ORIGINAL ARTICLE

Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review

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Methods: Meta-analysis and review of 14 occupational cohort and four case-control studies of workers exposed to trichloroethylene (TCE) to investigate the relation between TCE exposure and the risk of non-Hodgkin's lymphoma (NHL). Studies were selected and categorised based on a priori criteria, and results from random effects meta-analyses are presented.

Results: The summary relative risk estimates (SRRE) for the group of cohort studies that had more detailed information on TCE exposure was 1.29 (95% CI 1.00 to 1.66) for the total cohort and 1.59 (95% CI 1.21 to 2.08) for the seven studies that identified a specific TCE exposed sub-cohort. SRREs for three studies with cumulative exposure information were 1.8 (95% CI 0.62 to 5.26) for the lowest exposure category and 1.41 (95% CI 0.61 to 3.23) for the highest category. Comparison of SRREs by levels of TCE exposure did not indicate exposure-response trends. The remaining cohort studies that identified TCE exposure but lacked detailed exposure information had an SRRE of 0.843 (95% CI 0.72 to 0.98). Case-control studies had an SRRE of 1.39 (95% CI 0.62 to 3.10). Statistically significant findings for the Group 1 studies were driven by the results from the subgroup of multiple industry cohort studies (conducted in Europe) (SRRE = 1.86; 95% CI 1.27 to 2.71). The SRRE for single industry cohort studies was not significantly elevated (SRRE = 1.25; 95% CI 0.87 to 1.79).

Conclusions: Interpretation of overall findings is hampered by variability in results across the Group 1 studies, limited exposure assessments, lack of evidence of exposure response trends, lack of supportive information from toxicological and mechanistic data, and absence of consistent findings in epidemiologic studies of exposure and NHL. Although a modest positive association was found in the TCE sub-cohort analysis, a finding attributable to studies that included workers from multiple industries, there is insufficient evidence to suggest a causal link between TCE exposure and NHL.

Trichloroethylene (TCE) has been widely used as an industrial solvent and degreasing agent.[1] Animal studies have reported elevated risk of kidney, liver, lung, and some haematopoietic cancers with TCE exposure.[2–4] The evidence of TCE carcinogenicity in animals is inconsistent, with TCE causing cancers in some species, sexes, and strains of animals but not in others. Increased cancer incidence is typically seen in animals following exposure levels that are much higher than the levels that humans would encounter in environmental or workplace settings, and in some cases observed cancer incidence in animals may be secondary to organ damage.[5–8]

Epidemiological studies of TCE have included occupational cohort studies, nested and population based case-control studies, and community cancer assessments. Community studies, which analysed aggregate exposure and disease data (e.g. cancer rates by county), have evaluated cancer occurrence and proximity to hazardous waste sites or industrial facilities, as well as communities that have consumed drinking water potentially contaminated with TCE. Community studies have focused primarily on haematological cancers, particularly leukaemia, frequently in the context of reported cancer clusters.[9–15]

The main occupations involving TCE exposure that have been studied involve metal degreasing and aircraft/aerospace maintenance or manufacturing work. Other industries with potential for TCE exposure include the iron/steel industries, where TCE may have been used as a general solvent and degreaser; painting, where products may have been cleaned with TCE or TCE was used as a solvent in the paint; the electronics industry, where TCE was used as a degreaser; the chemical industry, where TCE was used in the production of various products; the printing industry, where TCE may have been used to clean machinery and as a solvent in dyes; shoe manufacturing, where TCE was used as a solvent in the glues; and jewellery manufacturing, where TCE may have been used as a general solvent.[1 16]

As in most occupational studies, few, if any, of the exposures to workers in these occupations are limited to one chemical alone. Other petroleum based products were common ingredients in degreasers and solvents such as mineral spirits used in cleaning machinery.[17] TCE use in the USA peaked in 1970 and began a significant decline over the next decades due to a combination of regulatory and economic factors.[18] Although it has decreased over time, US production has exceeded two hundred million pounds each year and it remains a common contaminant in ground water.[1] Similar use trends have been reported in European countries.[16]

Several epidemiological TCE carcinogenicity reviews have been published.[19–24] Emphasis in these reviews has been primarily on kidney cancers,[7 20 22 24] although other outcomes have also been assessed. Wartenberg *et al*, for example, evaluated over 20 cancer sites in their assessment of TCE.[21] Recent epidemiological studies from Denmark were not evaluated in these reviews.[25 26] Furthermore, there has not been a comprehensive, quantitative meta-analysis applied to

Abbreviations: NHL, non-Hodgkin's lymphoma; SRRE, summary relative risk estimate; PCE, perchloroethylene; TCE, trichloroethylene

NHL and TCE exposure. With this in mind, we conducted a review and meta-analysis to evaluate the potential association between TCE exposure and NHL in occupational epidemiological studies with specific TCE exposure information. This assessment included recent studies that were not considered in previous quantitative or qualitative reviews.

METHODS

Literature search methods

Using the bibliographic databases Medline and Embase, studies were identified that assessed the relationship between TCE exposure and NHL. An electronic search using ''trichloroethylene and cancer'' was initially undertaken to find a comprehensive listing of articles. This was supplemented with various combinations of the following key words: ''trichloroethylene'', ''TCE'', ''occupational'', ''exposure'', ''solvents'', ''chlorinated solvents'', ''case-control'', ''cohort'', ''degreasers'', ''cancer'', using ''AND'' and ''OR'' operating terms to narrow and expand the search as appropriate.

