Exhibit 279

Mortality of Aerospace Workers Exposed to Trichloroethylene

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We measured mortality rates in a cohort of 20,508 aerospace workers who were followed up over the period 1950–1993. A total of 4,733 workers had occupational exposure to trichloroethylene. In addition, trichloroethylene was present in some of the washing and drinking water used at the work site. We developed a job-exposure matrix to classify all jobs by trichloroethylene exposure levels into four categories ranging from "none" to "high" exposure. We calculated standardized mortality ratios for the entire cohort and the trichloroethylene-exposed subcohort. In the standardized mortality ratio analyses, we observed a consistent elevation for nonmalignant respiratory disease, which we attribute primarily to the higher background rates of respiratory disease in this region. We also compared trichloroethylene-exposed workers with workers in the "low" and "none" exposure categories. Mortality rate ratios for nonmalignant respiratory disease were near or less than 1.00 for trichloroethylene exposure groups. We observed elevated rate ratios for ovarian cancer among those with peak exposure at medium and high levels]relative risk (RR) = 2.74; 95% confidence interval (CI) = 0.84–8.99] and among women with high cumulative exposure (RR = 7.09; 95% CI = 2.14–23.54). Among those with peak exposures at medium and high levels, we observed slightly elevated rate ratios for cancers of the kidney (RR = 1.89; 95% CI = 0.85–4.23), bladder (RR = 1.41; 95% CI = 0.52–3.81), and prostate (RR = 1.47; 95% CI = 0.85–2.55). Our findings do not indicate an association between trichloroethylene exposure and respiratory cancer, liver cancer, leukemia or lymphoma, or all cancers combined. (Epidemiology 1998;9:424–431)

Keywords: aerospace workers, cancer, cohort study, healthy worker effect, respiratory disease, trichloroethylene.

Trichloroethylene (TCE) has been used in degreasing metal, processing food, and as an anesthetic agent. In 1992, the U.S. Environmental Protection Agency (EPA) withdrew its classification of TCE as a "probable human carcinogen."[1] In 1995, the International Agency for Research on Cancer (IARC) reclassified TCE to Category 2A, indicating that ". . . a positive association has been observed between exposure to the agent. . . and cancer. . . but chance, bias, or confounding could not be ruled out with reasonable confidence."[2] At least two reviewers questioned the IARC classification.[2,3]

Previous studies examined cohorts exposed either to TCE or to solvent mixtures containing TCE.[3–18] Of 15 published occupational mortality studies mentioning TCE, a few report positive associations, but among them, there is no consistent major increase in cancer mortality.[4–18] Weiss[3] recently reviewed studies of TCE production workers (Finland[19] and Sweden[4]), civilian air force employees (Utah[17]), and aerospace workers (Arizona; ENSR Health Sciences. Final Report: Historical Prospective Mortality Study of Hughes Aircraft Employees at Air Force Plant #44. ENSR Health Sciences, May 1990, unpublished report). He concluded that there was no excess cancer risk, with the possible exception of non-Hodgkin's lymphoma and cancers of the liver, biliary tract, and kidney.

Anttila *et al*[19] reported excess incidence of cancers of the stomach, liver, prostate, and lymphohematopoietic systems in Finnish workers exposed to organic solvents, including TCE. Henschler *et al*[20] reported excess incidence of renal cell cancers in a small (N = 169) heavily exposed cohort of German cardboard workers. In a study of aircraft maintenance workers, Spirtas *et al*[17] reported elevated standardized mortality ratios (SMRs) for biliary cancer among male employees and multiple myeloma and non-Hodgkin's lymphoma among female employees. Low SMRs were reported for all causes, all cancers combined, and nonmalignant respiratory diseases. Axelson *et al*[4] reported an excess of skin cancer among male Swedish workers identified through a TCE surveillance program. They also report standardized incidence ratios for men of 1.6 and 1.4 for non-Hodgkin's lymphoma and liver/biliary cancer, respectively. An earlier analysis of Hughes aircraft workers found no excess cancer risk or overall impact on mortality (ENSR Health Sciences, unpublished report).

Our study evaluates the mortality of the same cohort of employees working at a Hughes Aircraft manufactur-

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Funding for this research was provided by Hughes Aircraft Company.

Submitted October 25, 1996; final version accepted January 28, 1998.

ing site in Arizona. Most TCE exposure occurred in vapor degreasing units between 1952 and 1977. Before 1981, the plant had used some contaminated well water (TCE levels estimated between 730 and 2,200 parts per billion) for showers and drinking. Thus, workers were potentially exposed through both occupation (inhalation and skin exposure) and water. We have now followed the cohort through 1993, with more extended analyses than the 1990 study of this cohort (ENSR Health Sciences, unpublished report).

