Exhibit 223

ORIGINAL ARTICLE

Mortality and end-stage renal disease incidence among dry cleaning workers

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ABSTRACT

Objective Perchloroethylene (PCE) is a known animal carcinogen and probable human carcinogen. Dry cleaning exposures, particularly PCE, are also associated with renal toxicity. The objective was to follow-up a cohort of dry cleaners to evaluate mortality and assess end-stage renal disease (ESRD) morbidity.

Methods This study adds 8 years of mortality follow-up for 1704 dry cleaning workers in four cities. Employees eligible for inclusion worked for ≥1 year before 1960 in a shop using PCE as the primary solvent. Life table analyses for mortality and ESRD morbidity were conducted. Only employees alive on 1 January 1977 were included in ESRD analyses.

Results Overall cancer deaths were in significant excess in this cohort (standardised mortality ratio (SMR) 1.22, 95% CI 1.09 to 1.36). Oesophageal, lung and tongue cancers had significant excesses of deaths. Oesophageal cancer risk was highest among those employed in a PCE-using shop for ≥5 years with ≥20 years' latency since first such employment. Deaths from non-malignant underlying diseases of the stomach and duodenum were in significant excess. Hypertensive ESRD morbidity was significantly elevated in the entire cohort (standardised incidence ratio (SIR) 1.98, 95% CI 1.11 to 3.27), and among workers employed only in PCE-using dry cleaning shops for ≥5 years.

Conclusion Employment in the dry cleaning industry and occupational exposure to PCE are associated with an increased risk for ESRD and for cancer at several sites. The employment duration findings for oesophageal cancer and hypertensive ESRD further support an association with PCE exposure instead of lifestyle or socioeconomic factors.

What this paper adds

- Perchloroethylene (PCE) is widely used in the dry cleaning industry and is considered a probable human carcinogen.
- Exposure to PCE was found to be significantly associated with elevations in overall cancer, and cancers of the oesophagus, bladder and tongue.
- Although evidence suggests that dry cleaning exposures, and PCE in particular, are associated with renal toxicity, to our knowledge this is the first study to report a significant association between PCE exposure and hypertensive end-stage renal disease (ESRD).
- The magnitude of the risk elevations for oesophageal cancer, bladder cancer and hypertensive ESRD, and the fact that the risks were highest among those with the longest duration of PCE exposure and longest latency since initial PCE exposure, supports an association between these illnesses and PCE exposure instead of lifestyle or socioeconomic factors.

INTRODUCTION

Perchloroethylene (PCE) is widely used in the dry cleaning industry, despite being classified as a probable human carcinogen,[1] and as recently as the 1990s was being used by 85–90% of dry cleaning establishments.[2] Before its widespread use, dry cleaning workers were exposed to other solvents including carbon tetrachloride and petroleum solvents (eg, Stoddard solvent). Stoddard solvent is a petroleum-based mixture of alkane and aromatic hydrocarbons and is similar in content to unleaded gasoline. Because Stoddard solvent has shown limited evidence of carcinogenicity in animals, and because few human studies have explored its carcinogenic risk, it is currently not classifiable regarding its human carcinogenicity.[3 4]

This paper provides an update on a cohort of dry cleaning workers exposed to PCE and Stoddard solvent. After the original mortality study was published in 1987,[5] there were two subsequent updates.[6 7] The consistent finding of all three studies was a significantly increased bladder cancer mortality risk among dry cleaning workers. In addition, the two updates found significantly increased mortality risks for all cancers combined, oesophageal cancer, intestinal cancer, tongue cancer and diseases of the stomach and duodenum (eg, gastric and duodenal ulcers). The second update also reported significantly increased mortality risks for cervical cancer, pancreatic cancer (in multiple cause of death (MCOD) analyses only), hypertension without heart disease (in MCOD analyses only), lung cancer and pneumonia.[7]

An International Agency for Research on Cancer (IARC) review of PCE from 1995 found evidence for associations between PCE exposure and oesophageal cancer, bladder cancer and non-Hodgkin's lymphoma.[1] The previous update of our dry cleaning cohort summarised the literature on most health outcomes associated with PCE and Stoddard solvent exposure.[7] There is also evidence to suggest that dry cleaning exposures, and PCE in particular, are associated with renal toxicity.[8–12] A few reports have been published since 2001 on dry cleaners.[8 13 14] Blair *et al* studied dry cleaning workers in St Louis and found significant excesses in emphysema, oesophageal cancer, lung cancer and cervical cancer.[8]

Because of lack of information on socioeconomic and lifestyle factors and occupational exposures, the authors declined to attribute the excesses to dry cleaning exposures. Lynge *et al* conducted nested case–control studies for several cancers among laundry and dry cleaning workers employed in Scandinavia.[13] They found a significant excess of bladder cancer among dry cleaners and an excess of cervical cancer among non-dry cleaners employed in dry cleaning shops. The risk of bladder cancer did not increase monotonically with increasing duration of employment. No significant excess was found for the other cancers studied (eg, oesophageal). Lynge *et al* speculated that the lack of an association with oesophageal cancer may be because the Scandinavian workers had a lower dermal PCE exposure and lower PCE air exposures compared to US workers, and/or because the investigators were able to control for socioeconomic and lifestyle factors.[13] A large record-linkage study of dry cleaners, launderers and pressers in Sweden found excesses in Hodgkin's disease and leukaemia in women, and stomach and laryngeal cancer in men.[14]

This update further explores the association between dry cleaning exposures and mortality. The objective was to determine if the elevated disease risks identified in the earlier updates had persisted, and to determine if new disease risks appeared. Vital status was updated through 31 December 2004, adding 8 years of cohort follow-up. In addition, we conducted the first study of end-stage renal disease (ESRD) incidence in a cohort of PCE-exposed dry cleaning workers.