In addition, the bibliographies of recent reviews and of the individual published studies were examined to identify potentially relevant studies of TCE exposed populations that were not identified through electronic searches.

Criteria for study inclusion and classification

Epidemiological studies were considered for inclusion in this meta-analysis if they: (1) used a cohort or case-control study design; (2) identified occupational exposures to TCE by the use of quantitative or qualitative industrial hygiene assessment; (3) reported results for NHL in adults and expressed results in the form of a relative risk estimate with an associated measure of variability (confidence intervals or p values), or included data that allowed the calculation of these measures. When there were multiple published analyses based on updates to the same cohort, we included only the most recent update in our analyses. Axelson *et al*, Anttila *et al*, Blair *et al* and Morgan *et al* were updates to earlier reports.[27–30]

We classified cohort studies into two groups based on how TCE was measured in the workplace or monitored among workers. Inclusion in Group I (n = 8) required a study to have the following features: (1) sufficient enumeration of the workforce (i.e. the data source for cohort enumeration appeared to be a complete roster of workers as opposed to partial or incomplete lists); (2) a sub-cohort identifiable within the larger cohort that was more likely to have had TCE exposure; (3) cases identifiable as having NHL, as opposed to less specific classifications such as lymphoma (both Hodgkin's and non-Hodgkin's combined) or haematopoietic cancer. In some studies, the entire cohort was TCE exposed.

Group II occupational cohort studies (n = 6) either mentioned or identified TCE exposure and NHL disease categories, but no data were provided to verify actual exposure or to identify a TCE exposed sub-cohort. Because of the lack of specific TCE exposure information or other significant study design or data quality issues, these studies were considered less informative in evaluating the relation between TCE exposure and NHL.

Our meta-analysis included four case-control studies that specifically evaluated the association between TCE exposure and NHL. Two of the case-control studies used industrial hygienists to assess occupational exposures.[31 32] Of these, one study was a nested case-control study that developed a facility specific TCE job matrix.[31] In a population based case-control study, Siemiatycki developed a TCE job matrix based on self-reported job title information.[32] The other two case-control studies relied on self-reported TCE exposure information.[33 34]

Dry cleaning work may have involved some exposure to TCE prior to the 1960s and perchloroethylene (PCE) exposure has been predominant since that time.[35] Earlier, carbon tetrachloride and Stoddard solvent, a petroleum based product, were also used.[35] Dry cleaning studies did not meet our criteria due to limitations in assessing TCE exposure among dry cleaners. These limitations include the fact that there was little or no TCE exposure for a significant portion of these workers, predominant exposure to other solvents (e.g. PCE), a lack of a distinction between dry cleaners and laundry workers, as well as study design limitations (e.g. proportionate mortality ratio analyses for several of the studies). Some of the cohorts selected for this analysis, however, did contain small proportions of dry cleaners as part of a larger TCE cohort.[25 26]

For occupational cohort and case-control studies meeting the inclusion criteria, relative risk estimates and associated 95% confidence intervals (CI) were extracted from each publication for the following information: (1) the most inclusive analyses that reflected the total cohort under study, or the exposure category in case-control studies that included all TCE exposed workers (regardless of level or duration of exposure); (2) the sub-cohort of workers who were identified as being exposed to TCE; (3) the sub-cohort exposed to the highest and lowest intensity regardless of duration of exposure; and (4) the sub-cohort of workers who were exposed to TCE for the longest and shortest durations, with or without information on the quantitative level of exposure. Studies did not always use similar quantitative exposure cut-off points or duration categories to define higher exposed groups or longer exposure duration. However, the majority reported findings for workers potentially exposed for five years or greater to identify a longer duration of exposure. Thus, our extraction and grouping of results by ''intensity'' and ''duration'' should only be considered as a qualitative classification of higher exposed or longer exposed subgroups. The original data extraction process was reviewed and verified by two members of the study team.

For cohort studies that reported relative risk estimates based on both mortality and incidence,[29] we used the incidence data for subgroup analyses and mortality data for the overall cohort analysis, as per the way these data were reported. In some studies the results for sub-cohorts were not reported directly, but could be calculated based on the data provided. In those instances, 95% confidence intervals (CI) were calculated based on the Poisson distribution.[36]

Most epidemiological studies of NHL used the ICD (versions 7 and 9) codes of 200 (lymphosarcoma and reticulosarcoma) and 202 (other lymphomas) to represent NHL.[25–30 37 38] In the study by Morgan *et al*, code 200 was reported alone. One member of our research team (MAK) had access to the original Morgan *et al* data, and we were able to regroup data and calculate SMRs for ICD 200 and 202 codes combined. Thus among the Group I studies in our analyses, the only study where ICD 200 alone was used was Ritz.[38]

Statistical analysis

Although random effects and fixed effects models were both evaluated, we present only results from the random effects models. This model assumes that the study specific effect sizes come from a random distribution of effect sizes with a specific mean and variance. The estimates of the individual studies were combined weighted by the inverse of the variance. In addition to the results for the random effects model, we calculated the p value for the test for heterogeneity. When variability among studies is negligible (high level of homogeneity), the random effects model will reduce to a fixed effects model, and the results for the two models

will be identical.[39] All analyses were performed using ''Episheet'', a spreadsheet based analytical package for meta-analyses.[40]

A description of the statistical approach used is given in Appendix A (see *OEM* website: http://www.occenvmed.com/supplemental).

