Coronary Artery Disease and Cancer Mortality in a Cohort of Workers Exposed to Vinyl Chloride, Carbon Disulfide, Rotating Shift Work, and *o*-Toluidine at a Chemical Manufacturing Plant

Tania Carreón, PhD,[1]* Misty J. Hein, PhD,[1] Kevin W. Hanley, MSPH, CIH, REHS/RS,[1] Susan M. Viet, PhD, CIH,[2] and Avima M. Ruder, PhD[1]

Background *We updated through 2007 the mortality experience of 1,874 workers employed at a New York State chemical manufacturing plant between 1946 and 2006.*
Methods *Reassessed exposures to vinyl chloride, carbon disulfide, and shift work and categories of o-toluidine exposure were based on year, department and job title. Standardized mortality ratios (SMR) compared mortality to that of the US population. Internal comparisons used directly standardized rate ratios.*
Results *Hepatobiliary cancer mortality was elevated among workers ever exposed to vinyl chloride (SMR = 3.80, 95% confidence interval 1.89–6.80); directly standardized rates increased with increasing vinyl chloride exposure duration. No increase in non-Hodgkin lymphoma mortality was observed with vinyl chloride and shift work exposures. Internal comparisons showed increased coronary artery disease mortality among long-term workers exposed to carbon disulfide and shift work for 4 years or more.*
Conclusions *Excess coronary artery disease mortality confirms earlier results; further investigation is needed to understand risk factors.* Am. J. Ind. Med. 57:398–411, 2014.

KEY WORDS: cohort mortality; chemical manufacturing; vinyl chloride; carbon disulfide; o-toluidine; shift work; cancer; coronary artery disease

INTRODUCTION

Workers at a rubber and plastic chemical manufacturing plant in New York State have been studied repeatedly to evaluate the effects of occupational exposures [Carreón et al., 2010; Nicholson et al., 1975, 1984; Oliver and Weber, 1984; Prince et al., 2000; Ward et al., 1991, 1996]. The facility opened in 1946 for production of vinyl chloride monomer and polyvinyl chloride (PVC), and expanded in 1951, increasing the number of hourly employees, polymerization reaction vessels and monomer reactors. In 1960, on-site production of vinyl chloride monomer ceased, and vinyl chloride was received in tank cars for synthesis of PVC which continued until about 1996. Beginning in 1957, the plant made an antioxidant used in tire manufacturing using *o*-toluidine, aniline, hydroquinone, and toluene. The plant also produced a family of accelerators used in the manufacture of rubber from the mid-1950s until 1970, and one rubber accelerator from 1970 to 1994 using carbon disulfide, sulfur, aniline, benzothiazole, and nitrobenzene [Hanley et al., 2012; Nicholson et al., 1975]. Two departments have been the main

[1]Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio
[2]Westat, Rockville, Maryland
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*Correspondence to: Dr. Tania Carreón, PhD, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, Mailstop R-15, Cincinnati, OH 45226. E-mail: tcarreonvalencia@cdc.gov

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focus of previous studies, the PVC, Vinyl department and the Rubber Chemicals department; both were physically located on the same industrial site but in different buildings with mostly separate work forces.

In the 1970s and the 1980s, Nicholson et al. [1975, 1984] evaluated mortality among 296 workers exposed to vinyl chloride at this plant for at least 5 years. Although the population studied was relatively young, excess risk of all-cancer mortality was reported [standardized mortality ratio (SMR) = 1.77 ($P < 0.05$)]. Twenty-one deaths were due to cardiovascular diseases (SMR = 1.06) and six to hepatobiliary cancer (SMR = 31.58, $P < 0.001$).

In 1980, Oliver and Weber [1984] conducted a cross-sectional study of chest pain among 89 workers employed in the Rubber Chemicals department and exposed to, among other agents, carbon disulfide, hydrogen sulphide, *o*-toluidine, aniline, and nitrobenzene. The control group included 65 employees working in PVC production. The results showed an association between chest pain and angina and current employment in the Rubber Chemicals department, after controlling for age and cigarette smoking. The association was not dependent on duration of exposure; however, small numbers did not allow testing for longer latency nor assessing independently the possible effects of different exposures.

In 1988, the union representing workers at the plant requested that the National Institute for Occupational Safety and Health (NIOSH) investigate an apparent cluster of bladder cancer cases. Ward et al. [1991] investigated bladder cancer incidence among 1,749 workers employed at the plant from 1946 to 1988. Thirteen bladder cancer cases were observed, with only 3.61 expected, based on rates in New York State (excluding New York City) [standardized incidence ratio (SIR) = 3.6, 90% confidence interval (CI) 2.13–5.73]. Seven cases occurred among employees working in the Rubber Chemicals department.