METHODS

The cohort consists of 1704 workers who were identified from dry cleaning union records in four US cities (San Francisco/Oakland, Chicago, Detroit and New York). These workers were not known to ever have been exposed to carbon tetrachloride or trichloroethylene and all had worked for at least 1 year prior to 1960 in a shop using PCE as the primary cleaning solvent (in every dry cleaning shop, small amounts of a variety of solvents are present which are used for spotting stains). Cohort members could be actively employed, retired, deceased or lost to follow-up in 1960. The entire cohort shrank by four members between the 1996 and 2004 updates, because these four were discovered to have missing dates of birth and were excluded from analyses. This study was conducted under the review and approval of the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH).

Cohort members were employed in one or more of over 300 commercial dry cleaning shops. A complete or partial solvent history was available for approximately half of these shops.[5] If a shop had no solvent history, employment in that shop was not used to determine study eligibility. A subcohort of 618 subjects worked only in a shop or shops where PCE was the primary cleaning solvent (PCE-only subcohort). The other 1086 workers worked in a shop or shops where PCE was the primary cleaning solvent, but also had a history of employment in shops where the primary solvent in use could not be identified (these shops are referred to as 'other solvent' shops). The solvent used in the 'other solvent' shops could have been PCE or another solvent (most likely a petroleum solvent such as Stoddard solvent). Those who ever worked in both a PCE shop and one of the 'other solvent' shops were placed in a 'PCE-plus' subcohort. Some analyses were also conducted of the entire cohort but duration of employment included only time employed in shops using PCE as the primary cleaning solvent (PCE-using shops).

Prior to 1979, vital status was determined using records from the Social Security Administration, unions, state drivers licence and motor vehicle registration authorities, the Internal Revenue Service and the Postal Service. Copies of death certificates were obtained for the deceased. The National Death Index (NDI) was used to assess vital status from 1 January 1979 through 31 December 2004. Vital status follow-up through 31 December 2004 was successful for 95% of the cohort (ie, 5% were lost to follow-up). Follow-up was slightly less complete for women (94%) than for men (97%). Overall, 79 workers were lost to follow-up before NDI coverage began, and six after.

To evaluate ESRD incidence, we linked the cohort to the Renal Management Information System (REMIS) maintained by the US Centers for Medicare and Medicaid Services (CMS). This database includes every individual who received ESRD benefits from Medicare from 1977 and includes approximately 93% of US ESRD cases.[15]

Statistical methods

LTAS.NET, a modified life table analysis program, was used to conduct analyses.[16] Mortality rates for underlying causes of death (UCOD) used 1940–2004 data obtained from the National Center for Health Statistics (NCHS). Deaths were classified into one of 92 cause-of-death categories.[17] Additional analyses used the multiple-cause mortality rates and programs.[18] The UCOD indicates the single cause that ultimately led to death, whereas the MCOD represents all other medical conditions found on the death certificate that contributed to death. The MCOD analyses might identify mortality excesses not observed in the UCOD analyses.[18] Mortality rates for MCOD used 1960–2004 data obtained from NCHS. Deaths were classified into one of 119 MCOD categories.[17]

An ESRD rate file for 1977–2004 was created by using all incident cases of ESRD available in REMIS as the numerators and US Census data as the denominators. Rates were determined for all ESRD cases combined and for each specific ESRD type.

Analyses using local (ie, county) rate files were not conducted. The previous studies of this cohort found little difference in the analytical results when local versus national mortality rates were used. For the 1199 deaths with information on state of death, 81% occurred in the four states where the dry cleaning shops were located (only 70% of deaths between 1997 and 2004 were in these four states).

For the UCOD analyses, the period of observation started on 1 January 1940 (rate files are not available for earlier years) or after 1 year of employment in a unionised PCE plant, whichever was later, and ended at the date lost to follow-up, date of death or 31 December 2004, whichever was earlier. For the MCOD analyses, the person-years at risk (PYAR) began on 1 January 1960. For the ESRD analyses, PYAR began on 1 January 1977.

Age, race, sex and calendar-time adjusted standardised mortality ratios (SMRs) were derived. SMRs were calculated as the observed number of deaths divided by number expected on the basis of age, race, sex and calendar-time specific national rates. SMRs were calculated with and without stratification by duration of employment in PCE-using dry cleaning shops (1–5 years, 5+ years) as a surrogate for PCE exposure and by latency periods (less than 20 years, 20+ years). Standardised incidence ratios (SIRs) for ESRD were calculated for the entire cohort and the two subcohorts with and without stratification by duration of employment in dry cleaning shops using PCE. Two-sided 95% CIs for each SMR and SIR were calculated using either the exact Poisson distribution of the number (N) of observed deaths or incident ESRD cases for $N<5$ or Byar's approximation of the Poison distribution of N for $N\geq5$.[19] Two-sided 90% CIs for each SMR in the duration and latency analyses were calculated using exact Poisson distribution or the formulae

of Breslow and Day.[20] SMRs and SIRs were considered statistically significant if the confidence interval excluded 1.00. Significance testing for trends with duration and time since first employment were performed on the directly adjusted counterparts of the SMRs using Rothman's methods.[21]

RESULTS

Mortality

The cohort consisted of 1704 workers with 1255 deaths and 63 426 PYAR. The composition and status as of 31 December 2004 for the cohort and the subcohorts are provided in table 1. During the 8 years of extended follow-up, 260 members of the cohort died. Overall mortality was similar to national mortality (SMR 1.04, 95% CI 0.98 to 1.10).

