Exhibit 286

Published in final edited form as:
Occup Environ Med. 2017 March ; 74(4): 268–274. doi:10.1136/oemed-2016-103849.

Occupational exposure to chlorinated solvents and kidney cancer: a case-control study

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Abstract

Objectives—Trichloroethylene, a chlorinated solvent widely used for metal degreasing, is classified by the International Agency for Research on Cancer as a kidney carcinogen. Other chlorinated solvents are suspected carcinogens, most notably the cleaning solvent perchloroethylene, although it is unclear whether they are associated with kidney cancer. We investigated kidney cancer associations with occupational exposure to six chlorinated solvents (trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, chloroform, and methylene chloride) within a case-control study using detailed exposure assessment methods.

Methods—Cases (n = 1,217) and controls (n = 1,235) provided information on their occupational histories and, for selected occupations, on tasks involving potential exposure to chlorinated solvents through job-specific interview modules. Using this information, an industrial hygienist

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Author Contributions

JSC, FD, JR, KS, BIG, NR, and WHC contributed to the planning or execution of the case-control study. PAS, MPP, MCF, SJL, MJH, and MAW contributed to the exposure assessment. MPP, BIG, and JNH conducted or advised on the statistical analysis. MPP drafted the manuscript. All authors contributed to the writing of the manuscript.

Competing Interests

The authors have no competing interests to report.

assessed potential exposure to each solvent. We computed odds ratios (ORs) and 95% confidence intervals (CIs) for different exposure metrics, with unexposed subjects as the referent group.

Results—1,1,1-trichloroethane, carbon tetrachloride, chloroform, and methylene chloride were not associated with kidney cancer. Among jobs with high exposure intensity, high cumulative hours exposed to perchloroethylene was associated with increased risk, both overall (third tertile vs. unexposed: OR 3.1, 95% CI 1.3-7.4) and after excluding participants with ≥50% exposure probability for trichloroethylene (OR 3.0, 95% CI 0.99-9.0). A non-significant association with high cumulative hours exposed to trichloroethylene was observed (OR 1.7, 95% CI 0.8-3.8).

Conclusions—In this study, high exposure to perchloroethylene was associated with kidney cancer, independent of trichloroethylene. Additional studies are needed to further investigate this finding.

Keywords

case-control studies; chlorinated solvents; kidney cancer

BACKGROUND

Low-molecular weight chlorinated solvents are chlorine-containing methanes, ethanes, and ethenes that are widely used across different industries for a variety of applications, most notably degreasing of metal parts. The production and use of several of these chlorinated solvents has declined since the late 20th century due to concern over environmental and health effects, including their carcinogenic potential.[1, 2] Trichloroethylene (TCE), commonly used in vapor degreasing in the past, has been classified by the International Agency for Research on Cancer (IARC) as a (Group 1) human carcinogen.[3] The evidence for other chlorinated solvents is weaker. Perchloroethylene, a cleaning agent used for dry cleaning and degreasing, has been classified by IARC as a probable human carcinogen (Group 2A). Chloroform and carbon tetrachloride, used for the production of several chemicals and degreasing, are classified as possible human carcinogens (Group 2B). Methylene chloride and 1,1,1-trichloroethane, commonly used in paint stripping and metal degreasing, respectively, have not been classifiable as to their human carcinogenicity (Group 3).[3-5]

The kidney is an organ sensitive to chlorinated solvent effects; several of these chemicals have been found to induce nephrotoxic effects in animals and humans, and TCE is classified as a kidney carcinogen.[3-5] Associations with kidney cancer have also been noted in some epidemiologic studies of perchloroethylene, but not others.[3] This inconsistency may be due in part to limitations in exposure assessment, as many studies of chlorinated solvents, particularly those of case-control design, inferred occupational exposure based on job title or through the use of job-exposure matrices. These methods, which assume that all workers in the same occupation and/or industry in a given time period are identically exposed, can introduce substantial exposure misclassification.[6] Few studies of other chlorinated solvents have investigated associations with kidney cancer.[4, 5]

To clarify the association between these chlorinated solvents and kidney cancer risk, we conducted an analysis within the U.S. Kidney Cancer Study (USKC), a population-based case-control study designed to obtain detailed information regarding workplace exposure to solvents. Occupational exposure to six chemicals (1,1,1,-trichloroethane, carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, and trichloroethylene) was assessed by an expert industrial hygienist after a review of participants' occupational histories and data from job-specific questionnaires.

METHODS

Study Design

The design and enrollment methods of the USKC have been described.[7] Briefly, the USKC was conducted between in Detroit, MI (Wayne, Oakland, and Macomb Counties) and Chicago, IL (Cook County). Cases of histologically confirmed incident kidney cancer diagnosed were identified in Detroit through the Metropolitan Detroit Cancer Surveillance System, a contributor of data to the National Cancer Institute's Cancer Surveillance, Epidemiology, and End Results (SEER) program, from February 2002 until July 2006 (for white cases) or January 2007 (black cases). In Chicago, cases diagnosed in 2003 were identified through reviews of pathology reports from 56 hospitals located in Cook County. In both study centers, eligible controls were selected from the general population and frequency matched to cases on sex, age (five-year intervals), and race. Controls aged 20 to 64 were identified from Department of Motor Vehicle (DMV) records, while controls aged 65 to 79 were identified from Medicare eligibility files. As previously described, a complex sampling strategy was used to increase the number of black participants in the study.[7] We attempted to recruit all black cases, while some strata of white cases were sampled. Controls were frequency matched to cases at a 2:1 ratio for blacks and a 1:1 ratio for whites. As information on race was unavailable in the DMV records, the racial density of the census block group (according to the 2000 Census) was used for the purpose of sampling controls under age 65. People living in high-density black areas were oversampled to help achieve the targeted matching ratio for blacks.