Prince et al. [2000] conducted a retrospective mortality study of the same cohort of workers studied by Ward et al., to investigate whether ischemic heart disease was elevated among workers in the Rubber Chemicals department, since the union had observed an elevated number of heart attacks, coronary by-pass operations and elevated cholesterol levels among its members. The cohort was followed through December 31, 1994. Mortality was compared to population rates in the United States and to local county rates. Excess mortality for ischemic heart disease was found among workers in the Rubber Chemicals department compared to that of the US population (SMR 1.51, 95% CI: 0.94–2.3); the excess was most pronounced at younger ages (<50 years, SMR = 2.4, 95% CI: 1.1–4.6).

The purpose of this report is to update the NIOSH cohort [Prince et al., 2000] adding 13 years of vital status follow-up and expanding the exposure assessment. In addition to documented exposures to *o*-toluidine, aniline, and nitrobenzene, exposures at the plant included vinyl chloride, carbon disulfide and rotating shift work [Hanley et al., 2012]; therefore, we evaluated the effect of these exposures with outcomes selected *a priori*. We selected hepatobiliary cancers (cancers of the biliary passages, liver, and gallbladder) as the outcome of interest for vinyl chloride exposure; for carbon disulfide exposure, we investigated coronary artery disease; for shift work, coronary artery disease, colorectal, prostate, and breast cancers and non-Hodgkin lymphoma; and for *o*-toluidine, bladder cancer. For vinyl chloride exposure, we additionally considered non-Hodgkin lymphoma and pancreatic and brain cancers.

METHODS

Cohort Definition

The original cohort included 1,749 workers employed at the plant for 1 day or more from 1946 to 1988. For earlier studies [Ward et al., 1991; Prince et al., 2000], personnel records (as of August 1988) were microfilmed for all workers, including office and salaried personnel. Work history data (begin and end dates, department and job title) were coded and entered into an electronic database. For the update, a company-provided electronic work history database (complete as of April 2006) was merged with the existing NIOSH database. The cohort was expanded to include workers hired after the original cutoff date of August 1, 1988, and work history records were updated for workers who were actively employed on that date. When discrepancies between the two sources were identified, the data were manually reviewed and compared with existing microfilmed records. If no microfilm was available, data most recently provided were used.

Records were available for 1,887 workers. Ten workers with no work histories (three from the original cohort and seven hired after August 1, 1988) were excluded along with two workers missing date of birth. A worker who died in 1959 was also excluded from analyses because comparison mortality rate files began on January 1, 1960. Consequently, analyses of the expanded cohort included 1,874 workers employed for 1 day or more at the plant between 1946 and 2006. This number includes eighteen workers inadvertently excluded from previous analyses and 111 workers hired after August 1, 1988.

This study was approved by the NIOSH Institutional Review Board. As a records study, it was exempted from informed consent requirements.

Vital Status Ascertainment

Vital status was ascertained through 2007 by linking with records of the National Center for Health Statistics' National Death Index [Cowper et al., 2002]. Causes of death were

obtained by National Death Index Plus, and a special request was submitted to the Florida Department of Health for deaths that occurred in that state. The National Death Index is reported to have the highest sensitivity of all major U.S. mortality databases and high accuracy in cause of death coding [Sathiakumar et al., 1998; Cowper et al., 2002].

Causes of death were coded to the revision of the International Classification of Diseases in effect at the time of death. Cohort members with a valid Social Security Number who were known to be alive as of January 1, 1979 (the date from which death records are available at the National Death Index) and not found to be deceased, were considered alive.

Exposure Assessment

Since only scant legacy data were available for vinyl chloride in the electronic industrial hygiene sampling database provided by the company, we considered any worker assigned to the PVC, Vinyl department prior to 1995 exposed to vinyl chloride. In addition, several jobs assigned to other departments (i.e., Shipping, Packaging & Warehouse, Rubber Compounds, Quality Control, Laboratory, and Research & Development) were considered exposed to vinyl chloride (see Hanley et al. [2012] for the rationale), as were multiple jobs assigned to departments whose work was conducted throughout the plant (i.e., Maintenance, Yard/Janitor). In addition, guards, nurses, engineers, yardmen, co-op employees, workers on temporary assignment from company headquarters, and other jobs with no assigned department prior to 1995 were considered exposed to vinyl chloride, because they moved around the plant.

