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Occupational solvent exposure and adult chronic lymphocytic leukemia: No risk in a population-based case–control study in four Nordic countries

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The aim of this study was to assess the effect of occupational solvent exposure on the risk of adult chronic lymphocytic leukemia (CLL). The current case–control study was nested in the Nordic Occupational Cancer Study (NOCCA) cohort. 20,615 CLL cases diagnosed in 1961–2005 in Finland, Iceland, Norway, and Sweden, and 103,075 population-based controls matched by year of birth, sex, and country were included. Occupational histories for cases and controls were obtained from census records in 1960, 1970, 1980/1981, and 1990. Exposure to selected solvents was estimated by using the NOCCA job-exposure matrix (NOCCA-JEM). Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by using conditional logistic regression models. Overall, nonsignificant CLL risk elevations were observed for methylene chloride, perchloroethylene, and 1,1,1-trichloroethane. Compared to unexposed, significantly increased risks were observed for cumulative perchloroethylene exposure ≤13.3 ppm-years (OR = 1.85, 95% CI 1.16–2.96) and average life-time perchloroethylene exposure ≤2.5 ppm (1.61, 95% CI 1.01–2.56) among women, and cumulative methylene chloride exposure ≤12.5 ppm-years (OR = 1.19, 95% CI 1.01–1.41) and 12.5–74.8 ppm-years (OR = 1.23, 95% CI 1.01–1.51) among men in an analysis with 5 years lag-time, though without dose–response pattern. Decreased CLL risk was observed for aliphatic and alicyclic hydrocarbon solvents and toluene. This study did not support associations for solvent exposure and CLL. Observed weak associations for methylene chloride, perchloroethylene, 1,1,1-trichloroethane exposures, aliphatic and alicyclic hydrocarbons and toluene were not consistent across sexes, and showed no gradient with amount of exposure.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are two subtypes of non-Hodgkin lymphoma that affect B-cell lymphocytes.[1] They are essentially the same diseases, with the only difference being the location where they primarily occur. In CLL, most of the cancer cells are located in bloodstream and bone marrow, while in SLL, mostly lymph nodes are affected.[1]

Key words: chronic lymphocytic leukemia, solvent, case–control study, Nordic Occupational Cancer Study, job-exposure matrix
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CLL is the most common type of leukemia among adults in the Nordic countries. Its incidence is considerably higher in males than in females, and median age at diagnosis is about 72 years.[2]

The causes of CLL are poorly understood. Studies have suggested associations with smoking,[3,4] immune dysfunctions and infections,[5–7] familial history of CLL and other hematological malignancies[6,8] and adult height.[6] There is a weak evidence for modestly elevated CLL risk for power-line frequency electromagnetic field exposure.[9–12] Some studies reported associations with formaldehyde.[13,14] Farm work, farming-related exposures[6,15] and professional hairdressers[6] have also been linked to an increased CLL risk. There is also accumulating evidence on association between ionizing radiation and CLL.[16,17]

Evidence on the role of solvents in the development of CLL is limited and inconsistent. Some studies observed associations with toluene,[18] styrene and butadiene[19–21] and

What's new?

Exposure to organic solvents is associated with various negative health effects, including increased risk of certain blood cancers. Adult chronic lymphocytic leukemia (CLL) is potentially ranked among those malignancies, as causes for CLL remain poorly understood. In this population-based investigation of CLL patients in the Nordic Occupational Cancer Study cohort, nonsignificant increases in CLL risk were detected for exposure to methylene chloride, perchloroethylene and 1,1,1-trichloroethane. Relative to unexposed individuals, cumulative perchloroethylene exposure was linked to significantly increased CLL risk. Nonetheless, the absence of a dose–response pattern and inconsistent findings across sexes suggest that solvent exposure is unrelated to CLL.

ethylene oxide.[22,23] A nonsignificantly excess risk of CLL was reported for benzene in a study of Australian petroleum industry workers,[24] Italian multicenter case–control study[18] and in a meta-analysis.[25] Nonsignificant risk of CLL/SLL was observed for trichloroethylene in a meta-analysis of cohort and case–control studies,[26] and high levels of trichloroethylene exposure was significantly associated with increased risk of SLL/CLL in a case–control study by Purdue *et al.*[27] A population-based case–control study in the San Francisco Bay Area did not show association between CLL/SLL and occupational solvent exposure.[28]

It is suspected that immune system dysregulation may be responsible for CLL development. Some studies linked solvent exposure with impaired immune functioning[29,30] and it is possible that solvents may influence CLL development on this basis.[31]

The aim of this study was to assess associations of adult chronic lymphocytic leukemia with selected organic solvents.

