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Mortality patterns among industrial workers exposed to chloroprene and other substances I. General mortality patterns

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Abstract

We conducted an historical cohort study to investigate the mortality experience of industrial workers potentially exposed to chloroprene (CD) and other substances, including vinyl chloride (VC), with emphasis on cancer mortality, including respiratory system (RSC) and liver. In 1999, the International Agency for Research on Cancer (IARC) classified CD as a possible carcinogen (Group 2B); VC was classified in 1987 as a known human carcinogen (Group 1).

Subjects were 12,430 workers ever employed at one of two U.S. industrial sites (Louisville, KY ($n=5507$) and Pontchartrain, LA ($n=1357$)) or two European sites (Maydown, Northern Ireland ($n=4849$) and Grenoble, France ($n=717$)), with earliest CD production dates ranging from 1942 (L) to 1969 (P). Two sites (L and M) synthesized CD with the acetylene process that produced VC exposures. We determined vital status through 2000 for 95% of subjects and cause of death for 95% of the deaths. Historical exposures for individual workers were estimated quantitatively for CD and VC. Workers ever exposed to CD ranged from 92.3% (M) to 100% (G); to VC from 5.5% (M) to 22.7% (L). We computed standardized mortality ratios (SMRs) (using national and regional standard populations) in relation to selected demographic, work history and exposure factors. We used worker pay type (white or blue collar) as a rough surrogate for lifetime smoking history.

For the combined cohort, SMRs (95% CIs) for all causes combined, all cancers combined, RSC and liver cancer were, respectively, 0.72 (0.69–0.74), 0.73 (0.68–0.78), 0.75 (0.67–0.84) and 0.72 (0.43–1.13). Site-specific (L, M, P and G, respectively) SMRs were: for all cancers combined: 0.75 (0.69–0.80), 0.68 (0.56–0.80), 0.68 (0.47–0.95) and 0.59 (0.36–0.91); for RSC: 0.75 (0.66–0.85), 0.79 (0.58–1.05), 0.62 (0.32–1.09) and 0.85 (0.41–1.56); for liver cancer: 0.90 (0.53–1.44) (17 deaths), 0.24 (0.01–1.34) (1 death), 0.0 (0–2.39) (no deaths) and 0.56 (0.01–3.12) (1 death). Among all workers ever exposed to CD, SMRs were: for all cancers combined: 0.71 (0.66–0.76); for RSC: 0.75 (0.67–0.84); for liver cancer: 0.71 (0.42–1.14). We also observed no increased mortality risks among cohort subgroups defined by race, gender, worker pay type, worker service type (short/long term), time period, year of hire, age at hire, duration of employment, the time since first employment, and CD or VC exposure status (never/ever exposed).

In summary, our study has many strengths and is the most definitive study of the human carcinogenic potential of exposure to CD conducted to date. We conclude that persons exposed to chloroprene or vinyl chloride at the levels encountered in the four study sites did not have elevated risks of mortality from any of the causes of death examined, including all cancers combined and lung and

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liver cancer, the cancer sites of *a priori* interest. This conclusion is corroborated by our detailed analyses of mortality in relation to qualitative and quantitative exposures to CD and VC at each of the four study sites, reported in our companion paper (Marsh et al., submitted for publication).

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1. Introduction

Chloroprene (2-chloro-1,3-butadiene) (CD) is a monomer used almost exclusively for the production of synthetic rubber and latexes [1]. Epidemiologic studies of CD were stimulated by reports of angiosarcoma of the liver among vinyl chloride (VC) workers [2], a case report of a liver angiosarcoma among a worker exposed to CD but not to VC [3] and the structural similarity between CD and VC.

The earliest CD studies appeared in the Russian literature as case series studies of lung [4] and skin [5] cancers among workers with high exposure to CD. The first informative epidemiological study of CD exposed workers in the U.S. was conducted by Pell [6], who studied an historical cohort of DuPont Chemical Co. workers from two polychloroprene manufacturing plants, including the Louisville, KY plant in the current study. Pell found no consistent evidence of elevated mortality rates or cancer incidence rates among CD-exposed workers. Later cohort studies of CD production workers in China [7] and Armenia [8], and of shoe manufacturing workers in Russia [9] reported excesses in liver cancer among workers exposed to CD. Zaridze et al. [10] performed additional analyses of the Russian and Armenian cohorts that supported the liver cancer findings. The most recent cohort study of cancer incidence among chloroprene production workers in France found no excess in liver cancer, but limited evidence of a lung cancer excess associated with duration of employment [11].

Chloroprene was first evaluated by the International Agency for Research on Cancer (IARC) in 1978 as Group 3 (not classifiable as to its carcinogenicity to humans), and remained in Group 3 following the 1987 reevaluation [12,13]. On the basis of new bioassays that provided sufficient evidence of carcinogenicity in rats and mice [14,15], IARC reclassified chloroprene in 1999 from Group 3, to Group 2B (possibly carcinogenic to humans) [16]. The 1999 reevaluation considered only two epidemiology studies [6,9] whose evidence was deemed inadequate.

To provide more definitive epidemiological evidence regarding the long-term health effects of exposure to CD, a four-plant, multi-national epidemiologic study of workers with potential exposure to CD was commissioned in 1999 by the International Institute of Synthetic Rubber Producers (IISRP). The exposure assessment component of the study was conducted at the University of Oklahoma (UOk) and the University of Illinois at Chicago (UIC); the epidemiology and biostatistics component was conducted at the University of Pittsburgh (UPitt).

We report here the results of our analysis of general mortality patterns among the CD cohort. Detailed accounts of the historical exposure reconstruction and the results of our analyses of mortality in relation to CD exposure are presented elsewhere [17–21].

2. Methods

2.1. Study sites and subjects

The chloroprene (CD) cohort included all workers ($n = 12{,}430$) with potential CD exposure at any of four CD production sites from plant start-up date through the end of 2000 (1999 for one site). The sites include two DuPont/Dow Elastomers LLC (DDE) plants in the U.S. (Louisville, KY and Pontchartrain, LA), one DDE plant in Maydown, Northern Ireland (NI) and one Enichem Elastomers France plant in Grenoble, France (FR) (called here Plants L, P, M and G). CD production dates for each plant were: L (1942–1972), P (1969–date), M (1960–1998) and G (1966–date). In two Plants (L and M), CD production included an acetylene-based process that produced vinyl chloride (VC) as a by-product. Plant L made CD only through the acetylene process that was phased out between 1971 and 1976; Plant M made CD by the acetylene process from 1960 to 1980 then only by the butadiene process from 1980 to 1998. Plants P and G used only the butadiene process to produce CD. The newer butadiene process did not involve VC exposures and resulted in lower CD exposures for jobs related to monomer production than those associated with the early production years of the older Plants L and M. Details of the history, processes and chemical exposures associated with each study plant is described elsewhere [17–21].

