Exhibit 233

Risk of Selected Cancers due to Occupational Exposure to Chlorinated Solvents in a Case–Control Study in Montreal

Krista Yorita Christensen, MPH, PhD, David Vizcaya, MPH, PhD, Harriet Richardson, MSc, PhD, Jérôme Lavoué, MSc, PhD, Kristan Aronson, MSc, PhD, and Jack Siemiatycki, MSc, PhD

Objective: To evaluate the association between exposure to chlorinated solvents and cancer. **Methods:** We conducted a case–control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer. **Results:** The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9). **Conclusions:** There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

Chlorinated solvents are some of the most widespread and useful industrial chemicals. Because of their unique chemical properties, including good solvency and low flammability, chlorinated solvents have been used in a wide variety of workplaces since the beginning of the 20th century. Their most frequent uses have included degreaser, paint stripper, dry cleaning solvent, spot remover, chemical reaction intermediate, aerosol propellant, and anesthetic gas. Consequently, workers in many occupations and industries may have significant exposure to chlorinated solvents. Chlorinated solvents as a chemical family are defined as short-chain hydrocarbons in which one or several hydrogen atoms have been substituted by a chlorine atom. This substitution increases the boiling point of the molecule and reduces its flammability. Chlorinated solvents can be further separated into two main classes: chlorinated alkenes and chlorinated alkanes. Chlorinated alkanes are saturated molecules; that is, they do not contain any double bond. Chlorinated alkenes are unsaturated, which, all other things being equal, renders them more reactive.

The most widely used chlorinated alkenes are trichloroethylene (TCE) and perchloroethylene (PERC; also known as tetrachloroethylene), while the most widely used chlorinated alkanes are carbon tetrachloride, methylene chloride, 1,1,1-trichloroethane, and chloroform.[1] The frequency of the use of these compounds has changed over time in response to various factors, including discoveries about toxicity and environmental impact.[2–4] For example, the use of carbon tetrachloride was reduced because of its adverse effects on kidneys and liver, while 1,1,1-trichloroethane was banned in many countries because of its adverse effects on the ozone layer.

Experimental evidence suggests that some chlorinated solvents may be carcinogenic. Chlorinated solvents are generally metabolized in the liver via the cytochrome P450 oxidase pathway; this process generates reactive intermediates that may bind to proteins, lipids, DNA, RNA, and cell receptors.[5,6] Evidence from animal studies indicates that some chlorinated solvents may cause liver tumors in some animal models,[7,8] and possibly tumors in the kidney, bone marrow, and lung.[9] Nevertheless, epidemiologic evidence regarding carcinogenicity of solvents has been sparse and inconsistent. Although some studies reported an association between PERC exposure among dry cleaners and elevated risk of esophageal, lung, tongue, and cervical cancer,[10,11] other studies using different types of exposure assessment did not find increased risk for any type of cancer.[12,13] Recent reviews have generally concluded that TCE exposure increases the risk of kidney cancer, and possibly also the risk of liver cancer, and non-Hodgkin's lymphoma.[7,14–16] Among the chlorinated alkanes, some studies have found an association between occupational exposure and elevated risk of cancer at various sites including multiple myeloma and the nervous system with 1,1,1-trichloroethane,[12,17] the lymphatic system with carbon tetrachloride,[16,18] and liver and biliary tract cancer with methylene chloride.[19] Nevertheless, other studies have failed to find associations between occupational exposure to chlorinated alkanes and cancer.[20–22]

Given the widespread use of chlorinated solvents and the inconsistent findings on potential carcinogenicity of these substances, it is important to increase the epidemiologic information base. A large case–control study was conducted in Montreal, Quebec, Canada, aiming to detect and describe possible associations between each of 294 occupational exposures and each of 19 sites of cancer.[23] The study was not conducted to test any particular set of hypotheses, but rather to provide an estimate of risk for each of thousands of possible associations. In this spirit, the choice of cancer sites was conditioned by available financial resources and by opportunistic considerations. Thus, because we had to establish a registry-like case ascertainment system, we included only those cancer types that, at the time, were highly likely to be diagnosed in hospital pathology departments (which led to the exclusion of leukemia cases, which were often diagnosed in hematology laboratories) and we excluded those types of cancer that often led to communication difficulties (which led to the exclusion of brain, nasal, tongue, larynx). Nineteen cancer sites were eligible for recruitment. Information was collected on exposure to the six specific chlorinated solvents listed earlier as well as on the families of chlorinated alkenes and chlorinated alkanes. The calendar period during which this study population had occupational activity and, thus, exposure to the evaluated agents, coincides with the period in which the use of such agents was increasing. This study describes the associations between these chlorinated solvents and each of 11 sites of cancer. We exclude lung cancer findings from the present report because they will be reported separately in

From the University of Montreal Hospital Research Center (CRCHUM) (Drs Christensen, Vizcaya, Lavoué, and Siemiatycki), Montreal, Quebec, Canada; Department of Social and Preventive Medicine (Dr Siemiatycki), and Guzzo–Cancer Research Society Chair in Environment and Cancer, School of Public Health (Dr Siemiatycki), Université de Montréal, Montréal, Quebec, Canada; Department of Community Health and Epidemiology (Dr Richardson and Aronson), Queen's University, Kingston, Ontario, Canada.

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Address correspondence to Jack Siemiatycki, MSc, PhD, Environmental Epidemiology and Population Health Research Group, Research Centre of the University of Montreal Hospital Network (CRCHUM), 3875 rue Saint-Urbain, Montréal, QC H2W 1V1, Canada (j.siemiatycki@umontreal.ca).

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a pooled analysis including another lung cancer study. In an earlier report,[24] we published selected results from the multisite study, including some that overlap with results in this article. The present results should be taken as the definitive ones for several reasons: there has been some further refinement and correction of exposure information; the logistic regression analyses conducted here allowed for more effective control of multiple covariates than the Mantel–Haenszel analyses conducted earlier; the selection of covariates was more targeted here; some associations presented here were not presented in the earlier report; and there was no discussion of findings in the earlier report.

