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Mortality patterns among industrial workers exposed to chloroprene and other substances
II. Mortality in relation to exposure

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Abstract

As part of an historical cohort study to investigate the mortality experience of industrial workers exposed to chloroprene (CD) and other substances, including vinyl chloride monomer (VC), we analyzed mortality from all cancers combined, respiratory system (RSC) and liver cancer in relation to CD and VC exposures. Subjects were 12,430 workers ever employed at one of two U.S. sites (Louisville, KY ($n = 5507$) and Pontchartrain, LA ($n = 1357$)) or two European sites (Maydown, Northern Ireland ($n = 4849$) and Grenoble, France ($n = 717$)).

Historical exposures for individual workers were estimated quantitatively for CD and VC. For sites L, M, P and G, respectively, average intensity of CD exposures (median value of exposed workers in ppm) were 5.23, 0.16, 0.028 and 0.149 and median cumulative exposures (ppm years) were 18.35, 0.084, 0.133 and 1.01. For sites L and M, respectively, average intensity of VC exposures (median value of exposed workers in ppm) was 1.54 and 0.03 and median cumulative exposures (ppm years) were 1.54 and 0.094.

We performed relative risk (RR) regression modeling to investigate the dependence of the internal cohort rates for all cancers combined, RSC and liver cancer on combinations of the categorical CD or VC exposure measures with adjustment for potential confounding factors. We categorized exposure measures into approximate quartiles based on the distribution of deaths from all cancers combined. We also considered 5- and 15-year lagged exposure measures and adjusted some RR models for worker pay type (white/blue collar) as a rough surrogate for lifetime smoking history. All modeling was site-specific to account for exposure heterogeneity. We also computed exposure category-specific standardized mortality ratios (SMRs) to assess absolute mortality rates.

With the exception of a one statistically significant association with duration of exposure to CD and all cancers combined in plant M, we observed no evidence of a positive association with all cancers, RSC or liver cancer and exposure to CD and/or VC using both the unlagged and lagged exposure measures: duration, average intensity or cumulative exposure to CD or VC; time since first CD or VC exposure; and duration of CD exposure or time since first CD exposure in presence or absence of VC exposure. We observed elevated and statistically significantly elevated RRs for some analysis subgroups, but these were due to inordinately low death rates in the baseline categories. With the possible exception of all cancer mortality in plant G, our additional adjustment of RRs for pay type revealed no evidence of positive confounding by smoking.

We conclude that exposures to CD or VC at the levels encountered in the four study sites do not elevate mortality risks from all cancers, RSC or liver cancer. This conclusion is corroborated by our analysis of general mortality patterns among the CD cohort

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reported in our companion paper [G. Marsh, A. Youk, J. Buchanich, M. Cunningham, N. Esmen, T. Hall, M. Phillips, Mortality patterns among industrial workers exposed to chloroprene and other substances. I. General mortality patterns, Chem.-Biol. Interact., submitted for publication].

Keywords: Chloroprene; Cohort study; Liver cancer; Lung cancer; Mortality; Vinyl chloride; Exposure-response

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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]. The chemical structure of CD is similar to that of vinyl chloride, a known human carcinogen [2]. CD is classified by the International Agency for Research on Cancer as a possible human carcinogen (group 2B) based on sufficient evidence of carcinogenicity in experimental animals [3]. Epidemiological data on the carcinogenicity of CD are available from five cohort studies of chloroprene production workers in the U.S. [4], China [5], Armenia [6] and France [7], and the study of shoe manufacturing workers in Russia [8]. An increased risk of liver [5,6,8,9] and lung cancer [7] has been suggested by some of these studies. The inherent methodological limitations in the previous epidemiology studies raise questions; however, about their significance regarding human cancer risks [10,11].

To provide more definitive and comprehensive 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). Our analysis of general mortality patterns among the CD cohort, reported in a companion paper [12], found no evidence of elevated mortality risks from any of the causes of death examined, including all cancers combined and lung and liver cancer, the sites of *a priori* interest. We report here the results of our detailed analysis of mortality from all cancers combined, lung and liver cancer in relation to quantitative measures of CD and VC exposure.

2. Methods

2.1. Study sites and subjects

The chloroprene (CD) cohort included all workers ($n = 12{,}430$) with potential CD exposure at one 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 in 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 CD cohort and the history, processes and chemical exposures associated with each study plant are described elsewhere [12–16].

2.2. Exposure estimation

2.2.1. Chemical process-based exposure reconstruction

Historical individual worker exposure profiles were estimated using a chemical process-based exposure reconstruction approach detailed elsewhere by Esmen et al. [13–15]. In brief, the exposure reconstruction was based on mathematical models which utilized exposure models based on the physics and chemistry associated with a given chemical process as determined from process documentation and task performance habits gleaned from interviews with knowledgeable plant personnel. The mathematical models used were based on the dispersion of the contaminant in the breathing zone of the worker performing the task associated with the exposure of interest. The simplest models scaled the contaminant vapor pressure by task execution time; more sophisticated models considered the contamination generation and dispersion rates. To the extent possible, all mathe-

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Table 1
Chloroprene (CD) and vinyl chloride (VC) exposure level classes

Level	CD (ppm)		VC (ppm)	
	Range	Nominal	Range	Nominal
0	$N < 0.0005$	0	$N < 0.01$	0
1	0.0005–0.005	0.0016	0.01–0.1	0.03
2	0.005–0.05	0.016	0.1–1	0.3
3	0.05–0.5	0.16	1–10	3
4	0.5–5	1.6	10+	16
5	5–50	16		
6	50–100	71		
7	100+	160		

N: negligible exposure.

matical models were validated with existing air monitoring data available for the later years (1975–1992). In comparison to the available exposure measurement data, the estimated exposure levels could have been obtained for many job categories using only the existing exposure measures leading to the same results obtained through modeling. This suggested that the exposure assignment in job categories with sparse or missing exposure measurement data was satisfactory.

2.2.2. Estimated exposures to chloroprene and vinyl chloride

In each plant, CD and VC exposures were modeled for all unique job title classes using six exposure classes for CD and four exposure classes for VC (Table 1). The width of the exposure classes (one order of magnitude) was calculated to minimize exposure misclassification on the basis of the specificity available in the job dictionary [13–15]. The nominal values (geometric mean of the associated class limits) of each agent were used as the daily average intensity value for a specific job with the associated exposure level. Exposures were estimated for the entire period of CD production in each plant. Although the four plants varied considerably with respect to the mix of production methods, CD exposures were remarkably similar in both estimated and measured values. CD exposures were found to be much more dependent on the improvement of the production methods, rather than deliberate reduction in exposures for occupational hygiene considerations. CD exposures were generally lower than the contemporaneous exposure limits or guidelines. Specifically, average CD exposures were less than 20 ppm in the pre-1960 era, less than 10 ppm in the 1960–1980 era, less than 1 ppm in the 1980–1990 era and less than 0.5 ppm thereafter. VC exposures, which occurred only in monomer production, were estimated to be relatively high in the pre-1960 era of CD production, but the highest exposures for the CD monomer operator job class did not exceed 2 ppm. For the same job class, VC exposures in the 1960–1970 era were less than 0.5 ppm.

