Exhibit 317

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ORIGINAL ARTICLE

Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries

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ABSTRACT

Objectives Trichloroethylene (TCE) and Perchloroethylene (PER) are two chlorinated solvents that are applied widely as degreasers of metal parts, and in dry cleaning and other applications. In 2012, the International Agency for Research on Cancer classified TCE as carcinogenic to humans and PER as probably carcinogenic to humans. We explored exposure–response relations for TCE and PER and non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and cancers of the kidney and liver in the Nordic Occupational Cancer cohort.

Methods The cohort was set up by linking occupational information from censuses to national cancer registry data using personal identity codes in use in all Nordic countries. Country, time period, and job-specific exposure estimates were generated for TCE, PER and potentially confounding occupational exposures with a job-exposure matrix. A conditional logistic regression was conducted for exposure groups as well as for continuous cumulative exposure.

Results HRs for liver cancer, NHL and MM but not kidney cancer were slightly elevated in groups with high exposure to PER (compared to occupationally unexposed subjects). HRs for liver cancer and NHL also increased with increasing continuous exposure to PER. We did not observe evidence for an association between exposure to TCE and NHL, MM or liver and kidney cancer.

Conclusions Although this study was subject to limitations related to the low prevalence of exposure to PER and TCE in the Nordic population and a limited exposure assessment strategy, we observed some evidence indicative of an excess risk of cancer of the liver and NHL in subjects exposed to PER.

What is already known about this subject

- Trichloroethylene and perchloroethylene, two chlorinated solvents that have been applied widely as degreasers of metal parts, and in dry cleaning and other applications, have been classified by the International Agency for Research on Cancer as (*probably) carcinogenic to humans*.

What this paper adds:

- We observed evidence indicative of an association between exposure to perchloroethylene and cancer of the liver, non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).
- We did not observe evidence for an association between exposure to trichloroethylene and NHL, MM or liver and kidney cancer.

BACKGROUND

Trichloroethylene (TCE) and tetrachloroethylene or perchloroethylene (PER) are two chlorinated solvents that have been applied widely as degreasers of metal parts (primarily TCE) and in dry cleaning (primarily PER), among other applications.[1 2] In 2012, the International Agency for Research on Cancer (IARC) classified TCE as carcinogenic to humans (Group 1) based on sufficient evidence for kidney cancer in humans and sufficient evidence for multi-site cancers in experimental animals, and PER as probably carcinogenic to humans (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals.[3]

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Trichloroethylene

TCE was used extensively from the early 1920s through to the 1970s, mainly as a degreasing agent in metal fabricating operations. TCE has also been used in many other industries such as dry cleaning, and the production of textiles, electronics, leather and rubber. Furthermore, many products like adhesives, drugs, paints, inks and various industrial products contained TCE. After the 1970s, the use of TCE decreased because of environmental concerns. Occupational exposures probably also decreased due to better release controls and improvements in worker protection.[1 4] However, recent studies describing associations between occupational exposure to TCE, and kidney toxicity and cancer illustrate that exposure to TCE is still a relevant health concern.[5 6]

A considerable number of recent reviews and meta-analyses have assessed the epidemiological

evidence for excess cancer risks associated with exposure to TCE.[7–12] The body of literature provides the most convincing evidence of an association between TCE exposure and kidney cancer and to a lesser extent non-Hodgkin's lymphoma (NHL) and liver cancer.[7–12] The evidence for the association with liver cancer is somewhat more limited as many studies had limited quality of exposure assessment and small numbers of cases resulting in wide CIs and difficulties for the exploration of exposure-response relationships.[11 13] Further, limited evidence of an association with exposure to TCE is available for a number of other types of cancer, including cancers of the bladder, oesophagus, prostate, cervix, breast, and childhood leukaemia.[13]

Perchloroethylene

PER is a solvent used for dry cleaning clothes; cleaning and degreasing metal in a number of industries, including metal finishing, cleaning mining equipment and testing coal; cleaning animal coats in taxidermy; and cleaning and duplicating film.[2]

In a recent evaluation, the US Environmental Protection Agency (US EPA) concluded that evidence from multiple high quality epidemiological studies, unlikely to be confounded by common lifestyle factors, supported associations between exposure to PER and bladder cancer, NHL and multiple myeloma (MM).[14] The evidence was found to be especially convincing for bladder cancer and NHL, for which quantitative exposure–response relationships have been reported in several studies.[14] The evidence for MM was found to be slightly less convincing, primarily due to the smaller set of studies that was available.[14] US EPA concluded that more some evidence was available for a range of other sites, including cancers of the oesophagus, kidney, lung, liver, cervix and breast.[14] The findings by US EPA contrasted with the 2012 evaluation of the carcinogenicity of PER by an IARC working group that concluded that a consistent association with PER and bladder cancer only was observed across epidemiological studies.[3] The IARC working group classified the epidemiological evidence for the carcinogenicity of PER as limited because its employment in dry cleaning was the only indicator of exposure to PER in most studies, the number of exposed cases was small and the exposure–response relationship was weak.[3]

