Exhibit 258

Cancer Incidence Among Danish Workers Exposed to Trichloroethylene

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Human evidence regarding the carcinogenicity of the animal carcinogen trichloroethylene (TCE) is limited. We evaluated cancer occurrence among 803 Danish workers exposed to TCE, using historical files of individual air and urinary measurements of TCE-exposure. The standardized incidence ratio (SIR) for cancer overall was close to unity for both men and women who were exposed to TCE. Men had significantly elevated SIRs for non–Hodgkin's lymphoma (SIR = 3.5; n = *8) and cancer of the esophagus (SIR = 4.2;* n = *6). Among women, the SIR for cervical cancer was significantly increased (SIR = 3.8;* n = *4). No clear dose-response relationship appeared for any of these cancers. We found no increased risk for kidney cancer. In summary, we found no overall increase in cancer risk among TCE-exposed workers in Denmark. For those cancer sites where excesses were noted, the small numbers of observed cases and the lack of dose-related effects hinder etiological conclusions.* (J Occup Environ Med. *2001; 43:133–139*)

Trichloroethylene (TCE) is among the most widely used chlorinated organic solvents and is mainly used for degreasing metal products before painting.[1] TCE is carcinogenic in long-term animal assays; tumors of the liver, kidney, and testis and lymphomas have been reported.[1–3] Epidemiological data are limited and inconsistent, although some studies suggest an association between TCE exposure and risk of cancers of the liver and biliary passages, non–Hodgkin's lymphoma, and leukemia.[1,4,5] On the basis of experimental data and limited epidemiological evidence, the International Agency for Research on Cancer in 1995 classified TCE as a probable human carcinogen.[1] Since then, a potential association between occupational exposure to TCE and kidney cancer risk has been investigated, with conflicting results.[4,6–12]

Most studies of cancer risk have been based on indirect assessment of TCE exposure, which may lead to the misclassification of exposure and a tendency to dilute the observation of a potential carcinogenic effect.[13] Further, the largest studies[4,6,7,14] concerned mortality rather than incidence rates. Death certificate data may have a higher proportion of misclassified diagnoses and may fail to identify cancers with very high survival rates.[15,16] We conducted a cohort study in Denmark of cancer morbidity among workers with individual measurements of exposure to TCE.

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Material and Methods

Ascertainment of TCE Measurement Data

Since 1947, the Labor Inspection Services in Denmark has performed individual measurements of persons exposed to TCE. These measurements were initiated by the Services (1) as part of a routine measurement program; (2) during specific campaigns against exposure to hazardous chemicals; or (3) by request from medical officers, workers, or their employers after concern about exposure levels, poisoning accidents, etc. During the period 1947 to 1989, a total of 2397 samples were analyzed for the TCE-metabolite trichloroacetic acid (TCA) in the urine of exposed persons at 275 different companies.[17,18] The urine samples were taken uniformly through normal workdays, and no association was observed between the measured level of urinary TCA and the sampling weekday. The same measurement method (Fujiwara) was used during the entire period.[17] Samples of urinary TCA provide an indication of TCE exposure during the preceding week[19] (the biological half-life of TCA is about 100 hours[1]), and approximate linearity exists between the average concentration of inhaled TCE below about 375 mg/m^3 and urinary concentration of TCA ($TCE_{mg/m3} = 1.96 \cdot TCA_{mg/L\ urine} - 0.7$; 1 mg/L 6.1 μmol/L).[20] Since 1974, a total of 472 measurements of the individual concentration of TCE in the breathing zone were also performed at 81 different companies.[21,22] For both urinary-TCA and air-TCA measurements, information on each measurement (concentration, date, exposure conditions); the company (name, address, and type of production); and the worker (name, sex, birth date, address, and work tasks) was recorded and kept at the National Institute of Occupational Health.

