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Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case—control study

P Cocco,¹ A t'Mannetje,² D Fadda,¹ M Melis,¹ N Becker,³ S de Sanjosé,⁴ L Foretova,⁵ J Mareckova,⁶ A Staines,⁷ S Kleefeld,⁸ M Maynadié,⁹ A Nieters,³ P Brennan,¹⁰ P Boffetta¹¹

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¹Department of Public Health, Occupational Health Section, University of Cagliari, Cagliari, Italy

²Centre for Public Health Research, Massey University, Wellington, New Zealand

³German Cancer Research Centre, Heidelberg, Germany

⁴Catalan Institute of Oncology, Barcelona, and Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP) Spain

⁵Department of Cancer Epidemiology and Genetics, Brno, Czech Republic

⁶Institute of Public Health, Brno, Czech Republic

⁷Dublin City University, Dublin, Ireland

⁸National University of Ireland, Galway, Ireland

⁹Dijon University Hospital, Dijon, France

¹⁰International Agency for Research on Cancer, Lyon, France

¹¹The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY and International Prevention Research Institute, Lyon, France

Correspondence to

Pierluigi Cocco, Department of Public Health, Occupational Health Section, University of Cagliari, Asse Didattico — Policlinico Universitario, SS 554, km 4,500, 09042 Monserrato (Cagliari), Italy; coccop@medicina.unica.it

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ABSTRACT

Background Several studies have suggested an association between occupational exposure to solvents and lymphoma risk. However, findings are inconsistent and the role of specific chemicals is not known.

Objective To investigate the role of occupational exposure to organic solvents in the aetiology of B-cell non-Hodgkin's lymphoma (B-NHL) and its major subtypes, as well as Hodgkin's lymphoma and T-cell lymphoma.

Methods 2348 lymphoma cases and 2462 controls participated in a case—control study in six European countries. A subset of cases were reviewed by a panel of pathologists to ensure diagnostic consistency. Exposure to solvents was assessed by industrial hygienists and occupational experts based on a detailed occupational questionnaire.

Results Risk of follicular lymphoma significantly increased with three independent metrics of exposure to benzene, toluene and xylene (BTX) (combined $p=4\times 10^{-7}$) and to styrene ($p=1\times 10^{-5}$), and chronic lymphocytic leukaemia (CLL) risk increased with exposure to solvents overall ($p=4\times 10^{-6}$), BTX ($p=5\times 10^{-5}$), gasoline ($p=8\times 10^{-5}$) and other solvents ($p=2\times 10^{-6}$). Risk of B-NHL for ever exposure to solvents was not elevated (OR=1.1, 95% CI 1.0 to 1.3), and that for CLL and follicular lymphoma was 1.3 (95% CI 1.1 to 1.6) and 1.3 (95% CI 1.0 to 1.7), respectively. Exposure to benzene accounted, at least partially, for the association observed with CLL risk. Hodgkin's lymphoma and T-cell lymphoma did not show an association with solvent exposure.

Conclusion This analysis of a large European dataset confirms a role of occupational exposure to solvents in the aetiology of B-NHL, and particularly, CLL. It is suggested that benzene is most likely to be implicated, but we cannot exclude the possibility of a role for other solvents in relation to other lymphoma subtypes, such as follicular lymphoma. No association with risk of T-cell lymphoma and Hodgkin's lymphoma was shown.

INTRODUCTION

Several reports have suggested an association between non-Hodgkin's lymphoma (NHL) and occupational exposure to organic solvents.^{1–7} Various chemicals have been implicated, including benzene,^{4 8–11} toluene^{11 12} and styrene,^{13–16} trichloroethylene and tetrachloroethylene^{8 12 17–19} and gasoline.^{2 11 20} However, a pooled analysis of 26 cohorts of petroleum workers in the United States, the United Kingdom, Canada, Australia, Italy and Finland, reportedly exposed to benzene, did not

What this paper adds

- Occupational exposure to solvents has been repeatedly suggested as a risk factor for non-Hodgkin's lymphoma; however, contradictory findings, outdated pathological definitions and imprecision in the exposure assessment preclude conclusive statements.
- The Epilymph case—control study defined lymphoma and its subentities with the 2001 WHO classification; used state-of-the-art retrospective assessment of occupational exposure to solvents, subgroups of solvents and individual chemicals; and achieved the statistical power required to test the hypothesis also for the major lymphoma subentities.
- Occupational exposure to solvents, and particularly to benzene and technical solvents, appears to have a role in the aetiology of mature B-cell lymphomas, and particularly, chronic lymphocytic leukaemia.
- Effort should be made to achieve zero benzene content in fuels and solvents, and to further reduce its use in the chemical industry.
- The occupational origin of mature B-cell lymphomas among solvent-exposed workers should be acknowledged.

