Exhibit 214

Cancer Incidence among Finnish Workers Exposed to Halogenated Hydrocarbons

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Epidemiologic studies and long-term carcinogenicity studies in experimental animals suggest that some halogenated hydrocarbons are carcinogenic. To investigate whether exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane increases carcinogenic risk, a cohort of 2050 male and 1924 female workers monitored for occupational exposure to these agents was followed up for cancer incidence in 1967 to 1992. The overall cancer incidence within the cohort was similar to that of the Finnish population. There was an excess of cancers of the cervix uteri and lymphohematopoietic tissues, however. Excess of pancreatic cancer and non-Hodgkin lymphoma was seen after 10 years from the first personal measurement. Among those exposed to trichloroethylene, the overall cancer incidence was increased for a follow-up period of more than 20 years. There was an excess of cancers of the stomach, liver, prostate, and lymphohematopoietic tissues combined. Workers exposed to 1,1,1-trichloroethane had increased risk of multiple myeloma and cancer of the nervous system. The study provides support to the hypothesis that trichloroethylene and other halogenated hydrocarbons are carcinogenic for the liver and lymphohematopoietic tissues, especially for non-Hodgkin lymphoma. The study also documents excess of cancers of the stomach, pancreas, cervix uteri, prostate, and the nervous system among workers exposed to solvents.

The International Agency for Research on Cancer (IARC) has concluded that some halogenated hydrocarbons (carbon tetrachloride, chloroform, dichloromethane, 1,2-dichloroethane, tetrachloroethylene) are possibly carcinogenic to humans.[1] The evidence is based on animal data because of the inadequacies of the published epidemiologic literature, such as small population sizes, short follow-up times or latency intervals, and possible chance findings.

Both trichloroethylene and tetrachloroethylene have caused malignancies of the liver, kidney, and hematopoietic tissue in long-term carcinogenicity studies in experimental animals.[1–3] Trichloroethylene, tetrachloroethylene, and their metabolite trichloroacetic acid produce peroxisome proliferation, which may play a role in rodent hepatocarcinogenicity.[4] They appear to promote the growth of cells with spontaneously occurring H-*ras* mutations in mouse liver.[5] Animal studies on 1,1,1-trichloroethane have been negative or inadequate; in only one study did this agent appear to increase the risk of leukemia.[6] The similarities in at least one target site in exposed humans and experimental animals can help to generate a priori hypotheses for epidemiologic studies.[7] The present epidemiologic literature suggests that exposure to trichloroethylene, tetrachloroethylene, or other chemically related solvents may increase carcinogenic risk, especially of the liver and biliary passages,[8–13,15] pancreas,[11,14] the urinary tract,[12,14,16–19] and lymphohemato-

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poietic tissues.[11–13,16,19–21] For 1,1,1-trichloroethane, only one very small study has been performed in human populations.[12]

We have had access to a database of employees biologically monitored for occupational exposure to three halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane) during 1965 to 1983 at the Finnish Institute of Occupational Health (FIOH).[22,23] The aim of the present study was to assess the incidence of cancer among these workers, in comparison with the Finnish total population. As biologic measurements are usually done because the exposure at the workplace is known to be substantial and well-documented, we consider this workforce to be particularly suitable for the study.

Materials and Methods

Description and Ascertainment of the Cohort

The cohort analyzed in this study consisted of workers who had been biologically monitored for occupational exposure to three halogenated hydrocarbon solvents at the FIOH. The Finnish legislation on labor protection and occupational health care stipulates since 1958 that workers exposed to agents hazardous to health undergo regular health examinations. Therefore, workers regularly exposed to, for example, organic solvents have been monitored biologically to measure the uptake of the chemicals. The measurements recorded in the database were the concentration of trichloroacetic acid in the urine (U-TCA) for trichloroethylene during 1965 to 1982, the concentration of tetrachloroethylene (perchloroethylene) in the blood (B-Per) during 1974 to 1983, and the concentration of 1,1,1-trichloroethane in the blood (B-TC) during 1975 to 1983. The monitoring database included all the measurements for these solvents at the Institute since 1965, performed before the data collection in 1983 to 1984. In addition, the database included 109 workers for whom no U-TCA measurements were done. They were trichloroethylene poisoning cases, according to the registry of occupational diseases, or workers reported by the employers to have handled trichloroethylene sometime between 1965 to 1976.[24]

There were a total of 11,534 measurements for the three halogenated hydrocarbons. The unique personal identification code, given to everybody residing in Finland since January 1, 1967, could be ascertained from laboratory documents, various population registers (including records of deceased and emigrated persons), and from employers for 10,743 measurements (93.1%) or 3976 workers. The proportion of samples with an incomplete identification was higher during the earlier years, especially before 1970 (14.9% among women, 6.4% among men). After 1977, practically all samples could be identified. Only persons with full identification were included in the cancer study.

The computerized data included name, date of birth, personal identification code, and gender of the workers; date of sampling (if missing, the date of laboratory analysis, being usually within 1 week from the sampling, was recorded), workplace (if missing, then the sampling laboratory was recorded), solvent code, result, specific gravity (urine sample), time of day for the sampling (blood samples) and the analyzing laboratory at the FIOH. The measurements were analyzed at the Laboratory of Biochemistry (96.3% of the samples), and at the Regional Institute of Oulu (3.7%). About 600 different codes of workplaces or sampling laboratories were recorded from all over the country. Of the workers, 94.4% were monitored only for one solvent, 5.2% for two, and 0.4% for three solvents.