The Nordic Occupational Cancer study

In the Nordic Occupational Cancer (NOCCA), occupational information from censuses is linked to national cancer registry data from Denmark, Finland, Iceland, Norway and Sweden.[15] The NOCCA database includes up to 45 years of cancer incidence follow-up for 15 million people and contains occupational information from national censuses held in 1960, 1970, 1980–1981 and 1990.[15] Pukkala *et al*[15] described standardised incidence ratios (SIRs) for 49 cancer types and 53 occupational categories, and provided a discussion of strengths (high coverage, precision and validity of the linked files, large numbers of cases that diminished the role of chance variation even in the case of relatively rare cancers) and potential limitations (failure to capture occupational mobility, and confounding by lifestyle factors, tobacco smoking, alcohol consumption and dietary behaviour) of the NOCCA data. Kauppinen *et al*[16] developed country-specific and time-specific job-exposure matrices (JEMs) for the NOCCA database. With these JEMs, information about occupational histories can be transformed into quantitative exposure estimates for specific agents. JEMs were developed for more than 20 agents, including TCE and PER.[16]

We used the unique combination of vast sample size and quantitative exposure estimates for PER, TCE and a number of potentially confounding exposures in the NOCCA database to explore exposure response relationships of TCE and PER with NHL, MM, and cancers of the kidney and liver in four of the five Nordic countries.

MATERIAL AND METHODS

Study cohort

All subjects aged 30–64 years who participated in the 1960, 1970, 1980–1981 and/or 1990 censuses in Finland, Iceland, Norway and Sweden, and who were still alive and living in the respective countries on 1 January in the year following the census were included in the study cohort. Personal identification codes were used to link the census data of each individual to the national cancer registries to add cancer data, and to the national population registries for information on deaths and emigrations. The unique personal identity codes have been given to each individual alive in Sweden from 1947, in Iceland from 1953, in Norway from 1960 and in Finland from 1967. National cancer registration started in 1953 in Finland and Norway, in 1955 in Iceland and in 1958 in Sweden. In Sweden and Norway, the individual data from the 1960 census and later censuses have been computerised, whereas in Finland, the first computerised data are available from the 1970 census; in Iceland, only for the year 1981 only. Census questionnaires included questions related to the respondents' economic activity, occupation and industry. All questionnaires were centrally coded and computerised in the national statistical offices. Details concerning the structure of the population and history of the four Nordic countries; the culture, smoking and alcohol consumption habits of the population; living conditions and climate have been described previously.[15]

The cohort was followed up for cancer incidence during the period from 1 January of the year after the first available census through to emigration, death, or 31 December of the following years: 2005in Finland, 2004in Iceland, 2003in Norway and 2005in Sweden. The seventh revision of the International Classification of Diseases (ICD-7),[17] with country-specific modifications, served as a common coding system for all countries through the study period, as either the main system or as a system used in parallel with newer codes.[18 19]

Case ascertainment and control selection

All incident cases of liver cancer (ICD-7 155), kidney cancer (ICD-7 180), NHL (ICD-7 200, 202) and MM (ICD-7 203) were extracted from the cohort. For each case, five control subjects were randomly selected from all cohort members alive and free of cancer at the time of diagnosis of the case, by matching for age (±1 year), country and sex.

Exposure assessment

Quantitative estimates of exposure were assigned using JEMs that were developed for the NOCCA study. In the NOCCA JEMs, about 300 job categories were assigned estimates of the prevalence and level of exposure to 29 agents for four calendar periods covering 1945–1994. The development of the NOCCA JEMs is discussed in detail by Kauppinen *et al*.[16] Cases and controls were assigned an occupational code for each calendar year of his or her working career based on the occupational codes recorded in the censuses. We assumed that individuals kept the occupation reported in the census until the calendar year in which the census information was updated. To accumulate exposure in the period before the first census, we assumed that workers had worked in the job they reported in the first census

since the age of entry into the cohort (ie, 30 years). Cumulative exposure was calculated by multiplying prevalence (%) by the level of exposure and assigning this to each calendar year of a working career and then summing the assigned exposure estimates over the full working career. Accumulation of exposure started at the age of 20 years or the start of the working career, whichever occurred later, and ended at the incidence date of the case in the case–control set or at the age of 65 years, whichever occurred first.

Our primary focus for the current analysis is exposure to TCE and PER. The NOCCA JEMs also include estimates for several other organic solvent categories: chlorinated hydrocarbon solvents, aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, gasoline, 'other organic solvents', benzene, methylene chloride, toluene and 1,1,1-trichloroethane. To explore potential confounding by the other organic solvent categories included in the NOCCA JEM, we calculated the cumulative exposure for all agents listed above. Furthermore we assigned cumulative exposure to ionising radiation, a potential confounder of the risk of liver cancer, kidney cancer, NHL and MM that was included in the NOCCA JEM. In the NOCCA JEM, exposure levels of all solvents were estimated in parts per million, and exposure levels of ionising radiation was estimated in millisieverts. However, for each agent, we report cumulative exposure in unit-years. Estimates of other potential confounding factors such as smoking behaviour, viral infections, contraceptive use or alcohol consumption were not available.

Statistical analysis

We described the association between potential confounding cumulative exposure variables and PER or TCE with Pearson correlation coefficients. HRs and 95% CIs were estimated by conditional logistic regression. Tertile cut-off points for cumulative exposure were chosen to achieve approximately equal numbers of exposed control subjects in each category. For PER and TCE, 'high exposure' groups were defined following two approaches: (a) individuals exposed to levels higher than the 90th percentile of the distribution of cumulative exposure, and (b) individuals exposed to levels higher than the 90th percentile of the distribution of the average intensity × prevalence of exposure (calculated by dividing cumulative exposure by the duration of exposure). Occupationally unexposed individuals were used as reference group in all analyses.