2.2.3. Construction of worker summary exposure measures

For each plant, the job title classes and corresponding time-specific exposure class estimates for CD and VC were linked to the detailed subject work histories held by UPitt to enable the construction of working lifetime exposure profiles for each subject. These individual subject exposure profiles were used to compute three summary measures of CD and/or VC exposure for each subject as follows: duration of exposure (Dur) = the sum of the days spent in jobs with nonzero exposure to CD or VC (in years); cumulative exposure (Cum) = the product of the number of days in each job and the estimated average daily exposure to CD or VC (in ppm years); and average intensity of exposure (AIE) = the ratio of Cum to Dur (in ppm). The notation used to describe these summary measures is Agent_Measure, for example, CD_AIE refers to the average intensity of CD exposure.

We also considered a latent time-related exposure measure, time since first exposure to CD (or VC), expressed as Agent_TSFExp and constructed two composite summary measures, CD exposure in the presence of VC exposure (CDwVC_Measure) and CD exposure in the absence of VC exposure (CDwoVC_Measure). With the former composite measure, CD exposures are computed only for those jobs with concomitant VC exposure. Alternative characterizations of the CD and VC exposure measures described above were also computed using a lag period as described in detail by Youk et al. [17]. Simply put, the lag period refers to the fixed period of time before the time of observation during which exposures are not counted. Thus, with a 5-year lag period, exposures received up to five years before a given observation time are given zero weight, and exposures received five or more years before observation time are given full weight. Lagging attempts to characterize only the most etiologically relevant exposures and is particularly relevant for examining diseases, such as cancer, associated with long latent periods. We considered both a 5 and 15 years lag in our analysis of respiratory system cancer and liver cancer.

2.2.4. Worker exposures to chloroprene and vinyl chloride

Table 2 shows for each plant the distribution of subjects exposed to CD and/or VC. More than 92% of the workers at each plant were exposed to CD, with

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Table 2
Distribution of workers exposed to chloroprene and vinyl chloride

Plant	Number exposed (%)			Total subjects
	CD	VC	CD and VC	
Louisville	5468 (99.3)	1250 (22.7)	1250 (22.7)	5507
Maydown	4474 (92.3)	265 (5.5)	265 (5.5)	4849
Pontchartrain	1258 (92.7)	0 (0)	0 (0)	1357
Grenoble	717 (100.0)	0 (0)	0 (0)	717
All plants	11919 (95.9)	1515 (12.2)	1515 (12.2)	12430

Table 3
Summary statistics for chloroprene (CD) and vinyl chloride (VC) exposure measures by plant, exposed workers only

Exposure indicator	Louisville	Pontchartrain	Maydown	Grenoble
Chloroprene				
Person-years (total)	197919	30660	127036	17057
Person-years exposed	197034	26842	117640	17057
Person-years unexposed[a]	885	3818	9396	0
Duration (CD_Dur, years)				
25 percentile	0.997	3.08	0.003	5.71
Median	5.78	13.34	3.32	15.5
75 percentile	23.2	23.91	10.96	24.21
Maximum	45.2	30.998	42.5	33.996
Mean	12.15	14.12	7.11	15.51
Standard deviation	12.35	10.72	8.87	9.88
Coefficient of variation	101.6	75.91	124.8	63.74
Average intensity (CD_AIE, ppm)				
25 percentile	0.871	0.0016	0.0016	0.0160
Median	5.23	0.0283	0.160	0.149
75 percentile	16.00	0.552	1.60	1.39
Maximum	71.00	12.37	16.00	16.00
Mean	8.42	0.269	1.43	2.19
Standard deviation	10.40	0.552	3.27	4.54
Coefficient of variation	123.5	205.7	228.7	207.3
Cumulative (CD_Cum, ppm-years)				
25 percentile	1.52	0.0088	0.0022	0.0690
Median	18.35	0.133	0.0837	1.005
75 percentile	106.3	13.13	7.33	19.38
Maximum	1351.5	110.9	357.3	458.7
Mean	80.35	5.64	11.1	37.04
Standard deviation	134.9	10.33	32.79	85.93
Coefficient of variation	167.9	183.1	295.4	231.96
Vinyl chloride				
Person-years (total)	197919	n/a	127036	n/a
Person-years exposed	50401		8792	
Person-years unexposed[a]	147518		118244	
Duration (VC_Dur, years)				
25 percentile	0.392	n/a	0.296	n/a
Median	2.55		2.24	
75 percentile	12.39		5.57	
Maximum	29.42		27.23	
Mean	6.795		3.94	
Standard deviation	7.97		4.75	
Coefficient of variation	117.3		120.5	

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Table 3 (*Continued*)

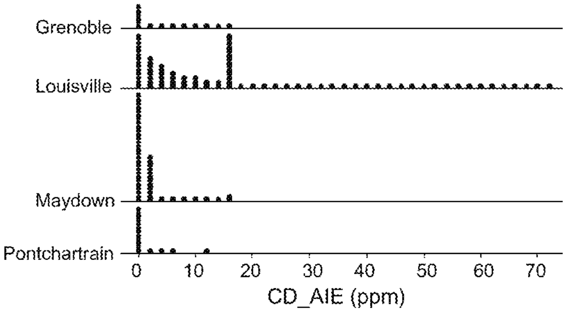
Exposure indicator	Louisville	Pontchartrain	Maydown	Grenoble
Average intensity (VC_AIE, ppm)				
25 percentile	0.265	n/a	0.030	n/a
Median	1.54		0.030	
75 percentile	3.00		0.030	
Maximum	3.00		0.300	
Mean	1.50		0.0648	
Standard deviation	1.26		0.0787	
Coefficient of variation	83.7		121.4	
Cumulative (VC_Cum, ppm-years)				
25 percentile	0.331	n/a	0.0089	n/a
Median	1.54		0.0941	
75 percentile	9.25		0.212	
Maximum	58.04		5.34	
Mean	8.66		0.335	
Standard deviation	13.55		0.672	
Coefficient of variation	156.4		200.8	

[a] Includes unexposed portion of person-years among subjects ultimately exposed.

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.