Trichloroethylene was mainly used in degreasing or cleaning of metal surfaces among the monitored workers. It was also used in rubber work, glueing, dry-cleaning (especially during the 1950s and 1960s), and as a component in cleaning fluids, for example, in the graphic industry. Tetrachloroethylene was used in dry-cleaning, and to a small extent also in degreasing and in the graphic industry; 1,1,1-trichloroethane substituted trichloroethylene in degreasing in many workplaces during the 1970s and 1980s. It was also used as a component in cleaning fluids and in glues.[22–26]

Concentrations in the Monitoring Data

Figure 1 shows the median and maximum level as well as other quartiles of the concentrations in the biologic samples. The only clear temporal decrease can be seen for the U-TCA levels. We do not know, however, whether the sampling procedures were reasonably similar during the period. There might also have been selection of the monitored tasks or workplaces. The overall median of U-TCA was higher for women (63 μmol/L) than for men (48 μmol/L). Before 1970, the U-TCA levels among men were higher, however (the median being 80 to 90 μmol/L among men and 60 to 80 μmol/L among women). For B-Per, the levels were slightly higher among men (median 0.7 μmol/L) than among women (median 0.4 μmol/L).

The biologic half-lives of the solvent concentrations are rather short, that is, the measurements describe exposure only during the last few days. The accuracy of sample timing could not be checked from the documents, however, affecting the interpretation of the monitored levels. There were on average 2.7 measurements per individual (2.0 for B-TC, 2.5 for U-TCA, and 3.2 for B-Per). Among those monitored for B-Per, only one sample was analyzed for 45% of the workers, and fewer than three samples for 60% of the workers (55 and 74% for U-TCA and 61 and 79% for B-TC, respectively).

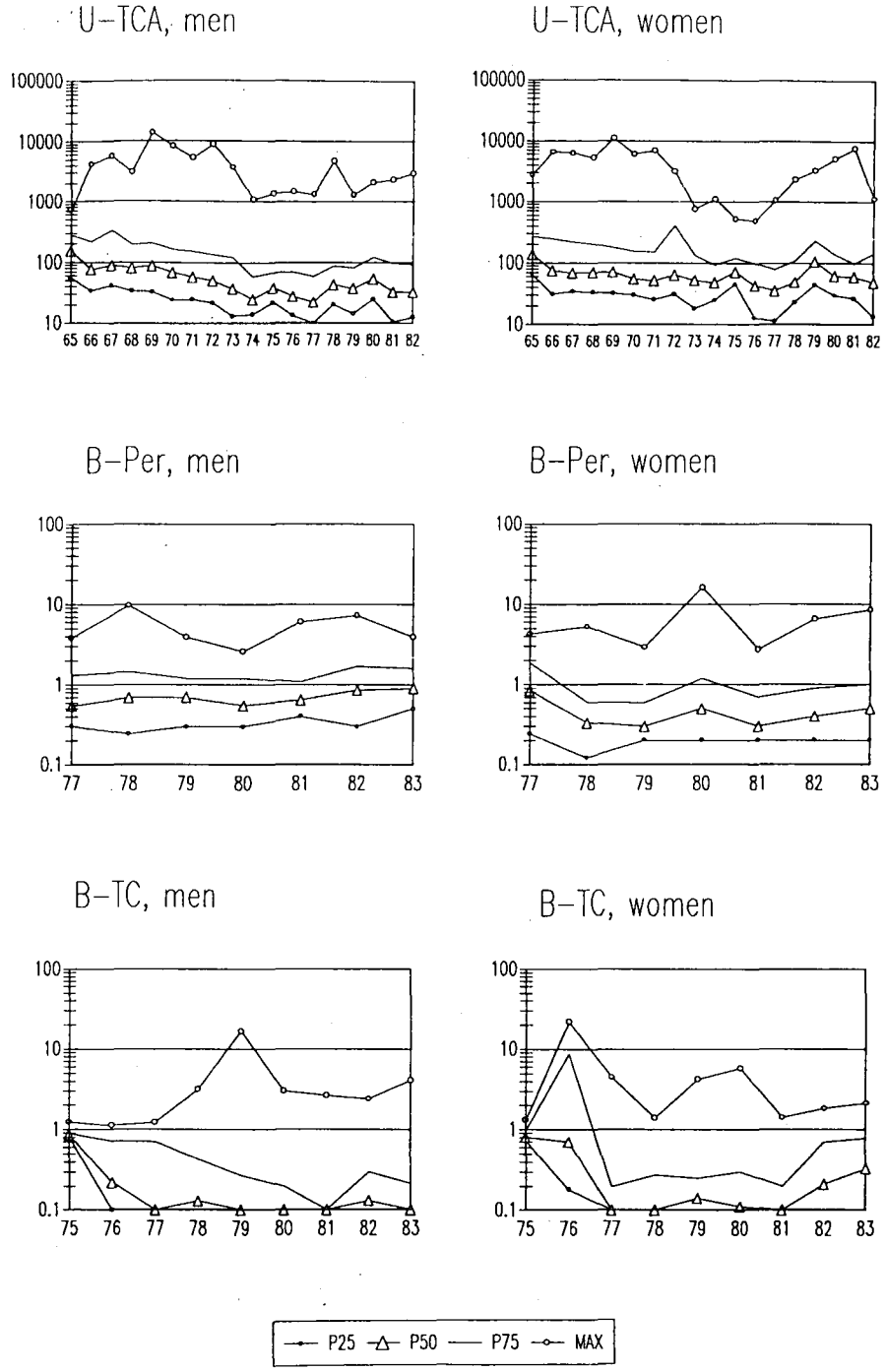

Fig. 1. The quartiles of the concentrations of monitored halogenated hydrocarbons (μmol/L) by the year of monitoring. For B-Per, only the morning samples are included (N = 1278).