We explored quantitative patterns in HRs for continuous cumulative exposure, denoted by d, by fitting a log-linear model, $HR(d)=\exp(\beta d)$. To allow a more flexible assessment of the shape of the patterns in HRs, we specified a penalised spline basis for cumulative exposure. The level of smoothness of the spline was determined by using the Akaike information criterion[20] to choose the optimal degrees of freedom. Analyses were conducted in SAS V.9.2 using the CORR and LOGISTIC procedures (SAS Institute Inc., Cary, North Carolina, USA) and in R, V.2.14 (R Core Development Group, Vienna, Austria) using the clogit and pspline functions of the survival package.

Lag times

We explored the impact of lag times on our results by comparing the fit of the models including cumulative exposure variables with 0, 1, 5, 10 and 20 years of lag-time. However, for all cancers and all exposures, inclusion of a lag time in the calculation of cumulative exposure had a negligible impact on the Akaike information criterion. This was true for the models that included parameter estimates for tertiles of cumulative exposure as well as the models that included cumulative exposure as a continuous variable (either as a linear or as a spline function). We therefore chose to conduct all analyses with unlagged exposure variables.

RESULTS

We present an overview of the demographic characteristics of the kidney, liver, NHL and MM case–control sets in table 1. All four datasets have similar demographic characteristics. The datasets contain slightly more men (ranging from 53–62%) than women. The majority of the case and control subjects are from Sweden (53–60%). The other case and control subjects are from Finland (19–27%) and Norway (13–27%), and a small percentage from Iceland (~1%). Most case and control subjects were born in 1900–1924 (53–65%) or in 1925–1949 (28–34%). A small percentage of subjects was born before 1900 (3–6%) or in 1950–1960 (2–4%). The data contains 76 130 cases of kidney cancer, 23 896 cases of liver cancer, 69 254 cases of NHL and 35 534 cases of MM.

Table 1 Demographic characteristics of the cases and control subjects

	Kidney		Liver		NHL		MM	
Stratum	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Sex								
Men	44708 (59%)	223540 (59%)	14702 (62%)	73510 (62%)	36487 (53%)	182435 (53%)	18777 (53%)	93885 (53%)
Women	31422 (41%)	157110 (41%)	9194 (38%)	45970 (38%)	32767 (47%)	163835 (47%)	16757 (47%)	83785 (47%)
Country								
Finland	17846 (23%)	89230 (23%)	6358 (27%)	31790 (27%)	18361 (27%)	91805 (27%)	6919 (19%)	34595 (19%)
Iceland	646 (1%)	3230 (1%)	104 (0%)	520 (0%)	456 (1%)	2280 (1%)	212 (1%)	1060 (1%)
Norway	15857 (21%)	79285 (21%)	3182 (13%)	15910 (13%)	12480 (18%)	62400 (18%)	9434 (27%)	47170 (27%)
Sweden	41781 (55%)	15857 (55%)	14252 (60%)	71260 (60%)	37957 (55%)	189785 (55%)	18969 (53%)	94845 (53%)
Year of birth								
<1900	3575 (5%)	17875 (5%)	1364 (6%)	6820 (6%)	1928 (3%)	9640 (3%)	1942 (5%)	9710 (5%)
1900–1924	44930 (59%)	224650 (59%)	15549 (65%)	77745 (65%)	36754 (53%)	183770 (53%)	23036 (65%)	115180 (65%)
1925–1949	25955 (34%)	129775 (34%)	6584 (28%)	32920 (28%)	27561 (40%)	137805 (40%)	10004 (28%)	50020 (28%)
1950–1960	1670 (2%)	8350 (2%)	399 (2%)	1995 (2%)	3011 (4%)	15055 (4%)	552 (2%)	2760 (2%)
Total	76130	380650	23896	119480	69254	346270	35534	177670

MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

Table 2 Association of liver and kidney cancer, non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) by tertiles of cumulative exposure*

	Liver		Kidney		NHL		MM	
Exposure tertile	N†	HR (95% CI)	N†	HR (95% CI)	N†	HR (95% CI)	N†	HR (95% CI)
Ionising radiation‡								
First	45	1.20 (0.86 to 1.66)	114	0.91 (0.74 to 1.11)	104	0.98 (0.79 to 1.21)	52	1.03 (0.77 to 1.39)
Second	39	1.03 (0.73 to 1.45)	114	0.91 (0.74 to 1.11)	99	0.94 (0.75 to 1.16)	57	1.14 (0.86 to 1.52)
Third	51	1.35 (0.99 to 1.84)	129	1.02 (0.85 to 1.24)	109	1.03 (0.84 to 1.26)	62	1.23 (0.93 to 1.62)
Benzene§								
First	373	1.00 (0.89 to 1.12)	1359	1.00 (0.94 to 1.06)	1259	0.99 (0.93 to 1.06)	584	1.01 (0.92 to 1.11)
2nd	497	1.04 (0.94 to 1.15)	1435	1.00 (0.95 to 1.06)	1289	1.01 (0.95 to 1.07)	663	1.00 (0.92 to 1.09)
3rd	485	1.14 (1.03 to 1.26)	1560	1.06 (1.00 to 1.12)	1212	0.97 (0.91 to 1.04)	577	0.93 (0.85 to 1.02)
Trichloroethylene¶								
First	340	1.03 (0.91 to 1.16)	1217	1.01 (0.95 to 1.07)	1213	1.01 (0.95 to 1.07)	468	0.93 (0.84 to 1.03)
Second	508	0.99 (0.90 to 1.09)	1556	1.02 (0.97 to 1.08)	1183	0.93 (0.88 to 1.00)	574	0.92 (0.84 to 1.01)
Third	422	1.00 (0.90 to 1.11)	1372	1.00 (0.95 to 1.07)	1211	0.97 (0.91 to 1.03)	541	0.96 (0.88 to 1.06)
Perchloroethylene**								
First	90	0.91 (0.73 to 1.14)	375	1.11 (0.99 to 1.24)	346	1.06 (0.94 to 1.19)	149	0.99 (0.83 to 1.18)
Second	121	1.18 (0.97 to 1.44)	333	0.96 (0.86 to 1.08)	337	1.04 (0.93 to 1.17)	140	0.93 (0.78 to 1.12)
Third	114	1.13 (0.92 to 1.38)	314	0.94 (0.83 to 1.06)	292	0.95 (0.84 to 1.08)	148	0.98 (0.82 to 1.17)