Methods

This study employed case–control design nested within the Nordic Occupational Cancer Studies (NOCCA) cohort. The NOCCA cohort includes 14.9 million persons from Finland, Iceland, Norway, Sweden and Denmark who participated in one or more population censuses in 1960, 1970, 1980/1981 and/or 1990.[32] Data from Denmark were not included in this study because we did not have an access to individual level data from this country.

All incident cases of adult CLL diagnosed between 1961 and 2005 in Finland, Iceland, Norway and Sweden—who did not have a previous history of cancer—were included in this study. Five controls per each case, who were alive and did not have a history of cancer prior to the date of diagnosis of the case (hereafter "index date"), were randomly selected from the NOCCA cohort. Cases and controls were matched by country, sex and year of birth. Study participants were 20 years or older at index date, and had at least one census record before that date.

Information on occupation was available from computerized census records from 1960, 1970, 1980 and 1990 censuses in Sweden; 1960, 1970 and 1980 censuses in Norway; 1970, 1980 and 1990 censuses in Finland; 1981 census in Iceland. Census questionnaires were self-administered and included questions related to economic activity, occupation and industry. In Finland, Norway and Sweden, they were filled in by the heads of households for all members of households, whereas each member of the household, who was at least 17 years old, personally filled in a questionnaire in Iceland.

Occupations in Finland, Norway and Sweden were coded according to the Nordic Occupational Classification (NYK),[33] a Nordic adaptation of the International Standard of Classification of Occupations (ISCO) from 1958.[34] In Iceland, a national adaptation of the ISCO-68[35] was originally used for occupational coding. Icelandic codes were also converted to ISCO-58 to homogenize occupational coding system in all Nordic countries.

Occupational solvent exposure estimates for each study participant were assigned by using the NOCCA job-exposure matrix (NOCCA-JEM). The NOCCA-JEM was developed by a Nordic expert panel, including experts from each of country based on the template of the Finnish job-exposure matrix (FINJEM).[36] It provides information on annual average (L) and prevalence of exposure (P) to 28 chemical and nonchemical agents for >300 specific occupational groups in four time periods: 1945–1959, 1960–1974, 1975–1984 and 1985–1994. By linking occupational codes to NOCCA-JEM, we assigned P and L solvent exposure estimates to each study participant. The number of P and L values assigned to each person corresponded to the number of occupational codes he/she had during employment career.

In this study, we assessed six individual solvents—benzene, methylene chloride, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane and toluene—and two grouped solvents—aliphatic and alicyclic hydrocarbon solvents and other organic solvents.

Employment period for each study participant was assumed to start at an age of 20 years and end at either 65 years or index date, whichever came first. Exposure duration was equal to the number of years a person was in an exposed occupation during employment period. If a person had different occupations in different censuses, we assumed that he/she changed an occupation in the middle of known census years. For the employment periods before 1945 and after 1994, we assumed that average exposure and exposure prevalence was the same as in 1945–1959 and 1985–1994, respectively.

We used three exposure metrics for each solvent: cumulative exposure, average life-time exposure and peak annual exposure. Cumulative exposures were calculated as a product of prevalence, annual average and duration of exposure. Average life-time exposures were estimated by averaging sum of annual exposures over employment period by duration of employment. The highest annual average exposure estimate during entire employment period was selected as a peak annual exposure for each study participant.

We estimated odds ratios (OR) and 95% confidence intervals (95% CI) by using conditional logistic regression models. All exposures of interest and co-factors were categorized using 50^{th} and 90^{th} percentiles of exposure distribution among exposed controls as cut-points. Hence, the resulting exposure categories were: unexposed, $\leq 50^{th}$ percentile, 50^{th}–90^{th} and $>90^{th}$ percentile. Unexposed categories were used as a reference in all analyses. We treated these exposure variables as continuous to test for dose–response relationship between exposure and CLL.

Selection of variables for the final main effect models were based on the "purposeful covariate selection" method.[37] The final main effect models included solvents as the main variables of interest, and formaldehyde and ionizing radiation exposure because they significantly contributed to the fit of the models. Because aliphatic and alicyclic hydrocarbons, toluene and benzene were highly correlated, we included them into separate models. The main results are presented as overall and sex-specific results for all exposure metrics.

