Exhibit 264

Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis

Sara Karami,[1] Bryan Bassig,[1] Patricia A Stewart,[2,3] Kyoung-Mu Lee,[3,4] Nathaniel Rothman,[1] Lee E Moore,[1] Qing Lan[1]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2012-101212).

[1]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA
[2]Stewart Exposure Assessments, LLC, Arlington, Virginia, USA
[3] Formerly of the Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA
[4]Department of Environmental Health, Korea National Open University, Seoul, Korea

Correspondence to
Dr Sara Karami and Dr Lee E Moore, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd, EPS 8102, Rockville, MD 20852, USA; moorele@mail.nih.gov

NR, LEM and QL co-supervised this work.

Received 28 September 2013
Revised 23 April 2013
Accepted 30 April 2013
Published Online First 30 May 2013

To cite: Karami S, Bassig B, Stewart PA, *et al*. *Occup Environ Med* 2013;**70**: 591–599.

ABSTRACT

The carcinogenic potential of trichloroethylene (TCE) continues to generate much controversy, even after the US Environmental Protection Agency raised its classification to 'carcinogenic to humans'. We conducted a meta-analysis of published cohort and case–control studies exploring occupational TCE exposure in relation to five different lymphatic and haematopoietic cancers: non-Hodgkin's lymphoma (NHL, N=24), Hodgkin's lymphoma (HL, N=13), multiple myeloma (MM, N=11), leukaemia (N=12) and chronic/small lymphocytic leukaemia (CLL/SLL, N=7). Studies published between 1950 and 2011 were identified through a PubMed Medline search. All studies included in analyses were classified as those that assessed either occupational TCE exposure specifically ('TCE-exposure' studies) or a broader classification of all chlorinated solvents ('chlorinated solvent-exposure' studies). A significantly raised summary estimate for NHL was seen for all cohort and case–control 'TCE-exposure' studies combined (N=19; relative risk (RR)=1.32, 95% CI 1.14 to 1.54; I^2=25.20; p-heterogeneity=0.12) and for cohort 'TCE-exposure' studies (N=10; RR=1.52, 95% CI 1.29 to 1.79; I^2=7.09; p-heterogeneity=0.63). A non-significant but raised summary estimate was seen for NHL case–control 'TCE-exposure' studies. No significant association with NHL risk was detected overall for any 'chlorinated solvent-exposure' studies. Summary estimates for occupational TCE exposure were not associated with risk of HL, MM, leukaemia or CLL/SLL. Our updated meta-analysis of NHL, which incorporates new analytical results from three cohort and four case–control studies, supports an association between occupational TCE exposure and NHL.

What this paper adds

- This review presents findings for updated meta-analyses of occupational trichloroethylene (TCE) exposure and risk of five different lymphatic and haematopoietic cancers.
- In efforts to reduce exposure misclassification, summary risk estimates for studies that assessed TCE specifically ('TCE-exposure' studies) were compared with those assessing any type of chlorinated solvent ('chlorinated solvent-exposure' studies).
- The meta-analysis for non-Hodgkin's lymphoma (NHL), which incorporated results for 293 NHL cases from 12 cohort (228 cases from 10 'TCE-exposure' and 65 cases from two 'chlorinated solvent-exposure') studies and 8140 NHL cases from 12 case–control (6095 cases from nine 'TCE-exposure' and 2045 cases from three 'chlorinated solvent-exposure') studies, was supportive of an association between occupational TCE exposure and increased risk.
- The association for NHL was not observed for studies that used the broader category of 'chlorinated solvent' exposure, suggesting that this exposure metric, which has been used in previous meta-analyses, may introduce exposure misclassification, resulting in bias towards the null.
- These findings indicate that efforts to reduce exposure misclassification by analysis of TCE specifically may strengthen the association between TCE exposure and cancer risk.

INTRODUCTION

Inconsistent epidemiological evidence, the difficulty of extrapolating findings from animal models to humans and debate over the interpretation of epidemiological results have fuelled controversy surrounding the toxicological and carcinogenic potential of trichloroethylene (TCE).[1–3] In 2006, the National Academy of Sciences recommended that additional meta-analytical studies be conducted to further examine the human health risk assessment of TCE exposure.[3] As a result, in 2011 the US Environmental Protection Agency released its human risk assessment of TCE, raising the agent's classification as 'carcinogenic to humans'.[1] Subsequently, in 2012, the International Agency for Research on Cancer (IARC) also raised TCE's classification from a group 2A 'probable human carcinogen' to a group 1 'human carcinogen'.[2]

Widely manufactured for commercial use as a solvent for nearly a century, TCE is primarily used in the vapour degreasing of metal parts.[4] This chlorinated solvent has also been used in the dry-cleaning, food and chemical processing, healthcare and electronics industries.[4–6] People working in degreasing operations are among the most heavily TCE-exposed workers.[5 7] According to the US National Institute for Occupational Safety and Health, about 3.5 million US workers are exposed to TCE.[8] In addition, the solvent continues to be classified as a hazardous waste pollutant, persists as a common groundwater contaminant and is one of the most commonly observed chemicals at Superfund sites, abandoned hazardous locations requiring long-term response in order to clean up pollutant material contaminates.[3 4 9] Since the

1970s TCE use worldwide has declined owing to economical, regulatory and public health concerns.[4 5 9] TCE use in most industries has diminished and it has been replaced by other chlorinated and non-chlorinated solvents. A limitation of some previous reviews is that they have examined exposure to chlorinated solvents as a surrogate for TCE exposure, which might have increased the likelihood of TCE-exposure misclassification.[10 11] To examine this subject, we conducted a meta-analytical review of published studies to explore the link between occupational TCE exposure and risk of lymphatic and haematopoietic cancers by assessing whether studies that evaluated TCE exposure differed explicitly from those that evaluated mixed chlorinated solvent exposures.

Both animal and human studies have shown an increased risk of lymphoid neoplasms after TCE exposure.[1–4 8 9] In humans, TCE exposure has been associated with reduced activity of markers of immune activation and major lymphocyte subsets (ie, CD4, CD27, CD30), which play a vital role in regulating the cellular activity of T, B and natural killers cells that are critical for immune response.[12] TCE exposure has also been shown to stimulate unscheduled DNA synthesis in vitro in human lymphocytes, a mechanism that has been associated with increased cancer risk.[13 14] Since TCE can dysregulate and impair immune functions, concerns about the solvent's immunotoxic effects have motivated numerous investigations of the association between TCE exposure and lymphoma risk, which have been associated with reduced immune function. Given that over the past half-century there have been substantial changes in the histological categorisation of lymphoid neoplasms (ie, the International Classification of Diseases (ICD), revision 7–9 and ICD for oncology revision 3), it has been challenging to discern the exact relationship between TCE exposure among the different subtypes of lymphoid neoplasms.[15–18] To deal with this concern, our review also evaluated the association between occupational TCE exposure and the risk of five different lymphatic and haematopoietic cancers using consistent criteria, defined according to ICD-9: non-Hodgkin lymphoma (NHL: ICD-9 200, 202), Hodgkin's lymphoma (HL: ICD-9 201), multiple myeloma (MM: ICD-9 203.0), leukaemia (ICD-9 204-208) excluding chronic/small lymphatic leukaemia (CLL/SLL) and CLL/SLL (ICD-9 204.1). To our knowledge, this is the first meta-analytical assessment of occupational TCE exposure in relation to CLL/SLL risk. Our review also incorporates new analytical results from both cohort (three NHL, five HL, four MM and five leukaemia) and case–control (four NHL, two HL and two MM) studies not assessed in previous meta-analyses of TCE.[10 19–21]