We calculated SRREs for the following subgroups of studies: Group I cohort studies, Group II cohort studies, case-control studies, Group I and Group II cohort studies combined, and all cohort studies and case-control studies combined. Influence analyses were conducted to evaluate the impact of any particular study on overall SRRE results. This was done by reanalysis of the summary relative risk estimate (SRRE) after each study was removed. Changes from the original SRRE were noted and the particular study was reviewed to determine whether it differed (e.g. on study design, data collection methods, or other potential biases) from the other studies in the analysis. In addition, among Group I studies, SRREs were calculated by exposure level (highest, lowest), duration (longest, shortest), and cumulative exposure (intensity × duration) groupings, by grouping based on exposure assessment (quantitative and qualitative), and by type of cohort (single industry/aerospace/aircraft workers and multiple industry) types.

RESULTS

Results from the initial electronic search using the search terms ''trichloroethylene and cancer'' identified 249 studies. On review of the relevant study features, 18 studies (14 cohort and 4 case-control) that met our inclusion criteria were identified, and assigned to Group I, II, or case-control categories. Tables 1 and 2 list the study information by study type. Descriptive summaries of these studies are contained in Appendix B (see *OEM* website: http://www.occenvmed.com/supplemental). The Group I studies collectively account for over 3 500 000 person-years, three quarters of which were from the aerospace/aircraft worker studies. The TCE sub-cohort represented a higher proportion of the multi-industry studies (42%) compared to the single industry studies (13%).

Individual study risk estimates for all cohorts (Groups I and II) ranged between 0.80 and 3.50. The summary relative risk estimate (SRRE) for all Group I studies was 1.29 (95% CI 1.0 to 1.66) (table 3). The p value for heterogeneity was significant for the total cohort analyses ($p < 0.0001$). Given this heterogeneity and the fact that the total cohorts included many workers who had little or no TCE exposure, we assessed the Group I studies according to methodological and exposure characteristics (see below).

Group I studies; subgroup analyses

Seven of the eight Group I cohort studies provided results for TCE exposed sub-cohorts and specific information on NHL (table 3). Ritz identified the NHL category in the total cohort and a TCE sub-cohort, but did not include the specific diagnostic category for NHL within the TCE sub-cohort.[38] This study was therefore included in the calculation of the SRRE for the total cohorts in Group I, but not in the sub-cohort SRRE. When combining results from the seven Group I studies for the TCE sub-cohorts, the SRRE was 1.59 (95% CI 1.21 to 2.08) and the p value for heterogeneity was 0.18 (table 3). Removal from the analysis of any individual study did not have a profound effect on the SRRE. For example, when one of the larger studies, Raaschou-Nielsen[26] was removed, the SRRE for the remaining six studies changed to 1.64 (95% CI 1.14 to 2.38, p value for heterogeneity = 0.12). When the Hansen study, one of the most influential due to its high SIR, was removed, the SRRE for the remaining six studies decreased by 9% to 1.44 (95% CI 1.17 to 1.77, with a higher p value for heterogeneity = 0.70).

We examined results when studies were stratified further into low and high TCE exposure categories (table 4). Based on results from the four individual studies that had some type of exposure level data, the SRREs across lowest and highest TCE exposure classifications did not indicate an exposure response gradient. The summary risk estimate for the lowest TCE exposure category (SRRE = 2.33, 95% CI 1.39 to 3.91) was similar to the estimate for the highest TCE exposure category (SRRE = 2.11, 95% CI 0.76 to 5.84).

For the two studies that evaluated duration of exposure, the SRRE for the shortest duration was 1.47 (95% CI 1.08 to 2.0) and for the longest was 1.60 (95% CI 1.2 to 2.1) (table 5). As with analyses of exposure intensity alone, cumulative exposures (intensity × duration) did not show a gradient between the lower (SRRE = 1.8, 95% CI 0.62 to 5.26) and higher exposure categories (SRRE = 1.41, 95% CI 0.61 to 3.23) (table 5).

Single industry cohort studies (all US based studies) used exposure assignment methods that involved job exposure matrices based on available industrial hygiene data, walk-through surveys, and expert opinion (tables 1 and 2). These studies demonstrated greater homogeneity ($p = 0.431$ *v* 0.159) and consistently lower SRREs across the categories of ''total cohort'', ''TCE exposed sub-cohort'', and ''highest exposed'', ''lowest exposed'', ''longest exposed'', and ''shortest exposed'' categories of exposure compared to the European multiple industry studies (table 6). Within the European studies, the total cohort SRRE was similar to the TCE sub-cohort (1.84 *v* 1.86). In comparing findings for the highest *v* lowest TCE exposure or between the longest and shortest cumulative TCE exposure, there were minimal differences between SRREs within the US and European studies; there was no consistent exposure or duration-response gradient observed for either subgroup of studies.

Group II and case-control studies

For Group II cohort studies, exposure information was less specific. For Costa *et al*, although TCE was not mentioned as a potential exposure, we included this study in these summaries because this type of industry and work activity was associated with TCE exposure in aerospace/aircraft worker studies.[41] Excluding the Costa *et al* study from the SRRE calculation did not alter the SRRE for the Group II studies. Across Group II studies the summary relative risk was not elevated (SRRE = 0.84; 95% CI 0.73 to 0.98, p value for heterogeneity = 0.85) (table 7). None of the individual Group II studies reported statistically significant SMRs. Three Group II studies reported relative risk estimates (SMRs or SIRs) greater than 1.0, ranging from 1.06 to 1.27,[42–44] and three reported relative risks that were less than 1.0, ranging from 0.8 to 0.93.[41 45 46]

The four case-control studies examining NHL had a wide range of findings, with odds ratios ranging from 0.8 to 7.20 (table 7). The overall SRRE across the four studies was 1.39 (95% CI 0.62 to 3.10) with a relatively low p value for heterogeneity ($p = 0.17$). Removal of one influential study changed the SRRE to 1.08 (95% CI 0.58 to 2.03) and the p value for heterogeneity increased ($p = 0.58$).