Of the 1,918 eligible cases identified, 171 died before contact or interview, 92 could not be located, and 21 moved out of the area; in addition, physicians of 63 declined to give permission to contact patients. Among the remaining 1,571 cases, 221 declined participation and 133 were not interviewed due to serious illness, impairment, or nonresponse after multiple contact attempts. Thus, 1,217 cases participated (77% of the 1,571 we attempted to recruit). Of 2,718 presumed eligible controls, 41 died before contact or interview, 345 were not locatable, and 63 had moved away. Among the 2,269 controls we attempted to recruit, 677 declined participation and 357 were not interviewed due to serious illness, impairment, or lack of response to multiple contact attempts. Thus, 1,235 eligible controls participated (54% of those we attempted to recruit). The study was approved by Institutional Review Boards at all institutions, and written informed consent was obtained from all participants before interview.

Copies of medical records were obtained for all cases to confirm the kidney cancer diagnosis and collect information on histologic and clinical factors. In addition, the original diagnostic

slides were obtained for 706 cases for review by an experienced pathologist. We assigned histology on the basis of the centralized histopathologic review if available; otherwise, information from the original diagnostic pathology reports was used.

Exposure Assessment

Participants were mailed a work history calendar asking them to list each job held for at least 12 months since the age of 16, along with the corresponding employer. During a subsequent home visit, a trained interviewer administered a computer-assisted personal interview (CAPI) covering a wide variety of topics, including occupational history. The occupational history gathered additional information on each job, usual number of hours worked per week, type of business or service, tasks, and a description of chemicals/materials and equipment used. All jobs were later coded using the Standard Industrial Classification (SIC) and Standard Occupational Classification (SOC) systems.[8, 9]

In addition, for selected occupations, one of 39 job- or industry-specific interview modules was administered based on the information collected in the occupational histories. Most modules focused on solvent exposures, asking for detailed information over the duration of employment in each job (e.g., machinist) or industry (e.g., dry cleaning). The information collected in these modules included the solvent(s) used, average frequency of various solvent-related tasks, work practices, and – in some modules – potential for dermal exposure.[10-12] A maximum of five modules were administered in an interview to minimize participant burden.

A systematic review of the industrial hygiene literature for uses of TCE and perchloroethylene provided important information for the exposure assessment.[1, 2] Personal and area measurement data and determinants of exposure (e.g., tasks and work practices) reported in the literature were collected, with the measurement data summarized by industry, job and “source of exposure” (e.g., cold degreasing, vapor degreasing, spot removal, and printing ink.). Job and task exposure matrices (N=38), developed for each of the six solvents by the industrial hygienist using information from the literature review, provided initial estimates of probability and frequency of solvent exposure for different combinations of occupation, industry, and decade of employment.

Using the literature review, the exposure matrices, the occupational histories, and the information collected in the job modules, the industrial hygienist assessed levels of exposure probability, frequency, and determinants of exposure intensity for each chlorinated solvent for each job. Probability, defined as the theoretical probability of exposure to the solvent, was assigned to one of five categories: 0%, <10%, 10-49%, 50-89%, or ≥90%. If the subject specifically reported use of a given chlorinated solvent, a probability of ≥90% was assigned. Otherwise, the probability was assigned by the industrial hygienist based on the likelihood of using that solvent during the decade(s) the job was held.

All jobs with a probability > 0% were also assigned an exposure frequency and determinants of exposure intensity. Exposure frequency was assigned by the industrial hygienist to one of four categories according to the estimated number of hours per week exposed to the given solvent: <2, 2-9, 10-19, or ≥ 20 hours per week. The assigned frequency was either the

reported frequency of performing the related task or, if missing, the average frequency of all reports for that task, or if the task was not asked about in the questionnaire, an estimate based on the IH's knowledge of the workplace. Determinants of chlorinated solvent exposure intensity, defined as the solvent concentration in a subject's breathing zone while exposed, were identified from previously developed predictive intensity models for three chlorinated solvents,[13] and estimated from the participants' responses to the occupational history and modules; these parameters included job location (indoors, outdoors, both), local exhaust ventilation (effective, ineffective, absent), mechanism of solvent release (evaporation, aerosolized, other active), proximity (near, far, both) and process temperature (room temperature, elevated, both). Using these parameters, an algorithm was developed to assign a qualitative job exposure intensity of "high" or "low" (Table 1). The industrial hygienist assigned varying levels of confidence, ranging from 1 (lowest) to 4, to the assigned scores for probability, frequency, and intensity parameters. The exposure assessment was performed without knowledge of the subject's case/control status.

The job-specific estimates of probability, frequency and intensity for each subject were integrated to develop several metrics of exposure for each chlorinated solvent. We defined a subject's exposure probability as the highest assigned exposure probability across all jobs. For subjects with an exposure probability ≥50%, we calculated the following additional exposure metrics: *duration of exposure* (years), defined as the sum of the number of years worked at each job across all jobs with exposure probability ≥50%; *cumulative hours exposed*, defined as the sum of the product of the job-specific frequency midpoint (1, 6, 15, or 30 hours/week) and the job duration in weeks across all jobs with an exposure probability ≥50% ; and *average weekly exposure* (hours per week), defined as the cumulative hours exposed divided by the duration of exposure in weeks. All of these metrics were set to 0 for subjects with an exposure probability of 0%. Subjects with exposure probability greater than 0% and less than 50% were excluded from analyses of exposure metrics. We also calculated these exposure metrics further restricting to jobs with high exposure intensity. Selected exposure metrics were also recalculated incorporating 5- and 15-year exposure lags, with subjects whose exposures were entirely within the lagged period excluded from analysis.