Cancer

Overall cancer deaths were in significant excess in the entire cohort (SMR 1.22) and the PCE-plus subcohort (SMR 1.26) (table 2). Specific cancer sites with significant excesses of deaths in the entire cohort were the oesophagus, lung and tongue. Oesophageal cancer was in non-significant excess in all four gender–race categories (data not shown). It was in significant excess in the PCE-plus subcohort and approached significance in the PCE-only subcohort. The greatest risk for oesophageal cancer was among those with both 5 or more years of employment in PCE-using shops and 20 or more years of latency (table 3). In the entire cohort, lung cancer death excesses approached statistical significance for non-white females (SMR 1.64, 95% CI 1.00 to 2.54) and non-white males (SMR 1.52, 95% CI 1.00 to 2.21). The risk of lung cancer death in white males and females was slightly above unity (1.01 and 1.09, respectively). Tongue cancer deaths were also in significant excess in the entire cohort for both non-white females (SMR 8.75, 95% CI 1.06 to 31.62) and non-white males (SMR 8.26, 95% CI 1.70 to 24.15). No tongue cancer deaths were observed in white workers. Tongue was the only cancer in significant excess in the PCE-only subcohort (table 2). The greatest risk for tongue and lung cancer was among those employed for less than 5 years in PCE-using shops and with 20 or more years of latency (table 3).

For several types of cancer, mortality was not significantly elevated in the overall cohort but was elevated in the PCE-plus subcohort. These included intestinal cancer, pancreatic cancer and bladder cancer (table 2). However, significant excesses were not consistent across all four gender–race categories in the PCE-plus subcohort. Only white females had a significant excess of intestinal cancer (13 deaths, SMR 2.22, 95% CI 1.18 to 3.79). Non-white males in the PCE-plus subcohort had a significant excess of bladder cancer (four deaths, SMR 4.97, 95% CI 1.35 to 12.72), but no bladder cancer cases were found in non-white females. All four gender–race categories had a non-significant excess of pancreatic cancer.

Several cancers were in significant excess in the MCOD analyses but not in the UCOD analyses. For cervical cancer, the UCOD SMR was 1.84 (13 deaths, 95% CI 0.98 to 3.14), while

Table 1 Composition of the entire cohort and subcohorts as of 31 December 2004: mortality and ESRD analyses

	Mortality			ESRD		
Characteristic	Entire cohort (n=1704)	PCE-only (n=618)	PCE-plus (n=1086)	Entire cohort (n=1704)	PCE-only (n=618)	PCE-plus (n=1086)
Excluded from analysis*	0	0	0	408 (24%)	124 (20%)	284 (26%)
Racial distribution						
Females	1112 (65%)	412 (67%)	700 (64%)	900 (53%)	345 (56%)	555 (51%)
White	514	186	328	396	151	245
Non-white	598	226	372	504	194	310
Males	592 (35%)	206 (33%)	386 (36%)	396 (23%)	149 (24%)	247 (23%)
White	298	106	192	182	70	112
Non-white	294	100	194	214	79	135
Vital status						
Females						
Alive†	350	172	178			
Dead	762	240	522			
Males						
Alive†	99	54	45			
Dead	493	152	341			
Mean year of birth±SD	1916±11.7	1919±12.0	1914±11.1	1918±10.3	1922±10.0	1916±9.9
Mean year first employed±SD	1951±5.7	1953±4.6	1949±5.7	1951±5.3	1954±4.1	1950±5.3
Mean age at first employment±SD	34.5±10.2	34.0±10.8	34.8±9.9	32.8±9.3	32.2±9.4	33.2±9.1
Mean duration of employment±SD‡	9.6±6.8	6.4±5.6	11.3±6.7	9.4±6.8	6.4±5.6	11.2±6.9
Using PCE	6.2±5.0	6.4±5.6	6.0±4.7	6.2±5.1	6.4±5.6	6.1±4.7
Using other solvents	3.4±4.8	–	5.3±5.1	3.2±4.7	–	5.1±5.0
Mean number of shops worked in	2.3±2.7	1.1±0.4	3.0±3.2§			
Range	(1–62)	(1–4)	(2–62)			
Person-years at risk from PCE exposure	63 426	22 735	40 691	22 974	9653	13 321
Latency <20 years	32 109	11 542	20 567	196	164	32
Latency ≥20 years	31 317	11 193	20 124	22 778	9489	13 289
1–5 years exposure	26 295	13 840	12 455	8405	5552	2854
≥5 years exposure	37 131	8895	28 236	14 569	4101	10 467

*In the ESRD analyses, these represent those who died before 1 January 1977.
†'Alive' includes 85 persons lost to follow-up in the entire cohort (68 females and 17 males).
‡Through 1982.
§By definition everyone in this subcohort worked in at least two shops (one where PCE was the primary cleaning solvent and one where it was not).
ESRD, end-stage renal disease; PCE, perchloroethylene.