Follow-up for Cancer Incidence

Follow-up for cancer was done automatically through the files of the Finnish Cancer Registry between 1967 and 1992. In the basic analysis, the follow-up was started on January 1, 1967, or at the date of the first measurement of the solvent category, whichever was later. In the analysis utilizing multiple measurements (eg, mean level), the calculation of person-years was started at the date of the last referred measurement. The calculation of person-years ended at emigration, at death, or on December 31, 1992, whichever occurred first. The full 26-year follow-up was possible only for trichloroethylene. The follow-up for death and emigration was done automatically in the Population Register Center using the personal identification code. There were no losses for follow-up among the originally identified cohort members. Two persons had died before 1967, and they were therefore excluded from the cancer incidence study.

The numbers of observed cases and person-years at risk were counted, by gender and 5-year age groups, separately for three calendar periods: 1967 to 1975, 1976 to 1984, and 1985 to 1992. The expected numbers of cases for total cancer and for specific cancer types were calculated by multiplying the gender and age-specific number of person-years in each age group by the corresponding average cancer incidence in Finland during the period of observation. Further division was made by the time elapsed from the first personal measurement. The data were also grouped by the lifetime mean level of the concentrations.

The specific cancer types selected a priori comprised those with known or suspected exceptional risk for the solvents in earlier studies. Thus, the most important primary sites were (1) liver (trichloroethylene, tetrachloroethylene), also including the biliary tract and the pancreas, even though evidence is lacking for these in animal studies; (2) kidney, bladder (trichloroethylene, tetrachloroethylene); (3) lymphatic and hematopoietic tissues; (4) brain and other nervous system, due to the known toxicity of these chemicals to the central nervous system; and (5) those primary sites that are usually in direct contact with solvents (mouth, pharynx, nose, sinuses, larynx, trachea, lung, skin). Also, cancers of the genital organs, potentially influenced by hormonal factors, were included in the analysis. Because solvents or their metabolites are spread also to several other tissues in the

TABLE 1
Number of Persons under the Follow-Up of Cancer Incidence and Number of Person-Years at Risk in 1967 to 1992, by Gender, Age, and Solvent Type*

Category	Men		Women	
	N	P-Years	N	P-Years
Total cohort	2,050	36,053	1,924	35,747
Age <30 y	1,033	6,275	592	3,442
Age 30–59 y	977	26,181	1,275	25,513
Age 60+ y	40	3,597	57	6,792
Trichloroethylene	1,698	31,552	1,391	28,353
Tetrachloroethylene	292	3,895	557	8,063
1,1,1-trichloroethane	140	1,720	131	1,653

* The same person may have measurements of various solvent types.
P-Years, person-years.

body, one cannot rule out the possibility of carcinogenic risks in some other primary sites either.

To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. The statistical significance was tested by the Mantel-Haenszel χ^2 test, on the presumption that the number of observed cases followed a Poisson distribution.

There were altogether 2050 men and 1924 women in the study. The mean age at the time of the first personal measurement was 32.8 years for men and 37.7 years for women. Those monitored for B-TC were slightly older than the average (men 38.2 years, women 39.9 years). The number of person-years was around 36,000 for each gender (Table 1). The mean length of follow-up was 18 years, 71,800/3,974. There were 27,547 person-years for the follow-up of 10 to 19 years from the entry, and 5877 person-years for the follow-up of ≥20 years.

Mortality

The data were also linked with cause-of-death statistics through 1965 to 1991 in the Central Statistical Office of Finland. The methods used for the follow-up of mortality were, as far as possible, similar to those used for the study of cancer incidence.

Results

During the entire 26-year follow-up period, 112 (98 expected) cases of cancer were found among men and 125 (130 expected) among women. The SIR of total cancer, both genders combined, was close to unity (Table 2). Significant increases were found in the SIRs of cancers of the cervix uteri, lymphatic and hematopoietic tissues combined, and non-Hodgkin lymphoma. There was an increase in the incidence of pancreatic cancer and non-Hodgkin lymphoma in the follow-up category of ≥10 years.

The SIRs among men and women were rather similar. Significant excesses were found, however, in the follow-up category ≥10 years among men only for cancers of the liver (SIR 4.3, 95% CI 1.2 to 11) and bone (SIR 11, 95% CI 1.4 to 40). Among women there was a significant excess of multiple myeloma (SIR 3.2, 95% CI 1.0 to 7.4, five subjects).