Statistical Analysis

We developed sample weights to reduce the potential for bias arising from differential sampling rates for controls and cases, from survey nonresponse, and from deficiencies in coverage of the population at risk in the DMV and Medicare files. Sample weights for controls also include a post-stratification adjustment, so that the weighted distribution of controls across the matching variables matched exactly the weighted distribution of cases. In addition to being consistent with the objectives of the frequency matching, the post-stratification adjustment reduces the variability of the weights.[14]

Estimates of exposure duration, average weekly exposure, and cumulative hours exposed for each chlorinated solvent were categorized using the tertiles among exposed controls as cutpoints, with unexposed participants defined as the referent category. We described case-control differences across categorized exposure metrics (both overall and restricted to high-intensity exposures) using odds ratios (ORs) and 95% confidence intervals (CIs) computed

from unconditional logistic regression modeling, with adjustment for the post-stratification weights using the jackknife replicate weight method to estimate standard errors.[15] Regression models were adjusted for study center, age at reference date (20-44, 45-54, 55-64, 65-74, 75+ years), self-reported race (white, black), sex, education (<12 years, high school graduate, some college, 4+ years of college), smoking history as of two years before the reference date (never, occasional [smoked more than 100 cigarettes but never smoked one cigarette daily for six months or couldn't provide a definitive answer], regular former, regular current), body mass index (BMI, based on height at interview and weight five years prior to interview, <25, 25-<30, 30-<35, 35+ kg/m^2, unknown), and self-reported history of hypertension as of two years before the reference date. The reported results were not adjusted for self-reported diagnosed chronic renal failure given the possibility that nephrotoxic effects could be a mediating factor along the causal pathway between solvent exposure and kidney cancer; we note however that models additionally adjusting for this risk factor generated virtually identical results. Tests for trend of exposure duration, average frequency, and cumulative hours exposed were performed by modeling the intra-category median among controls as a continuous variable, with values for unexposed subjects set to zero. Our tests for trend, which include the unexposed subjects, offer better power to detect a monotonic exposure-response relationship in this study population than a trend test restricted to exposed subjects, given the low exposure prevalence. However, we caution that our trend test results should not be interpreted as independent of the results of exposure categories.

To assess the robustness of our findings, we conducted analyses incorporating 5- and 15-year exposure lags, restricting to participants for whom the IH assessed exposure with high confidence, and excluding participants with ≥50% probability of TCE exposure. We also conducted analyses stratified on study center, sex, race, age group, smoking status, hypertension history, and BMI. Interactions between two variables were assessed by including multiplicative terms for the variables in the logistic regression models, and testing for the joint significance of the additional terms using the Wald chi-square test, which is appropriate for weighted data.[16] We also conducted separate analyses for clear cell adenocarcinoma, the most common kidney cancer histologic subtype, and other kidney cancers using polytomous regression models. Tests of OR heterogeneity across cancer subgroups were performed using case-only analysis. Analyses were conducted with SAS software version 9.2 using procedures appropriate for sample-weighted data. All statistical tests were determined to be significant at a two-sided $p<0.05$ without adjustment for multiple comparisons.

RESULTS

A summary of selected characteristics of study cases and controls is provided in Tables 2 and, stratified by study center, S1. Controls had on average a higher level of education than cases, both overall and in each study center. As expected, cases were more likely than controls to be current smokers and to have a BMI greater than 25 kg/m^2 and a history of hypertension.

As summarized in Table 3, few study participants were assessed as having been exposed to individual chlorinated solvents in the workplace; the proportion of controls with an exposure

probability ≥50% varied from 2.4% (chloroform) to 11.9% (methylene chloride). Degreasing was the most commonly assessed task for TCE, accounting for 65% of participants assessed as having a ≥50% exposure probability, as well as for carbon tetrachloride (79%) and 1,1,1-trichloroethane (80%). Of the participants with exposure probability ≥50% for other chlorinated solvents, the most common exposure-related tasks were as follows: for perchloroethylene, degreasing (41% of participants) and dry cleaning (32%); for chloroform, degreasing (33%), surgery (22%), and dry cleaning (17%); and for methylene chloride, gluing (68%), stripping paint or floors (33%), and degreasing (30%). Some participants were exposed through multiple tasks. In analyses among controls, after excluding subjects unexposed to any chlorinated solvent, solvent exposure probabilities were moderately correlated with one another (see Table S2), with Spearman coefficients ranging from 0.12 (TCE and methylene chloride) to 0.61 (1,1,1-trichloroethane and methylene chloride).

No statistically significant differences in exposure probability were observed between kidney cancer cases and controls for any chlorinated solvent (Table 3). However, more detailed analyses of perchloroethylene exposure were suggestive of an association with risk (Table 4). While analyses of perchloroethylene exposure duration, average weekly exposure, and cumulative hours of exposure were null including all exposure intensities, in analyses restricted to jobs involving high-intensity exposure, high cumulative hours exposed was significantly associated with increased risk of kidney cancer (>1,820 hours vs. unexposed: OR 3.1, 95% CI 1.3-7.4; P_{trend} = 0.03). In other high-intensity exposure analyses, ORs generally increased across increasing levels of exposure duration and average weekly exposure (ORs 0.9, 1.4, 1.4 and 1.1, 1.2, 2.5 for first, second and third tertiles vs. unexposed, respectively), although confidence intervals included the null, and tests of trend were not statistically significant (P = 0.78 and 0.15 respectively).

TCE exposure metrics were generally not associated with kidney cancer in this study population (Table 5), although in analyses restricted to jobs with high-intensity exposure, a non-significant association with high cumulative hours exposed was observed (>1,560 exposure hours vs. unexposed: OR 1.7, 95% CI 0.8-3.8; P_{trend} = 0.28). Trichloroethylene exposure duration and average weekly intensity were not associated with kidney cancer, both overall and restricting to high-intensity jobs. Our findings for the other chlorinated solvents were not suggestive of an association with kidney cancer (see Table S3).

We conducted additional analyses to assess the robustness of our finding for cumulative hours of exposure to perchloroethylene in jobs with high-intensity exposures. The association remained in analyses incorporating exposure lag periods of 5 years (>1,820 exposure hours vs. unexposed: OR 3.5, 95% CI 1.3-10.0; P_{trend} = 0.03) and 15 years (6.2, 1.8-21.3; P_{trend} = 0.003), as well as in analyses restricted to subjects in the (larger) Detroit study center (2.3, 0.9-6.3; P_{trend} = 0.13) and to jobs where the industrial hygienist assigned exposure probability with a high level of confidence (5.1, 1.5-7.2; P_{trend} = 0.12). In an unlagged analysis excluding participants with a ≥50% probability of TCE exposure (17 cases, 14 controls), the association with perchloroethylene was essentially unchanged in magnitude, although no longer statistically significant (OR 3.0, 95% CI 0.99-9.0; P trend = 0.08). The perchloroethylene association did not significantly differ by age group, sex, study center, race, smoking status, BMI, hypertension history, or tumor histology (see Table S4).