Identification of Persons With Measurement Records

To follow each person for cancer occurrence and/or date of death or emigration, the unique 10-digit personal identification number assigned to each resident in Denmark was obtained from the Central Population Registry (which began on April 1, 1968), using information on name, sex, address, and birth date recorded in the measurement files. For urinary measurements performed before approximately 1965, and for air measurements performed before 1980, the amount and quality of individual data recorded have been somewhat limited, particularly because of incomplete registration of birth dates. Furthermore, persons who died before the start of the Central Population Registry could not be identified. Thus, for 36% of the urinary-TCA and 48% of the air-TCE measurements, the individual worker could not be identified for certain. For the remaining 1519 urinary-TCA and 245 air-TCE measurements, a total of 658 men and 145 women, born between 1901 and 1979, were identified as exposed to TCE and comprised our study cohort. Among the 803 identified persons, 712 had urinary-TCA measurement records, 89 had air-measurement records, and 2 had records of both types. For 37 persons with a measurement below the lowest measured value (detection limit), one-half of this value was assigned instead (2.5 mg/L before 1979; 0.5 mg/L 1979 and after). On average, 2.2 measurements were performed per individual, with a maximum of 27 measurements. By far, the largest fraction of measurements came from persons working in the iron and metal industry.

Employment History

No information on start and end dates for jobs involving TCE exposure was available from the measurement files. Nevertheless, job information was reconstructed from the files of the national Pension Fund using the personal identification number, company name, and dates of exposure. Membership in this Pension Fund has been mandatory for all employees in Denmark since its establishment in 1964, and information on all employment since 1964 is computerized and retained even after the employee retires or dies.[23,24] The employment history was identified from the pension fund files for 654 of 662 workers with measurements from 1964 or later. For the remaining 149 persons (19%), only the measurement dates before 1964 were available. Among the identified persons with pension fund records, 131 (20%) were employed in the relevant company on the first day of the pension scheme, indicating that their true start date of work would likely have been before this date. The mean and median durations of employment (taking 1964 as the first possible employment year) were 102 months and 75 months, respectively.

Follow-Up for Cancer

Each person was linked to the files of the nationwide Danish Cancer Registry by use of the personal identification number.[25] Information on type of cancer and date of diagnosis was abstracted for all notified cases of cancer among cohort members. Tumors were classified according to a modified version of the International Classification of Diseases, Seventh Revision.[26] The period of follow-up for cancer occurrence began on the later of April 1, 1968, or the date of first employment. Unknown dates of employment were replaced with the first date of monitoring (after April 1, 1968). Follow-up ended on the date of death, emigration, or December 31, 1996, whichever occurred first. We calculated the expected numbers of cancers from Danish national incidence rates of site-specific cancers by sex, 5-year age group, and calendar year. Each person was categorized according to period of first known employment (pre-1965 and 1965 and later) and duration of employment ($<$75 months and $\leqq$75 months). Further,

each person was grouped according to the median air concentration of TCE (19 mg/m^3), and if duration of employment was available, also to the calculated median (1080 months · mg/m^3) cumulative exposure. Persons who ended employment before the establishment of the Pension Fund in 1964, and for whom a duration period could not be calculated, were categorized separately. Finally, 10- and 20-year lag periods were included to allow for latency time. Tests of significance and 95% confidence intervals (CI) for the standardized incidence ratio (SIR), the ratio of observed-to-expected cancers, were calculated assuming that the observed number of cancers followed a Poisson distribution.[27]

After it was determined that a high proportion of esophageal cancers among TCE-exposed workers were adenocarcinomas, we ascertained the proportions of adenocarcinomas, squamous cell carcinomas, and other esophageal cancers by using the International Classification of Diseases of all male subjects with esophageal cancer in the Danish Cancer Registry who were born in the same period (1910 to 1935) and were diagnosed in the same median calendar period (1990 to 1996) as the TCE-exposed workers.

Results

Table 1 shows the characteristics of the measurements of the cohort members. Downward trends in the mean and median concentrations of urinary TCA were seen during the period 1947 to 1989. The mean and median concentrations of urinary TCA for the entire period were 40 mg/L and 15 mg/L, respectively. The corresponding figures for air measurements (1974 to 1989) were 101 mg/m^3 and 28 mg/m^3. The calculated mean and median air concentrations of TCE (after transforming the urinary-TCA measurements to air concentrations; thus, air- and urinary-TCA measurements together) were 65 mg/m^3 (TCA = 34 mg/L) and 19 mg/m^3 (TCA = 10 mg/L), respectively.