A total of 208 of the 237 cancer cases in the whole cohort had been monitored for U-TCA. The SIRs for the U-TCA subcohort were similar to those of all halogenated hydrocarbons combined. The risks for the follow-up period ≥20 years were significantly increased for overall cancer as well as for cancer of the stomach, liver, prostate, and lymphatic and hematopoietic tissues combined (Table 3). The increase in the overall cancer incidence for the follow-up of ≥20 years was the same both in women and men and similar for the specific primary sites other than liver.

Table 4 shows the SIRs for selected cancers according to the mean U-TCA level of the employees. One cancer case of thyroid gland was excluded from this analysis, because the last measurement was taken after diagnosing. The SIR of cancer of the cervix uteri was increased especially among those with relatively high U-TCA results. There is a weak indication that the SIRs of the cancers of the lymphohematopoietic tissues also were increased in the higher U-TCA group. Due to small numbers in the higher U-TCA group, the data in this analysis were not split further according to the time elapsed from the first personal measurement.

For tetrachloroethylene, the numbers of the cancer cases were small, and no significant excess was found (Table 5). Among workers monitored for 1,1,1-trichloroethane, there were increases in the incidence of cancer of the nervous system, and of myeloma, and the overall cancer incidence was elevated nonsignificantly (Table 5). There were no significantly increased risks related to a follow-up time of ≥10 years from the entry or when the material was grouped according to the level of personal mean B-Per or B-TC. Both of the multiple myeloma cases were women (SIR 33.8, 95% CI 4.1 to 122 for trichloroethane among women).

Mortality

The observed number of all deaths (222) was as expected (222.6) among the men. Among the women, there was a slight decline in the observed deaths (133/156.9, SMR 0.8, 95% CI 0.7 to 1.0). Cancer mortality was close to that expected (47/46.0 among men, 42/46.8 among women). For circulatory diseases, there was a small deficit (98/103.8 among men, 60/72.1 among women). Mortality from chronic liver disease was slightly but insignificantly higher than expected (5/4.3 for men; 4/1.6 for women). The overall mortality was similar to that expected in the U-TCA and B-TC subcohorts. In the subcohort for B-Per, there was a

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TABLE 2
Observed Numbers of Cancer Cases and SIRs in 1967 to 1992 with 95% Confidence Intervals for Selected Primary Sites among Workers Exposed to Halogenated Hydrocarbons, Both Genders Combined, by Years since the First Measurement*

Primary Site (ICD 7)	Years since First Measurement								
	0–9			10+			Whole Cohort		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All sites (140–204)	82	1.03	0.82–1.28	155	1.04	0.88–1.22	237	1.04	0.91–1.17
Mouth, pharynx (143–148)	1	1.39	0.04–7.74	2	1.52	0.18–5.47	3	1.47	0.30–4.30
Esophagus (150)	1	1.28	0.03–7.14	0	E1.64	0–2.25	1	0.41	0.01–2.29
Stomach (151)	8	1.45	0.62–2.85	11	1.18	0.59–2.11	19	1.28	0.77–1.99
Colon (153)	3	0.92	0.19–2.70	5	0.65	0.21–1.53	8	0.74	0.32–1.44
Rectum (154)	4	1.62	0.44–4.15	9	1.63	0.75–3.10	13	1.63	0.87–2.78
Liver (155.0)	0	E0.72	0–5.12	5	2.84	0.92–6.63	5	2.01	0.65–4.68
Gallbladder, bile ducts (155.1)	2	2.47	0.30–8.92	2	0.94	0.11–3.41	4	1.36	0.37–3.48
Pancreas (157)	1	0.43	0.01–2.42	**11**	**2.04**	**1.02–3.65**	12	1.56	0.81–2.72
Larynx (161)	0	E0.91	0–4.05	2	1.59	0.19–5.73	2	0.92	0.11–3.32
Lung, bronchus (162.0–162.1)	13	1.19	0.63–2.03	16	0.84	0.48–1.36	29	0.97	0.65–1.38
Breast (170)	12	0.84	0.44–1.48	22	0.85	0.53–1.28	34	0.85	0.59–1.18
Cervix uteri (171)	**6**	**2.82**	**1.04–6.13**	3	1.76	0.36–5.16	**9**	**2.35**	**1.08–4.46**
Corpus uteri (172)	0	E3.21	0–1.15	4	0.68	0.19–1.75	4	0.44	0.12–1.12
Ovary (175)	2	0.61	0.07–2.19	2	0.38	0.05–1.39	4	0.47	0.13–1.20
Prostate (177)	3	1.36	0.28–3.98	11	1.39	0.69–2.49	14	1.38	0.76–2.32
Testis (178)	1	1.75	0.04–9.77	1	2.04	0.05–11.4	2	1.89	0.23–6.81
Kidney (180)	1	0.42	0.01–2.33	6	1.09	0.40–2.37	7	0.89	0.36–1.82
Bladder, ureter, urethra (181)	1	0.52	0.01–2.87	4	0.82	0.22–2.10	5	0.73	0.24–1.71
Skin melanoma (190)	3	1.14	0.23–3.32	2	0.46	0.06–1.65	5	0.71	0.23–1.66
Other skin (191)	1	0.86	0.02–4.80	1	0.32	0.01–1.77	2	0.46	0.06–1.67
Nervous system (193)	3	0.76	0.16–2.21	9	1.53	0.70–2.90	12	1.22	0.63–2.12
Thyroid gland (194)	3	1.70	0.35–4.98	4	1.60	0.44–4.10	7	1.65	0.66–3.39
Bone (196)	0	E0.39	0–9.46	2	6.06	0.73–21.9	2	2.79	0.34–10.1
Lymphohematopoietic tissues (200–204)	11	1.91	0.95–3.42	14	1.47	0.80–2.46	**25**	**1.63**	**1.06–2.41**
Non-Hodgkin lymphoma (200, 202)	2	1.21	0.15–4.38	**9**	**2.55**	**1.17–4.84**	**11**	**2.13**	**1.06–3.80**
Hodgkin's disease (201)	3	2.65	0.55–7.76	0	E0.94	0–3.92	3	1.45	0.30–4.23
Multiple myeloma (203)	3	3.53	0.73–10.3	3	1.55	0.32–4.52	6	2.15	0.79–4.66
Leukemia (204)	3	1.41	0.29–4.12	2	0.64	0.08–2.31	5	0.95	0.31–2.21
Basal cell carcinoma of the skin†	12	1.08	0.56–1.88	21	0.74	0.46–1.13	33	0.83	0.57–1.17