With the exception of Plant G, the study population was enumerated from computerized employee databases

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Table 1
Key features of cohort study design

Characteristic	Louisville, KY	Maydown, NI	Pontchartrain, LA	Grenoble, FR	All plants
Subjects	5507	4849	1357	717	12,430
Person-years	197,919	127,036	30,660	17,057	372,672
Earliest hire date	1942	1947	1962	1966	–
CD production dates	1942–1972[a]	1960–1998	1969–date	1966–date	–
CD production process	Acetylene	Butadiene and acetylene	Butadiene	Butadiene	–
Observation period	1949–2000[b]	1960–2000	1962–2000	1966–1999[c]	–
Maximum observation period through 2000	52 years	41 years	39 years	34 years	–

[a] Monomer production ended in 1972, CD currently in use at plant.
[b] Dates chosen to avoid fifth revision of International Classification of Diseases (ICD).
[c] Follow-up through 1999 only.

and by manual review of hard copy personnel records. We verified the completeness of the cohorts for all but Plant G by cross checking names among the various data sources, including the corporate mortality registry and earlier cohort study files of Plant L and Plant P held by the DuPont Chemical Company. For Plant P, we identified but could not locate, the records of 191 employees who had transferred to other DDE sites; however, these were mostly salaried workers with little potential for CD exposure. Eighteen potential subjects from Plant M chose not to participate in the study. The Plant G cohort was enumerated and verified by French investigators as an expansion and update of their earlier cohort study of cancer incidence [11].

The total CD cohort includes 12,430 subjects who contributed 372,672 person-years of observation, with Plants L and M comprising the bulk of the subjects and person-years (Table 1). Plant L is the oldest and largest with CD production dates extending back to 1942. With the exception of Plant L, study periods roughly coincided with CD production dates and ranged in length from 34 to 52 years. The observation period for Plant L began in 1949 to avoid methodological problems associated with the earlier fifth revision of the International Classification of Diseases (ICD).[1] These problems include establishing comparability with later revisions and cohort selection factors associated with employment during World War II. Because the four study sites are highly diverse with respect to geographic location, cohort size, cohort entry period, CD exposure period and CD exposure levels [21], we approached all aspects of this investigation in a site-specific manner, combining activities or data across two or more sites only if warranted by evidence of sufficient homogeneity.

Table 2 shows that the CD cohort predominantly comprised white males employed in blue collar (wage earning) positions who terminated employment before the end of the study period. The pay type (blue, white collar) variable was constructed by two of the authors (NE and TH) from detailed work history data for use in our exposure–response analysis for respiratory system cancer as a rough surrogate of education/socioeconomic status [21]. A substantial number of subjects in each plant worked 20 or more years or were followed for mortality 30 or more years. Plants L and M included the largest percentages of short-term workers (less than 5 years). In all plants, the majority of subjects were hired between ages 20 and 29. More than 92% of the workers at each plant were exposed to CD, with 99% of the Louisville workers exposed and all Grenoble workers exposed. Exposure to VC occurred only in Plants L and M with 22.7% and 5.5% of subjects exposed, respectively. By nature of the production process involved, all workers exposed to VC were also exposed to CD.

2.2. *Vital status and cause of death ascertainment*

Study members for U.S. plants with unconfirmed vital status (not known from company-held records to be alive or dead as of the study end date) were entered into the standard UPitt vital status tracing protocol developed by Schall et al. [22,23]. This included a combination of federal and state government sources (e.g., Pension Benefit Information (PBI), the National Death Index (NDI), Social Security Administration (SSA)). A limitation found with this protocol in fall 2004 [24] revealed that relying upon PBI as the first stage of the tracing protocol may not identify all deaths. Due to time limitations, the revised two-stage protocol proposed by Buchanich et al. [24] was not used; instead all cohort members identified

[1] Truncating the Plant L cohort at 1949 resulted in the loss of only three subjects. Two of these had died before 1949 (one from cancer of the intestines (ICD5 = 046e) and one from an automobile accident (ICD5 = 170c)) and one subject was lost to follow-up. Thus, this truncation had negligible effect on our mortality analysis.

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Table 2
Distribution of CD cohort by selected study factors

Characteristic	Louisville, KY		Maydown, NI		Pontchartrain, LA		Grenoble, FR		All plants	
	Number	%	Number	%	Number	%	Number	%	Number	%
Subjects	5507	44.3	4849	39.0	1357	10.9	717	5.8	12,430	100.0
Race										
White	3425	62.1	4849	100.0	698	51.4	717	100	9689	77.9
Non-white	568	10.3	0	0	175	12.9	0	0	743	6.0
Unknown	1514	27.6	0	0	484	35.7	0	0	1998	16.1
Sex										
Male	4895	88.9	4359	89.9	1108	81.6	646	90.1	11,008	88.6
Female	612	11.1	490	10.1	249	18.4	71	9.9	1422	11.4
Worker pay type[a]										
Blue collar	5317	96.6	4503	92.8	947	69.8	518	72.2	11,285	90.8
White collar	190	3.4	346	7.2	410	30.2	199	27.8	1145	9.2
Worker service type										
Short-term (<5 years)	2615	47.5	2713	56.0	426	31.4	150	20.9	5904	47.5
Long-term (5+ years)	2892	52.5	2136	44.1	931	68.6	567	79.1	6526	52.5
Vital status (as of 31 December 2000)										
Alive	3095	56.2	4414	91.0	1255	92.5	630	87.9	9394	75.6
Assumed	(2715)	(87.7)	(4089)	(92.6)	(837)	(66.7)	(374)	(59.4)	(8015)	(85.3)
Confirmed	(380)	(12.3)	(325)	(7.4)	(418)	(33.3)	(256)	(40.6)	(1379)	(14.7)
Dead	2403	43.6	435	9.0	102	7.5	62	8.7	3002	24.2
Cause of death known	(2282)	(95.0)	(412)	(94.7)	(100)	(98.0)	(56)	(90.3)	(2850)	(94.9)
Cause of death unknown	(121)	(5.0)	(23)	(5.3)	(2)	(2.0)	(6)	(9.7)	(152)	(5.1)
Untraceable	9	0.2	0[b]		0		25	3.5	34	0.3
Working status (31 December 2000)										
Active	380	6.9	325	6.7	418	30.8	256	35.7	1379	11.1
Separated	5127	93.1	4501	92.8	912	67.2	461	64.3	11,001	88.5
Died while employed	0	0	23	0.5	27	2.0	0	0	50	0.4
Age at hire										
<20	339	6.2	1172	24.2	112	8.3	36	5.0	1659	13.3
20–29	3280	59.6	2515	51.9	839	61.8	369	51.5	7003	56.3
30+	1888	34.3	1162	24.0	406	29.9	312	43.5	3768	30.3
Duration of employment (years)										
<5	2615	47.5	2713	56.0	426	31.4	150	20.9	5904	47.5
5–19	1100	20.0	1276	26.3	459	33.8	307	42.8	3142	25.3
20+	1792	32.5	860	17.7	472	34.8	260	36.3	3384	27.2
Time since first employment (years)										
<20	497	9.0	1107	22.8	575	42.4	234	32.6	2413	19.4
20–29	1213	22.0	1709	35.2	298	30.0	245	34.2	3465	27.9
30+	3797	69.0	2033	41.9	484	35.7	238	33.2	6552	52.7
CD exposure status										
Unexposed	37	0.7	375	7.7	99	7.3	0	0	511	4.1
Exposed	5470	99.3	4474	92.3	1258	92.7	717	100.0	11,919	95.9
VC exposure status										
Unexposed	4257	77.3	4584	94.5	n/a		n/a		8841	85.4
Exposed	1250	22.7	265	5.5					1515	14.6

[a] Pay type = blue collar if blue collar duration of employment > white collar duration of employment, else pay type = white collar.
[b] An estimated 5% of the NI cohort was lost-to-follow-up and presumed alive for the statistical analysis.

