 1.92 | 18 | 1.75 | 0.89, 3.46 |
| > 1364.3 - 2470.7 | 40 | 1.16 | 0.75, 1.78 | 17 | 1.98 | 0.98, 4.02 |
| > 2470.7 | 47 | 1.31 | 0.86, 2.00 | 13 | 2.17 | 1.03, 4.56 |
| Age in Years | | 1.04 | 1.02, 1.07 | | 1.02 | 0.96, 1.08 |
| | | | | | | |
| Hexane[a] | | | | | | |
| Unexposed to hexane | 81 | 1.00 | Referent | 25 | 1.00 | Referent |
| > 0 - 33.7 | 33 | 0.73 | 0.51, 1.04 | 13 | 0.77 | 0.41, 1.42 |
| > 33.7 | 41 | 0.94 | 0.68, 1.29 | 22 | 1.26 | 0.76, 2.11 |
| Age in Years | | 1.05 | 1.02, 1.07 | | 1.04 | 0.99, 1.10 |
| | | | | | | |
| Hexane + acetone[b] | | | | | | |
| Unexposed to hexane | 81 | 1.00 | Referent | 25 | 1.00 | Referent |
| > 0 - 17.1 | 23 | 0.65 | 0.43, 0.99 | 11 | 0.84 | 0.45, 1.57 |
| > 17.1 | 41 | 1.15 | 0.84, 1.57 | 20 | 1.62 | 0.97, 2.72 |
| Age in Years | | 1.04 | 1.02, 1.07 | | 1.04 | 0.99, 1.10 |

Abbreviations: CI, confidence interval; PR, prevalence ratio

[a] 689 total participants and 338 participants age ≤ 60

[b] 607 total participants and 291 participants age ≤ 60

**Table 4** Prevalence Ratios for Any Color Vision Defect and Cumulative Exposure (mg/m$^3$-year) to Non-hexane Solvents, Hexane, and Hexane in the Presence of Acetone Using Log-binomial Regression Among Participants Completing Lanthony Test, Bay Area Solvent Study, 2007-2013

| Covariate | All Participants | | | Participants Age ≤ 50 | | |
|---|---|---|---|---|---|---|
| | No. of Cases | PR | 95% CI | No. of Cases | PR | 95% CI |
| Non-hexane solvents[a] | | | | | | |
| 0 - 670.9 | 45 | 1.00 | Referent | 19 | 1.00 | Referent |
| > 670.9 - 1364.3 | 57 | 1.19 | 0.85, 1.65 | 24 | 1.42 | 0.83, 2.43 |
| > 1364.3 - 2470.7 | 62 | 1.18 | 0.85, 1.64 | 27 | 1.73 | 1.02, 2.94 |
| > 2470.7 | 72 | 1.28 | 0.93, 1.76 | 18 | 1.72 | 0.97, 3.08 |
| Age in Years | | 1.04 | 1.02, 1.06 | | 1.04 | 0.99, 1.09 |
| | | | | | | |
| Hexane[a] | | | | | | |
| Unexposed to hexane | 125 | 1.00 | Referent | 35 | 1.00 | Referent |
| > 0 - 33.7 | 56 | 0.81 | 0.62, 1.05 | 24 | 1.01 | 0.64, 1.58 |
| > 33.7 | 55 | 0.82 | 0.63, 1.07 | 29 | 1.14 | 0.75, 1.74 |
| Age in Years | | 1.04 | 1.02, 1.06 | | 1.06 | 1.01, 1.10 |
| | | | | | | |
| Hexane + acetone[b] | | | | | | |
| Unexposed to hexane | 125 | 1.00 | Referent | 35 | 1.00 | Referent |
| > 0 - 17.1 | 41 | 0.77 | 0.58, 1.04 | 21 | 1.05 | 0.66, 1.67 |
| > 17.1 | 53 | 0.94 | 0.73, 1.22 | 23 | 1.33 | 0.86, 2.06 |
| Age in Years | | 1.04 | 1.02, 1.06 | | 1.06 | 1.02, 1.11 |

Abbreviations: CI, confidence interval; PR, prevalence ratio

[a] 754 total participants and 359 participants age ≤ 60

[b] 669 total participants and 310 participants age ≤ 60

## Chapter 3: Direct exposure to metalworking fluid aerosols and chronic obstructive pulmonary disease in a cohort of automotive industry workers

### Introduction

Metalworking fluids (MWF) are used in industrial metalworking operations such as machining, cutting, and grinding to cool and lubricate the tool and working surface. Exposure to MWF is a common occupational health hazard, with the 1998 NIOSH Criteria Document for MWF reporting an estimate of 1.2 million workers exposed to MWF in the US and many millions more worldwide (2). Little data are available on worldwide worker exposure to MWF, but at present the global region responsible for the greatest consumption of MWF production is Asia, with increasing demand predicted in Southeast Asian countries (1). While they are a heterogeneous group of complex mixtures, they can be usefully grouped into straight, soluble, and synthetic fluids. Straight fluids are composed of highly refined petroleum oils, soluble fluids are mineral oils dispersed with emulsifiers in water, and synthetics are composed of non-petroleum-based compounds dispersed in water (2). The fluids can also be classified as oil-based (straight) and water-based (combining soluble and synthetic fluids). MWF contain additives, which are determined by the process and type of metal being worked; common additives include biocides, ethanolamines, detergents, and corrosion inhibitors (2,3).

Although MWF exposure was first associated with dermal cancers, respiratory health effects from inhalation of MWF aerosols have generated more concern in recent years as fluids have become increasingly refined (reducing carcinogenic contaminants) and dermal exposure decreases (4). Associations have been reported between all three types of MWF and respiratory symptoms including cough, chronic bronchitis, and dyspnea in studies of pulmonary function and respiratory outcomes in machinists (5–10). Hypersensitivity pneumonitis has been associated with exposure to water-based MWF (11). Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by obstructed airflow that is typically progressive and not fully reversible with bronchodilator medication; wheezing, dyspnea, chronic cough, excess phlegm, and chest tightness are symptoms of COPD, and chronic bronchitis increases risk of COPD (12). The major cause of COPD is cigarette smoking; however, occupational exposures also contribute substantially to the global burden of COPD. An American Thoracic Society analysis estimated a population attributable risk of 15% for COPD due to occupational exposures to particulate matter (PM), fumes, and gases (13).

Little research has been done on the association between MWF exposure and COPD mortality. The only positive evidence comes from publications based on the General Motors-United Autoworkers (GM-UAW) cohort, the largest study of MWF-exposed workers with quantitative exposure estimates (4,14,15). Initial results were null, with standardized mortality ratios consistently below 1.0 (4, 17). Subsequent studies by Chevrier et al. (14) and Picciotto et al. (15) using g-estimation to adjust for healthy worker survivor bias in internal analyses were positive. They found that reductions in exposure to MWF, particularly oil-based fluids, would result in decreased risk of COPD mortality (14) and increased years of life saved among COPD cases (15). Although data on cigarette smoking were available for approximately 5% of the cohort, neither of these analyses adjusted for the cigarette smoking as a potential confounder of the MWF exposure and COPD mortality relationship. The goal of this analysis is to estimate the association between MWF exposure and COPD mortality in the GM-UAW cohort data adjusting for potential confounding by cigarette smoking using the indirect adjustment method described by Axelson and Steenland (16).

**Methods**

Cohort data

The design of the GM-UAW cohort study has been previously described in detail (4,17). The cohort consists of 46 316 hourly workers from three Michigan auto parts manufacturing facilities who had ever worked for at least 3 years before January 1, 1985. Work history data is available from the date of hire until the date of termination or December 31, 1994, and mortality follow-up for each subject starts either three years after hire or January 1, 1941, whichever came later. Follow-up for this analysis ends on December 31, 2004 (17). Date of birth, sex, race, and work history were abstracted from employment records. Mortality follow-up was performed by obtaining vital status from the Social Security Administration, the National Death Index, and plant and union records (17).

A cross-sectional survey of 1811 actively employed subjects was performed in 1985 in order to study pulmonary function and respiratory symptoms in relation to MWF exposure, adjusting for self-reported cigarette smoking habits (9). The cross-sectional study population included males only, and African Americans were oversampled. We used this cross-sectional slice of the population as the basis for an indirect adjustment for smoking. In order to maximize comparability between the cross-sectional population and the mortality cohort, we restricted the COPD mortality analysis to workers who were hired after January 1, 1938 (incident hires) and were alive as of January 1, 1985. Subjects with work histories less than 50% complete (3.0%) were excluded. After applying the exclusion criteria 33 301 subjects remained in the study with 1661 included in the pulmonary function survey. For analyses, subjects of unknown race (16.9%) were classified as white based on the changes in the racial composition of the workforce over time and across the three plants (4). COPD mortality was defined as underlying causes of death listed as COPD or allied conditions in the International Classification of Disease (ICD-9-CM 490-496 and ICD-10 J40-J44, J47).

Exposure

Exposure assessment was based on 541 personal and area samples of PM collected by industrial hygienists, combined with historical exposure monitoring data (18,19). Plant records were used to determine which types of fluids were used for each job type, department, and plant throughout the operational history of the plant, and this was combined with particulate sampling data to assign the measured quantities of total and respirable PM for each job to a specific fluid type (18). Quantitative information on changes in exposure levels over time was used to create scale factors to extrapolate historical exposure levels (18–20). Individual exposure histories were created by applying the job-specific exposures and scale factors to each subject's work history. Subjects with missing work history had exposures interpolated by averaging the exposure levels before and after the data gap (21). Cumulative average annual exposure to $PM_{9.8}$ (thoracic fraction) and $PM_{3.5}$ (alveolar fraction) were expressed as $mg/m^3$-year and lagged by 10 years. This lag was consistent with the chronic nature of COPD and accounted for the time difference between the end of exposure information in 1994 and mortality follow-up in 2004.