When analyses were conducted that combined the Group I and Group II studies, the SRRE = 1.13 (95% CI 0.94 to 1.34, p value for heterogeneity = 0.001). When case-control and both cohort types were all analysed together, the most inclusive analysis, the SRRE was 1.14 (95% CI 0.95 to 1.38, with indications of heterogeneity (p value for heterogeneity = 0.001).

DISCUSSION

This meta-analysis focused on occupational cohort and case-control studies that had specific TCE exposure information

Table 1 Occupational cohort studies that assessed TCE exposure and NHL

Author(s) and year	Workforce size	Person-years	Follow up period	Number of exposed NHL cases or deaths	Cohort description	Exposure
GROUP I						
European studies						
Anttila *et al*, 1995[28]	3974 3089 (TCE)	71 800 total 59 905 TCE	1967–92	8 cases	Solvent workers bio-monitored for TCE (Finland)	Urinary TCA bio-monitoring levels
Axelson *et al*, 1994[27]	1670	22 446	1958–87	5 cases	Male workers ⩽79 years bio-monitored for TCE from facilities where TCE was used (Sweden)	Urinary TCA bio-monitoring levels
Hansen *et al*, 2001[25]	803	16 730	1968–96	8 cases	Cohort of TCE workers who were monitored for uTCA or had breathing zone air measurements	Urinary TCA or breathing zone TCE measurements. Average 2.2 measurements per individual, mostly uTCA measures. uTCA, mean 40 mg/l, median 15 mg/l. Air TCE measurements: mean 101 mg/m^3, median 28 mg/m^3. For 36% of uTCA and 48% of air measurements, worker could not be identified
Raaschou-Nielsen *et al*, 2003[26]	40 049 total 14 360 TCE	706 317 total 339 486 TCE	1964–97	96 cases	Blue-collar workers (Denmark) Presumed highly exposed sub-cohort: at least one year employment that started <1980	Identified TCE using companies, restricted cohort to smaller (<200 workers) companies. Final cohort included iron and metal, electronics, chemical, and other industries. Restricted to smaller companies on assumption of larger proportion of TCE exposed workers
US studies						
Blair *et al*, 1998[29]	14 457 7204 TCE	NR	1953–90	49 deaths	Update of Spirtas *et al* (1991), aircraft maintenance facility (Utah)	Walk-through survey, interviews, record review, chemical inventory, review of available industrial hygiene data
Boice *et al*, 1999[37]	77 965 45 323 factory 2267 TCE (routine exposure)	1 889 795 total 1 121 639 factory 66 183 TCE	1960–96	215 deaths	Aircraft manufacturing (Burbank, California)	Walk-through survey, interviews, review of available industrial hygiene data. Factory/non-factory workers, TCE and other solvent sub-cohorts, internal cohort
Morgan *et al*, 1998[30]	20 508 4733 TCE	461 617 total 105 852 TCE	1950–93	9 deaths	Aerospace manufacturing (Arizona) TCE exposed sub-cohort	Job classifications used to define TCE sub-cohort (high/medium/low/none), cumulative and peak exposure, TCE also in drinking water
Ritz, 1999[38]	120 237	120 237	1951–89	8 deaths (ICD-8 code 200, lymphosarcoma and reticulosarcoma)	Male uranium processing workers (Ohio)	Plant industrial hygienists and others classified jobs into TCE exposure categories: none, light, moderate, high
GROUP II						
Blair *et al*, 1989[42]	1767 inspectors 1914 others	36 720 55 571	1942–80	4 deaths (lymphoma and reticulosarcoma)	US Coast Guard marine inspectors vs. non-inspectors	Exposed to various chemicals including TCE but could not assess exposure to any specific chemicals
Chang *et al*, 2003[43]	86 868	1 022 094	1985–97	15 deaths (other lymphatic and haematopoietic)	Electronics manufacturing factory (Taiwan)	TCE in wells near waste disposal sites of facility, but no worker exposure information available.
Costa *et al*, 1989[41]	8626	113 120	1954–81	12 deaths (lymphatic and haematopoietic)	Aircraft manufacturing factory (Italy)	Solvents listed among hazardous substances used; TCE not specifically mentioned
Garabrant *et al*, 1988[45]	14 067	222 100	1958–82	13 deaths (lymphosarcoma and reticulosarcoma)	Aircraft manufacturing (San Diego County, California)	37% of cohort had TCE exposure, based on interviews of small sample of workers

Table 1 Continued

Author(s) and year	Workforce size	Person-years	Follow up period	Number of exposed NHL cases or deaths	Cohort description	Exposure
Henschler *et al*, 1995[44]	359	11 288 total 5188 exposed 6100 unexposed	1956–92	2 deaths (exposed and unexposed: lymph and haematopoietic)	Cardboard manufacturers, exposed at least 1 year (Germany)	Walk-through surveys and interviews
Selden and Ahlborg 1991[46]	2176	21 463	1975–84	3 cases (lymphatic tissue)	Members of Swedish Armed Forces (SAF) with jet fuel exposure	TCE used for metal degreasing to a limited extent but no data on individual exposure available