METHODS

Study identification, data extraction and exposure assessment

We conducted a PubMed Medline (http://www.ncbi.nlm.nih.gov/sites/entrez) search using the following key words: *trichloroethylene exposure and cancer*, *organochlorine exposure and cancer*, *chlorinated solvents and cancer*, *solvent exposure and cancer* and *occupational exposures and lymphoma*. All published cohort and case–control studies written in English from 1950 through 2011 that assessed occupational TCE or chlorinated solvent exposure and risk of NHL, HL, MM, leukaemia or CLL/SLL were included in our review. References in all identified publications were also reviewed for additional studies. As a result, we excluded community-based studies of TCE exposure from drinking water, since the level and route of exposure differ from those found in occupational settings.[10] We also excluded standardised incidence ratio/standardised mortality ratio (SIR/SMR) studies that evaluated cancer risk among a wide range of workers for whom the likelihood of TCE exposure is considered lower than for other solvents (ie, paints, benzyl chloride, diesel, etc). Except for one study that specifically assessed TCE in the industry,[22] studies of dry-cleaners and launderers were excluded from our analysis as most of these studies either had low or unknown specificity of TCE exposure.[5]

Subsequent exclusions of cohort studies that reported proportionate mortality ratios/proportionate cancer mortality ratios were made,[23–27] as well as those reporting SMRs without providing information on the number of observed/exposed cases.[28 29] When risk estimates were not presented, where possible, we calculated crude risk estimates using the number of subjects provided in the manuscripts (ie, expected/observed cases and unexposed/exposed subjects).[22 30–34] When more than one manuscript was published on the same cohort, we chose the publication with the highest quality and most precise exposure assessment. Thus, Zhao *et al*[35] and Boice *et al*[36] both published manuscripts on the same cohort using different inclusion criteria; in our analysis, we included results from the Boice *et al*[36] study which had a longer follow-up of more participants and assessed TCE exposure separately for lymphoma subtypes. We also identified three manuscripts on the same cohort of US aircraft workers[28 31 37]; the study with the most recent follow-up was included in our review.[31] Likewise, two other US studies conducted on the same cohort of aircraft workers were identified[38 39]; only results from the extended follow-up study were used.[39]

For a number of case–control studies, overlapping sets of participants from the same population were recruited. Two Swedish studies enrolled cases and controls from the same population during similar time periods[33 40]; only NHL results from the larger study were included in our review.[40] However, HL results from this population were only reported in the smaller study and were therefore used in our analysis of HL risk.[33] Additionally, an overlapping number of cases and controls from a German case–control study[34] was also included in a larger European multicentre study.[32] Because the larger European multicentre study did not evaluate HL risk, findings from the German case–control study were included in our analysis of HL risk. In total, our final analysis included 12 cohort (12 NHL, 10 HL, 9 MM, 11 leukaemia and 2 CLL/SLL) and 16 case–control (12 NHL, 3 HL, 2 MM, 1 leukaemia and 5 CLL/SLL) studies.

To evaluate the specificity of the TCE-exposure data available in each study, an expert industrial hygienist (PAS) blinded to the epidemiological results categorised each study into two groups: 'TCE-exposure' and 'chlorinated solvent-exposure' studies. Cohort studies that assessed TCE exposure using job-exposure matrices (JEMs) or biomonitoring data, and case–control studies that assessed TCE exposure specifically or covered metal degreasing/cleaning industry workers were classified as 'TCE-exposure' studies. Studies that assessed exposure to a broader group of chlorinated solvents or covered aircraft manufacturing, iron or metal workers were classified as 'chlorinated solvent-exposure' studies. Consistent categorisation of studies as 'TCE-exposure' or 'chlorinated solvent-exposure' was found between the expert industrial hygienist and the authors.

For two studies, the subcohort analysis was selected that assessed TCE exposure using more restrictive inclusion criteria, thereby reducing the likelihood of TCE-exposure misclassification.[30 39] However, similar results but with less precise risk estimates were observed when all cohort members were included in the analysis. Additionally, since the industrial use of TCE has declined over recent decades, we also evaluated the association

between occupational TCE exposure and cancer risk by the median publication year for cohort and for case–control studies separately, the median of the maximum length of years of follow-up for cohort studies, the median year that follow-up was initiated for cohort studies and the median recruitment year for case–control studies.

Statistical analysis

Summary risk estimates for NHL, HL, MM, leukaemia and CLL/SLL were calculated individually. Initially, separate analyses were carried out for cohort and case–control studies; subsequently, we performed analyses for cohort and case–control studies combined. Likewise, we evaluated estimates for 'TCE-exposure' studies and for 'chlorinated solvent-exposure' studies, separately and combined. Because of the potential for overlap between the Axelson *et al*[41] cohort and three Swedish case–control studies,[33 40 42] sensitivity analyses were performed with and without these three studies for analyses of all studies combined. Also, since a small proportion of subjects in the Purdue *et al*[43] case–control study might have overlapped with participants in two US cohorts that included California residents from the same area,[36 39] sensitivity analyses were conducted by including and excluding the Purdue *et al*[43] case–control study from analyses of all studies combined. Overall, sensitivity analyses showed no major differences in risk estimates. Subgroup-specific summary estimates by study location (ie, Europe or USA), study type (ie, SIR or SMR), sex and use of different exposure metrics (ie, high vs low intensity or duration) were also performed. Given the dissimilar use of quantitative exposure cut-off points and duration categories in previous studies to define higher exposed groups or longer exposure duration, we conducted subgroup analyses for TCE exposure by the highest and lowest intensity regardless of duration of exposure and by the longest and shortest durations regardless of information on the quantitative level of exposure.

After merging data from all studies into a single dataset, we estimated summary relative risks (RRs) or odds ratios (ORs) and 95% confidence intervals (CIs) using random-effects models. The Higgin's I^2 statistic and Cochrane's Q test were used to evaluate heterogeneity across the studies.[44] Where heterogeneity was seen, an influence analysis was conducted; each study was omitted one at a time from that analysis and the summary risk estimate was recalculated. Publication bias was assessed statistically using the Egger and Begg methods and through evaluation of funnel plots.[45] The influence of potential publication bias on risk estimates was further evaluated by implementing the Duval and Tweedie non-parametric 'trim-and-fill' method.[46] Statistical tests were determined to be significant using a two-sided p value <0.05. All analyses were conducted using STATA software V.10 (College Station, Texas, USA).