*Occupationally unexposed individuals were used as a reference group in all analyses.
†Number of exposed cases.
‡Median exposure (unit-years) first tertile: 0.01 (liver), 0.01 (kidney), 0.01 (NHL), 0.01 (MM); second tertile: 0.03 (liver), 0.03 (kidney), 0.03 (NHL), 0.03 (MM); third tertile: 0.05 (liver), 0.05 (kidney), 0.05 (NHL), 0.06 (MM).
§Median exposure (unit-years) first tertile: 0.01 (liver), 0.01 (kidney), 0.00 (NHL), 0.01 (MM); second tertile: 0.04 (liver), 0.04 (kidney), 0.03 (NHL), 0.04 (MM); third tertile: 0.09 (liver), 0.09 (kidney), 0.09 (NHL), 0.09 (MM).
¶Median exposure (unit-years) first tertile: 0.04 (liver), 0.04 (kidney), 0.04 (NHL), 0.04 (MM); second tertile: 0.25 (liver), 0.13 (kidney), 0.12 (NHL), 0.13 (MM); third tertile: 0.77 (liver), 0.72 (kidney), 0.72 (NHL),0.74 (MM).
**Median exposure (unit-years) first tertile: 0.03 (liver), 0.03 (kidney), 0.02 (NHL), 0.03 (MM); second tertile: 0.12 (liver), 0.12 (kidney), 0.12 (NHL), 0.12 (MM); third tertile: 0.77 (liver), 0.77 (kidney), 0.77 (NHL),0.77 (MM).

In online supplementary table S1, we show Pearson correlation coefficients (r) among cumulative exposure estimates of PER, TCE, other organic solvent metrics and potential confounding factors. We observed moderate correlations between PER and TCE (r=0.58–0.63), PER and chlorinated hydrocarbon solvents (r=0.61–0.63), TCE and 'chlorinated hydrocarbon solvents' (r=0.56–0.61), and TCE and 1,1,1-trichloroethane (r=0.37–0.43) across datasets. No association was observed between PER or TCE and other organic solvent indices. Additionally, no association was observed between PER or TCE and the potential confounding factors benzene and ionising radiation.

In table 2, we report the results from univariate conditional logistic regression of tertiles of cumulative exposure to PER, TCE, ionising radiation and benzene, and cancer of the liver and kidney, NHL and MM. The HR for cancer of the liver increased slightly with increasing tertiles of cumulative exposure to PER. Cumulative exposure to PER was not associated with increased HRs for the other cancers. Similarly, we did not observe evidence for an association between cumulative exposure to TCE and cancer of the liver and kidney, NHL and MM. We did observe a positive exposure–response relationship between the tertiles of cumulative exposure to benzene or ionising radiation and cancer of the liver, and between tertiles of ionising radiation and MM.

In table 3, we report the results from univariate conditional logistic regression analyses for tertiles of cumulative exposure to TCE and PER stratified by sex. HRs for NHL and cancer of the liver and kidney were slightly increased for some tertiles of cumulative exposure to TCE among women. However, exposure–response patterns for these cancers were not clear and HRs for these exposures were not increased among men. HRs for liver cancer increased with increasing tertiles of cumulative exposure to PER among men. Among women, the HR for liver cancer was elevated only in the second tertile. No associations were observed between PER and any of the other cancers among either men or women.

In table 4, we report results from univariate conditional logistic regression analyses for individuals in the high exposure groups for PER or TCE. The reference group consisted of individuals who were not occupationally exposed to PER or TCE. HRs for cancer of the liver and kidney, NHL and MM were not convincingly elevated for individuals exposed to TCE, regardless of the exposure metric that was used. For PER, HRs for NHL were significantly elevated among men and women combined (HR 1.23, 95% CI 1.00 to 1.52), among men (HR 1.74, 95% CI 1.15 to 2.64) based on the intensity × prevalence of exposure metric and among men (HR 1.54, 95% CI 0.99 to 2.42) based on the cumulative exposure metric. HRs for liver cancer were non-significantly elevated among men and women combined (HR 1.26, 95% CI 0.88 to 1.80), among men (HR 1.31, 95% CI 0.67 to 2.56), among women (HR 1.24, 95% CI 0.81 to 1.89) based on the intensity × prevalence of exposure metric and among men (1.25, 95% CI 0.65 to 2.43) based on the cumulative exposure metric. HRs for MM were non-significantly elevated among women (HR 1.28, 95% CI 0.92 to 1.78) based on the intensity × prevalence of exposure metric and among men (1.22, 95% CI 0.65 to 2.30) based on the cumulative exposure metric.