In additional analyses for high-intensity TCE cumulative hours of exposure, lagged results were similar to the unlagged finding (e.g., for 15-year lag: OR 2.1, 95% CI 0.9-4.7 for >1,560 exposure hours vs. unexposed; $P_{trend} = 0.16$), as were results restricted to Detroit participants (OR 1.9, 95% CI 0.8-4.5; $P_{trend} = 0.17$). Lagged and Detroit-restricted analyses of other chlorinated solvents were null (results not shown).

DISCUSSION

In this case-control investigation of occupational exposure to six chlorinated solvents and kidney cancer risk, we observed a statistically significant association for high cumulative hours exposed to perchloroethylene among jobs where the probability of exposure was likely to be ≥50% and exposure intensity was likely to be high. The same magnitude of association remained in sensitivity analyses incorporating lagging and excluding participants with ≥50% probability of exposure to TCE. In other analyses, we observed weak, statistically non-significant evidence of an association with TCE. Our findings for the other evaluated chlorinated solvents do not support an association with kidney cancer.

Previous epidemiologic studies of perchloroethylene have generally yielded weak and inconsistent evidence of an association with kidney cancer,[3] although crude methods of exposure assessment were often used. Most studies used employment in the dry cleaning industry as a surrogate for exposure, while a few studies employed generic job-exposure matrices (JEMs) to estimate perchloroethylene exposure. These methods, which assume uniform exposure levels across all workers in the same occupation and/or industry in a given time period, can introduce substantial measurement error that could attenuate or obscure an actual association.

Five epidemiologic studies (three cohort, two case-control) employed more detailed exposure assessment methods, beyond the use of job title or generic JEMs, in order to directly assess PCE exposure. Anttila et al., in a cohort study of 849 Finnish workers biologically monitored for perchloroethylene exposure between 1974 and 1983, observed a non-significant excess of kidney cancer among workers relative to the number expected from population rates (standardized incidence ratio 1.8, 95% CI 0.2-6.5), based on 2 observed cases of kidney cancer.[17] Lipworth et al. updated follow-up of a cohort of aircraft manufacturing workers exposed to different solvents who were assessed for perchloroethylene exposure using a job-exposure matrix based on job descriptions and historical chemical usage patterns; for 5,830 workers assessed as having intermittent or routine perchloroethylene exposure, the standardized mortality ratio (SMR) for kidney cancer was 0.8 (0.4-1.4; 13 deaths).[18] In the most recent follow-up of a cohort of 1,704 workers in dry cleaning facilities with documented records of perchloroethylene use, Calvert et al. reported a standardized mortality ratio of 1.14 (0.37-2.67); in an analysis restricted to participants exposed only to perchloroethylene, a SMR of 1.35 (0.16-4.89) was observed.[19] Christensen et al. conducted a case-control investigation of chlorinated solvents and kidney cancer and 10 other cancer sites, with occupational exposures derived from self-reported occupational histories, selected job-specific interview modules, and expert assessment by a team of chemists and industrial hygienists.[20] In analyses using population controls, kidney cancer ORs of 1.6 (95% CI 0.3-9.4) and 3.1 (0.4-24) were observed for

having any exposure (four exposed cases) and substantial exposure (2 cases) to perchloroethylene, respectively. Pesch et al., in a case-control investigation of occupational risk factors for kidney cancer, used participants' reported work histories and answers to supplemental questions on selected exposure-specific work tasks to estimate perchloroethylene exposure through the use of a job-task-exposure matrix; ORs for "substantial" exposure were 1.3 (0.7-2.3; 15 exposed cases) and 2.0 (0.5-7.8; 3 exposed cases) for men and women, respectively, versus no exposure.[21] In summary, the evidence from past studies directly assessing perchloroethylene exposure and kidney cancer, although in some cases suggestive of an association, are inconclusive given small numbers of exposed participants and imprecise risk estimates.

Other lines of evidence suggest that perchloroethylene exposure adversely affects the kidney. Multiple studies have shown exposure to induce nephrotoxicity in mice and rats,[3] and associations with early renal effects and end-stage renal disease among exposed dry cleaning industry workers have been reported.[19, 22] Experimental evidence of renal carcinogenicity is, however, limited; kidney tumors, rare in rats, were more frequent with increasing exposure in a single bioassay, although not at a level of statistical significance.[23]

We did not observe statistically significant evidence of an association with TCE, classified by IARC as a Group 1 kidney carcinogen.[3] We note that our statistical power to detect a moderately-sized TCE association was limited, given the low prevalence of high-probability TCE exposure in this general-population study. It is noteworthy that the overall magnitude of association between TCE and kidney cancer in the epidemiologic literature is generally moderate in size, with summary relative risks of 1.27 and 1.58 from meta-analyses of findings for any exposure and highest exposure levels, respectively.[24] These summary findings are comparable in magnitude to the non-significant ORs we observed in analyses of cumulative hours of TCE exposure restricted to high-intensity jobs.