show an increased risk of NHL.²¹ On the other hand, the conclusion of two out of three published reviews stated that exposure to benzene or solvents or products containing benzene is causally related to NHL^{22–24}; a meta-analysis of the cohort and case—control studies of NHL risk associated with trichloroethylene exposure argued that variability in results of cohort studies, weakness of the exposure assessment, lack of dose—response trends and lack of supportive information from toxicological and mechanistic data limit the interpretation of the overall findings.²⁵ The heterogeneous array of pathological entities in NHL complicates evaluation. However, linking specific exposures to lymphoma subtypes would strengthen the observed positive associations.⁶ Although few studies are available, solvent-associated risk was observed to vary by major groups of lymphomas,²⁶ being more pronounced for B-cell lymphoma.³ Also, exposure to chlorinated hydrocarbons reportedly conveyed a more pronounced increased risk for follicular

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lymphoma and marginal zone lymphoma.¹² Multiple myeloma and chronic lymphocytic leukaemia (CLL), which the 2001 WHO Classification of Lymphoma categorises as mature B-cell neoplasms,²⁷ were also reported in association with exposure to benzene^{28–29} and trichloroethylene,¹⁷ although cohort studies were mostly negative.^{29–30} Further study of solvents and NHL subtypes is needed.

Using the opportunity provided by the detailed occupational information available for subjects who participated in a large European case–control study, we evaluated the role of solvents, subgroups of solvents and specific chemicals used as solvents, in the aetiology of B-cell NHL, and its major subtypes, as well as Hodgkin's lymphoma and T-cell lymphoma.

METHODS

The Epilymph study, a multicentre case–control study on environmental exposures and lymphoid neoplasms, was conducted in the Czech Republic, France, Germany, Ireland, Italy and Spain from 1998 to 2004. Details of the study have been described elsewhere.³¹ Briefly, cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres. The diagnosis was classified according to the 2001 World Health Organization (WHO) Classification of Lymphoma,²⁷ and slides of about 20% of cases from each centre were reviewed centrally by a panel of pathologists, coordinated by MMA. Controls from Germany and Italy were selected by random sampling from the general population, and matched to cases by gender, 5-year age group, and residence area. The rest of the centres used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases and immunodeficient diseases. Approval by the relevant ethics committees was obtained in all centres. Informed consent was obtained for the 2348 lymphoma cases and 2462 controls who participated in the study. All cases and controls were interviewed during the study period. Overall participation rate was 88% in cases, 81% in hospital controls and 52% in population controls.

Trained interviewers conducted in-person interviews with cases and controls, using the same structured questionnaire translated to the local language. Questions sought information on socio-demographic factors, lifestyle, health history and a list of all full-time jobs held for 1 year or longer. Industrial hygienists in each participating centre coded the occupations and industries using the five-digit 1968 International Labour Office International Standard Classification of Occupations (ISCO)³² and the four-digit codes of the 1996 EEC Classification of Economic Activities, revision 1 (NACE, revision 1).³³ Overall, the work histories included 19129 job entries, identified by a combination of occupational title and industry type, representing an average of 4.0 jobs for each study subject. Country-specific averages ranged from 2.4 to 5.0, being 4.1 among cases, and 4.0 among controls. For each job, information on the description of the activity of the company, the tasks performed and the machines used was sought, as well as a list of exposures of interest. Fourteen special questionnaire modules for specific occupations were used to gather additional details on jobs and exposures of a priori interest. Most job modules used in this study are modified versions of similar tools originally developed at the US National Cancer Institute, Occupational and Environmental Epidemiology Branch by Stewart P and colleagues. The original NCI job modules can be obtained from the NCI (<http://dceg.cancer.gov/oeeb> (accessed 26 September 2009)). The job modules newly

developed for the purpose of this study can be obtained from the authors.

Occupational exposure assessment

Industrial hygienists in each participating centre reviewed the general and specific questionnaires and assessed exposure to 43 agents, including the organic solvents listed in table 1, according to the following exposure metrics:

- Confidence, representing the industrial hygienist's degree of certainty that the worker had been truly exposed to the agent, based upon two criteria: 1. a summary evaluation of the probability of the given exposure (1=possible, but not probable; 2=probable; 3=certain); and 2. the proportion of workers exposed in the given job (1=<40%; 2=40–90%; 3=>90%);
- Intensity of exposure, expressed on a four-point scale (0=unexposed; 1=low; 2=medium; 3=high). Agent-specific cut-off points of intensity categories were defined based on the respective most recent threshold limit value or benchmark occupations; individual assessments took into account the available questionnaire information on whether the job consisted of manual or process operations; whether skin contact was likely to occur; whether exhaust ventilation was in place and personal protective equipment was used; as well as whether job tasks were performed indoors or outdoors and at what distance from the source of exposure. When grouping individual agents, the group intensity level was that of the contributing agent attaining the highest intensity level;
- Frequency of exposure, expressed according to the proportion of work time involving contact with the agent (0=unexposed; 1=1–5% work time; 2=>5–30% work time; 3=>30% work time).