Finally, we performed a series of sensitivity analysis to evaluate robustness of the main findings. These included analyses with 5, 10, and 20 years lag-time, analysis with tertile categorizations, and analyses excluding Icelandic data and economically inactive persons. The lag-time analyses were performed under the assumption that CLL may develop over a number of years and recent exposures may not have an effect on disease risk. Therefore, in 5, 10 and 20 years lag-time analyses, we did not count exposures occurring during 5, 10 and 20 years before the index date, respectively. We excluded Icelandic data ($n = 118$ cases and $n = 590$ controls) from these subanalyses because occupational information in this country was available from a single census in 1981. We also conducted sensitivity analysis excluding economically inactive persons, because the main analysis included 9,678 (7.8%) persons who were economically inactive.

Results

Overall, 20,615 CLL cases and 103,075 matched controls were included in this study. Of the CLL cases, 60.1% were
T1 males and 39.9% females (Table 1). Mean age at diagnosis was 70 years (median 71 years, standard deviation 10 years), and about 80% of study participants were born before 1930. The majority of study participants were from Sweden (57%), about 21% from Finland and Norway, respectively, and <1% from Iceland.

Table 1. Demographic characteristics of chronic lymphocytic leukemia cases and controls

	Cases		Controls	
Characteristic	*n*	%	*n*	%
Sex				
Male	12,393	60.1	61,965	60.1
Female	8,222	39.9	41,110	39.9
Country				
Finland	4,353	21.1	21,765	21.1
Iceland	118	0.6	590	0.6
Norway	4,346	21.1	21,730	21.1
Sweden	11,798	57.2	58,990	57.2
Age at index[1]				
<39	63	0.3	320	0.3
40–49	638	3.1	3,198	3.1
50–59	2,553	12.4	12,740	12.4
60–69	5,542	26.9	27,687	26.9
70–79	7,397	35.8	36,924	35.8
≥80	4,422	21.5	22,206	21.5
Year of birth				
≤1920	11,491	55.7	57,455	55.7
1921–1930	4,990	24.2	24,950	24.2
1931–1940	2,526	12.3	12,630	12.3
1941–1950	1,347	6.5	6,735	6.5
1951–1960	261	1.3	1,305	1.3
Total	20,615	100.0	103,075	100.0

[1]Index date is defined as the date of diagnosis of case for both case and its matched controls.

High exposure levels were more common among men than women for most solvent types. For example, about 5% of men and only <0.5% of women were exposed to cumulative benzene exposure >4.55 parts per million years (ppm-years) (Table 2). T2

Analysis of cumulative exposures showed small, nonsignificantly increased overall risks for some strata of methylene chloride, other organic solvents and 1,1,1-trichloroethane exposure (Table 2). Significantly increased risk was observed for perchloroethylene exposure ≤13.3 ppm-years (OR = 1.85, 95% CI 1.16–2.96) among women. Significantly decreasing risk with increasing exposure was observed for aliphatic and alicyclic hydrocarbons and toluene (Table 2).

We did not observe associations between CLL and peak annual exposure (Supporting Information Table S1), and average life-time exposure (Supporting Information Table S2). The only significantly increased risk was observed for average life-time perchloroethylene exposure ≤2.5 ppm (OR = 1.61, 95% CI 1.01–2.56) among women (Supporting Information Table S2).

In a sensitivity analysis with a 5 years lag-time, significantly increased risks were found for cumulative methylene

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Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for cumulative solvent exposure[1] and chronic lymphocytic leukemia