In this study we did not observe evidence of an association with kidney cancer for exposures to 1,1,1-trichloroethane, carbon tetrachloride, chloroform, or methylene chloride. As noted for TCE, our power to detect ORs of moderate size for these exposures was generally limited, and as such we cannot rule out the possibility of a weak association with kidney cancer for these chemicals. However, our findings are consistent with the previously published epidemiologic evidence, which is not suggestive of a kidney cancer excess among workers exposed to these chemicals.[4, 5]

An important strength of our study is the detailed information collected on workplace tasks related to chlorinated solvent exposure. By collecting a general work history and including task-, job-, and industry-specific interview modules administered to elicit specific information regarding solvent use, we generated a rich data resource to inform the expert retrospective exposure assessment. This approach enabled the calculation of exposure metrics restricted to jobs with high exposure probability and intensity, thereby likely increasing the expected specificity of exposure assessment which, in studies such as this where exposure prevalence is low, is vital to minimizing potential bias from exposure misclassification.[6] Another strength is our assessment of occupational exposure to six different chlorinated solvents. With this comprehensive assessment, we were able to

investigate potential associations with kidney cancer for rarely studied chemicals like 1,1,1-trichloroethane, carbon tetrachloride, and chloroform. Importantly, this also enabled us to account for exposure to TCE, an established kidney carcinogen, in our analysis of perchloroethylene. Our observed association with perchloroethylene remained upon excluding participants assessed as having probably been exposed to TCE, thus arguing against confounding by TCE as an explanation for this finding.

Our case-control study had a comparatively large sample size, which enabled the identification of a sizable number of individuals highly exposed to these chlorinated solvents, who are rare in the general population. However, in spite of this overall sample size, the number of highly-exposed participants for each solvent was small, giving us limited statistical power to detect an association of moderate size for the other chemicals. A factor limiting our perchloroethylene finding as evidence of causation is the fact that it was observed as part of an analysis in which scores of statistical tests were conducted; as a consequence, we cannot rule out the possibility that this association may have arisen due to chance. Another limitation of this study was the low response rate among controls, which is typical of recent population-based case-control studies. The use of sample weights should have reduced the potential for bias arising from nonresponse, as the weights accounted for differential nonresponse across subgroups defined by factors such as age, sex, and county of residence, for which data were available for both respondents and non-respondents. However, we cannot entirely rule out the possibility that selection bias influenced our results. Lastly, as with other case-control studies collecting participant-reported information, we cannot eliminate the possibility that bias due to differential recall of occupational tasks and their characteristics by cases and controls may have been introduced into the study.

In conclusion, findings from this study, employing a detailed expert assessment of multiple chlorinated solvents based on extensive information regarding solvent-related workplace tasks, are compatible with an association between high exposure to perchloroethylene and kidney cancer risk. Additional studies investigating this relationship are warranted. In order to best inform a future evaluation of perchloroethylene as a potential kidney carcinogen, such studies should employ high-quality exposure assessment methodology and be able to address the potential concern for confounding from TCE. A meta-analysis of the published epidemiologic evidence, taking into account differences in exposure assessment quality between studies, may also be informative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This research was supported by the Intramural Research Program of the NIH and the National Cancer Institute.

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WHAT THIS PAPER ADDS

- Trichloroethylene, a chlorinated solvent used to clean metal parts, has been classified by the International Agency for Research on Cancer (IARC) as a human kidney carcinogen (Group 1).
- To assess whether other chlorinated solvents are associated with kidney cancer, we conducted an analysis within a case-control study using detailed exposure assessment methods.
- Kidney cancer cases were significantly more likely than controls to have had high estimated cumulative hours of exposure to perchloroethylene, a solvent commonly used in the dry cleaning industry.
- Our finding for perchloroethylene, currently classified by IARC as a probable human carcinogen, warrants further evaluation in other studies of kidney cancer using high-quality exposure assessment methods.

Table 1

Algorithm developed to qualitatively estimate solvent exposure intensity (high vs. low)

Job Location	Proximity	Local Exhaust Ventilation	Mechanism of Release (Primary and Secondary)	Process Temperature	Intensity
Outdoors					Low
Indoors/Both	Far	Effective			Low
Indoors/Both	Far	Absent/Ineffective	Evaporation	Room	Low
Indoors/Both	Far	Absent/Ineffective	Evaporation	Elevated/Both	High
Indoors/Both	Far	Absent/Ineffective	Any active		High
Indoors/Both	Near/Both				High

Shaded cells represent factors that do not influence the intensity assignment for a given row.

Occup Environ Med. Author manuscript; available in PMC 2018 January 10.

Table 2

Selected characteristics of cases and controls in the U.S. Kidney Cancer Study.

	Cases (N = 1,217)	Controls (N = 1,235)
Characteristic	**N (%)***	**N (%)***
Age (years)		
20–44	147 (10.5)	179 (10.5)
45–54	287 (21.6)	270 (21.6)
55–64	372 (29.3)	350 (29.3)
65–74	303 (27.1)	329 (27.1)
75+	108 (11.4)	107 (11.4)
Sex		
Male	720 (61.8)	689 (61.4)
Female	497 (38.2)	546 (38.6)
Race		
Black	361 (26.1)	523 (26.1)
White	856 (73.9)	712 (73.9)
Study Center		
Chicago	199 (16.7)	197 (17.3)
Detroit	1,018 (83.3)	1,038 (82.7)
Education		
≤11 Years	200 (16.7)	165 (12.0)
12 Years/HS Graduate/GED/Voc/Tech	419 (34.5)	390 (31.5)
1–3 Years College	328 (26.3)	356 (27.3)
4+ Years College/College Graduate	270 (22.5)	324 (29.3)
Smoking Status		
Never	432 (35.3)	471 (38.4)
Occasional/Don't Know	55 (4.7)	55 (4.0)
Regular, Former	410 (34.7)	445 (37.9)
Regular, Current	320 (50.6)	264 (19.7)
Body Mass Index (kg/m^2)		
<25	240 (19.3)	366 (29.0)
25–<30	436 (37.0)	493 (41.6)
30–<35	298 (24.6)	221 (18.3)
35+	230 (18.0)	147 (10.8)
Unknown	13 (1.1)	8 (<1)
History of Hypertension		
No	500 (40.2)	718 (58.5)
Yes	701 (58.4)	508 (40.7)
Unknown	16 (1.4)	9 (<1)
Chronic Kidney Disease		
No	1,165 (96.1)	1,222 (99.1)

Characteristic	Cases (N = 1,217) N (%)*	Controls (N = 1,235) N (%)*
Yes	51 (3.9)	13 (<1)
Unknown	1 (<1)	0 (0)

Abbreviations: HS, high school; GED, General Education Development test; Voc, vocational school; Tech, technical college.