Consistency in the occupational coding and exposure assessments was sought through several meetings of the industrial hygienists. In such meetings, exercises based on true occupational histories and questionnaire extracts were conducted, and reference manuals were implemented and delivered to the participants. Based on the assessments, a cumulative exposure score to each solvent was determined for each study subject by summing the cumulative exposure scores over his own work history as follows³⁴:

$$C_i = \sum (y_i * f_i / 3)^{x_i}$$

where, C=cumulative exposure score; *i*=study subject; *j*=*j*th job in the work history of *i*th study subject *i*; *y*=duration of exposure (in years); *x*=exposure intensity level; *f*=exposure frequency level.

Cumulative exposure to each agent was then categorised according to the tertiles among the exposed controls. Duration of exposure was also analysed separately.

Statistical methods

We assessed the risk of B-cell NHL, and its major subtypes, including diffuse large B-cell lymphoma (DLBCL), CLL, follicular lymphoma and multiple myeloma, as well as the risk of T-cell lymphoma and Hodgkin's lymphoma, associated with ever exposure to organic solvents (all types), solvent subgroups (benzene, toluene and xylene (BTX); chlorinated aliphatic hydrocarbons (CAH); other solvents), and the individual solvents listed in table 1. The analysis was led by PC, supported by DF and MMe, on all the exposed subjects, and after restriction to subjects whose exposure was assessed with high confidence. Linear trends by all exposure metrics were also explored. The OR was calculated with unconditional logistic regression, adjusting for age, gender, education and centre. Two-tailed 95% CIs of the OR were

Table 1 Selected characteristics of lymphoma cases and controls

	Lymphoma cases (n=2348) n (%)	Controls (n=2462) n (%)
Centre		
Spain	591 (25.2)	631 (25.6)
France	298 (12.7)	276 (11.2)
Germany	703 (29.9)	710 (28.8)
Italy	262 (11.2)	336 (13.6)
Ireland	203 (8.6)	206 (8.4)
Czech Republic	291 (12.4)	303 (12.3)
Gender*		
Male	1314 (56.0)	1320 (53.6)
Female	1033 (44.0)	1142 (46.4)
Age*		
≤30	220 (9.4)	227 (9.2)
31–40	242 (10.3)	253 (10.3)
41–50	303 (12.9)	316 (12.8)
51–60	462 (19.7)	515 (20.9)
61–70	646 (27.5)	655 (26.6)
71–80	427 (18.2)	448 (18.2)
81+	47 (2.0)	48 (1.9)
Education*		
Low	1081 (46.0)	1123 (45.6)
Medium	937 (39.9)	999 (40.6)
High	329 (14.0)	340 (13.8)
Exposed to organic solvents	1008 (100.0)	1011 (100.0)
Confidence		
Low	43 (4.2)	24 (2.4)
Medium	236 (23.4)	258 (25.5)
High	729 (72.3)	729 (72.1)
Exposed to BTX	422 (100.0)	403 (100.0)
Confidence		
Low	29 (6.9)	30 (7.4)
Medium	149 (35.3)	138 (34.2)
High	244 (57.8)	235 (58.3)
Exposed to CAH	347 (100.0)	370 (100.0)
Confidence		
Low	48 (13.8)	32 (8.6)
Medium	147 (42.4)	159 (43.0)
High	152 (43.8)	179 (48.4)
Exposed to gasoline	424 (100.0)	440 (100.0)
Confidence		
Low	13 (3.1)	11 (2.5)
Medium	111 (26.2)	148 (33.6)
High	300 (70.8)	281 (63.9)
Exposed to mineral spirits	305 (100.0)	317 (100.0)
Confidence		
Low	24 (7.9)	19 (6.0)
Medium	115 (37.7)	144 (45.4)
High	166 (54.4)	154 (48.6)
Exposed to styrene	78 (100.0)	58 (100.0)
Confidence		
Low	12 (15.4)	11 (19.0)
Medium	45 (57.7)	28 (48.3)
High	21 (26.9)	19 (32.8)
Exposed to other solvents	469 (100.0)	450 (100.0)
Confidence		
Low	20 (4.3)	16 (3.6)
Medium	190 (40.5)	192 (42.7)
High	259 (55.2)	242 (53.8)

*Information on gender, age and education was missing for one case.

BTX, benzene, toluene and xylene; CAH, chlorinated aliphatic hydrocarbons.

calculated with the Wald statistics ($e^{\beta \pm (z_{\alpha/2} * se_{\beta})}$). Subjects unexposed to any solvent comprised the reference category used for all the analyses. Trends in the ORs were assessed using the Wald test for trend. Overall, 49 associations were explored. To deal with the multiple comparison problem, we also calculated the CI of the ORs by applying the appropriate Bonferroni correction to the two-tailed 5% probability associated with the normal standard deviate value ($z_{\alpha/2}$) used in its calculation. Besides, assuming independence between intensity (x), frequency (f) and duration (y), the threshold α error to reject the null hypothesis of an upward trend in risk was defined as $\alpha_x * \alpha_f * \alpha_y = 0.000125$, so expressing the combined probability of independent events. A Bonferroni correction was also applied to the 32 comparisons and cumulative exposure trend calculations among the exposed study subjects classified with the highest level of confidence. Heterogeneity in risk across the participating centres was formally tested with a Cochrane χ^2 test.