Agent (ppm-years)[2,3]	Male					Female					Total				
	Cases	Controls	OR	95% CI	p trend[7]	Cases	Controls	OR	95% CI	p trend[7]	Cases	Controls	OR	95% CI	p trend[7]
Solvents															
Benzene[4]															
≤4.55	500	2,523	0.92	0.79–1.06		118	589	1.15	0.90–1.46		618	3,112	0.97	0.86–1.09	
4.55–14.8	424	2,303	0.86	0.73–1.01		28	186	0.78	0.51–1.20		452	2,489	0.89	0.77–1.02	
>14.8	123	602	0.94	0.74–1.19	0.16	3	21	0.79	0.22–2.85	0.42	126	623	0.98	0.78–1.22	0.19
Methylene chloride[4]															
≤12.5	477	2,469	1.11	0.93–1.31		39	240	0.66	0.43–1.03		516	2,709	1.04	0.89–1.21	
12.5–74.8	415	1,933	1.16	0.96–1.42		27	179	0.71	0.43–1.16		442	2,112	1.09	0.92–1.30	
>74.8	82	529	0.78	0.54–1.12	0.43	3	7	2.96	0.61–14.4	0.75	85	536	0.79	0.56–1.11	0.46
Other organic solvents[4]															
≤95.2	184	1,045	0.88	0.73–1.05		48	211	1.36	0.95–1.95		232	1,256	0.94	0.79–1.09	
95.2–378	184	936	1.05	0.83–1.32		10	68	0.75	0.35–1.64		194	1,004	1.02	0.82–1.26	
>378	43	234	1.17	0.78–1.76	0.98	3	18	1.06	0.29–3.89	0.59	46	252	1.10	0.75–1.62	0.89
Perchloroethylene[4]															
≤13.3	97	554	0.93	0.73–1.17		39	180	1.87	1.17–2.98		136	734	1.03	0.84–1.27	
13.3–99.8	76	366	1.11	0.85–1.44		35	220	1.04	0.64–1.68		111	586	1.02	0.82–1.26	
>99.8	5	42	0.65	0.25–1.69	0.69	23	105	1.24	0.61–2.53	0.38	28	147	1.00	0.64–1.57	0.99
Trichloroethylene[4]															
≤20	434	2,414	0.92	0.79–1.05		83	545	0.62	0.40–0.94		517	2,959	0.87	0.77–0.99	
20–125	407	2,085	0.97	0.84–1.12		39	232	0.69	0.41–1.16		446	2,317	0.95	0.83–1.09	
>125	90	455	0.99	0.78–1.27	0.17	27	131	0.78	0.39–1.53	0.46	117	586	0.99	0.78–1.24	0.16
1,1,1-trichloroethane[4]															
≤5.6	884	4,618	0.99	0.86–1.13		96	560	1.11	0.76–1.62		980	5,178	0.99	0.88–1.13	
5.6–12.9	352	1,911	0.95	0.81–1.12		41	259	1.19	0.73–1.96		393	2,170	0.96	0.82–1.14	
>12.9	180	756	1.18	0.95–1.45	0.39	6	59	0.70	0.28–1.75	0.19	186	815	1.16	0.95–1.42	0.77
Toluene[5]															
≤55.4	544	2,783	0.90	0.78–1.04		62	358	0.91	0.68–1.20		606	3,141	0.92	0.81–1.04	
55.4–706	464	2,352	0.86	0.73–1.01		18	161	0.65	0.37–1.14		482	2,513	0.87	0.75–1.00	
>706	96	606	0.63	0.39–0.99	0.05	5	21	0.81	0.15–4.40	0.07	101	627	0.65	0.42–1.01	0.02

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for cumulative solvent exposure and chronic lymphocytic leukemia (Continued)

Agent (ppm-years)[2,3]	Male					Female					Total				
	Cases	Controls	OR	95% CI	p trend[7]	Cases	Controls	OR	95% CI	p trend[7]	Cases	Controls	OR	95% CI	p trend[7]
Aliphatic and alicyclic hydrocarbon solvents[6]															
≤19.9	528	2,662	0.87	0.72–1.06		31	213	0.76	0.50–1.14		559	2,875	0.89	0.75–1.04	
19.9–340	369	1,890	0.81	0.65–1.00		70	409	0.83	0.52–1.32		439	2,299	0.81	0.68–0.97	
>340	80	535	0.63	0.44–0.92	0.01	3	40	0.36	0.09–1.41	0.02	83	575	0.61	0.43–0.86	<0.01

[1] 50th and 90th percentiles of exposure distribution among exposed controls used as cut-points.
[2] Occupationally unexposed were used as a reference category.
[3] ppm-years, parts per million.
[4] Results from model including benzene, methylene chloride, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, formaldehyde and ionizing radiation.
[5] Results from model including toluene, methylene chloride, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, formaldehyde and ionizing radiation.
[6] Results from model including aliphatic and alicyclic hydrocarbons, methylene chloride, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, formaldehyde and ionizing radiation.
[7] *p* trend: test for linear trend was performed by using categorical exposures as continuous variables.