MATERIALS AND METHODS

Design and Study Subjects

The Montreal Cancer Case–Control Study is a study of male Canadian citizens aged 35 to 70 years, living in Montreal. Eligible cancer cases occurring from 1979 to 1985 were ascertained from the 18 largest hospitals in the Montreal metropolitan area; only incident, histologically confirmed cancer cases were included.

For the present analysis, we excluded seven sites that had very small numbers, and lung cancer, which will be the object of a separate evaluation; the present analysis focuses on the following 11 types of cancer: esophagus (International Classification of Diseases, 9th Revision [ICD-9] code 150), stomach (ICD-9 code 151), colon (ICD-9 code 153), rectum (ICD-9 code 154), liver (ICD-9 code 152), pancreas (ICD-9 code 157), prostate (ICD-9 code 185), bladder (ICD-9 code 188), kidney (ICD-9 code 189), melanoma (ICD-9 code 172), and non-Hodgkin's lymphoma (ICD-9 codes 200 and 202).

Population controls were randomly sampled from population-based electoral lists, stratified by sex and age to the distribution of cases. In Quebec, Canada, electoral lists were maintained by means of active enumeration of households and are thought to represent nearly complete listings of Canadian citizens residing in the province. Ethical approval was obtained from each participating hospital and university. All participating subjects provided informed consent. Additional details of subject ascertainment and data collection have been presented previously.[24–26]

Data Collection

Among 4576 eligible cancer patients, 3730 (82%) were successfully interviewed, whereas among 740 eligible population controls, 533 (72%) were successfully interviewed. Interviews were divided into two parts: a structured section requested information on sociodemographic and lifestyle characteristics, and a semistructured section elicited a detailed description of each job held by the subject in his or her working lifetime. The sociodemographic and lifestyle factors assessed included ethnicity, median family income of the neighborhood of residence, education level attained, residential history, smoking history, alcohol and coffee consumption, selected dietary factors, selected medical history conditions, and household heating and cooking practices. On average, male subjects had held 4.2 jobs each. For each job held, a trained interviewer asked the subject about the company, its products, the nature of the worksite, the subject's main and subsidiary tasks, and any additional information (eg, equipment maintenance, the use of protective equipment, activities of coworkers) that could provide clues about work exposures and their intensity. The job history part of the interview typically lasted from 20 to 60 minutes. Occupations were coded according to the Canadian Classification and Dictionary of Occupations (1971) and the Canadian Standard Industrial Classification (1980). For some occupations, supplementary questionnaires were used to assist interviewers with detailed technical probing.[27] A team of chemists and industrial hygienists examined each completed questionnaire and translated each job into a list of potential exposures, using a checklist of 294 agents.[24]

Altogether, approximately 16,000 jobs were evaluated. The team of coders spent about 40 person-years on this project, including helping to develop the methodology, monitoring the quality of the interviewing, conducting background research on exposures in different occupations, coding the individual participants' files, and recoding after the initial complete round of coding was finished. The final exposure codes attributed to a subject were based on consensus among the coders. Coders were blind with regard to the subject's case or control status. For each substance considered present in each job, the coders noted three dimensions of information, each on a three-point scale: their degree of confidence that the exposure had actually occurred (possible, probable, definite), the frequency of exposure in a normal workweek (less than 5%, 5% to 30%, more than 30% of the time), and the relative level of concentration of the agent (low, medium, and high). Concentration levels were established with reference to certain benchmark occupations in which the substance is found. Specifically, we identified some hypothetical workplace situations a priori, which would correspond to low, medium, and high exposure for each substance, and the experts rated each real job against these benchmarks. Unfortunately, it proved impossible to reliably estimate absolute concentration values corresponding to the relative levels coded. Nonexposure was interpreted as exposure up to the level that can be found in the general environment. If subjects volunteered information about chemical exposures, this was noted, but it was not accepted at face value unless our experts concurred that such an exposure was likely. The exposure assessment was based not only on the worker's occupation and industry but also on individual characteristics of the workplace and tasks as reported by the subject; an illustrative example is given in the Appendix of Parent et al.[28] Periodic tests showed a satisfactory degree of reproducibility among our experts and between our experts and others.[29–31] There was no evidence that cases provided more complete or more valid job histories than controls, as judged by the numbers of jobs reported per subject and as judged by the interviewers' subjective ratings of the quality of interviews. Because the job histories were collected retrospectively, it is very difficult to confirm the validity of the exposure assessment.

Included among the agents assessed were chlorinated alkanes as a family as well as each of four specific ones: carbon tetrachloride, methylene chloride, 1,1,1-trichloroethane, and chloroform. Also on the list were chlorinated alkenes as a family as well as each of two specific ones: TCE and PERC. The assignment of exposure to a family was not simply the sum of assignments to component agents, because we sometimes assigned exposure to the family without enough information to designate the specific agent.

Statistical Analysis

The study design involved a population control series and a number of cancer case series. In the analysis of each case series, we thus had the opportunity to use the population control group and we also had the opportunity to fashion a control group consisting of other cancer patients (a cancer control group). There are pros and cons with cancer controls and population controls and we cannot affirm that one is necessarily more valid than the other.[32,33] For each case series, we created a distinct cancer control group, using the following principles: (1) exclude contiguous sites as controls for the index cancer series (eg, do not use stomach as control for esophagus and vice versa), (2) exclude lung cancer from the pool of controls, and (3) subsample so that no cancer site constitutes more than 20% of any cancer control series. Thus, for any solvent-site association, the odds ratio (OR) estimate would not be greatly biased except in the implausible scenario that a solvent is a risk factor for most cancer sites, in which case it should be detectable by the analysis using population controls.

Unconditional logistic regression was used to estimate ORs and corresponding 95% confidence intervals (CIs) for risk of each

cancer site, in relation to each control group. We first carried out analyses by comparing the cases separately with population controls and with cancer controls. To maximize precision of estimates, we also conducted an analysis including both cancer controls and population controls but weighted them equally, in consequence of our prior belief that the two control groups are equally likely to represent the study base. Operationally, this was done by assigning weights to the cancer controls so that in aggregate the cancer control group would carry the same statistical weight as the population control group with 533 subjects. For example, for the esophagus cancer series, we had a population control group of 533 and a cancer control group of 2299. To give equal weight to the two control series, we implemented a regression routine that gave each population control a weight of 1 and each cancer control a weight of 0.232 (ie, 533/2299). For each agent-cancer association, we thus estimated ORs separately with three distinct sets of controls: (1) population controls, (2) all eligible cancer controls, and (3) pooled controls, with cancer controls given equal weight to population controls.