On April 5, 1974, the Occupational Safety and Health Administration (OSHA) issued an emergency temporary standard reducing the Permissible Exposure Limit (PEL) ceiling for vinyl chloride from 500 to 50 ppm, and on October 4, 1974, OSHA issued a permanent standard reducing the 8-hr PEL to 1 ppm; however, the emergency temporary standard remained in effect until April 1, 1975 [Levine et al., 1975]. According to Union and Company officials, the ambient concentrations in the PVC, Vinyl department averaged 53 ppm vinyl chloride in 1973 and 40–50 ppm in 1974 until late 1974, when they dropped to less than 10 ppm. Because of the presumptive change in exposure levels at the plant, we additionally considered exposures to vinyl chloride occurring prior to January 1, 1975 in separate analyses.

We considered any worker assigned to the Rubber Chemicals department from 1954 to 1994 as exposed to carbon disulfide. Multiple jobs assigned to other departments (i.e., Shipping, Packaging & Warehouse, Quality Control, Laboratory and Research & Development; see Hanley et al. [2012] for the rationale) and departments whose work was conducted throughout the plant (i.e., Maintenance, Yard/Janitor) were also considered exposed to carbon disulfide. In addition, we considered some jobs in the PVC, Vinyl department as exposed to carbon disulfide when the job title specifically indicated work in the Rubber Chemicals department. Furthermore guards, nurses, engineers, yardmen, co-op employees, workers on temporary assignment from company headquarters, and other jobs with no assigned department from 1954 to 1994 were considered exposed to carbon disulfide, because they moved around the plant. We selected these years, departments and jobs based on reported use of carbon disulfide at the plant and partial industrial hygiene data.

The plant operated 24 hr a day, 7 days a week, and numerous workers were in a forward rotating shift work schedule. For example, each of four groups worked Wednesday to Tuesday evening shift; off 2 days; Friday to Thursday day shift; off 2 days; Saturday/Sunday to Friday/Saturday overnight shift; off 4 days, on a rotating basis. Maintenance workers worked only on the day shift, unless called in for emergency repair work. Jobs considered exposed to rotating shift work in the PVC, Vinyl department included area manager, various chemical operators, general utility operator, various production operators, foreman, and supervisor; Rubber Chemicals department jobs included area manager, antioxidant packaging operator, various chemical operators, various production operators, foreman, and supervisor.

For *o*-toluidine, we developed an exposure classification scheme that incorporated year, department and job title. The exposure categories include: definitely exposed moderate/high and regularly, probably exposed low and regularly, probably exposed low and irregularly/occasionally, and probably not exposed. These categories broadly account for intensity and frequency of exposure. A detailed description of the methods used to develop these categories and examples of jobs assigned to each category are provided by Hanley et al. [2012].

Workers were considered unexposed to the agents analyzed in this study during employment at other company locations and after separation from the company.

Statistical Analysis

We used the NIOSH Life Table Analysis System (LTAS.NET Version 3.0.4) [Schubauer-Berigan et al., 2011] to conduct the statistical analyses. Standardized mortality ratios, adjusted for gender, race, age (in 5-year categories), and calendar year (in 5-year categories), were based on US mortality rates (beginning in 1960) for 119 underlying cause of death categories [Robinson et al., 2006]. Additional analyses used New York State (excluding New York City) underlying cause mortality rates or US multiple cause of death rates (i.e., considering all causes of death listed on the death certificate). For all analyses, person-years-at-risk began on the later of January 1, 1960 (the rate file begin date) or the

date of first employment at the plant. Person-years-at-risk ended at the earliest of the date of death (for deceased cohort members), the date last observed (for cohort members lost to follow-up), or December 31, 2007. Estimated 95% confidence intervals (CIs) for the SMRs were based on the Poisson distribution. Life table analyses were conducted for the total cohort and separately for those employed less than 90 days and 90 days or more.

We used directly standardized rate ratios (SRR) for internal analyses with 95% CIs estimated using approximate methods [Rothman and Greenland, 1998]. We conducted linear trend tests using the Rothman trend test [Rothman and Greenland, 1998] for all *a priori* outcomes using quartiles of employment duration (or duration of exposure to vinyl chloride, carbon disulfide, and/or shift work) defined by the distribution of the metric among decedents. Cohort studies have shown that the average latency between initial vinyl chloride exposure and liver cancer diagnosis is approximately 22 years [Lelbach, 1996]. Consequently, we allowed for varying periods of cancer induction/latency by lagging exposure duration by 20 years for hepatobiliary cancer and by 10 and 20 years for other cancer outcomes.