Cumulative exposure as a continuous variable

Exposure–response relationships for exposure to PER and cancer of the liver, NHL and MM were further explored with univariate conditional logistic regression analysis including cumulative exposure as a continuous variable. Analyses were conducted among men and women separately. Specification of

Table 3 Association of liver and kidney cancer, non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) by tertiles of cumulative exposure to trichloroethylene (TCE) and perchloroethylene (PER), stratified by sex*

	Liver		Kidney		NHL		MM	
Exposure tertile	N†	HR (95% CI)	N†	HR (95% CI)	N†	HR (95% CI)	N†	HR (95% CI)
TCE men								
First	277	1.01 (0.89 to 1.15)	978	0.99 (0.93 to 1.07)	950	1.02 (0.95 to 1.10)	364	0.93 (0.83 to 1.04)
Second	431	0.99 (0.89 to 1.10)	1282	1.00 (0.94 to 1.07)	943	0.90 (0.84 to 0.97)	452	0.90 (0.82 to 1.00)
Third	373	0.98 (0.87 to 1.10)	1234	1.03 (0.97 to 1.10)	1039	0.97 (0.91 to 1.04)	455	0.94 (0.85 to 1.04)
TCE women								
First	63	1.11 (0.84 to 1.46)	239	1.07 (0.93 to 1.23)	263	0.95 (0.83 to 1.08)	104	0.94 (0.76 to 1.17)
Seccond	77	1.00 (0.78 to 1.27)	274	1.12 (0.98 to 1.28)	240	1.10 (0.95 to 1.26)	122	1.00 (0.83 to 1.22)
Third	49	1.16 (0.85 to 1.59)	138	0.83 (0.69 to 0.99)	172	0.95 (0.80 to 1.12)	86	1.10 (0.87 to 1.39)
PER men								
First	67	0.91 (0.70 to 1.18)	280	1.14 (1.00 to 1.30)	243	1.06 (0.92 to 1.22)	114	1.13 (0.92 to 1.38)
Second	96	1.17 (0.93 to 1.46)	252	0.94 (0.82 to 1.08)	234	1.00 (0.87 to 1.15)	98	0.89 (0.72 to 1.10)
Third	55	1.21 (0.90 to 1.63)	124	0.93 (0.76 to 1.12)	114	1.02 (0.84 to 1.25)	48	0.85 (0.63 to 1.16)
PER women								
First	23	0.91 (0.58 to 1.43)	95	1.01 (0.81 to 1.26)	103	1.06 (0.86 to 1.31)	35	0.71 (0.50 to 1.02)
Second	25	1.23 (0.79 to 1.90)	81	1.04 (0.82 to 1.32)	103	1.17 (0.94 to 1.45)	42	1.06 (0.76 to 1.48)
Third	59	1.06 (0.80 to 1.41)	190	0.95 (0.81 to 1.11)	178	0.91 (0.78 to 1.07)	100	1.06 (0.85 to 1.32)

*Occupationally unexposed individuals were used as a reference group in all analyses.
†Number of exposed cases.

Table 4 Association of non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM), and cancer of the liver and kidney with the trichloroethylene (TCE) and perchloroethylene (PER) high-exposure groups*†

	Liver		Kidney		NHL		MM	
Exposure metric	N‡	HR (95% CI)	N‡	HR (95% CI)	N‡	HR (95% CI)	N‡	HR (95% CI)
Men and women TCE								
Cumulative§	106	1.02 (0.82 to 1.25)	251	0.86 (0.75 to 0.98)	353	0.95 (0.84 to 1.06)	132	1.01 (0.84 to 1.22)
Intensity × prevalence¶	137	1.08 (0.90 to 1.30)	387	1.00 (0.90 to 1.12)	269	0.96 (0.84 to 1.09)	174	1.03 (0.88 to 1.22)
Men TCE								
Cumulative**	69	1.01 (0.78 to 1.31)	159	0.92 (0.77 to 1.09)	257	0.96 (0.84 to 1.10)	71	0.95 (0.73 to 1.22)
Intensity × prevalence††	99	1.07 (0.86 to 1.33)	297	1.10 (0.97 to to 1.25)	176	0.94 (0.80 to 1.11)	113	1.00 (0.81 to 1.22)
Women TCE								
Cumulative‡‡	37	1.02 (0.72 to 1.46)	92	0.92 (0.77 to 1.09)	96	0.92 (0.74 to 1.15)	61	1.09 (0.83 to 1.44)
Intensity × prevalence§§	38	1.12 (0.79 to 1.59)	90	0.78 (0.62 to 0.97)	93	0.99 (0.79 to 1.24)	61	1.11 (0.84 to 1.46)
Men and women PER								
Cumulative¶¶	40	1.11 (0.79 to 1.57)	88	0.81 (0.65 to 1.01)	102	1.04 (0.84 to 1.29)	64	1.15 (0.88 to 1.51)
Intensity***× prevalence¶¶	38	1.26 (0.88 to 1.80)	103	1.01 (0.82 to 1.25)	113	1.23 (1.00 to 1.52)	53	1.18 (0.87 to 1.59)
Men PER								
Cumulative†††	11	1.25 (0.65 to 2.43)	17	0.79 (0.47 to 1.31)	25	1.54 (0.99 to 2.42)	12	1.22 (0.65 to 2.30)
Intensity × prevalence‡‡‡	11	1.31 (0.67 to 2.56)	19	0.78 (0.48 to 1.26)	30	1.74 (1.15 to 2.64)	9	0.85 (0.42 to 1.72)
Women PER								
Cumulative§§§	29	1.07 (0.71 to 1.59)	71	0.82 (0.63 to 1.05)	77	0.94 (0.74 to 1.20)	52	1.14 (0.84 to 1.54)
Intensity × prevalence¶¶¶	27	1.24 (0.81 to 1.89)	84	1.08 (0.85 to 1.37)	83	1.12 (0.88 to 1.42)	44	1.28 (0.92 to 1.78)