For each job in which the subject was exposed to a solvent, we expressed the duration in years and a set of ordinal values for confidence, frequency, and concentration. In the analyses for each solvent, two measures of exposure were used. The most basic measure was ever/never exposed; because of latency considerations, exposures occurring within 5 years of diagnosis or interview were excluded. The second was a simple cumulative exposure measure that combined duration, confidence, frequency, and concentration into categories as follows: unexposed, exposed at nonsubstantial level, and exposed at substantial level. To be classified as exposed at the substantial level, a subject had to have been exposed at a confidence level of probable or definite, a concentration and frequency of medium or high, and a duration greater than 5 years. All other exposed subjects were then classified in the nonsubstantial category. We consider this nonsubstantial/substantial dichotomy to be a simple proxy for cumulative exposure. If a subject was exposed in two or more jobs, then lifetime values of confidence, frequency, and concentration were calculated by taking averages, weighted by the durations of the various jobs in which exposure occurred. For each cancer site, the reference group for analyses consisted of those subjects who were never exposed to any of the six chlorinated solvents evaluated as well as to any of the two generic families of chlorinated hydrocarbons. Thus, for each cancer site, there is a single reference category for association analyses. Each solvent was treated the same way.

To control for the effect of potential confounders, multivariate models were constructed. Specific confounders were selected separately for each cancer site. All models were adjusted for age, ethnicity (French Canadian or other), socioeconomic status (median family income of the neighborhood of residence), and proxy/self-respondent. In addition, the following covariates were adjusted for in cancer-site-specific models: *esophagus*—smoking, coffee, tea, and alcohol intake; *stomach, colon, and liver*—smoking and alcohol intake; *rectum*—smoking and beer intake; *pancreas and kidney*—smoking, coffee, and alcohol intake; *prostate*—smoking, alcohol intake; *bladder*—smoking, coffee intake, and aromatic amine exposure. Smoking was accounted for in the models as *cigarette-years*.

RESULTS

Table 1 presents selected sociodemographic characteristics of study participants by control status and cancer site. The study participants had a median age of approximately 60 years. The proportion of interviews completed by proxy respondents varied by cancer site, from a low of 11.6% (melanoma) to a high of 60.4% (liver cancer); 12.6% of population control interviews were completed by proxy. The majority of study participants were French Canadian, and the majority reported a medium level of family income and less than 13 years of education. Nearly all study subjects were current or former smokers, with the proportion of never smokers ranging from 7.1% (esophageal cancer) to 20.8% (liver cancer). Among ever smokers, the largest proportion had been smoking for 40 years or more; the median number of cigarettes smoked per day was 25.

Among the population controls, 12.4% were deemed to have been exposed, at some time in their careers, to any chlorinated alkane, while 4.7% were assigned exposure to any chlorinated alkene. Among the alkanes, the most prevalent exposure was carbon tetrachloride (5.2%), followed by methylene chloride (2.2%), 1,1,1-trichloroethane (1.9%), and chloroform (0.9%). Among the alkenes, more controls were exposed to TCE (2.8%) than to PERC (0.7%). In our data set, as coded by our experts, it was possible to discern that exposure prevalence of most of these agents increased steadily from the 1930s to the 1970s. The main exceptions were carbon tetrachloride, which peaked and then decreased sharply in prevalence after 1960, and chloroform, which exhibited a quite uniform trend in time. For each agent, Table 2 shows the top-five occupations in terms of the numbers of subjects who were exposed to that agent, using the three-digit occupation classification as the unit of observation. For these agents, the top five (three-digit Canadian Classification and Dictionary of Occupations) accounted cumulatively for between 50% and 75% of all subjects exposed. Metalworking occupations represented the most important sector in terms of numbers exposed to these agents.

Table 3 describes the adjusted OR between each of the eight agents and each of the 11 types of cancer, at two exposure levels—any exposure and substantial exposure. The majority of ORs were close to the null or were based on very small numbers, providing very low power to detect risks. Only two of the OR estimates in Table 3 were significantly elevated at the $P = 0.05$ level, while none were significantly less than 1.0.

On the basis of reasonably large numbers, we found an association between PERC exposure and prostate cancer (OR = 2.2, 95% CI: 0.8 to 5.7, for any exposure; OR = 4.3, 95% CI: 1.4 to 13, for substantial exposure). Melanoma was associated with the exposure to TCE (OR = 3.0, 95% CI: 1.2 to 7.2, for any exposure; and OR = 3.2, 95% CI: 1.0 to 9.9, for substantial exposure), and, in general, with substantial exposure to chlorinated alkenes (OR = 2.6, 95% CI: 1.0 to 7.1). Based on only two exposed subjects, there was an OR of 10.6 (95% CI: 1.2 to 93) between pancreatic cancer and substantial exposure to chloroform. For other associations that have been previously reported in other studies, we found no statistically significant or suggestive evidence of excess risks.

To evaluate the possibility that the higher proportion of proxy respondents among cases than among controls might have led to differential quality of information, we conducted a series of analyses restricted to self-respondents; the results (not shown) were similar to those shown in Table 3.

DISCUSSION

We used data from a large case–control study to explore the association between exposure to chlorinated solvents, and risk of 11 different sites of cancer (Supplemental Digital Content Table 1, http://links.lww.com/JOM/A111). According to our results, there is an indication of increased risk of prostate cancer among people highly exposed to PERC. Likewise, those subjects with high occupational exposure to TCE presented a threefold risk of having melanoma. On the contrary, we found no noteworthy association between any other agent and the 11 evaluated cancers. The few statistically significant results must be interpreted in light of the multiple comparisons context. We note that there is no marked departure from the global null hypothesis of no true associations.