Methods

From company records, we identified all workers who were employed at the plant for at least 6 months between January 1, 1950, and December 31, 1985. We determined vital status through the Social Security Administration (SSA) and National Death Index (NDI). We excluded 27 persons from the cohort because of missing information, leaving a cohort of 20,508 workers. Personnel data included name, Social Security number, date of birth, sex, race, date of hire, job title, and termination date. After ascertaining deaths through either SSA or NDI, we obtained death certificates from each state and coded cause of death according to the *International Classification of Diseases* (ICD) in use at time of death (revisions 7–9).

Because limited industrial hygiene measurements were available for the Hughes plant before 1975, Hughes employees with at least 30 years of experience rated TCE exposure for each job classification. Hughes industrial hygienists then compiled these ratings into a master exposure matrix that was reviewed and confirmed by the Hughes employees.

From the ratings, jobs were classified into exposure categories of high, medium, low, or none. The highest rating involved work on degreaser machines using TCE, which the industrial hygienists estimate were equivalent to exposures above 50 parts per million. Jobs with a medium rating were near the degreasing area, with more than occasional contact with TCE. A low exposure rating was given to jobs away from the degreasing area, but entailing occasional contact with TCE. All other jobs were assigned zero exposure. Most TCE-exposed workers had more than one category of exposure. We did not consider potential exposure to drinking or wash water in classifying occupational TCE exposure.

We assigned exposure scores of 0 for none, 1 for low, 4 for medium, and 9 for high exposure, which assumes a potential exponential exposure-response relation. We assigned a zero level to anyone with less than 6 months of any TCE exposure (N = 1,025). Then, for each job, we multiplied months of exposure by the TCE rating (0, 1, 4, or 9) and summed the results to arrive at a cumulative (total) exposure score. For internal cohort analyses, we created exposure groups using both cumulative exposure and the job with the highest TCE exposure rating ("peak" exposure). (We used "peak" exposure to evaluate hypotheses that high-level exposure involves different metabolic pathways and may, thus, be more important in assessing cancer risk.) In the SMR analyses, we used cumulative exposure scores and a dichotomous measure (none/any) to define exposure groups.

Statistical Analyses

We used the OCMAP-PC computer program to calculate SMRs and 95% confidence limits for the overall cohort and TCE-exposed subcohorts.[21] For internal cohort analyses, we used Mantel-Haenszel procedures and Cox proportional hazard models that included exposure classification, age at hire, and gender.[22] Data concerning race were too sparse to use in the stratified analyses or Cox models. Because we found that decade of hire did not influence relative risk estimates, we did not include it in the final Cox models. We analyzed all causes of death, nonmalignant respiratory disease, and selected cancer outcomes using three exposure classification systems (ever/never, peak, and cumulative).

To analyze peak exposure, we combined jobs with no and low exposure into one group and jobs with medium and high exposure into a second group. To define cumulative exposure categories, we examined the distribution of cumulative exposure scores to identify any obvious cutpoints. The distribution was approximately lognormal, with no obvious modes. Therefore, we divided the TCE-exposed group into "low" and "high" based on cumulative exposure score. Exposure groups were roughly equal (50%), with the low group including any workers with the equivalent of up to 5 years of exposure to jobs at low exposure or 1.4 years of medium exposure. The high-exposure group includes all other TCE-exposed workers.

Our SMR analyses include most causes of death. For internal cohort analyses, we selected outcomes either on the basis of previous reports or because of elevated SMRs in our analyses. Because results from the Mantel-Haenszel and Cox proportional hazards models were so similar, we present only Cox modeling results. Although we used the ever/never exposure classification in both SMR and internal cohort analyses, we do not report those results, because they are highly correlated with both peak and cumulative exposure classifications. (A full set of analytical tables is available upon request.)

For cancer sites previously identified as possibly TCE associated, we combined our data with previously published cohorts to calculate a series of meta-SMRs and associated confidence limits. We derived the meta-SMRs from the sums of observed and expected deaths.

Results

The cohort is composed primarily of white men, nearly half of whom were hired before 1960. Of 4,052 deaths, we were unable to locate 112 death certificates. Some occupational TCE exposure was experienced by 23% of the cohort (Table 1).

