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The Relationship between Multiple Myeloma and Occupational Exposure to Six Chlorinated Solvents

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Abstract

Objectives—Few studies have examined whether exposure to chlorinated solvents is associated with increased risk of multiple myeloma (MM). Using occupational exposure information, we evaluated associations between the risk of MM and exposure to six chlorinated solvents: 1,1,1-trichloroethane (TCA), trichloroethylene (TCE), methylene chloride (DCM), perchloroethylene (PCE), carbon tetrachloride, and chloroform.

Methods—MM cases were identified through cancer registries and controls were identified in the general population. In-person interviews obtained lifetime occupational histories and additional information on jobs with likely solvent exposure. We reviewed each job and assigned exposure metrics of probability, frequency, intensity, and confidence using job-exposure matrices modified by job-specific questionnaire information. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between MM and having ever been exposed to each, and any, chlorinated solvent and also analyzed whether associations varied by duration and cumulative exposure. We also considered all occupations that were given the lowest confidence scores as unexposed and repeated all analyses.

Results—Risk of MM was significantly elevated for subjects ever exposed to TCA (OR (95% CI): 1.8 (1.1–2.9)). Ever-exposure to TCE or DCM also entailed elevated, but not statistically significant, risks of MM; these became statistically significant when occupations that had low confidence scores were considered unexposed (TCE: 1.7 (1.0–2.7); DCM: 2.0 (1.2–3.2)). Increasing duration and cumulative exposure to TCE were associated with significantly increasing risk of MM when jobs given low confidence were considered unexposed. Increasing cumulative exposure to PCE was also associated with increasing MM risk. We observed non-significantly increased MM risks with exposure to chloroform; however, few subjects were exposed.

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Conclusions—Evidence from this relatively large case-control study suggests that exposures to certain chlorinated solvents may be associated with increased incidence of MM; however, the study is limited by relatively low participation (52%) among controls.

Keywords

multiple myeloma; chlorinated solvents; 1,1,1-trichloroethane (TCA); trichloroethylene (TCE); methylene chloride (DCM); perchloroethylene (PCE); carbon tetrachloride; chloroform

INTRODUCTION

Multiple myeloma (MM) is an incurable plasma cell malignancy that accounts for about 20% of deaths from hematopoietic cancers and 2% of deaths from all cancers.[1] While the etiology of this cancer is poorly understood, several studies have reported associations between MM and occupations that may entail exposure to chlorinated solvents, including chemical work,[2,3] construction work,[4,5] painting,[6–8] metal work,[8–11] farm work, [5,12–14] and hairdressing.[15–17]

Few studies have specifically examined whether exposure to chlorinated solvents is associated with increased risk of MM. No relationship has been found between trichloroethylene (TCE) and MM in cohort studies,[18–24] but these studies were based on small numbers of MM cases. Two small cohort studies found increased risks associated with exposure to 1, 1, 1-trichloroethane (TCA).[21,25] In a recent cohort study, a fumigant mixture composed of carbon tetrachloride and carbon disulfide was significantly associated with monoclonal gammopathy of undetermined significance (MGUS),[26] a benign proliferation of plasma cells that likely precedes most MM cases.[27] Additionally, other lymphohematopoietic cancers that may have similar etiologies to MM have been linked to occupational exposure to chlorinated solvents. For example, TCE has been associated with increased risks of non-Hodgkin lymphoma (NHL). [22,28] Occupational exposures to carbon tetrachloride, chloroform, methylene chloride (DCM), and perchloroethylene (PCE) have not been evaluated with respect to MM risk, but PCE has been linked to NHL[21,29] and carbon tetrachloride has been associated with leukemia[30,31] and NHL.[32]

Using occupational exposure information obtained from job-specific questionnaires in a population-based case control study, we evaluated associations between the risk of MM and exposure to six major chlorinated solvents that were widely used occupationally during the time period in which our study subjects were working: TCA, TCE, DCM, PCE, carbon tetrachloride, and chloroform.

METHODS

Identification of cases and controls

MM cases were identified through the Surveillance, Epidemiology, and End Results (SEER) cancer registries in the Seattle-Puget Sound region of Washington and the Detroit metropolitan area of Michigan. These registries identified cases by reviewing medical records at all the hospitals in the region, as well as by reviewing records of selected pathology laboratories, oncologists, radiologists, and state death certificates. The frequency of these reviews enabled the identification of cases within one to two months of diagnosis. Cases eligible to participate in this study were 35 to 74 years old and were diagnosed with MM (ICD-O-2/3 9731:9732) between January 1, 2000 and March 31, 2002. Of the 365 cases who appeared to be eligible to participate in this study, 64 (18%) died before they could be contacted, 28 (8%) were unable to be located, and the physicians of 18 (5%) refused. Of the remaining 255 that we were able to contact, 74 (29%) refused to participate,

leaving a total of 181 cases. Thus, of cases who were alive, able to be located, and whose eligibility could be confirmed, 71% (181/255) participated in this study. Case participation was not associated with study site, age, or gender. General population controls were selected from a case-control study of NHL that was undertaken at the same time and included the same geographic areas as the MM case recruitment.[33] Controls under 65 years were identified using random digit dialing; controls 65 to 74 years were identified from the Center for Medicare and Medicaid Services files. We selected controls for our MM study from the NHL study controls who 1) were not previously diagnosed with MM, plasmacytoma, NHL, or HIV (the latter were excluded because of the association between the virus and lymphoma development);[34] 2) were between 35 and 74 years old; 3) were identified as residents of the Detroit or Seattle-Puget Sound areas between September 1998 and December 2002; and 4) spoke English. Of the 1133 potential controls who were eligible to participate in this MM study, 52% (481/1133) participated as NHL study controls. Control participation was not associated with study site or gender, but individuals in the youngest (35–50) and oldest (65–74) age groups were less likely to have participated than those in the middle age group. Informed consent was obtained from each participant before the interview and approval was obtained from the appropriate Institutional Review Boards.