Findings from previous studies on the human carcinogenicity of chlorinated solvents have been mixed. There have been scattered reports of excess risk related to PERC for esophageal, lung, tongue, and cervical cancer.[10,11] We were not able to evaluate the association between PERC and cancer of the esophagus in this study

TABLE 1. Selected Demographic Characteristics by Cancer Site or Control Status

	Population Controls ($N = 533$)	Colon ($N = 496$)	Bladder ($N = 484$)	Prostate ($N = 449$)	Stomach ($N = 251$)	Rectum ($N = 248$)	Non-Hodgkin's Lymphoma ($N = 215$)	Kidney ($N = 177$)	Pancreas ($N = 116$)	Melanoma ($N = 103$)	Esophagus ($N = 99$)	Liver ($N = 48$)
Median age (Q1–Q3),* yrs	61 (54–66)	61 (55–66)	60 (54–65)	64 (59–67)	60 (53–66)	60 (54–65)	57 (48–63)	59 (52–65)	60 (53–65)	55 (46–62)	61 (54–66)	61 (53–66)
Proxy response, *n* (%)	67 (12.6)	93 (18.7)	70 (14.5)	62 (13.8)	54 (21.5)	39 (15.7)	47 (21.9)	25 (14.1)	59 (50.9)	12 (11.6)	32 (32.3)	29 (60.4)
Ethnicity, *n* (%)												
French	342 (64.2)	266 (53.6)	278 (57.4)	287 (63.9)	145 (57.8)	143 (57.7)	134 (62.3)	94 (53.1)	67 (57.8)	39 (37.9)	65 (65.7)	28 (58.3)
Other	191 (35.8)	230 (46.4)	206 (42.6)	162 (36.1)	106 (42.2)	105 (42.3)	81 (37.7)	83 (46.9)	49 (42.2)	64 (62.1)	34 (34.3)	20 (41.7)
Family income,† *n* (%)												
Below 30th percentile	127 (23.8)	131 (26.4)	145 (30.0)	147 (32.7)	85 (33.9)	68 (27.4)	60 (27.9)	39 (22.0)	30 (25.9)	13 (12.6)	27 (27.3)	17 (35.4)
Between 30th and 70th	221 (41.5)	204 (41.1)	169 (34.9)	160 (35.6)	102 (40.6)	94 (37.9)	73 (33.9)	75 (42.4)	56 (48.3)	37 (35.9)	47 (47.5)	21 (43.7)
Over 70th percentile	185 (34.7)	161 (32.5)	170 (35.1)	142 (31.6)	64 (25.5)	86 (34.7)	82 (38.1)	63 (35.6)	30 (25.9)	53 (51.4)	25 (25.2)	10 (20.8)
Education, *n* (%)												
0–7 yrs	163 (30.6)	152 (30.7)	155 (32.0)	159 (35.4)	100 (39.8)	101 (40.7)	61 (28.4)	56 (31.6)	50 (43.1)	16 (15.5)	41 (41.4)	17 (35.4)
8–12 yrs	244 (45.8)	240 (48.5)	206 (42.6)	211 (47.0)	117 (46.6)	100 (40.3)	108 (51.2)	91 (51.4)	49 (42.2)	38 (36.9)	44 (44.4)	20 (41.7)
13+ yrs	126 (23.6)	103 (20.8)	123 (49.4)	79 (17.6)	34 (13.6)	47 (19.0)	46 (21.4)	30 (17.0)	17 (14.7)	49 (47.6)	14 (14.1)	11 (22.9)
Cigarette smoking, *n* (%)												
Never smoker	105 (19.7)	93 (18.7)	43 (8.9)	75 (16.7)	32 (12.7)	49 (19.8)	37 (17.2)	34 (19.2)	14 (12.1)	37 (35.9)	7 (7.1)	10 (20.8)
Less than 765 cigarette-years	162 (30.4)	168 (33.9)	133 (27.5)	130 (29.0)	79 (31.5)	87 (35.1)	84 (39.1)	59 (33.3)	40 (34.5)	39 (37.9)	19 (19.2)	16 (33.3)
765–1240 cigarette-years	152 (28.5)	132 (26.6)	175 (36.2)	113 (25.2)	71 (28.3)	60 (24.2)	58 (27.0)	43 (24.3)	24 (20.7)	15 (14.6)	37 (37.4)	10 (20.8)
More than 1240 cigarette-years	114 (21.4)	103 (20.8)	133 (27.5)	131 (29.2)	69 (27.5)	52 (21.0)	36 (16.7)	41 (23.2)	38 (32.8)	12 (11.7)	36 (36.4)	12 (25.0)

*Interquartile range.
†Median household income in census tract of residence.

TABLE 2. Occupations (3-digit CCDO) With the Highest Exposure Prevalence* to Six Chlorinated Solvents and Two Chemical Families