chloride ≤12.5 ppm-years (1.19, 95% CI 1.01–1.41) and 12.5–74.8 ppm-years (OR = 1.23, 95% CI 1.01–1.51) among men, and for cumulative perchloroethylene ≤13.3 ppm-years (1.68, 95% CI 1.05–2.67) among women. In an analysis with 10 years lag-time, significantly increased risks were seen for cumulative other organic solvents ≤95.2 ppm-years (OR = 1.45, 95% CI 1.02–2.06) and cumulative perchloroethylene ≤13.3 ppm-years (OR = 1.81, 95% 1.14–2.89) among women. Odds ratio for the low categories of methylene chloride among men and other organic solvents among women was significantly increased also in an analysis with 20 years lag-time. Small nonsignificant risk elevations were observed for 1,1,1-trichloroethane in both 5 and 10 years lag-time analyses. The model with 5 years lag-time had a better fit than the model with 20 years lag-time when Akaike information criteria (AIC) were compared. Analysis with tertile categorization of cumulative exposures yielded significantly increased risk for methylene chloride > 15.9 ppm-years (OR = 1.28, 95% CI 1.02–1.59) among men, and nonsignificantly increased odds ratios for other organic solvents, perchloroethylene and 1,1,1-trichloroethane among females. There was no dose–response pattern of the risk estimates in sensitivity analyses. Exclusion of Iceland and economically inactive persons from the main analysis did not materially change the main findings (*data from sensitivity analyses are not shown*).

Discussion

This study did not support associations between organic solvent exposure and adult CLL. In particular, the risk estimates did not reflect monotonic gradient by exposure levels, and they were not consistent across genders. Gender-specific differences are likely to result from low statistical power of analysis in women, who had lower exposures in this study and are also known to have lower CLL incidence.

One of the main advantages of this study was completeness and accuracy of cancer incidence data. A validation study showed high degree of completeness, comparability, accuracy and timeliness of cancer registration in Norway.[38] Data from cancer registries of Finland and Iceland were compared to hospital discharge reports in linkage studies and 99% completeness of registry data was observed in both countries.[39,40] Validation studies linking deaths certificate with Swedish cancer registry data also demonstrated reasonably high completeness and accuracy.[41]

Another advantage is the accuracy of occupational classification. Previous validity studies demonstrated high accuracy of occupational classifications based on census records in the Nordic countries.[42,43]

The main limitation was potential exposure misclassification, which could be a result of the following reasons. First, exposure misclassification is inherent to all JEMs because they assign average exposure estimates to all members of an occupational group ignoring the true exposure variation within an occupation. We do not know the extent of misclassification of solvent exposure in this study because there is no evidence on reliability of solvent exposure estimation using the NOCCA-JEM. Some previous studies assessed reliability of FINJEM, from which NOCCA-JEM was adopted. For example, a moderate reliability (weighted kappa 0.40, 95% CI 0.32–0.52) was observed for estimation of polycyclic aromatic hydrocarbons using FINJEM in a Dutch cohort study.[44] A poor to fair reliability was observed for formaldehyde, lead, insecticides, welding fumes and asbestos.[44,45] Exposure misclassification rate by FINJEM seemed to be dependent on the type of exposure agent.[45] In a recent study, a fair-to-moderate reliability was observed for NOCCA-JEM for estimation of cosmic radiation exposure among airline workers.[46]

Misclassification of continuous cumulative exposures was likely to be nondifferential in this study because it was independent from the disease status. However, categorization of continuous exposures with nondifferential classification into multilevel categorical exposures can produce differential misclassification.[47,48] Therefore, misclassification of multilevel categorical solvent exposures in this study could be differential.

Second, NOCCA-JEM does not account for industries but only occupational groups. Exposure intensity and prevalence may vary by industry included in the same occupational group [49]. Thus, not accounting for industry may lead to exposure misclassification and biased estimate of association between exposure and outcome of interest [50].

Finally, annual job histories of study participants were not available, and therefore, they were imputed from census records by assuming the person changed occupation in the middle between available censuses. This assumption was the weakest for persons with high occupational mobility and for Iceland because annual job history for entire working career was based on a single census from 1981. However, Icelandic part of the data constituted only <1% of overall study population, and excluding it from the main analysis did not change the main findings. In addition, previous studies demonstrated low occupational mobility in the Nordic countries, particularly among men and in occupations requiring higher education.[32,42] Therefore, limited job history is unlikely to strongly bias the main results in this study.