RESULTS

A detailed summary of all cohort[22 30 31 36 39 41 47–52] and case–control[32–34 40 42 43 53–63] studies included in our analysis of NHL, HL, MM, leukaemia and CLL/SLL are presented in online supplementary table S1. Data for study size, location, exposure assessment methods, risk estimates and person-years and length of follow-up (for cohort studies) are provided for each study.

NHL cohort and case–control studies combined

A summary estimate of 1.21 (95% CI 1.06 to 1.38; I^2=35.91; p-heterogeneity=0.04) was observed for cohort and case–control studies combined. This risk estimate remained significantly increased after excluding an outlier study that introduced the greatest variability (RR=1.17; 95% CI 1.04 to 1.32; I^2=29.64; p-heterogeneity=0.13).[22] A slightly stronger estimate was detected for cohort and case–control 'TCE-exposure' studies combined (RR=1.32, 95% CI 1.14 to 1.54; I^2=25.20; p-heterogeneity=0.12). For 'chlorinated solvent-exposure' studies, risk was not increased (RR=0.96, 95% CI 0.80 to 1.14; I^2=2.49; p-heterogeneity=0.65).

Analysis by the median publication year for cohort and for case–control studies, the median of the maximum number of years of follow-up and the median year that follow-up was initiated for cohort studies, as well as the median recruitment year for case–control studies showed similar risk estimates (data not shown). Overall, no evidence of publication bias, assessed using the Begg and Egger tests as well as funnel plots, was seen for analyses involving NHL cohort and case–control studies combined (data not shown).

NHL cohort studies

A significantly increased summary risk estimate of 1.52 (95% CI 1.29 to 1.79; I^2=7.09; p-heterogeneity=0.63) was seen for NHL cohort studies of TCE-exposed workers (table 1 and figure 1). In contrast, risk was not increased for cohort studies of chlorinated solvent-exposed workers (RR=0.85, 95% CI 0.66 to 1.10; I^2=0.02; p-heterogeneity=0.89). For all cohort studies combined, a significantly increased summary of 1.33 (95% CI 1.07 to 1.66) was seen with some evidence of heterogeneity (I^2=21.12; p-heterogeneity=0.03); however, risk remained raised (RR=1.45, 95% CI 1.22 to 1.73; I^2=11.08; p-heterogeneity=0.35) after removal of a cohort that introduced the greatest variability.[52]

When studies of cancer incidence (SIR) and mortality (SMR) and European and US, 'TCE-exposure' studies were compared, a stronger risk estimate was seen for SIR and European (RR=1.66, 95% CI 1.29 to 2.14; I^2=3.19; p-heterogeneity=0.36) than for SMR and US (RR=1.41, 95% CI 1.11 to 1.78; I^2=3.13; p-heterogeneity=0.68) studies. A somewhat similar pattern was seen when we combined all cohort studies, with lower SMR risk estimates observed (RR=1.15, 95% CI 0.90 to 1.47; I^2=11.23; p-heterogeneity=0.13). Comparable summary estimates were detected for studies that included only male participants compared with those of both sexes.

Among cohort 'TCE-exposure' studies that examined duration of occupational exposure (N=4), a significant summary risk estimate of 1.56 (95% CI 1.02 to 2.40; I^2=4.66; p-heterogeneity=0.20) was seen among workers who had a longer duration of exposure (≥6.25 years,[22] ≥5 years,[31 39] ≥2 years[41]) compared with those with a shorter exposure duration (<6.25 years,[22] <5 years,[31 39] <2 years [41]) (RR=1.30, 95% CI 0.92 to 1.84; I^2=3.75; p-heterogeneity>0.29). No significant pattern of association was seen for studies that assessed intensity of TCE exposure.[20 31 37 38 40 42] Additionally, a statistically significant twofold increased risk (RR=2.15, 95% CI 1.34 to 3.45; I^2=1.47; p-heterogeneity=0.48) was detected among studies that identified TCE exposure through urinary biomonitoring data.[22 41 47]

Overall, no evidence of publication bias, assessed using funnel plots or the Begg and Egger tests, was identified among NHL cohort studies.

NHL case–control studies

A similar non-significant risk estimate was observed for both 'TCE-exposure' studies (OR=1.14, 95% CI 0.93 to 1.40;

Table 1 Summary estimates of cohort studies of occupational TCE exposure and NHL risk

				Test for heterogeneity		Test for publication bias	
	Number of studies	RR	95% CI	I^2	p Value	p Value (Begg)	p Value (Egger)
TCE-exposed studies							
All†	10	1.52	(1.29 to 1.79)*	7.09	0.63	0.42	0.67
US studies	6	1.41	(1.11 to 1.78)*	3.13	0.68	0.09	0.08
European studies	4	1.66	(1.29 to 2.14)*	3.19	0.36	1.00	0.36
Male participant studies	4	1.48	(1.09 to 2.01)*	2.72	0.44	0.50	0.37
Female participant studies	0						
Male and female participant studies	6	1.53	(1.27 to 1.86)*	4.33	0.50	0.85	0.70
Incident studies	4	1.66	(1.29 to 2.14)*	3.19	0.36	1.00	0.36
Mortality studies	6	1.41	(1.11 to 1.78)*	3.13	0.68	0.09	0.08
Low-intensity studies	5	1.68	(1.14 to 2.46)*	0.41	0.98	0.33	0.54
High-intensity studies	5	1.27	(0.83 to 1.96)	2.81	0.59	0.62	0.67
Low-duration studies	4	1.30	(0.92 to 1.84)	3.75	0.29	1.00	0.95
High-duration studies	4	1.56	(1.02 to 2.40)*	4.66	0.20	0.50	0.70
Chlorinated solvent-exposed studies							
All‡	2	0.85	(0.66 to 1.10)	0.02	0.89		
US studies	1	0.82	(0.44 to 1.41)				
European studies	0						
Male participant studies	0						
Female participant studies	0						
Male and female participant studies	2	0.85	(0.66 to 1.10)	0.02	0.89		
Incident studies	0						
Mortality studies	2	0.85	(0.66 to 1.10)	0.02	0.89		
Low-intensity studies	0						
High-intensity studies	1	0.84	(0.42 to 1.51)				
Low-duration studies	0						
High-duration studies	0						
All cohort studies							
All§	12	1.33	(1.07 to 1.66)*	21.12	0.03¶	0.41	0.84
US studies	7	1.31	(1.05 to 1.62)*	5.99	0.43	0.10	0.14
European studies	4	1.66	(1.29 to 2.14)*	3.19	0.36	1.00	0.36
Male participant studies	4	1.48	(1.09 to 2.01)*	2.72	0.44	0.50	0.37
Female participant studies	0						
Male and female participant studies	8	1.30	(0.98 to 1.72)	17.39	0.02**	1.00	0.58
Incident studies	4	1.66	(1.29 to 2.14)*	3.19	0.36	1.00	0.36
Mortality studies	8	1.15	(0.90 to 1.47)	11.23	0.13	0.46	0.90
Low-intensity studies	5	1.68	(1.14 to 2.46)*	0.41	0.98	0.33	0.54
High-intensity studies	6	1.12	(0.78 to 1.60)	3.94	0.56	0.35	0.49
Low-duration studies	4	1.30	(0.92 to 1.84)	3.75	0.29	1.00	0.95
High-duration studies	4	1.56	(1.02 to 2.40)*	4.66	0.20	0.50	0.70