SMR Analysis

For the full cohort, most SMRs were below 1.00 (Table 2), with elevations for Hodgkin's disease (1.25) and

TABLE 1. Distribution of Aerospace Worker Cohort by Sex, Race, Birth Decade, Hire Decade, and Exposure Classification

Demographic Factor	Nonexposed				TCE Exposed				Totals			
	N	%	PY*	%PY	N	%	PY	%PY	N	%	PY	%PY
Sex												
Male	11,187.0	70.9	250,410.0	70.4	2,555.0	54.0	57,879.0	54.7	13,742.0	67.0	308,289.0	66.8
Female	4,588.0	29.1	105,355.0	29.6	2,178.0	46.0	47,973.0	45.3	6,766.0	33.0	153,328.0	33.2
									20,508.0		461,617.0	
Race												
White	14,698.0	93.2	331,072.0	93.1	4,132.0	87.3	91,561.0	86.5	18,830.0	91.8	422,633.0	91.6
Nonwhite	1,077.0	6.8	24,693.0	6.9	601.0	12.7	14,291.0	13.5	1,678.0	8.2	38,984.0	8.4
									20,508.0		461,617.0	
Birth year												
1920	3,168.0	20.1	88,953.0	25.0	1,022.0	21.6	29,711.0	28.1	4,190.0	20.4	118,664.0	25.7
1920–1929	3,171.0	20.1	96,152.0	27.0	893.0	18.9	23,950.0	22.6	4,064.0	19.8	120,102.0	26.0
1930–1939	3,252.0	20.6	89,186.0	25.1	803.0	17.0	19,382.0	18.3	4,055.0	19.8	108,568.0	23.5
1940–1949	2,288.0	14.5	37,968.0	10.7	1,008.0	21.3	19,779.0	18.7	3,296.0	16.1	57,747.0	12.5
1950–1959	2,840.0	18.0	33,669.0	9.5	749.0	15.8	10,558.0	10.0	3,589.0	17.5	44,227.0	9.6
≤1960	1,056.0	6.7	9,838.0	2.8	258.0	5.5	2,472.0	2.3	1,314.0	6.4	12,310.0	2.7
									20,508.0		461,618.0	
Hire date												
<1960†	6,941.0	44.0	222,557.0	62.6	1,563.0	33.0	48,779.0	46.1	8,504.0	41.5	271,336.0	58.8
1960–1969	1,782.0	11.3	44,080.0	12.4	913.0	28.8	23,045.0	21.8	2,695.0	13.1	67,125.0	14.5
1970–1979	2,448.0	15.5	42,545.0	12.0	1,322.0	18.9	24,625.0	23.3	3,770.0	18.4	67,170.0	14.6
1980–1989	4,604.0	29.2	46,584.0	13.1	935.0	16.5	9,403.0	8.9	5,539.0	27.0	55,987.0	12.1
Totals	15,775.0	76.9	355,766.0	77.1	4,733.0	23.1	105,852.0	18.7	20,508.0	100	461,618.0	100.0

* PY = person-years.
† Only 27 employees started before 1950.

kidney cancer (1.14), although confidence intervals (CI) were wide (95% CI = 0.60–2.30 and 0.78–1.61, respectively). SMRs for all respiratory diseases and for suicide were also elevated. For these conditions, Arizona rates are considerably higher than national rates. When we used Arizona rates for comparison instead of U.S. rates, SMRs were lower (data not shown).

The TCE-exposed subcohort results resembled the total cohort SMRs for most causes of death (Table 2). SMRs for respiratory disease (1.14; 95% CI = 0.92–1.41) and kidney cancer (1.32; 95% CI = 0.57–2.60) were elevated, but with wide confidence intervals. SMRs for prostate (1.18; 95% CI = 0.73–1.80), respiratory (1.12; 95% CI = 0.91–1.35), bladder (1.36; 95% CI = 0.59–2.68), and ovarian (1.21; 95% CI = 0.52–2.38) cancers, which were all below 1.00 in the overall cohort analysis, were slightly elevated in the TCE-exposed subcohort analysis, although, again, with wide confidence intervals. For respiratory cancers, we observed higher SMRs in the low-exposure category than in the high-exposure group. We also examined SMRs among the nonexposed subcohort (data not shown). These results were similar to the SMRs for the overall cohort.

Internal Cohort Analysis

Our Cox proportional hazards modeling results are presented in Tables 3–5. For all cancers and nonmalignant respiratory disease, all risk ratios for peak and cumulative exposure classifications were near 1.00 (Table 3). The risk ratio for respiratory cancers in the low-cumulative-exposure group was 1.47 (95% CI = 1.07–2.03); however, both peak- and high-cumulative-exposure groups had risk ratios near 1.00 (Table 3).