Role of the funding sources

The private and public institutions that sponsored this study did not influence or intervene in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

Mean age was substantially similar between cases and controls (cases: 56.2 years, SD 15.99; controls: 56.1 years, SD 16.12), as was distribution by 10-year age groups, indicating that frequency matching by age was successful. Mean age was also identical by gender (men: 56.1 years, SD 15.99; women: 56.1 years, SD 16.44), and the male/female ratio among cases was 1.3:1. Table 1 shows the number of cases and controls by participating centre, and their frequency distribution by selected variables. Overall, for 72% of the exposed cases and 72% of the exposed controls, solvent exposure was classified with high degree of confidence. Confidence was lower for most specific subgroups of solvents and individual chemicals.

A significant increasing trend in CLL risk was observed by confidence in exposure to organic solvents ($p < 0.02$), BTX ($p < 0.02$), benzene ($p < 0.03$) and other solvents ($p < 0.01$). Risk of follicular lymphoma increased significantly by confidence in exposure to BTX ($p < 0.01$), benzene ($p < 0.04$), toluene ($p < 0.01$) and xylene ($p < 0.004$) (see supplementary online table 1 for detailed results). Risk for B-NHL, DLBCL, multiple myeloma, T-cell lymphoma and Hodgkin's lymphoma did not differ by confidence of exposure to organic solvents, subgroups of solvents or individual chemicals.

Table 2 shows combinations of pairwise exposures represented by the ratio between subjects ever exposed to both solvents over those exposed to one or the other. The most severe overlapping was observed between exposure to BTX and the other solvent subgroups, as well as between CAH and mineral spirits. Substantial overlapping was also observed between CAH and

Table 2 Ratio of study subjects exposed to two groups of solvents and those exposed to either one

	BTX	CAH	Gasoline	Mineral spirits	Styrene
CAH	0.32				
Gasoline	0.33	0.26			
Mineral spirits	0.35	0.29	0.22		
Styrene	0.12	0.10	0.08	0.09	
Other solvents	0.29	0.23	0.17	0.22	0.07

BTX, benzene, toluene and xylene; CAH, chlorinated aliphatic hydrocarbons.

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gasoline; mineral spirits and other solvents; and mineral spirits and gasoline.

Table 3 shows the OR and 95% CI for ever exposed—that is, all the confidence levels combined, as well as the results of the test for trend by increasing levels of three independent exposure metrics. Several risks associated with ever exposure attained statistical significance, although none remained significant after Bonferroni correction (see supplementary online table 1). Significant upward trends were observed for B-NHL with styrene exposure (combined $p=1\times 10^{-5}$), follicular lymphoma with BTX ($p=4\times 10^{-7}$) and styrene ($p=1\times 10^{-5}$), and CLL with all solvents ($p=4\times 10^{-6}$), BTX ($p=5\times 10^{-5}$), gasoline ($p=8\times 10^{-5}$) and other solvents ($p=2\times 10^{-6}$). After Bonferroni correction, CAH did not show a significant association with B-NHL or any lymphoma subtype. Risk of multiple myeloma, T-cell lymphoma and Hodgkin's lymphoma did not show an association (see supplementary online table 1 for detailed ORs and uncorrected 95% CIs, associated with each level of the individual exposure metrics).

We further explored the risk of B-NHL and its major subtypes, including DLBCL, follicular lymphoma, CLL and multiple myeloma against exposure to the agents showing an association in table 3, limiting the analysis to those subjects classified with high confidence of exposure to specific chemicals in the BTX group, trichloroethylene and gasoline. When restricting the analysis to such assessments, styrene was not included because of the small number of exposed and small number of cases. Table 4 shows ORs and Bonferroni uncorrected 95% CIs for ever exposed. OR point estimates are also shown by increasing level of cumulative exposure, along with the result of the corresponding test for trend.