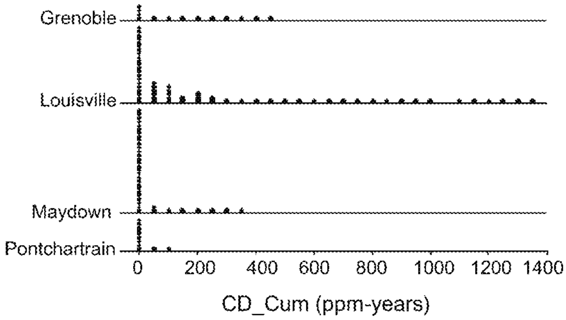
Table 3 shows selected summary statistics for CD and VC exposures in each study plant. For each plant, the bulk of the accumulated person-years occurred during periods of exposure to CD. The median CD_Dur computed across individual workers ranged from 3.32 years at plant M to 15.5 years at plant G; the median CD_AIE ranged from 0.028 ppm (plant P) to 5.23 ppm (plant L) and the median CD_Cum ranged from 0.084 ppm years (plant M) to 18.35 ppm years (plant L). The median VC_Dur, VC_AIE and VC_Cum values for plants L and M were, respectively, 2.55 and 2.24 years, 1.54 and 0.03 ppm and 1.54 and 0.094 ppm years. For both CD and VC, the corresponding means of the three exposure measures were considerably greater than the medians, reflecting the positive skewness of the subjects' exposure distributions.

Figs. 1 and 2 provide plant-specific dot plots of the individual worker values for CD_AIE and CD_Cum; Figs. 3 and 4 provide corresponding dot plots for VC. The clustering of points at various levels of CD_AIE and VC_AIE corresponds with the nominal exposure values shown in Table 1. The figures show that plant L had, by far, the largest exposures to both CD and VC, due to its earlier period of operation and use of the acetylene process. Figs. 5 and 6 show for plants L and M, respectively, scattergrams of individual worker values of CD_AIE by VC_AIE. These are relevant to the composite exposure measures CDwVC_AIE and CDwoVC_AIE described above. The figures show that the CD_AIE and VC_AIE values were essentially uncorrelated.



Exposed workers only, each dot represents up to 62 subjects.

Fig. 1. Average intensity of chloroprene exposure by plant.



Exposed workers only, each dot represents up to 84 subjects.

Fig. 2. Cumulative chloroprene exposure by plant.

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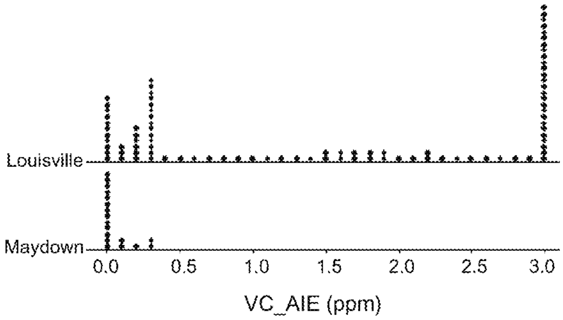
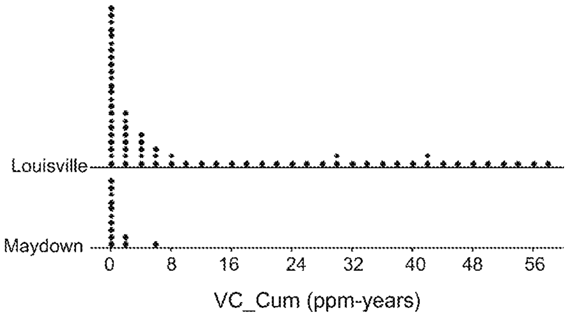


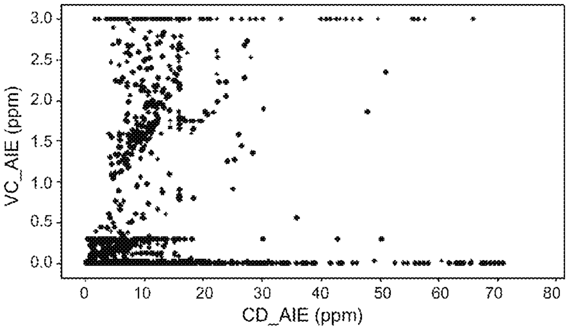
Exposed subiects only, each dot represents up to 11 subjects.

Fig. 3. Average intensity of vinyl chloride exposure by plant.



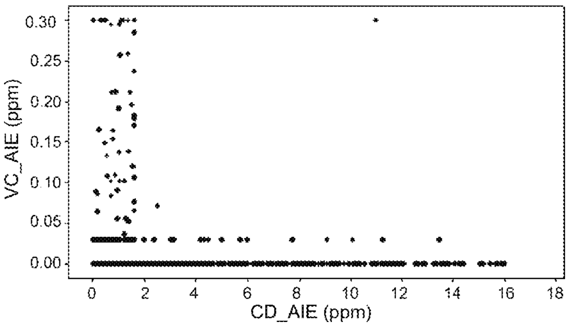
Exposed workers only, each dot represents up to 16 subjects.

Fig. 4. Cumulative vinyl chloride exposure by plant.



CD-exposed workers only

Fig. 5. Louisville plant, VC_AIE by CD_AIE.



CD-exposed workes only

Fig. 6. Maydown plant, VC_AIE by CD_AIE.

2.3. Statistical analyses

2.3.1. Exposure-response based on internal comparisons

We used relative risk (RR) regression modeling to investigate the dependence of the internal cohort rates (modeled as time to death) for all cancers combined, respiratory system cancer (RSC) and liver cancer (categorized as "cancer of the biliary passages and liver" [12]) on combinations of the various CD and VC exposure measures, with adjustment for potential confounding factors. In our analysis of all cancers combined (each plant) and respiratory system cancer (plant L only), we also included adjustment for worker pay type, which was dichotomized as blue collar or white collar and analyzed as a time-dependent variable. The worker pay type 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 and socioeconomic status, which are highly correlated with smoking prevalence in both the U.S. and Europe [18]. In our analysis of general mortality patterns among the CD cohort reported elsewhere [12], we observed SMRs for all cancers combined and RSC were generally higher among blue collar workers, giving this variable the potential to confound exposure-response associations.

We categorized all exposure measures *a priori* into approximate quartiles based on the distribution of deaths from all cancer. The equal subgroup sizes approximately balance the precision of the risk estimates across subgroups; the use of the all cancer category standardizes comparability across cause of death categories and produces nearly equal subgroup sizes for many of the cause of death categories examined. We analyzed no alternative categorizations. For each cause of death, risk sets were explicitly constructed from the cohort data file with age as the primary time dimension, using the RISKSET program module in OCMAP-PLUS [19]. Risk sets were matched further on year of birth to control for cohort effects, and time-dependent exposures and the time-dependent variable, worker pay type, were evaluated for each individual at each event time they were at risk. Multiplicative relative risk models of the form $\lambda(t) = \lambda_0(t)\exp\{x(t)\beta\}$ were fit to the internal cohort rates [20,21], and the stratified conditional logistic regression programs in Stata [22] were used to estimate β from the explicitly constructed risk sets. For plants with less than 20 deaths for the causes of interest, the stratified exact conditional logistic regression program in LogXact was used to estimate β [23]. To parallel the descriptive SMR analysis of mortality in relation to exposure

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(described below), categorized forms of the covariates were considered. Demographic and exposure variables were first considered univariately as categorical variables to identify patterns of univariate associations with outcome variables and possible sparse data problems. Possible exposure-response associations were then evaluated with a forward stepwise approach to adjust for possible confounders. Effect modification was assessed if warranted by the main effects.