Chemical	Occupation With Highest Prevalence of Exposure	Number Exposed	% Exposed	Cumulative % Exposed
Chlorinated alkenes ($N = 419$)	Mechanics and repairmen	80	19.1	19.1
	Metal machining occupations	55	13.1	32.2
	Fabricating, assembling, installing, and repairing occupations: electrical, electronic, and related equipment	48	11.5	43.7
	Metal shaping and forming occupations, except machining	37	8.8	52.5
	Personal service occupations	25	6.0	58.5
Perchloroethylene ($N = 76$)	Apparel and furnishings service occupations	20	26.3	26.3
	Mechanics and repairmen	13	17.1	43.4
	Metal machining occupations	6	7.9	51.3
	Metal shaping and forming occupations, except machining	5	6.6	57.9
	Printing and related occupations	4	5.3	63.2
Trichloroethylene ($N = 207$)	Mechanics and repairmen	53	25.6	25.6
	Metal machining occupations	38	18.4	44
	Fabricating, assembling, installing, and repairing occupations: electrical, electronic, and related equipment	26	12.6	56.5
	Metal shaping and forming occupations, except machining	22	10.6	67.1
	Fabricating and assembling occupations metal products	9	4.3	71.5
Chlorinated alkanes ($N = 704$)	Mechanics and repairmen	142	20.2	20.2
	Metal machining occupations	79	11.2	31.4
	Fabricating, assembling, installing, and repairing occupations: electrical, electronic, and related equipment	67	9.5	40.9
	Metal shaping and forming occupations, except machining	42	6.0	46.9
	Protective service occupations	40	5.7	52.6
1,1,1-Trichloroethane ($N = 109$)	Mechanics and repairmen	37	33.9	33.9
	Metal machining occupations	14	12.8	46.8
	Fabricating, assembling, installing, and repairing occupations: electrical, electronic, and related equipment	11	10.1	56.9
	Metal shaping and forming occupations, except machining	8	7.3	64.2
	Occupations in physical sciences	5	4.6	68.8
Carbon tetrachloride ($N = 304$)	Mechanics and repairmen	54	17.8	17.8
	Metal machining occupations	44	14.5	32.2
	Protective service occupations	39	12.8	45.1
	Fabricating, assembling, installing, and repairing occupations: electrical, electronic, and related equipment	35	11.5	56.6
	Metal shaping and forming occupations, except machining	13	4.3	60.9
Chloroform ($N = 59$)	Nursing, therapy, and related assisting occupations	12	20.3	20.3
	Other occupations in medicine and health	7	11.9	32.2
	Occupations in physical sciences	6	10.2	42.4
	Health diagnosing and treating occupations	6	10.2	52.5
	Chemicals petroleum, rubber, plastic, and related materials-processing occupations	5	8.5	61
Methylene chloride ($N = 102$)	Other construction trades occupations	39	38.2	38.2
	Mechanics and repairmen	11	10.8	49
	Chemicals petroleum, rubber, plastic, and related materials-processing occupations	10	9.8	58.8
	Fabricating, assembling, and repairing occupations, wood products	8	7.8	66.7
	Other product fabricating, assembling, and repairing occupations	7	6.9	73.5

CCDO, Canadian Classification and Dictionary of Occupations.
*Percentages reflect the proportion of individual jobs that were assigned as exposed to each chlorinated solvent over the total number of individual jobs with assigned exposure to that particular chlorinated solvent.

TABLE 3. Association Between Different Cancers and the Exposure-Chlorinated Solvents Using Population* and Cancer† Controls in Two Studies From Montreal

		Bladder Cancer				Prostate Cancer				Colon Cancer			
	N_{pcon} (533)	N_{cacon} (2299)	N_{cas} (484)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (1550)	N_{cas} (449)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (2050)	N_{cas} (496)	OR (95% CI)*	OR (95% CI)†
Never exposed-chlorinated solvents	403	1398	372	1	1	1158	335	1	1	1542	365	1	1
Chlorinated alkenes													
Any exposure	25	100	17	0.8 (0.4–1.5)	0.7 (0.4–1.2)	71	23	1.3 (0.7–2.3)	1.2 (0.7–2.1)	95	27	1.2 (0.7–2.2)	1.2 (0.7–2.0)
Substantial exposure	14	46	8	0.6 (0.2–1.5)	0.6 (0.3–1.4)	29	14	1.3 (0.6–3.0)	1.5 (0.8–3.1)	47	12	1.0 (0.4–2.1)	1.0 (0.5–2.0)
Perchloroethylene													
Any exposure	4	32	2	0.5 (0.1–3.0)	0.3 (0.1–1.4)	17	9	2.9 (0.8–9.9)	2.2 (0.8–5.7)	26	7	2.3 (0.7–8.3)	1.5 (0.6–4.1)
Substantial exposure	2	20	2	0.9 (0.1–7.3)	0.5 (0.1–2.5)	9	9	**6.0 (1.2–30)**	**4.3 (1.4–13)**	21	3	1.8 (0.3–11)	0.9 (0.2–3.7)
Trichloroethylene													
Any exposure	15	57	10	0.7 (0.3–1.7)	0.7 (0.3–1.4)	42	14	1.3 (0.6–2.8)	1.3 (0.7–2.6)	56	14	1.0 (0.5–2.2)	1.0 (0.5–2.0)
Substantial exposure	9	30	5	0.6 (0.2–1.7)	0.6 (0.2–1.5)	21	7	1.1 (0.4–3.1)	1.2 (0.5–3.1)	30	9	1.1 (0.4–2.9)	1.2 (0.5–2.7)
Chlorinated alkanes													
Any exposure	66	190	48	0.7 (0.5–1.1)	0.8 (0.6–1.2)	155	50	1.0 (0.6–1.5)	1.1 (0.8–1.6)	205	46	0.8 (0.5–1.1)	0.9 (0.6–1.2)
Substantial exposure	34	73	21	0.6 (0.3–1.1)	0.8 (0.5–1.4)	68	18	0.7 (0.4–1.3)	0.8 (0.5–1.4)	85	21	0.7 (0.4–1.2)	0.8 (0.5–1.4)
1,1,1-trichloroethane													
Any exposure	10	21	5	0.6 (0.2–1.8)	0.7 (0.2–1.9)	19	5	0.7 (0.2–2.1)	0.8 (0.3–2.4)	28	5	0.6 (0.2–1.7)	0.6 (0.2–1.7)
Substantial exposure	6	14	3	0.5 (0.1–2.2)	0.6 (0.2–2.4)	12	5	1.3 (0.4–4.6)	1.6 (0.5–5.1)	18	4	0.7 (0.2–2.7)	0.8 (0.3–2.6)
Carbon tetrachloride													
Any exposure	28	88	21	0.8 (0.5–1.5)	0.8 (0.5–1.4)	73	25	1.1 (0.6–2.0)	1.2 (0.7–2.0)	88	27	1.0 (0.6–1.8)	1.2 (0.7–1.9)
Substantial exposure	11	28	13	1.3 (0.6–3.1)	1.5 (0.7–3.0)	31	11	1.3 (0.6–3.1)	1.3 (0.6–2.8)	38	12	1.1 (0.5–2.5)	1.2 (0.6–2.5)
Chloroform													
Any exposure	5	15	3	0.6 (0.1–2.5)	0.7 (0.2–2.4)	8	6	2.3 (0.7–8.4)	2.9 (0.9–8.9)	16	2	0.4 (0.1–2.4)	0.5 (0.1–2.3)
Substantial exposure	1	5	1	1.4 (0.1–23)	1.0 (0.1–10)	4	1	4.5 (0.3–76)	2.5 (0.2–29)	5	1	1.5 (0.1–25)	1.1 (0.1–12)
Methylene chloride													
Any exposure	12	36	9	0.7 (0.3–1.8)	0.8 (0.3–1.8)	24	10	0.9 (0.4–2.3)	1.2 (0.5–2.7)	41	7	0.7 (0.3–1.9)	0.7 (0.3–1.7)
Substantial exposure	4	14	3	0.6 (0.1–3.1)	0.8 (0.2–3.0)	8	1	0.3 (0.0–3.4)	0.5 (0.1–4.0)	11	3	1.0 (0.2–4.4)	1.0 (0.3–3.9)