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as presumed alive using the Schall et al. [22,23] methodology were sent to the NDI. This revised methodology ensured that we did not miss deaths for study members who had been presumed alive because NDI has independent agreements with each state to receive all deaths and is not subject to the restrictions identified by Buchanich et al. [24] from relying on information from PBI.

Cause of death acquisition proceeded as described by Schall et al. [22,23]. NDI-Plus was utilized to obtain the coded cause of death for all persons identified as deceased from 1 January 1979 through 31 December 2000. For all study members identified as deceased prior to 1979, a copy of the death certificate was requested from the state health department where the death occurred. We also obtained some coded causes of death for deaths prior to 1979 from the Dupont employee registry. All death certificates were coded to the underlying cause of death by a U.S. National Center for Health Statistics nosologist using the International Classification of Diseases (ICD) rules in effect at the time of death.

Subjects in the Plant M cohort whose vital status was unknown from company-held records were traced for deaths via computerized and manual searches of files available at the General Registry Office (GRO) in Belfast, NI. This activity was performed by GRO staff under the direction of UPitt researchers and a DuPont Chemical Co. consultant based in England. Because GRO did not have access to the mortality registers for the Republic of Ireland, some relatively small percentage of deaths (estimated to be about 5%) that occurred in that area may have been missed. These subjects were assumed alive for purposes of the mortality analysis. For subjects in the Plant G cohort, vital status and cause of death was determined through 1999 (1 year earlier than the remaining sites) by the French investigators who conducted the earlier cancer incidence study of this site [11] and provided the cohort file to UPitt. As for Plant M, a small percentage of deaths in the Plant G cohort may have been missed among subjects who emigrated from France.

Table 2 shows that 3002 deaths were identified among the total CD cohort and underlying cause of death was determined for 2850 or 95%. Cause of death ascertainment rates ranged from 90.3% for Plant G to 98% for Plant P. Lost-to-follow-up rates were 0% for Plant P, 0.2% for Plant L and 3.5% for Plant G.

2.3. Statistical analysis

We examined the total and cause-specific mortality experience of subjects from each CD plant during their respective study period (see Table 1). Cohort analyses were performed using a modified life table procedure from the Occupational Cohort Mortality Program (OCMAP) [25]. Person-years at risk contributed by each subject were jointly classified by race, sex, age group, calendar time, duration of employment (DOE) and the time since first employment (TSFE). Person-year counts began at the beginning of the study period or date of hire (whichever occurred later) and continued until date of death or the end of the study period. For workers lost-to-follow-up, person-year counts stopped at the last date of known vital status, which was employment termination date. Person-years for subjects of unknown race were assigned to white or non-white categories in proportion to the person-year distribution of study members with known race. This same approach was applied separately to assign race to observed deaths of unknown race.

We computed expected numbers of deaths by multiplying average annual race, sex, age and time-specific standard population death rates by the person-years at risk in the corresponding race–sex–age–time intervals. For Plants L and P, expected deaths were computed using as standard populations the total U.S. and the local plant areas (aggregates of counties or parishes) from which the plant workforces were largely drawn (for Plant L: Jefferson and Bullitt KY, Clark, Floyd and Harrison IN; for Plant P: E. Baton Rouge, Jefferson, Ascension, St. Charles, St. James, Tangipahoa and St. John LA). Population-weighted county rates were obtained from the Mortality and Population Data System (MPDS) maintained by UPitt [26]. Due to MPDS data limitations, expected numbers of non-cancer deaths for Plant L were limited to 1960–1994 (with 1962–1964 rates applied to 1960–1964 person-years). Because local death rates usually provide the most valid external mortality comparisons (as they help to adjust for the social, cultural and economic factors related to disease) our analysis of general mortality patterns for the U.S. plants focused primarily on the local county comparisons. Moreover, because the counties or parishes involved represent large population areas, the local rates are measured with good precision. For Plants M and G, we used only the respective national death rates to compute expected deaths.

For each study plant, standardized mortality ratios (SMRs) and their 95% confidence intervals (CI) were computed for all subjects and for selected subgroups. A limited number of SMRs were computed for all study plants combined by forming the ratio of the sum of the plant-specific observed to expected numbers of deaths taken from the plant-specific total study periods. Statistically significant deviations of the SMRs below and above 1.00 were identified using Poisson probabilities [27]. All tests were done at the .05 significance level

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Table 3
Observed (Obs) deaths and SMRs for selected causes of death (total Louisville cohort, U.S. and local county comparisons, 1949–2000[a])

Cause of death (ninth revision ICD codes)	Obs	U.S.		Local county	
		SMR	95% CI	()[b] SMR	95% CI
All causes of death (001–999)	2403	0.82**	0.79–0.86	(2357) 0.74**	0.71–0.77
All cancer (140–208)	652	0.91*	0.84–0.98	0.75**	0.69–0.80
Buccal cavity and pharynx (140–149)	13	0.76	0.41–1.31	0.51**	0.27–0.86
Digestive organs and peritoneum (150–159)	168	0.94	0.80–1.09	0.83*	0.71–0.96
Esophagus (150)	20	0.99	0.60–1.53	0.71	0.44–1.10
Stomach (151)	24	0.92	0.59–1.37	1.10	0.70–1.64
Large intestine (153)	70	1.14	0.89–1.44	0.94	0.73–1.19
Rectum (154)	12	0.87	0.45–1.52	0.80	0.41–1.40
Biliary passages and liver primary (155, 156)	17	1.04	0.60–1.66	0.90	0.52–1.44
Pancreas (157)	22	0.62*	0.39–0.94	0.57**	0.36–0.86
All other digestive (152, 158, 159)	3	0.55	0.11–1.61	0.48	0.10–1.40
Respiratory system (160–165)	266	1.06	0.94–1.19	0.75**	0.66–0.85
Larynx (161)	10	1.13	0.54–2.08	0.75	0.36–1.39
Bronchus, trachea, lung (162)	252	1.05	0.92–1.19	0.75**	0.66–0.85
All other respiratory (160, 163, 164, 165)	4	1.66	0.45–4.25	1.29	0.35–3.30
Breast (174, 175)	10	0.97	0.47–1.79	0.91	0.44–1.67
All uterine (females only) (179, 180, 181, 182)	2	0.71	0.09–2.57	0.61	0.07–2.22
Prostate (males only) (185)	47	0.72*	0.53–0.95	0.68**	0.50–0.91
Kidney (189.0, 189.1, 189.2)	15	0.92	0.52–1.52	0.83	0.46–1.37
Bladder and other urinary organs (188, 189.3, 189.4, 189.8, 189.9)	14	0.77	0.42–1.30	0.69	0.38–1.16
Malignant melanoma of skin (172)	5	0.55	0.18–1.29	0.58	0.19–1.36
Central nervous system (191, 192)	13	0.77	0.41–1.32	0.69	0.37–1.18
Lymphatic–hematopoietic tissue (200–208)	63	0.96	0.74–1.23	0.88	0.68–1.13
Hodgkin's disease (201)	4	0.99	0.27–2.54	0.86	0.23–2.19
Non-Hodgkin's lymphoma (200, 202.0, 202.1, 202.8, 202.9)	23	0.97	0.62–1.46	0.92	0.58–1.37
Leukemia and aleukemia (204–208)	26	1.03	0.68–1.52	0.93	0.60–1.36
All other lymphopoietic tissue (202.2, 202.3, 202.4, 202.5, 202.6, 203)	10	0.79	0.38–1.45	0.74	0.36–1.37
All other malignant neoplasms (171, 173, 195–199)	34	0.62**	0.43–0.87	0.56**	0.39–0.78
Diabetes (250)	47	0.84	0.62–1.12	(47) 0.72*	0.53–0.96
Cerebrovascular disease (430–438)	139	0.79**	0.67–0.94	(138) 0.71**	0.60–0.84
All heart disease (390–398, 402, 404, 410–429)	825	0.77**	0.72–0.83	(817) 0.71**	0.66–0.76
Non-malignant respiratory disease (460–519)	158	0.67**	0.57–0.79	(158) 0.56**	0.47–0.65
Ulcer of stomach and duodenum (531–533)	8	0.68	0.29–1.34	(6) 0.63	0.23–1.38
Cirrhosis of liver (571)	32	0.53**	0.37–0.75	(32) 0.51**	0.35–0.72
Nephritis and nephrosis (580–589)	32	1.11	0.76–1.57	(30) 0.90	0.61–1.29
All external causes of death (E800–999)	130	0.61**	0.51–0.72	(118) 0.63**	0.52–0.75
Accidents (E800–949)	80	0.58**	0.46–0.72	(74) 0.68**	0.53–0.85
Suicides (E950–959)	33	0.72	0.49–1.00	(31) 0.66*	0.45–0.93
Homicides and other external (E960–978, E980–999)	17	0.57*	0.33–0.91	(13) 0.41**	0.22–0.70
Unknown causes	121			(116) 121	