We assessed the statistical significance of each main effect (expressed as a global p-value) with a likelihood ratio statistic. For the exposure variables that exhibited a monotonic increasing or decreasing pattern in the parameter estimates, we conducted a test for linear trend (expressed as a trend p-value). All tests on RRs were done at the 0.05 significance level and no adjustment was made for multiple comparisons. All modeling was plant-specific to account for the marked heterogeneity in CD and VC exposures and other large disparities (e.g., vital records systems, time periods, culture, ethnicity, etc.) across the two U.S. and two European study plants. Models for liver cancer were limited by small numbers of deaths.

2.3.2. *Exposure-response based on external comparisons*

Mortality excesses and deficits in relation to CD and VC exposure levels were also determined via external mortality comparisons expressed as standardized mortality ratios (SMRs) along with their 95% confidence intervals (CI). The methods used to compute SMRs for the CD cohort study are described in detail elsewhere [12]. SMRs were computed for the categories of the CD and VC exposure measures used in the RR analysis described above. Person-year counts in the unexposed baseline categories included the observation time of workers prior to their first exposure. Statistically significant deviations of the SMRs below and above 1.00 were identified using Poisson probabilities [24]. All tests were done at the 0.05 significance level and no adjustment was made for multiple comparisons.

3. Results

Tables 4–8 show for plants L, M, P and G, respectively, the results of our exposure-response analyses based on internal and external comparisons. Results for the internal comparisons include for each category of the exposure measures considered, the number of observed deaths (cases) and associated non-cases summed across individual risk sets. The external comparisons include the number of person-years accumulated in each exposure category. For plant L (Table 4), none of the exposure measures was positively associated with mortality from all cancers combined or RSC using either internal or external comparisons. RRs fluctuate sporadically around 1.00 and the corresponding SMRs are consistently less than 1.00 and almost always statistically significant. For liver cancer, we observed elevated RRs in all non-baseline categories of each exposure measure. However, none of the RRs was statistically significant and there was no evidence of a positive association with any exposure measure. The elevated RRs result mainly from the exceedingly low death rates associated with the baseline categories of each measure, as reflected by the correspondingly low SMRs (i.e., the RR for a given non-baseline category is roughly related to the ratio of the corresponding SMR for that category to the SMR for the baseline category).

For plant M (Table 5), we observed a statistically significant positive association with CD_Dur and all cancers combined based on RRs and the associated non-baseline RRs were statistically significant (RRs = 1.53 (95% CI = 1.00–2.34) and 1.78 (95% CI = 1.11–2.84) for CD_Dur 10–19 and 20+ years, respectively, trend $p = 0.007$). However, as noted for liver cancer in Table 4, the elevated RRs and positive association with CD_Dur appear to be due mainly to an inordinately low death rate associated with the baseline category, as reflected by corresponding statistically significant SMR of 0.53 (95% CI = 0.41–0.67). In fact, both elevated RRs for CD_Dur arise as the ratio of death rates that are less than those of the corresponding external standard population (i.e., SMR = 0.85 and 0.97 for CD_Dur 10–19 and 20+ years, respectively). There is no evidence in Table 5 of a positive association with all cancers combined and the other exposure measures considered, and the corresponding SMRs are consistently less than 1.00. For RSC, we observed some limited evidence of a positive association with CD_AIE and CD_Cum along with a marginally statistically significant ($0.05 < p < 0.10$) trend test for CD_AIE, however, this appears again to be driven by inordinately low baseline death rates for both exposure measures as reflected by the statistically significant baseline SMRs (SMR for baseline CD_AIE = 0.47 (95% CI = 0.23–0.83) and SMR for baseline CD_Cum = 0.54 (95% CI = 0.29–0.90)).

For plants P and G (Tables 6 and 7), the evaluation of exposure-response was made more difficult by the smaller numbers of observed deaths, particularly for RSC. In plant P (Table 6), none of the exposure measures was positively associated with mortality from all cancers combined or RSC using either internal or external comparisons. We observed one statistically significant

Table 4
Exposure-response analysis for chloroprene and selected cancer sites by exposure metric, Louisville plant, relative risks (RR) and standardized mortality ratios (SMR)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR[d] (95% CI)	p-Value	Person-years[e]	SMR (95% CI)
All cancer combined						
CD_Dur						
<10	326	60363	1.00	Global = 0.71	131276	0.70** (0.63–0.78)
10–19	64	9559	1.06 (0.80–1.41)	Trend = 0.42	30404	0.68** (0.53–0.87)
20+	262	39856	1.07 (0.90–1.27)		36239	0.82** (0.72–0.93)
CD_AIE						
<3.6216	163	29840	1.00	Global = 0.27	69274	0.73** (0.62–0.83)
3.6216–8.1245	163	22373	1.19 (0.94–1.50)	Trend = 0.97	27933	0.88 (0.75–1.02)
8.1246–15.99	97	16147	0.93 (0.71–1.21)		28689	0.65** (0.53–0.79)
16.0+	229	40418	1.07 (0.86–1.32)		72023	0.72** (0.63–0.82)
CD_Cum						
<4.747	163	30338	1.00	Global = 0.35	68918	0.75** (0.64–0.87)
4.747–55.918	163	29222	0.98 (0.78–1.23)	Trend = 0.83	56737	0.71** (0.60–0.82)
55.919–164.052	163	24222	1.14 (0.91–1.43)		39840	0.79** (0.68–0.92)
164.053+	163	24996	0.93 (0.73–1.17)		32424	0.70** (0.60–0.82)
Respiratory system cancer						
CD_Dur						
<10	137	25995	1.00	Global = 0.98	131276	0.74** (0.62–0.87)
10–19	23	3806	0.98 (0.62–1.57)	Trend = 0.84	30404	0.66** (0.42–0.99)
20+	106	17174	0.97 (0.75–1.27)		36239	0.79* (0.65–0.96)
CD_AIE						
<3.6216	56	12642	1.00	Global = 0.06	69274	0.63** (0.48–0.82)
3.6216–8.1245	70	9812	1.34 (0.93–1.95)	Trend = 0.20	27933	0.90 (0.70–1.14)
8.1246–15.99	33	6950	0.88 (0.56–1.38)		28689	0.56** (0.38–0.78)
16.0+	107	17571	1.36 (0.97–1.91)		72023	0.83 (0.68–1.00)
CD_Cum						
<4.747	62	12961	1.00	Global = 0.07	68918	0.71** (0.55–0.91)
4.747–55.918	67	12656	1.00 (0.71–1.43)	Trend = 0.71	56737	0.71** (0.55–0.90)
55.919–164.052	77	10471	1.32 (0.94–1.88)		39840	0.92 (0.73–1.15)
164.053+	60	10887	0.85 (0.58–1.23)		32424	0.65** (0.50–0.84)
Liver cancer[f]						
CD_Dur						
<10	6	1500	1.00	Global = 0.24	131276	0.61 (0.22–1.32)
10–19	4	216	3.85 (0.76–17.09)	Trend = 0.36	30404	2.08 (0.57–5.33)
20+	7	965	1.75 (0.49–6.44)		36239	0.99 (0.40–2.04)
CD_AIE						
<3.6216	3	714	1.00	Global = 0.22	69274	0.62 (0.13–1.80)
3.6216–8.1245	7	568	3.81 (0.77–25.76)	Trend = 0.84	27933	1.73 (0.70–3.56)
8.1246–15.99	3	388	1.84 (0.22–15.74)		28689	0.94 (0.19–2.74)
16.0+	4	1011	1.31 (0.20–10.07)		72023	0.59 (0.16–1.52)
CD_Cum						
<4.747	2	744	1.00	Global = 0.17	68918	0.43 (0.05–1.55)
4.747–55.918	3	725	1.90 (0.21–23.81)	Trend = 0.09	56737	0.59 (0.12–1.74)
55.919–164.052	7	653	5.10 (0.88–54.64)		39840	1.62 (0.65–3.33)
164.053+	5	559	3.33 (0.48–39.26)		32424	1.00 (0.33–2.34)