(*continues*)

TABLE 3. (*Continued*)

		Stomach Cancer				Rectum Cancer				Non-Hodgkin's Lymphoma			
		N_{cacon} (2279)	N_{cas} (251)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (1295)	N_{cas} (248)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (2341)	N_{cas} (215)	OR (95% CI)*	OR (95% CI)†
Never exposed-chlorinated solvents	403	1710	195	1	1	974	192	1		1775	155	1	1
Chlorinated alkenes													
Any exposure	25	112	8	0.8 (0.3–1.8)	0.7 (0.3–1.5)	68	16	1.4 (0.7–2.7)	1.3 (0.7–2.3)	105	14	1.6 (0.8–3.3)	1.5 (0.8–2.9)
Substantial exposure	14	53	3	0.5 (0.1–1.8)	0.5 (0.1–1.7)	32	4	0.6 (0.2–1.9)	0.6 (0.2–1.8)	50	4	0.8 (0.2–2.5)	0.8 (0.3–2.5)
Perchloroethylene													
Any exposure	4	28	4	2.2 (0.5–9.3)	1.5 (0.5–5.0)	19	4	2.1 (0.5–8.7)	1.5 (0.5–5.0)	28	3	2.2 (0.5–10)	1.7 (0.5–6.2)
Substantial exposure	2	22	2	2.1 (0.3–17)	1.0 (0.2–5.1)	15	1	1.1 (0.1–13)	0.6 (0.1–4.8)	21	2	2.6 (0.4–19)	1.7 (0.3–8.5)
Trichloroethylene													
Any exposure	15	67	4	0.6 (0.2–2.1)	0.6 (0.2–1.8)	37	13	1.8 (0.8–4.0)	1.8 (0.9–3.6)	65	7	1.3 (0.5–3.4)	1.2 (0.5–2.9)
Substantial exposure	9	34	2	0.5 (0.1–2.5)	0.5 (0.1–2.4)	18	3	0.7 (0.2–2.6)	0.7 (0.2–2.6)	30	3	0.9 (0.2–3.4)	1.0 (0.3–3.5)
Chlorinated alkanes													
Any exposure	66	229	25	0.8 (0.5–1.3)	0.9 (0.6–1.4)	141	31	1.0 (0.6–1.6)	1.0 (0.7–1.6)	233	20	0.7 (0.4–1.3)	0.9 (0.5–1.4)
Substantial exposure	34	99	8	0.5 (0.2–1.1)	0.6 (0.3–1.3)	59	11	0.7 (0.3–1.4)	0.8 (0.4–1.5)	96	10	0.8 (0.4–1.7)	1.0 (0.5–1.9)
1,1,1-Trichloroethane													
Any exposure	10	27	4	1.1 (0.3–3.8)	1.2 (0.4–3.8)	25	2	0.4 (0.1–2.0)	0.4 (0.1–1.8)	29	5	1.2 (0.4–4.0)	1.5 (0.5–4.3)
Substantial exposure	6	19	2	0.8 (0.2–4.3)	0.9 (0.2–4.4)	16	2	0.6 (0.1–3.3)	0.6 (0.1–3.0)	21	2	0.8 (0.1–4.0)	0.9 (0.2–4.2)
Carbon tetrachloride													
Any exposure	28	115	5	0.5 (0.2–1.3)	0.5 (0.2–1.2)	58	19	1.5 (0.8–2.8)	1.6 (0.9–2.8)	110	6	0.6 (0.3–1.6)	0.6 (0.3–1.5)
Substantial exposure	11	50	0	. . .	. . .	23	3	0.6 (0.2–2.2)	0.6 (0.2–2.2)	45	2	0.6 (0.1–3.0)	0.6 (0.1–2.5)
Chloroform													
Any exposure	5	18	2	0.7 (0.1–4.2)	1.0 (0.2–4.7)	11	4	1.7 (0.4–6.5)	1.8 (0.5–6.2)	19	1	0.4 (0.0–3.5)	0.5 (0.1–3.9)
Substantial exposure	1	7	0		. . .	3	2	4.5 (0.4–52)	4.0 (0.5–31)	7	0		. . .
Methylene chloride													
Any exposure	12	45	4	0.6 (0.2–2.1)	0.7 (0.2–2.0)	30	7	1.3 (0.5–3.4)	1.2 (0.5–2.9)	47	3	0.6 (0.1–2.1)	0.6 (0.2–2.2)
Substantial exposure	4	14	1	0.4 (0.0–3.9)	0.5 (0.1–4.2)	7	5	2.6 (0.7–10)	2.7 (0.8–9.3)	17	0		

(*continues*)

TABLE 3. (*Continued*)