* If Obs = 0, expected value (E) is given instead of the SIR.
† Not included with above categories.
Obs, observed; SIR, standardized incidence ratios; CI, confidence interval; statistically significant results are indicated in boldface type.

deficit in the overall mortality, especially among women (men: 10/15.0, SMR 0.7, 95% CI 0.3 to 1.2; women: 12/23.5, SMR 0.5, 95% CI 0.3 to 0.9).

Discussion

There were excess cancers of the cervix uteri and lymphohematopoietic tissues, particularly non-Hodgkin lymphoma, among the workers monitored for exposure to the halogenated hydrocarbons. After 10 years from the first measurement, an excess was found for pancreatic cancer and non-Hodgkin lymphoma. There was no indication of an increase of cancers of the mouth, pharynx, nose, nasal sinuses, larynx, lung, or skin; or of urinary organs or genital organs combined. In the U-TCA subcohort, the overall cancer risk and the risk of cancers of the stomach, liver, prostate, and lymphohematopoietic tissues were increased in the follow-up category of ≥20 years. For the B-Per subcohort, no statistically significant excesses were found. For B-TC exposure, excesses of multiple myeloma and cancer of the nervous system were seen, although the number of cases was small.

There are five previous cohort studies[12,13,20,24,27] and five population-based case-control studies[9,10,21,28,29] on trichloroethylene or chemically related solvents.[1,30] Because the studied cohorts have been small, their power to detect potential effects has been rather low. Two of the cohorts[12,13] and two case-control studies[9,10] showed elevated rates for cancer of the liver or biliary passages. Four of the studies reported an increase in the risk in the lymphohematopoietic tissue (lymphosarcoma or non-Hodgkin lymphoma,[12,13,21] or leukemia[20]). Risk of cancers of the

TABLE 3
Observed Numbers of Cancer Cases and SIRs in 1967 to 1992 for Selected Primary Sites with 95% Confidence Intervals among Workers Exposed to Trichloroethylene, Both Genders Combined, by Years since the First Measurement*

Primary Site (ICD 7)	Years since First Measurement											
	0–9			10–19			20+			Whole Period		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All sites (140–204)	65	1.07	0.82–1.36	83	0.84	0.67–1.04	**60**	**1.57**	**1.20–2.02**	208	1.05	0.92–1.20
Stomach (151)	6	1.32	0.48–2.87	4	0.63	0.17–1.60	**7**	**2.98**	**1.20–6.13**	17	1.28	0.75–2.04
Colon (153)	3	1.23	0.25–3.59	3	0.62	0.13–1.80	2	0.92	0.11–3.31	8	0.84	0.36–1.66
Rectum (154)	3	1.59	0.33–4.64	8	2.22	0.96–4.36	1	0.67	0.02–3.72	12	1.71	0.88–2.98
Liver (155.0)	0	E0.56	0–6.59	2	1.74	0.21–6.29	**3**	**6.07**	**1.25–17.7**	5	2.27	0.74–5.29
Men	0	E0.34	0–10.8	1	1.54	0.04–8.56	**3**	**13.0**	**2.68–37.9**	4	3.26	0.89–8.34
Women	0	E0.22	0–16.8	1	2.01	0.05–11.2	0	E0.26	0–14.0	1	1.02	0.03–5.70
Gallbladder, bile ducts (155.1)	2	3.28	0.40–11.8	1	0.75	0.02–4.17	1	1.62	0.04–9.02	4	1.56	0.43–4.00
Pancreas (157)	1	0.56	0.01–3.10	8	2.30	0.99–4.52	2	1.31	0.16–4.74	11	1.61	0.81–2.88
Lung, bronchus (162.0–162.1)	11	1.19	0.59–2.13	9	0.67	0.30–1.26	5	1.11	0.36–2.58	25	0.92	0.59–1.35
Cervix uteri (171)	**6**	**3.39**	**1.24–7.38**	1	0.84	0.02–4.67	1	2.89	0.07–16.1	**8**	**2.42**	**1.05–4.77**
Prostate (177)	2	1.09	0.13–3.91	3	0.56	0.12–1.64	**8**	**3.57**	**1.54–7.02**	13	1.38	0.73–2.35
Kidney (180)	1	0.53	0.01–2.95	5	1.39	0.45–3.24	0	E1.48	0–2.48	6	0.87	0.32–1.89
Bladder, ureter, urethra (181)	1	0.65	0.02–3.59	2	0.61	0.07–2.22	2	1.51	0.18–5.44	5	0.82	0.27–1.90
Nervous system (193)	0	E2.92	0–1.26	8	2.00	0.86–3.93	1	0.76	0.02–4.26	9	1.09	0.50–2.07
Lymphohematopoietic tissues (200–204)	8	1.79	0.77–3.53	5	0.78	0.25–1.81	**7**	**2.98**	**1.20–6.14**	20	1.51	0.92–2.33
Non-Hodgkin lymphoma (200, 202)	1	0.83	0.02–4.64	4	1.75	0.48–4.47	3	3.24	0.67–9.45	8	1.81	0.78–3.56
Hodgkin's disease (201)	3	3.33	0.69–9.74	0	E0.71	0–5.23	0	E0.16	0–22.9	3	1.70	0.35–4.96
Multiple myeloma (203)	1	1.52	0.04–8.44	1	0.79	0.02–4.38	2	3.78	0.46–13.7	4	1.62	0.44–4.16
Leukemia (204)	3	1.76	0.36–5.16	0	E2.18	0–1.69	2	2.72	0.33–9.83	5	1.08	0.35–2.53