Table 2 Dry cleaners, USA: mortality (through 31 December 2004) in the entire cohort, the PCE-only subcohort and PCE-plus subcohort* for selected underlying causes of death

		Entire cohort			PCE-only			PCE-plus		
Cause of death	**ICD-9 codes**	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**	**Obs**	**SMR**	**95% CI**
All cancers	140–208	322	1.22‡	1.09 to 1.36	100	1.13	0.92 to 1.37	222	1.26‡	1.10 to 1.44
Buccal and pharyngeal cancer	140–149	9	1.83	0.84 to 3.48	4	2.42	0.66 to 6.20	5	1.54	0.50 to 3.59
Tongue	141	5	4.48†	1.45 to 10.45	3	8.03†	1.66 to 23.46	2	269	0.33 to 9.73
Digestive organ cancer	150–159	92	1.25†	1.01 to 153	20	0.84	0.51 to 1.29	72	1.45‡	1.13 to 1.82
Oesophagus	150	16	2.44‡	1.40 to 3.97	6	2.68	0.98 to 5.83	10	2.32†	1.11 to 4.27
Intestine (except rectum)	152–153	36	1.36	0.95 to 1.88	8	0.93	040 to 1.83	28	1.56†	1.04 to 2.26
Liver and biliary	155, 156	1	0.13‡	0.00 to 0.73	0	–		1	0.20	0.01 to 1.10
Rectal cancer	154	7	1.26	0.51 to 2.59	0	–		7	1.81	0.73 to 3.74
Pancreas	157	22	1.51	0.95 to 2.29	4	0.82	0.22 to 2.10	18	1.86†	1.10 to 2.94
Respiratory system cancer	160–165	81	1.32†	1.05 to 1.64	27	1.24	0.82 to 1.81	54	1.36†	1.02 to 1.77
Larynx	161	3	1.40	0.29 to 4.09	0	–		3	2.11	0.43 to 6.16
Trachea, bronchus, lung	162	77	1.31†	1.04 to 1.64	26	1.25	0.82 to 1.83	51	1.35†	1.00 to 1.77
Breast cancer	174–175	28	1.05	0.70 to 1.52	10	1.06	0.51 to 1.94	18	1.05	0.62 to 1.66
Female genital organ cancer	179–184	27	1.20	0.79 to 1.75	11	1.44	0.72 to 2.58	16	1.08	0.62 to 1.75
Cervix uteri	180	13	1.84	0.98 to 3.14	5	2.10	0.68 to 4.90	8	1.70	0.74 to 3.36
Male genital organ cancer	185–187	14	0.96	0.52 to 1.61	2	0.51	0.06 to 1.84	12	1.13	0.58 to 1.97
Urinary organ cancer	188–189	15	1.52	0.85 to 2.50	2	0.64	0.08 to 2.30	13	1.93†	1.02 to 3.29
Kidney cancer	189.0–189.2	5	1.14	0.37 to 2.67	2	1.35	0.16 to 4.89	3	1.04	0.21 to 3.04
Bladder and other urinary cancer	188, 189.3–189.9	10	1.81	0.87 to 3.33	0	–		10	2.59†	1.24 to 4.76
Other and unspecified sites	170–173, 190–199	37	1.25	0.88 to 1.72	13	1.30	0.69 to 2.23	24	1.22	0.78 to 1.81
Lymphatic and haematopoietic cancer	200–208, 273.3	19	0.88	0.53 to 1.38	11	1.51	0.75 to 2.70	8	0.56	0.24 to 1.11
Non-Hodgkin's lymphoma	200–202, 273.3	11	1.57	0.78 to 2.81	6	2.46	0.90 to 5.36	5	1.10	0.36 to 2.56
Tuberculosis	010–018	0	–		0	–		0	–	
Benign neoplasms	201–239	0	–		0	–		0	–	
Diabetes mellitus	250	25	0.71	0.46 to 1.05	6	0.51	0.19 to 1.10	19	0.82	0.49 to 1.28
Blood and blood-forming diseases	281–289	6	1.28	0.47 to 2.78	3	1.96	0.40 to 5.71	3	0.95	0.20 to 2.77
Alcoholism and mental disorders	290–319	8	0.60	0.26 to 1.19	2	0.45	0.05 to 1.63	6	0.68	0.25 to 1.48
Nervous system diseases	320–337, 349–389	13	0.70	0.37 to 1.20	10	1.57	0.76 to 2.90	3	0.25‡	0.05 to 0.72
Diseases of the heart	390–398, 402–404, 410, 414, 420–429	434	1.01	0.92 to 1.11	140	1.08	0.91 to 1.27	294	0.98	0.87 to 1.10
Ischaemic heart disease	410–414	360	1.10	0.99 to 1.22	121	1.24†	1.03 to 1.48	239	1.05	0.92 to 1.19
Diseases of the circulatory system	401, 403, 405, 415–417, 430–438, 440–459	143	0.92	0.77 to 1.08	36	0.77	0.54 to 1.06	107	0.98	0.80 to 1.10
Cerebrovascular disease	430–438	103	0.91	0.75 to 1.11	25	0.74	0.48 to 1.10	78	0.99	0.78 to 1.23
Diseases of arteries, veins and pulmonary circulation	415, 417, 440–459	28	0.84	0.56 to 1.22	6	0.60	0.22 to 1.30	22	0.95	0.60 to 1.44
Pulmonary system diseases	460–466, 470–478, 480–487, 490–519	100	1.19	0.97 to 1.45	31	1.17	0.80 to 1.66	69	1.20	0.93 to 1.52
Pneumonia	480–486	48	1.33	0.98 to 1.76	12	1.13	0.58 to 1.97	36	1.41	0.99 to 1.96
COPD	490–492, 496	33	1.15	0.79 to 1.62	13	1.33	0.71 to 2.28	20	1.06	0.65 to 1.64
Digestive system diseases	520–537, 540–543, 550–553, 555–558, 560, 562–579	54	1.13	0.85 to 1.47	16	1.02	0.58 to 1.65	38	1.18	0.83 to 1.62
Diseases of the stomach and duodenum	531–537	12	2.21†	1.14 to 3.87	1	0.64	0.02 to 3.55	11	2.86‡	1.42 to 5.11
Cirrhosis of the liver	571	21	1.20	0.74 to 184	9	1.45	0.66 to 2.76	12	1.06	0.55 to 1.86
Genitourinary system disease	580–608, 610, 611, 614–629	33	1.06	0.73 to 1.49	8	0.83	0.36 to 1.63	25	1.17	0.76 to 1.72
Acute glomerulonephritis, nephrotic syndrome, acute renal failure	580, 581, 584	4	1.62	0.44 to 4.16	2	2.60	0.31 to 9.39	2	1.18	0.14 to 4.27
Chronic and unspecified nephritis, renal failure, other renal sclerosis	582, 583, 585–587	11	0.74	0.37 to 133	2	0.42	0.05 to 1.52	9	0.89	0.41 to 1.70
Calculi of urinary system	592	2	4.30	0.52 to 15.54	2	15.61†	1.89 to 56.39	0	–	
Other genitourinary system diseases	588, 589, 591, 593, 595–599	9	1.06	0.48 to 2.01	0	–		9	1.54	0.71 to 2.93
Skin and subcutaneous tissue diseases	680–686, 690–709	2	0.72	0.09 to 2.58	0	–		2	1.03	0.13 to 3.73
Musculoskeletal diseases	710–739	1	0.23	0.01 to 1.27	0	–		1	0.35	0.01 to 1.96
Symptoms and ill-defined conditions	780–796, 798, 799	2	0.12‡	0.01 to 0.44	1	0.19	0.00 to 1.07	1	0.09‡	0.00 to 0.49
Accidents	E800–848, E850–888, E890–949	11	0.29‡	0.14 to 0.51	4	0.32‡	0.09 to 0.81	7	0.27‡	0.11 to 0.56
Suicide and homicide	E950–978	16	0.95	0.54 to 1.54	6	1.03	0.38 to 2.24	10	0.90	0.43 to 1.66
Other causes	Residual ICD codes	30	1.01	0.68 to 1.44	9	0.92	0.42 to 1.74	21	1.05	0.65 to 1.61
Cause of death not obtained		55			20			35		
Total deaths		1255	1.04	0.98 to 1.10	392	1.03	0.93 to 1.14	863	1.04	0.98 to 1.12