Table 2 Occupational case-control studies that assessed TCE exposure and NHL

Author(s) and year	Study population	Diagnostic period	Number of cases and controls	Number of exposed cases	Study description
Greenland *et al*, 1994[31]	Deceased transformer assembly workers	1969–84	15 eligible lymphoma cases with job history information available 1202 controls	Specific number of TCE exposed cases was not available	Nested case control study that examined cancer mortality and occupational exposure to seven chemicals or chemical groups among transformer assembly workers. Agent specific job-exposure matrices (JEM) were created based on chemical inventories and detailed work history information
Hardell *et al*, 1994[33]	Swedish men admitted to the Dept of Oncology in Umea and population registered controls	1974–78	105 cases 335 controls	4 TCE exposed cases	Evaluated the relationship between exposure to phenoxyacetic acids, chlorophenols, or organic solvents and NHL. Exposure information was obtained by questionnaire and telephone interviews. Occupations were classified according to the Nordic Working Classification system
Persson *et al*, 1989[34]	Swedish male and female hospital registered cases and population registered controls	1964–86	106 cases 275 controls	8 TCE exposed cases	Evaluated the relationship between occupational risk factors and malignant lymphomas in men and women A nine page questionnaire was used to ascertain occupational exposure information. Qualitative information regarding exposure to solvents was obtained directly from the questionnaires
Siemiatycki, 1991[32]	Males aged 35–70 residing in the Montreal Metropolitan area	1979–85	215 cases 2357 ''other'' cancer patient controls 533 population controls	6 TCE exposed cases	Evaluated TCE as one of over 290 substances. Self-reported information on occupational exposure was evaluated by industrial hygienists to determine whether there was potential for TCE exposure

Table 3 Summary of individual and meta-analysis results for Group I

Author(s) and year	Type of risk estimate	Number of exposed cases or deaths	Risk estimate	95% CI
Cohort studies from multiple industries (Europe)				
Anttila *et al*, 1995[28]*	SIR	8	1.81	0.78 to 3.56
Axelson *et al*, 1994[27]*	SIR	5	1.52	0.49 to 3.54
Hansen *et al*, 2001[25]*	SIR	8	3.50	1.50 to 6.90
Raaschou-Nielsen *et al*, 2003[26]*	SIR	65	1.50	1.20 to 2.00
Summary risk estimate: random effects model	SRRE	86	1.86	1.27 to 2.71
Test for heterogeneity	p=0.159			
Cohort studies involving aerospace and aircraft industry (USA)				
Blair *et al*, 1998[29]†	RR	28	2.00	0.90 to 4.60
Boice *et al*, 1999[35]‡	SMR	14	1.19	0.65 to 1.99
Morgan *et al*, 1998[30]§	SMR	9	1.01	0.46 to 1.92
Summary risk estimate: random effects model	SRRE	51	1.25	0.87 to 1.79
Test for heterogeneity	p=0.431			
Overall summary risk estimate: random effects model	SRRE subcohorts	137	1.59	1.21 to 2.08
	SRRE total cohorts	429	1.29	1.0 to 1.66
Overall test for heterogeneity				
Sub-cohorts	p=0.181			
Total cohorts	p=0.0001			

Ritz (1999) included in overall SRRE but not in sub-cohort (number of exposed cases=10; SMR=1.03; 95% CI 0.49 to 1.89).
*Results based on ICD-7 codes 200 and 202.
†Results based on ICD-8 codes 200 and 202.
‡Results based on ICD-9 codes 200 and 202.
§Results based on ICD-7, -8, -9 codes 200 and 202 (as per the version in use at the time of death).

available. As such, it is the first comprehensive review to provide a detailed quantitative evaluation of epidemiological studies and address heterogeneity and exposure response trends. In an attempt to minimise exposure heterogeneity and rely only on studies of assumed better quality and study design, we did not include PMR studies or community studies.

We assumed that the focus on occupational exposures would provide a better and less biased assessment of occupational TCE exposures compared to other study types. The incorporation of exposure levels along with more accuracy in defining exposure has recognised value in minimising heterogeneity in meta-analysis studies.[47]

Heterogeneity

Heterogeneity was pronounced when both cohort and case-control studies were combined ($p < 0.0001$). When cohort studies of aerospace/aircraft worker and multiple industry studies were included in the analysis, the overall SRRE was 1.29 (95% CI 1.0 to 1.66). The p value for heterogeneity was still highly significant for this analysis ($p < 0.0001$). There were methodological differences in the multiple industry and single industry study groups. For example, the former studies reported findings for NHL incidence, and had cohorts that were generally formed more recently (1960s), whereas the single industry studies reported findings for NHL mortality with cohorts assembled earlier (1950s). When we examined potential sources of variability within each of these sub-groups, we found that heterogeneity decreased within each of these subgroups (compared to the combined analysis). A greater decrease was evident for the single-industry studies (table 3). Whether the source of variability was related to different exposures in these two groups or from other

Table 4 Individual and meta-analysis results for Group I sub-cohort studies of occupational TCE exposure and non-Hodgkin's lymphoma by lowest and highest TCE exposure categories