Exposure to organic solvents (OR=1.5; 95% CI 1.1 to 1.9) and gasoline (OR=1.7; 95% CI 1.2 to 2.3) showed significant associations with CLL risk, retained significance after Bonferroni correction (not shown in the tables) and showed significant upward trends by increasing cumulative exposure (organic solvents: $p=0.002$; gasoline: $p=0.001$). No clear association was observed for DLBCL and follicular lymphoma. The association between gasoline exposure and B-NHL risk persisted after excluding 21 gas station attendants (11 cases and 10 controls), indicating that risk associated with use of gasoline as a solvent was not biased by concurrent exposures among gas station attendants. Risks and trends associated with BTX, and benzene, toluene and xylene were all elevated, although not significantly. However, adjusting B-NHL risk and CLL risk from exposure to gasoline by BTX exposure reduced the association (B-NHL: OR=1.0, 95% CI 0.8 to 1.2; CLL: OR=1.0, 95% CI 0.7 to 1.4). Conversely, the slight B-NHL risk and the CLL risk associated with ever exposure to BTX was not affected by adjustment for gasoline exposure (OR=1.3, 95% CI 1.0 to 1.8). No such confounding effect was seen for concurrent exposure to BTX and other solvents, while associations with CLL risk persisted unchanged after reciprocal exclusion or adjustment (BTX: OR=1.4, 95% CI 0.9 to 2.0; other solvents: OR=1.4, 95% CI 1.0 to 2.1). BTX-associated and other solvents-associated risk of B-NHL and CLL did not change after excluding farmers from the analysis, or after adjusting by farm work, another occupation previously associated with lymphoma.

To explore whether confounding from associated benzene exposure explained the excess CLL risks observed also for toluene and xylene, we assessed their separate effects, although the pairwise overlapping ratio was much larger within the BTX group, than that seen between different groups of solvents, ranging from 0.74 (benzene and toluene) to 0.93 (toluene and xylene). Table 5 shows that isolated ever exposure to benzene was

always consistently associated with CLL risk. Excluding co-occurrence of benzene exposure did not change the OR for toluene and xylene; however, isolated ever exposure to toluene did not show an association; and study subjects with isolated exposure to xylene were too few to confirm or exclude an association.

When between-centre heterogeneity in solvent-associated B-NHL risk was evaluated, the risk was not elevated in four of the six centres, with no heterogeneity detected ($Q=2.00$; degrees of freedom=5; $p=0.85$). Solvent-associated CLL risk was more consistently raised with risks >1 in five out of six centres, and again no heterogeneity ($Q=1.34$; degrees of freedom=5; $p=0.93$). CLL risk associated with benzene exposure was consistently raised in all six centres, and it was statistically significant after Bonferroni correction ($p<0.025/6=0.004$) in four, and again no heterogeneity was detected ($Q=6.13$; degrees of freedom=5; $p=0.29$). The proportion of those exposed to benzene ranged from 17% to 23% in the three centres showing the most elevated CLL risks in association with solvent exposure, while it varied between 5% and 8% in the three centres where the association was weaker. Therefore, the proportion of benzene exposed subjects apparently accounted for the between-centre variation in CLL risk associated with solvent exposure.

DISCUSSION

Our results support the hypothesis that occupational exposure to solvents may contribute to lymphomagenesis.^{23 35} The association appears to be stronger with mature B-cells malignancies, such as CLL. Because of the small numbers of exposed subjects among cases with specific lymphoma subtypes, it was not possible to explore in more detail the association of follicular lymphoma with those exposed to BTX and styrene. Risk of CLL and follicular lymphoma increased by confidence level of exposure to BTX, and particularly, benzene. Among subjects with high confidence exposure, after reciprocal adjustment, the BTX subgroup was consistently associated with a significant increase in CLL risk, whilst the association observed with gasoline exposure disappeared, indicating confounding by concurrent exposure to BTX. Overlapping exposure was substantial; although discriminating the reciprocal effects of individual chemicals in an epidemiological analysis of real world occurrences is unlikely to be completely achievable, our strategy aimed at minimising its effect.

Our results are consistent with several published reports in finding a significant increase in B-NHL risk in relation to occupational exposure to solvents.^{2–20} In our study, the association was stronger for CLL, with benzene and solvents other than the specific agents considered in this paper accounting for the excess risk. Although benzene content in technical solvents and gasoline has been regulated in the last decades, it frequently occurs in both as a contaminant. Significant increases in lymphoma risk associated with gasoline exposure or aliphatic hydrocarbons were previously reported.^{2 11 20} Also, a large Italian case-control study reported excess risks of B-NHL more consistent with toluene than benzene exposure. Besides, other solvents in our study and technical solvents in the multicentre Italian study,¹¹ represented mostly by mixtures of different chemicals in both studies, also showed consistent upward trends in risk of B-NHL and, specifically, CLL. None of the previous studies adjusted for or stratified the analysis by benzene exposure. Our results suggest that technical grade benzene and benzene as a component of solvent mixtures is likely to be responsible for the observed associations. Other yet to be identified technical mixtures of solvents may also have a role.