*618 Cohort members were exposed only to PCE; the rest were exposed to PCE and other dry-cleaning solvents.
†95% CI excludes the null value (1.0).
‡99% CI excludes the null value (1.0).
COPD, chronic obstructive pulmonary disease; ICD-9, International Classification of Diseases, 9th Revision; Obs, observed number of deaths; PCE, perchloroethylene; SMR, standardised mortality ratio; CI, confidence interval.

Table 3 Dry cleaners, USA: SMRs* for selected cancers by time since first employment in PCE-using shops and duration of employment in PCE-using shops

Site	Time <20 years Duration <5 years	Time <20 years Duration 5+ years	Time 20+ years Duration <5 years	Time 20+ years Duration 5+ years	p Value† By time	p Value† By duration
All	24 deaths	32 deaths	136 deaths	130 deaths	<0.001	0.52
	0.61‡ (0.42 to 0.85)	1.16 (0.84 to 1.55)	1.43§ (1.24 to 1.65)	1.33§ (1.14 to 1.54)		
Tongue	0	0	4	1	NP	0.25
	0.00	0.00	11.33§ (3.87 to 25.93)	2.84 (0.15 to 13.49)		
Oesophagus	0	0	5	11	NP	0.085
	0.00	0.00	2.16 (0.85 to 4.54)	4.78§ (2.68 to 7.91)		
Intestine	2	4	17	13	0.20	0.52
	0.59 (0.10 to 1.86)	1.64 (0.56 to 3.76)	1.75‡ (1.12 to 2.63)	1.22 (0.72 to 1.94)		
Lung	4	6	42	25	0.009	0.35
	0.63 (0.21 to 1.44)	1.27 (0.55 to 2.50)	1.75§ (1.33 to 2.26)	1.08 (0.75 to 1.51)		
Cervix	2	4	4	3	0.23	0.66
	0.84 (0.15 to 2.66)	2.63 (0.90 to 6.03)	2.75 (0.94 to 6.30)	2.08 (0.57 to 5.38)		
Bladder	0	0	1	9	NP	0.12
	0.00	0.00	0.53 (0.03 to 2.52)	4.08§ (2.13 to 7.12)		

*Approximate 90% CIs on SMRs calculated using exact Poisson distribution or the formulae of Breslow and Day.[20]
†The effect of time since first employment is based on the confidence interval for a directly adjusted standardised rate ratio comparing the 20+ group with the <20 group, ignoring employment duration. The effect of employment duration is based on the confidence interval for a directly adjusted standardised rate ratio comparing the 5+ group with the <5 group, ignoring time since first employment. NP indicates that the test could not be performed due to zero deaths in the lower category.
‡95% CI excludes the null value (1.0).
§99% CI excludes the null value (1.0).
PCE, perchloroethylene; SMR, standardised mortality ratio; CI, confidence interval.

the MCOD SMR was 2.30 (14 deaths, 95% CI 1.26 to 3.87). For pancreatic cancer, the UCOD SMR was 1.51 (22 deaths, 95% CI 0.95 to 2.29), while the MCOD SMR was 1.63 (24 deaths, 95% CI 1.04 to 2.42).