*Occupationally unexposed individuals were used as a reference group in all analyses.
†HRs for the group of individuals exposed above the 90th percentile of the exposure distribution among exposed controls. 90th percentile is 0.8 unit-years for cumulative exposure and 0.03 units for intensity × prevalence for all cancer outcomes for TCE, and 1.05 unit-years for cumulative exposure and 0.05 units for intensity × prevalence for all cancer outcomes for PER.
‡Number of exposed cases.
§Median exposure (unit-years): 1.06 (liver), 1.07 (kidney), 0.83 (NHL), 1.86 (MM).
¶Median exposure (units): 0.04 (liver), 0.04 (kidney), 0.04 (NHL), 0.04 (MM).
**Median exposure (unit-years): 0.84 (liver), 0.84 (kidney), 0.82 (NHL), 0.84 (MM).
††Median exposure (units): 0.03 (liver), 0.03 (kidney), 0.03 (NHL), 0.03 (MM).
‡‡Median exposure (unit-years): 2.43 (liver), 2.44 (kidney), 2.44 (NHL), 2.45 (MM).
§§Median exposure (units): 0.09 (liver), 0.10 (kidney), 0.09 (NHL), 0.10 (MM).
¶¶Median exposure (unit-years): 1.17 (liver), 1.17 (kidney), 1.15 (NHL), 1.11 (MM).
***Median exposure (units): 0.08 (liver), 0.08 (kidney), 0.08 (NHL), 0.08 (MM).
†††Median exposure (unit-years): 1.32 (liver), 1.22 (kidney), 1.41 (NHL), 1.47 (MM).
‡‡‡Median exposure (units): 0.06 (liver), 0.08 (kidney), 0.08 (NHL), 0.08 (MM).
§§§Median exposure (unit-years): 1.17 (liver), 1.14 (kidney), 1.12 (NHL), 1.09 (MM).
¶¶¶Median exposure (units): 0.08 (liver), 0.08 (kidney), 0.08 (NHL), 0.08 (MM).