[a] Observation period is 1960–2000 for all causes combined and non-malignant causes of death based on local comparisons.
[b] Observed number of deaths during 1960–2000 study period.
* $p < .05$.
** $p < .01$.

and no adjustment was made for multiple comparisons. The *a priori* statistical power[2] of our study to detect a 2.0-fold or greater excess in lung cancer was 0.87 and 0.97 for Plants G and P, respectively, and essentially 1.00 for Plants L and M and the combined cohort. For liver cancer, the corresponding statistical power was less than 0.25 for Plants G and P, 0.41 for Plant M, 0.97 for Plant L and 0.99 for the combined cohort.

3. Results

Tables 3–6 show for Plants L, P, M and G, respectively, observed deaths and SMRs for the corresponding

[2] The *a priori* statistical power is the probability of obtaining an SMR statistically significantly greater than 1.00 at the 0.05 level (one-sided) assuming no excess risk and estimated numbers of expected deaths.

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Table 4
Observed (Obs) deaths and SMRs for selected causes of death (total Pontchartrain cohort, U.S. and local county comparisons, 1962–2000)

Cause of death (ninth revision ICD codes)	Obs	U.S.		Local county	
		SMR	95% CI	SMR	95% CI
All causes of death (001–999)	102	0.57**	0.46–0.69	0.53**	0.43–0.65
All cancer (140–208)	34	0.74	0.51–1.04	0.68*	0.47–0.95
Digestive organs and peritoneum (150–159)	7	0.66	0.26–1.35	0.63	0.25–1.29
Large intestine (153)	3	0.84	0.17–2.46	0.78	0.16–2.27
Rectum (154)	2	2.62	0.32–9.47	3.06	0.37–11.04
Biliary passages and liver primary (155, 156)	0	–	0–3.11	–	0–2.39
Respiratory system (160–165)	12	0.72	0.37–1.26	0.62	0.32–1.09
Larynx (161)	1	1.81	0.05–10.11	1.46	0.04–8.12
Bronchus, trachea, lung (162)	10	0.63	0.30–1.16	0.55	0.26–1.00
All other respiratory (160, 163, 164, 165)	1	6.00	0.15–33.42	4.25	0.11–23.68
Malignant melanoma of skin (172)	2	1.97	0.24–7.10	2.03	0.25–7.34
Central nervous system (191, 192)	3	1.88	0.39–5.50	1.95	0.40–5.70
Lymphatic–hematopoietic tissue (200–208)	5	1.05	0.34–2.45	1.03	0.33–2.40
Non-Hodgkin's lymphoma (200, 202.0, 202.1, 202.8, 202.9)	2	1.05	0.13–3.78	0.99	0.12–3.57
Leukemia and aleukemia (204–208)	2	1.13	0.14–4.07	1.11	0.13–4.01
All other malignant neoplasms (171, 173, 195–199)	2	0.52	0.06–1.89	0.44	0.05–1.58
Cerebrovascular disease (430–438)	2	0.30	0.04–1.06	0.28	0.03–1.01
All heart disease (390–398, 402, 404, 410–429)	26	0.49**	0.32–0.72	0.44**	0.29–0.64
Non-malignant respiratory disease (460–519)	3	0.28*	0.06–0.80	0.33*	0.07–0.96
All external causes of death (E800–999)	18	0.65	0.38–1.02	0.59*	0.35–0.93
Accidents (E800–949)	14	0.89	0.48–1.49	0.82	0.45–1.37
Suicides (E950–959)	2	0.31	0.04–1.12	0.28	0.03–1.01
Homicides and other external (E960–978, E980–999)	2	0.36	0.04–1.30	0.31	0.04–1.12
Unknown causes (in all causes category only)	2				

* $p < .05$.
** $p < .01$.

total study period. Shown in each table are all cause of death categories from our MPDS listing [26] that included at least two observed deaths (or at least one death for liver cancer). For Plant L (Table 3), the local county comparisons revealed statistically significant deficits in deaths for all causes of death combined (SMR = 0.74, 95% CI = 0.71–0.77) and all cancers combined (SMR = 0.75, 95% CI = 0.69–0.80). Deficits in deaths were also observed for nearly all the malignant and non-malignant cause of death categories examined, and many were statistically significant. We observed a statistically significant 25% deficit in respiratory system cancer (RSC) based on 266 deaths (SMR = 0.75, 95% CI = 0.66–0.85). Of these, 252 or 95% were due to cancer of the bronchus, trachea or lung, which yielded a similar deficit (SMR = 0.75, 95% CI = 0.66–0.85). For the other cancer site of *a priori* interest in this study, liver cancer (categorized as cancer of the biliary passages and liver), we observed a 10% local county rate-based deficit in mortality based on 17 deaths (SMR = 0.90, 95% CI = 0.52–1.44). Based on their ICD codes, the 17 liver cancer deaths included seven "liver primary" (ICD9 = 155.0), four "extrahepatic bile ducts" (ICD9 = 156.1), three "gall bladder" (ICD9 = 156.0), one "intrahepatic bile ducts" (ICD9 = 155.1), one "liver cell carcinoma" (ICD10 = C22.0), and one "biliary tract, unspecified" (ICD10 = C24.9). With only a few exceptions, the corresponding SMRs based on U.S. rates are higher, reflecting the generally higher total and cause-specific rates of the Louisville, KY regional area. This disparity for many of the chronic disease categories is at least partly due to the higher prevalence of cigarette smoking associated with the state of Kentucky and presumably the Louisville regional area. In fact, Kentucky had the highest prevalence of cigarette smoking of any state in 1997 [28,29].