		Kidney Cancer				Melanoma				Pancreas Cancer			
		N_{cacon} (1999)	N_{cas} (177)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (2525)	N_{cas} (103)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (2448)	N_{cas} (116)	OR (95% CI)*	OR (95% CI)†
Never exposed-chlorinated solvents	403	1497	134	1	1	1895	69	1	1	1834	95	1	1
Chlorinated alkenes													
Any exposure	25	103	9	1.1 (0.5–2.5)	1.0 (0.5–2.1)	120	9	**2.3 (1.0–5.7)**	1.9 (0.9–4.2)	115	3	0.8 (0.2–3.0)	0.7 (0.2–2.4)
Substantial exposure	14	50	4	0.9 (0.3–2.8)	0.9 (0.3–2.5)	51	6	2.8 (0.9–8.5)	**2.6 (1.0–7.1)**	55	0	. . .	. . .
Perchloroethylene													
Any exposure	4	31	2	1.6 (0.3–9.4)	1.0 (0.2–4.5)	32	2	3.4 (0.5–22)	2.8 (0.6–14)	30	0	. . .	. . .
Substantial exposure	2	20	2	3.1 (0.4–24)	1.6 (0.3–8.1)	22	1	2.6 (0.2–33)	2.2 (0.2–19)	22	0	. . .	. . .
Trichloroethylene													
Any exposure	15	63	5	1.0 (0.3–2.9)	0.9 (0.4–2.4)	68	8	**4.0 (1.5–11)**	**3.0 (1.2–7.2)**	69	2	1.0 (0.2–4.9)	0.8 (0.2–3.6)
Substantial exposure	9	34	2	0.7 (0.1–3.2)	0.6 (0.1–2.8)	32	5	**4.0 (1.1–14)**	**3.2 (1.0–9.9)**	36	0	. . .	. . .
Chlorinated alkanes													
Any exposure	66	194	20	0.9 (0.5–1.5)	1.0 (0.6–1.7)	258	11	0.9 (0.4–2.0)	1.0 (0.5–2.0)	255	8	0.5 (0.2–1.1)	0.6 (0.3–1.3)
Substantial exposure	34	76	12	1.1 (0.5–2.2)	1.3 (0.7–2.6)	110	3	0.5 (0.2–1.9)	0.6 (0.2–1.9)	103	6	0.6 (0.2–1.5)	0.8 (0.3–2.1)
1,1,1-Trichloroethane													
Any exposure	10	26	4	1.1 (0.3–3.7)	1.3 (0.4–4.0)	31	2	0.9 (0.2–4.5)	0.9 (0.2–4.3)	31	1	0.6 (0.1–5.7)	0.8 (0.1–6.0)
Substantial exposure	6	19	3	1.2 (0.3–5.0)	1.5 (0.4–5.3)	21	1	0.5 (0.1–4.8)	0.6 (0.1–5.3)	20	1	0.8 (0.1–7.5)	1.1 (0.1–8.8)
Carbon tetrachloride													
Any exposure	28	90	9	1.0 (0.4–2.1)	1.0 (0.5–2.2)	117	7	1.7 (0.7–4.3)	1.6 (0.7–3.8)	121	3	0.5 (0.1–1.9)	0.6 (0.2–2.0)
Substantial exposure	11	31	5	1.3 (0.4–4.0)	1.6 (0.6–4.4)	50	1	0.5 (0.1–4.2)	0.5 (0.1–4.1)	50	1	0.3 (0.0–2.7)	0.4 (0.0–3.1)
Chloroform													
Any exposure	5	14	1	0.5 (0.1–4.8)	0.7 (0.1–5.3)	19	1	0.5 (0.0–4.4)	0.6 (0.1–5.2)	18	2	1.7 (0.2–12)	2.3 (0.4–12)
Substantial exposure	1	5	0			6	1	3.0 (0.2–50)	2.1 (0.2–25)	5	2	9.9 (0.7–148)	**10.6 (1.2–93)**
Methylene chloride													
Any exposure	12	38	6	1.5 (0.5–4.2)	1.6 (0.6–4.0)	51	2	1.2 (0.2–6.1)	1.2 (0.3–5.3)	51	0	. . .	. . .
Substantial exposure	4	12	2	1.6 (0.3–9.3)	1.7 (0.3–8.3)	17	1	2.1 (0.2–20)	1.6 (0.2–14)	17	0	. . .	. . .

(*continues*)

TABLE 3. (*Continued*)

		Esophagus Cancer				Liver Cancer			
		N_{cacon} (2299)	N_{cas} (99)	OR (95% CI)*	OR (95% CI)†	N_{cacon} (1834)	N_{cas} (33)	OR (95% CI)*	OR (95% CI)†
Never exposed-chlorinated solvents	403	1711	75	1	1	1834	33	1	1
Chlorinated alkenes									
Any exposure	25	120	1	0.4 (0.0–3.0)	0.3 (0.0–2.0)	123	2	1.4 (0.3–7.7)	1.4 (0.3–6.3)
Substantial exposure	14	53	1	0.7 (0.1–5.3)	0.5 (0.1–4.1)	58	2	2.6 (0.4–15)	2.7 (0.6–13)
Perchloroethylene									
Any exposure	4	30	0	. . .	. . .	35	1	3.3 (0.2–60)	2.8 (0.3–25)
Substantial exposure	2	21	0	. . .	. . .	23	1	4.4 (0.2–103)	3.9 (0.4–38)
Trichloroethylene									
Any exposure	15	71	1	0.5 (0.1–4.3)	0.4 (0.1–3.4)	72	1	1.1 (0.1–11)	1.1 (0.1–8.5)
Substantial exposure	9	34	1	0.9 (0.1–7.7)	0.9 (0.1–6.7)	38	1	2.5 (0.3–25)	2.1 (0.2–18)
Chlorinated alkanes									
Any exposure	66	236	9	0.7 (0.3–1.6)	0.8 (0.4–1.7)	259	2	0.3 (0.1–1.4)	0.4 (0.1–1.9)
Substantial exposure	34	103	2	0.4 (0.1–1.7)	0.4 (0.1–1.8)	104	1	0.3 (0.0–2.5)	0.5 (0.1–3.6)
1,1,1-Trichloroethane									
Any exposure	10	27	2	1.4 (0.3–7.5)	1.9 (0.4–8.7)	31	1	1.8 (0.2–17)	2.3 (0.3–19)
Substantial exposure	6	19	1	1.1 (0.1–10)	1.4 (0.2–12)	21	1	2.2 (0.2–22)	3.2 (0.4–28)
Carbon tetrachloride									
Any exposure	28	116	4	0.7 (0.2–2.4)	0.9 (0.3–2.5)	119	0	. . .	. . .
Substantial exposure	11	50	1	0.6 (0.1–5.1)	0.6 (0.1–4.5)	46	0	. . .	. . .
Chloroform									
Any exposure	5	18	0	. . .	. . .	19	0	. . .	. . .
Substantial exposure	1	7	0	. . .	. . .	5	0	. . .	. . .
Methylene chloride									
Any exposure	12	47	2	1.4 (0.3–6.6)	0.9 (0.2–4.2)	54	1	0.7 (0.1–8.1)	1.0 (0.1–9.4)
Substantial exposure	4	16	1	2.4 (0.2–24)	1.7 (0.2–15)	20	0	. . .	. . .