*Percentages incorporate post-stratified sample weights.

Table 3

Probability of exposure to individual chlorinated solvents and kidney cancer risk

		Cases	Controls	
Solvent	**Exposure Probabliity**	**N (%)***	**N (%)**	**OR** ** **(95% CI)**
1,1,1-Trichloroethane	Unexposed	579 (48.5)	652 (54.4)	1.0
	<50%	562 (47.5)	512 (41.2)	1.2 (1.0–1.4)
	50%–89%	41 (3.5)	43 (3.9)	1.0 (0.6–1.6)
	≥90%	7 (0.5)	4 (0.5)	1.2 (0.4–4.1)
Carbon tetrachloride	Unexposed	772 (63.7)	826 (67.6)	1.0
	<50%	331 (28.5)	301 (25.0)	1.1 (0.9–1.4)
	50%–89%	14 (1.1)	16 (1.1)	1.2 (0.6–2.7)
	≥90%	72 (6.7)	68 (6.3)	1.1 (0.8–1.5)
Chloroform	Unexposed	795 (66.8)	836 (69.8)	1.0
	<50%	365 (30.9)	346 (27.7)	1.1 (0.9–1.3)
	50%–89%	15 (1.2)	16 (1.4)	0.8 (0.4–1.9)
	≥90%	14 (1.2)	13 (1.0)	1.0 (0.4–2.1)
Methylene chloride	Unexposed	558 (46.8)	619 (52.6)	1.0
	<50%	469 (39.9)	447 (35.5)	1.2 (0.9–1.4)
	50%–89%	130 (10.6)	120 (9.5)	1.2 (0.8–1.6)
	≥90%	32 (2.7)	25 (2.4)	0.9 (0.6–1.6)
Perchloroethylene	Unexposed	652 (54.0)	705 (59.0)	1.0
	<50%	499 (42.8)	469 (38.1)	1.1 (0.9–1.4)
	50%–89%	17 (1.3)	21 (1.3)	0.9 (0.4–1.9)
	≥90%	22 (1.9)	16 (1.6)	1.2 (0.6–2.3)
Trichloroethylene	Unexposed	521 (42.9)	582 (48.0)	1.0
	<50%	608 (52.6)	565 (46.7)	1.2 (0.9–1.4)
	50%–89%	18 (1.6)	27 (1.9)	0.8 (0.4–1.6)
	≥90%	32 (2.8)	32 (3.3)	0.8 (0.4–1.5)

Abbreviations: OR, odds ratio; CI, confidence interval.

*Percentages incorporate post-stratified sample weights.

**Adjusted for age, sex, race, study center, education level, smoking status, BMI, and history of hypertension.

Table 4

Analysis of estimated occupational perchloroethylene exposure and kidney cancer risk

Exposure Metric	Any Exposure Intensity*		High-Intensity Exposure Only**	
	N_{Ca}/N_{Co}	OR# (95% CI)	N_{Ca}/N_{Co}	OR (95% CI)
Years Exposed				
Unexposed	652/705	1.0	652/705	1.0
1 – 3	13/12	1.1 (0.4–2.9)	10/10	0.9 (0.3–2.6)
4 – 9	13/14	1.0 (0.4–2.5)	11/8	1.4 (0.5–4.0)
≥10	13/11	1.1 (0.5–2.5)	13/8	1.4 (0.6–3.4)
		P_{trend} = 0.77		P_{trend} = 0.78
Average Weekly Exposure (hours/week)				
Unexposed	652/705	1.0	652/705	1.0
≤1	18/15	1.0 (0.5–2.0)	18/13	1.1 (0.5–2.3)
>1 – 15	10/7	1.4 (0.5–4.1)	9/7	1.2 (0.4–3.7)
>15	11/14	1.1 (0.4–3.1)	7/5	2.5 (0.6–10.6)
		P_{trend} = 0.83		P_{trend} = 0.15
Cumulative Hours Exposed##				
Unexposed	652/705	1.0	652/705	1.0
Tertile 1	16/12	1.2 (0.5–2.8)	13/9	1.4 (0.5–3.8)
Tertile 2	15/13	1.1 (0.6–2.1)	7/8	0.5 (0.2–1.4)
Tertile 3	8/11	0.9 (0.3–3.3)	14/8	**3.1 (1.3–7.4)**
		P_{trend} = 0.95		P_{trend} = 0.03

Abbreviations: N_{Ca}, number of cases; N_{Co}, number of controls; OR, odds ratio; CI, confidence interval.

*Restricted to unexposed participants and participants with ≥50% exposure probability.

**Exposed participants further restricted to those with jobs involving a potentially high exposure intensity.

#Adjusted for age, sex, race, study center, education level, smoking status, BMI, and history of hypertension.

##Tertile cut-points for cumulative hours exposed: ≤936, 937 – 4,680, >4,680 for any exposure intensity; ≤624, 625-1,820, >1,820 for high exposure intensity.