[a] Categories based on approximate quartiles of all cancer deaths; decimal places of cutpoints reflect precision needed for computational purposes only and not precision of exposure assessment.

[b] Local county rates.

[c] The number of persons in decedent's risk set used in calculation of RR.

[d] Also adjusted for sex.

[e] The number of person-years used in calculation of SMR.

[f] Analyzed using LogXact.

* $p < 0.05$.

** $p < 0.01$.

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Table 5
Exposure-response analysis for chloroprene and selected cancer sites by exposure metric, Maydown plant, relative risks (RR) and standardized mortality ratios (SMR)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR[d] (95% CI)	p-Value	Person-years[e]	SMR (95% CI)
All cancers combined						
CD_Dur						
<10	66	9674	1.00	Global = 0.03	102413	0.53** (0.41–0.67)
10–19	35	2965	1.53* (1.00–2.34)	Trend = 0.007	17257	0.85 (0.59–1.18)
20+	27	2349	1.78* (1.11–2.84)		7366	0.97 (0.64–1.41)
CD_AIE						
<0.1538	43	5660	1.00	Global = 0.98	57453	0.54** (0.39–0.73)
0.1538–1.269	28	2931	1.02 (0.60–1.72)	Trend = 0.97	22489	0.83 (0.55–1.20)
1.270–1.69	36	3973	1.07 (0.67–1.71)		32973	0.70* (0.49–0.96)
1.70+	21	2424	0.95 (0.54–1.65)		14121	0.70 (0.43–1.07)
CD_Cum						
<0.0387	43	6062	1.00	Global = 0.92	63130	0.50** (0.36–0.67)
0.0387–6.7310	28	3266	1.12 (0.67–1.89)	Trend = 0.75	32527	0.74 (0.49–1.07)
6.7311–24.50	29	3065	0.94 (0.53–1.66)		19539	0.79 (0.53–1.13)
24.51+	28	2595	0.95 (0.53–1.70)		11840	0.85 (0.56–1.22)
Respiratory system cancer						
CD_Dur						
<10	28	3649	1.00	Global = 0.82	102413	0.73 (0.48–1.05)
10–19	12	1143	0.81 (0.36–1.79)	Trend = 0.84	17257	0.86 (0.44–1.50)
20+	8	992	1.17 (0.23–5.92)		7366	0.83 (0.36–1.64)
CD_AIE						
<0.1538	11	2180	1.00	Global = 0.08	57453	0.47** (0.23–0.83)
0.1538–1.269	12	1133	2.83* (1.09–7.38)	Trend = 0.09	22489	1.08 (0.56–1.89)
1.270–1.69	16	1522	2.63* (1.11–6.23)		32973	0.93 (0.53–1.51)
1.70+	9	949	2.23 (0.83–5.97)		14121	0.87 (0.40–1.65)
CD_Cum						
<0.0387	14	2300	1.00	Global = 0.39	63130	0.54* (0.29–0.90)
0.0387–6.7310	9	1263	1.65 (0.66–4.15)	Trend = 0.10	32527	0.74 (0.34–1.40)
6.7311–24.50	12	1181	1.89 (0.72–4.96)		19539	0.97 (0.50–1.69)
24.51+	13	1040	2.28 (0.86–6.01)		11840	1.13 (0.60–1.92)

[a] Categories based on approximate quartiles of all cancer deaths; decimal places of cutpoints reflect precision needed for computational purposes only and not precision of exposure assessment.

[b] National rates.

[c] The number of persons in decedent's risk set used in calculation of RR.

[d] Also adjusted for worker service type and duration of employment.

[e] The number of person-years used in calculation of SMR.

[*] $p < 0.05$.

[**] $p < 0.01$.

RR for all cancers combined in the second category of CD_AIE (RR = 4.76; 95% CI = 1.39–6.27); however, this appears to be an isolated finding. RRs for RSC were also elevated in all baseline categories of each exposure measure, again driven by the inordinately low baseline death rates (i.e., baseline SMRs for CD_Dur, CD_AIE and CD_Cum = 0.28 (95% CI = 0.03–1.00), 0.33 (95% CI = 0.09–0.85) and 0.40 (95% CI = 0.08–1.18), respectively. In plant G (Table 7), none of the exposure measures was positively associated with mortality from all cancers combined using either internal or external comparisons. There is some limited evidence of a positive association with CD_AIE and CD_Cum and RSC; however, the linear trends and the exposure category-specific RRs were not statistically significant. While the death rates for RSC associated with the baseline categories of CD_AIE and CD_Cum were not as low as those in the other plants, they were still about 25% less