Reference and level of exposure	Type of risk estimate	Lowest exposure category		Highest exposure category	
		Risk estimate	95% CI	Risk estimate	95% CI
Anttila *et al*, 1995[28]					
TCE exposed sub-cohort					
Low: <100 μmol/l uTCA					
High: ≥100 μmol/l uTCA	SIR	2.01	0.65 to 4.69	1.40	0.17 to 5.04
Axelson *et al*, 1994[27]					
TCE exposed sub-cohort (≥2 years of exposure and 10 years of latency)					
Low: <50 mg/l mean uTCA					
High: ≥100 mg/l mean uTCA	SIR	1.64	0.20 to 5.92	8.33	0.22 to 46.43
Hansen *et al*, 2001[25]					
Low: individual mean exposure (<19 mg/m^3)					
High: individual mean exposure (≥19 mg/m^3)	SIR	3.90	1.10 to 10.0	3.2	1.10 to 10.0
Morgan *et al*, 1998[30]*					
TCE exposed sub–cohort					
Low: approx <50 ppm					
High: approx. ≥50 ppm	SMR	1.79	0.22 to 6.46	0.50	0.01 to 2.79
Summary risk estimate: random effects model	SRRE	2.33	1.39 to 3.91	2.11	0.76 to 5.84
Test for heterogeneity	p value	0.63		0.109	

*Results for lymphosarcoma, reticulosarcoma.

Table 5 Individual and meta-analysis results of occupational TCE exposure and non-Hodgkin's Lymphoma for Group I sub-cohorts by shortest and longest cumulative exposure and duration categories of exposure

Reference and exposure level	Type of risk estimate	Shortest exposure category		Longest exposure category	
		Risk estimate	95% CI	Risk estimate	95% CI
Cumulative exposure (intensity × duration)					
Blair *et al*, 1998[29]					
TCE exposed sub-cohort					
Shortest: <5 unit-years					
Longest: >25 unit-years (units = intensity/year × duration/day for each job × frequency)	RR	0.85	0.39 to 1.62	0.98	0.45 to 1.86
Hansen *et al*, 2001[25]					
Cumulative TCE exposed sub-cohort					
Shortest: <1080 months × mg/m^3					
Longest: ⩾1080 months × mg/m^3	SIR	3.90	0.80 to 11.0	3.10	0.6 to 9.10
Morgan *et al*, 1998[30]*					
Shortest: cumulative and low TCE exposed sub-cohort					
Longest: cumulative and highly TCE exposed sub-cohort (based on intensity and duration of exposure)	RR	2.25	0.46 to 11.1	0.81	0.10 to 2.20
Summary risk estimate: random effects model	SRRE	1.8	0.62 to 5.26	1.41	0.61 to 3.23
Test for heterogeneity	p value	0.041		0.179	
Duration of exposure (time)					
Boice *et al*, 1999[35]					
TCE exposed sub-cohort					
Shortest: 1–4 years exposed					
Longest: ⩾5 years exposed	RR	1.33	0.64 to 2.78	1.62	0.82 to 3.22
Raaschou-Nielsen *et al*, 2003[26]					
Cumulative TCE exposed sub-cohort					
Shortest: 1–4.9 years					
Longest: ⩾5 years	SIR	1.50	1.10 to 2.10	1.60	1.10 to 2.20
Summary risk estimate: random effects model	SRRE	1.47	1.08 to 2.0	1.60	1.20 to 2.10
Test for heterogeneity	p value	0.771		0.974	

*Results for ICD codes 200 and 202.

methodological issues is not known. Exposure misclassification in the multiple industry studies would likely be higher because this cohort comprised multiple categories of industry with multiple types within these main categories. Job related exposures would vary accordingly as would the ability to capture exposure accurately in each of these settings. For example, in Denmark, the main industries represented were iron and steel (48%), electronics (11%), painting (11%), printing (8%), chemical (5%), and dry cleaning (5%).[25]

When we examined the association between TCE and NHL exclusively within the aerospace industry cohorts in the USA, the meta-analysis for this group did not show a significant association between TCE and NHL (SRRE = 1.25, 95% CI 0.87 to 1.79, p value for heterogeneity = 0.431). Implicit in this assessment was the increased likelihood of more uniform exposures. However, the aerospace studies incorporated both manufacturing and maintenance work within that industry. An exposure assessment within that industry demonstrated a wide variety of job tasks and accompanying exposures.[48]

Our meta-analysis findings highlight a pattern of elevated relative risk estimates among studies of multiple industries. These studies used incidence data and three of the four studies used bio-monitoring to ascertain exposures in the cohort. Studies of single industries (aerospace/aircraft maintenance workers (Group I), and also Group II studies of cohorts of coast guard personnel, cardboard manufacturing workers, electronics workers as well as aerospace/aircraft maintenance workers) did not observe statistically significant elevations in relative risks.

The Group II studies are limited in that TCE exposure information is less specific than in Group I studies. Other limitations of the Group II studies include short latency (electronics workers[43]) and small study size (cardboard workers[44]). The case-control study results were consistent with no association between TCE exposure and NHL, with one clear ''outlier'' study that reported an odds ratio of 7.2 based on self-reported TCE exposure.[33] The numbers of exposed cases in each of the studies were small, and the individual odds ratio estimates were imprecise.