High-level occupational exposure to benzene among subjects with a familial history of haematological neoplasms was

Table 3 Risk of major lymphoma subtypes associated with solvent exposure in the Epilymph study (all degrees of IH confidence combined)

Solvent	B-NHL Case/controls OR 95% CI	T-lymphoma Case/controls OR 95% CI	Hodgkin's lymphoma Case/controls OR 95% CI	DLBCL Case/controls OR 95% CI	Follicular lymphoma Case/controls OR 95% CI	CLL Case/controls OR 95% CI	Multiple myeloma Case/controls OR 95% CI
Unexposed	1061/1451 1.0 -	78/1451 1.0 -	195/1451 1.0 -	325/1451 1.0 -	140/1451 1.0 -	217 /1451 1.0 -	160/1451 1.0 -
All solvents: ever exposed	808/1009 1.1 1.0 to 1.3	55/1009 0.9 0.7 to 1.4	144/1009 1.1 0.9 to 1.4	213/1009 1.0 0.8-1.2	111/1009 1.3 1.0 to 1.7	196/1009 1.3 1.1 to 1.6	117/1009 1.1 0.8 to 1.4
Test for trend (p)	0.000189	0.239400	0.072352	0.491244	0.000644	0.000004	0.056672
BTX: ever exposed	343/402 1.2 1.0 to 1.4	30/402 1.3 0.8 to 2.1	49/402 1.0 0.7 to 1.4	91/402 1.0 0.8-1.4	53/402 1.7 1.2 to 2.5	86/402 1.4 1.0 to 1.9	50/402 1.1 0.8 to 1.6
Test for trend (p)	0.000500	0.007425	0.397296	0.623904	0.0000004	0.000048	0.075480
CAH: ever exposed	284/370 1.1 0.9 to 1.3	20/370 1.0 0.6 to 1.7	42/370 0.9 0.6 to 1.4	68/370 0.8 0.6 to 1.1	44/370 1.5 1.0 to 2.2	74/370 1.4 1.0 to 1.9	38/370 0.9 0.6 to 1.3
Test for trend (p)	0.034276	0.784827	0.461916	0.078624	0.000162	0.005016	0.272958
Gasoline: ever exposed	353/439 1.1 0.9 to 1.3	24/439 1.1 0.6 to 1.8	46/439 0.7 0.5 to 1.1	91/439 0.9 0.7-1.2	33/439 1.0 0.6 to 1.6	84/439 1.3 0.9 to 1.8	60/439 1.2 0.8 to 1.7
Test for trend (p)	0.000405	0.079680	0.027000	0.354000	0.177660	0.000084	0.002070
Mineral spirit: ever exposed	240/317 1.0 0.9 to 1.3	22/317 1.2 0.7 to 2.0	43/317 1.1 0.7 to 1.6	63/317 0.9 0.7-1.2	30/317 1.2 0.8 to 1.9	56/317 1.2 0.8 to 1.6	41/317 1.2 0.8 to 1.7
Test for trend (p)	0.083249	0.005520	0.480004	0.480200	0.151767	0.028800	0.017612
Styrene: ever exposed	66/58 1.6 1.1 to 2.3	2/58 0.6 0.1 to 2.7	10/58 1.1 0.5 to 2.3	20/58 1.5 0.9-2.5	11/58 2.6 1.3 to 5.2	10/58 1.2 0.6 to 2.5	6/58 0.9 0.4 to 2.2
Test for trend (p)	0.000096	0.474815	0.700728	0.004158	0.000097	0.268464	0.511200
Other solvents: ever exposed	369/449 1.2 1.0 to 1.4	25/449 1.0 0.6 to 1.6	75/449 1.2 0.9 to 1.6	120/449 1.2 1.0-1.6	59/449 1.5 1.1 to 2.0	88/449 1.5 1.1 to 2.0	52/449 1.1 0.8 to 1.5
Test for trend (p)	0.000130	0.308884	0.005720	0.000144	0.000266	0.000002	0.029240

For each association, the α error probability (p) associated with positive trends in risk by three independent exposure metrics (Wald tests for trend) is also shown (see text). $p \leq 0.000125$ was defined as the threshold to reject the null hypothesis. BTX, benzene, toluene and xylene combined; B-NHL, B-cell non-Hodgkin's lymphoma; CAH, chlorinated aliphatic hydrocarbons; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma.

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Table 4 Risk of major lymphoma subtypes associated with cumulative exposure to individual solvents in the Epilymph study (only subjects whose exposure was assessed with high degree of confidence)