* Odd ratios and 95% confidence intervals from logistic regression analyses adjusted by age, census tract median income, educational attainment (years), ethnicity (French Canadian vs others), questionnaire respondent (self vs proxy), smoking (cigarettes-years) using only population controls. For some specific cancer sites, we included further adjustment: BLADDER: coffee intake, aromatic amines exposure; PROSTATE, COLON, STOMACH AND LIVER: beer, wine, and spirit intake, RECTUM: beer intake; PANCREAS AND KIDNEY: coffee, beer, wine, and spirit intake; ESOPHAGUS: coffee, tea, beer, wine, and spirit intake.

† Same models using population and cancer controls weighting proportionately (N_{pcon} (533) /N_{cacon}).

CI, confidence interval; N_{pcon}, number of population controls; N_{cacon}, number of cancer controls; N_{cas}, number of cases; OR, odds ratio.

because of small numbers. Lung cancer will be evaluated in a separate analysis. Tongue and cervical cancers were not included in the list of selected cancers in the design. To our knowledge, no previous study has reported an association between PERC and prostate cancer. For TCE, there have been scattered reports of associations with non-Hodgkin's lymphoma,[34] stomach, liver, prostate, and lymphohematopoietic system[12] with the strongest evidence for kidney cancer.[15,16] Among those exposed to TCE in this study population, there was a suggestive, but not significant, association with kidney cancer, which has been the most plausible target organ for TCE carcinogenesis in previous research.[7,14,16,35] An association between TCE and melanoma, such as we found, has not been reported in any previous study, and a previous study even found a protective association.[13] We found little indication of excess risk for other sites of cancer and chlorinated solvents. Of the studies evaluating exposure to various chlorinated alkanes, there have been reports of associations between the following exposures and cancer sites: 1,1,1-trichloroethane and multiple myeloma and the nervous system,[12] methylene chloride and liver and biliary tract cancer,[19] carbon tetrachloride and lymphosarcomas, lymphatic leukemia,[36,37] and non-Hodgkin's lymphoma.[18] We did not evaluate cancers of the nervous system or multiple myeloma and found no effect of methylene chloride exposure on risk of liver cancer or carbon tetrachloride exposure on risk of non-Hodgkin's lymphoma. In contrasting our findings with previous research, it is important to note that because we included exposures across a wide spectrum of occupations and industries, the average concentration of exposure was likely much lower in this study base than in that of cohort studies that focused on particular high-exposure industries. On the contrary, the exposures to chlorinated solvents among cases and controls took place mainly in the period 1940 to 1970, when the use of these substances was increasing and before some of them were substituted by other chemicals.[2–4]

There were both strengths and limitations to this analysis. In terms of exposure assessment, we did not have quantitative measurements of personal exposure to each solvent. Nevertheless, we did have semiquantitative exposure information, based on expert assessment after detailed interviews regarding occupational history, using an approach that has been shown to have good reliability.[31,38] and validity.[29,39,40] Using our exposure data, we were able to estimate temporal trends and industry and occupation-specific profiles that provided a portrait of chlorinated solvents exposure that is compatible with the available literature.[2–4,41] Subjects reported their job histories and job descriptions to interviewers specially trained and supervised in the conduct of occupation history interviews, and the resulting responses were filtered through a team of experts blinded to the disease status of the subjects. Thus, although there surely was some degree of error in the retrospective exposure assessment, such misclassification would likely have been nondifferential between cases and population controls, and certainly between cases and cancer controls. This is indeed one of the advantages of using cancer controls. To the extent that there was exposure misclassification, it would have biased OR estimates to the null. Although the study population was quite large, because of the low prevalence of exposure to chlorinated solvents and rarity of certain types of cancer, we could not investigate some associations, particularly when stratifying by level of exposure. As in any observational epidemiology study, there could be confounding by unmeasured risk factors or residual confounding by measured risk factors. In this analysis, which covered 11 different types of cancer and several different agents, it is inconceivable that one or a small number of covariates could lead to massive bias across all the associations studied. This is particularly true in our situation for a few reasons. The different sites of cancer likely have very distinct sets of risk factors. The factor that has the best chance of affecting multiple sites is smoking. Smoking was well measured and, we believe, well controlled, by the inclusion of cigarette-years. Furthermore, some of the sites in this analysis have not been shown to be associated with smoking and none of the others are among sites with very strong smoking associations, thereby diminishing any possibility of residual confounding. Smoking patterns among the subjects between different cancer sites were relatively similar, further reducing the possibility of residual confounding when we use cancer controls. Finally, the exposures of interest are agents that were attributed to subsets of workers in varying occupations and industries, and it is not likely that personal or lifestyle characteristics would differ greatly according to exposure to solvents. If there is widespread confounding by other factors, it is likely that these would be occupational exposures. But even this is not very likely, because of the fact that the exposures to solvents occurred in so many different types of occupational environments, and the fact that the putative occupational confounder would have to be a risk factor for multiple cancer sites. Additional strengths of the study are the inclusion of incident and histologically confirmed cancer cases and the availability of cancer and population control groups. In addition, all those groups had high response rates. By contrast with most cohort studies conducted in the past, we were able to control for many potentially important confounders in our analyses. Finally, approximately two-thirds of the study participants were of French Canadian origin, which limits the potential for confounding by variation in genetic and social characteristics.

CONCLUSION

We found that among persons participating in the Montreal case–control studies, there was little evidence that exposure to chlorinated solvents was associated with increased risk of 11 types of cancer. The main exceptions to this general finding were possible associations between PERC and prostate cancer and between melanoma and TCE, but neither of these is supported by other research in the literature. Nevertheless, limited power precludes strong inferences about absence of risk.

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