We defined three exposure groups; the straight MWF group consisted of subjects who had ever been directly exposed to straight MWF, likewise for the soluble and synthetic exposure groups. A subject exposed to more than one fluid type would be in multiple exposure groups. The reference group was defined to include those who had always worked as assemblers and were never directly exposed to MWF. Each fluid group was divided into quartiles based on the

exposure distribution of the COPD mortality cases, and analyses were duplicated for $PM_{9.8}$ and $PM_{3.5}$.

Statistical Methods

We used Cox proportional hazards models to estimate the hazard ratios (HRs) for COPD mortality in quartiles of exposure to each MWF type compared to the common reference group. Age was the time metric, and models for each fluid type were adjusted for cumulative exposure to the two other fluid types, plant, and calendar year. Models excluding female (10.4%) and non-white (18.8%) subjects were fit for indirect adjustment for confounding by smoking because female workers had been excluded from the cross-sectional survey and evidence of effect modification by race has been noted in analyses of GM-UAW data (22).

Potential confounding by cigarette smoking was accounted for by using indirect adjustment (16). The risk of COPD due to smoking alone in each exposure group was calculated by combining the relative risk of COPD from the relevant literature (23) with the smoking habits (current, former, or never smoker) of the cross-sectional survey subjects as a proxy for the smoking habits of the study cohort. The observed relative risk for each exposure group, uncorrected for smoking, was then divided by weighted relative risk due to smoking alone in that exposure group, yielding a relative risk for the exposure indirectly adjusted for the confounding effect of smoking. Confidence intervals were adjusted for sampling error introduced by adjustment using the method described by Larkin et al. (24). Cox regressions were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Confidence interval calculations were performed using Microsoft Excel (2010). Potential bias due to informative censoring by cardiovascular disease mortality was assessed using the method of Fine and Gray using the R *cmprsk* package (R, version 3.1.2; R Development Core Team, Vienna, Austria) (25,26). This method results in an estimate of the subdistribution hazard ratio (SHR): the instantaneous risk of dying of the cause of interest, given that the subject has not yet died of that cause.

**Results**

There were 438 COPD deaths in total, 30 of which occurred among the reference group (Tables 1 and 2). When the cohort was considered as a whole (unadjusted for smoking), elevated HRs were observed for all exposure quantiles of straight and soluble MWF (Table 3). As $PM_{9.8}$ and $PM_{3.5}$ exposures are highly correlated, models for exposure to $PM_{3.5}$ (not shown) did not differ notably from those for $PM_{9.8}$. While all 95% confidence intervals (95% CI) included the null, the strongest association occurred in the third quartile of exposure to straight MWF, with a HR of 1.46 (95% CI 0.91 to 2.33). Associations were weakest for synthetic MWF, the least common exposure.

When the cohort was restricted to white male subjects, the associations strengthened and all HRs were elevated (Table 4). Indirect adjustment for confounding by smoking was based on 1,043 subjects in total; 664 of these had straight MWF exposure, 959 had soluble, and 490 had synthetic exposure. At the time of the survey, subjects had a median age of 34 years. Among all MWF exposure groups 46-59% of subjects were current smokers. Indirect adjustment resulted in percent changes in effect estimates ranging in magnitude from 0.4%-6.6% (Table 4). Hazard ratios for all MWF types and exposure levels remained elevated after adjustment. In the straight and soluble groups there was an increase in estimates in the first exposure quartile, with the HR for soluble exposure increasing to 1.69 (96% CI 0.99, 2.87).

Subdistribution hazard ratios estimated using the Fine and Gray method to account for cardiovascular disease mortality as a potential competing event were increased in the lower two exposure quartiles compared to the cause-specific HR for COPD mortality unadjusted for competing risks (Table 5). The increase resulted in 95% CI excluding the null for soluble MWF in the lower two exposure quartiles, both with a HR of 1.71 (95% CI 1.03, 2.87). Conversely, the HR estimates decreased in the higher two exposure quartiles when adjusted for competing risks.

**Discussion**

We found elevated HRs for COPD mortality in autoworkers directly exposed to MWF compared to those who were never directly exposed to MWF. These associations were stronger among white males, and the elevated HRs persisted when indirectly adjusted for confounding by cigarette smoking and when CVD mortality was accounted for as a competing risk.

Previous studies of exposure to MWF in this and other U.S. study populations reported associations between acute decrements in pulmonary function over a single work shift and exposure to straight and synthetic fluids (27), straight and soluble fluids (5), and total $PM_{10}$ (6). Self-reported chronic respiratory symptoms and MWF exposure were associated in several of these studies as well as two other cross-sectional studies of Scandinavian workers (5–8), but the results were inconsistent in implicating specific symptoms and fluid types. A longitudinal study of newly hired machinists found an association between MWF exposure, especially synthetic fluids, and asthma-like symptoms after two years of follow-up (28). An early standardized mortality ratio analysis of the GM-UAW cohort found no association with non-malignant respiratory mortality (4), although analyses of the respiratory health survey detected associations between MWF exposure and cough, wheeze, excess phlegm, and chronic bronchitis (9), as well as higher asthma incidence in those exposed to synthetic MWF (10). While these studies provide evidence for the association of MWF exposure and acute and chronic respiratory outcomes, none specifically examined COPD incidence or mortality until several recent studies applying g-estimation methods in the GM-UAW cohort to address time varying confounding affected by prior exposure (14,15). Chevrier et al. reported an elevated HR for COPD mortality of 1.23 (95% CI: 1.13, 1.38) comparing five years of exposure to straight MWF to no exposure, in contrast with null results in conditional Cox models (14). Piccotto et al. estimated that eliminating MWF exposure, particularly soluble, would result in up to 1550 years of life saved among COPD cases (15). The present analysis of the GM-UAW data support these conclusions, with HRs elevated for all MWF types and exposure levels when comparing ever-exposed to never exposed subjects.

Previous analyses of the GM-UAW data did not examine potential confounding by cigarette smoking, an exposure which is strongly associated with COPD. We found evidence of modest confounding by cigarette smoking resulting in percent changes of up to 6.6% in the unadjusted effect estimates. While these changes are consistent with the conclusions of Kriebel et al. (2004) that unadjusted confounding by smoking is unlikely to cause more than a 20% change in relative risk in large cohorts such as this one, it raises concern that the small effect estimates seen in many occupational exposure studies could be subject to enough confounding to shift statistically significant estimates so that a 95% CI includes one (29). This was seen here, as well as in an analysis of diesel exhaust PM and lung cancer with indirect adjustment for smoking (24).

In this analysis, indirect adjustment was performed using data from a 4.4% sample of the cohort of subjects at work in 1985. Both the small sample and inability to account for subjects who left work before 1985 may have biased estimates of the relative risk of COPD due to smoking.

However, we compare workers directly exposed to MWF particles to workers in the same factories who were never directly exposed, resulting in a reference group more likely to be comparable in smoking habits than these exposed workers would be to an external comparison group. The higher smoking rates in subjects more highly exposed to MWF could be explained by the "healthy smoker" hypothesis proposed by Becklake (30), or by unmeasured factors associated with smoking and MWF exposure.

When comparing the cause-specific HRs for COPD mortality to the SHRs, we discovered some evidence that CVD mortality was a competing risk. Recent studies of heart disease in the GM-UAW cohort have reported associations between MWF exposure, particularly straight, and ischemic heart disease mortality (14,20) as well as all CVD mortality (31). In the lower exposure quartiles for all MWF types, the HRs increased after adjusting for competing risks suggesting an association between CVD and MWF exposure that attenuated the cause-specific HR for COPD.

It is likely that the exposure-response relationships in this analysis are biased downward by the healthy worker survivor effect (HWSE). This is supported by the stronger effect estimates reported by Chevrier et al. and Picciotto et al. adjusting for time-varying health status as a confounder affected by prior exposure using g-estimation; this cannot be addressed in an unbiased fashion in Cox proportional hazards models (14,15). Because respiratory symptoms progressively worsen with COPD, workers in the early stages of this chronic respiratory disease are more likely to leave work earlier than those not affected by diseases characterized by gradually declining health (32). This would result in workers affected by lung disease opting out of jobs with higher exposures, accruing more time off work, or leaving work (33). The cohort was also restricted to subjects alive in 1985 in order to be most comparable in composition to the respiratory health survey. This further selection may have enhanced HWSE: subjects who had survived to 1985 were likely to be the more resilient workers.

Although the findings did not consistently attain statistical significance, the elevated HRs for all exposures remained after adjustments for confounding by cigarette smoking and the competing risk of CVD mortality. This supports previous evidence that MWF exposure is associated with COPD mortality – particularly given that the effect estimates are likely to be biased downwards by the HWSE. According to research published by a private agency, 2.3 million tons of MWF were consumed globally in 2013, with 42% of the consumption occurring in Asia; despite changes in technology that reduce the amount of fluid needed for metalworking procedures, they predict a 3.3% mean annual growth rate in Southeast Asia through 2020 due to growth of the automotive industry (1). While soluble fluids are the most commonly used, synthetics are becoming more popular. The presence and enforcement of occupational health regulations vary widely within this large region. With widespread exposure, even small elevations in the hazard of COPD mortality could result in many preventable deaths.