Table 5

Analysis of estimated occupational trichloroethylene exposure and kidney cancer risk

Exposure Metric	Any Exposure Intensity*		High-Intensity Exposure Only**	
	N_{Ca}/N_{Co}	OR# (95% CI)	N_{Ca}/N_{Co}	OR (95% CI)
Years Exposed##				
Unexposed	521/582	1.0	521/582	1.0
Tertile 1	18/20	0.9 (0.4–1.9)	9/9	1.3 (0.5–3.6)
Tertile 2	9/19	0.4 (0.1–1.1)	5/8	0.6 (0.2–2.2)
Tertile 3	23/20	0.9 (0.5–1.9)	11/9	1.1 (0.5–2.4)
		P_{trend} = 0.41		P_{trend} = 0.93
Average Weekly Exposure (hours/week)				
Unexposed	521/582	1.0	521/582	1.0
≤1	18/32	0.6 (0.3–1.3)	5/13	0.6 (0.2–1.9)
>1 – 6	20/20	0.7 (0.3–1.5)	11/9	1.0 (0.4–2.3)
>6	12/7	1.4 (0.5–3.7)	9/4	2.0 (0.5–7.4)
		P_{trend} = 0.89		P_{trend} = 0.30
Cumulative Hours Exposed†				
Unexposed	521/582	1.0	521/582	1.0
Tertile 1	12/20	0.7 (0.3–2.0)	4/9	0.8 (0.2–3.5)
Tertile 2	15/20	0.6 (0.3–1.3)	3/8	0.3 (0.1–1.3)
Tertile 3	23/19	0.9 (0.5–1.9)	18/8	1.7 (0.8–3.8)
		P_{trend} = 0.69		P_{trend} = 0.28

Abbreviations: N_{Ca}, number of cases; N_{Co}, number of controls; OR, odds ratio; CI, confidence interval.

*Restricted to unexposed participants and participants with ≥50% exposure probability.

**Exposed participants further restricted to those with jobs involving a potentially high exposure intensity.

#Adjusted for age, sex, race, study center, education level, smoking status, BMI, and history of hypertension.

##Tertile cut-points for years exposed: ≤5, 6-10, >10 for any exposure intensity; ≤4, 5-8, >8 for high exposure intensity.

†Tertile cut-points for cumulative hours exposed: ≤416, 417 – 2,184, >2,184 for any exposure intensity; ≤364, 365 – 1,560, >1,560 for high exposure intensity.

Supplemental Material

Occupational exposure to chlorinated solvents and kidney cancer: a case-control study

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Supplemental Table 1. Selected characteristics of cases and controls in the U.S. Kidney Cancer Study stratified by study center.

	Detroit (Wayne, Oakland, Macomb Counties)		Chicago (Cook County)	
	Cases (N = 1,018)	Controls (N = 1,038)	Cases (N = 199)	Controls (N = 197)
Characteristic	**N (%)***	**N (%)***	**N (%)***	**N (%)***
Age (years)				
20-44	123 (10.5)	148 (11.2)	24 (10.5)	31 (7.3)
45-54	234 (21.4)	232 (21.9)	53 (22.8)	38 (20.3)
55-64	320 (30.0)	287 (28.5)	52 (26.1)	63 (33.3)
65-74	257 (27.4)	278 (26.5)	46 (25.4)	51 (29.9)
75+	84 (10.7)	93 (11.9)	24 (15.2)	14 (9.2)
Sex				
Male	588 (60.8)	581 (61.8)	132 (66.9)	108 (59.4)
Female	430 (39.2)	457 (38.2)	67 (33.1)	89 (40.6)
Race				
Black	280 (24.6)	427 (24.9)	81 (33.1)	96 (31.6)
White	738 (75.4)	611 (75.1)	118 (66.9)	101 (68.4)
Education				
≤11 Years	163 (16.2)	141 (11.8)	37 (19.3)	24 (12.6)
12 Years / HS Graduate / GED / Voc / Tech	354 (34.8)	339 (32.8)	65 (33.2)	51 (25.1)
1-3 Years College	276 (26.6)	289 (26.5)	52 (24.9)	67 (30.9)
4+ Years College / College Graduate	225 (22.4)	269 (28.8)	45 (22.6)	55 (31.4)
Smoking Status				
Never	360 (35.1)	387 (37.8)	72 (36.4)	84 (41.0)
Occasional / Don't Know	45 (4.7)	47 (4.0)	10 (5.0)	8 (3.8)
Regular, Former	347 (35.1)	377 (37.6)	63 (32.7)	68 (39.4)
Regular, Current	266 (25.2)	227 (20.5)	54 (25.9)	37 (15.9)
Body Mass Index (kg/m^2)				
<25	199 (18.9)	313 (30.1)	41 (21.0)	53 (23.8)
25-<30	360 (36.7)	417 (41.7)	76 (38.4)	76 (40.8)
30-<35	248 (24.4)	180 (17.4)	50 (25.5)	41 (22.3)
35+	200 (18.9)	121 (10.4)	30 (13.7)	26 (13.0)
Unknown	11 (1.0)	7 (<1)	2 (1.3)	1 (<1)

(continued on next page)

History of Hypertension	408 (39.1)	605 (59.8)	92 (45.8)	113 (52.7)
No	599 (59.8)	426 (39.5)	102 (51.2)	82 (46.1)
Yes	11 (1.1)	7 (<1)	5 (3.0)	2 (1.2)
Unknown				
Chronic Kidney Disease	976 (96.2)	1027 (99.1)	189 (95.6)	195 (99.3)
No	41 (3.8)	11 (<1)	10 (4.4)	2 (<1)
Yes	0 (0)	1 (<1)	0 (0)	0 (0)
Unknown				

Abbreviations: HS, high school; GED, General Education Development test; Voc, vocational school; Tech, technical college.
*Percentages incorporate post-stratified sample weights.

Supplemental Table 2. Spearman rank correlation coefficients between exposure probabilities of chlorinated solvents among U.S. Kidney Cancer Study controls with exposure probability >0% for any solvent (N=753)

	Spearman Rank Correlation Coefficient (*P*-value)					
	1,1,1-Trichloroethane	**Carbon Tetrachloride**	**Chloroform**	**Methylene Chloride**	**Trichloroethylene**	**Perchloroethylene**
1,1,1-Trichloroethane	1.00					
Carbon tetrachloride	0.43 <0.0001	1.00				
Chloroform	0.33 <0.0001	0.60 <0.0001	1.00			
Methylene chloride	0.61 <0.0001	0.37 <0.0001	0.41 <0.0001	1.00		
Trichloroethylene	0.15 <0.0001	0.36 <0.0001	0.23 <0.0001	0.12 0.0007	1.00	
Perchloroethylene	0.38 <0.0001	0.46 <0.0001	0.53 <0.0001	0.48 <0.0001	0.28 <0.0001	1.00

Supplemental Table 3. Associations with kidney cancer for estimated cumulative hours of exposure to other chlorinated solvents (1,1,1-trichloroethane, carbon tetrachloride, chloroform, and methylene chloride), restricted to jobs qualitatively assessed as high-intensity.