* If Obs = 0, expected value (E) is given instead of the SIR.
Obs, observed; SIR, standardized incidence ratios; CI, confidence interval; statistically significant results are indicated in boldface type.

nose, sinus and nasopharynx,[28] cervix uteri,[12] prostate and testis,[13] urinary organs,[12] skin,[13] and brain[29] have been reported in single studies. An excess of overall cancer mortality among women, not described in detail, has also been reported.[13] No excess of cancer mortality was found in two small cohort studies.[24,27] In one of the cohorts, exposure to 1,1,1-trichloroethane was also assessed; mortality from multiple myeloma was increased among women, based on only two cases.[12]

Tetrachloroethylene has been studied more extensively, especially among laundry and dry-cleaning workers.[8,11,14–17,19,31] Other solvents, including trichloroethylene, petroleum solvents, and carbon tetrachloride, have also been used in that industry. It may be impossible to separate the overall solvent effects. In these occupations, a large proportion of the workers were women. Excesses in line with those found in the present cohort as a whole have been reported for the liver,[8,11,15] pancreas,[14] cervix uteri,[14,16,19] and lymphohematopoietic tissues (lymphoma or lymphosarcoma,[16,19] multiple myeloma[11]). The previous studies have indicated increased risks also for cancers of the esophagus,[14,19] colon or rectum,[14,19,31] lung,[11,17,19] urinary organs,[14,16–19] and skin.[16]

Of the potential confounders for lymphohematopoietic cancer in occupational cohorts, benzene and radiation are the most important ones. According to our knowledge, these exposures are not related to the monitored work in our study (except for the occasional use of petroleum solvents in dry-cleaning). In general, the use of benzene as a solvent in Finnish industry has been minimal since 1955, after a mass poisoning detected in a shoe factory.[32] Exposure to aromatic amines, vinyl chloride, and other chemicals in rubber work may be related to the risk of lymphoma, leukemia, and stomach cancer.[1] However, because the proportion of rubber workers is small in our cohort, it is unlikely that rubber

TABLE 4
Observed Numbers of Cancer Cases and SIRs in 1967 to 1992 with 95% Confidence Intervals among Workers Exposed to Trichloroethylene, Both Genders Combined, by Mean Personal U-TCA Level*

Primary Site	Mean personal U-TCA level μmol/L†					
	<100			100+		
	Obs	SIR	95% CI	Obs	SIR	95% CI
All sites (140–204)	127	1.17	0.98–1.39	63	0.97	0.74–1.23
Stomach (151)	12	1.65	0.85–2.88	4	0.91	0.25–2.32
Rectum (154)	**9**	**2.34**	**1.07–4.44**	2	0.85	0.10–3.07
Liver (155.0)	2	1.64	0.20–5.92	2	2.74	0.33–9.88
Pancreas (157)	6	1.61	0.59–3.50	3	1.31	0.27–3.82
Lung, bronchus (162.0–162.1)	16	1.02	0.58–1.66	7	0.83	0.33–1.71
Cervix uteri (171)	3	1.86	0.38–5.45	**5**	**4.35**	**1.41–10.1**
Prostate (177)	8	1.43	0.62–2.82	2	0.68	0.08–2.44
Nervous system (193)	7	1.52	0.61–3.13	2	0.76	0.09–2.74
Lymphohematopoietic tissues (200–204)	10	1.36	0.65–2.49	9	2.08	0.95–3.95
Non-Hodgkin lymphoma (200, 202)	5	2.01	0.65–4.69	2	1.40	0.17–5.04
Hodgkin's disease (201)	2	2.00	0.24–7.22	1	1.83	0.05–10.2
Multiple myeloma (203)	2	1.48	0.18–5.35	2	2.41	0.29–8.71
Leukemia (204)	1	0.39	0.01–2.19	4	2.65	0.72–6.78

* 1 μmol/L = 0.1634 mg/L.
† There were 237 employees for whom no adequate result was available (the specific gravity of the urine sample <1.008 [N = 128], or no sample available [N = 109]). Among these persons there were registered 17 cancers (18.1 expected); one in liver (0.2 expected), two in pancreas (0.6 expected), three in prostate (0.8 expected), and one in lymphohematopoietic tissues (1.1 expected).
Obs, observed; SIR, standardized incidence ratios; CI, confidence interval; statistically significant results are indicated in boldface type.