Exposure assessment

In-person interviews were conducted using a computer-assisted personal interview program. Surrogates were not permitted to complete interviews on behalf of study participants but were allowed to aid in recalling occupational histories, dates, and frequencies of exposures. Information on all jobs held for at least one year between 1941 for cases and 1946 for controls and the date of enrollment in the study was collected. Participants reported job start and stop years, job titles, and employers for every job they held since age 18. The participants were also asked to describe what the employer made or what service was provided, their main duties, and how many months per year and hours per week they worked each job. Additionally, for 20 occupations with potential solvent exposure, job-specific questionnaires developed by an industrial hygienist were administered.[35] These included questions on the work environment (e.g. ventilation practices), job-specific tasks performed by the subject, chemicals used, and other factors relevant to exposure assessment.[36] To minimize interview time, job-specific modules were administered only when participants held the relevant job for at least two years.

All jobs were coded according to the Standard Occupational Classification (SOC) System.[37] In addition, all jobs held by each participant, regardless of whether job-specific questionnaires were used, were assessed for exposure to each of the six chlorinated solvents; a total of 2,264 jobs were reviewed. Exposure metrics of probability, frequency, intensity, and confidence were assigned by modifying job-exposure matrices (JEMs) based on the subjects' answers to the work history and the job module sections of the questionnaire. The JEMs were developed by an industrial hygienist after reviewing over 600 published papers and reports on chlorinated solvents (e.g. see Bakke et al.[38] and Gold et al.[39]). These JEMs were developed for each decade for specific 1) industries, such as the chemical or rubber industry; 2) occupations, such as auto mechanics or hair dressers; and 3) tasks, such as degreasing, gluing, and painting.

Exposure *probability* was defined as the theoretical percentage of workers reporting the same information who would have been likely to have had exposure to the solvent. Probability was scored as: *0* = <1% of subjects were likely to have had exposure; *1* = 1 to <10% of subjects were likely to have had exposure; *2* = 10 to <50% of subjects were likely to have had exposure; *3* = 50 to <90% of subjects were likely to have had exposure; and, *4* = self-reported use or ≥90% of subjects were likely to have had exposure. For jobs with probability scores of at least 1, frequency and intensity scores were also assigned. *Frequency*

was defined as the average hours per week of exposure to a particular solvent, averaged over the job, and was categorized as: *0* = <15 min/week; *1* = 15 minutes to <1 hour/week; *2* = 1 to 10 hours/week; *3* = >10 to 20 hours/week; and, *4* = >20 hours/week. The *intensity* score was the concentration of solvent estimated to have been in the subject's breathing zone, in parts per million (ppm), during the exposure period (not necessarily for a full-shift) and was coded as: *1* = <1 to 10 ppm; *2* = >10 to 100 ppm; *3* = >100 to 200 ppm; and, *4* = >200 ppm. Finally, the *confidence* level was assigned as: *1* = literature contradictory or no information was available; *2* = one metric (probability, frequency, or intensity) was based on the literature or self-report; *3* = two metrics were based on the literature or self-report; and, *4* = all three metrics were based on the literature or directly from the subject's report.

Some general rules were applied across all jobs. If the subject reported information that contradicted the appropriate JEM scores, the subject-specific data were used. If chlorinated solvent exposure was not specifically mentioned but would normally have occurred when performing reported tasks (e.g. an auto mechanic reported doing tune-ups and clutch or brake work, but did not report degreasing), the subject was assessed as having been exposed and given probability, frequency, and intensity scores from the JEM, but the confidence score was lowered by 1. If a subject reported working in an industry that likely involved tasks entailing chlorinated solvent exposure (e.g., auto manufacturing) and the job title was manager or a similar that indicated s/he was not likely to do hands-on work in the production area, the frequency and intensity scores from the JEMs were lowered by 1. If dermal exposure was likely (e.g. the subject reported degreasing with a rag), the intensity score was raised by 1. All assignments were conducted by an occupational epidemiologist (LSG) and reviewed by an industrial hygienist (PAS); both were blinded to case-control status.

We did not have information about non-occupational sources of chlorinated solvent exposure, such as use of glues or paints for hobbies, so we were not able to include these in each subject's cumulative solvent exposure. However, we did not expect these to be major sources of chlorinated solvent exposure relative to occupational exposures.

Statistical Analysis

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between the risk of MM and having ever been exposed (defined as a probability score of at least 2 in any job) to *any* of the six chlorinated solvents and to *each* of the six chlorinated solvents. We also analyzed whether the risk of MM varied by duration, using the summed total years worked in jobs considered to have been exposed to each chlorinated solvent. We performed analyses examining cumulative exposure over each subject's lifetime (for each exposed job, the midpoint of intensity (in ppm) x the midpoint of frequency (in hours/week) x total years worked, summed over all exposed jobs), again for jobs with a probability score of 2 or greater for a particular solvent. Finally, assuming MM develops over a number of years and recent exposures may be less relevant than those that took place in the more distant past, we conducted analyses in which potential exposures that occurred within ten years of the reference date were considered unexposed. Each of the continuous exposure metrics (duration, cumulative, and lagged cumulative exposure) was categorized into four groups according to quartiles of the control exposure distribution. Tests of trend were conducted using a linear term for the median duration and cumulative scores among controls in each category. The reference group in each model consisted of study participants who were assessed to have never been exposed (probability<2 in all jobs) to that particular chlorinated solvent.