*p Value <0.05. Summary estimate for:
†Cohort TCE-exposure studies.
‡Cohort chlorinated solvent-exposure studies.
§All cohort studies
¶Exclusion of the McLean D, 2006 study removed heterogeneity: RR=1.45, 95% CI 1.22 to 1.73; I^2=11.08; p-heterogeneity=0.35; p-Begg=0.31; p-Egger=0.54.
**Exclusion of the McLean D, 2006 study removed heterogeneity: RR=1.43, 95% CI 1.12 to 1.83; I^2=8.34; p-heterogeneity=0.21; p-Begg=0.65; p-Egger=0.97.
NHL, non-Hodgkin lymphoma; RR, relative risk; TCE, trichloroethylene; CI, confidence interval.

I^2=10.51; p-heterogeneity=0.23) and 'chlorinated solvent-exposure' studies (OR=1.05, 95% CI 0.83 to 1.33; I^2=1.05; p-heterogeneity=0.59) (table 2 and figure 2). Owing to evidence of publication bias for 'TCE-exposure' studies (p-Eggers=0.01), we applied the 'trim-and-fill' method; four studies were added and the magnitude of the association decreased but was not statistically significant (OR=1.04, 95% CI 0.84 to 1.28). Overall, no significant association was seen for all case–control studies combined (OR=1.09; 95% CI 0.94 to 1.25; I^2=11.63; p-heterogeneity=0.39; p-Eggers=0.003). This association was similar after five additional studies were added through the 'trim-and-fill' method (OR=1.03, 95% CI 0.89 to 1.19).

Stratification by study location and sex did not disclose significant associations and were similar after applying the 'fill-and-trim' method to address publication bias. Associations were not found when studies were evaluated by exposure intensity[43 53 54 56 63] or duration.[43 56 62]

Analyses of HL, MM, leukaemia and CLL/SLL

Meta-analytical results for cohort and case–control studies combined did not show significant associations between occupational TCE exposure and HL (RR=1.14, 95% CI 0.87 to 1.49; I^2=14.63; p-heterogeneity=0.26), MM (RR=1.05, 95% CI 0.88 to 1.27; I^2=6.69; p-heterogeneity=0.76), leukaemia

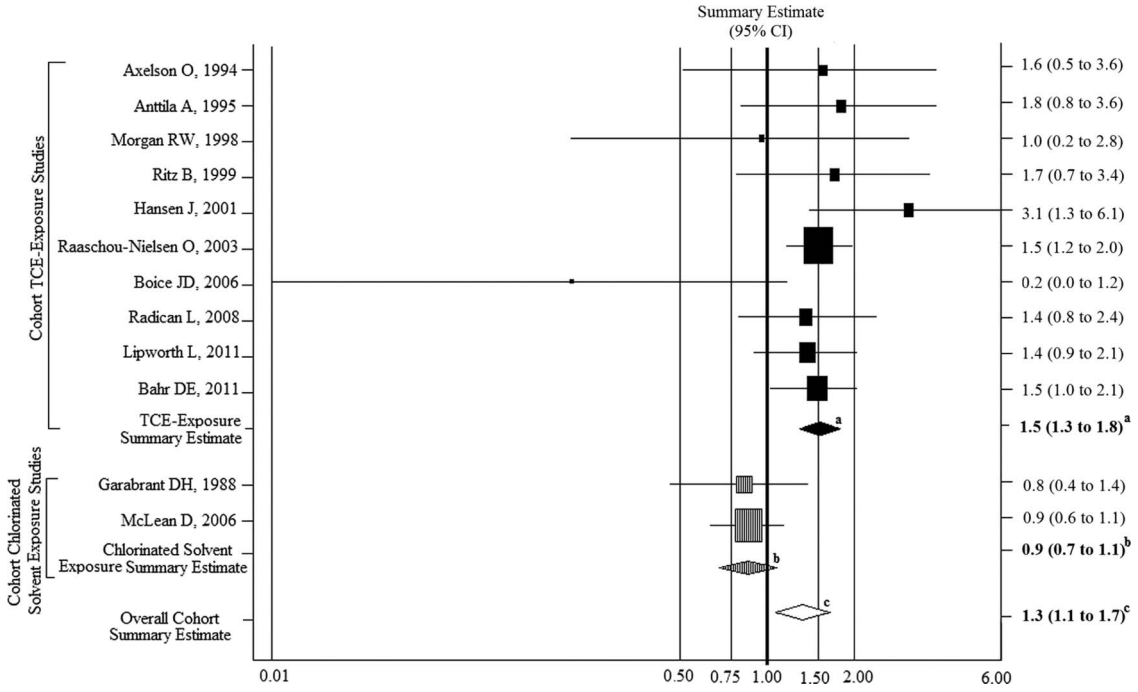

Figure 1 Summary estimates of cohort studies of occupational TCE exposure and NHL risk. NHL, non-Hodgkin's lymphoma; TCE, trichloroethylene. Summary estimate for: [a]cohort TCE-exposure studies; [b]cohort chlorinated solvent-exposure studies; [c]all cohort studies; CI confidence interval.

(RR=1.03, 95% CI 0.91 to 1.17; I^2=7.21; p-heterogeneity=0.78) or CLL/SLL (RR=0.98, 95% CI 0.69 to 1.41; I^2=8.14; p-heterogeneity=0.23) risk (see online supplementary figures S1–S4). Findings did not differ for any of the cancer subtypes when analyses were restricted to 'TCE-exposure' cohort, case–control, or cohort and case–control studies combined. However for HL, a significantly increased summary estimate of 2.07 (95% CI 1.13 to 3.78; I^2=1.22; p-heterogeneity=0.88) was seen among the five mortality 'TCE-exposure' studies, but not among the three cancer incidence studies. Non-significant risk estimates for HL, MM, leukaemia and CLL/SLL were observed for analyses of cohort, case–control and cohort and case–control combined 'chlorinated solvent-exposure' studies. No evidence of publication bias was found for studies of HL, MM, leukaemia and CLL/SLL.