These results further support the hypothesis that MWF exposure increases the risk of COPD mortality, with the strongest associations with soluble fluids. Previous analyses of COPD mortality did not adjust for confounding by cigarette smoking; indirect adjustment showed modest confounding, but all HRs remained elevated. Elevated HRs persisted when CVD mortality was considered as a competing risk for COPD mortality. These findings suggest that MWF exposures make a substantial contribution to the global burden of occupational COPD.

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**Table 1** Characteristics of Subjects Alive in 1985, GM-UAW Cohort, 1941-2005

| Characteristic | All subjects | | COPD cases | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Number | 33301 | 100 | 438 | 1.3 |
| COPD cases[a] | 438 | 1.3 | - | |
| Sex | | | | |
| Male | 28805 | 86.5 | 387 | 88.4 |
| Female | 4496 | 13.5 | 51 | 11.6 |
| Race | | | | |
| White | 21418 | 64.3 | 255 | 58.2 |
| African-American | 6261 | 18.8 | 52 | 11.9 |
| Unknown | 5622 | 16.9 | 131 | 29.9 |
| Plant | | | | |
| 1 | 7416 | 22.3 | 117 | 26.7 |
| 2 | 14258 | 42.8 | 221 | 50.5 |
| 3 | 11627 | 34.9 | 100 | 22.8 |
| | Median | IQR | Median | IQR |
| Year of birth | 1941 | 1927, 1950 | 1922 | 1916, 1928 |
| Year of hire | 1967 | 1953, 1976 | 1953 | 1949, 1959 |
| Years of follow-up | 19 | 11, 28 | 21 | 10, 32 |
| 10-year lagged cumulative MWF exposure (mg/m$^3$-year) | | | | |
| PM$_{3.5}$ | | | | |
| Straight | 0.02 | 0, 0.26 | 0.03 | 0, 0.45 |
| Soluble | 1.05 | 0.21, 2.75 | 2.04 | 0.65, 5.56 |
| Synthetic | 0 | 0, 0.06 | 0 | 0, 0.08 |
| PM$_{9.8}$ | | | | |
| Straight | 0.04 | 0, 0.60 | 0.08 | 0, 1.01 |
| Soluble | 2.26 | 0.48, 5.97 | 4.27 | 1.53, 11.74 |
| Synthetic | 0 | 0, 0.14 | 0 | 0, 0.17 |

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MWF, metalworking fluid

[a] Percent cases among exposure group subjects

Table 2. Characteristics of Exposure Subcohorts of Subjects Alive in 1985, GM-UAW Cohort, 1941-2005

| Characteristic | Never MWF exposed | | Ever exposed to MWF type | | | | | |
| | | | Straight | | Soluble | | Synthetic | |
| | No. | % | No. | % | No. | % | No. | % |
|---|---|---|---|---|---|---|---|---|
| Subjects[a] | 3008 | 9.0 | 18744 | 56.3 | 28789 | 86.5 | 11752 | 35.3 |
| COPD cases[b] | 30 | 1.0 | 253 | 1.3 | 399 | 1.4 | 137 | 1.2 |
| Sex | | | | | | | | |
| Male | 2364 | 78.6 | 16425 | 87.6 | 25171 | 87.4 | 10111 | 86.0 |
| Female | 644 | 21.4 | 2319 | 12.4 | 3618 | 12.6 | 1641 | 14.0 |
| Race | | | | | | | | |
| White | 1920 | 63.8 | 12882 | 68.7 | 18708 | 65.0 | 8669 | 73.8 |
| African-American | 494 | 16.4 | 3078 | 16.4 | 5504 | 19.1 | 1517 | 12.9 |
| Unknown | 594 | 19.7 | 2784 | 14.9 | 4577 | 15.9 | 1566 | 13.3 |
| Plant | | | | | | | | |
| 1 | 616 | 20.5 | 2797 | 14.9 | 6499 | 22.6 | 151 | 1.3 |
| 2 | 1080 | 35.9 | 9605 | 51.2 | 12551 | 43.6 | 9301 | 79.1 |
| 3 | 1312 | 43.6 | 6342 | 33.8 | 9739 | 33.8 | 2300 | 19.6 |
| | Median | IQR | Median | IQR | Median | IQR | Median | IQR |
| Year of birth | 1944 | 1929, 1950 | 1941 | 1927, 1950 | 1941 | 1927, 1950 | 1944 | 1929, 1953 |
| Year of hire | 1968 | 1960, 1976 | 1967 | 1953, 1976 | 1967 | 1953, 1976 | 1969 | 1954, 1977 |
| Years of follow-up | 17 | 7, 24 | 20 | 14, 29 | 20 | 13, 28 | 20 | 15, 28 |
| 10-year lagged cumulative MWF exposure (mg/m$^3$-year) | | | | | | | | |
| $PM_{3.5}$ | | | | | | | | |
| Straight | - | | 0.21 | 0.07, 0.75 | 0.05 | 0, 0.32 | 0.1 | 0.02, 0.28 |
| Soluble | - | | 1.34 | 0.59, 3.09 | 1.32 | 0.52, 3.31 | 1.28 | 0.63, 2.49 |
| Synthetic | - | | 0 | 0, 0.16 | 0 | 0, 0.09 | 0.15 | 0.05, 0.55 |
| $PM_{9.8}$ | | | | | | | | |
| Straight | - | | 0.48 | 0.15, 1.71 | 0.11 | 0, 0.72 | 0.24 | 0.04, 0.65 |
| Soluble | - | | 2.91 | 1.29, 6.90 | 2.85 | 1.15, 7.23 | 2.66 | 1.34, 5.35 |
| Synthetic | - | | 0 | 0, 0.33 | 0 | 0, 0.19 | 0.33 | 0.11, 1.17 |

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MWF, metalworking fluid

[a] Percent of all subjects alive in 1985

[b] Percent cases among exposure group subjects

26

**Table 3** Hazard ratios[a] for COPD Mortality and Cumulative Metalworking Fluid Exposure (10 Year Lag, mg/m$^3$-yr) by Exposure Subcohort, Estimated with Cox Proportional Hazards Models Among Subjects Alive in 1985, GM-UAW Cohort,1941-2005

| Exposure category | No. of Cases | HR | 95% CI |
|---|---|---|---|
| Straight (21 752 subjects) | | | |
| Unexposed | 30 | 1.00 | Referent |
| > 0 - 0.22 | 63 | 1.17 | 0.74, 1.84 |
| > 0.22 - 0.83 | 63 | 1.20 | 0.76, 1.90 |
| > 0.83 - 2.34 | 63 | 1.46 | 0.91, 2.33 |
| > 2.34 | 64 | 1.27 | 0.79, 2.03 |
| | | | |
| Soluble (31 797 subjects) | | | |
| Unexposed | 30 | 1.00 | Referent |
| > 0 - 2.06 | 99 | 1.26 | 0.83, 1.90 |
| > 2.06 - 5.12 | 100 | 1.34 | 0.89, 2.03 |
| > 5.12 - 12.58 | 100 | 1.19 | 0.79, 1.80 |
| > 12.58 | 100 | 1.12 | 0.74, 1.70 |
| | | | |
| Synthetic (14 760 subjects) | | | |
| Unexposed | 30 | 1.00 | Referent |
| > 0 - 0.24 | 34 | 1.01 | 0.56, 1.80 |
| > 0.24 - 0.72 | 34 | 1.42 | 0.79, 2.54 |
| > 0.72 - 1.62 | 34 | 1.21 | 0.66, 2.20 |
| > 1.62 | 35 | 0.95 | 0.52, 1.74 |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MWF, metalworking fluid

[a] Time metric is age, adjusted for continuous cumulative exposure to other MWF types, sex, race, plant, and calendar year

**Table 4** Hazard ratios[a] for COPD Mortality and Cumulative Metalworking Fluid Exposure (10 Year Lag, mg/m$^3$-yr) by Exposure Subcohort, Estimated with Cox Proportional Hazards Models, Unadjusted and Indirectly Adjusted for Cigarette Smoking, Among White Male Subjects Alive in 1985, GM-UAW Cohort, 1941-2005

| Exposure category | No. of Cases | Unadjusted for smoking | | Indirectly adjusted for smoking[b] | |
|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI |
| **Straight (16 009 subjects)** | | | | | |
| Unexposed | 18 | 1.00 | Referent | 1.00 | Referent |
| > 0 - 0.23 | 50 | 1.48 | 0.84, 2.61 | 1.54 | 0.86, 2.76 |
| > 0.23 - 0.89 | 51 | 1.37 | 0.77, 2.41 | 1.38 | 0.76, 2.48 |
| > 0.89 - 2.44 | 51 | 1.83 | 1.02, 3.27 | 1.71 | 0.94, 3.11 |
| > 2.45 | 51 | 1.55 | 0.87, 2.76 | 1.50 | 0.83, 2.71 |
| | | | | | |
| **Soluble (22 721 subjects)** | | | | | |
| Unexposed | 18 | 1.00 | Referent | 1.00 | Referent |
| > 0 - 2.142 | 78 | 1.64 | 0.98, 2.75 | 1.69 | 0.99, 2.87 |
| > 2.14 - 5.27 | 78 | 1.66 | 0.99, 2.78 | 1.65 | 0.97, 2.81 |
| > 5.27 - 12.58 | 78 | 1.49 | 0.89, 2.51 | 1.41 | 0.82, 2.42 |
| > 12.58 | 78 | 1.38 | 0.82, 2.32 | 1.35 | 0.79, 2.33 |
| | | | | | |
| **Synthetic (11 003 subjects)** | | | | | |
| Unexposed | 18 | 1.00 | Referent | 1.00 | Referent |
| > 0 - 0.24 | 28 | 1.14 | 0.57, 2.28 | 1.17 | 0.58, 2.38 |
| > 0.24 - 0.73 | 29 | 1.55 | 0.78, 3.11 | 1.53 | 0.75, 3.10 |
| > 0.73 - 1.58 | 29 | 1.44 | 0.71, 2.93 | 1.49 | 0.72, 3.07 |
| > 1.58 | 29 | 1.02 | 0.5, 2.08 | 1.07 | 0.51, 2.24 |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio

[a] Time metric is age, adjusted for continuous cumulative exposure to other MWF types, plant, and calendar year

[b] Based on smoking (current, past, or former) data available from 664 subjects for straight, 959 subjects for soluble, 490 subjects for synthetic

**Table 5** Subdistribution hazard ratios[a] for COPD Mortality and Cumulative Metalworking Fluid Exposure (10 Year Lag, mg/m$^3$-year) by Exposure Subcohort, Estimated by Method of Fine & Gray, Among White Male Subjects Alive in 1985, GM-UAW Cohort, 1941-2005

| Exposure category | No. of Cases | SHR | 95% CI |
|---|---|---|---|
| Straight (16 009 subjects) | | | |
| Unexposed | 18 | 1.00 | Referent |
| > 0 - 0.23 | 50 | 1.58 | 0.90, 2.78 |
| > 0.23 - 0.89 | 51 | 1.44 | 0.82, 2.53 |
| > 0.89 - 2.44 | 51 | 1.73 | 0.95, 3.14 |
| > 2.45 | 51 | 1.40 | 0.78, 2.50 |
| | | | |
| Soluble (22 721 subjects) | | | |
| Unexposed | 18 | 1.00 | Referent |
| > 0 - 2.142 | 78 | 1.71 | 1.02, 2.87 |
| > 2.14 - 5.27 | 78 | 1.71 | 1.02, 2.88 |
| > 5.27 - 12.58 | 78 | 1.33 | 0.79, 2.23 |
| > 12.58 | 78 | 1.21 | 0.73, 2.03 |
| | | | |
| Synthetic (11 003 subjects) | | | |
| Unexposed | 18 | 1.00 | Referent |
| > 0 - 0.24 | 28 | 1.24 | 0.62, 2.45 |
| > 0.24 - 0.73 | 29 | 1.77 | 0.87, 3.60 |
| > 0.73 - 1.58 | 29 | 1.40 | 0.68, 2.87 |
| > 1.58 | 29 | 0.97 | 0.48, 1.96 |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SHR, subdistribution hazard ratio

*Time metric is age, adjusted for continuous cumulative exposure to other MWF types, plant, and calendar year

## Chapter 4: Exposure to metalworking fluid and mortality due to natural causes and cardiopulmonary disease in a prospective study of a cross-sectional subset of the UAW-GM cohort of automotive industry workers

**Background**

Exposure to airborne particulate matter (PM) from air pollution and cigarette smoking has been associated with all-cause mortality and reduced life expectancy in many epidemiologic studies. These associations are strongest between respiratory and cardiovascular disease (CVD) mortality and traffic-related fine particles with aerodynamic diameter < 2.5μm ($PM_{2.5}$), with less evidence for coarse respirable material ($PM_{10}$) (1–5). The majority of ambient $PM_{2.5}$ is generated by combustion (including cigarette smoke), producing polycyclic aromatic hydrocarbons (PAHs) adsorbed to small particles, which may then cross the lung-blood barrier upon inhalation (6). Several recent analyses and re-analyses of ambient PM exposure and mortality in large cohorts in the United States, Canada, and Europe have indicated that these associations are robust to different statistical and spatial modeling techniques, and that the strongest associations are between $PM_{2.5}$ and CVD (7–12). While the majority of the literature linking PM to CVD mortality is based on air pollution, many workers are occupationally exposed to PM with exposures frequently an order of magnitude or higher than those to ambient air pollution (13). A systematic review of occupational PM exposure and CVD studies published during 2000-2009 found associations between PM exposure and ischemic heart disease, and strong evidence for elevation of systemic inflammatory markers with exposure (14).

Machinists are occupationally exposed to PM in a range of size fractions generated by the aerosolization of metalworking fluids (MWF) sprayed to cool and lubricate tools and materials during machining, grinding, and drilling operations. While they are complex mixtures of chemicals, water, and mineral oil, MWF can be classified as straight (mineral oil based), soluble (mineral oil dispersed in water), or synthetic (non-petroleum chemicals in water); all fluid types contain a variety of additives such as detergents and corrosion inhibitors (15). Unlike other air contaminants, most of the PAHs in MWF are not generated by combustion but rather are present in the base mineral oil which is then aerosolized by mechanical means or by the condensation of vapor generated by hot operations (16).

The General Motors-United Auto Workers (GM-UAW) study includes a large cohort of workers at three automobile manufacturing plants in Michigan with quantitative exposure assessment and mortality follow-up lasting from 1941 through 2009, with detailed health and cigarette smoking data in a cross-sectional survey of subjects who were at work in 1985 (17,18). We explore the associations between MWF exposure, measured as the respirable fraction ($PM_{3.5}$), and natural cause mortality and cardiopulmonary disease (CPD) mortality in the subset of the GM-UAW cohort who participated in the 1985 survey, adjusting for cigarette smoking and respiratory health status as potential confounders of the exposure-response relationship. Previous analyses of the cohort have not adjusted for cigarette smoking, which is strongly associated with mortality and may be associated with MWF exposure. There are two potential sources of bias induced by studying only those subjects in the cross-section. The first is a form of artificial censoring: subjects can be considered censored when they leave work or die before 1985 and become ineligible for the cross-sectional study (19). Because only active workers are included in the cohort, inclusion in the study is conditioned on active work status, which is itself an effect of both past exposure and underlying health, resulting in informative censoring. By conditioning on a common effect (work status), we introduce selection bias that can result in bias downwards

towards the null - and even beyond - making a true hazard even appear protective (20). The second potential source of bias is that subjects were selected into the cross-sectional study non-randomly based on being alive and at work, sex, race and current exposure characteristics; when selection criteria are associated with both outcome and exposure, selection bias may be introduced.

Inverse probability weights (IPW) were used to address both sources of selection bias described above, by calculating the inverse probability of being jointly alive and at work in 1985 (eligible for the study) and for being selected into the study. Using methods described by Hernan et al. and Cole et al. (20–22), we applied the product of these IPWs in a weighted Cox proportional hazards regression to estimate hazard ratios for natural cause and CPD mortality. By applying higher weights to subjects more similar to those who either left work or died prior to 1985 and to those who were least likely to be included in the study, we created a pseudo-population of workers more closely resembling the full GM-UAW cohort. We interpret increases in the weighted effect estimates for MWF exposure compared to the unweighted results as evidence that we have mitigated some of the downward bias due to selection.

The objective of this analysis is to assess relationships between exposure to MWF and mortality due to natural causes or CPD in a follow-up study of a cross-section of the GM-UAW cohort with cigarette smoking and health data, using IPW to address potential bias due to informative censoring and sample selection.

**Methods**
Study Population

The GM-UAW cohort study design has been described in detail previously (17,23). Hourly workers who had ever worked for at least 3 years before January 1, 1985 at three Michigan automobile parts manufacturing facilities were enrolled and followed for vital status from the later date of either January 1, 1941 or three years after the subject's date of hire, until December 31, 2009. Work histories were available from date of hire until termination or December 31, 1994, which ever occurred first. This analysis includes 38,622 subjects who were hired after January 1, 1938 and had work histories more than 50% complete. Work history, date of birth, sex, and race were obtained from employment records. Race was not systematically collected until the late 1970s at one of the three plants and subjects of unknown race (22%) were classified as white for analyses based on the racial composition of the workforce across time at the three plants (17).

In 1985 a survey was administered to collect detailed information on respiratory health history and smoking habits in a cross-sectional sample of 1811 actively employed subjects (18). Measurements of pulmonary function, weight, and blood pressure were also collected. Of these, 1661 with complete work history data were included in this prospective analysis of the cross-sectional cohort. Only male subjects were included in the survey and researchers over-sampled assembly workers without direct exposure to MWF, as well as machinists exposed to a single MWF type. African-American workers were also over-sampled.

Exposure

Quantitative exposure measurements were based on 541 personal and area PM samples collected by study industrial hygienists as well as historical exposure monitoring performed by industrial hygienists employed by GM (24,25). A job-exposure matrix was constructed based on the sampling data and plant records of the types of fluid used for each job type, department, and

plant; this was used to assign the measured quantities of total and respirable PM as well as the fluid type for each job throughout the operational history of the plant (24). Scale factors were calculated using quantitative information on the changes in exposure levels over time to extrapolate historical exposure levels (16,24,25). Measurements of PM levels were performed using particle impactors with a cutoff of $PM_{3.5}$ defining the respiratory size fraction, consistent with guidelines promulgated by the American Conference of Governmental Industrial Hygienists (25). The work history of each subject was used in conjunction with the job-exposure matrix and scale factors to create an individual exposure history. Subjects with missing work history had exposures interpolated by averaging exposures before and after the missing interval (26). Cumulative average annual exposure to MWF was expressed in $mg/m^3$-year and lagged by 15 years. This lag accounted for the time difference between the end of work history records in 1994 and mortality follow-up in 2009.