During the follow-up period, TCE-exposed men and women contributed 13,796 and 2934 person-years, respectively. A total of 246 cohort members (21%) died during the follow-up period. Overall, 128 primary cancers (including non-melanoma skin cancers) were identified among 115 workers. The total observed number of cancer cases was close to expected among both men and women who were exposed to TCE (Table 2). Among the men, significantly elevated SIRs were found for non–Hodgkin's lymphoma (SIR = 3.5; 95% CI = 1.5 to 6.9; n = 8) and cancer of the esophagus (SIR = 4.2; 95% CI = 1.5 to 9.2; n = 6). The original notification forms from the hospital departments to the Cancer Registry were retrieved for all patients with non–Hodgkin's lymphoma and esophageal cancer, and all were histologically confirmed. Five (83%) of the six observed esophageal cancers were adenocarcinomas, and one was a squamous cell carcinoma. The proportions of adenocarcinomas, squamous cell carcinomas, and other esophageal cancers among the comparable Danish male population during the period 1990 to 1996 (n = 1529) were 38%, 46%, and 16%, respectively. For alcohol-related cancers combined (buccal cavity and pharynx, esophagus, liver, and larynx) among TCE-exposed men, the SIR was 2.3 (95% CI = 1.3 to 3.6), based on 20 observed cases. Among women, only the risk for cervical cancer (SIR = 3.8; 95% CI = 1.02 to 9.8; n = 4) was significantly different from unity. The SIR for kidney cancer among both sexes combined was 1.1 (95% CI = 0.3 to 2.7; n = 4); three of these cancers were renal cell carcinomas (hypernephroma), and one was a ureter carcinoma. Inclusion of lag time showed no material changes in the results for men or women (data not shown).

SIRs for non–Hodgkin's lymphoma and esophageal cancer among men and cervical cancer among women, according to period of first exposure, duration of employment, calculated individual mean measurement level, and cumulative exposure, are shown in Table 3.

Occupational and time-related characteristics of workers with non–Hodgkin's lymphoma, esophageal cancer, and cervical cancer are given in Table 4. Most patients with known duration of employment had relatively long employment periods (mean >9 years). The only patient with esophageal cancer having a squamous cell carcinoma was born in 1910, and the urinary-TCA concentration was at detection level.

TABLE 1
Characteristics of Measurements for 803 TCE-Exposed Persons Included in the Follow-Up Study*

	Urinary-TCA Measurements (mg/L)				Air-TCA Measurements (mg/m^3)			
Period of Measurement	*n*	Mean	SD	Median	*n*	Mean	SD	Median
1947–1964	401	62	98	25	0	–	–	–
1965–1973	399	43	72	15	0	–	–	–
1974–1979	562	30	57	10	18	372	502	138
1980–1989	157	9	33	2	227	79	151	25
Total period	1519	40	74	15	245	101	211	28

* TCE, trichloroethylene; TCA, trichloroacetic acid.