All models included the covariates gender, age (35–50 years (referent), 51–64 years, and 65–74 years), race (only white (referent), any black, any Asian, and other), education (less

than 12 years (referent), 12–15 years, and 16 or more years), and SEER site (Seattle and Detroit). Reported p-values are two-sided and p-values of <0.05 were considered to be statistically significant.

As a sensitivity analysis, we considered all occupations that were given confidence scores of 1 as unexposed and repeated all of the analyses. Evidence has shown that the main source of non-differential misclassification that falsely attenuates odds ratios toward the null is incorrect classification of unexposed individuals as exposed in population-based case-control studies in which the prevalence of exposure is low. Incorrectly classifying an equal proportion of exposed individuals as unexposed has been reported not to have a substantial effect on risk estimates.[40–42] We also performed an additional sub-analysis with stratification by SEER site to evaluate whether the different case-to-control ratios in Seattle and Detroit may have influenced our results (because a greater proportion of controls than cases were from Seattle and the prevalence of industries, occupations, and chlorinated solvent exposures also differed by study site). For the site-stratified results, we note associations that were present in only one site. Finally, because uses of TCA, TCE, DCM, and carbon tetrachloride may have been correlated, we report the percentages of control subjects exposed to these chemicals alone and to two of these chemicals and provide an estimate of the association to MM for subjects who were exposed to all four.

RESULTS

One case was excluded because of missing covariate information, leaving 180 cases and 481 controls in our final study population. Cases were more likely to be male (55%) than female (45%), were frequently age 65 and older (39%), African American (28%), and most (85%) had at least 12 years of education. Overall, the distributions of sex, age, education and race were similar between cases and controls in Seattle. In Detroit, sex and education were similarly distributed between cases and controls but cases were more likely than controls to be in the middle versus the oldest age group and were less likely to be of white race only.

Among the most commonly held occupations, management and administrative occupations (SOCs 12, 13, and 14; n=190 jobs reported) tended not to entail exposure to any of the chlorinated solvents, but occupations such as mechanics and repairers (SOC 61; n=79 jobs reported), construction trades (SOC 64; n=70 jobs reported), machine operators and tenders (SOCs 75 and 76; n=128 jobs reported), fabricators, assemblers, and hand working occupations (SOC 77; n=85 jobs reported) and handlers, equipment cleaners, and laborers (SOC 87; n=84 jobs reported) generally were assessed as entailing exposure to one or more of the chlorinated solvents.

Exposure to any of the six chlorinated solvents of interest was associated with a statistically significant increased risk of MM (OR (95% CI): 1.5 (1.0–2.3), data not shown). Associations between exposure to each of the six chlorinated solvents and the risk of MM are shown in Tables 1–6. Risk of MM was significantly elevated for subjects ever exposed to TCA (OR (95% CI): 1.8 (1.1–2.9), Table 1). However, MM risk did not increase by exposure duration or with increased cumulative exposure; in fact, the highest increased risk was observed in the second highest categories for each. Similar results were seen when jobs with low confidence scores were considered unexposed except the highest increased risk was seen in the first exposure categories for the cumulative and lagged cumulative scores (Table 1).

Exposure to TCE in any job entailed elevated, but not statistically significant, risk of MM (OR (95% CI): 1.4 (0.9–2.1), Table 2) and this result was seen only in subjects from Detroit (data not shown). MM risk associated with TCE exposure showed increases in magnitude by

increasing cumulative exposure and lagged cumulative exposure, although these trends were not statistically significant. When occupations that had low confidence scores were included in the unexposed category, the increased MM risk associated with ever-exposure to TCE became statistically significant (OR (95% CI): 1.7 (1.0–2.7), Table 2) and showed a trend of increasing risk with increasing duration of exposure in which the highest OR was seen in the third highest duration category. Increasing cumulative exposure to TCE was also associated with a statistically significant trend of increasing risk of MM in the analysis with low confidence exposures recoded as unexposed and this trend remained when the cumulative exposure scores were lagged by ten years, with the highest risks in the highest categories.

Ever-exposure to DCM was associated with elevated risk of MM that was not statistically significant (OR (95% CI): 1.5 (0.9–2.3), Table 3). The increased MM risk associated with DCM exposure did not show an apparent trend by increased duration or cumulative exposure. However, when occupations that had low confidence scores were included in the unexposed category, the increased MM risks associated with ever-exposure to DCM became statistically significant (OR (95% CI): 2.0 (1.2–3.2), Table 3) and showed a significant trend of increasing risk with increasing duration of exposure, with the highest OR in the third highest duration category. In these analyses with jobs given low confidence scores considered unexposed, there was no trend of risk with increasing cumulative or lagged cumulative exposure (Table 3).

Subjects ever-exposed to PCE were at slightly elevated, but not statistically significant, risk of MM when the low confidence assessments were considered either exposed (OR (95% CI): 1.4 (0.9–2.4)) or unexposed (OR (95% CI): 1.5 (0.8–2.9), Table 4). Trends of increasing risk with increasing duration of exposure were not statistically significant, but we did observe statistically significant trends for increasing cumulative and lagged cumulative exposure both when the low confidence occupations were considered exposed and unexposed. In all cumulative exposure analyses of PCE, the highest ORs were seen in the highest exposure categories (Table 4).

Exposure to carbon tetrachloride was not associated with an increased risk of MM when jobs with low confidence scores were included among the exposed (OR (95% CI): 1.1 (0.7–1.8), Table 5), but when these jobs were included among the unexposed, we observed a non-statistically significant increase in risk of MM (OR (95% CI): 1.6 (0.8–3.0)) and a trend of significantly increased risk with increasing duration of exposure that was only observed among Seattle participants (data not shown). We did not observe any trends of increased risk of MM with increasing cumulative or lagged cumulative exposure to carbon tetrachloride.