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Table 6
Exposure-response analysis for chloroprene and selected cancer sites by exposure metric, Pontchartrain plant, relative risks (RR) and standardized mortality ratios (SMR)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR (95% CI)	*p*-Value	Person-years[d]	SMR (95% CI)
All cancers combined						
CD_Dur						
<10	15	2039	1.00	Global = 0.71	19067	0.75 (0.42–1.24)
10–19	12	2095	0.71 (0.32–1.58)	Trend = 0.56	7668	0.59 (0.31–1.03)
20+	7	1473	0.83 (0.27–2.53)		3926	0.57 (0.23–1.18)
CD_AIE						
<0.0017	17	2735	1.00	Global = 0.17	15858	0.55** (0.32–0.88)
0.0017–0.1329	4	298	4.76* (1.39–16.27)	Trend = 0.44	1574	2.76 (0.75–7.06)
0.1330–0.8174	7	1409	1.58 (0.57–4.37)		5522	0.76 (0.31–1.57)
0.8175+	6	1165	1.34 (0.49–3.65)		7707	0.69 (0.26–1.51)
CD_Cum						
<0.0193	15	1794	1.00	Global = 0.31	15354	0.75 (0.42–1.24)
0.0193–1.8944	6	1434	0.52 (0.20–1.37)	Trend = 0.91	6363	0.41* (0.15–0.90)
1.8945–16.1918	6	766	1.50 (0.55–4.11)		6027	1.07 (0.39–2.32)
16.1919+	7	1613	0.80 (0.29–2.16)		4916	0.61 (0.24–1.25)
Respiratory system cancer[e]						
CD_Dur						
<10	2	653	1.00	Global = 0.33	19067	0.28 (0.03–1.00)
10–19	7	799	3.08 (0.62–15.31)	Trend = 0.32	7668	0.85 (0.34–1.75)
20+	3	747	2.09 (0.26–16.85)		3926	0.60 (0.12–1.76)
CD_AIE						
<0.0017	4	932	1.00	Global = 0.25	15858	0.33* (0.09–0.85)
0.0017–0.1329	1	102	7.28 (0.09–167.13)	Trend = 0.14	1574	2.05 (0.05–11.44)
0.1330–0.8174	4	646	5.03 (0.59–58.02)		5522	1.11 (0.30–2.85)
0.8175+	3	519	3.50 (0.37–33.64)		7707	0.90 (0.19–2.62)
CD_Cum						
<0.0193	3	600	1.00	Global = 0.70	15354	0.40 (0.08–1.18)
0.0193–1.8944	3	468	1.60 (0.20–12.77)	Trend = 0.34	6363	0.52 (0.11–1.53)
1.8945–16.1918	2	322	2.90 (0.20–34.11)		6027	0.96 (0.12–3.48)
16.1919+	4	809	2.32 (0.30–21.83)		4916	0.85 (0.23–2.18)

[a] Categories based on approximate quartiles of all cancer deaths; decimal places of cutpoints reflect precision needed for computational purposes only and not precision of exposure assessment.
[b] Local county rates.
[c] The number of persons in decedent's risk set used in calculation of RR.
[d] The number of person-years used in calculation of SMR.
[e] Analyzed using LogXact.
[*] $p < 0.05$.
[**] $p < 0.01$.

than those in the external comparison populations (i.e., baseline SMRs for CD_AIE and CD_Cum were 0.76 and 0.72, respectively). As noted for the other plants, the low baseline rates at least partly explain the elevated RRs for many of the non-baseline categories.

Table 8 shows our exposure-response analyses for VC that was limited to plant L. For all cancers combined and RSC, deficits in deaths based on RRs and SMRs were observed in all exposure categories; many were statistically significant. Fifteen of the 17 liver cancer deaths in plant L occurred among unexposed workers; RRs and SMRs in the non-baseline categories were unremarkable.

While not shown, our analysis of mortality among plant L and M workers in relation to the four composite exposure measures, CDwVC_AIE, CDwVC_Cum, CDwoVC_AIE and CDwoVC_Cum, produced risk estimates similar to those based on the marginal CD exposure measures (i.e., exposure to CD regardless of VC exposure) and none of the composite measures revealed evidence of increasing cancer risks with increasing expo-

Table 7
Exposure-response analysis for chloroprene and selected cancer sites by exposure metric, Grenoble plant, relative risks (RR) and standardized mortality ratios (SMR)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR (95% CI)	p-Value	Person-years[d]	SMR (95% CI)
All cancers combined						
CD_Dur						
<10	9	934	1.00	Global = 0.43	9813	0.63 (0.29–1.20)
10–19	5	819	0.60 (0.20–1.80)	Trend = 0.82	4900	0.40* (0.13–0.94)
20+	6	585	1.32 (0.43–4.08)		2344	0.83 (0.31–1.82)
CD_AIE						
<0.0051	5	551	1.00	Global = 0.99	3393	0.60 (0.20–1.41)
0.0051–0.0880	5	477	1.21 (0.35–4.22)	Trend = 0.95	4694	0.55 (0.18–1.28)
0.0881–1.2246	5	616	1.21 (0.34–4.40)		3189	0.67 (0.22–1.56)
1.2247+	5	694	1.04 (0.29–3.76)		5781	0.56 (0.18–1.31)
CD_Cum						
<0.0497	5	584	1.00	Global = 0.92	4267	0.56 (0.18–1.31)
0.0497–1.4149	5	532	1.16 (0.33–4.08)	Trend = 0.57	4749	0.53 (0.17–1.23)
1.4150–23.9306	5	683	1.07 (0.30–3.84)		4619	0.55 (0.18–1.28)
23.9307+	5	539	1.54 (0.43–5.60)		3422	0.79 (0.26–1.85)
Respiratory system cancer[e]						
CD_Dur						
<10	3	500	1.00	Global = 0.70	9813	0.64 (0.13–1.87)
10–19	5	448	1.84 (0.44–7.77)	Trend = 0.58	4900	1.16 (0.38–2.71)
20+	2	272	1.46 (0.22–9.61)		2344	0.71 (0.09–2.58)
CD_AIE						
<0.0051	2	294	1.00	Global = 0.45	3393	0.76 (0.09–2.80)
0.0051–0.0880	1	260	0.63 (0.06–6.96)	Trend = 0.19	4694	0.32 (0.01–1.76)
0.0881–1.2246	3	325	2.29 (0.22–34.16)		3189	1.06 (0.22–3.09)
1.2247+	4	341	2.99 (0.36–41.87)		5781	1.25 (0.34–3.19)
CD_Cum						
<0.0497	2	312	1.00	Global = 0.40	4267	0.72 (0.09–2.61)
0.0497–1.4149	1	288	0.61 (0.05–6.76)	Trend = 0.17	4749	0.30 (0.01–1.69)
1.4150–23.9306	4	356	2.87 (0.35–39.70)		4619	1.19 (0.32–3.04)
23.9307+	3	264	3.14 (0.30–47.99)		3422	1.28 (0.26–3.73)

[a] Categories based on approximate quartiles of all cancer deaths; decimal places of cutpoints reflect precision needed for computational purposes only and not precision of exposure assessment.

[b] National rates.

[c] The number of persons in decedent's risk set used in calculation of RR.

[d] The number of person-years used in calculation of SMR.

[e] Analyzed using LogXact.

[*] $p < 0.05$.

sure. Also not shown, our analyses of RSC and liver cancer mortality in relation to 5 and 15 year lagged measures of CD_Dur, CD_AIE and CD_Cum did not materially alter the findings from the unlagged analyses. Likewise, for RSC and liver cancer, we observed no evidence of an association with time since first exposure to CD or to VC (not shown).