DISCUSSION

Our updated meta-analysis, evaluating NHL risk and occupational TCE exposure incorporated three recently published cohort analyses[39 50 52] and four case–control studies.[59–61 63] Significantly increased risk estimates were seen for cohort studies overall, for those that specifically assessed TCE-exposed workers and for combined cohort and case–control 'TCE-exposure' studies. A non-significant but increased summary estimate was seen for NHL case–control 'TCE-exposure' studies. The stronger risk estimates found for 'TCE-exposure' studies compared with 'chlorinated solvent-exposure' studies suggest that the latter group might have been prone to TCE-exposure misclassification since they included broader groups of chlorinated solvents.

The raised NHL risk estimates seen in our study are consistent with review findings reported by Wartenberg *et al*,[10] Scott and Jinot,[19] and Mandel *et al*.[20] In 2000, Wartenberg and colleagues first reported a borderline significant increased association for NHL in the tier 1 study group that included studies with the most extensive exposure assessment; tier 1 studies used biomarkers, JEMs, or other worksite exposure evaluations to assess TCE exposure for individual study subjects.[10] With the inclusion of results from additional studies, a statistically significant increased association between occupational TCE exposure and NHL risk for cohort studies has been reported in two independent reviews.[19 20] Similar to our study, NHL risk estimates were calculated for case–control studies but no statistically significant increased pooled risk was reported by these reviews.[10 19 20]

Our review is unique in that an expert industrial hygienist classified TCE-exposure specificity while blinded to the study results; this classification allowed us to evaluate the potential effect of exposure misclassification by comparing whether summary estimates from studies that assessed TCE exposure separately differed from those that assessed exposure to the broad classifications of chlorinated solvents. The reviews by Mandel *et al*[20] and Scott and Jinot[19] also evaluated risk among a subcohort of workers with the greatest potential for TCE exposure who, compared with all exposed workers, had a similar but slightly greater risk estimate. With the exception of one dry-cleaning industry study that evaluated TCE specifically, other dry-cleaning/laundry studies assessed in the Wartenberg *et al*[10] review were excluded for reasons described previously.

In contrast to the most recent meta-analysis of TCE exposure and NHL risk,[19] our review integrated results from an updated cohort study with 12 additional years of follow-up.[39] Our study also included results from two recently published occupational cohort studies not previously assessed in previous reviews.[50 52] One of these cohorts, which was categorised as a 'chlorinated solvent-exposure' study, did not observe an increase in NHL risk.[52] One would expect risk of TCE-related disease to be diluted in 'chlorinated solvent-exposure' studies given the increased likelihood of non-differential exposure misclassification. Furthermore, in comparison with all previous reviews,[10 19 20] our study also incorporated data from 376 NHL cases and 463 controls in a US case–control study that assessed exposure among metal cleaning/degreasing industry workers.[59]

Table 2 Summary estimates of case–control studies of occupational TCE exposure and NHL risk

				Test for heterogeneity		Test for publication bias	
	Number of studies	RR	95% CI	I^2	p Value	p Value (Begg)	p Value (Egger)
TCE-exposed studies							
All*	9	1.14	(0.93 to 1.40)	10.51	0.23	0.14	0.01†
US studies	3	1.23	(0.95 to 1.58)	0.30	0.86	0.60	0.68
European studies	5	1.20	(0.78 to 1.84)	8.76	0.07	0.14	0.01‡
Male participant studies	3	1.65	(0.78 to 3.50)	3.92	0.14	0.12	0.08
Female participant studies	2	1.18	(0.89 to 1.58)	0.02	0.89		
Male and female participant studies	4	1.04	(0.77 to 1.38)	4.17	0.24	0.50	0.14
Low-intensity studies	3	1.06	(0.79 to 1.42)	2.49	0.29	0.60	0.82
High-intensity studies	3	1.42	(0.86 to 2.33)	1.78	0.41	0.60	0.80
Low-duration studies	2	1.46	(0.78 to 2.73)	1.62	0.20		
High-duration studies	2	1.18	(0.60 to 2.34)	0.50	0.48		
Chlorinated solvent-exposed studies							
All§	3	1.05	(0.83 to 1.33)	1.05	0.59	0.60	0.53
US studies	2	1.03	(0.79 to 1.36)	0.98	0.32		
European studies	0						
Male participant studies	1	0.91	(0.62 to 1.30)				
Female participant studies	0						
Male and female participant studies	2	1.16	(0.86 to 1.57)	0.06	0.80		
Low-intensity studies	1	1.03	(0.64 to 1.66)				
High-intensity studies	1	1.81	(0.52 to 6.23)				
Low-duration studies	0						
High-duration studies	1	0.73	(0.41 to 1.30)				
All case-control studies							
All¶	12	1.09	(0.94 to 1.25)	11.63	0.39	0.08	0.003**
US studies	5	1.13	(0.94 to 1.36)	2.10	0.72	0.62	0.42
European studies	5	1.20	(0.78 to 1.84)	8.76	0.07	0.14	0.01‡
Male participant studies	4	1.26	(0.76 to 2.10)	6.09	0.11	0.04††	0.051
Female participant studies	2	1.18	(0.89 to 1.58)	0.02	0.89		
Male and female participant studies	6	1.04	(0.87 to 1.25)	4.98	0.42	0.35	0.07
Low-intensity studies	4	1.05	(0.84 to 1.32)	2.50	0.48	1.00	0.74
High-intensity studies	4	1.47	(0.93 to 2.32)	1.91	0.59	0.34	0.91
Low-duration studies	2	1.46	(0.78 to 2.73)	1.62	0.20		
High -duration studies	3	0.89	(0.57 to 1.39)	1.60	0.45	0.12	0.01‡‡

Summary estimate for:
*Case–control TCE-exposure studies.
†Four studies, OR=1.04, 95% CI 0.84 to 1.28.
‡Three studies, OR=0.91, 95% CI 0.61 to 1.38.
§Case–control chlorinated solvent-exposure studies.
¶All case–control studies. Application of the 'trim-and-fill' method added.
**Five studies, OR=1.03, 95% CI 0.89 to 1.19.
††Two studies, OR=0.97, 95% CI 0.57 to 1.66.
‡‡Two studies, OR=0.73. 95% CI 0.48 to 1.11.
NHL, Non-Hodgkin's Lymphoma; TCE, trichloroethylene; CI, confidence interval.

Given that individuals in degreasing operations are among the most heavily TCE-exposed workers,[5 7] this study was assessed as a 'TCE-exposure' study.[59] Data from three 'chlorinated solvent-exposure' studies, which included 2045 cases and 2656 population-based controls, were also assessed in our study.[60 61 63] Unlike previous reviews,[10 19 20] we chose to exclude the results of the Greenland *et al*[55] case–control study given that TCE exposure was assessed in relation to NHL and HL risk combined as opposed to NHL risk specifically.