TABLE 2
Cancer Incidence (1968–1996) Among 803 Danish Workers Exposed to TCE*

	Men (*n* = 658; 13,796 person-years)				Women (*n* = 145; 2,934 person-years)			
Site (ICD-7)	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Total (140–205)	109	104.8	1.0	0.9–1.3	19	18.6	1.0	0.6–1.6
Buccal cavity and pharynx (140–148)	7	3.1	2.3	0.9–4.7	0	0.2	–	–
Esophagus (150)	6	1.4	4.2	1.5–9.2	0	0.1	–	–
Stomach (151)	3	3.8	0.8	0.2–2.3	1	0.4	2.8	0.04–16
Colon (153)	5	7.3	0.7	0.2–1.6	1	1.4	0.7	0.01–4.0
Rectum (154)	7	5.4	1.3	0.5–2.7	0	0.7	–	–
Liver and biliary passages (155)	5	2.0	2.6	0.8–6.0	0	0.4	–	–
Pancreas (157)	3	2.9	1.0	0.2–3.0	1	0.5	2.2	0.03–13
Larynx (161)	2	1.9	1.1	0.1–3.9	0	0.1	–	–
Lung (162)	16	19.9	0.8	0.5–1.3	1	1.5	0.7	0.01–3.8
Breast (170)	0	0.2	–	–	4	4.5	0.9	0.2–2.3
Cervix uteri (171)	–	–	–	–	4	1.1	3.8	1.0–9.8
Corpus uteri (172)	–	–	–	–	1	1	1.0	0.01–5.4
Ovary (175)	–	–	–	–	2	0.9	2.1	0.2–7.6
Prostate (177)	6	10.1	0.6	0.2–1.3	–	–		
Testis (178)	1	1.4	0.7	0.01–4.0	–	–		
Kidney (180)	3	3.3	0.9	0.2–2.6	1	0.4	2.4	0.03–14
Bladder (181)	10	9.4	1.1	0.5–2.0	0	0.5	–	–
Melanomas of skin (190)	2	2.1	0.9	0.1–3.4	0	0.5	–	–
Other skin (191)	15	15.1	1.0	0.6–1.6	0	2.3	–	–
Brain and nervous system (193)	1	2.7	0.4	0.01–2.1	0	0.5	–	–
Non–Hodgkin's lymphoma (200,202)	8	2.3	3.5	1.5–6.9	0	0.3	–	–
Hodgkin disease (201)	0	0.5	–	–	0	0.1	–	–
Multiple myeloma (203)	1	1.2	0.9	0.01–4.7	0	0.2	–	–
Leukemia (204)	5	2.7	1.9	0.6–4.4	1	0.3	3.1	0.04–18
Other and unspecified	3	6.1	0.5	0.1–1.4	2	0.7	2.9	0.4–104

* TCE, trichloroethylene; ICD-7, International Classification of Diseases, 7th revision; Obs, observed; Exp, expected; SIR, standardized incidence ratio; CI, confidence interval.

Discussion

The workers included in this study were selected because of measurements taken specifically for assessing their exposure to TCE, and some workers were followed-up for as long as 50 years after their exposure, which allowed the detection of cancers with long latency periods.

The main findings in this study are that the observed and expected numbers of cancers among both men and women are approximately equal, that significantly elevated SIRs for non–Hodgkin's lymphoma and esophageal cancer among men and cervical cancer among women exposed to TCE were seen, and that no increased risk for kidney cancer was observed.

Non–Hodgkin's lymphoma was also reported in excess, albeit not with statistical significance, in similar cohorts of TCE-exposed workers from Sweden and Finland.[28,29] In addition, a non-significantly elevated risk of non–Hodgkin's lymphoma was reported in two recent cohort studies[4,7] but not in two others.[6,14] Case-control studies have been limited in their ability to evaluate TCE and cancer risks, and the results have been inconsistent.[1] Finally, some ecological studies on TCE-contaminated groundwater have reported an elevated risk of non–Hodgkin's lymphoma, although such a study design is useful in generating but not in testing hypotheses.[30] The etiology of non–Hodgkin's lymphoma remains largely unknown, although the risk is generally higher among the higher social classes and elevated risks associated with immunosuppression and occupational phenoxy herbicide exposures have been observed.[31]

A major cause of esophageal cancer and cancers of the oral cavity, pharynx, larynx, and liver in Denmark is consumption of alcoholic beverages.[32,33] SIRs for these cancers were all in excess among men in this study, suggesting that alcohol intake among cohort members might have been higher than in the general population. On the other hand, only one of the six esophageal cancers was a squamous cell carcinoma (which is generally strongly associated with alcohol), whereas the association, if any, between alcohol and adenocarcinomas is weak.[34] Levels of alcohol drinking and smoking are often correlated[35]; however, we did not observe excesses of the major tobacco smoking–related cancers (lung, bladder, and larynx). Because no information on individual alcohol intake was available for the present study, it was not possible to separate the effects of TCE exposure and alcohol on known alcohol-related cancer sites. TCE has generally not been associated with esophageal can-