For cancers of the lymphatic and hematopoietic systems (Table 4), risk ratios were close to 1.00 for all of these cancers combined and for leukemia. For lymphosarcoma and reticulosarcoma, the risk ratios were slightly elevated for the peak-exposure and the low-cumulative-exposure groups; however, these estimates had wide confidence intervals. For the high-cumulative-exposure group, the risk ratio was 0.81, indicating lack of a dose-response effect. There were 11 cases of Hodgkin's disease in the cohort; because only one case was in the TCE-exposed group (Table 2), we did not conduct internal cohort analyses on this outcome.

For liver, kidney, bladder, prostate, and ovarian cancer, we observed somewhat higher associations with TCE exposure, but with varying confidence intervals (Table 5). These are based on only a few exposed cases, uniformly leading to wide confidence intervals. For bladder and ovarian cancers in the high-exposure categories, the confidence intervals were 1.10–6.65 and 2.14–23.54, respectively. For liver cancers, there was no association with the peak exposure classification, nor was there an apparent dose-response trend for cumulative exposure. Kidney cancers had a higher association (RR = 1.89; 95% CI = 0.85–4.23) with peak exposure than high cumulative exposure (RR = 1.59; 95% CI = 0.68–3.71). Ovarian cancers had the highest associations with TCE exposure for peak (RR = 2.74) and high cumulative exposures (RR = 7.09).

TABLE 2. Standardized Mortality Ratios* for Selected Causes of Death: Overall Cohort and Occupationally Exposed Trichloroethylene Subcohort

Cause of Death†,‡	Overall Cohort (N = 20,508)				TCE-Exposed Subcohort (N = 4,733)			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All causes of death	4,052	4,772.5	0.85	0.82–0.88	917	1,088.8	0.84	0.79–0.90
All malignant neoplasms	1,100	1,267.3	0.87	0.82–0.92	270	295.0	0.92	0.81–1.03
Cancer of digestive organs and peritoneum	255	307.8	0.83	0.73–0.94	55	71.3	0.77	0.58–1.00
Cancer of rectum	18	25.3	0.71	0.42–1.13	6	5.7	1.06	0.39–2.31
Cancer of biliary passages and liver	20	26.0	0.77	0.47–1.19	6	6.1	0.98	0.36–2.13
Cancer of pancreas	47	61.9	0.76	0.56–1.01	11	14.4	0.76	0.38–1.37
Cancer of respiratory system	401	424.0	0.95	0.86–1.04	103	92.4	1.12	0.91–1.35
Cancer of bronchus, trachea, lung	388	404.9	0.96	0.87–1.06	97	88.3	1.10	0.89–1.34
Cancer of breast	47	62.8	0.75	0.55–1.00	16	21.3	0.75	0.43–1.22
Cancer of uterus (women only)	6	17.4	0.34	0.13–0.75	1	6.1	0.16	0.00–0.91
Cancer of cervix uteri (women only)	1	10.0	0.10	0.00–0.56	0	3.5	0.00	0.00–1.07
Cancer of ovary (women only)	13	19.4	0.67	0.36–1.15	8	6.6	1.21	0.52–2.38
Cancer of prostate (men only)	76	81.4	0.93	0.74–1.17	21	17.8	1.18	0.73–1.80
Cancer of kidney	32	28.0	1.14	0.78–1.61	8	6.1	1.32	0.57–2.60
Cancer of bladder	23	27.3	0.84	0.53–1.26	8	5.9	1.36	0.59–2.68
Cancer of central nervous system	28	33.3	0.84	0.56–1.22	4	7.3	0.55	0.15–1.40
Cancer of all lymphatic, hematologic tissue	107	111.5	0.96	0.79–1.16	25	25.2	0.99	0.64–1.47
Lymphosarcoma and reticulosarcoma	11	14.2	0.78	0.39–1.39	3	3.1	0.96	0.20–2.81
Hodgkin's disease	10	8.0	1.25	0.60–2.30	1	1.7	0.60	0.02–3.35
Leukemia and aleukemia	42	42.8	0.98	0.71–1.33	10	9.5	1.05	0.50–1.93
Cancer of all other lymphopoietic tissue	44	46.5	0.95	0.69–1.27	11	10.9	1.01	0.51–1.81
All heart disease	1,409	1,751.5	0.80	0.76–0.85	290	387.5	0.75	0.67–0.84
Cerebrovascular disease	170	278.0	0.61	0.52–0.71	40	67.4	0.59	0.42–0.81
Nonmalignant respiratory disease	389	337.7	1.15	1.04–1.27	87	76.1	1.14	0.92–1.41
Bronchitis, emphysema, asthma	116	71.1	1.63	1.35–1.96	27	15.7	1.72	1.13–2.50
Emphysema	66	51.5	1.28	0.99–1.63	15	11.1	1.36	0.76–2.23
Other nonmalignant respiratory disease	171	153.9	1.11	0.95–1.29	39	34.8	1.12	0.80–1.53
Cirrhosis of liver	65	115.0	0.57	0.44–0.72	14	25.3	0.55	0.30–0.93
All external causes of death	293	366.7	0.80	0.71–0.90	68	80.1	0.85	0.66–1.08
Accidents	156	225.0	0.69	0.59–0.81	41	48.9	0.84	0.60–1.14
Suicides	115	89.1	1.29	1.07–1.55	20	18.4	1.09	0.67–1.68
Other causes of death	379	483.9	0.78	0.71–0.87	101	114.2	0.89	0.72–1.08