TABLE 5
Observed Numbers of Cancer Cases and SIRs with 95% Confidence Intervals for Selected Primary Sites among Workers Exposed to Tetrachloroethylene (1974 to 1992) or 1,1,1-Trichloroethane (1975 to 1992), Both Genders Combined*

Primary Site	Tetrachloroethylene			1,1,1-Trichloroethane		
	Obs	SIR	95% CI	Obs	SIR	95% CI
All sites (140–204)	31	0.90	0.61–1.27	17	1.58	0.92–2.52
Pancreas (157)	3	3.08	0.63–8.99	0	E0.34	0–10.8
Lung, bronchus (162.0–162.1)	5	1.92	0.62–4.48	2	1.31	0.16–4.71
Cervix uteri (171)	2	3.20	0.39–11.6	1	8.28	0.21–46.1
Kidney	2	1.82	0.22–6.56	0	E0.40	0–9.16
Nervous system (193)	2	1.15	0.14–4.15	**3**	**6.05**	**1.25–17.7**
Lymphohematopoietic tissues (200–204)	3	1.38	0.28–4.02	3	4.23	0.87–12.3
Non-Hodgkin lymphoma (200, 202)	3	3.76	0.77–11.0	1	3.87	0.10–21.5
Multiple myeloma (203)	0	E0.38	0–9.80	**2**	**15.98**	**1.93–57.7**

* If Obs = 0, expected value (E) is given instead of the SIR.
Obs, observed; SIR, standardized incidence ratio; CI, confidence interval; statistically significant results are indicated in boldface type.

chemicals can explain much of the excess.

It is not probable that chemicals other than solvents, or life-style patterns (such as alcohol consumption, smoking, sexual habits) explain the excesses in the present cohort, because excesses of the same primary sites were not seen in a parallel, in many respects comparable, cohort of workers monitored for lead exposure.[33] For instance, the reported use of alcohol was similar between the solvent and lead cohort members in the previous studies on spontaneous abortion.[22,23,34,35] Moreover, Hernberg et al.[10] found that alcohol was a negative confounder in their study on liver cancer and solvent exposure.

An excess of cervical cancer has been reported rather consistently among female solvent workers.[12,14,16,19] This has usually been explained by socioeconomic factors. In the present study, the incidence of cancer of the cervix uteri was increased for halogenated hydrocarbons combined and for trichloroethylene. For trichloroethylene, the increase was greatest among the women with high mean U-TCA level. This suggests that occupational factors may play a role.

As most or all of the solvent workers are usually exposed to more than one solvent (concomitantly from a mixture, or in different jobs or periods), it is not possible to separate the effects of other solvents from the

monitored ones. Particularly, in the present cohort the number of workers exposed to more than one of the monitored solvents may have been higher than that seen from the monitoring data. It is also possible that a wrong exposure test had been used: during the 1960s some of the U-TCA analyses had possibly been taken from exposure to tetrachloroethylene.[24] In 1,1,1-trichloroethane, small amounts (<1 to 5%) of 1,4-dioxane were used as stabilizer.[26] We do not believe that this small concentration of 1,4-dioxane can explain the excesses in the B-TC subcohort.

The identification of the cohort members through population registers was incomplete in the earlier years, especially for women. If the incompleteness was associated with health status, this would have caused some underestimation in the cancer risk among women. However, there was no difference in cancer risk by calendar period. The follow-up for death and emigration among those whose identification was ascertained was complete for the period of this study, 1967 to 1992. The cancer registration system in Finland is virtually complete,[36] and the computerized record linkage procedures are accurate.[37]

Because both observed and expected numbers of cases are based on same source, it is not likely that any misclassification of the disease status greatly affects the results. As only about 48% of the incident cancer cases died from cancer before 1993, it is clear that the statistical power of the study was much better when cancer incidence was used instead of mortality. Moreover, the relative risk of cancer tends to be smaller when using the mortality data than when using incidence.[13,38] The underestimation holds especially for those cancers whose survival rates are high. This may be due to problems in defining the underlying cause of death and selection in survival after diagnosing a cancer.

As biologic measurements are usually done on exposures considered substantial at the workplaces, it is reasonable to assume that virtually all the cohort members were exposed to the monitored agents. No further inclusion criteria were needed. We also considered that the statistical power was best for the analysis including the whole cohort (or subcohorts for the three solvents, respectively). For some cohort members, the monitored levels were increased only slightly compared with the values for the general population, which may weaken the potential effects seen for the solvents. It is not possible to say whether low values reflect low exposures or improper timing of the sampling. By contrast, a rather high level reflects the true burden better, but we are not able to estimate a dose for a longer period, or for the duration of exposure. More repeated measurements would have been needed to obtain adequate information on individual variability.[39,40] Taken together, the feasibility of the biologic monitoring data as such for a historical classification of exposure was limited, preventing reliable internal comparison within the cohort.