Solvent	Cumulative exposure	B-NHL			DLBCL			Follicular lymphoma			CLL			Multiple myeloma		
		Case/controls	OR	95% CI	Case/controls	OR	95% CI	Case/controls	OR	95% CI	Case/controls	OR	95% CI	Case/controls	OR	95% CI
Unexposed		1061/1451	1.0	-	325/1451	1.0	-	140/1451	1.0	-	217/1451	1.0	-	160/1451	1.0	-
All solvents	All the exposed	586/728	1.1	1.0 to 1.3	151/728	0.9	0.7 to 1.1	80/728	1.3	1.0 to 1.8	150/728	1.5	1.1 to 1.9	86/728	1.1	0.8 to 1.5
	Low	140/233	0.9		39/233	0.7		25/233	1.3		34/233	1.2		15/233	0.7	
	Medium	200/265	1.1		51/265	0.9		25/265	1.1		49/265	1.4		35/265	1.3	
	High	246/230	1.4		61/230	1.2		30/230	1.6		67/230	1.7		36/230	1.2	
	Test for trend (p)	2.40	(0.02)		0.12	(0.90)		2.23	(0.03)		3.12	(0.002)		1.19	(0.23)	
BTX	All the exposed	208/235	1.2	1.0 to 1.5	55/235	1.1	0.8 to 1.5	28/235	1.6	1.0 to 2.5	56/235	1.5	1.1 to 2.2	27/235	1.0	0.6 to 1.6
	Low	58/74	1.1		17/74	1.0		8/74	1.4		14/74	1.4		5/74	0.6	
	Medium	61/74	1.1		17/74	1.0		10/74	1.8		19/74	1.7		6/74	0.7	
	High	89/87	1.3		21/87	1.1		10/87	1.5		23/87	1.5		16/87	1.4	
	Test for trend (p)	1.45	(0.15)		0.14	(0.89)		1.77	(0.08)		2.22	(0.03)		0.71	(0.48)	
Benzene	All the exposed	118/138	1.1	0.8 to 1.4	28/138	0.9	0.6 to 1.4	17/138	1.6	0.9 to 2.9	34/138	1.4	0.9 to 2.2	16/138	0.9	0.5 to 1.6
	Low	34/51	0.9		9/51	0.8		5/51	1.3		11/51	1.4		4/51	0.7	
	Medium	29/35	1.1		8/35	1.0		8/35	3.0		6/35	1.0		2/35	0.4	
	High	55/52	1.3		11/52	0.9		4/52	1.0		17/52	1.8		10/52	1.4	
	Test for trend (p)	0.96	(0.34)		-0.42	(0.67)		1.65	(0.10)		1.47	(0.14)		1.47	(0.14)	
Toluene	All the exposed	151/184	1.1	0.9 to 1.4	42/184	1.0	0.7 to 1.4	20/184	1.5	0.9 to 2.4	37/184	1.3	0.9 to 1.9	20/184	0.9	0.6 to 1.6
	Low	46/61	1.0		16/61	1.1		7/61	1.5		7/61	0.8		5/61	0.8	
	Medium	37/62	0.8		10/62	0.7		5/62	1.1		11/62	1.1		4/62	0.5	
	High	68/61	1.5		16/61	1.1		8/61	1.8		19/61	1.8		11/61	0.4	
	Test for trend (p)	0.93	(0.35)		-0.42	(0.67)		1.27	(0.20)		1.46	(0.14)		0.40	(0.69)	
Xylene	All the exposed	121/151	1.1	0.8 to 1.4	32/151	0.9	0.6 to 1.4	18/151	1.6	0.9 to 2.7	32/151	1.4	0.9 to 2.1	14/151	0.8	0.4 to 1.4
	Low	32/53	0.8		7/53	0.6		7/53	1.7		6/53	0.8		4/53	0.6	
	Medium	32/49	0.9		11/49	1.0		4/49	1.1		9/49	1.1		3/49	0.5	
	High	57/49	1.5		14/49	1.2		7/49	1.9		17/49	2.1		7/49	1.1	
	Test for trend (p)	0.89	(0.37)		0.07	(0.94)		1.47	(0.14)		1.66	(0.10)		-0.43	(0.67)	
CAH	All the exposed	119/179	0.9	0.7 to 1.2	35/179	0.9	0.6 to 1.3	15/179	1.1	0.6 to 1.9	28/179	1.0	0.7 to 1.6	16/179	0.8	0.4 to 1.3
	Low	34/63	0.7		10/63	0.6		7/63	1.4		8/63	1.0		2/63	0.3	
	Medium	31/59	0.7		9/59	0.7		2/59	0.4		5/59	0.6		7/59	1.0	
	High	54/57	1.2		16/57	1.2		6/57	1.3		15/57	1.5		7/57	0.9	
	Test for trend (p)	-0.32	(0.75)		-0.63	(0.53)		0.12	(0.90)		0.58	(0.56)		-0.42	(0.67)	
Trichloroethylene	All the exposed	71/117	0.8	0.6 to 1.1	17/117	0.7	0.4 to 1.1	11/117	1.2	0.6 to 2.3	18/117	0.9	0.5 to 1.5	9/117	0.6	0.3 to 1.2
	Low	26/37	0.9		6/37	0.7		7/37	2.4		6/37	1.0		1/37	0.2	
	Medium	16/43	0.5		4/43	0.4		1/43	0.3		3/43	0.4		4/43	0.7	
	High	29/37	1.0		7/37	0.9		3/37	1.0		9/37	1.2		4/37	0.8	
	Test for trend (p)	-1.40	(0.16)		-1.39	(0.16)		-0.45	(0.65)		-0.08	(0.94)		-1.22	(0.22)	
Gasoline	All the exposed	248/281	1.2	1.0 to 1.5	63/281	0.9	0.7 to 1.3	18/281	0.8	0.5 to 1.5	67/281	1.7	1.2 to 2.3	41/281	1.3	0.9 to 1.9
	Low	58/94	0.9		17/94	0.7		9/94	1.3		14/94	1.3		8/94	0.9	
	Medium	77/94	1.2		22/94	1.0		4/94	0.6		24/94	1.8		9/94	0.9	
	High	113/93	1.5		24/93	1.1		5/93	0.7		29/93	1.8		24/93	2.0	
	Test for trend (p)	2.68	(0.01)		0.24	(0.81)		-1.04	(0.30)		3.19	(0.001)		2.37	(0.02)	