Smoking Adjustment

Selected results for coronary artery disease mortality were indirectly adjusted for cigarette smoking [Axelson and Steenland, 1988], using three sources of cohort smoking data (described below), published US smoking rates among men in 1987 (the median year of the available cohort smoking data) [National Center for Health Statistics, 1988], and rate ratios for coronary artery disease mortality and smoking among men [Thun et al., 2000]. To incorporate uncertainty into the adjustment, we used Monte Carlo sensitivity analyses that resulted in 95% Monte Carlo limits for the smoking bias factor and subsequent smoking-adjusted SMRs and SRRs [Steenland and Greenland, 2004].

Tobacco smoking data were available for a subset of the cohort from three sources:

(1) Company medical records for a 5% random sample of current and former workers collected in 1989 (n = 143) [Ward et al., 1991].
(2) Completed questionnaires (n = 98) from then current workers in the Rubber Chemicals (n = 64) and PVC, Vinyl (n = 52) departments who participated in a biomonitoring study in 1990 [Ward et al., 1996].
(3) Company historical medical records for a non-random subset of current and former workers collected by NIOSH in 2006 (n = 167).

These sources captured varying information regarding smoking; however, all provided, at a minimum, smoking status at the time the information was obtained from the workers. When all three sources were considered, 18% of cohort members had smoking data; however, the indirect adjustment was repeated using only data from the first source since the other two sources did not constitute random samples.

RESULTS

The cohort of 1,874 workers was followed through 2007 for a total of 59,966 person-years-at-risk (mean 32 years; Table I). A majority of workers (1,739) were men. As of December 31, 2007, 76% were still alive (median age 58 years), 24% were deceased (median age at death 64 years), and 2% had been lost to follow up (median age 27 years). Seventy eight percent of the workers were considered ever exposed ($\geq$1 day) to vinyl chloride, and 58% ever exposed ($\geq$1 day) to vinyl chloride in 1974 or earlier. Sixty-seven percent of workers were classified as ever exposed ($\geq$1 day) to carbon disulfide, and a larger percentage (77%) had performed some shift work ($\geq$1 day). Exposure durations ranged from less than 1 year to 40 years or longer. For *o*-toluidine, 69% had ever been exposed ($\geq$1 day), with 49% considered to be definitely exposed with moderate to high and regular exposure.

Observed causes of death, corresponding SMRs based on US rates and 95% CIs are presented in Table II, overall and by duration of employment. Among all workers combined, all-cause and all-cancer mortality were not elevated, but excess mortality was observed for the following *a priori* causes of death: hepatobiliary cancers, non-Hodgkin lymphoma and coronary artery disease (in addition to diseases of the heart). No other cause of death showed a statistically significant excess, but reduced risks were observed for intestinal cancer (also an *a priori* cause) and transportation injuries.

Among short-term workers (employed less than 90 days), all-cause mortality was elevated, largely due to increased mortality from diseases of the heart. Mortality due to tuberculosis and human immunodeficiency virus (HIV)-related disease were also elevated. Among long-term workers (employed 90 days or more), hepatobiliary cancer mortality remained elevated; non-statistically significant elevations were observed for coronary artery disease and non-Hodgkin lymphoma.

Similar results were observed among men (not shown); the results for women were largely uninformative (12 deaths) and are not shown. Similar results were observed when we used New York State (excluding New York City) mortality rates (results not shown). When we used multiple cause of death US rates, results (not shown) were similar to those based on underlying cause of death US rates, but excess mortality was observed for conduction disorder (an impairment of transmission of the cardiac electrical impulse; 118 observed deaths, SMR = 1.43, 95% CI: 1.18–1.71).