TABLE 3
Cancer Incidence Among 803 Danish Workers Exposed to TCE, According to Exposure-Related Characteristics*

Characteristics	Non-Hodgkin's Lymphoma (men)			Esophageal Cancer (men)			Cervical Cancer		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Period of first employment									
1947–1964	4	3.5	0.9–8.9	2	2.6	0.3–9.5	3	5.2	1.1–16
1965–1989	4	3.5	0.9–8.9	4	6.0	1.6–15.3	1	2.1	0.03–12
Duration of employment (months)									
Unknown†	2	3.7	0.4–13	0	–	–	2	6.4	0.7–23
<75	2	2.5	0.3–9.2	2	4.4	0.5–16	1	3.8	0.1–21
≥75	4	4.2	1.1–11	4	6.6	1.8–17	1	2.1	0.03–12
Individual mean exposure (mg/m^3)									
<19‡	4	3.9	1.1–10	5	8.0	2.6–19	2	3.4	0.4–12
≥19	4	3.2	1.1–10	1	1.3	0.02–7.0	2	4.3	0.5–16
Cumulative exposure (months · mg/m^3)									
Unknown†	2	3.6	0.4–13	0	–	–	2	6.4	0.7–23
<1080‡	3	3.9	0.8–11	3	6.5	1.3–19	1	2.9	0.04–16
≥1080	3	3.1	0.6–9.1	3	4.2	1.5–9.2	1	2.6	0.03–14

* For definition of abbreviations, see Table 2.
† Persons with urinary-TCA or air-TCE measurements before 1964 for whom employment history could not be reconstructed from the National Pension Fund.
‡ Median.

TABLE 4
Characteristics of Patients With Non–Hodgkin's Lymphoma, Esophagal Cancer, and Cervical Cancer

Urinary TCA* mean concentration mg/L/ no. of measurements (min–max)	Measurement Period	First Known Employment† (duration in months)	Type of Industry	Job Type	Birth Year	Diagnosis Year
Non–Hodgkin's lymphoma						
35/1	1969	1964 (180)	Iron and metal	Unskilled worker	1908	1972
6/14 (0–20)	1967–1972	1964 (144)	Electronics	Galvanizer	1910	1991
Detection limit/1	1978	1976 (39)	Iron and metal	Spray-painter assistant	1923	1996
Detection limit/1	1979	1964 (122)	Printing	Typographer	1927	1996
20/1	1954	Before 1964	Iron and metal	Machine-repair worker	1938	1991
1/9 (0–2)	1986–1987	1974 (259)	Iron and metal	Painter	1941	1988
127/3 (20–180)	1958	Before 1964	Iron and metal	Metal-product cleaner	1942	1996
93 mg/m^3‡/1	1986	1986 (60)	Iron and metal	Cleaning-machine operator	1955	1990
Esophageal cancer						
5/1	1966	1966 (2)	Machine	Painter	1902	1988
Detection limit/1	1960	1964 (67)	Machine	Cleaning metal products	1910	1985
5/1	1966	1964 (180)	Cable	Cleaning metal products	1912	1991
Detection limit	1978	1970 (114)	Printing	Plumber	1932	1995
22/3 (10–40)	1972–1974	1970 (96)	Iron and metal	Cleaning metal products	1932	1995
5/14 (0–10)	1971–1978	1971 (141)	Electronics	Welder	1933	1992
Cervical cancer						
23/2 (5–40)	1965–1969	1964 (103)	Iron and metal	Unknown	1917	1975
Detection limit/1	1979	1974 (16)	Dry cleaning	Dry cleaner	1930	1989
27/1	1949	Before 1964	Iron and metal	Cleaning metal products	1931	1995
5/1	1961	Before 1964	Machine	General cleaner	1934	1991

* TCA, trichloroacetic acid.
† Information from the Pension Fund (backdating to 1964).
‡ Air measurement.

cer in prior studies,[7,36] whereas perchloroethylene has been linked to esophageal cancer (primarily, squamous cell carcinomas) among dry cleaners.[37] Risk factors for esophageal adenocarcinomas include cigarette smoking, obesity, and gastroesophageal reflux diseases,[34] but we are aware of no epidemiological reports of occupational hazards for this cell type.