In our NHL review, stronger risk estimates were found for cohort versus case–control studies and for incidence versus mortality studies. These findings were also seen in previously published meta-analyses of occupational TCE exposure and NHL risk.[10 19] Exposure estimates in cohort studies are more likely to have greater validity than other study designs, since investigators can obtain site-specific exposure information reflective of historical exposures. Results from occupational cohort studies that compared cancer risk with the general population, however, may also be biased towards the null since mortality and morbidity rates within workforces are likely to be lower than those of the general population owing to the healthy-worker effect.[64] For studies that depended on death certificates as the only source of case ascertainment, a large proportion of cancer cases could be missed if survival is high and the reported cause of death differed from the cancer of interest or lacked histological information that is particularly important in studies of lymphoma owing to the heterogeneity of the disease. Compared with mortality studies, incidence studies are less likely to be biased by outcome misclassification and more accurately reflect exposure-related risk.[11]

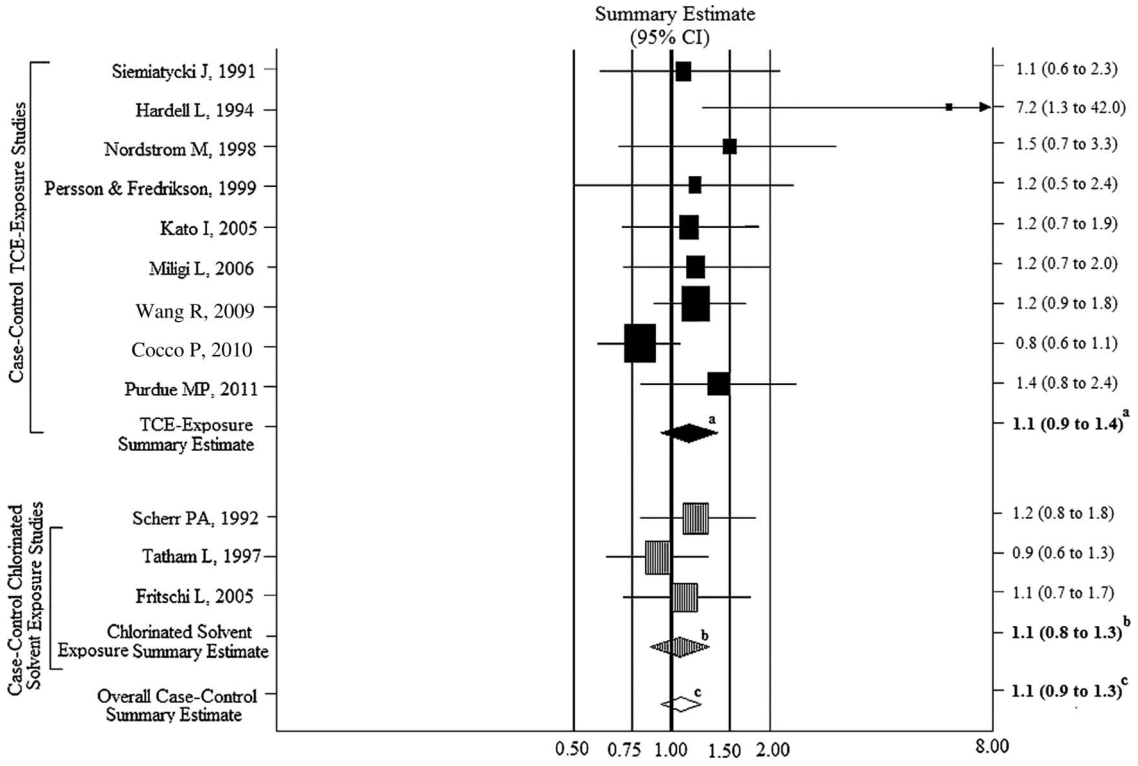

Figure 2 Summary estimates of case–control studies of occupational TCE exposure and NHL risk. NHL, non-Hodgkin's lymphoma; TCE, trichloroethylene. Summary estimate for: [a]cohort TCE-exposure studies; [b]cohort chlorinated solvent-exposure studies; [c]all cohort studies; CI confidence interval.

Given the attenuation of TCE use in most industries,[4 5 9] stronger risk estimates were expected for earlier studies in our evaluation of NHL studies by median publication year, median of maximum number of years of follow-up, median year that follow-up was initiated and median recruitment year. Although similar risks were found between the time periods, summary estimates for more recent studies may reflect improvements in the validity and reliability of exposure assessment techniques used in occupational epidemiology.[65–67] For assessment of low and high intensity and duration of exposure, dose–response relationships were not observed except for longer duration of exposure among 'TCE-exposure' cohort studies. Yet, given our extraction and grouping of results by duration, our findings should only be considered as a qualitative classification of a longer-exposed subgroup.

Overall, our meta-analytical review of occupational TCE exposure and risk of HL, MM, leukaemia and CLL/SLL did not disclose any significant findings. To date, only one other review has evaluated HL risk in relation to TCE exposure.[10] That review assessed results from two incidence and four mortality cohort studies. A borderline significant association was reported for incidence studies. Similar to our review, a significant twofold increased association with exposure for mortality studies was observed.[10] Our study, however, included new analytical HL results from five additional cohort[30 31 36 39 52] and two case–control[34 56] studies. Raised MM risk estimates were reported for both incidence and mortality cohort studies in an earlier review; but, results were based on only 10 cases from three SIR studies and 18 cases from two SMR studies, respectively.[10] The most recent review, evaluating findings from seven epidemiological studies, found no association between TCE exposure and MM risk.[21] Similar null results were found in our MM review, now including results from six additional studies not previously evaluated.[31 32 36 39 52 58] Our study also found similar results to those of two previous reviews that reported no association between TCE exposure and risk of leukaemia,[10 21] but with the inclusion of findings from five additional cohorts.[31 36 39 50 52] To our knowledge, our study is the only review to assess CLL/SLL risk in relation to occupational TCE exposure; no significant findings were found.

Increasing evidence from molecular epidemiological investigations of TCE has suggested that an association between TCE exposure and lymphoma and NHL in particular, may be biologically plausible. Exposure to TCE has demonstrated relevant immune-related effects in occupationally exposed workers, with declines in total lymphocytes and lymphocyte subpopulations including CD4 T cells and alterations in serum cytokine levels involved in immunoregulation.[12 68] Notably, immunosuppression is one of the few known risk factors for NHL and additional evidence has indicated that alterations in markers associated with immune regulation, such as cytokines and immune activation biomarkers, are related to NHL risk and/or progression.[69–71] Moreover, animal and human studies have indicated a role for TCE in the development of autoimmunity.[72] Associations with several autoimmune conditions, NHL and particular subtypes have been described.[73] Collectively, findings indicate that exposure to TCE may result in immune-related changes that are associated with NHL in other settings and disease contexts and provide plausibility for the association seen in our study.