TABLE I. Demographic and Employment Characteristics of Workers Employed at a Chemical Manufacturing Plant

Characteristic	No. (%)	Median (range)
Total workers[a]	1,874	
From original study	1,431 (76%)	
From original study with work history updated after 8/1/1988	314 (17%)	
Missed from original study[b]	18 (1%)	
Hired after 8/1/1988	111 (6%)	
Vital status as of 12/31/2007		
Alive	1,382 (74%)	
Dead	443 (24%)	
Unknown (considered alive until the date lost to follow-up)	49 (2%)	
Gender, race		
Female, white	70 (4%)	
Female, other than white	16 (1%)	
Female, race unknown[c]	49 (3%)	
Male, white	712 (38%)	
Male, other than white	61 (3%)	
Male, race unknown[c]	966 (52%)	
Person-years at-risk	59,966	
Age at first employment (years)		23 (17–65)
Age at death, among deceased (years)		64 (20–97)
Age at date last observed, among alive (years)		58 (28–93)
Duration of employment (years)		1.6 (0.005–46)
Active at work history end (on 04/27/2006)	73 (4%)	
Duration (years) of vinyl chloride exposure[d]		1.5 (0.003–43)
None	416 (22%)	
>0–<1 year	635 (34%)	
1–<5 years	327 (17%)	
5–<10 years	121 (6%)	
10+ years	375 (20%)	
Duration (years) of vinyl chloride exposure in 1974 or earlier[d]		1.3 (0.003–41)
None	788 (42%)	
>0–<1 year	482 (26%)	
1–<5 years	255 (14%)	
5–<10 years	106 (6%)	
10+ years	243 (13%)	
Duration (years) of carbon disulfide exposure[d]		1.2 (0.003–40)
None	615 (33%)	
>0–<1 year	587 (31%)	
1–<5 years	265 (14%)	
5–<10 years	122 (7%)	
10+ years	285 (15%)	
Duration (years) of shift work exposure[d]		0.98 (0.005–42)
None	430 (23%)	
>0–<1 year	727 (39%)	
1–<5 years	292 (16%)	
5–<10 years	153 (8%)	
10+ years	272 (15%)	
4-category classification for *o*-toluidine		
Probably not exposed	590 (31%)	
Possibly exposed low and irregularly/occasionally	169 (9%)	

(*Continued*)

TABLE I. (*Continued*)

Characteristic	No. (%)	Median (range)
Possibly exposed low and regularly	199 (11%)	
Definitely exposed moderate/high and regularly	916 (49%)	

[a]After excluding 10 workers with no work history information, two workers with missing date of birth, and 1 worker who died prior to 1/1/1960 (rate file begin date).
[b]Records were located for 18 workers hired prior to 8/1/1988 but not included in earlier studies.
[c]Race/ethnicity was not available for the some cohort members. For the analysis, race was assumed to be White, based on racial demographics in the geographic area of the study.
[d]Among workers with 1 day or more of the indicated exposure.

The coronary artery disease SMR of 1.24 (95% CI: 1.04–1.48) among all workers was adjusted for gender, race, age, and calendar year, but not for possible smoking differences between the cohort and the US population. The distribution of smoking was 31.4% never, 26.9% former, and 41.6% current among workers in the cohort with smoking data (using all three sources) and 36.6% never, 29.9% former, and 33.5% current among US males in 1987 (age-adjusted to the cohort). Using estimated coronary artery disease mortality rate ratios (compared to non-smokers) of 1.3 and 1.9 for former and current smokers, respectively, the estimated bias factor (f) for the coronary artery disease SMR expected from smoking-related differences is given by

$$f = \frac{1 \times 0.314 + 1.3 \times 0.269 + 1.9 \times 0.416}{1 \times 0.366 + 1.3 \times 0.299 + 1.9 \times 0.335} = 1.05$$

using an indirect adjustment method described by Axelson and Steenland [1988]. Consequently, the smoking-adjusted SMR was 1.19. Ninety-five percent Monte Carlo limits for the bias factor (1.01–1.08) and the smoking-adjusted SMR (0.99–1.42) were estimated using methods described by Steenland and Greenland [2004]. Similar results were observed when only source one of the smoking data was used (estimated median bias factor 1.06, bias-adjusted SMR 1.17, and 95% Monte Carlo limits 0.98–1.41).

Vinyl Chloride Exposure and Hepatobiliary Cancer

Eleven deaths were in the category of "Malignant neoplasms of biliary passages, liver, and gall bladder"; of these, five were "liver, primary," five were "liver, unspecified," and one was intrahepatic bile duct. Compared to the US population, hepatobiliary cancer mortality in the cohort was highest in the 1970s (two deaths, SMR 10.04, 95% CI: 1.22–36.2) and the 1980s (three deaths, SMR 6.93, 95% CI: 1.43–20.2); the excess was not statistically significant in the 1990s (two deaths, SMR 1.86, 95% CI: 0.23–6.73) and 2000s (four deaths, SMR 2.43, 95% CI: 0.66–6.23).