To examine the role of PCE exposure in more detail, table 3 provides SMRs for selected cancers by time since first employment in PCE shops and duration of employment in these shops (PCE-using shops). For no cancer was there a statistically significant trend of increased risk by longer employment duration. There was a statistically significant trend of increased risk by longer time since first employment in a PCE-using shop for all cancers combined and for lung cancer. As with oesophageal cancer, the risk of bladder cancer was highest among those with both 5 or more years of employment in PCE-using shops and 20 or more years of latency.

Non-malignant diseases

In the UCOD (table 2) and MCOD analyses, deaths from ischaemic heart disease were in significant excess in the PCE-only subcohort (UCOD 121 deaths, SMR 1.24; MCOD 167 deaths, SMR 1.19; 95% CI 1.02 to 1.39) and were non-significantly elevated in the entire cohort and PCE-plus subcohort. In the UCOD analyses of the PCE-only subcohort, deaths from ischaemic heart disease were in non-significant excess in all four gender–race categories. Hypertension without heart disease was much more likely to be a contributing cause of death and not the underlying cause of death. In the MCOD analyses, deaths due to hypertension without heart disease were in significant excess in the entire cohort (91 deaths, SMR 1.35, 95% CI 1.09 to 1.66) and the PCE-plus subcohort (63 deaths, SMR 1.45, 95% CI 1.12 to 1.86). The only gender–race category with a significant excess was non-white males in each of these cohorts. In the UCOD analyses, hypertension without heart disease was not significantly elevated. Mortality from conductive disorders of the heart, a cause-of-death category not found in the UCOD analyses, was significantly elevated in the entire cohort in the MCOD analyses (281 deaths, SMR 1.22, 95% CI 1.08 to 1.37) and among white women in the PCE-plus cohort.

Deaths from non-malignant diseases of the stomach and duodenum were in significant excess in the entire cohort and in the PCE-plus subcohort. In the entire cohort, deaths from this cause were in non-significant excess in three gender–race categories, but were in non-significant deficit among non-white males.

No significant excesses in non-malignant pulmonary disease were observed in the entire cohort or the subcohorts. However, when females were examined separately, an elevation in chronic obstructive pulmonary disease was observed in the entire cohort (SMR 1.69, 95% CI 1.08 to 2.51) and in the PCE-only subcohort (SMR 2.00, 95% CI 1.00 to 3.58). In both the entire cohort and the PCE-only subcohort, the excess was present among females in both race groups, but statistically significant only among non-white females. For pneumonia, the UCOD SMR in the entire cohort was 1.33 (48 deaths, 95% CI 0.98 to 1.76) (table 2), while the MCOD SMR was 1.29 (128 deaths, 95% CI 1.08 to 1.54).

Kidney disease

A non-significant deficit in chronic renal disease mortality was observed in the entire cohort (SMR 0.74) (table 2). Among females in both race categories, chronic renal disease mortality was close to unity (white females SMR 1.08, non-white females SMR 1.04). For acute glomerulonephritis with renal failure, the UCOD SMR was 1.62 (four deaths, 95% CI 0.44 to 4.16) (table 2), while the MCOD SMR was 1.70 (20 deaths, 95% CI 1.04 to 2.62).

ESRD incidence

Of the 1704 workers in the cohort, 1296 (76%) were eligible for the ESRD analysis (table 1). The risk for ESRD in the entire cohort was non-significantly elevated (SIR 1.34), based on 30 cohort members identified with ESRD (table 4). The risk for systemic ESRD was significantly elevated in the entire cohort (SIR 1.55). Hypertensive ESRD was also significantly elevated in the entire cohort (SIR 1.98). All of the remaining types of systemic ESRD were non-significantly elevated in the entire cohort.

Most of the cohort members with ESRD were non-white females (N=19, SIR 1.39, 95% CI 0.84 to 2.18). Those non-white female workers with the longest duration of dry cleaning employment (5 or more years) had a significantly elevated risk for all ESRD combined (N=16, SIR 1.87, 95% CI 1.07 to 3.03),

Table 4 End-stage renal disease incidence (through 31 December 2004) for the entire cohort of dry cleaning workers and the subcohorts

	Entire cohort			PCE-only			PCE-plus		
Type of ESRD	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Systemic ESRD	27	1.55*	1.02 to 2.25	12	1.64	0.85 to 2.86	15	1.48	0.83 to 2.44
Diabetes mellitus	9	1.02	0.47 to 1.94	3	0.78	0.16 to 2.27	6	1.21	0.44 to 2.63
Hypertension	15	1.98*	1.11 to 3.27	8	2.66*	1.15 to 5.23	7	1.53	0.62 to 3.16
Obstructive nephropathy	1	4.38	0.11 to 24.39	0	–	–	1	7.02	0.18 to 39.13
Malignancy	1	3.55	0.09 to 19.77	1	8.50	0.22 to 47.35	0	–	–
Cystic nephropathy	1	3.67	0.09 to 20.45	0	–	–	1	6.64	0.17 to 36.98
Non-systemic ESRD	2	1.20	0.15 to 4.35	0	–	–	2	2.06	0.25 to 7.43
Glomerulonephritis	2	1.57	0.19 to 5.68	0	–	–	2	2.71	0.33 to 9.77
Interstitial nephritis	0	–	–	0	–	–	0	–	–
Other	1	2.47	0.06 to 13.74	0	–	–	1	4.25	0.11 to 23.65
Total	30	1.34	0.90 to 1.91	12	1.30	0.67 to 2.26	18	1.37	0.81 to 2.17