For Plant P (Table 4), the local county comparisons revealed a statistically significant 47% deficit in deaths for all causes of death combined (SMR = 0.53, 95% CI = 0.43–0.65) and a statistically significant 32% deficit for all cancers combined (SMR = 0.68, 95% CI = 0.47–0.95). We observed elevated SMRs for several of the cancer site categories examined, however, most were based on small numbers of observed deaths and none was statistically significant. SMRs for all non-malignant cause of death categories exam-

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Table 5
Observed (Obs) deaths and SMRs for selected causes of death (total Maydown study cohort, Northern Ireland comparison, 1960–2000)

Cause of death (ninth revision ICD codes)	Obs	SMR	95% CI
All causes of death (001–999)	435	0.60**	0.55–0.67
All cancer (140–208)	128	0.68**	0.56–0.80
Digestive organs and peritoneum (150–159)	39	0.65**	0.46–0.89
Esophagus (150)	2	0.23*	0.03–0.84
Stomach (151)	17	1.23	0.72–1.98
Large intestine (153)	7	0.45*	0.18–0.93
Rectum (154)	7	1.07	0.43–2.21
Biliary passages and liver (155, 156)	1	0.24	0.01–1.34
Pancreas (157)	4	0.49	0.13–1.26
Respiratory system (160–165)	48	0.79	0.58–1.05
Bronchus, trachea, lung (162)	43	0.78	0.56–1.05
Prostate (males only) (185)	8	0.84	0.36–1.65
Central nervous system (191, 192)	6	0.84	0.31–1.82
Bone (170)	2	2.69	0.33–9.73
Lymphatic–hematopoietic tissue (200–208)	15	0.90	0.51–1.49
Hodgkin's disease (201)	2	0.31	0.04–1.12
Leukemia and aleukemia (204–208)	3	0.55	0.11–1.62
Benign neoplasms (210–229)	3	0.75	0.16–2.20
Diabetes mellitus (250)	2	0.60	0.07–2.18
Cerebrovascular disease (430–438)	31	0.69*	0.47–0.98
All heart disease (390–398, 402, 404, 410–429)	151	0.60**	0.51–0.70
Non-malignant respiratory disease (460–519)	22	0.34**	0.21–0.51
Cirrhosis of liver (571)	4	0.55	0.15–1.42
Nephritis and nephrosis (580–589)	5	1.16	0.38–2.70
All external causes of death (E800–999)	32	0.38**	0.26–0.54
Accidents (E800–949)	32	0.61**	0.42–0.86
Unknown causes (in all causes category only)	23		

* $p < .05$.
** $p < .01$.

ined were less than 1.00 and some deficits were statistically significant. We observed a 38% deficit in respiratory system cancer (RSC) based on 12 deaths (SMR = 0.62, 95% CI = 0.32–1.09). Of these, 10 or 83% were due to cancer of the bronchus, trachea or lung, which yielded an even larger deficit (SMR = 0.55, 95% CI = 0.26–1.00). No deaths from liver cancer were observed at Plant P. SMRs based on U.S. rates were gen-

Table 6
Observed (Obs) deaths and SMRs for selected causes of death (total Maydown study cohort, Northern Ireland comparison, 1966–1999)

Cause of death (ninth revision ICD codes)	Obs	SMR	95% CI
All causes of death (001–999)	62	0.65**	0.50–0.83
All cancer (140–208)	20	0.59*	0.36–0.91
Buccal cavity and pharynx (140–149)	2	0.65	0.08–2.34
Digestive organs and peritoneum (150–159)	4	0.43	0.12–1.09
Large intestine (153)	2	1.19	0.14–4.28
Biliary passages and liver primary (155, 156)	1	0.56	0.01–3.12
Respiratory system (160–165)	10	0.85	0.41–1.56
Larynx (161)	3	1.88	0.39–5.49
Bronchus, trachea, lung (162)	4	0.47	0.13–1.20
All other respiratory (160, 163, 164, 165)	3	2.55	0.53–7.46
All heart disease (390–398, 402, 404, 410–429)	14	1.06	0.58–1.78
All external causes of death (E800–999)	12	0.72	0.37–1.25
Unknown causes (in all causes category only)	6		

* $p < .05$.
** $p < .01$.

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Table 7
Observed (Obs) deaths and SMRs for all cancers combined by selected study factors and plant, local county comparisons (KY and LA), national comparisons (NI and FR)

Study factor	Louisville, KY (1949–2000)		Maydown, NI (1960–2000)		Pontchartrain, LA (1962–2000)		Grenoble, FR (1966–1999)		All plants	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
All workers	652	0.75** (0.69–0.80)	128	0.68** (0.56–0.80)	34	0.68* (0.47–0.95)	20	0.59* (0.36–0.91)	834	0.73** (0.68–0.78)
Race										
White	561	0.77** (0.71–0.84)	128	0.68** (0.56–0.80)	30	0.66* (0.44–0.94)	20	0.59* (0.36–0.91)	739	0.74** (0.69–0.80)
Non-white	91	0.62** (0.50–0.75)	–	–	4	0.91 (0.25–2.32)	–	–	95	0.62** (0.51–0.76)
Sex										
Male	616	0.75** (0.69–0.81)	126	0.71** (0.59–0.85)	32	0.69* (0.47–0.97)	19	0.59* (0.35–0.92)	793	0.74** (0.69–0.79)
Female	36	0.67* (0.47–0.93)	2	0.16** (0.02–0.59)	2	0.60 (0.07–2.17)	1	0.70 (0.02–3.92)	41	0.58** (0.41–0.78)
Worker pay type										
Blue collar	636	0.75** (0.69–0.81)	123	0.70** (0.49–0.95)	20	0.59* (0.36–0.91)	16	0.67 (0.38–1.09)	795	0.74** (0.68–0.79)
White collar	16	0.67 (0.38–1.09)	5	0.28** (0.09–0.66)	14	0.84 (0.46–1.42)	4	0.40 (0.11–1.03)	39	0.57** (0.41–0.78)
Worker service type										
Short-term (<5 years)	281	0.74** (0.66–0.83)	39	0.47** (0.34–0.65)	3	0.53 (0.11–1.55)	5	0.89 (0.29–2.07)	328	0.69** (0.62–0.77)
Long-term (5+ years)	371	0.75** (0.67–0.83)	89	0.80* (0.64–0.98)	31	0.70* (0.48–0.99)	15	0.53* (0.30–0.88)	506	0.75** (0.68–0.81)
Duration of employment										
<5	281	0.73** (0.65–0.82)	39	0.45** (0.32–0.62)	3	0.42 (0.09–1.23)	5	0.71 (0.23–1.65)	328	0.68** (0.60–0.75)
5–19	107	0.63** (0.51–0.76)	51	0.72* (0.53–0.94)	22	0.86 (0.54–1.31)	9	0.46* (0.21–0.88)	189	0.66** (0.57–0.76)
20+	264	0.82** (0.72–0.93)	38	1.02 (0.72–1.40)	9	0.44** (0.20–0.84)	6	0.83 (0.31–1.82)	317	0.82* (0.73–0.91)
Time since first employment										
<20	51	0.52** (0.39–0.68)	30	0.53** (0.36–0.76)	16	0.93 (0.53–1.51)	9	0.61** (0.42–0.86)	106	0.57** (0.47–0.69)
20–29	118	0.72** (0.59–0.86)	58	0.77* (0.58–0.99)	11	0.56 (0.28–1.01)	8	0.57 (0.24–1.12)	195	0.71** (0.62–0.82)
30+	483	0.79** (0.72–0.86)	40	0.64** (0.45–0.87)	7	0.53 (0.21–1.09)	3	0.83 (0.17–2.43)	533	0.77** (0.71–0.84)
CD exposure status										
Unexposed	1	0.99 (0.03–5.51)	14	1.26 (0.69–2.12)	8	1.44 (0.62–2.85)	5	0.61 (0.20–1.42)	28	1.08 (0.72–1.56)
Exposed	651	0.74** (0.69–0.80)	114	0.62** (0.51–0.75)	26	0.57** (0.37–0.84)	15	0.59* (0.33–0.97)	806	0.71** (0.66–0.76)
VC exposure status										
Unexposed	524	0.80** (0.73–0.87)	113	0.64** (0.53–0.77)	34	0.68* (0.47–0.95)	20	0.59 (0.36–0.91)	691	0.75** (0.70–0.81)
Exposed	128	0.58** (0.49–0.69)	15	0.80 (0.44–1.31)	–	–	–	–	143	0.60* (0.50–0.70)