Compared to the US population, hepatobiliary cancer mortality was elevated in the highest three quartiles of overall employment duration; compared to the lowest quartile, we observed a statistically significant trend in the standardized rates with employment duration, among all workers and when short-term workers were excluded (Table III).

Vinyl chloride exposed workers had increased hepatobiliary cancer mortality compared to the US population (11 observed deaths, SMR = 3.80, 95% CI: 1.89–6.80). All 11 deaths occurred among workers considered ever exposed to vinyl chloride in 1974 or earlier (SMR = 4.20, 95% CI: 2.09–7.51). When results were stratified by duration of vinyl chloride exposure (lagged 20 years), a 10-fold increase in hepatobiliary cancer mortality was observed among workers exposed to vinyl chloride 16 or more years, and mortality increased 13-fold among those with 16 or more years of vinyl chloride exposure prior to 1975 (Table III). Compared to workers with lower duration of vinyl chloride exposure, clear trends were observed for the two metrics. Similar results were observed in analyses limited to long-term workers.

Shift Work and Vinyl Chloride Exposures and Non-Hodgkin Lymphoma

Among workers who performed shift work, non-Hodgkin lymphoma mortality was increased compared to the US population (eight observed deaths, SMR = 2.31, 95% CI: 1.00–4.55), but not compared to fellow workers who did not perform shift work (SRR = 0.69, 95% CI: 0.18–2.69). Workers with vinyl chloride exposure had increased non-Hodgkin lymphoma mortality compared to the US population, but it was not statistically significant (SMR = 2.03, 95% CI: 0.88–4.00), and no increase was observed in internal comparisons (SRR = 0.46, 95% CI: 0.10–2.13). When only exposure to vinyl chloride in 1974 or earlier was considered, similar results were observed (SMR = 2.22, 95% CI: 0.96–4.37 and SRR = 0.61, 95% CI: 0.12–3.21).

No increase in mortality was observed with overall employment or increased shift work or vinyl chloride duration (Table IV). These results were generally unchanged when short-term workers were excluded or when exposure lag periods of 10 and 20 years were applied (results not shown).

TABLE II. Standardized Mortality Ratios Overall and by Duration of Employment for Workers Employed at a Chemical Manufacturing Plant