Health Outcome

Mortality follow-up was performed based on vital status searches of the National Death Index. We combined CVD and respiratory disease mortality into a single category, cardiopulmonary disease (CPD), to maximize power and because previous analyses of the GM-UAW cohort reflect increased risks of both CVD (16,27,28) and respiratory disease (18,29,30). Natural cause mortality was defined as all-cause mortality less external causes of death, and included ICD-9-CM codes < 800 and ICD-10 code groups A00-R99. Cardiopulmonary disease mortality was defined as ICD-9-CM codes 400-519 and ICD-10 codes I00-J99.

Statistical methods

We calculated weights consisting of three components: the inverse probability of being alive in 1985 ($W^D(t)$), being employed in 1985 given alive ($W^L(t)$), and of being selected ($W^S$) into the cross-section given alive and employed at the time of the cross-sectional study. The product $W^D(t)*W^L(t)$ represents the inverse of the joint probability of being alive and at work in 1985 (i.e., eligible for inclusion in the cross-section). Because only males were included in the cross-sectional study, females are excluded from the IPW calculations. All of the predicted probabilities were estimated using the SAS procedure LOGISTIC.

Let $T$ denote the time in years from the date entering follow-up to either death or January 1, 1985, whichever occurs first. $D(t)$ represents an indicator of being alive in year $t$ (0: alive, 1: dead), $L(t)$ is an indicator for having left work in year $t$ (0: at work, 1: left work), and $S$ is being selected into the cross sectional study in 1985 (0: selected, 1: not selected). Cumulative days off work and exposure to MWF (categorized by quartiles) are denoted by $E(t)$, with $\bar{E}(t)$ representing the history of the exposure from study entry to time $t$. $R(t)$ represents cumulative duration of employment in years. A subscript $S$ is used to denote the value of a variable in the year of selection into the cross-sectional study: $D_S$ represents vital status in 1985, $L_S$ active work status in 1985, $E_S$ one year lagged cumulative exposure in 1985, and $R_S$ duration of employment in 1985. The baseline covariates of race, plant, date of birth, and date entered study follow-up are denoted by $V$.

All three IPW components were stabilized to increase efficiency, as suggested by Hernán et al (21). The component $W^D(t)$ is proportional to the cumulative product across each person-year of the inverse of the probability of being alive in year $t$, given by:

$$W^D(t) = \prod_{k=0}^{t} \frac{\Pr[D(k) = 0|D(k-1) = 0, V]}{\Pr[D(k) = 0|D(k-1) = 0, \bar{E}(k-1), R(k), V]}$$

The numerator of the weight is the cumulative product of the predicted probability of being alive at the end of year $t$, conditional on baseline covariates and an indicator of being alive at the end of year $t-1$. The denominator of the weights is the cumulative product of the predicted probability of being alive at year $t$ conditional on having been alive in the previous year, baseline covariates $V$, and cumulative days off work and MWF exposure in the previous year $\bar{E}(t)$, and duration of employment $R(t)$.

$$W^L(t) = \prod_{k=0}^{t} \frac{\Pr[L(k) = 0|L(k-1) = 0, V]}{\Pr[L(k) = 0|L(k-1) = 0, \bar{E}(k-1), R(k), V]}$$

$W^L(t)$ is estimated among subjects alive in 1985. The numerator is the cumulative product of the predicted probability of being at work at the end of year $t$, given having been at work the previous year and baseline covariates. The denominator is the cumulative product of the predicted probability of being at work in year $t$, conditioned on having been at work the previous year, with the same model covariates $\bar{E}(t)$, $R(t)$, and V as described for $W^D(t)$. Predicted probabilities for $W^D(t)$ and $W^L(t)$ were estimated using pooled logistic regression (21).

The numerator of $W^S$ is the marginal probability of being selected and the denominator of $W^S$ is the predicted probability of having been selected into the cross-sectional survey given being at work and alive in 1985, cumulative exposure and days off work as of 1984, and baseline covariates. $W^S$ was estimated with logistic regression.

$$W^S = \frac{\Pr[S = 0|D_S = 0, L_S = 0]}{\Pr[S = 0|D_S = 0, L_S = 0, \bar{E}_S, R_S, V]}$$

We used Cox proportional hazards regression to estimate the association between quartiles of straight MWF exposure, with unexposed (assembly work) person-years as the referent, and natural cause mortality and CPD mortality. Each person-year in the Cox regressions is weighted by the product of the subject's weights, $W^D(t)*W^L(t)*W^S$, denoted by $W^{prod}$; in the weighted Cox models $W^{prod}$ was truncated at the 99th percentile to avoid extreme weights due to near-positivity violations (22) . The outcome models were fit by specifying the *covs* option for robust standard errors and the *weights* statement in the SAS procedure PHREG (31).

All Cox models for mortality included continuous measures of cumulative exposure to soluble and synthetic MWF, location of employment, race, less than 12th grade education, cigarette smoking status in 1985, work status at time of death, year of hire before 1970, calendar year, and duration of employment in years as of 1985. In addition, the models for natural-cause mortality included self-reported pre-hire physician diagnosis of asthma. All calculations were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

**Results**

The characteristics of the cohort as a whole and subcohorts used to predict IPW are shown in Table 1. Comparing subjects selected for the cross-sectional survey to all those at work in 1985, selected subjects were much more likely to be African-American (36.4% vs 22.5%) or work at Plant 1 (where the majority of African-American workers were employed), and cumulative exposure to straight MWF was over twice as high. Table 2 shows detailed characteristics of subjects included in the cross-section. Most subjects had a 12$^{th}$ grade education, and over 50% were current cigarette smokers in 1985. There were 322 natural-cause deaths, of which 155 were due to cardiopulmonary disease. The median forced expiratory volume in one second (FEV$_1$) was 98.2% of predicted and the median duration of employment was 11.8 years, indicating that the subjects were, on average, healthy long-term workers.

The properties of W$^A$($t$), W$^E$($t$), and W$^S$ as well as W$^{prod}$ are presented in Table 3. A description of the IPW denominator models is included in Appendix A-1. All of the components, as well as W$^{prod}$ have a mean of approximately 1, however, the maxima of W$^S$ and W$^{prod}$ are large, 115.17 and 114.57 respectively. The weights were truncated at the 99$^{th}$ percentile (2.23) for weighted analyses.

The results of Cox models for natural cause mortality and quartiles of straight MWF are presented in Table 4. Effect estimates in models adjusted for cigarette smoking are higher compared to the models unadjusted for smoking in all straight MWF exposure quartiles, with the greatest increases in the first and fourth. In all models, the greatest HR is in the second quartile, although all 95% confidence intervals (95% CI) include 1. While the robust standard errors estimated in the IP-weighted models are conservative and much larger, the HRs for exposure increase to exceed 1 in the first, second, and fourth exposure quartiles reaching a maximum in the second quartile of 1.25 (95% CI: 0.79, 2.00). The strongest risk factors for natural cause mortality in both unweighted and IP-weighted models are cigarette smoking and pre-hire asthma (Appendix A-2).

Few CPD deaths occurred among asthmatics so CPD models are not adjusted for pre-hire asthma. Adjustment for smoking in the unweighted model results in increased HRs in the first, second, and fourth quartiles again with the largest changes in the first and fourth quartiles (Table 5). The estimates for straight MWF exposure in the unweighted smoking-adjusted model were elevated in the first and second quartiles, with an HR of 2.30 (95% CI: 1.36, 3.89) in the second; in the IPW model this HR decreases slightly (1.86, 95% CI: 0.97, 3.55). The HRs in the two high quartiles increased, but remained below the null.

**Discussion**

We used IPW as a means to adjust for bias due to informative censoring and non-random sample selection in a prospective cohort mortality study of automobile industry workers exposed to mineral oil-based MWF. The 95% CI for all weighted HRs for exposure contained 1, however, most HRs for all natural cause mortality were elevated in the weighted model and the standard errors were conservative. For CPD, evidence of persistent downward HWSE bias was observed ever after weighting to reduce initial selection into the study. Confounding by cigarette smoking was observed, with an increase in HRs for MWF of up to 12% in adjusted unweighted models. Cigarette smoking was the strongest predictor of mortality for both natural causes and CPD.

There is a large body of literature detailing the associations between PM and health outcomes. In a systematic review and meta-analysis of publications on long-term exposure to air pollution

published during 1950-2007, Chen at al. found statistically significant elevated summary risk ratios for natural cause and CVD mortality for each increase of $10\mu g/m^3$ $PM_{2.5}$ in air (32). The 2010 update to the American Heart Association Scientific Statement on Particulate Matter Air Pollution and Cardiovascular Disease concluded that short- or long-term exposure to ambient $PM_{2.5}$ increases CVD mortality and reduces life expectancy, and that evidence for plausible biological mechanisms supports this assessment (33). A 2010 review of 37 articles in the occupational health literature by Fang et al. reported a summary RR of 1.15 (95% CI: 1.06, 1.26) for ischemic heart disease mortality, and while they did not find an elevated meta-RR for all CVD, they did report that lack of control for confounding and use of external comparison groups (which can induce healthy worker bias) were frequent problems (14). They reported consistent evidence that occupational PM exposure is associated with markers of systemic inflammation, atherosclerosis, and decreased heart rate variability (14). Several more recent studies not included in the Fang et al. review have also reported associations between occupational exposure to PM and CVD endpoints (16,27,34–36).