* $p < .05$.
** $p < .01$.

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Table 8
Observed (Obs) deaths and SMRs for respiratory system cancer by selected study factors and plant, local county comparisons (KY and LA), national comparisons (NI and FR)

Study factor	Louisville, KY (1949–2000)		Maydown, NI (1960–2000)		Pontchartrain, LA (1962–2000)		Grenoble, FR (1966–1999)		All plants	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
All workers	266	0.75** (0.66–0.85)	48	0.79 (0.58–1.05)	12	0.62 (0.32–1.09)	10	0.85 (0.41–1.56)	336	0.75** (0.67–0.84)
Race										
White	233	0.78** (0.69–0.89)	48	0.79 (0.58–1.05)	10	0.55* (0.23–0.96)	10	0.85 (0.41–1.56)	301	0.77** (0.69–0.87)
Non-white	33	0.59** (0.40–0.83)	–	–	2	1.56 (0.17–4.91)	–	–	35	0.61** (0.42–0.85)
Sex										
Male	256	0.75** (0.66–0.85)	48	0.82 (0.60–1.08)	11	0.59 (0.30–1.06)	10	0.86 (0.41–1.58)	325	0.76** (0.68–0.84)
Female	10	0.72 (0.34–1.31)	0	– (0–2.01)	1	1.38 (0.04–7.71)	0	– (0–30.70)	11	0.66 (0.33–1.18)
Worker pay type										
Blue collar	262	0.76** (0.67–0.86)	46	0.81 (0.60–1.08)	8	0.62 (0.27–1.21)	9	1.09 (0.50–2.06)	325	0.77** (0.69–0.86)
White collar	4	0.41 (0.11–1.04)	2	0.36 (0.04–1.29)	4	0.63 (0.17–1.61)	1	0.29 (0.01–1.59)	11	0.44** (0.22–0.78)
Worker service type										
Short-term (<5 years)	123	0.80* (0.66–0.95)	14	0.57* (0.30–0.93)	0	– (0–2.08)	2	1.04 (0.13–3.77)	139	0.76* (0.64–0.90)
Long-term (5+ years)	143	0.72** (0.60–0.84)	34	0.92 (0.64–1.28)	12	0.69 (0.36–1.20)	8	0.81 (0.35–1.60)	197	0.75** (0.65–0.86)
Duration of employment (years)										
<5	123	0.79** (0.66–0.95)	14	0.54* (0.29–0.90)	0	– (0–1.70)	2	0.86 (0.10–3.12)	139	0.75** (0.63–0.88)
5–19	37	0.58** (0.41–0.79)	24	1.03 (0.66–1.53)	8	0.81 (0.35–1.59)	6	0.90 (0.33–1.96)	75	0.72* (0.57–0.91)
20+	106	0.79** (0.64–0.95)	10	0.78 (0.37–1.43)	4	0.48 (0.13–1.22)	2	0.71 (0.09–2.58)	122	0.77* (0.64–0.92)
Time since first employment (years)										
<20	15	0.46** (0.26–0.76)	14	0.83 (0.45–1.39)	4	0.68 (0.18–1.73)	4	0.74 (0.20–1.89)	37	0.61** (0.43–0.84)
20–29	50	0.72* (0.53–0.95)	19	0.77 (0.46–1.20)	5	0.63 (0.20–1.47)	6	1.17 (0.43–2.55)	80	0.75* (0.59–0.93)
30+	201	0.80** (0.69–0.92)	15	0.73 (0.41–1.21)	3	0.56 (0.12–1.65)	0	– (0–2.95)	219	0.79* (0.69–0.90)
CD exposure status										
Unexposed	0	– (0–8.99)	4	1.15 (0.31–2.93)	0	– (0–1.88)	2	0.79 (0.10–2.84)	6	0.71 (0.26–1.55)
Exposed	266	0.75** (0.66–0.85)	44	0.75 (0.54–1.01)	12	0.68 (0.35–1.18)	8	0.87 (0.37–1.70)	330	0.75** (0.67–0.84)
VC exposure status										
Unexposed	232	0.89 (0.78–1.02)	43	0.77 (0.56–1.04)	12	0.62 (0.32–1.09)	10	0.85 (0.41–1.56)	297	0.85* (0.76–0.96)
Exposed	34	0.36** (0.25–0.50)	5	0.78 (0.25–1.82)	–	–	–	–	39	0.39** (0.27–0.53)

* $p < .05$.
** $p < .01$.

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erally somewhat higher than those based on the local parishes.

For Plant M (Table 5), the Northern Ireland national comparisons revealed statistically significant deficits in deaths for all causes of death combined (SMR = 0.60, 95% CI = 0.55–0.67) and all cancers combined (SMR = 0.68, 95% CI = 0.56–0.80). Deficits in deaths were also observed for nearly all the malignant and non-malignant cause of death categories examined, and many were statistically significant. We observed a not statistically significant 21% deficit in respiratory system cancer (RSC) based on 48 deaths (SMR = 0.79, 95% CI = 0.58–1.05). Of these, 43 or 90% were due to cancer of the bronchus, trachea or lung, which yielded a similar deficit (SMR = 0.78, 95% CI = 0.56–1.05). One death from liver cancer was observed in Plant M (SMR not calculated) and was coded as "liver cancer-unspecified" (ICD10 = C22.9).

For Plant G (Table 6), the French national comparisons revealed statistically significant deficits in deaths for all causes of death combined (SMR = 0.65, 95% CI = 0.50–0.83) and all cancers combined (SMR = 0.59, 95% CI = 0.36–0.91). We observed elevated SMRs for some of the cancer sites and non-malignant disease categories examined, however, most were based on small numbers of observed deaths and none was statistically significant. We observed a 15% deficit in respiratory system cancer (RSC) based on 10 deaths (SMR = 0.85, 95% CI = 0.41–1.56). Of these, only 4 or 40% were due to cancer of the bronchus, trachea or lung, which yielded a much larger deficit (SMR = 0.47, 95% CI = 0.13–1.20). One death from liver cancer was observed in Plant G (SMR = 0.56, 95% CI = 0.01–3.12), and was coded as "liver, not specified as primary or secondary" (ICD9 = 155.2).