	All workers (n = 1,874)			Workers employed ≥90 days (n = 1,362)			Workers employed <90 days (n = 512)		
Underlying cause of death[a]	**OBS**	**SMR[b]**	**95% CI**	**OBS**	**SMR**	**95% CI**	**OBS**	**SMR**	**95% CI**
All causes	443	1.02	0.92–1.12	336	0.92	0.83–1.03	107	1.48	1.21–1.79
All cancers	121	1.08	0.90–1.30	95	1.01	0.82–1.23	26	1.50	0.98–2.19
MN of buccal cavity and pharynx	1	0.39	0.01–2.16	0	0	0–1.73	1	2.26	0.06–12.58
MN of digestive organs and peritoneum	36	1.32	0.92–1.83	30	1.31	0.88–1.87	6	1.38	0.51–3.00
MN of esophagus	4	1.12	0.30–2.86	3	1.02	0.21–2.99	1	1.54	0.04–8.60
MN of stomach	5	1.64	0.53–3.83	4	1.54	0.42–3.94	1	2.22	0.06–12.38
MN of intestine except rectum	3	0.33	0.07–0.97	3	0.39	0.08–1.14	0	0	0–2.82
MN of rectum	2	0.97	0.12–3.50	1	0.58	0.01–3.21	1	3.06	0.08–17.07
MN of biliary passages, liver, and gall bladder	11	3.20	1.60–5.73	10	3.57	1.71–6.57	1	1.57	0.04–8.77
MN of pancreas	11	1.90	0.95–3.40	9	1.85	0.85–3.52	2	2.14	0.26–7.74
MN of respiratory system	40	1.02	0.73–1.39	33	0.99	0.68–1.39	7	1.21	0.48–2.48
MN of larynx	2	1.55	0.19–5.62	2	1.84	0.22–6.66	0	0	0–18.33
MN of trachea, bronchus, and lung	37	0.98	0.69–1.36	30	0.94	0.63–1.34	7	1.26	0.51–2.60
MN other parts of respiratory system	1	3.75	0.09–20.88	1	4.64	0.12–25.85	0	0	0–71.86
MN of breast	1	0.85	0.02–4.73	1	0.95	0.02–5.31	0	0	0–28.84
MN of male genital organs	4	0.56	0.15–1.43	2	0.31	0.04–1.12	2	2.78	0.34–10.06
MN of prostate	4	0.59	0.16–1.51	2	0.32	0.04–1.17	2	3.29	0.40–11.89
MN of urinary organs	6	1.06	0.39–2.30	5	1.04	0.34–2.42	1	1.16	0.03–6.46
MN of kidney	2	0.64	0.08–2.33	1	0.39	0.01–2.18	1	1.84	0.05–10.24
MN of bladder and other urinary organs	4	1.55	0.42–3.98	4	1.77	0.48–4.54	0	0	0–11.58
MN of other and unspecified sites	17	1.04	0.60–1.66	12	0.9	0.46–1.57	5	1.65	0.53–3.84
MN brain & other parts of nervous system	2	0.54	0.07–1.95	2	0.68	0.08–2.46	0	0	0–4.75
Neoplasms of lymphatic and hematopoietic tissue	16	1.39	0.79–2.25	12	1.26	0.65–2.19	4	2.03	0.55–5.19
Hodgkin disease	1	1.38	0.04–7.72	0	0	0–6.58	1	6.18	0.16–34.44
Non–Hodgkin lymphoma	11	2.38	1.19–4.26	8	2.10	0.91–4.13	3	3.7	0.76–10.81
Multiple myeloma	1	0.55	0.01–3.08	1	0.65	0.02–3.61	0	0	0–13.81
Leukemia and aleukemia	3	0.69	0.14–2.00	3	0.82	0.17–2.41	0	0	0–5.02
Benign and unspecified neoplasms	3	2.12	0.44–6.19	3	2.54	0.52–7.43	0	0	0–15.61
Tuberculosis and HIV related disease	7	1.07	0.43–2.21	0	0	0–0.81	7	3.54	1.42–7.29
Diabetes mellitus	8	0.80	0.34–1.57	6	0.72	0.26–1.57	2	1.17	0.14–4.22
Mental, psychoneurotic, and personality disorders	4	0.67	0.18–1.71	3	0.62	0.13–1.81	1	0.86	0.02–4.79
Disorders of the nervous system and sense organs	5	0.60	0.19–1.40	5	0.70	0.23–1.63	0	0	0–3.06
All cardiovascular disease	179	1.13	0.97–1.31	143	1.04	0.88–1.23	36	1.73	1.28–2.39
Diseases of the heart	155	1.20	1.02–1.40	124	1.11	0.92–1.32	31	1.79	1.22–2.55
Hypertension with heart disease	4	1.01	0.28–2.59	3	0.92	0.19–2.67	1	1.47	0.04–8.17
Coronary artery disease	130	1.24	1.04–1.48	104	1.14	0.93–1.38	26	1.91	1.25–2.80
Cardiomyopathy	7	1.44	0.58–2.97	4	1.01	0.28–2.59	3	3.37	0.69–9.84
Conduction disorder	6	0.97	0.36–2.12	6	1.15	0.42–2.49	0	0	0–3.95
Other diseases of the heart	8	1.21	0.52–2.39	7	1.21	0.49–2.49	1	1.25	0.03–6.97
Other diseases of the circulatory system	24	0.82	0.53–1.23	19	0.74	0.45–1.16	5	1.4	0.45–3.27
Cerebrovascular disease	17	0.93	0.54–1.50	13	0.81	0.43–1.38	4	1.88	0.51–4.81
Diseases of the arteries, veins, and lymphatic vessel	7	0.76	0.30–1.56	6	0.75	0.27–1.63	1	0.83	0.02–4.61
Diseases of the respiratory system	27	0.90	0.59–1.30	24	0.90	0.58–1.34	3	0.85	0.18–2.48
Influenza	1	5.77	0.15–32.12	1	6.44	0.16–35.89	0	0	0–202.39
Pneumonia (except newborn)	8	1.00	0.43–1.96	7	0.99	0.40–2.04	1	1.05	0.03–5.84

(*Continued*)