We did not observe an increased risk of MM with exposure to chloroform when jobs with low confidence scores were considered exposed (OR (95% CI): 1.4 (0.7–2.8), Table 6). However, exposure to chloroform was associated with elevated, but not statistically significant, risk of MM when subjects with low confidence were included in the unexposed group (OR (95% CI): 2.5 (0.8–7.6), Table 6). We did not observe significant trends with increased duration or cumulative exposure to chloroform in either the analysis in which jobs with low confidence scores were considered exposed or unexposed, but the highest odds ratios were in the highest exposed categories in these analyses. However, few subjects were assessed as being exposed to chloroform (n=41) and we were not able to assess site-specific trends.

Finally, we found that 16% of controls were exposed to both TCE and carbon tetrachloride (13% were exposed to TCE but not carbon tetrachloride; 2.5% were exposed to carbon tetrachloride but not TCE); 13% of controls were exposed to both TCE and DCM (16% were exposed to TCE but not DCM; 6.2% were exposed to DCM but not TCE); 11% of

controls were exposed to TCA and TCA (17% were exposed to TCE but not TCA; 2.1% were exposed to TCA but not TCE); 9.1% of controls were exposed to carbon tetrachloride and DCM (9.1% were exposed to carbon tetrachloride but not DCM; 9.8% were exposed to DCM but not carbon tetrachloride); 11% were exposed to DCM and TCA (2.5% were exposed to TCA but not DCM; 7.9% were exposed to DCM but not TCA); 6.7% were exposed to carbon tetrachloride and TCA (12% were exposed to carbon tetrachloride but not TCA; 6.9% were exposed to TCA but not carbon tetrachloride). Ever exposure to TCE, TCA, DCM, *and* carbon tetrachloride was non-significantly associated with increased risk of MM (OR (95% CI): 1.7 (0.8–3.5), data not shown).

DISCUSSION

Evidence from this relatively large case-control study suggests that exposures to certain chlorinated solvents were associated with increased incidence of MM. We observed elevated risk estimates for each of the six chlorinated solvents we examined; however, increased risks were not always statistically significant and we did not always observe linear exposure-response patterns. The most consistent results were observed for TCE, with MM risk increasing with greater exposure when low confidence exposure assignments were considered unexposed. We also observed elevated risks for MM from exposure to TCA, DCM, and PCE; however, all showed non-linear exposure-response gradients, in which the highest risks were associated with moderate (rather than high) exposure in at least one analysis. While a non-linear dose-response is biologically possible and potentially relevant for certain exogenous exposures, the more traditional expectation is that risks rise with increasing levels of exposure. Exposure to carbon tetrachloride was associated with elevated, but usually not statistically significant, increased risk of MM, with a significant trend of increasing risk with greater duration of exposure when low confidence exposure assignments were considered unexposed. We also observed a suggestion that exposure to chloroform was associated with increased MM risk; however, few subjects in our study were exposed to chloroform and we were not able to make firm conclusions regarding its association with MM.

The most common task that entailed exposure to TCA, TCE, and carbon tetrachloride was degreasing of metal parts. Many of the subjects who were considered as having been possibly exposure to these chemicals through degreasing were machine operators and were employed at automotive manufacturing companies in Detroit and at aircraft manufacturing companies and in the military in Seattle. Workers at auto plants in Detroit and at airplane plants in Seattle who were involved in finishing tasks such as packaging were assessed as possibly exposed to TCA and TCE through glues. Janitors and custodians were considered to have been possibly exposed to TCE through the use of furniture polishing and floor-stripping products.

Possible exposure to DCM and PCE likely occurred most often through the use of glues. In Detroit, subjects who worked at automotive manufacturing companies were assessed to have possibly used glues on assembly lines or when packaging products whereas in Seattle, glues were more often associated with aircraft manufacturing companies and tire repair at service stations. Another commonly assessed source of possible exposure to DCM and PCE was from degreasing in car garages and in aircraft manufacturing plants. Janitors and cleaners were considered to have been exposed to DCM through the use of cleaning products. Although a less common source of PCE exposure than glues, work in the dry cleaning industry was associated with high intensity PCE exposure.

Although previous studies have not examined exposure to chlorinated solvents and MM specifically, associations between occupations that might entail exposure to chlorinated

solvents and MM have been noted. A meta-analysis of associations between chemical workers and many types of cancer found these workers were at significantly increased risk of incidence of MM (meta-standardized incidence ratio (95% CI) 2.2 (1.3–3.8)), [2] but particular exposures that these workers had that may have led to MM were not clear from this study. Many studies have found that occupation in agriculture was associated with increased risk of MM, [43] but these jobs tended to include exposure to many potentially carcinogenic substances, and specific exposures that might increase risk of MM have not been identified.

One mechanism through which chlorinated solvents may induce cancer is by damaging or altering DNA. TCE and carbon tetrachloride have been shown to form DNA adducts and mutations in brain, testis, pancreas, kidney, liver, lung, and spleen cells in rodents.[44,45] DNA hypomethylation of protooncogenes, which is hypothesized to precede several types of cancer,[46] has also been associated with exposure to TCE[46] and chloroform.[47]

Solvents can also affect the immune system, which may be relevant since MM is increased in patients experiencing immune system dysregulation, such as patients with the human immunodeficiency virus (HIV),[48–50] certain autoimmune diseases,[51] and organ transplants.[52,53] Suppressed immunity may lead to susceptibility to viruses that could potentially cause critical cytogenetic transformations, leading to MM. Stimulated immunity is associated with proliferation of plasma cells, which could in turn increase the chance of errors in DNA replication that may lead to MM. Another hypothesis is that the breakdown of immunological responses may compromise the ability of T-cells to eliminate cancer-causing cells.[54] Long-term exposure to occupationally relevant levels of TCE in air has been shown to lead to greater numbers of activated CD4+ T-cells, and higher levels of markers of increased immune response were significant at lower (0.1 and 0.5 mg/ml), but not higher (2.5 mg/ml) doses of TCE,[55] which suggests that carcinogenesis that is preceded by stimulated immunity may not follow a typical dose-response pattern. These studies suggest that immune alterations may lie on the etiologic pathway between chlorinated solvent exposure and development of MM, but further research is necessary to clarify this as a possible mechanism.