			Cumulative Hours Exposed (High-Intensity Exposure Only)						
	Unexposed		Low		Medium		High		
Chemical	N_{Ca} / N_{Co}	OR*	N_{Ca} / N_{Co}	OR (95% CI)	N_{Ca} / N_{Co}	OR (95% CI)	N_{Ca} / N_{Co}	OR (95% CI)	P_{trend}
1,1,1-Trichloroethane**	579 / 652	1.0	9 / 15	0.6 (0.2-1.6)	14 / 15	0.8 (0.3-2.0)	21 / 14	1.6 (0.8-3.2)	0.30
Carbon Tetrachloride#	772 / 826	1.0	27 / 27	1.1 (0.6-2.0)	18 / 23	0.8 (0.4-1.4)	32 / 25	1.5 (0.9-2.6)	0.23
Chloroform##	795 / 836	1.0	4 / 9	0.4 (0.1-1.8)	11 / 9	1.0 (0.4-2.5)	12 / 9	1.1 (0.4-2.6)	0.88
Methylene Chloride†	558 / 619	1.0	45 / 42	1.1 (0.7-2.0)	46 / 42	0.9 (0.6-1.6)	51 / 41	1.4 (0.9-2.2)	0.21

Abbreviations: N_{Ca}, number of cases; N_{Co}, number of controls; OR, odds ratio; CI, confidence interval.
*Adjusted for age, sex, race, study center, education level, smoking status, BMI, and history of hypertension.
**Cutpoints (hours): tertile 1 = ≤520, tertile 2 = 521 – 1,456, tertile 3 = >1,456.
#Cutpoints (hours): tertile 1 = ≤572, tertile 2 = 573 – 1,456, tertile 3 = >1,456. ##Cutpoints (hours): tertile 1 = ≤312, tertile 2 = 313 – 1,768, tertile 3 = >1,768. †Cutpoints (hours): tertile 1 = ≤624, tertile 2 = 625 – 2,340, tertile 3 = >2,340.

Supplemental Table 4. Analysis of estimated cumulative perchloroethylene exposure and kidney cancer across selected strata and by tumor histology

	Cumulative Hours Exposed (High-Intensity Only)*							
	Unexposed		Tertiles 1 & 2		Tertile 3			
	N_{Ca} / N_{Co}	OR**	N_{Ca} / N_{Co}	OR (95% CI)	N_{Ca} / N_{Co}	OR(95% CI)	P_{trend}	$P_{interaction}$
By Sex								
Female	345 / 387	1.0	4 / 5	0.6 (0.1-4.0)	1 / 2	-	0.99	0.80
Male	307 / 318	1.0	16 / 12	1.0 (0.5-2.4)	13 / 6	3.5 (1.4-8.9)	0.006	
By Age Group								
20-54	215 / 263	1.0	7 / 4	0.9 (0.2-3.6)	6 / 0	-	0.005	0.15
55-64	221 / 204	1.0	7 / 8	0.6 (0.2-1.6)	3 / 3	1.7 (0.2-1.6)	0.74	
65+	216 / 238	1.0	6 / 5	1.5 (0.4-6.0)	5 / 5	2.6 (0.7-9.5)	0.14	
By Race								
Black	177 / 180	1.0	6 / 6	1.3 (0.4-4.5)	5 / 7	1.6 (0.4-5.7)	0.47	0.06
White	475 / 425	1.0	14 / 11	0.8 (0.3-2.0)	9 / 1	9.8 (2.5-39.0)	0.001	
By Region								
Chicago	128 / 110	1.0	1 / 1	-	4 / 1	16.2 (1.9-140)	0.01	0.07
Detroit	542 / 577	1.0	19 / 16	0.8 (0.4-1.8)	10 / 7	2.3 (0.9-6.3)	0.13	
By Smoking Status								
Never	251 / 317	1.0	6 / 8	0.7 (0.2-2.4)	3 / 2	2.6 (0.5-14.8)	0.34	0.91
Regular Former	219 / 230	1.0	11 / 5	1.5 (0.4-5.1)	4 / 3	3.9 (0.9-17.3)	0.05	
Regular Current	149 / 126	1.0	3 / 3	0.3 (0.1-3.7)	7 / 3	4.1 (0.7-24.6)	0.14	
By Body Mass Index								
<25	140 / 221	1.0	1 / 1	-	1 / 4	-	0.82	0.76
25-<30	224 / 278	1.0	7 / 10	0.7 (0.2-2.0)	8 / 3	3.8 (0.8-17.9)	0.10	
30+	280 / 199	1.0	12 / 6	1.2 (0.4-3.8)	5 / 1	-	0.12	
By Hypertension History								
Never Diagnosed	284 / 425	1.0	5 / 4	1.7 (0.3-8.9)	8 / 4	3.5 (1.0-12.1)	0.04	0.61
Ever Diagnosed	360 / 277	1.0	15 / 13	0.8 (0.3-1.7)	5 / 3	3.0 (0.7-13.8)	0.25	
By Tumor Histology								
Clear Cell	400 / 705	1.0	9 / 17	0.7 (0.3-1.7)	10 / 8	3.7 (1.5-9.1)	0.09	0.90#
Other	252 / 705	1.0	11 / 17	1.2 (0.5-2.8)	4 / 8	2.2 (0.5-9.6)	0.23	

Abbreviations: N_{Ca}, number of cases; N_{Co}, number of controls; OR, odds ratio; CI, confidence interval
*Cut-points (hours): tertiles 1 & 2 = ≤1,820, tertile 3 = >1,820.
**Adjusted for age, sex, race, study center, education level, smoking status, BMI, and history of hypertension.
#P-value form case-only test of OR heterogeneity.