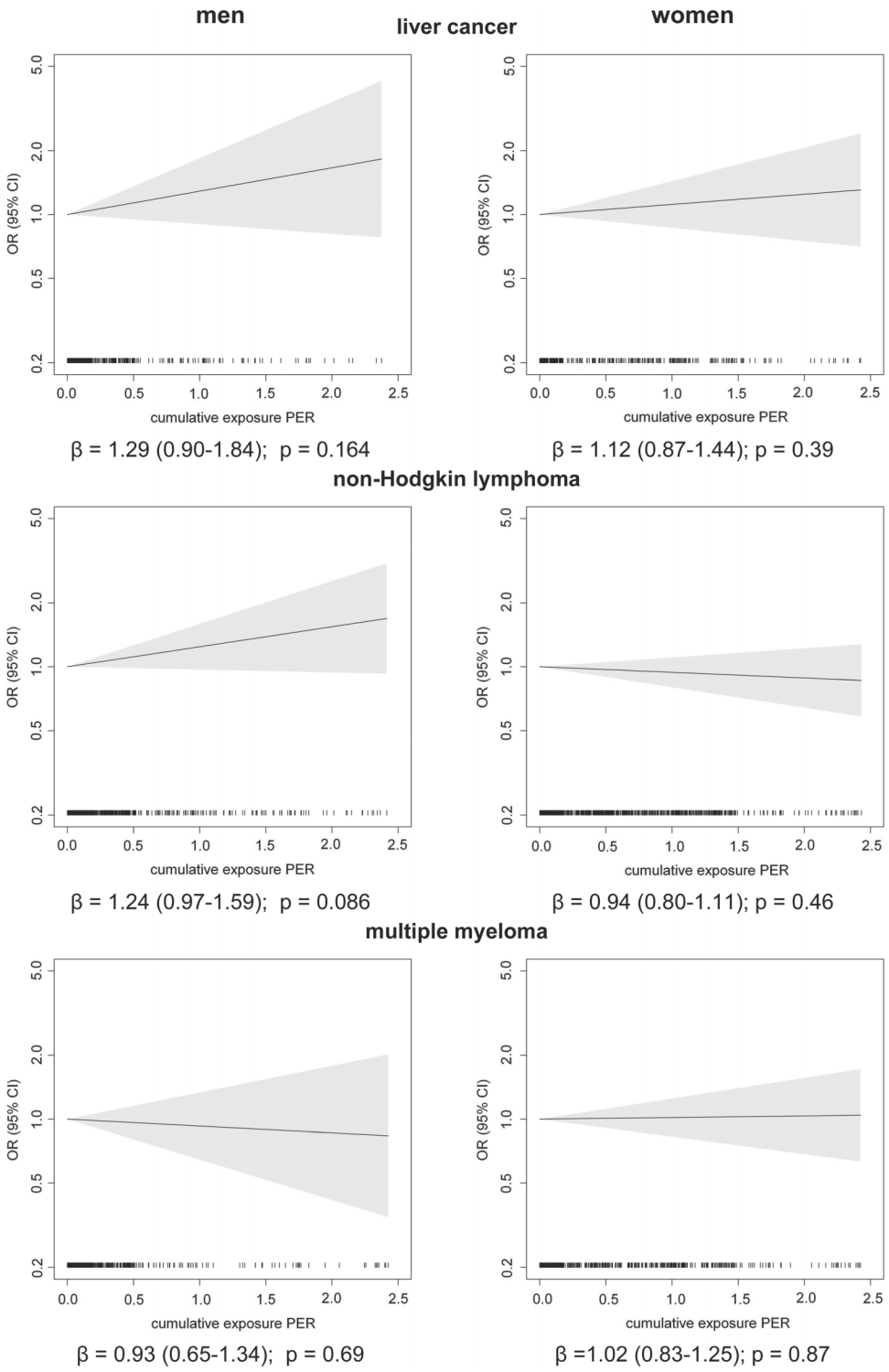

Figure 1 Univariate linear analysis of continuous cumulative exposure to perchloroethylene and the HR of liver cancer, non-Hodgkin's lymphoma and multiple myeloma stratified by sex. Slope of the exposure response relationship (β) indicated under each plot with 95% CI and associated p value. The rug plot indicates the distribution of cumulative exposure for cases and controls.

a penalised spline basis for cumulative exposure did not significantly improve the fit to the data over a linear model in any of the analyses (p value of the likelihood ratio test: ~1). We therefore report results from the linear models only. The results are shown in figure 1. We observed positive slopes for liver cancer in men (β=1.29, 95% CI 0.90 to 1.84, p=0.164) and in women (β=1.12, 95% CI 0.87 to 1.44, p=0.39) and for NHL in men (β=1.24, 95% CI 0.97 to 1.59, p=0.086), although none of the slopes were significantly different from 1. We did not observe a trend with cumulative exposure to PER for NHL in women or for MM in either men or women. In analyses conducted on men and women combined, we observed a positive slope for cumulative exposure to PER and cancer of the liver (β=1.17, 95% CI 0.95 to 1.44, p=0.14), but observed no association with NHL or MM (results not shown).

In online supplementary table S2, we compare a multivariate conditional logistic regression model for cancer of the liver that included parameters for the linear functions of the continuous exposure variables for PER and for the potential confounding factors benzene and ionising radiation with a univariable conditional logistic regression model that included only a linear function of the continuous exposure variable for PER. This model was fitted on men and women combined. Although the inclusion of parameters for benzene and ionising radiation resulted in a significantly better fit of the model to the liver cancer data (p value likelihood ratio test: 0.0007), the parameter estimate for PER was only marginally different from the parameter estimate of the univariate model.

DISCUSSION

In this study, which was conducted in the general population of Finland, Iceland, Norway and Sweden, and which used census data in combination with a specifically designed JEM, we observed some evidence indicative of an association between exposure to PER and liver cancer among men and women, and between exposure to PER and NHL among men. In addition, we observed a slight excess risk for MM in men and women with high exposure to PER. We did not observe evidence for an association between PER and kidney cancer. Neither did we observe evidence for an association between exposure to TCE and NHL, MM, and cancers of the liver and kidney.

There is limited evidence for the association between exposure to PER and liver cancer in the literature, as most studies that assessed this association suffered from small numbers of exposed cases or the limited quality of the exposure assessment.[14] To our knowledge, this is the first study of liver cancer that includes quantified estimates of exposure to PER. A study of laundry workers by Blair *et al*[21] did develop semiquantitative estimates for exposure to 'dry cleaning solvents', but did not report risk estimates for the group with 'medium/high exposure'. Excess risks for liver cancer have been observed in studies that classified subjects by exposure to PER[22 23] or that used employment as a dry cleaning or laundry worker as a proxy for exposure to PER.[24–26] Within the NOCCA database, a SIR of 1.23 (95% CI 1.02 to 1.49) was observed for laundry workers (including dry cleaning workers),[15] but an earlier study of cancer in persons working only in dry cleaning in the Nordic countries, including Denmark and highly overlapping with the NOCCA database, reported a rate ratio of 0.76 (95% CI 0.38 to 1.72).[27] Studies that focus on dry cleaners only are thought to be more informative, as the exposure prevalence of PER in this group is high (75–85%).[2]

Non-significantly elevated risks were reported for NHL in case–control studies using experts to estimate exposure to PER.[23 28–30] A cohort study that monitored workers for exposure to PER[31] and two cohort studies using employment as a dry cleaning or laundry worker as a proxy for exposure to PER also reported non-significantly elevated risks.[26 32] In the NOCCA database, a SIR of 0.96 (95% CI 0.72 to 1.25) was observed for the category of laundry workers.[15]

Although the 2012 IARC evaluation of the carcinogenicity of TCE concluded that there was convincing evidence in the epidemiological literature for an association with kidney cancer and, to a lesser extent, NHL,[3] we did not observe these associations in our study. Below we discuss factors that might have contributed to our inability to do so.