This study was the first case-control study to analyze exposure to these six chlorinated solvents in relation to incidence of MM. The use of detailed occupational information improved assessment of solvent exposure compared to analyses based solely on job titles. However, our study had several weaknesses. Even with the additional efforts undertaken to improve exposure assessment, exposure misclassification likely occurred. Also, participation rates were relatively low among cases and controls. Although case participation was not associated with age, sex, or study site, control participation did vary by age category. We were not able to assess whether non-participants were similar to participants in terms of race or socioeconomic status, which are tied to occupation and, potentially, solvent exposure. This might have resulted in selection bias if, for example, controls in certain types of jobs with likely solvent exposure were less likely to have participated in our study than cases in those jobs, although we observed no evidence that this occurred. Although every effort was made to contact MM patients within 1–2 months of diagnosis, a substantial proportion of cases (18%) died before they could be contacted and 29% of those we did contact refused to participate, possibly because they were too ill. Our findings, therefore, might reflect relationships between chlorinated solvents and less aggressive forms of MM. In addition, we cannot rule out the possibility of recall bias affecting our results. However, this bias was likely minimized since the questions in the job-specific questionnaires focused on job tasks rather than specific chemical exposures.

Small numbers of participants exposed to certain chlorinated solvents, increased the possibility false positive and false negative chance findings and the potential impact that misclassification could have had on the associations. In addition, the possibility of false associations was increased by the number of associations we examined. Also, concomitant exposures likely occurred in many of the occupations that entailed exposure to chlorinated solvents, so we cannot rule out the possibility that these confounded the relationship between chlorinated solvent exposure and the risk of MM. However, it is unlikely that these other exposures were so highly correlated with chlorinated solvent exposure that they caused substantial degrees of confounding.[56] Finally, another limitation of our findings is that assignments of some of the chlorinated solvents were likely correlated, especially TCE, DCM, TCA, and carbon tetrachloride, which were commonly used as degreasers. In many situations, we were not able to determine which specific chlorinated solvent was used. We attempted to overcome this challenge by assigning probabilities of exposure, based on published information on the probability that that given solvent was being used in a particular decade.[38,39] However, it is still likely that the correlation of assignments led to some misclassification of exposure. Therefore, it is possible that not all of the solvents we examined are truly involved in MM etiology, but instead appeared to be associated with MM because their uses and exposure assignments were correlated.

In summary, this research provides some evidence that certain chlorinated solvents – notably TCE – are associated with increased incidence of MM. While results were less clear, exposure to TCA, DCM, PCE, carbon tetrachloride, and chloroform may also confer increased risk of MM. In order to establish causality, larger studies including more MM cases should be undertaken. Ideally, these studies would pool cases diagnosed from several sites and would obtain detailed lifestyle data in order to assess chlorinated solvent exposure even more thoroughly than this study. Additional studies of biologic effects of occupational chlorinated solvent exposure may also provide clues to possible mechanisms by which these chemicals may cause MM.

What this article adds to the literature:

- The etiology of multiple myeloma (MM) is poorly understood.
- The purpose of this research was to examine relationships between occupational exposures to chlorinated solvents and MM.
- This research provides evidence that certain chlorinated solvents, most notably TCE, are associated with increased incidence of MM.
- While results were less clear, exposure to TCA, DCM, PCE, carbon tetrachloride, and chloroform also conferred increased risk of MM in our population.

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Table 1

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to 1,1,1-trichloroethane (TCA).

Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed			
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	65 (14%)	36 (20%)	1.8 (1.1–2.9)	Ever exposed [B]	23 (4.8%)	17 (9.4%)	2.2 (1.1–4.4)
		Duration				Duration	
Unexposed	416 (86%)	144 (80%)	Referent	Unexposed	458 (95%)	163 (91%)	Referent
1–3 years	16 (3.3%)	7 (3.9%)	1.6 (0.6–4.3)	1–5 years	9 (1.8%)	5 (2.8%)	1.8 (0.6–5.7)
4–8 years	16 (3.3%)	11 (6.1%)	2.3 (1.0–5.3)	6–16 years	3 (0.6%)	6 (3.3%)	6.7 (1.5–29)
9–21 years	15 (3.1%)	11 (6.1%)	1.9 (0.8–4.5)	17–25 years	7 (1.5%)	4 (2.2%)	1.6 (0.4–6.0)
22–45 years	18 (3.7%)	7 (3.9%)	1.3 (0.5–3.3)	26–45 years	4 (0.8%)	2 (1.1%)	1.3 (0.2–7.4)
			p-trend 0.17				p-trend 0.27
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	416 (86%)	144 (80%)	Referent	Unexposed	458 (95%)	163 (91%)	Referent
1–53	17 (3.5%)	7 (3.9%)	1.7 (0.7–4.4)	1–378	5 (1.0%)	5 (2.8%)	3.7 (1.0–13)
54–605	16 (3.3%)	10 (5.6%)	2.2 (0.9–5.3)	379–1938	6 (1.3%)	2 (1.1%)	1.1 (0.2–5.8)
606–3750	16 (3.3%)	8 (4.4%)	1.4 (0.5–3.4)	1939–10012	6 (1.3%)	6 (3.3%)	3.0 (0.9–10)
3751–57000	16 (3.3%)	11 (6.1%)	1.9 (0.8–4.4)	10013–57000	6 (1.3%)	4 (2.2%)	1.5 (0.4–5.8)
			p-trend 0.19				p-trend 0.33
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	417 (87%)	147 (82%)	Referent	Unexposed	459 (95%)	164 (91%)	Referent
1–49	16 (3.3%)	7 (3.9%)	1.8 (0.7–4.6)	1–303	6 (1.3%)	5 (2.8%)	3.1 (0.9–11)
50–342	16 (3.3%)	7 (3.9%)	1.5 (0.6–3.3)	304–1690	5 (1.0%)	0	NA
343–2781	16 (3.3%)	8 (4.4%)	1.3 (0.5–3.3)	1691–4500	6 (1.3%)	5 (2.8%)	2.3 (0.6–8.0)
2782–49500	16 (3.3%)	11 (6.1%)	1.8 (0.8–4.1)	4501–49500	5 (1.0%)	6 (3.3%)	2.8 (0.8–9.9)
			p-trend 0.21				p-trend 0.07