Table 9
Observed (Obs) deaths and SMRs for liver cancer by selected study factors, Louisville Plant, local county comparisons

Study factor	Louisville, KY (1949–2000)		All plants combined[a]	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)
All workers	17	0.90 (0.53–1.44)	19	0.72 (0.43–1.13)
Race				
White	16	1.02 (0.58–1.65)	18	0.78 (0.46–1.23)
Non-white	1	0.32 (0.01–1.77)	1	0.30 (0.004–1.67)
Sex				
Male	16	0.89 (0.51–1.45)	18	0.72 (0.43–1.13)
Female	1	1.06 (0.03–5.93)	1	0.87 (0.01–4.87)
Worker pay type				
Blue collar	17	0.93 (0.54–1.49)	18	0.73 (0.43–1.16)
White collar	0	– (0–6.91)	1	0.66 (0.009–3.67)
Worker service type				
Short-term (<5 years)	4	0.49 (0.13–1.26)	4	1.54 (0.41–3.94)
Long-term (5+ years)	13	1.21 (0.64–2.07)	15	0.88 (0.49–1.45)
Duration of employment (years)				
<5	4	0.49 (0.13–1.25)	4	0.41 (0.11–1.06)
5–19	6	1.68 (0.62–3.66)	7	1.02 (0.41–2.09)
20+	7	0.98 (0.40–2.03)	8	0.97 (0.42–1.91)
Time since first employment (years)				
<20	1	0.56 (0.01–3.11)	1	0.29 (0.004–1.60)
20–29	3	0.91 (0.19–2.66)	4	0.71 (0.19–1.81)
30+	13	0.95 (0.50–1.62)	14	0.88 (0.48–1.47)
CD exposure status				
Unexposed	0	– (0–134.59)	2	2.56 (0.29–9.25)
Exposed	17	0.90 (0.53–1.44)	17	0.71 (0.42–1.14)
VC exposure status				
Unexposed	15	1.07 (0.60–1.77)	17	0.80 (0.47–1.29)
Exposed	2	0.44 (0.05–1.49)	2	0.40 (0.05–1.46)

[a] Includes observed and expected deaths from all four study plants.

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Tables 7–9 show for all cancers combined, RSC and liver cancer, respectively, observed deaths and SMRs by selected study factors and plant, including the four plants combined. SMRs for Plants L and P are based on local county rates; those for Plants M and G on the respective national rates. For all cancers combined (Table 7), the aggregate SMR reflects a statistically significant 27% deficit in deaths based on 834 observed deaths (SMR = 0.73, 95% CI = 0.68–0.78) for the total CD cohort. For nearly all of the study variables and subcategories examined, including the variables that are surrogates of occupational exposure to CD or other substances (i.e., worker pay type, worker service type, duration of employment and the time since first employment), we observed deficits in deaths within and across the four plants and many are statistically significant. None of the few elevated SMRs in Table 7 was statistically significant. Because most of the cohort was exposed to CD, most of the cancer deaths occurred among CD-exposed persons (806/834), resulting in a statistically significant 29% deficit in all cancer mortality. Although plant-specific SMRs for CD-unexposed subjects are relatively imprecise due to the much smaller numbers of observed deaths, all cancer SMRs are higher within and across plants for CD-unexposed subjects compared with subjects who had some CD exposure. For Plants L and M where potential VC exposure occurred, we observed a combined statistically significant 40% deficit in all cancer deaths (SMR = 0.60, 95% CI = 0.50–0.70) based on 143 deaths. SMRs for workers both exposed and unexposed to VC were less than 1.00 in each plant.

For RSC (Table 8), the aggregate SMR reflects a statistically significant 25% deficit in deaths based on 336 observed deaths (SMR = 0.75, 95% CI = 0.67–0.84) for the total CD cohort. For nearly all of the study variables and subcategories examined, including the CD exposure variable and the variables that act as surrogates of exposure to CD or other substances, we observed deficits in deaths within and across the four plants and many are statistically significant. None of the few elevated SMRs in Table 8 was statistically significant. With the exception of a slight RSC excess among workers unexposed to CD in Plant M, SMRs for workers unexposed and exposed to CD or VC were less than 1.00.

Because 17 of the 19 total liver cancer deaths occurred in Plant L, the subgroup analysis was limited to Plant L and the combined four plants (Table 9). Based on the 19 deaths, we observed a 28% deficit in liver cancer deaths for the total CD cohort. All but one death occurred among white male, blue collar subjects. All of the 17 liver cancer deaths in Plant L occurred among subjects who had been exposed to CD, resulting in 10% deficit in deaths (SMR = 0.90, 95% CI = 0.53–1.44). For the combined plants, elevated SMRs were observed among short-term workers, workers employed 5–19 years, and among workers unexposed to CD; however, none was statistically significant.

4. Discussion and conclusions

Our historical cohort study of workers from four CD production sites in the U.S. and Europe represents the largest and the most comprehensive and rigorous investigation of the long-term health effects of exposure to CD conducted to date. It overcomes most of the shortcomings and uncertainties noted by Rice and Boffetta [30] and Acquavella and Leonard [31] that have limited the interpretation of findings from the five previous cohort studies, that is, the studies of chloroprene production workers in the U.S. [6], China [7], Armenia [8] and France [11] and the study of shoe manufacturing workers in Russia [9].

Our combined cohort of 12,430 subjects contributed over one-third of a million person-years of observation, of which 151,691 or 41% were among workers followed for 20 or more years from first employment. Through 2000 (1999 for Plant G), we observed 3002 deaths, including 834 from all cancers combined. For the two cause of death categories of *a priori* interest in this study (respiratory system cancer and liver cancer (categorized as cancer of the biliary passages and liver)), we observed 336 and 19 deaths, respectively. Other major strengths of the study include: diversity of site location and production processes; long observation periods; substantial proportion of workers employed 20 or more years; nearly complete cohort enumeration with cross-validation, vital status tracing and cause of death determination; excellent statistical power to detect two-fold or greater overall mortality excess for all cause of death categories of *a priori* interest; a rigorous and innovative, chemical process-based exposure reconstruction for chloroprene and vinyl chloride; and the use of national and local county mortality comparisons and robust statistical modeling of internal cohort rates.

During the course of the study, we attempted to locate, from records held by the two U.S. plants and Plant M, tobacco-smoking histories for all subjects who died from RSC and a series of control subjects to permit adjustment for potential confounding by smoking via a nested case-control study. Because we found that only 28% of the RSC cases from Plant L and 54% from Plant M had smoking history information, we decided that the case-control study of RSC was unfeasible. Two features of our cohort study, however, enabled at least

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some crude adjustment for potential confounding by smoking. First, in the two U.S. plants, our use of local county mortality comparisons afforded some adjustment for geographic variability in tobacco use. This was particularly evident in Plant L where SMRs for RSC and most other smoking-related chronic diseases based on local rates were considerably less than those based on U.S. rates. Second, in the exposure–response analyses for CD and VC described in our companion paper [21], we categorized workers by pay type (blue/white collar) and used this variable as a rough surrogate of education and socioeconomic status, which are highly correlated with smoking prevalence in both the U.S. and Europe.