	Low (N = 2,357)				High (N = 2,376)			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All causes of death	345	402.44	0.86	0.77–0.95	572	686.31	0.83	0.77–0.91
All malignant neoplasms	114	109.31	1.04	0.86–1.25	156	185.73	0.84	0.71–0.98
Cancer of digestive organs and peritoneum	21	25.92	0.81	0.50–1.24	34	45.41	0.75	0.52–1.05
Cancer of rectum	1	2.03	0.49	0.01–2.74	5	3.63	1.38	0.45–3.21
Cancer of biliary passages and liver	3	2.28	1.32	0.27–3.85	3	3.85	0.78	0.16–2.28
Cancer of pancreas	5	5.25	0.95	0.31–2.22	6	9.16	0.66	0.24–1.43
Cancer of respiratory system	46	31.59	1.46	1.07–1.94	57	60.81	0.94	0.71–1.21
Cancer of bronchus, trachea, lung	45	30.2	1.49	1.09–1.99	52	58.1	0.90	0.67–1.20
Cancer of breast	11	10.72	1.03	0.51–1.84	5	10.55	0.47	0.15–1.11
Cancer of uterus (women only)	1	3.28	0.31	0.01–1.70	0	2.84	0.00	0.00–1.30
Cancer of cervix uteri (women only)	0	1.91	0.00	0.00–1.93	0	1.54	0.00	0.00–2.39
Cancer of ovary (women only)	2	3.4	0.61	0.07–2.21	6	3.4	1.79	0.66–3.88
Cancer of prostate (men only)	7	5.42	1.29	0.52–2.66	14	12.41	1.13	0.62–1.89
Cancer of kidney	1	2.13	0.47	0.01–2.62	7	3.94	1.78	0.72–3.66
Cancer of bladder	1	1.97	0.51	0.01–2.83	7	3.90	1.79	0.72–3.69
Cancer of central nervous system	2	2.7	0.73	0.09–2.64	2	4.6	0.44	0.05–1.58
Cancer of all lymphatic, hematologic tissue	10	9.37	1.07	0.51–1.96	15	15.81	0.95	0.53–1.57
Lymphosarcoma and reticulosarcoma	2	1.12	1.79	0.22–6.46	1	2.00	0.50	0.01–2.79
Hodgkin's disease	1	0.65	1.55	0.04–8.64	0	1.02	0.00	0.00–3.61
Leukemia and aleukemia	3	3.55	0.85	0.17–2.47	7	5.98	1.17	0.47–2.41
Cancer of all other lymphopoietic tissue	4	4.05	0.99	0.27–2.53	7	6.80	1.03	0.41–2.12
All heart disease	77	136.78	0.56	0.44–0.70	213	250.72	0.85	0.74–0.97
Cerebrovascular disease	17	25.71	0.66	0.39–1.06	23	41.73	0.55	0.35–0.83
Nonmalignant respiratory disease	32	27.00	1.19	0.81–1.67	55	49.06	1.12	0.84–1.46
Bronchitis, emphysema, asthma	11	5.42	2.03	1.01–3.63	16	10.27	1.56	0.89–2.53
Emphysema	5	3.66	1.37	0.44–3.19	10	7.42	1.35	0.65–2.48
Other nonmalignant respiratory disease	13	12.11	1.07	0.57–1.84	26	22.66	1.15	0.75–1.68
Cirrhosis of liver	9	9.49	0.95	0.43–1.80	5	15.85	0.32	0.10–0.74
All external causes of death	27	32.77	0.82	0.54–1.20	41	47.36	0.87	0.62–1.18
Accidents	18	19.68	0.92	0.54–1.45	23	29.18	0.79	0.50–1.18
Suicides	6	7.23	0.83	0.31–1.81	14	11.14	1.26	0.69–2.11
Other causes of death	46	44.00	1.05	0.77–1.39	55	70.16	0.78	0.59–1.02

* U.S. mortality rates, 1950–1992, provided by OCMAP software (see Ref 21). SMR = standardized mortality ratio.
† Totals do not add up to "All causes" total deaths because not all specific causes are presented.
‡ "Other causes" does not include all other cause ICD codes (see Appendix).