Table 6 Comparison of summary risk estimates (SRRE) from single industry cohorts versus cohorts from multiple companies within Group I cohorts studies of occupational TCE exposure and non-Hodgkin's lymphoma

	Group I studies involving single industry cohorts*		Group I studies involving multiple industry cohorts†	
	SRRE (95% CI)	p value for heterogeneity	SRRE (95% CI)	p value for heterogeneity
Total cohort	1.00 (0.80 to 1.24)	0.119	1.84 (1.10 to 3.07)	0.012
TCE exposed sub-cohort	1.25 (0.87 to 1.79)	0.431	1.86 (1.27 to 2.71)	0.159
Highest TCE exposure	0.90 (0.50 to 1.65)	0.472	2.96 (1.20 to 7.32)	0.257
Lowest TCE exposure	1.00 (0.55 to 1.81)	0.31	2.45 (1.39 to 4.32)	0.47
Longest TCE exposure	1.21 (0.77 to 1.92)	0.535	1.81 (1.09 to 2.99)	0.248
Shortest TCE exposure	1.10 (0.69 to 1.75)	0.44	2.13 (0.86 to 5.26)	0.09

*Includes the following: Blair *et al*, 1998;[29] Boice *et al*, 1999;[35] Morgan *et al*, 1998.[30]
†Includes the following: Anttila *et al*, 1995;[28] Axelson *et al*, 1994;[27] Hansen *et al*, 2001[25]; Raaschou-Nielsen *et al*, 2003.[26]

Table 7 Individual and meta-analysis results for Group II cohort studies and case-control studies of occupational TCE exposure and non-Hodgkin's lymphoma

Reference	Type of risk estimate	Risk estimate	95% CI
Group II cohort studies			
Garabrant *et al*, 1988[45]	SMR	0.80	0.68 to 0.95
Blair *et al*, 1989[42]	SMR	1.06	0.34 to 2.47
Selden *et al*, 1991[46]	SIR	0.93	0.19 to 2.73
Costa *et al*, 1989[41]	SMR	0.80	0.41 to 1.40
Henschler *et al*, 1995[44]	SMR	1.10	0.12 to 3.99
Chang *et al*, 2003[43] (men)	SMR	1.27	0.41 to 2.97
Chang *et al*, 2003[43] (women)	SMR	1.14	0.55 to 2.10
Summary risk estimate: random effects model	SRRE	0.84	0.73 to 0.98
Test for heterogeneity	p value	0.846	
Case-control studies			
Greenland *et al*, 1994[31]*	OR	0.76	0.24 to 2.42
Hardell *et al*, 1994[33]	OR	7.20	1.30 to 42.0
Persson *et al*, 1989[34]	OR	1.52	0.59 to 3.73
Siemiatycki *et al*, 1991[32]†	OR	0.80	0.15 to 3.12
Summary risk estimate: random effects model	SRRE	1.39	0.62 to 3.10
Test for heterogeneity	p value	0.17	
Summary risk estimate: excluding Hardell	SRRE	1.08	0.58 to 2.03
Test for heterogeneity	p value	0.58	

*Results for ICD-8 lymphomas 200–202.
†Substantial exposure group.

The SRRE for all four case-control studies was 1.39 (95% CI 0.62 to 3.10) (table 6). It is noteworthy that the Hardell study, which reported the highest association for NHL, relied on self-report for assigning TCE exposure. Two other case-control studies, which applied a job exposure matrix methodology for TCE exposure assessment, with work histories provided by company records or self-report, both observed odds ratios less than 1.0.[31 32]

In summary, considering only the Group I studies that we identified a priori as potentially more informative, there was less variability in the studies assessing single industry cohorts. The SRREs based on these studies are lower than from multiple industry cohorts, which had significantly elevated relative risk estimates and evidence of greater variability. Random error in the multiple industry studies does not appear as a likely explanation given the relatively narrow confidence intervals around the summary relative risk estimate. However, the potential role of systematic error (bias) should be considered including information bias (e.g. exposure and/or disease misclassification), selection bias, and confounding.

Exposure classification

A finding of exposure response trends would provide additional evidence that the observed positive associations are related to TCE exposure. Using available exposure response data, evaluated by duration, intensity and cumulative exposure, no apparent patterns were observed. These analyses were limited, however, because only two categories of exposure levels could be defined across studies, and not all studies could be included in these analyses. Neither subgroup of the Group I studies (single industry or multiple industry) provided indications of exposure response trends, assessed by exposure level, duration or cumulative exposure. The lack of exposure response is consistent with the findings of no exposure-related association. Disease latency analyses were not presented in any of the cohort studies. Such analyses would provide additional insights into causal associations, providing that the NHL latency is sufficiently long.

The aerospace/aircraft worker studies and the multiple industry studies differed considerably in their methods, especially as it involved exposure assessment. Within the latter grouping, three out of four studies used urinary trichloroacetic acid (uTCA) measures to define those with highest exposures. They averaged only several urinalyses per individual, despite following the overall cohort for over 40 years or more in some cases.[25] In addition to how representative a few biomarker measurements might be of lifetime TCE exposure, an additional concern is the potential for selection bias. Participation rates in the monitoring programmes were not reported, so it is unclear how well the bio-monitoring data represented the universe of exposed workers. Since the monitoring participation was not selected at random, it is possible that participating workers with more health problems may have higher participation and could be more at risk for NHL on the basis of underlying disease, not exposure. Nevertheless, while the limited biomarker data may not accurately reflect a worker's entire exposure history, it does represent a point in time where exposure can be uniquely quantified in that individual. It is potentially a very useful tool in studies assessing disease risk. Its use in some of the multiple-industry studies (European) of TCE is commendable, but needs to be interpreted with caution for the reasons above. This same criticism could be raised for the exposure assessments that rely on air monitoring, where sampling results may not be representative of actual working conditions.

The fourth and largest multiple-industry study used a previous quantitative exposure assessment to identify the TCE worker cohort.[26] This initial exposure assessment identified several hundred companies as using TCE from a central exposure registry. The study focused on companies with less than 200 employees because they were likely to have higher TCE exposures than larger companies.[25] No individual exposure measurements were performed for the epidemiological analyses, so although smaller companies tended to have a larger proportion of TCE workers exposed, there were still likely to be workers within the smaller companies who did not receive significant TCE exposure.