By using the NOCCA JEM, we could generate quantitative exposure estimates for PER, TCE and a number of potentially confounding exposures. A clear advantage of this approach was the ability to explore exposure–response relations beyond analyses of 'exposed' versus 'non-exposed' individuals or analysis by job title. However, the disadvantages of using a generic JEM to assess exposure levels are known and include poor sensitivity and failure to account for heterogeneity in exposure levels within jobs and over time.[33 34] The misclassification of the NOCCA JEM is likely to be considerable (a considerable number of individuals working in a job classified as 'exposed' might, in fact, not have been exposed and vice versa). In the NOCCA JEM, for the majority of occupational groups that were assigned with exposure to TCE or PER, the prevalence of exposure was estimated to be as low as 5%, which means that the potentially exposed group assigned by the JEM is seriously 'diluted' in terms of exposure. Similar misclassification among the tertiles of exposure and within continuous exposure metrics are likely to have attenuated the observed exposure–response relationships. Another source contributing to exposure misclassification in our analysis is the resolution of the available work history data. Individual work histories were based on census data which provide a snapshot of an individual's job at a specific point in time (census), but do not provide detailed information with regards to changes in jobs or tasks over a full working career. Similar, the census data classified individuals in relatively broad job categories, without having the possibility to differentiate between specific jobs or tasks. To assess the impact of occupational mobility on our results, we conducted sensitivity analyses restricted to the group of individuals younger than 40 years old at the time of their first census, as this group were likely to have had a more complete assessment of occupational history (ie, they were more likely to be included in more than one census). HRs based on these sensitivity analyses changed little (and in both directions) compared to our original analysis, while CIs widened.

Because our study is based on a sample of the general population of Finland, Sweden, Iceland and Norway, only a small percentage of the study population received considerable exposure to PER or TCE. In the JEM, high exposure to PER was primarily assigned to laundry workers, contributing 0.12% of the person-years (py) for men and 0.45% of the py in women in the NOCCA database.[15] High exposure to TCE was primarily assigned to shoe and leather workers (0.29% of the py for men; 0.23% of the py for women), mechanics (7.71% of the py for men; 0.54% of the py for women), and laundry workers and, to a lesser extent, smelting workers (1.31% of the py for men; 0.07% of the oy forwomen).[15] As a result, although there was considerable contrast among exposed workers (see the notes to table 1 and figure 1), the exposure prevalence was low, affecting the ability to assess exposure–response relationships. This might explain why we observed considerably increased HRs for NHL and MM in some of our high exposure groups for PER, while HRs in our analysis based on tertiles remained around unity and might have contributed to the inability to reproduce the modestly but significantly elevated risks that have been observed in other studies, especially for TCE and cancers of the kidney and NHL.

We included an assessment of NHL in our analysis. To allow the inclusion of historical cancer registry data in the NOCCA database, all incident cases (including NHL cases) were coded according to ICD-7 classifications. Unfortunately, the ICD-7 system offers limited ability to differentiate between NHL subtypes. However, NHL is a heterogenic group of diseases. If some NHL subtypes (eg, diffuse large B-cell lymphoma or follicular lymphoma) are associated with TCE or PER, while others are not, any NHL HR would have been attenuated

because of the inclusion of unassociated NHL subtypes. Further consideration of the associations between TCE or PER and NHL will therefore require delineation of the risks by NHL subtype. A recent large European case–control study did explore the association of TCE exposure with NHL subtypes, but observed no increased risk for any of the subtypes.[35]

We could not control for potential confounding factors such as tobacco smoking, alcohol consumption, and the hepatitis B and C virus in this study. Because the prevalence of the hepatitis B and C virus is low in the Nordic countries and both are unlikely to be associated with exposure to PER or TCE, these are unlikely to be confounding factors for the observed associations with liver cancer and NHL. Alcohol consumption and tobacco smoking are risk factors for liver cancer, but moderate risks have generally been reported (Relative Risk (RR)<2),[36 37] which makes substantial confounding in our analyses unlikely.

Although exposure is likely to have decreased over the last decades, even in the modern occupational setting, exposure to PER and TCE is still widespread. In addition, the general population might be exposed to PER and TCE through drinking water.[13 14] Assessment of potential health effects associated with exposure to PER and TCE, especially in more recent cohorts, is therefore necessary. Our current analysis provides some insight into the potential associations of these chlorinated solvents with NHL, MM and cancers of the liver and kidney. Our finding of evidence that suggests an association between exposure to PER, and NHL and cancer of the liver should be followed up in other studies. This study was subject to limitations related to the low prevalence of exposure to PER and TCE in the Nordic population and a limited exposure assessment strategy. New studies of cancer risks associated with exposure to PER and TCE should focus on high quality quantitative exposure assessment, inclusion of information on potential confounding factors and a more detailed classification of cancer outcomes.

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Table S1 Pearson correlation coefficients for cumulative exposure PER and TCE with other organic solvents and potential confounding factors

Exposure	**PER** [a]	**TCE** [a]
Aliphatic and alicyclic hydrocarbon solvents	0.08 - 0.09	0.05 - 0.06
Aromatic hydrocarbon solvents	0.08 - 0.09	0.04 - 0.05
Chlorinated hydrocarbon solvents	0.61 - 0.63	0.56 - 0.61
Gasoline	-0.01 - 0	0.02 - 0.03
Other organic solvents	0	-0.01
Benzene	0.01	0.04 - 0.06
Methylene chloride	0	0.01 0.02
Toluene	0.01	-0.01 - 0
Perchloroethylene	1	0.58 - 0.63
1,1,1-trichloroethane	0.07 - 0.08	0.37 - 0.43
Trichloroethylene	0.58 - 0.63	1
Ionizing radiation	0	-0.01

[a] Table shows minimum and maximum observed Pearson correlation coefficient within case-control datasets for kidney and liver cancer, NHL, and MM.

Table S2 Multivariate model PER and cancer of the liver

Model	Log likelihood	parameter	beta	p-value
univariable	-42815	PER	1.17 (0.95-1.44)	0.1400
multivariable	-42808	PER	1.17 (0.95-1.43)	0.1500
		benzene	3.69 (1.59-8.55)	0.0023
		ionizing radiation	31.00 (2.08-462.9)	0.0130

Likelihood ratio test with two degrees of freedom: p=0.0007