TABLE 3. All Cancers and Respiratory Diseases: Internal Cohort Analyses for Peak and Cumulative Trichloroethylene Exposure Classifications Using Cox Proportional Hazards Models

	Exposed (N)	Unexposed (N)	RR*	95% CI
All cancers				
Peak: medium and high *vs* low and no exposure	177	923	1.06	0.90–1.24
Cumulative (low)	114	830	1.22	0.99–1.49
Cumulative (high)	156	830	1.01	0.85–1.19
Nonmalignant respiratory disease				
Peak: medium and high *vs* low and no exposure	59	330	0.97	0.73–1.28
Cumulative (low)	32	302	1.01	0.70–1.47
Cumulative (high)	55	302	0.99	0.75–1.33
Cancer of bronchus, trachea, lung				
Peak: medium and high *vs* low and no exposure	64	324	1.07	0.82–1.40
Cumulative (low)	45	291	1.47	1.07–2.03
Cumulative (high)	52	291	0.96	0.72–1.29

* RR = relative risk.

The meta-SMRs, which combine results from the four TCE cohorts cited by Weiss,[3] were all near 1.00, ranging from 1.09 for prostate and kidney cancers to 1.25 and 1.32 for non-Hodgkin's lymphoma and liver cancer, respectively (Table 6).

Discussion

Our data offer little support for an association between TCE exposure and cancer mortality from leukemia, cancer in hematopoietic tissues, and digestive, liver, and respiratory cancers. Our findings for kidney, bladder, prostate, and ovarian cancers are limited by small numbers, lack of information on smoking, and lack of quantitative exposure information.

Our finding of a potential association between TCE and ovarian cancer has not been previously reported. Among the TCE studies, Anttila *et al*[19] found no excess risk, and Spirtas *et al*[17] reported similar findings (SMR = 1.01). A hospital-based case-control study in the Washington DC area found no important association between ovarian cancer and occupational solvent or polycyclic aromatic hydrocarbon exposures; however, only a few participants in this study held manufacturing jobs.[23] We observed 13 such cancers in the entire cohort and 8 among the TCE-exposed subcohort. The expected numbers in the SMR analyses were 19.4 and 6.6, respectively. That six of the eight exposed cases were classified as "high" TCE exposure accounts for the high rate ratios.

Risk factors for ovarian cancer include family history of ovarian cancer, use of infertility drugs, and a long history of unprotected intercourse.[24] Protective factors for ovarian cancer include use of oral contraceptives, number of pregnancies, breastfeeding, and history of gynecologic surgery.[23,24] We reviewed the death certificates for these deaths and did not find any similarity in last names that could suggest a potential cluster of ovarian cancer cases among the same families. This review is limited because we relied only on names of workers in the cohort; we did not conduct interviews or collect other data on family history of ovarian cancer. Our results are dependent on six exposed cases, and exposure misclassification or another cause from a competing risk factor in one or two cases could substantially reduce the association. The lack of previous research suggesting ovarian cancer risk, the small number of cases involved, the largely unknown etiology of ovarian cancer, and the numerous unmeasured potential confounding factors limit our ability to interpret these findings.

TABLE 4. Lymphatic and Hematopoietic Cancers: Internal Cohort Analyses for Peak and Cumulative Trichloroethylene Exposure Using Cox Proportional Hazards Models

	Exposed (N)	Unexposed (N)	RR*	95% CI
Lymphatic and hematopoietic cancers				
Peak: medium and high *vs* low and no exposure	17	90	1.08	0.64–1.82
Cumulative (low)	10	82	1.09	0.56–2.14
Cumulative (high)	15	82	1.03	0.59–1.79
Leukemia				
Peak: medium and high *vs* low and no exposure	7	35	1.10	0.49–2.49
Cumulative (low)	3	32	0.69	0.21–2.32
Cumulative (high)	7	32	1.14	0.50–2.60
Lymphosarcoma and reticulosarcoma				
Peak: medium and high *vs* low and no exposure	2	9	1.31	0.28–6.08
Cumulative (low)	2	8	2.25	0.46–11.09
Cumulative (high)	1	8	0.81	0.10–6.49

* RR = relative risk.