For tetrachloroethylene and 1,1,1-trichloroethane, as well as for the analysis by grouped U-TCA level, the statistical power was low. The small excesses of cancers of the nervous system and multiple myeloma among workers exposed to 1,1,1-trichloroethane differed from the findings among those exposed to other halogenated hydrocarbons. In the only previous study suggesting brain cancer risk for halogenated hydrocarbons, the exposure classification was based on codes of industry and occupation.[29] The study could not separate individual solvents reliably. The risk was not clearly related to tetrachloroethylene or trichloroethylene. Exposure to 1,1,1-trichloroethane was not classified.

It was estimated that there were about 4000 workers in Finland exposed to 1,1,1-trichloroethane, correspondingly about 2000 for tetrachloroethylene, and fewer than 1000 to trichloroethylene at the end of the 1980s.[26] The total economically active workforce in Finland was about 2.4 million. In the industrial hygienic measurements, performed by FIOH between 1982 to 1985, the concentration of trichloroethylene in degreasing was usually less than the hygienic standard 30 ppm (8-hour time-weighted average). The concentrations of 1,1,1-trichloroethane sometimes exceeded the hygienic standard 100 ppm (the range 1–444 ppm, mean 79 ppm, 8-hour time-weighted average; 17 degreasers were measured). The concentrations of tetrachloroethylene in dry-cleaning were usually below the hygienic standard 50 ppm.[26] Because of the common use, the carcinogenic risk of exposure to 1,1,1-trichloroethane should be studied further.

At present the mechanisms of potential solvent effects are not known. However, there is some biologic plausibility for carcinogenic risks from experimental systems. Trichloroethylene, and also tetrachloroethylene to a lesser extent, generate epoxide intermediates when metabolized and display at least some degree of genotoxicity.[2] Trichloroethylene and tetrachloroethylene have caused tumors of the liver, kidney, and hematopoietic system in experimental animals, and 1,1,1-trichloroethane some leukemias. All the three chlorinated hydrocarbons studied are toxic to the central nervous system, trichloroethylene and tetrachloroethylene also to the liver, and trichloroethylene additionally to the kidney.[2,6]

Concluding Remarks

Earlier epidemiologic and animal studies suggest that occupational exposure to halogenated hydrocarbons may be associated with an increased risk of cancer of the liver, pancreas, lung, kidney, bladder, nervous system, or lymphohematopoietic tissues. Because solvents or their metabolites also are spread to several other tissues in the body, one cannot rule out the possibility of carcinogenic risk for other primary sites. Among the members of the present

cohort, excess cancers of the cervix uteri and lymphohematopoietic tissues combined, particularly non-Hodgkin lymphoma were found. Analysis focusing on a follow-up period of more than 10 years from the first personal measurement showed an excess of pancreatic cancer and of non-Hodgkin lymphoma. For trichloroethylene, the overall cancer incidence was increased for a follow-up period of more than 20 years; the incidence of cancers of the stomach, liver, prostate, and lymphohematopoietic tissues was increased in this group. Workers exposed to 1,1,1-trichloroethane showed excess of multiple myeloma and cancer of the nervous system. The study provides support to the hypothesis that trichloroethylene and other halogenated hydrocarbons are carcinogenic for the liver and lymphohematopoietic tissues, especially non-Hodgkin lymphoma. The results also suggest that exposure to these solvents may increase the risk of pancreatic cancer. The study further suggests that the risk of cancers of the stomach, cervix uteri, prostate, and nervous system is increased among workers exposed to halogenated hydrocarbons. However, at present the mechanisms for such possible carcinogenic effects are not known. We intend to continue the follow-up of the cohort and to collect more detailed information on the exposure history and potential confounders in a nested case-referent design.

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Caviar: A Health Hazard?

For caviar lovers, time is running out. The sturgeon, whose eggs were highly prized by Russian royalty, has swum in the Caspian Sea since the days of the dinosaurs. . . . But today, following the collapse of the Soviet Union, it is under intense threat. . . . The Caspian produces 90% of the world's sturgeon and 95% of the black caviar harvest. In the late seventies the Soviet Union was exporting 2,000 tons of roe a year. In 1991 that figure dropped to 500 tons. Last year, only 180 tons of Caspian caviar were exported.

One central problem is poachers whose catch now exceeds the quotas once rigidly enforced by the Soviet Union. Netting sturgeon in the Caspian Sea was forbidden because the fish—which mature for 12 to 20 years in the sea before returning to the rivers to spawn—would be caught before they could reproduce. But now, free from the threat of punishment, fishermen in newly independent Kazakhstan, Azerbaijan, and Turkmenistan are massively overfishing the Caspian. . . . Consequently, fewer sturgeon are returning to the spawning grounds and the population has been steadily diminishing.

Because poachers are taking the sturgeon before they enter the rivers, when their eggs are still immature, they have flooded the world market with inferior caviar that is frequently overly salted and even unsanitary. . . . So buying caviar at low prices in supermarkets is a gamble. The roe could have been legally caught but illegally exported and be quite delicious. Or it could have been illegally fished and amateurishly packed and be dangerous to your health. A tip: Buy a small can and open it. If it is good, go back and demand the cans with exactly the same numbers stamped on the lids. If you are careful, now is the time to buy. Prices won't drop further, and they will skyrocket as the sturgeon heads toward extinction.

From "Caviar: A Health Hazard," by C. Pala in *Condé Nast Traveler,* October 1994, p 48.