BTX, benzene, toluene and xylene combined; B-NHL, B-cell non-Hodgkin's lymphoma; CAH, chlorinated aliphatic hydrocarbons; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma.

associated with an almost 30-fold excess risk of NHL, and subjects exposed to benzene with a history of immune system diseases ran a 16-fold excess risk.⁷ Although generated by small numbers, both findings seem to indicate immune system disruption as a mechanism of lymphomagenesis among benzene-exposed workers. Benzene is also genotoxic, and it induces t(14;18), t(8;21), and t(15;17) translocations, long-arm deletion of chromosome 6, as well as trisomy of chromosomes 2, 4, 6, 11,

12, 14 and 18.^{36 37} Such conditions, and particularly the last two conditions, are frequently observed in patients with lymphoma. Larger international collaborative efforts are warranted to replicate such findings; to explore in more detail the risk of follicular lymphoma and marginal zone lymphoma, suggested in association with exposure to CAH¹²; and to exclude or confirm a role for other less frequently used specific solvents, such as trichloroethylene, tetrachloroethylene and styrene.

Table 5 Chronic lymphocytic leukaemia risk associated with individual and combined ever exposure to benzene, toluene and xylene

	Benzene Case/controls OR 95% CI	Toluene Case/controls OR 95% CI	Xylene Case/controls OR 95% CI
All exposed	70/295 1.5 1.1 to 2.2	65/333 1.5 1.0 to 2.1	61/309 1.5 1.0 to 2.2
Isolated exposure	19/62 1.8 1.0 to 3.2	1/23 0.4 0.1 to 3.0	1/1 11.3 0.7 to 198
Unexposed to benzene	—	14/103 1.3 0.7 to 2.4	14/81 1.7 0.9 to 3.3
Unexposed to toluene	19/65 1.7 1.0 to 3.0	—	1/4 2.0 0.2 to 21
Unexposed to xylene	23/67 2.0 1.2 to 3.5	5/28 1.5 0.5 to 4.0	—

Our study had the advantage of a very detailed exposure assessment, which allowed several independent exposure metrics to be designed, and the consistency of the results to be assessed, coupled with an up-to-date pathological definition of disease entities. Such conditions represent substantial improvements in the assessment of occupational exposures and in lessening exposure and disease misclassification, which would help in revealing true associations. While this differentiates our effort from most previous publications, loss of statistical power is the unavoidable consequence.

Multiple comparisons are also a concern in subgroup analyses, as several significant findings might be generated simply by chance.³⁸ We used Bonferroni correction for the individual risk estimates, and we defined the α -error threshold to reject the null hypothesis of an upward trend as the combined probability of three independent exposure metrics. Perhaps, the strategy we used was too conservative, as exposures to the different concurrent solvents were unlikely to be independent from each other. The use of hospital controls in several centres contributing to this multinational effort, and the low response rate in the two centres from which the controls were obtained, were further limitations in this study.

In conclusion, our analysis of a large European dataset confirms a role of occupational exposure to solvents in the aetiology of B-NHL, and particularly, CLL. We suggest that benzene is most likely implicated, but we cannot exclude the possibility of a role for other solvents in relation to other less prevalent lymphoma subtypes, such as follicular lymphoma. We did not show any association with risk of T-cell lymphoma and Hodgkin's lymphoma.

Contributors All co-authors participated in planning the study design, in conducting the study and data acquisition (PBo, SdS, PBr, PC, LF, MMA, AN, AS), AtM conducted the occupational experts training and prepared the reference materials for the exposure assessment, PC and AtM supervised the occupational exposure assessment which was conducted in collaboration with MME, JM and SK. PC conducted the epidemiological analysis in collaboration with DF and MME, and wrote the manuscript. All the co-authors reviewed the manuscript and have seen and approved the final version.

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Competing interests PBo participated as a co-author in a review on styrene presented by the Styrene Information and Research Center (STIRC) as a public comment to the US National Toxicology Program's Board of Scientific Counselors. None of the co-authors declare financial interests or other connections, direct or indirect, related to the work reported or the conclusions, implications, or opinions stated in this paper.

Ethics approval This study was conducted with the approval of the relevant ethics committees at all centres participating in the study.

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