The proposed mechanism for mortality caused by PM is through pathways of systemic and pulmonary oxidative stress and inflammation resulting in intermediate outcomes such as vascular dysfunction, increased platelet aggregation, and decreased heart rate variability (32,33). The deposition of PM in the respiratory tract depends on the size fraction, with $PM_{2.5}$ penetrating to the alveoli, while larger particles deposit further up in the lungs, bronchi, and nasal cavity (6). Due to their size and composition, these small particles have higher biological activity and more efficiently induce oxidative stress than larger particles (6,33). Overall exposures dropped sharply in 1970 at all three plants (thus the decision to include an indicator for hire previous to 1970 in this analysis) (16), and the PAH content of base mineral oils declined over time (37). In the context of the mechanism of $PM_{2.5}$ toxicity, we would anticipate that these changes would result in a lower rate of CVD events due to short-term exposure following 1970, but persistent effects of long term exposure to higher MWF levels prior to 1970 may remain. In this analysis an indicator of having been hired before 1970 was associated with an increased HR for both natural cause and CPD mortality, however, confidence intervals included 1 (Appendix A-2). A previous analysis of ischemic heart disease (IHD) in the GM-UAW cohort found evidence for an association between contemporaneous exposure to MWF and IHD before 1971, and cumulative exposure afterwards (16).

Three of the more recent analyses of occupational PM and heart disease were performed with GM-UAW cohort data. Costello et al. found modest increases in ischemic heart disease mortality risk associated with straight MWF ($PM_{3.5}$), and as with the present analysis, the exposure-response relationship was non-monotonic and occasionally resulted in apparently-protective HRs (16). Using g-estimation to account for time-varying confounding, Picciotto et al. found that reducing exposure to MWF could result in years of life saved in cases of both all-cause and IHD mortality (27). An analysis of IHD mortality focusing on differences in mortality patterns by race and gender found that African-American and female workers may have a higher incidence of IHD due to socioeconomic factors (28); while female workers were not included in this analysis, we found elevated HRs for African-American men that approached the level of statistical significance in unweighted models (Appendix A-2). Because African-American men were heavily oversampled for the cross-sectional study, it is likely that they were often down-weighted in the IP-weighted models. We used educational attainment as a proxy for socioeconomic status and found elevated HRs for having failed to complete 12th grade, although all 95% CIs included

1. The analyses by Costello et al. and Picciotto et al. did not address cigarette smoking; if the findings discussed here were relevant to those associations, their results may still be biased downwards.

The utility of IP-weighting schemes in reducing the magnitude of selection bias depends on the accurate estimation of the predicted probabilities that constitute the weights. This depends on the availability of a set of predictors sufficient to allow the correct specification of the models used to predict the probabilities, as well as large enough sample to permit the efficient estimation of the probabilities (21,22). In the present analysis, a limited set of covariates were available for estimating the weights, and all were included in the prediction models. We chose logistic regression to model censoring and selection, and categorized the exposures to reduce the chance of random non-positivity (38) and because non-monotonic exposure-response relationships have been noted in other analyses of the GM-UAW cohort (16,23,28). While correct model specification is not empirically provable, when the model is correctly specified the mean of the stabilized weights will be 1 (39), and as seen in Table 3, the means of our IPW components are all very close to 1. An indicator of the predictive ability of a model, the $c$-statistic, is presented for each IPW component in Appendix A-1. The $c$-statistics range from 0.61 to 0.79 (0.5 represents random chance); this statistic can be inflated by including covariates that are not predictive of selection (40), so although the model fit is not particularly impressive, the covariates were chosen *a priori* from the limited set of measured variables as likely predictors of active employment status, mortality by 1985, or selection into the cross-sectional study. In addition, Howe et al. showed in simulations that when a limited number of measured variables are available for predicting the weights, IPW to adjust for censoring may fail to fully eliminate bias (38). We were unable to include some potential predictors that were available only for the cross-sectional study (e.g., cigarette smoking, education) in the models for estimating probabilities of censoring and selection. Large IPW values are indicative of sparse cells defined by combinations of covariates; while $W^D(t)$ and $W^L(t)$ have relatively narrow distributions, the maximum value for $W^S$ is over 100 (Table 3), indicating poor predictability due to a relatively small number of subjects selected into the cross-section (8% of subjects at work in 1985). We selected models for the denominators of all IPW that use more predictors but had larger variances and then truncated $W^{prod}$ at the 99th percentile in order to maximize predictive accuracy without increasing variability (22), which resulted in a maximum weight of 2.2. Thus, subjects in the cross-section were up-weighted to represent at most just over two subjects from the full cohort.

There is an overall decreasing trend (though non-monotonic) for both outcomes even after applying IPW to adjust for the healthy worker bias due to artificial censoring, which suggests the presence of bias due to the healthy worker survivor effect (HWSE). For example, a subject may leave work due to exposure, resulting in decreased future exposure as well as increased risk of the outcome. In this scenario underlying health status causes both leaving work and the outcome, and thus acts as both a confounder of the exposure-response relationship and is on the causal pathway (41). The presence of the HWSE in this cohort is supported by previous analyses which found increased risks of exposure on mortality after correcting for time-varying confounding using g-estimation (27,28,42,43). The bias due to HWSE is often more extreme in the case of a chronic health outcome such as lung disease (included in the CPD category) where workers become progressively more ill and are likely to transfer out of highly exposed jobs, as opposed to cancer (included in natural cause mortality) where progressively worsening health is less likely (44). In previous analyses of GM-UAW data, the magnitude of increase in effect estimates is

36

greater for chronic obstructive pulmonary disease and ischemic heart disease than for all-cause mortality or cancers, indicating a stronger HWSE for these chronic diseases (42). Cox proportional hazards models are ineffective in adjusting for time-varying confounding caused by prior exposure, an important aspect of the HWSE. Another limitation of this analysis is our use of robust standard errors, which offer a conservative estimate of variance for inference; it is possible that this is obscuring a true association between MWF exposure and mortality (45). Using the bootstrap method of resampling to calculate confidence intervals could reveal stronger associations (22,45).

Although we do not adjust for time-varying confounding by health status, the use of IPW appears to alleviate some of the downward bias induced by the cross-sectional selection from active workers. Overall, the effect estimates for straight MWF exposure increase in the IP-weighted models, with an increase of 18% in the fourth quartile for natural cause mortality. The decreased HR in the second quartile for CPD and third for natural cause may reflect that the subjects in the cross-section had exposure characteristics unlike those in the full cohort, which is plausible because subjects with single MWF exposure types or who were unexposed in 1985 were oversampled and these workers do not typify the cohort as a whole. A strength of this analysis is accounting for cigarette smoking as a potential confounder. Few occupational cohorts include data on smoking, so these cross-sectional data provided an important opportunity to assess the role of cigarette smoking in the relationship between MWF exposure and mortality. We found that while confounding by smoking was not strong, adjustment increased effect estimates in the lowest and highest exposed groups. The magnitude of the change, at most 11%, is consistent with the assessment by Kriebel et al. (2004) that uncontrolled confounding by smoking will cause no more than a 20% change in relative risks in large studies (46).

Previous analyses of the cross-sectional study that did not account for selection into the cohort found largely null (and sometimes even protective) associations between MWF exposure and respiratory health outcomes (18,47). For the most part, HRs increased in IP-weighted models in this analysis, indicating that some of the selection bias was ameliorated. However, HRs for CPD mortality remained below the null in the highest exposure categories. In the presence of strong prior evidence of causal effects of MWF exposure on both heart and lung disease mortality based on g-estimation (27,30), our results underscore the persistence of HWSE bias in traditional conditional analysis, particularly for CPD mortality. Cigarette smoking was a modest confounder of the exposure-response relationship and the strongest predictor of mortality.

At present, the U.S. Occupational Safety and Health Administration regulates MWF as oil mist (for straight fluids) or as particulates not otherwise regulated, with an 8-hour time-weighted average exposure limit of $5mg/m^3$ (48). Average exposures in the GM-UAW cohort were nearly an order of magnitude below this level even in years prior to 1970 (16); the health effects seen in this and other analyses of the cohort provide evidence that this exposure limit is not sufficiently protective of worker health.

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**Table 1** Characteristics of GM-UAW Cohort and Subcohorts, 1941-2009

| | Cohort | | Subcohorts | | | | | |
| | | | Alive in 1985 | | At work in 1985 | | 1985 cross-sectional survey | |
| Characteristic | No. | % | No. | % | No. | % | No. | % |
|---|---|---|---|---|---|---|---|---|
| Cohort[a] | 38622 | - | 33232 | 86.0 | 19435 | 50.3 | 1661 | 4.3 |
| Person-years[a] | 724600 | - | 613052 | 84.6 | 247397 | 34.1 | 38206 | 5.3 |
| Plant | | | | | | | | |
| 1 | 9143 | 23.7 | 7331 | 22.1 | 3622 | 18.6 | 719 | 43.3 |
| 2 | 17095 | 44.3 | 14268 | 42.9 | 7872 | 40.5 | 733 | 44.1 |
| 3 | 12384 | 32.1 | 11633 | 35 | 7941 | 40.9 | 209 | 12.6 |
| Race | | | | | | | | |
| African-American | 7139 | 18.5 | 6261 | 18.8 | 4368 | 22.5 | 604 | 36.4 |
| White | 31483 | 81.5 | 26971 | 81.2 | 15067 | 77.5 | 1057 | 63.6 |
| Sex | | | | | | | | |
| Female | 4756 | 12.3 | 4500 | 13.5 | 2987 | 15.4 | 0 | 0 |
| Male | 33866 | 87.7 | 28732 | 86.5 | 16448 | 84.6 | 1661 | 100 |
| | Median | IQR | Median | IQR | Median | IQR | Median | IQR |
| Year of hire | 1965 | 1953, 1974 | 1967 | 1953, 1976 | 1973 | 1966, 1977 | 1973 | 1967, 1977 |
| Age at hire | 25 | 20, 33 | 24 | 20, 30 | 23 | 20, 28 | 23 | 20, 28 |
| Year of birth | 1938 | 1923, 1949 | 1941 | 1927, 1950 | 1947 | 1939, 1953 | 1949 | 1940, 1955 |
| Years of employment[a] | 11.7 | 7.3, 19.4 | 18.5 | 10.6, 26.7 | 12.3 | 8.3, 18.5 | 11.8 | 7.8, 18 |
| Cumulative days off work[a] | 234 | 46, 664 | 255 | 52, 692 | 319 | 83, 741 | 279 | 71, 612 |
| Cumulative MWF exposure among exposed (mg/m³-yr)[a] | | | | | | | | |
| Straight | 0.68 | 0.22, 2.38 | 0.64 | 0.21, 2.31 | 0.57 | 0.21, 2.09 | 1.25 | 0.18, 4.95 |
| Soluble | 4.12 | 1.55, 11.96 | 3.59 | 1.39, 10.46 | 2.78 | 1.16, 7.39 | 2.85 | 0.96, 9.28 |
| Synthetic | 0.38 | 0.14, 1.51 | 0.34 | 0.13, 1.38 | 0.27 | 0.13, 0.86 | 0.34 | 0.08, 1.23 |