Although a strength of our review is the way in which we classified studies by TCE-exposure assessment specificity, assuming that greater specificity minimised potential TCE-exposure misclassification, exposure assessment limitations must be acknowledged. Studies that estimated exposure based solely on job titles or JEMs were limited in that exposure might have varied considerably among individuals in the same industry or among those with the same job title. While the NHL risk

estimate was significant raised for urinary biomonitoring studies of individual study subjects,[22 41 47] most of these studies lack subject-specific exposure measurements. In contrast, biomarkers studies may not capture long-term exposure levels that are relevant to cancer studies, particularly if the monitoring was conducted at a single moment or a few points in time. Also, exposure to other chemicals may alter, modify, or confound urinary biomonitoring measurement. Findings from previous meta-analyses have always been questioned owing to concerns about exposure misclassification and unmeasured confounding. However, these factors would probably bias risk estimates towards the null, as exposure misclassification is typically non-differential. In order for unmeasured confounding to truly affect results, associations between the confounding factor and both the disease and the exposure of interest must be strong.[74] In most occupational epidemiological studies, such relationships are extremely rare, although we acknowledge that results might be biased away from the null by chance. Other limitations include the likelihood of selection bias among studies that did not match controls to cases, and the chance of outcome misclassification for studies lacking histologically confirmed cancers. Subgroup-specific risk estimates in our review might have been underpowered given the limited number of TCE-exposed cases for rare cancers, such as CLL/SLL. Finally, publication bias in meta-analyses may potentially skew positive results away from the null, though this type of bias did not appear to be a major concern in our review.

In summary, our meta-analysis differentiated between studies that assessed TCE exposure specifically and those that evaluated exposure to broader groups of chlorinated solvents, demonstrating that reduced TCE-exposure misclassification strengthened the association between exposure and risk. Our updated NHL meta-analysis incorporated analytical results from seven additional studies (three 'TCE-exposure' and four 'chlorinated solvent-exposure' studies) and supports an association between occupational TCE exposure and NHL risk, particularly for cohort studies. Our meta-analytical findings for TCE exposure and NHL risk still warrant further exploration given the limited dose–response patterns observed in our review and the recent conclusion by IARC that the carcinogenic evidence for TCE and NHL is limited.[2] Assessment for leukaemia and other lymphoid neoplasms also merits additional investigation.

Contributors All authors included on this paper fulfil the criteria of authorship.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Integrated Risk Information System. Trichloroethylene (CASRN 79-01-6). http://www.epa.gov/IRIS/subst/0199.htm (accessed 11 Mar 2012).
2 Guha N, Loomis D, Grosse Y, *et al*. Carcinogenicity of trichloroethylene, tetrachloroethylene, some other chlorinated solvents and their metabolites. *Lancet Oncol* 2012;13:1192–3.
3 National Academies of Science. Assessing the human health risks of trichloroethylene: key scientific issues; 2006. http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/trichloroethylene_brief_final.pdf (accessed 30 Aug 2011).
4 Agency for Toxic Substances and Disease Registry. Toxicological profile for trichloroethylene; 1997. http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf (accessed 29 Jun 2011).
5 Bakke B, Stewart PA, Waters MA. Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. *J Occup Environ Hyg* 2007;4:375–90.
6 Kelsh AM, Alexander DD, Mink PJ, *et al*. Occupational Trichloroethylene exposure and kidney cancer. *Epidemiology* 2010;21:95–102.
7 International Agency for Research on Cancer. Dry cleaning, some chlorinated solvents and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum* 1995;63:33–477. http://monographs.iarc.fr/ENG/Monographs/vol63/volume63.pdf (accessed 11 Nov 2011).
8 Agency for Toxic Substances and Disease Registry. Trichloroethylene (TCE) Toxicity; 2007. http://www.atsdr.cdc.gov/hec/csem/tce/docs/tce.pdf (accessed 4 Jun 2012).
9 National Toxicology Program. Reports on carcinogens. trichloroethylene; 2000. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc10/TCE.pdf (accessed 29 Jun 2011).
10 Wartenberg D, Reyner D, Scott CS. Trichloroethylene and cancer: epidemiologic evidence. *Environ Health Perspect* 2000;108(Suppl 2):161–76.
11 Scott CS, Chiu WA. Trichlorethylene cancer epidemiology: a consideration of select issues. *Environ Health Perspect* 2006;114:1471–8.
12 Lan Q, Zhang L, Tang X, *et al*. Occupational exposure to trichloroethylene is associated with a decline in lymphocyte subsets and soluble CD27 and CD30 markers. *Carcinogenesis* 2010;31:1592–6.
13 Perocco P, Prodi G. DNA damage by haloalkanes in human lymphocytes cultured in vitro. *Cancer Lett* 1981;13:213–18.
14 Gu ZW, Sele B, Jalbert P, *et al*. Induction of sister chromatide exchange by trichloroethylene and its metabolites (author's transl)]. *Toxicol Eur Res* 1981;3:63–7.
15 Aisenberg AC. Historical review of lymphomas. *Br J Haematol* 2000;109:466–76.
16 Harris NL, Jaffe ES, Diebold J, *et al*. Lymphoma classification—from controversy to consensus: the R.E.A.L. and WHO classification of lymphoid neoplasms. *Ann Oncol* 2000;11(Suppl 1):3–10.
17 Linet MS, Schubauer-Berigan MK, Weisenburger DD, *et al*. Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. *Br J Haematol* 2007;139:672–86.
18 Morton LM, Turner JJ, Cerhan JR, *et al*. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood* 2007;110:695–708.
19 Scott CS, Jinot J. Trichloroethylene and cancer: systematic and quantitate review of epidemiological evidence for identifying hazards. *Int J Environ Res Public Health* 2011;8:4238–72.
20 Mandel JH, Kelsh MA, Mink PJ, *et al*. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. *Occup Environ Med* 2006;63:597–607.
21 Alexander DD, Mink PJ, Mandel JH, *et al*. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. *Occup Med (Lond)* 2006;56:485–93.
22 Hansen J, Raaschou-Nielsen O, Christensen JM, *et al*. Cancer incidence among Danish workers exposed to trichloroethylene. *J Occup Environ Med* 2001;43:133–9.
23 Blair A. Mortality among workers in the metal polishing and plating industry, 1951–1969. *J Occup Med* 1980;22:158–62.
24 Dubrow R, Gute DM. Cause-specific mortality among Rhode Island jewelry workers. *Am J Ind Med* 1987;12:579–93.
25 Park RM, Silverstein MA, Green MA, *et al*. Brain cancer mortality at a manufacturer of aerospace electromechanical systems. *Am J Ind Med* 1990;17:537–52.
26 Hayes RB, Dosemeci M, Riscigno M, *et al*. Cancer mortality among jewelry workers. *Am J Ind Med* 1993;24:743–51.
27 Clapp RW. Mortality among US employees of a large computer manufacturing company: 1969–2001. *Environ Health* 2006;19;:30.
28 Blair A, Hartge P, Stewart PA, *et al*. Mortality and cancer incidence of aircraft maintenance workers to trichloroethylene and other organic solvents and chemicals: extended follow-up. *Occup Environ Med* 1998;55:161–71.
29 Blair A, Mason TJ. Cancer mortality in United States counties with metal electroplating industries. *Arch Environ Health* 1980;35:92–4.
30 Raaschou-Nielsen O, Hansen J, McLaughlin JK, *et al*. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. *Am J Epidemiol* 2003;158:1182–92.
31 Radican L, Blair A, Stewart P, *et al*. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow up. *J Occup Environ Med* 2008;50:1306–19.
32 Cocco P, t'Mannetje A, Fadda D, *et al*. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup Environ Med* 2010;67:341–7.
33 Persson B, Dahlander AM, Fredriksson M, *et al*. Malignant lymphomas and occupational exposures. *Br J Ind Med* 1989;46:516–20.
34 Seidler A, Möhner M, Berger J, *et al*. Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. *J Occup Med Toxicol* 2007;2:2.
35 Zhao Y, Krishnadasan A, Kennedy N, *et al*. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. *Am J Ind Med* 2005;48:249–58.
36 Boice JD Jr, Marano DE, Cohen SS, *et al*. Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. *J Occup Environ Med* 2006;48:1070–92.
37 Spirtas R, Stewart PA, Lee JS, *et al*. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br J Ind Med* 1991;48:515–30.
38 Boice JD Jr, Marano DE, Fryzek JP, *et al*. Mortality among aircraft manufacturing workers. *Occup Environ Med* 1999;56:581–97.