While the *a priori* statistical power of our study to detect an overall two-fold or greater excess in liver cancer was 99%, the power was much lower in all plants but Plant L (which included 17 of the total 19 liver cancer deaths) and in other cohort subgroups examined. However, the issue of statistical power for liver cancer in this study was rendered mostly moot, as most of the SMRs were less than the null hypothesis value of 1.00 that was tested with a one-tailed test (i.e., with a one-tailed statistical test of the null hypothesis SMR = 1.00 versus the alternative hypothesis SMR > 1.00, power only applies to values observed under the alternative hypothesis).

In addition to CD and to VC in Plants L and M, subjects in our study plants were also potentially exposed to other agents, including 1,3-butadiene, 1,4-dichloro-2-butene, 3,4-dichloro-1-butene and methylene chloride. However, because exposures to these agents were brief, intermittent and process-specific, they would have had negligible or no impact on long-term worker health effects, thus, we made no attempt to characterize these or other co-exposures.

About one-half of the CD cohort were short-term workers (defined as working less than 5 years) although 27% of subjects worked 20 or more years. Contrary to many other occupational cohort studies, short-term workers did not exhibit a differential mortality pattern often associated with increased mortality for both malignant and non-malignant diseases. The long length of follow-up in this study may have mitigated the mortality influence of short-term workers. Potential selection bias from the subjects lost to follow-up in Plant M or the transferred workers missed in Plant P, or underestimation of cause-specific SMRs in Plant G may be operating in our study, but the overall effects would be minimal due to the small percentage of subjects involved. Because we did not adjust p-values for multiple comparisons, some of our statistically significant SMRs may be simply chance occurrences.

The total and cause-specific mortality patterns observed in this study were generally quite consistent across plants and indicated a statistically significant reduced mortality risk from all causes combined, all cancer sites combined and from many of the other malignant and non-malignant disease categories examined. Moreover, these reduced risks were maintained in all cohort subgroups examined, including the CD and VC exposure variables (never/ever exposed to CD or VC), and the variables that serve as surrogates of exposure to CD or other substances found in the study plants (worker pay type (blue/white collar), worker service type (short/long term), duration of employment and the time since first employment). These favorable mortality patterns, particularly those for the long-term chronic diseases examined, are probably influenced in part by the "healthy worker effect", a relative absence of deleterious health risks in relation to employment, and the effects of continuing employment with its many benefits, such as improved health care and quality of life.

Of particular importance is our finding of no elevated mortality risks for all cancers combined or for the two *a priori* cancer sites of interest, lung (evaluated separately and within the slightly broader respiratory system cancer category) and liver (categorized as cancer of the biliary passages and liver). Our finding of no excess risk for liver cancer is reassuring, considering that during the course of this investigation, we learned that the acetylene manufacturing process for chloroprene used in Plants L and M produced vinyl chloride exposures as a by-product [17–20]. VC is an established risk factor for a rare form of liver cancer (angiosarcoma) and is also linked to other forms of cancer including hepatocellular carcinoma, brain tumors, lung tumors and malignancies of the lymphatic and hematopoietic system [32]. Excess liver cancers were also reported in experimental studies of animals exposed to CD [16] and in three previous epidemiology studies of workers with potential exposure to CD: workers in a chloroprene monomer production facility in China [7], shoe manufacturing workers in Moscow [9] and chloroprene production workers in Armenia [8]. The inherent methodological limitations in the previous epidemiology studies raise questions, however, about their significance regarding human cancer risks [30,31].

In our study, we examined liver cancer within the broader cause of death category "biliary passages and liver" and found no evidence of an increased risk of death in the total cohort (Plant L included 17 of 19 deaths) or within any of the cohort subgroups examined. Of the 19 deaths coded to this broader liver cancer category, only eight were coded as a primary liver cancer. We found no evidence of increased mortality risks for the other

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cancer sites linked to VC exposure. As noted in our companion papers, the absence of any elevated cancer risks among VC-exposed subjects in our study is most likely explained by the relatively low historical VC exposures in Plants L and M [17–21].

While the possible occurrence of the rare VC-related cancer, angiosarcoma of the liver, was of interest in this study, methodological limitations precluded a full evaluation. Because angiosarcoma of the liver does not have a specific ICD code until the 10th revision (1999+), it can only be roughly identified in earlier revisions by manually reviewing text fields of death certificates. A comprehensive death certificate review was not possible in this study as we obtained death certificates for the two U.S. plants only for deaths that occurred before the National Death Index (before 1979) and in some cases cause of death for pre-1979 deaths was obtained as an ICD code from the DuPont mortality registry. For Plant G we obtained ICD codes only from our French collaborators and in Plant M we obtained only a limited number of death certificates. What we were able to glean from available data follows.

Seventeen of the 19 deaths coded to cancer of "biliary passages and liver" occurred in Plant L. Only four of these occurred before 1979 and death information was obtained for three from the DuPont mortality registry as an ICD code only. Thus, of the 17 Plant L deaths, we had a copy of the death certificate for only one death. The cause of death on this certificate was noted as "liver cancer". Two of the 17 Plant L deaths occurred during the time-period of the ICD10 (1999 and 2000). One was coded as C249 "malignant neoplasms of digestive organs – malignant neoplasm of other and unspecified parts of biliary tract – biliary tract, unspecified" and one was coded as C220 "malignant neoplasms of digestive organs – malignant neoplasm of liver and intrahepatic bile ducts – liver cell carcinoma". The one Plant M liver cancer death was coded to ICD10 as C229 "malignant neoplasm of liver and intrahepatic bile ducts—liver, unspecified". The exact wording on that death certificate was "cancer of the liver". The possible occurrence of angiosarcoma of the liver would be best evaluated in a cancer incidence study that would utilize more detailed histo-pathological and other information not available on death certificates.

Our finding of no excess risk for respiratory system cancer (of which more than 90% were cancers of the bronchus, trachea or lung, i.e., lung cancer) is also reassuring considering the suggestion of a lung cancer excess in the cohort incidence study of chloroprene production workers in France [11] that formed the basis of our mortality study in Plant G. For several reasons, the results of our cohort mortality study for Plant G are not directly comparable with the previously published cancer incidence study. While both studies included the same facility, the cancer incidence study was limited by entrance criteria not used in the mortality study. Specifically, the cancer incidence study did not include women, employees who worked less than 2 years or subjects who left the Isère region of France before 1979. Also, the cancer incidence and vital status tracing done for the two studies used independent French government data sources. The cancer incidence study used the cancer registry of the Department of Isère for the identification of cancer cases. This regional cancer registry covers the area surrounding the plant and includes cancer diagnosis information for approximately one million inhabitants. The cohort mortality tracing used the nationwide INSERM death registry; this agency records the death information for all residents of France. Because the two agencies cover different populations and record different events, the results of tracing the same study cohort through each service cannot be directly compared. Our finding of no excess lung cancer risk among CD-exposed workers was not entirely unexpected, considering what is now known from experimental animal studies about substantial interspecies differences in sensitivity to CD-induced lung tumorigenicity and how these findings can be extrapolated to estimate human lung cancer risk [14,33,34].

In summary, our study has many strengths and is the most definitive study of the human carcinogenic potential of exposure to CD conducted to date. We conclude from this analysis of general mortality patterns that persons exposed to chloroprene at the levels encountered in the four study sites did not have elevated risks of mortality from any of the causes of death examined, including all cancers combined and lung and liver cancer, the cancer sites of *a priori* interest. This conclusion is corroborated by our detailed analyses of mortality in relation to qualitative and quantitative exposures to CD and VC at each of the four study sites, reported in our companion paper [21].

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