TABLE 5. Liver, Kidney, Bladder, Prostate, and Ovarian Cancers: Internal Cohort Analyses for Peak and Cumulative Trichloroethylene Exposure Using Cox Proportional Hazards Models

	Exposed (N)	Unexposed (N)	RR*	95% CI
Liver cancer†				
Peak: medium and high *vs* low and no exposure	3	17	0.98	0.29–3.35
Cumulative (low)	3	14	2.12	0.59–7.66
Cumulative (high)	3	14	1.19	0.34–4.16
Kidney cancer†				
Peak: medium and high *vs* low and no exposure	8	24	1.89	0.85–4.23
Cumulative (low)	1	24	0.31	0.04–2.36
Cumulative (high)	7	24	1.59	0.68–3.71
Bladder cancer‡				
Peak: medium and high *vs* low and no exposure	5	18	1.41	0.52–3.81
Cumulative (low)	1	15	0.69	0.09–5.36
Cumulative (high)	7	15	2.71	1.10–6.65
Prostate cancer‡				
Peak: medium and high *vs* low and no exposure	16	60	1.47	0.85–2.55
Cumulative (low)	7	55	1.05	0.48–2.32
Cumulative (high)	14	55	1.35	0.75–2.44
Ovarian cancer‡				
Peak: medium and high *vs* low and no exposure	4	9	2.74	0.84–8.99
Cumulative (low)	2	5	3.45	0.66–17.97
Cumulative (high)	6	5	7.09	2.14–23.54

* RR = relative risk.
† Cox models include age and sex as independent variables.
‡ Cox models include age only as independent variable.

To compare these updated results with previous research, we calculated meta-SMRs for liver, prostate, and kidney cancers and non-Hodgkin's lymphoma across the studies evaluated in the recent review by Weiss.[3] Although these four studies do not represent the complete set of TCE studies, IARC considered three of them to be the most relevant for assessing TCE carcinogenicity.[4,17,19] In general, the meta-SMRs offer little support for a relation between TCE exposure and non-Hodgkin's lymphoma or cancers of the kidney, bladder, and prostate (Table 6). Small numbers of cases (except for prostate cancer), even aggregated across all four studies, further limit causal interpretation of these findings.

To address the pronounced healthy worker effect (HWE) in this cohort, we used Cox proportional hazards models, using peak and cumulative exposures. In our study, however, the Cox method is limited by small numbers of cancers in the exposed, unexposed, or both

TABLE 6. Meta-Analysis of Four Occupational Cohort Mortality Studies with Exposure to Trichloroethylene

Cancer Site	Finnish*	Swedish†	Civilian Air Force‡	Aerospace Workers§	Total	Meta-SMR‖	95% CI
Liver							
Observed	5	4	2	6	17	1.32	0.77–2.11
Expected	2.2	2.8	1.8	6.1	12.9		
Prostate							
Observed	13	26	22	21	82	1.09	0.87–1.36
Expected	9.4	20.7	27.6	17.8	75.5		
Kidney							
Observed	6	6	8	8	28	1.09	0.72–1.58
Expected	6.9	5.2	7.5	6.1	25.7		
Bladder							
Observed	5	8	11	8	32	1.15	0.78–1.62
Expected	6.1	7.9	7.9	5.9	27.8		
Non-Hodgkin's lymphoma							
Observed	8	5	14	14	41	1.25	0.89–1.70
Expected	4.4	3.2	11.2	14	32.8		

* Anttila *et al*, 1995.[19]
† Axelson *et al*, 1994.[4]
‡ Spirtas *et al*, 1991.[17]
§ Present study.
‖ SMR = standardized mortality ratio.

groups. Thus, narrowly defining exposure groups, although reducing potential exposure misclassification, creates smaller groups and thereby produces more imprecise estimates of relative risk. These factors have to be considered in interpreting the results of our internal comparisons. The small number of cases in the TCE subcohort limits our ability to assess the risks for rare cancers. In addition, although nearly two-thirds of the TCE-exposed cohort were followed for more than 20 years (Table 1), it is possible that higher risks could occur later.

In addition to its limited data, this study has other limitations. We lack data on potential confounders such as smoking, diet, or exposure to other solvents. Furthermore, with no direct measurement of personal exposure, we had to rely on experts to assign estimated levels of TCE exposure, although we believe the extensive review process should have helped to reduce exposure misclassification.

The recent IARC review of TCE carcinogenicity considered positive findings from three occupational studies[4,17,19] for liver/biliary cancer and non-Hodgkin's lymphoma as suggestive of TCE carcinogenicity.[2] Our results and the meta-SMRs do not indicate strong effects on cancer risk for these outcomes.