In our study, painters, cookers and furnacemen and telecommunication workers were the occupations with the highest annual average methylene chloride exposure levels. Laundry workers and metal workers were exposed to the highest perchloroethylene exposures. Exposure to 1,1,1-trichloroethane was the highest among upholsterers, metal workers, smelters,
T3 shoe workers, machine and engine mechanics (Table 3). Some of these occupations have been linked to an increased CLL risk in previous studies; however, the literature is sparse. Excess CLL incidence (SIR = 1.54, 95% CI 1.05–2.12) was observed among female launderers and dry cleaners in Sweden.[51] Associations with metal work (OR = 8.4, 95% CI 1.4–50.6) and telecommunication work (OR = 3.1, 1.2–8.0) were observed in two case–control studies conducted in Kansas and Nebraska.[15] Kato *et al.* observed increased risk of B-cell NHL (OR = 1.52, 95% CI 1.08–2.14) following exposure to paint thinners.[52] In studies investigating individual solvents, nonsignificantly increased risk of CLL was observed for high/medium levels of methylene chloride (OR = 1.6, 95% CI 0.3–8.6).[18] Wang *et al.* observed associations for solvent exposure and diffuse large B-cell lymphoma, but not for CLL/SLL.[49]

Table 3. The list of selected occupational groups with the highest annual average solvent exposure

Solvent	Occupation
Aliphatic and alicyclic hydrocarbons (annual average exposure >10 ppm)	Upholsterers; lasters and sole fitters; occupation in graphics; cookers and furnacemen; refinery workers, other occupations in the chemical industry; rubber product workers; laundry workers.
Benzene (annual average exposure >1 ppm)	Laboratory assistants; upholsterers; lasters and sole fitters; footwear workers; machine and engine mechanics; painters, lacquerers and floor layers; printers; occupation in graphics; cookers and furnacemen; refinery workers, other occupations in the chemical industry; rubber product workers.
Methylene chloride (annual average exposure >10 ppm)	Upholsterers; lasters and sole fitters; machine and engine mechanics; painters, lacquerers and floor layers; printers; bookbinders; cookers and furnacemen; refinery workers, other occupations in the chemical industry; telecommunication workers.
Other organic solvents (annual average exposure >10 ppm)	Lasters and sole fitters; printers; lithographers; bookbinders; occupation in graphics; paper and cardboard mill workers; refinery workers, other occupations in the chemical industry.
Perchloroethylene (annual average exposure >10 ppm)	Metal plating and coaring workers; distillers; laundry workers.
Trichloroethylene (annual average exposure >20 ppm)	Lasters and sole fitters; metal plating and coating work; laundry workers; smelting, foundry and metallurgical work; turners, tool makers and machine-tool setters; machine and engine mechanics.
1,1,1-trichloroethane (annual average exposure >20 ppm)	Upholsterers; metal plating and coating work; smelters; lasters and sole fitters; machine and engine mechanics.
Toluene (annual average exposure >40 ppm)	Painters, lacquerers and floor layers; printers; occupation in graphics; cookers and furnacemen; refinery workers, other occupations in the chemical industry.

Observed small risk elevations for methylene chloride, perchloroethylene and 1,1,1-trichloroethane did not reflect an exposure-response gradient and they were not consistent for both sexes. Therefore, they are likely to be chance findings. In addition, the pattern of some risk estimates suggested a high nondifferential exposure misclassification. For example, observed protective effect for aliphatic and alicyclic hydrocarbon solvents and toluene could be an indication of crossover bias. Crossover bias in the middle and high exposure categories of multilevel exposures may occur when misclassification rate is very high in nonadjacent categories.[53] In this case, a detrimental effect ($OR > 1$) may appear as protective ($OR < 1$), and conversely, a true protective effect may appear detrimental.

In summary, this study did not demonstrate the association between solvent exposure and adult CLL. Observed suggestive evidence for methylene chloride, perchloroethylene, 1,1,1-trichloroethylene, aliphatic and alicyclic hydrocarbon solvents and toluene is likely to be due to chance because there was no a dose–response pattern and estimates were inconsistent across sexes. Because we cannot exclude the possibility of exposure misclassification, further investigations with more robust exposure estimation methods are needed to overcome the limitations of this study.

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