39 Lipworth L, Sonderman JS, Mumma MT, *et al*. Cancer mortality among aircraft manufacturing workers: an extended follow-up. *J Occup Environ Med* 2011;53:992–1007.
40 Persson B, Fredrikson M. Some risk factors for non-Hodgkin's lymphoma. *Int J Occup Med Environ Health* 1999;12:135–42.
41 Axelson O, Seldén A, Andersson K, *et al*. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J Occup Med* 1994;36:556–62.
42 Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage and anatomical localization of non-Hodgkin's lymphoma. *Cancer Res* 1994;54:2386–9.
43 Purdue MP, Bakke B, Stewart P, *et al*. A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. *Environ Health Perspect* 2011;119:232–8.
44 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
45 Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *J Epidemiol* 2005;15:235–43.
46 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
47 Anttila A, Pukkala E, Sallmén M, *et al*. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. *J Occup Environ Med* 1995;37:797–806.
48 Morgan RW, Kelsh MA, Zhao K, *et al*. Mortality of aerospace workers exposed to trichloroethylene. *Epidemiology* 1998;9:424–31.
49 Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. *J Occup Environ Med* 1999;41:556–66.
50 Bahr DE, Aldrich TE, Seidu D, *et al*. Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant. *Int J Occup Med Environ Health* 2011;24:67–77.
51 Garabrant DH, Held J, Langholz B, *et al*. Mortality of aircraft manufacturing workers in southern California. *Am J Ind Med* 1988;13:683–93.
52 McLean D, Pearce N, Langseth H, *et al*. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry: an international collaborative study. *Environ Health Perspect* 2006;114:1007–12.
53 Siemiatycki J. *Risk factors for cancer in the workplace*. Boca Raton, FL: CRC Press, 1991.
54 Wang R, Zhang Y, Lan Q, *et al*. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. *Am J Epidemiol* 2009;169:176–85.
55 Greenland S, Salvan A, Wegman DH, *et al*. A case-control study of cancer mortality at a transformer-assembly facility. *Int Arch Occup Environ Health* 1994;66:49–54.
56 Miligi L, Costantini AS, Benvenuti A, *et al*. Occupational exposure to solvents and the risk of lymphomas. *Epidemiology* 2006;17:552–61.
57 Nordström M, Hardell L, Magnuson A, *et al*. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. *Br J Cancer* 1998;77:2048–52.
58 Gold LS, Stewart PA, Milliken K, *et al*. The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. *Occup Environ Med* 2011;68:391–9.
59 Kato I, Koenig KL, Watanabe-Meserve H, *et al*. Personal and occupational exposure to organic solvents and risk of non-Hodgkin's lymphoma (NHL) in women (United States). *Cancer Causes Control* 2005;16:1215–24.
60 Scherr PA, Hutchison GB, Neiman RS. Non-Hodgkin's lymphoma and occupational exposure. *Cancer Res* 1992;52(19 Suppl):5503s–9s.
61 Tatham L, Tolbert P, Kjeldsberg C. Occupational risk factors for subgroups of non-Hodgkin's lymphoma. *Epidemiology* 1997;8:551–8.
62 Holly EA, Lele C, Bracci P. Non-Hodgkin's lymphoma in homosexual men in the San Francisco Bay Area: occupational, chemical and environmental exposures. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:223–31.
63 Fritschi L, Benke G, Hughes AM, *et al*. Risk of non-Hodgkin lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). *Cancer Causes Control* 2005;16:599–607.
64 Li CY, Sung FC. A review of the healthy worker effect in occupational epidemiology. *Occup Med (Lond)* 1999;49:225–9.
65 Stewart PA, Stewart WF, Heineman EF, *et al*. A novel approach to data collection in a case-control study of cancer and occupational exposures. *Int J Epidemiol* 1996;25:744–52.
66 Stewart PA, Stewart WF, Siemiatycki J, *et al*. Questionnaires for collecting detailed occupational information for community-based case control studies. *Am Ind Hyg Assoc J* 1998;59:39–44.
67 Karami S, Lan Q, Rothman N, *et al*. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occup Environ Med* 2012;69:858–67.
68 Iavicoli I, Marinaccio A, Carelli G. Effects of occupational trichloroethylene exposure on cytokine levels in workers. *J Occup Environ Med* 2005;47:453–7.
69 Saberi Hosnijeh F, Krop EJ, Scoccianti C, *et al*. Plasma cytokines and future risk of non-Hodgkin lymphoma: a case-control study nested in the Italian European Prospective Investigation into Cancer and Nutrition. *CEBP* 2010;19:1577–84.
70 Purdue MP, Lan Q, Bagni R, *et al*. Prediagnostic serum levels of cytokines and other immune markers and risk of non-Hodgkin lymphoma. *Cancer Res* 2011;71:4898–907.
71 El-Far M, Fouda M, Yahya R, *et al*. Serum IL-10 and IL-6 levels at diagnosis as independent predictors of outcome in non-Hodgkin's lymphoma. *J Physiol Biochem* 2004;60:253–8.
72 Cooper GS, Makris SL, Nietert PJ, *et al*. Evidence of autoimmune-related effects of trichloroethylene exposure from studies in mice and humans. *Environ Health Perspect* 2009;117:696–70.
73 Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors and lymphoma characteristics. *CEBP* 2006;15:2069–77.
74 Blair A, Stewart P, Lubin J, *et al*. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. *Am J Ind Med* 2007;50:199–207.

Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis

Sara Karami, Bryan Bassig, Patricia A Stewart, et al.

Occup Environ Med 2013 70: 591-599 originally published online May 30, 2013
doi: 10.1136/oemed-2012-101212