A fourfold elevation in the SIR for cervical cancer ($n = 4$) was found in this study among the TCE-exposed women. Twofold elevated risks of this cancer were reported in two

previous cohort studies,[4,29] whereas no increased risk was found in other studies.[6,7] The main cause of cervical cancer is infection with human papilloma virus, which is strongly associated with social class.[38] In Denmark, the risk of cervical cancer is twofold higher among factory workers compared with academics.[39] Because the majority of the female population included in this study were unskilled factory workers, the observed increase in risk of cervical cancer was likely a socioeconomic phenomenon reflecting infection by the human papilloma virus rather than causation by solvent exposure.

A greater than tenfold increased risk of renal cell cancer was recently reported among German TCE-exposed workers,[8,9,12] although most epidemiological studies have shown no increase in renal cancer risk associated with TCE exposure.[10] We observed four patients with kidney cancer (both sexes combined) versus the 3.7 expected. In the two other methodologically similar Nordic studies,[28,29] no association was found between TCE and renal cancer. Thus, our findings and those of other investigators do not support the hypothesis that TCE exposure increases the risk of renal cancer.

Our assessment of exposure is based on measurements performed by the Labor Inspection Services before the onset of cancer; thus, recall and information biases were unlikely. However, the exposed persons were not sampled at random, and the measured levels may not necessarily represent the general levels at Danish workplaces. Furthermore, the urinary measurements represent exposure at the time of sampling, and the air measurements represent thumbnail sketches as opposed to average cumulative exposure to TCE. Nevertheless, the individualized exposure data provide an advantage in objectively classifying workers' exposure.

A positive dose-response relationship is a key element in the evaluation of causality between exposure and disease.[40] No clear dose-response relationships were indicated for non–Hodgkin's lymphoma, esophageal cancer, or cervical cancer (Table 3), based on estimates for either the individual exposure level or cumulative exposure. However, because of the small numbers of patients, chance may play a role in the lack of dose-response effects. Further, because the biological half-life of TCE is relatively short,[41] sample timing is important, but it could not be controlled by using the available measurement files. Therefore, it is unknown whether low (or high) measured concentrations reflect truly low (or high) long-term average exposures or inappropriate timing of the sampling. In contrast, the more precisely measured duration of employment may represent a more reliable measure of cumulative dose;[40] for non–Hodgkin's lymphoma and esophageal cancer a tendency of increasing SIRs with increasing duration of employment was apparent, although neither trend was statistically significant.

Although monitoring data were available for some individuals back to 1947, only those alive as of April 1, 1968 (when the Central Population Registry was established) were included in the present study. Thus, risk periods before the start of the follow-up period could not be evaluated. For about 38% of the performed measurements, the measured worker could not be uniquely identified. Nevertheless, the mean and median exposures were almost identical for the measurements with and without an identified person, which indicated no selection associated with exposure level. On the other hand, if the inability to identify exposed workers was associated with poor (or good) health status, this may have caused underestimation (or overestimation) of cancer risk.

In conclusion, our investigation found no overall cancer increase among TCE-exposed workers, but it identified increased SIRs for non–Hodgkin's lymphoma and for cancers of the esophagus and cervix. Nevertheless, alternative explanations, such as confounding and chance due to multiple comparisons, cannot be excluded. Indeed, a higher prevalence of papilloma virus infection among female workers is likely to be the major contributor to the observed excess of cervical cancers, whereas the relevant confounders for non–Hodgkin's lymphomas are less apparent. Therefore, our findings for lymphoma and the increased risk of esophageal adenocarcinomas warrant further attention. Finally, we found no support for a TCE-associated increased risk for renal cell cancer.

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