We attempted to roughly additionally adjust RRs for RSC for potential confounding by smoking, via the surrogate variable worker pay type (blue/white collar). Because of the small number of white-collar RSC deaths among the white-collar workers in each plant (3, 0, 2 and 0 white collar RSC deaths for plants L, M, P and G, respectively), the adjusted analysis was limited to plant L. For all cancers combined, additional adjustment for potential confounding by worker pay type had little effect on the all cancer RRs for either CD_AIE or CD_Cum. For plant P, additionally adjusted RRs were higher for all exposure categories of both measures, suggesting negative confounding by smoking; for plant G,

Table 8
Exposure-response analysis for vinyl chloride monomer and selected cancer sites by exposure metric, Louisville plant, relative risks (RR) and standardized mortality ratios (SMR)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR[d] (95% CI)	*p*-Value	Person-years[e]	SMR (95% CI)
All cancers combined						
VC_Dur						
Unexposed	524	77268	1.00	Global = 0.0002	147518	0.80** (0.73–0.87)
>0–5	71	17509	0.66* (0.52–0.84)	Trend = 0.0001	31911	0.58** (0.45–0.73)
5–9	9	2444	0.78 (0.55–1.11)		6122	0.47* (0.21–0.88)
10+	48	11557	0.50* (0.29–0.85)		12369	0.60** (0.18–0.61)
VCM_AIE						
Unexposed	524	77268	1.00	Global = 0.0004	147518	0.80** (0.73–0.87)
>0–0.27	32	6335	0.80 (0.56–1.15)	Trend = 0.0001	10880	0.71 (0.49–1.00)
0.28–1.75	34	9312	0.59* (0.41–0.83)		14543	0.52** (0.36–0.73)
1.751–2.99	15	4087	0.56* (0.35–0.87)		5768	0.46** (0.26–0.76)
3.0+	47	11776	0.70* (0.51–0.97)		19210	0.47** (0.35–0.63)
VCM_Cum						
Unexposed	524	77268	1.00	Global = 0.0004	147518	0.80** (0.73–0.87)
>0–0.4476	32	7057	0.72 (0.50–1.03)	Trend < 0.0001	14506	0.63** (0.43–0.89)
0.4477–1.9482	32	6747	0.82 (0.57–1.18)		11583	0.58** (0.39–0.81)
1.9483–14.5832	32	9578	0.57* (0.40–0.82)		14267	0.44** (0.30–0.62)
14.5833+	32	8128	0.60* (0.42–0.86)		10045	0.53** (0.36–0.75)
Respiratory system cancer						
VC_Dur						
Unexposed	232	33132	1.00	Global < 0.0001	147518	0.89 (0.78–1.02)
>0–5	20	8732	0.38* (0.24–0.59)	Trend < 0.0001	31911	0.38** (0.23–0.59)
5–9	2	3313	0.48* (0.25–0.90)		6122	0.25* (0.03–0.89)
10+	12	1798	0.15* (0.04–0.60)		12369	0.35** (0.18–0.61)
VCM_AIE						
Unexposed	232	33132	1.00	Global < 0.0001	147518	0.89 (0.78–1.02)
>0–0.27	12	2743	0.64 (0.35-1.15)	Trend < 0.0001	10880	0.62 (0.31–1.08)
0.28–1.75	6	4035	0.22* (0.10–0.50)		14543	0.22** (0.08–0.47)
1.751–2.99	3	2443	0.23* (0.09–0.62)		5768	0.22** (0.05–0.65)
3.0+	13	4622	0.41* (0.23–0.73)		19210	0.31** (0.16–0.53)
VCM_Cum						
Unexposed	232	33132	1.00	Global < 0.0001	147518	0.89 (0.78–1.02)
>0–0.4476	13	3009	0.64 (0.36–1.12)	Trend < 0.0001	14506	0.60 (0.32–1.02)
0.4477–1.9482	8	2964	0.42* (0.21–0.86)		11583	0.34** (0.15–0.67)
1.9483–14.5832	6	4232	0.22* (0.10–0.49)		14267	0.19** (0.07–0.42)
14.5833+	7	3638	0.27* (0.13–0.58)		10045	0.27** (0.11–0.57)
Liver cancer[f]						
VC_Dur						
Unexposed	15	1952	1.00	Global = 0.24	147518	1.07 (0.60–1.77)
>0–5	1	407	2.49[g] (0.41–∞)	Trend = 0.23	31911	0.37 (0.01–2.08)
5–9	1	61	0.69[g] (0.02-∞)		6122	2.38 (0.06–13.29)
10+	0	261	3.96[g] (0.10-∞)		12369	– (0–2.05)
VCM_AIE						
Unexposed	15	1952	1.00	Global = 0.46	147518	1.07 (0.60–1.77)
>0–0.27	1	139	1.04 (0.02–7.04)	Trend = 0.20	10880	0.98 (0.03–5.48)
0.28–1.75	0	223	0.49[g] (−∞, 2.98)		14543	– (0–2.59)
1.751+	1	367	0.43 (0.01–2.92)		24978	0.37 (0.01–2.04)
VCM_Cum						
Unexposed	15	1952	1.00	Global = 0.54	147518	1.07 (0.60–1.77)

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Table 8 (*Continued*)

Metric[a]	Deaths	Internal rate analysis			External rate analysis[b]	
		Noncases[c]	RR[d] (95% CI)	*p*-Value	Person-years[e]	SMR (95% CI)
>0–0.4476	0	164	0.66[g] (-∞,4.00)	Trend = 0.31	14506	–(0–3.25)
0.4477–1.9482	1	168	0.97 (0.02–6.67)		11583	0.86 (0.02–4.79)
1.9483+	1	397	0.38 (0.01–2.58)		24312	0.36 (0.01–1.99)

[a] Categories based on approximate quartiles of all cancer deaths; decimal places of cutpoints reflect precision needed for computational purposes only and not precision of exposure assessment.

[b] Local county rates.

[c] The number of persons in decedent's risk set used in calculation of RR.

[d] Also adjusted for sex.

[e] The number of person-years used in calculation of SMR.

[f] Analyzed using LogXact.

[g] Median-unbiased estimate.

[*] $p < 0.05$.

[**] $p < 0.01$.

the opposite pattern emerged, suggesting positive confounding by smoking. In neither case; however, did the additional adjustment for worker pay type materially alter the unadjusted findings of no association with either exposure measure. In plant L, additional adjustment for pay type had little effect on the RSC RRs for CD_AIE or CD_Cum (data not shown).

4. Discussion and conclusions

As described in detail in our analysis of general mortality patterns [12], 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 Bofetta [10] and Acquavella and Leonard [11] that have limited the interpretation of findings from the five available cohort studies [4–8]. A particular strength of our study was the rigorous, chemical process-based exposure reconstruction for chloroprene and vinyl chloride conducted by Esmen et al. [13–15] and Hall et al. [16] that enable us to examine mortality from all cancers combined and from the *a priori* sites of interest, lung and liver cancer, in relation to several quantitative measures of CD and/or VC exposure.