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Appendix

TABLE A1. ICD Codes Used in Mortality Analysis of Aerospace Workers Cohort (1950–1993)

Cause of Death	6th and 7th Revisions (1950–1967)	8th Revision (1968–1978)	9th Revision (1979+)
All causes of death	001–999	000–999	001–999
All malignant neoplasms	140–205	140–209	140–208
Digestive organs and peritoneum	150–159	150–159	150–159
Biliary passages and liver primary	155	155, 156	155, 156
Pancreas	157	157	157
Respiratory system	160–164	160–163	160–165
Bronchus, trachea, lung	162–163	162	162
Breast	170	174	174, 175
All uterine (women only)	171, 172–174	180, 181, 182.0, 182.9	179, 180, 181, 182
Cervix (women only)	171	180	180
Other female genital organs (ovary)	175, 176	183–184	183–184
Prostate (men only)	177	185	185
Kidney	180	189.0, 189.1, 189.2	189.0, 189.1, 189.2
Bladder, other urinary organs	181	188, 189.9	188, 189.3, 189.4, 189.8, 189.9
All lymphatic and hematopoietic	200–205	200–209	200–208
Lymphosarcoma, reticulosarcoma	200	200	200
Hodgkin's disease	201	201	201
Leukemia and aleukemia	204	204–207	204–208
All other lymphopoietic tissue	202, 203, 205	202, 203, 208, 209	202, 203
Cerebrovascular disease	330–334	430–438	430–438
All heart disease	400–402, 410–443	390–398, 400.1, 400.9, 402, 404, 410–414, 420–429	390–398, 402, 404, 410–429
Nonmalignant respiratory disease	241, 470–527	460–519	460–519
Bronchitis, emphysema, asthma	501, 502, 527.1, 241	490–493	490–493
Emphysema	527.1	492	492
Other nonmalignant respiratory	470–475, 500, 510–527.0, 527.2	460–466, 500–519	460–466, 470–478, 494–496, 500–519
Cirrhosis of the liver	581	571	571
All external causes of death	800–999	800–999	E800–999
Accidents	800–962	800–949	E800–949
Suicides	963, 970–979	950–959	E950–959
Other causes of death	020–138, 206–207, 240, 242–254, 270–326, 340–398, 450–468, 530–539, 542–580, 582–587, 600–795	000–009, 020–136, 240–246, 251–389, 440–458, 520–530, 534–570, 572–577, 590–796	001–009, 020–139, 240–246, 251–389, 440–459, 520–530, 534–570, 572–579, 590–799

plausibility for the association.[3] Other EMF studies relying on metrics that are subject to calculation errors, may be subject to similar concerns depending upon the relative importance of calculation and temporal errors in each study. We hope that our paper will increase the attention paid to EMF exposure metrics and we thank Feychting and Ahlbom for their commentary.

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ERRATA

One of the authors of the article entitled "Mortality of aerospace workers exposed to trichloroethylene," by Robert W. Morgan, Michael A. Kelsh, Ke Zhao, and Shirley Heringer, published in Epidemiology 1998;9:424–431, informed us of some errors in one of the tables.

In Table 5, the authors had inadvertently included both genders in counting person-years, rather than presenting gender-specific risk ratios for prostate and ovarian cancer. In addition, one subject, in the high trichloroethylene (TCE) exposure category, had been incorrectly classified with a diagnosis of ovarian cancer, instead of "other female genital cancer." The authors report that correction of these errors did not change the overall conclusions of the study.

The correct estimates of effect for prostate and ovarian cancer are presented in the Table below.

TABLE 5. Prostate and Ovarian Cancers: Internal Cohort Analyses for Peak and Cumulative Trichloroethylene Exposure Using Cox Proportional Hazards Models

	Exposed N	Unexposed N	RR*	95% CI
Prostate cancer				
Peak: medium and high vs. low and no exposure	16	60	1.39	0.80–2.41
Cumulative (low)	7	55	1.72	0.78–3.80
Cumulative (high)	14	55	1.53	0.85–2.75
Ovarian cancer				
Peak: medium and high vs. low and no exposure	3	9	2.66	0.70–10.04
Cumulative (low)	2	5	1.54	0.29–8.22
Cumulative (high)	5	5	4.75	1.31–17.28

*RR = relative risk.
Cox models include age only as independent variable.

The name of the first author of the brief report entitled "Reproductive risk factors for mucinous and non-mucinous epithelial ovarian cancer" is Jolanda Wittenberg. (Epidemiology 1999;10:761–763 and Epidemiology 2000;11:95). We regret the printed errors.