*95% CI excludes the null value.
ESRD, end-stage renal disease; PCE, perchloroethylene; SIR, standardised incidence ratio; CI, confidence interval.

but a significantly positive dose–response trend for ESRD was not observed. The risk for ESRD among non-white females was elevated among those employed in PCE-using shops for 5 or more years (N=11, SIR 1.81, 95% CI 0.90 to 3.24) and among those employed for 5 or more years in shops where the primary solvent in use could not be identified (N=4, SIR 1.77, 95% CI 0.48 to 4.52).

Most of the hypertensive ESRD cases were observed in the PCE-only subcohort (eight (53%) of the 15 cases) (SIR 2.66, 95% CI 1.15 to 5.23). In the PCE-only subcohort, females had a significantly elevated risk for hypertensive ESRD (N=6, SIR 2.86, 95% CI 1.05 to 6.23) and there was a non-significant excess in all four gender–race categories.

Furthermore, the risk for hypertensive ESRD was highest among those in the PCE-only subcohort employed for 5 or more years (N=5, SIR 3.39, 95% CI 1.10 to 7.92), especially among non-white females (N=4, SIR 4.13, 95% CI 1.13 to 10.58).

Twenty-three (77%) of the 30 workers with ESRD had died by the end of the study. Renal failure was mentioned on the death certificate of 11 (48%) of the 23 workers who had died, and three others had 'renal disease not otherwise specified'. On the other hand, when we examined the causes of death of all cohort members who died in 1977 or later (when the ESRD REMIS began), we found five workers with 'chronic renal failure' listed as the underlying cause of death who were not in the ESRD REMIS. Medical records were obtained for three of these individuals and showed that two had ESRD. One refused treatment for ESRD and the other was under 65 years of age and died less than a month after ESRD was diagnosed (those under age 65 are not captured by ESRD REMIS if they die before completing 60–90 days of chronic maintenance dialysis). The third worker had chronic renal insufficiency complicated by prerenal azotaemia caused by congestive heart failure, but was never diagnosed with ESRD. The medical records had been destroyed for two other workers, and their ESRD status could not be determined. A total of 49 workers had 'chronic renal failure' listed as a contributing cause of death, of whom eight (16%) were in the ESRD REMIS.

DISCUSSION

In this third update of a dry cleaning cohort compiled by NIOSH, excess mortality for several causes of death continues to be significantly elevated in the entire cohort (eg, overall cancer, lung cancer, oesophageal cancer, tongue cancer and diseases of the stomach and duodenum), as was hypertensive ESRD morbidity. In addition, cervical and pancreatic cancer, conductive disorders of the heart, hypertension without heart disease and pneumonia were significantly elevated in the MCOD but not the UCOD analyses.

Strengths and limitations

Although this study has added 8 years of cohort follow-up and was the first study of ESRD incidence in a PCE-exposed cohort, it is subject to several limitations. First, work histories were not updated after 1982 because many records were no longer available and therefore duration of exposure for some cohort members is likely underestimated. Second, job titles were not available for most cohort members and no personal exposure measurements were available at all. Underestimates of exposure duration and lack of information on exposure intensity would tend to bias our findings towards the null. Third, some members of the PCE-plus subcohort were exposed to other dry cleaning solvents in addition to PCE. The identity of these other solvents is unknown but they are thought most often to have been Stoddard solvent. Fourth, information on possible confounders such as smoking and alcohol consumption was not available. Fifth, the period of observation for the ESRD analyses was much shorter than that for the mortality analyses, and therefore had less statistical power. Sixth, the diagnoses on the death certificate may be erroneous or incomplete, leading to disease misclassification.[22] In addition, some individuals with ESRD will not be found in REMIS, leading to possible ESRD underestimation. An unknown number of individuals would not have been treated for ESRD due to old age, poor prognosis, refusal of treatment or misdiagnosis,[23] and those who received all treatment for ESRD from the military or the Department of Veterans Affairs may have been missed by REMIS. Seventh, NIOSH was less successful in this update than in the past at obtaining causes of deaths. In the previous update, causes of death were not obtained for 3% of deaths (34/995); since the previous update, causes of death were not obtained for 8% (21/260).

ESRD incidence

All ESRD is hypothesised to have a multifactorial aetiology involving complex interactions between systemic diseases, toxins, nutritional status and genetic susceptibility.[24] Little is known about the aetiological role of occupational and environmental exposures in the development of renal disease. Although previous studies provide evidence for an association between renal toxicity and PCE (described below), to our knowledge this is the first study to report an association with hypertensive ESRD. This finding was strongest among workers employed only in PCE-using shops, especially among females. Hypertensive ESRD is the second most frequent type of ESRD