Another strength of our exposure-response analyses was the use of national and local county mortality comparisons and robust statistical modeling of internal cohort rates. The strengths of the internal study group comparison are that it will usually reduce the healthy worker effect [25], and it allows direct comparison of relative risk across strata. However, internal comparisons can be unstable when the study population is small and/or the disease under study is rare (producing wider confidence limits), and may be misleading if workers included in the baseline category (i.e., least exposed) have different underlying cancer risks than workers in the exposed groups. On the other hand, external comparisons based on regional rates have the strengths of being able to adjust for geographic variability in social, cultural and economic factors related to disease [26] and are generally very stable. The disadvantages of the external comparison group are an inability to adjust for the healthy worker effect and a difficulty in comparing standardized mortality ratios between groups when their confounder distributions differ [27].

When we used external comparisons of the surrounding county populations of each study plant, we observed many deficits in death from all cancers combined, RSC and liver cancer that were often largest among the unexposed workers, but still present among workers in the non-baseline exposure categories. This pattern of findings by exposure category in the external population-based SMRs led to elevated relative rates (RRs) of disease when rates for non-baseline categories were compared to the baseline (unexposed) rates. For example, for RSC by CD_AIE in plant P (Table 6), an RR of 3.50 (95%CI = 0.37–33.64) for the highest exposure category (0.8175+ ppm), or an apparent 3.5-fold excess, results because a small 10% deficit in deaths in the highest exposure category (SMR = 0.90; 95% CI = 0.19–2.62) is essentially being compared to a exceedingly large, statistically significant 67% deficit in the baseline category (SMR = 0.33; 95%CI = 0.09–0.85). Thus, the question arises as to whether the ratio of small to large deficits in deaths (essentially, but not exactly, what is expressed

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via RRs) should be interpreted as a meaningful "excess" in deaths. This enigmatic feature of exposure-response analyses created by inordinately low baseline rates has been observed in other major occupational cohort studies, such as the cohort studies of formaldehyde [28–30] and acrylonitrile [31] workers conducted by the National Cancer Institute, and has stimulated reanalyses and reinterpretation of the NCI cohort data [32–34]. Although RRs for the cancer sites and exposure measures considered were elevated in many non-baseline categories due to the low baseline rates, we observed no consistent evidence that RRs were positively associated with increasing exposure in any of the study plants.

There are at least two possible explanations for the large differences in the cancer relative risks in the CD cohort when internal or external comparison rates are used. The first is that internal comparisons produce more valid results because selection bias stemming from the "healthy worker effect" can reduce the putative effect of high exposure to CD (or VC) when external comparison rates are used. The healthy worker effect is evident in this population by the low relative risks for all causes of death for CD-exposed (SMR = 0.71; 95% CI = 0.69–0.73) and CD-unexposed workers (SMR = 0.88; 95% CI = 0.69–1.10). However, the selection for workers who are healthy at time of hire is usually more relevant for cardiovascular and nonmalignant respiratory diseases than lung cancer, which has a relatively sudden onset, short survival time and high case-fatality rate [35].

A second explanation is that the external comparisons produce more valid results because the unexposed group has a different underlying cancer risk than the exposed group. As shown above, the risk in the highest exposure category when internal comparisons are used may simply be the result of an unusually low lung cancer death rate among workers in the unexposed baseline category. In fact, had the death rates for all cancer, RSC or liver cancer among the unexposed workers been closer to or equal to those of the general regional populations from which the four plant workforces were drawn, the internal RRs calculated for quartiles of CD (or VC) exposure across the total cohort would probably have been uniformly near or less than 1.00.

The very low SMRs for all cancer, lung and liver cancer, especially among unexposed workers, are puzzling given that we used regional standard population rates. Although a small percentage of deaths (estimated at about 5%) may have been missed among transferees in plant P and among subjects who emigrated in plants M and G [12], under-ascertainment of deaths is an unlikely explanation for these low SMRs. Also, because regional rates can help adjust for the social, cultural and economic factors related to diseases such as lung cancer, and even help to adjust for geographic variability in tobacco use [26], it is difficult to postulate what non-occupational factors may have had such a profound influence on the cancer mortality experience of this cohort. It was hoped that our additional model adjustment for worker pay type, a correlate of education/socioeconomic status, and thus, smoking history, might help to explain the inordinately low and often statistically significant baseline SMRs for all cancers combined and RSC found for each study plant in the baseline categories of each exposure measure. For example, if subjects at risk in the baseline exposure categories were lighter smokers than subjects at risk in the non-baseline categories, this would negatively confound baseline SMRs for RSC relative to non-baseline SMRs and positively confound the corresponding non-baseline RRs. To a lesser extent, the same pattern could occur for all cancers combined. However, with the possible exception of plant G, where pay type-adjusted RRs for all cancers combined were uniformly less, suggesting positive confounding by smoking, the additional adjustment for worker pay type did not materially alter the pattern of RRs for all cancer and RSC found in the unadjusted models.

With the possible exception of liver cancer in plant L (based on small numbers of death), chance alone does not appear to be an explanation for the cancer deficits observed among unexposed workers in this study. Our U.S. and regional rate-based SMRs (and RRs) for all cancers and RSC in all categories of the CD exposures examined were based on sufficiently large numbers of observed deaths to provide stable risk estimates, and deficits were generally consistent across the CD exposure categories considered. Also, the general quality of the follow-up and cause of death ascertainment in this study rule out under-ascertainment of cancer deaths as a reason for the deficits. Given the absence of a viable explanation derived from the available study data, what remains is the possibility that some heretofore unknown selection factors for low cancer incidence or mortality were operating on the unexposed subjects in this cohort, or that some type of protective effect for lung cancer arose from a particular exposure or combination of exposures encountered at the study plants. Without further formal investigation of this phenomenon in the CD cohort, the reason(s) for the marked deficits in cancer in unexposed workers will remain unknown.

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

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evaluation. A full account of our evaluation of angiosarcoma was provided in our companion paper [12]. In brief, 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. These limitations notwithstanding, "angiosarcoma of the liver" was not mentioned on any death certificates available for our review.

In summary, our analysis of the cancer mortality experience of the CD cohort provides no evidence that exposure to CD or VC, at the levels encountered in the four study plants, increases the risk of death from all cancers or the sites of *a priori* interest, lung (included within the broader category respiratory system cancer) and liver (categorized as "cancer of the biliary passages and liver"). Our findings based on external comparisons using regional rates produced exposure category-specific risks very different than those based on internal rates due largely to inordinately low death rates among workers in the unexposed categories. We conclude that chance or selection bias in the form of the healthy worker effect were unlikely explanations for these differences. Further investigation of the CD cohort may help to explain the reasons for the differences in risk estimates based on internal and external rates.

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