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to TCA and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.

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Table 2

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to trichloroethylene (TCE).

	Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed		
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	138 (29%)	66 (37%)	1.4 (0.9–2.1)	Ever exposed [B]	75 (16%)	43 (24%)	1.7 (1.0–2.7)
		Duration				Duration	
Unexposed	343 (71%)	114 (63%)	Referent	Unexposed	406 (84%)	137 (76%)	Referent
1–4 years	32 (6.7%)	13 (7.2%)	1.4 (0.7–3.0)	1–4 years	23 (4.8%)	6 (3.3%)	0.9 (0.3–2.4)
5–11 years	35 (7.3%)	16 (8.9%)	1.3 (0.6–2.5)	5–7 years	15 (3.1%)	6 (3.3%)	1.3 (0.5–3.6)
12–29 years	36 (7.5%)	23 (13%)	1.5 (0.8–2.8)	8–24 years	19 (4.0%)	20 (11%)	2.5 (1.2–5.1)
30–51 years	35 (7.3%)	14 (7.8%)	1.2 (0.6–2.6)	25–47 years	18 (3.7%)	11 (6.1%)	1.9 (0.8–4.5)
			p-trend 0.41				p-trend 0.04
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	345 (72%)	116 (64%)	Referent	Unexposed	409 (85%)	139 (77%)	Referent
1–318	35 (7.3%)	15 (8.3%)	1.3 (0.7–2.6)	1–471	18 (3.7%)	6 (3.3%)	1.1 (0.4–2.9)
319–2218	33 (6.9%)	11 (6.1%)	1.0 (0.4–2.1)	472–3000	20 (4.2%)	11 (6.1%)	1.6 (0.7–3.5)
2219–7793	34 (7.1%)	14 (7.8%)	1.3 (0.6–2.6)	3001–7644	16 (3.3%)	7 (3.9%)	1.5 (0.6–3.9)
7794–57000	34 (7.1%)	24 (13%)	1.7 (0.9–3.3)	7645–57000	18 (3.7%)	17 (9.4%)	2.3 (1.1–5.0)
			p-trend 0.10				p-trend 0.03
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	345 (72%)	116 (64%)	Referent	Unexposed	409 (85%)	139 (77%)	Referent
1–311	34 (7.1%)	16 (8.9%)	1.4 (0.7–2.8)	1–415	18 (3.7%)	6 (3.3%)	1.1 (0.4–2.9)
312–2089	34 (7.1%)	11 (6.1%)	0.9 (0.4–2.0)	416–3000	20 (4.2%)	11 (6.1%)	1.6 (0.7–3.5)
2090–7285	34 (7.1%)	12 (6.7%)	1.1 (0.5–2.4)	3001–6592	16 (3.3%)	6 (3.3%)	1.4 (0.5–3.8)
7286–50000	34 (7.1%)	25 (14%)	1.8 (0.9–3.4)	6593–49500	18 (3.7%)	18 (10%)	2.3 (1.1–5.0)
			p-trend 0.08				p-trend 0.02

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to TCE and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.

Table 3

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to Methylene Chloride (DCM).

	Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed		
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	91 (19%)	47 (26%)	1.5 (0.9–2.3)	Ever exposed [B]	54 (11%)	37 (21%)	2.0 (1.2–3.2)
		Duration				Duration	
Unexposed	390 (81%)	133 (74%)	Referent	Unexposed	427 (89%)	143 (79%)	Referent
1–4 years	22 (4.6%)	9 (5.0%)	1.2 (0.5–2.9)	1–4 years	15 (3.1%)	8 (4.4%)	2.0 (0.8–5.1)
5–11 years	19 (4.0%)	11 (6.1%)	1.8 (0.8–4.1)	5–7 years	15 (3.1%)	6 (3.3%)	1.1 (0.4–3.1)
12–29 years	26 (5.4%)	17 (9.4%)	1.8 (0.9–3.5)	8–24 years	11 (2.3%)	13 (7.2%)	2.7 (1.1–6.5)
30–51 years	24 (5.0%)	10 (5.6%)	1.1 (0.5–2.6)	25–47 years	13 (2.7%)	10 (5.6%)	2.1 (0.9–5.2)
			p-trend 0.35				p-trend 0.01
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	392 (82%)	135 (75%)	Referent	Unexposed	430 (89%)	144 (80%)	Referent
1–318	22 (4.6%)	7 (3.9%)	1.2 (0.5–2.9)	1–102	12 (2.5%)	5 (2.8%)	1.6 (0.5–4.7)
319–2218	22 (4.6%)	17 (9.4%)	2.2 (1.1–4.6)	103–1122	14 (2.9%)	13 (7.2%)	2.8 (1.2–6.6)
2219–7793	23 (4.8%)	7 (3.9%)	0.8 (0.3–1.9)	1123–5493	13 (2.7%)	8 (4.4%)	1.6 (0.6–3.8)
7794–57000	22 (4.6%)	14 (7.8%)	1.6 (0.8–3.4)	5494–57000	12 (2.5%)	10 (5.6%)	2.4 (1.0–5.9)
			p-trend 0.27				p-trend 0.08
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	398 (83%)	138 (77%)	Referent	Unexposed	437 (91%)	147 (82%)	Referent
1–311	21 (4.4%)	8 (4.4%)	1.4 (0.6–3.3)	1–71	11 (2.3%)	4 (2.2%)	1.3 (0.4–4.4)
312–2089	20 (4.2%)	12 (6.7%)	1.6 (0.7–3.6)	72–437	11 (2.3%)	10 (5.6%)	2.9 (1.1–7.5)
2090–7285	22 (4.6%)	10 (5.6%)	1.2 (0.5–2.8)	438–3903	11 (2.3%)	9 (5.0%)	1.9 (0.7–5.0)
7286–50000	20 (4.2%)	12 (6.7%)	1.5 (0.7–3.2)	3904–49500	11 (2.3%)	10 (5.6%)	2.4 (1.0–6.1)
			p-trend 0.39				p-trend 0.06

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to DCM and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.

Table 4

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to Perchloroethylene (PCE).

Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed			
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	63 (13%)	29 (16%)	1.4 (0.9–2.4)	Ever exposed [B]	28 (5.8%)	16 (8.9%)	1.5 (0.8–2.9)
		Duration				Duration	
Unexposed	418 (87%)	151 (84%)	Referent	Unexposed	453 (94%)	164 (91%)	Referent
1–4 years	19 (4.0%)	4 (2.2%)	0.8 (0.3–2.5)	1–4 years	9 (1.9%)	3 (1.7%)	0.9 (0.2–3.5)
5–11 years	14 (2.9%)	8 (4.4%)	1.9 (0.8–4.9)	5–7 years	5 (1.0%)	3 (1.7%)	2.0 (0.4–9.2)
12–29 years	13 (2.7%)	8 (4.4%)	1.5 (0.6–3.9)	8–24 years	7 (1.5%)	4 (2.2%)	1.3 (0.3–4.6)
30–51 years	17 (3.5%)	9 (5.0%)	1.6 (0.7–3.9)	25–47 years	7 (1.5%)	6 (3.3%)	2.1 (0.7–6.8)
			p-trend 0.20				p-trend 0.18
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	419 (87%)	151 (84%)	Referent	Unexposed	453 (94%)	164 (91%)	Referent
1–318	16 (3.3%)	5 (2.8%)	1.3 (0.4–3.8)	1–353	7 (1.5%)	1 (0.6%)	0.3 (0.04–3.0)
319–2218	15 (3.1%)	6 (3.3%)	1.4 (0.5–3.8)	354–1430	7 (1.5%)	1 (0.6%)	0.5 (0.1–4.4)
2219–7793	16 (3.3%)	4 (2.2%)	0.7 (0.2–2.1)	1431–4875	7 (1.5%)	4 (2.2%)	1.5 (0.4–5.4)
7794–57000	15 (3.1%)	14 (7.8%)	2.5 (1.1–5.4)	4876–13500	7 (1.5%)	10 (5.6%)	3.3 (1.2–9.5)
			p-trend 0.04				p-trend 0.02
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	424 (88%)	154 (86%)	Referent	Unexposed	457 (95%)	164 (91%)	Referent
1–311	13 (2.7%)	4 (2.2%)	1.2 (0.4–3.8)	1–194	6 (1.3%)	1 (0.6%)	0.4 (0.04–3.2)
312–2089	17 (3.5%)	4 (2.2%)	0.7 (0.2–2.3)	195–1586	6 (1.3%)	1 (0.6%)	0.5 (0.1–4.7)
2090–7285	13 (2.7%)	5 (2.8%)	1.1 (0.4–3.3)	1587–4875	6 (1.3%)	4 (2.2%)	1.7 (0.5–6.5)
7286–50000	14 (2.9%)	13 (7.2%)	2.5 (1.1–5.6)	4876–13500	6 (1.3%)	10 (5.6%)	4.1 (1.4–12)
			p-trend 0.03				p-trend 0.01

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to PCE and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.

Table 5

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to Carbon Tetrachloride.

Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed			
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	88 (18%)	33 (18%)	1.1 (0.7–1.8)	Ever exposed [B]	37 (7.7%)	17 (9.4%)	1.6 (0.8–3.0)
		Duration				Duration	
Unexposed	393 (82%)	147 (82%)	Referent	Unexposed	444 (92%)	163 (91%)	Referent
1–2 years	14 (2.9%)	1 (0.6%)	0.2 (0.03–1.9)	1–4 years	18 (3.7%)	4 (2.2%)	0.8 (0.3–2.6)
3–4 years	26 (5.4%)	6 (3.3%)	0.7 (0.3–1.7)	5–7 years	5 (1.0%)	3 (1.7%)	1.7 (0.4–7.6)
5–11 years	26 (5.4%)	16 (8.9%)	1.7 (0.8–3.5)	8–24 years	10 (2.1%)	4 (2.2%)	1.1 (0.3–4.0)
12–44 years	22 (4.6%)	10 (5.6%)	1.4 (0.6–3.2)	25–42 years	4 (0.8%)	6 (3.3%)	6.9 (1.8–27)
			p-trend 0.30				p-trend 0.01
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	399 (83%)	148 (82%)	Referent	Unexposed	449 (93%)	164 (91%)	Referent
1–204	20 (4.2%)	8 (4.4%)	1.4 (0.6–3.4)	1–215	8 (1.7%)	2 (1.1%)	0.9 (0.2–4.6)
205–1280	21 (4.4%)	5 (2.8%)	0.7 (0.2–1.9)	216–1500	9 (1.9%)	4 (2.2%)	1.5 (0.4–5.1)
1281–3750	24 (5.0%)	7 (3.9%)	0.8 (0.3–2.1)	1501–5625	7 (1.5%)	6 (3.3%)	3.2 (1.0–10)
3751–48000	17 (3.5%)	12 (6.7%)	1.9 (0.8–4.4)	5626–48000	8 (1.7%)	4 (2.2%)	1.3 (0.4–4.7)
			p-trend 0.16				p-trend 0.51
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	399 (83%)	148 (82%)	Referent	Unexposed	449 (93%)	164 (91%)	Referent
1–204	20 (4.2%)	9 (5.0%)	1.6 (0.7–3.9)	1–215	8 (1.7%)	3 (1.7%)	1.5 (0.4–5.9)
205–1280	21 (4.4%)	5 (2.8%)	0.7 (0.2–1.8)	216–1500	9 (1.9%)	4 (2.2%)	1.4 (0.4–4.9)
1281–3750	24 (5.0%)	7 (3.9%)	0.8 (0.3–2.1)	1501–5625	7 (1.5%)	5 (2.8%)	2.6 (0.8–8.8)
3751–48000	17 (3.5%)	11 (6.1%)	1.7 (0.7–4.1)	5626–48000	8 (1.7%)	4 (2.2%)	1.3 (0.4–4.7)
			p-trend 0.29				p-trend 0.52

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to carbon tetrachloride and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.

Table 6

Odds Ratios[A] and 95% Confidence Intervals (CI) for Multiple Myeloma and Occupational Exposure to Chloroform.

Primary Analysis				Reanalysis: Jobs Assessed with Low Confidence Considered Unexposed			
	Controls (n=481)	**Cases (n=180)**	**Odds ratio (95% CI)**		**Controls (n=481)**	**Cases (n=180)**	**Odds ratio (95% CI)**
Ever exposed [B]	27 (5.6%)	14 (7.8%)	1.4 (0.7–2.8)	Ever exposed [B]	6 (1.3%)	7 (3.9%)	2.5 (0.8–7.6)
		Duration				Duration	
Unexposed	454 (94%)	166 (92%)	Referent	Unexposed	475 (99%)	173 (96%)	Referent
1–4 years	9 (1.9%)	2 (1.1%)	0.4 (0.1–2.2)	1–3 years	2 (0.4%)	0	NA
5–7 years	6 (1.3%)	3 (1.7%)	1.8 (0.4–7.7)	4–10 years	1 (0.2%)	2 (1.1%)	4.5 (0.4–53)
8–17 years	6 (1.3%)	4 (2.2%)	2.0 (0.5–8.0)	11–17 years	2 (0.4%)	1 (0.6%)	1.2 (0.1–14)
18–45 years	6 (1.3%)	5 (2.8%)	2.1 (0.6–7.4)	18–40 years	1 (0.2%)	4 (2.2%)	7.5 (0.8–72)
			p-trend 0.16				p-trend 0.09
		Cumulative exposure [C,D]				Cumulative exposure [C,D]	
Unexposed	454 (94%)	167 (93%)	Referent	Unexposed	475 (99%)	174 (97%)	Referent
1–18	6 (1.3%)	3 (1.7%)	1.7 (0.4–7.2)	1–204	1 (0.2%)	2 (1.1%)	4.1 (0.4–47)
19–204	7 (1.5%)	2 (1.1%)	0.9 (0.2–4.8)	205–1908	2 (0.4%)	0	NA
205–3223	8 (1.7%)	2 (1.1%)	0.5 (0.1–2.4)	1909–12750	2 (0.4%)	1 (0.6%)	0.9 (0.1–11)
3224–57106	6 (1.3%)	6 (3.3%)	2.6 (0.8–9.2)	12751–49500	1 (0.2%)	3 (1.7%)	7.7 (0.8–79)
			p-trend 0.12				p-trend 0.11
		10-year-lagged cumulative exposure [C,D]				10-year-lagged cumulative exposure [C,D]	
Unexposed	455 (95%)	167 (93%)	Referent	Unexposed	475 (99%)	174 (97%)	Referent
1–21	7 (1.5%)	4 (2.2%)	2.4 (0.7–8.9)	1–204	1 (0.2%)	2 (1.1%)	4.1 (0.4–47)
22–204	5 (1.0%)	1 (0.6$)	0.5 (0.1–4.8)	205–1627	2 (0.4%)	0	NA
205–3223	8 (1.7%)	2 (1.1%)	0.5 (0.1–2.4)	1628–4500	2 (0.4%)	1 (0.6%)	0.9 (0.1–11)
3224–54000	6 (1.3%)	6 (3.3%)	2.7 (0.8–9.3)	4501–4950	1 (0.2%)	3 (1.7%)	7.9 (0.8–82)
			p-trend 0.12				p-trend 0.09

[A] All models adjusted for age, race, study site, gender, and years of education.

[B] Ever exposed defined as having at least 1 job with a probability score of 2 for exposure to chloroform and all jobs with a probability score of <2 were considered as unexposed.

[C] Some participants were unexposed in the cumulative scores but not the ever/never and duration analyses because they were exposed <15 minutes per week and therefore had a frequency of 0.

[D] Cumulative score calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.