after diabetes mellitus. Hypertensive ESRD is a heterogeneous category and includes most of the vascular diseases related to ESRD. Vascular diseases of the kidney can both cause and arise from hypertension. It is thought that most hypertensive ESRD is caused by hypertensive nephrosclerosis, which is itself a consequence of hypertension.[25] Renal disease that causes hypertension is less common and includes renal artery stenosis leading to atherosclerotic renovascular disease.[26] Population studies have shown that black subjects are at higher risk of ESRD, although their risk of ESRD caused by atherosclerotic renovascular disease is lower than among white subjects.[26] This suggests that the increased risk of hypertensive ESRD observed among non-white PCE-exposed females may be related to hypertensive nephrosclerosis. PCE may have related effects on the cardiovascular system. Workers employed only in PCE-using shops (PCE-only) also had a significantly elevated risk for ischaemic heart disease. In the MCOD analyses, deaths due to hypertension without heart disease and conductive disorders of the heart were in significant excess in the entire cohort and in the PCE-plus subcohort, but not in the PCE-only subcohort. Hypertension with heart disease was not significantly elevated in either the UCOD or the MCOD analyses. Although we are unaware of any studies that explored hypertension prevalence among PCE-exposed workers, short term exposure to PCE has been shown to raise blood pressure.[27]

Evidence suggests that PCE is associated with subclinical renal changes, and the evidence is strongest for tubular changes compared with glomerular changes.[9–11] At least one case series documented renal disease among PCE-exposed workers.[12] In addition, Blair *et al* found significantly elevated mortality from chronic nephritis among PCE-exposed dry cleaners.[8] It is possible that PCE may raise ESRD risk through an interplay between direct renal toxicity and PCE-induced hypertension.

Heart disease mortality

Risk factors that may help explain the observed ischaemic heart disease findings include PCE exposure, workplace stress and non-occupational factors (low socioeconomic status and smoking). Although these dry cleaning workers may have a higher smoking prevalence, the fact that some other smoking-related causes of death were not significantly elevated suggests that other explanatory factors may be involved. The excess ischaemic heart disease risk among those with low socioeconomic status may be partly related to their higher likelihood of hazardous occupational exposures.[28] It should be noted that our cohort consisted of unionised workers thought to have good health insurance benefits, and these characteristics may have placed them in a higher socioeconomic status. Some studies have observed an association between cardiovascular disease and stress from high-demand and low-control jobs[29]; however, others have failed to find such an association.[30] Focus groups in southwest Ohio found that dry cleaning workers had low pay and sometimes worked long hours, but enjoyed their job-related autonomy (ie, self-paced work without constant supervision),[31] suggesting that dry cleaning jobs are demanding but that workers may have a fair degree of control. With the exception of carbon disulfide[32] and styrene,[33] few mortality studies of solvent-exposed workers have found excesses of cardiovascular disease. Apart from our cohort study, we are aware of only one other dry cleaner cohort study that reported heart disease risk.[8] Blair *et al* did not find an elevated risk for arteriosclerotic heart disease in a dry cleaner cohort.[8] Several mechanisms of action have been proposed to explain how organic solvents may cause cardiovascular disease.[34] These include direct toxicity on the myocardium or arterial walls, disturbances of lipid metabolism and development of hypertension (either essential hypertension or secondary hypertension from renal tubular damage). How these various occupational and non-occupational risk factors comingle to produce an elevated heart disease risk among PCE-exposed workers is not clear.

Cancer mortality

All three of the cancers (ie, lung, oesophagus and tongue) in significant excess in the entire cohort are also related to smoking.[35] As such, the increased risks for these cancers may be related to an increased prevalence of smoking among dry cleaning workers. Data obtained between 1987 and 1994 by the National Health Interview Survey, which provides nationally representative data on the civilian, non-institutionalised US population, found that the overall smoking prevalence was higher among laundering and dry cleaning machine operators than among all workers combined (34.8% vs 27.9%).[36] However, some smoking-related diseases and cancers were not significantly elevated (eg, chronic obstructive pulmonary disease, laryngeal cancer and pancreatic cancer). The inconsistent findings across smoking-related causes of death leaves unclear the role smoking plays in the increased disease risks experienced by dry cleaning workers.

The increased risk for oesophageal cancer by longer duration of employment, and elevations in both subcohorts supports the association between PCE exposure and this cancer. Oesophageal cancer was in excess in all four gender–race categories in the entire cohort. Furthermore, the SMR for oesophageal cancer was higher than would be expected by smoking alone. It was also found to be in significant excess in one other study of dry cleaning workers,[8] but two other studies did not support an association between PCE exposure and oesophageal cancer.[13 14]

The evidence is not as consistent for tongue and lung cancer. The risk for both cancers was greatest among those employed for less than 5 years in PCE shops. The small elevation in lung cancer could be explained by smoking alone,[37] and the tongue cancer findings were based on five deaths only.

The difference in cancer mortality SMRs between the PCE-only and PCE-plus subcohorts (table 2) could be due to differences in the types of exposures experienced by these two subcohorts. Because intestinal and pancreatic cancers were elevated in the PCE-plus subcohort only, it is possible that these cancers are related to exposure to another solvent (eg, Stoddard solvent). In contrast, although bladder cancer was significantly elevated in the PCE-plus subcohort, it was also significantly elevated among those with the longest duration of PCE exposure, suggesting a role for PCE.

Conclusion

This update of a cohort of dry cleaning workers exposed to PCE and Stoddard solvent provides additional evidence that employment in the dry cleaning industry and occupational exposure to PCE are associated with an increased risk for ESRD and cancers at several sites. The magnitude of the risk elevations for oesophageal cancer and hypertensive ESRD and the fact that the risks were highest among those with the longest duration of PCE exposure further supports an association between these illnesses and PCE exposure instead of lifestyle or socioeconomic factors.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Competing interests None.

Ethics approval This study was conducted with the approval of the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH).

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