Abbreviations: IQR, interquartile range; MWF, metalworking fluid

[a] percent of full cohort

[b] measured in 1985

**Table 2** Detailed Characteristics of 1646 Subjects[a] in 1985 Cross-sectional Study of GM-UAW Cohort, 1941-2009

| Characteristic | No. | % |
|---|---|---|
| Less than 12th grade education | 418 | 25.4 |
| Asthma diagnosis pre-hire | 82 | 4.9 |
| Smoking Status | | |
|     Current | 847 | 51.5 |
|     Ever | 372 | 22.6 |
|     Never | 427 | 25.9 |
| Cause of death | | |
|     All-cause | 354 | 21.5 |
|     Natural cause | 322 | 19.6 |
|     Cardiopulmonary | 155 | 9.4 |
| | Median | IQR |
| Year of death | 2001 | 1995, 2006 |
| Body mass index | 27.3 | 24.7, 30.3 |
| Percent predicted $FEV_1$[b] | 98.2 | 88.9, 107.1 |

Abbreviations: IQR, interquartile range; FEV1, forced expiratory volume in one second

[a] 15 subjects were missing values for one or more of the covariates included in Cox proportional hazards models and are omitted

[b] 26 additional subjects were missing pulmonary function (n=1620)

**Table 3** Properties of stabilized inverse probability weight components and product, GM-UAW cohort, 1941-2009

| | $W^A(t)$ | $W^E(t)$ | $W^S$ | $W^{prod}$ |
|---|---|---|---|---|
| Mean | 1.00 | 0.99 | 1.00 | 1.00 |
| Standard Deviation | 0.15 | 0.16 | 0.99 | 1.00 |
| Quantile | | | | |
|     Maximum | 2.93 | 2.10 | 115.17 | 114.57 |
|     99% | 1.65 | 1.42 | 2.16 | 2.23 |
|     75% | 1.00 | 1.04 | 1.03 | 1.08 |
|     50% Median | 1.00 | 1.00 | 0.94 | 0.96 |
|     25% | 0.99 | 0.95 | 0.92 | 0.92 |
|     1% | 0.56 | 0.57 | 0.29 | 0.29 |
|     Minimum | 0.17 | 0.39 | 0.17 | 0.17 |

**Table 4** Hazard Ratios[a] for Natural Cause Mortality and Cumulative Straight Metalworking Fluid Exposure (15 Year Lag, $mg/m^3$-year) in 1985 Cross-sectional Study of GM-UAW Cohort, 1941-2009

| Exposure Category | No. of Cases | Unweighted model | | Unweighted model, smoking-adjusted | | IP-weighted | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| 0 | 180 | 1.00 | Referent | 1 | Referent | 1.00 | Referent |
| > 0 - 0.21 | 35 | 0.85 | 0.58, 1.24 | 0.94 | 0.64, 1.38 | 1.12 | 0.72, 1.76 |
| 0.22 - 0.79 | 36 | 1.18 | 0.82, 1.70 | 1.22 | 0.84, 1.76 | 1.25 | 0.79, 2.00 |
| 0.80 - 4.40 | 35 | 0.87 | 0.60, 1.26 | 0.88 | 0.61, 1.27 | 0.71 | 0.42, 1.18 |
| > 4.40 | 36 | 0.84 | 0.58, 1.22 | 0.93 | 0.63, 1.35 | 1.12 | 0.68, 1.86 |

Abbreviations: CI, confidence interval; HR, hazard ratio; IP, inverse probability

[a] Model adjusted for plant location, race, education, pre-hire asthma diagnosis, cigarette smoking (never, past or current smoker), active work status at time of death, calendar year, hire previous to 1970, and cumulative years of employment


**Table 5** Hazard Ratios[a] for Cardiopulmonary Disease Mortality and Cumulative Straight Metalworking Fluid Exposure (15 Year Lag, $mg/m^3$-year) in 1985 Cross-sectional Study of GM-UAW Cohort, 1941-2009

| Exposure Category | No. of Cases | Unweighted model | | Unweighted model, smoking-adjusted | | IP-weighted | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| 0 | 85 | 1.00 | Referent | 1 | Referent | 1.00 | Referent |
| > 0 - 0.19 | 17 | 0.90 | 0.52, 1.54 | 1.02 | 0.59, 1.76 | 1.12 | 0.57, 2.17 |
| 0.20 - 0.50 | 18 | 2.30 | 1.36, 3.89 | 2.26 | 1.34, 3.82 | 1.86 | 0.97, 3.55 |
| 0.51 - 3.21 | 17 | 0.68 | 0.40, 1.16 | 0.73 | 0.43, 1.25 | 0.79 | 0.40, 1.55 |
| > 3.21 | 18 | 0.69 | 0.40, 1.17 | 0.76 | 0.45, 1.29 | 0.80 | 0.39, 1.63 |

Abbreviations: CI, confidence interval; HR, hazard ratio; IP, inverse probability

[a] Models are adjusted for plant location, race, education, cigarette smoking (never, past or current smoker), active work status at time of death, calendar year, hire previous to 1970, and cumulative years of employment

## Chapter 5: Conclusion

Occupational health is an important contributor to overall human health, and work-related injuries and illnesses are preventable. When many workers experience the same exposure, even small associated elevations in the risk of disease or mortality can cause a great burden of disease; understanding these associations is key to protecting workers and preventing deaths and illness. While working populations can offer the opportunity to study exposure-response relationships at higher exposures than seen in the general population, the healthy worker effect can result in underestimation of the effect of a truly hazardous exposure. This dissertation explores the associations between common industrial exposures and chronic health outcomes, providing evidence that exposures to *n*-hexane and particulate matter among industrial workers may result in preventable morbidity and mortality, and that current regulatory exposure limits may not be sufficiently protective of worker health.

In chapter two, I find modest evidence for an association between acquired color vision defects and exposure to *n*-hexane in automotive repair cleaning solvents. The associations are strongest among younger participants and blue-yellow color vision defects, consistent with the hypothesis that the neurotoxic effect of *n*-hexane results in damage to the retina and the increase in blue-yellow defects occurring due to age alone in older participants. Although this analysis was limited by the cross-sectional design of the study, the assessments of exposure and color vision were rigorous and the inclusion of retired workers served to reduce bias due to the healthy worker survivor effect. The workers in this group, the largest epidemiologic study of *n*-hexane exposure and color vision to date, were exposed to levels of hexane far below existing regulatory limits. Although modest, the elevations in color vision defect prevalence associated with hexane exposure may suggest that these limits may not be sufficiently protective of worker health.

I shifted focus to PM exposure among automobile industry workers in Chapter 3, where I investigate different types of MWF and COPD mortality. Results provide evidence for an elevated risk of COPD among workers exposed to MWF, especially soluble, compared to workers who were never directly exposed to MWF. Although 95% confidence intervals generally included 1, effect estimates remained elevated after indirect adjustment for confounding by cigarette smoking and accounting for potential competing risks; previous analyses of COPD risk in the cohort did not address confounding by cigarette smoking or the effect of competing risks. The results of this analysis are consistent with existing literature on MWF exposure and COPD, and contribute to on the literature by assessing the role of cigarette smoking (which is frequently unavailable in occupational cohort data) as a confounder. Because occupational exposure to PM is so widespread, even very small increases in risk could result in many COPD deaths – already a major source of occupational disease worldwide.

The fourth chapter explores the association between exposure to mineral oil-based MWF and natural cause and cardiopulmonary mortality using IPW to address selection bias due to the healthy worker survivor effect and non-random study sample selection. Although the effect estimates for exposure had wide confidence intervals including 1, HRs were generally higher in the IP-weighted models, indicating that some downward bias was alleviated. The analysis did not account for time-varying confounding by health status, so residual downward bias is likely to exist, especially given evidence from previous analyses of the GM-UAW cohort showing this type of bias. Cigarette smoking status was a modest confounder of the association between MWF and mortality; omitting smoking from the model attenuated effect estimates. While there are

important assumptions to consider, IP-weighting is a relatively straightforward method for addressing bias due to a selection bias element of the healthy worker survivor effect.