The aerospace/aircraft worker studies followed one primary cohort with multiple types of exposures and did not use biomarkers of exposure. The total cohorts were generally

larger and the studies relied on industrial hygiene walk-through job assessments and job exposure matrices to classify individual workers. The exposure assessment protocols for both the aerospace/aircraft worker and multiple industry studies have limitations and it is difficult to characterise any of these study types as having more or less misclassification bias. Even though the aerospace/aircraft worker studies involved larger total cohort sizes, TCE exposure was limited to a relatively small sub-cohort in some studies, compared to the overall cohort size.[30 37] Actual exposure to TCE may have been limited as some companies changed to other chemicals.[37] The exposure potential in the aerospace/aircraft industry has been described as complex, with multiple potential exposures.[49]

As a part of our effort to understand further the heterogeneity of exposure among these cohorts, we conducted a review of each Group I cohort exposure description. This review was based on the published information of these cohorts and was independently done by two individuals experienced in exposure assessment. Both quantitative and qualitative exposure information were assessed, in an effort to rank the exposures from highest to lowest. Some of the cohort studies were accompanied by more detailed, formal separate publications on their exposure assessment methods and results.[48–50]

From this review, several important exposure assessment issues were identified among these studies. First, the quality of these exposure assessments is difficult to characterise because methodologies were so different. The multiple industry study approach was more quantitative and biological, but suffered from having samples that were not randomly selected. On the other hand, it was not entirely clear how representative air monitoring was in single industry studies. In addition, it was difficult to quantitatively describe exposures in all of the cohorts, particularly when TCE exposures occurred prior to the mid-1960s, a time when industrial hygiene sampling was not routinely undertaken.

Consideration of the results of all analyses conducted in this study indicates a lack of consistency across various groupings of the cohort and case control studies. In terms of a biological gradient, within the Group I TCE sub-cohorts, those studies with elevated risk estimates did not have increased risk estimates with estimated higher cumulative exposures[25] and had slightly different SRREs, with longer duration of exposures.[26] There were no trends for elevations in risk estimates with increasing urinary TCA concentrations.

Disease classification

Both European and US study groups combined ICD categories (ICD versions 7 and 9) 200 (lymphosarcoma and reticulosarcoma) and 202 (other lymphoma). There is evidence to suggest that more recently developed schemes for identifying and categorising NHL types may play an important role in understanding risk factors and prognosis of this disease.[51 52] Until recently, few epidemiological studies have analysed data according to type of NHL. The increases in SIRs demonstrated in two of the Group I studies could be influenced by the presence of one or more particular types of lymphoma. If this were true, an analysis of all lymphoma types could bias the results downward. Information concerning incidence trends by NHL type is limited as are potential links between occupational factors and specific types of NHL.[51] None of the studies used in this meta-analysis incorporated these more recent types of diagnostic information.

The European multi-industry cohort studies and the Blair (1998) study relied on cancer incidence rather than mortality data. When SIR and SMR study types are both considered in the context of TCE in its association to NHL, it is difficult to explain why morbidity and mortality would be different. The increases for NHL in the general population over the past several decades have been for both morbidity and mortality.[53 54]

Confounding

Occupational cohort studies typically lack individual data on potential confounding factors, whereas case-control studies often collect information that is more detailed. This should not be a serious limitation if the cancer outcome of interest is not associated strongly with the potential confounding factors. Even if other risk factors exist, their association with exposure must be sizably stronger in the study cohort relative to the comparison population to act as material confounders.

Established risk factors for NHL include increasing age,[55] male gender,[55] family history of NHL or other haematolymphoproliferative cancers,[56 57] certain autoimmune disorders (e.g. rheumatoid arthritis, Sjogren's syndrome),[58–60] and infectious agents such as human immunodeficiency virus (HIV),[61–63] human herpes virus 8 (HHV-8),[64 65] and Epstein-Barr virus (EBV).[66–68] Although the factors related to family history, immune function, and infectious agents appear to play a role in the aetiology of NHL they do not explain a majority of the cases due to their relatively low prevalence in the population. Other factors, such as pesticide exposure,[69–76] occupational or environmental exposure to other chemicals,[23 77–79] dietary factors,[80–82] hair dye exposure,[83] obesity,[84 85] and sunlight exposure[86–88] have been reported in some studies as associated with NHL. Although smoking prevalence may be higher among TCE exposed workers,[26] smoking has not been consistently associated with NHL and it is unlikely that it would confound the association between TCE and NHL.

In summary, based on current understanding of NHL risk factors, none of them appear to be plausible as important confounders either because of a lack of association with exposure (i.e. TCE) or because the magnitude of any association would not be strong enough to meaningfully confound an association between TCE and NHL.

Summary and conclusions

This meta-analysis demonstrated significant heterogeneity of study findings among the total group of studies considered. There was also evidence for heterogeneity in the meta-analysis limited to Group I cohort studies, which exhibited the best information on TCE exposure. We found no statistically significant increase in the SRRE for the single industry cohort group. The SRRE for the multiple industry group was significantly elevated but there appeared to be more variability among these studies and little in the way of positive exposure response trends. Exposure assessments varied widely between these two types of cohorts, and although exposure may have contributed to the heterogeneity, given the available information from accompanying exposure assessments, it is difficult to determine whether single or multiple industry cohorts were likely to have had more TCE exposure. The associations of TCE with NHL in the studies that included workers from multiple industries were not consistent with broader guidelines for causality.

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