As a whole, the chapters of this dissertation present a set of analyses of associations between exposures faced by many industrial workers and a subclinical marker of neurotoxicity (Chapter 2) as well as mortality outcomes. The three papers address the healthy worker effect using different methods, but clear evidence of residual downward bias both indicates that the estimated associations are likely to be underestimates, and also illustrate the challenges of overcoming a source of bias unique to occupational epidemiologic studies.

These works add to the current scientific understanding of the health effects of *n*-hexane and PM exposure – two exposures with evidence supporting the inadequacy of current occupational and safety health regulatory levels in the U.S. In Chapter 2, even the 99th percentile of hexane exposure among study participants was well below regulatory limits. Metalworking fluids do not have a regulatory limit of their own, but are regulated as oil mists or particulate matter; average exposures in Chapters 3 and 4 are levels of respirable PM approximately an order of magnitude below the regulatory limit even during the early years of highest exposures. This information should be used to inform efforts to protect workers worldwide, many of whom are exposed at levels far above those measured in these studies.

# Appendix

**Appendix A-1** Models for Inverse Probability Weight Components, GM-UAW Cohort, 1941-2009

| | $W^D(t)$ | $W^L(t)$ | $W^S$ |
|---|---|---|---|
| No. | 38 622 | 33 232 | 19 435 |
| Person-years | 724 600 | 613 052 | NA |
| Model $c$-statistic | 0.77 | 0.61 | 0.79 |
| Covariate | OR | OR | OR |
| **Plant** | | | |
| 1 (Reference) | 1.00 | 1.00 | 1.00 |
| 2 | 1.44 | 1.25 | 0.56 |
| 3 | 1.77 | 1.67 | 0.10 |
| **Race** | | | |
| White (Reference) | 1.00 | 1.00 | 1.00 |
| Black | 1.22 | 1.49 | 1.48 |
| Year entered follow-up | 0.97 | 0.98 | 0.77 |
| Year of birth | 1.08 | 1.02 | 1.01 |
| Cumulative years employed | 0.97 | 0.96 | 0.75 |
| **Quartiles of 1-year lagged cumulative MWF (mg/m3-year)** | | | |
| Straight | | | |
| Unexposed (Reference) | 1.00 | 1.00 | 1.00 |
| 1st | 1.03 | 0.95 | 0.90 |
| 2nd | 0.97 | 0.92 | 0.52 |
| 3rd | 1.00 | 1.01 | 0.98 |
| 4th | 0.98 | 1.05 | 1.75 |
| Soluble | | | |
| Unexposed (Reference) | 1.00 | 1.00 | 1.00 |
| 1st | 1.09 | 0.90 | 0.78 |
| 2nd | 1.08 | 0.89 | 0.49 |
| 3rd | 1.10 | 1.06 | 0.47 |
| 4th | 1.09 | 1.08 | 0.50 |
| Synthetic | | | |
| Unexposed (Reference) | 1.00 | 1.00 | 1.00 |
| 1st | 0.93 | 1.04 | 0.49 |
| 2nd | 0.87 | 1.07 | 0.43 |
| 3rd | 0.93 | 1.01 | 0.45 |
| 4th | 0.90 | 0.78 | 0.75 |
| **Quartiles of 1-year lagged days off work** | | | |
| No days off (Reference) | 1.00 | 1.00 | 1.00 |
| 1st | 0.83 | 0.93 | 1.40 |
| 2nd | 0.68 | 0.77 | 1.29 |
| 3rd | 0.54 | 0.71 | 1.34 |
| 4th | 0.62 | 0.72 | 1.08 |

Abbreviations: GM-UAW, General Motors-United Auto Workers; MWF, metalworking fluid; OR, odds ratio

**Appendix A-2** Hazard Ratios[a] for Natural Cause and Cardiopulmonary Disease Mortality and Cumulative Straight Metalworking Fluid Exposure (15 Year Lag, mg/m³-year) in 1985 Cross-sectional Study of GM-UAW Cohort, 1941-2009

**Natural cause mortality (n=322)**

| Covariate | No. cases | Unweighted HR | Unweighted 95% CI | IP-weighted HR | IP-weighted 95% CI |
|---|---|---|---|---|---|
| Straight MWF | | | | | |
| 0 | 180 | 1.00 | Referent | 1.00 | Referent |
| > 0 - 0.21 | 35 | 0.94 | 0.64, 1.38 | 1.12 | 0.72, 1.76 |
| 0.22 - 0.79 | 36 | 1.22 | 0.84, 1.76 | 1.25 | 0.79, 2.00 |
| 0.80 - 4.40 | 35 | 0.88 | 0.61, 1.27 | 0.71 | 0.42, 1.18 |
| > 4.40 | 36 | 0.93 | 0.63, 1.35 | 1.12 | 0.68, 1.86 |
| Soluble MWF | | 0.97 | 0.94, 0.99 | 0.97 | 0.94, 0.99 |
| Synthetic MWF | | 0.91 | 0.76, 1.09 | 0.89 | 0.73, 1.08 |
| Plant | | | | | |
| 1 | 118 | 1.00 | Referent | 1.00 | Referent |
| 2 or 3 | 204 | 0.90 | 0.66, 1.22 | 0.81 | 0.55, 1.18 |
| Race | | | | | |
| White | 160 | 1.00 | Referent | 1.00 | Referent |
| African-American | 162 | 1.23 | 0.95, 1.61 | 1.02 | 0.73, 1.45 |
| Education | | | | | |
| ≥ 12th grade | 171 | 1.00 | Referent | 1.00 | Referent |
| < 12th grade | 151 | 1.10 | 0.86, 1.42 | 1.30 | 0.93, 1.81 |
| Smoking[a] | | | | | |
| Never | 35 | 1.00 | Referent | 1.00 | Referent |
| Past | 69 | 1.43 | 0.95, 2.17 | 1.37 | 0.81, 2.32 |
| Current | 218 | 3.00 | 2.09, 4.31 | 3.13 | 1.96, 5.00 |
| Pre-hire asthma | | | | | |
| Did not report | 290 | 1.00 | Referent | 1.00 | Referent |
| Reported asthma | 32 | 2.37 | 1.55, 3.62 | 2.46 | 1.44, 4.19 |
| Active at time of death | | | | | |
| Not at work | 279 | 1.00 | Referent | 1.00 | Referent |
| Still at work | 43 | 0.48 | 0.31, 0.76 | 0.56 | 0.31, 1.01 |
| Year of hire | | | | | |
| > 1970 | 98 | 1.00 | Referent | 1.00 | Referent |
| ≤ 1970 | 224 | 1.31 | 0.89, 1.93 | 1.24 | 0.78, 1.99 |
| Calendar year | | 0.97 | 0.95, 1.00 | 0.97 | 0.94, 1.00 |
| Years worked[a,b] | | 1.00 | 0.97, 1.02 | 1.00 | 0.97, 1.03 |

**Cardiopulmonary disease mortality (n=155)**

| Covariate | No. cases | Unweighted HR | Unweighted 95% CI | IP-weighted HR | IP-weighted 95% CI |
|---|---|---|---|---|---|
| Straight MWF | | | | | |
| 0 | 85 | 1.00 | Referent | 1.00 | Referent |
| > 0 - 0.19 | 17 | 1.02 | 0.59, 1.76 | 1.12 | 0.57, 2.17 |
| 0.20 - 0.50 | 18 | 2.26 | 1.34, 3.82 | 1.86 | 0.97, 3.55 |
| 0.51 - 3.21 | 17 | 0.73 | 0.43, 1.25 | 0.79 | 0.40, 1.55 |
| > 3.21 | 18 | 0.76 | 0.45, 1.29 | 0.80 | 0.39, 1.63 |
| Soluble MWF | | 0.97 | 0.94, 1.01 | 0.95 | 0.90, 0.99 |
| Synthetic MWF | | 0.94 | 0.79, 1.13 | 0.93 | 0.79, 1.10 |
| Plant | | | | | |
| 1 | 54 | 1.00 | Referent | 1.00 | Referent |
| 2 or 3 | 101 | 1.01 | 0.65, 1.57 | 0.80 | 0.46, 1.41 |
| Race | | | | | |
| White | 69 | 1.00 | Referent | 1.00 | Referent |
| African-American | 86 | 1.41 | 0.96, 2.07 | 1.16 | 0.72, 1.88 |
| Education | | | | | |
| ≥ 12th grade | 82 | 1.00 | Referent | 1.00 | Referent |
| < 12th grade | 73 | 0.95 | 0.66, 1.35 | 1.07 | 0.66, 1.76 |
| Smoking[a] | | | | | |
| Never | 16 | 1.00 | Referent | 1.00 | Referent |
| Past | 30 | 1.30 | 0.70, 2.40 | 1.33 | 0.62, 2.88 |
| Current | 109 | 3.17 | 1.86, 5.38 | 3.90 | 1.98, 7.69 |
| Active at time of death | | | | | |
| Not at work | 133 | 1.00 | Referent | 1.00 | Referent |
| Still at work | 22 | 0.70 | 0.37, 1.32 | 0.85 | 0.37, 1.98 |
| Year of hire | | | | | |
| > 1970 | 41 | 1.00 | Referent | 1.00 | Referent |
| ≤ 1970 | 114 | 0.97 | 0.93, 1.00 | 0.95 | 0.91, 1.00 |
| Calendar year | | 1.31 | 0.75, 2.28 | 1.09 | 0.58, 2.06 |
| Years worked[a,b] | | 1.00 | 0.97, 1.04 | 1.02 | 0.98, 1.06 |

Abbreviations: CI, confidence interval; HR, hazard ratio; MWF, metalworking fluid

[a] Measured in 1985

[b] Cumulative