TABLE II. *(Continued)*

Underlying cause of death[a]	All workers (n = 1,874) OBS	SMR[b]	95% CI	Workers employed ≥90 days (n = 1,362) OBS	SMR	95% CI	Workers employed <90 days (n = 512) OBS	SMR	95% CI
Chronic obstructive pulmonary disease	10	0.62	0.30–1.14	9	0.62	0.29–1.19	1	0.56	0.01–3.15
Other pneumoconioses	1	4.99	0.13–27.80	1	5.34	0.14–29.76	0	0	0–279.53
Other respiratory diseases	7	1.49	0.60–3.06	6	1.47	0.54–3.20	1	1.57	0.04–8.74
Diseases of the digestive system	18	0.87	0.52–1.38	12	0.72	0.37–1.26	6	1.52	0.56–3.31
Hernia and intestinal obstruction	1	1.41	0.04–7.85	0	0	0–5.92	1	11.61	0.29–64.66
Cirrhosis and other chronic liver disease	8	0.69	0.30–1.36	6	0.66	0.24–1.43	2	0.80	0.10–2.90
Other diseases of digestive system	9	1.29	0.59–2.45	6	1.04	0.38–2.26	3	2.51	0.52–7.34
Diseases of the musculoskeletal system and connective tissue	2	1.81	0.22–6.53	1	1.07	0.03–5.97	1	5.79	0.15–32.24
Diseases of the genitourinary system	9	1.56	0.71–2.96	8	1.58	0.68–3.12	1	1.37	0.03–7.65
Symptoms and ill-defined conditions	7	1.37	0.55–2.82	4	0.99	0.27–2.53	3	2.82	0.58–8.24
Transportation injuries	11	0.55	0.27–0.98	5	0.35	0.11–0.81	6	1.06	0.39–2.30
Falls	1	0.33	0.01–1.85	1	0.41	0.01–2.27	0	0	0–6.62
Other injury	9	0.65	0.30–1.23	7	0.69	0.28–1.41	2	0.54	0.07–1.95
Intentional self-harm	10	0.70	0.33–1.28	3	0.29	0.06–0.84	7	1.80	0.72–3.71
Assault and homicide	2	0.32	0.04–1.16	2	0.45	0.05–1.64	0	0	0–2.03
Residual causes	4	0.36	0.10–0.91	2	0.23	0.03–0.81	2	0.86	0.10–3.12
Unknown causes	16			12			4		

OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; MN, malignant neoplasm.

[a]International Classification of Disease (ICD) codes were mapped to 119 cause of death categories as described in Robinson et al. [2006] and tabulated on the NIOSH website (http://www.cdc.gov/niosh/ltas/rates.html). Major cause of death categories with zero deaths (MN of female genital organs, diseases of the skin and subcutaneous tissue and diseases of the blood and blood forming organs) were omitted from the table.

[b]SMRs are based on US underlying cause of death rates, 1960–2007. Results exclude 1 observed death and 758 person-years at risk prior to January 1, 1960 (rate file begin date).

Carbon Disulfide and Shift Work Exposures and Coronary Artery Disease

Coronary artery disease mortality was not associated with duration of employment (Table V). As many workers exposed to carbon disulfide also performed shift work, we evaluated the risk of coronary artery disease mortality in groups defined by duration of exposure to these agents (Table V). Compared to the US population, statistically significant increases in mortality were observed among workers with both exposures for 90 days or more, and among workers with fewer than 90 days of both exposures. Using cutpoints of 4 years (median exposure duration among long-term cases), the results were no longer statistically significant.

The elevation in coronary artery disease mortality among workers exposed 90 days or more to both shift work and carbon disulfide (SMR 1.36, 95% CI: 1.03–1.76) was adjusted for gender, race, age, and calendar year, but not for smoking. The distribution of smoking was 26.9% never, 29.0% former, and 44.1% current among similarly exposed workers in the cohort with all sources of smoking data and 35.3% never, 31.8% former, and 32.9% current among US males in 1987 (age-adjusted to the exposed). The estimated bias factor (f) for the coronary artery disease SMR expected from smoking-related differences is given by

$$f = \frac{1 \times 0.269 + 1.3 \times 0.290 + 1.9 \times 0.441}{1 \times 0.353 + 1.3 \times 0.318 + 1.9 \times 0.329} = 1.07$$

The smoking-adjusted SMR was 1.28 with 95% Monte Carlo limits of 1.03–1.11 for the bias factor and 0.98–1.66 for the smoking-adjusted SMR. Similar results were observed when only source 1 of the smoking data was used (estimated median bias factor 1.09, bias-adjusted SMR 1.24, and 95% Monte Carlo limits 0.96–1.62).

Coronary artery disease mortality was significantly higher among workers with more than 4 years of exposure to both shift work and carbon disulfide compared to workers with less than 4 years of exposure to both shift work and carbon disulfide, but only when short-term workers were excluded (Table V). Compared to the same referent group, mortality was not higher among workers with 4 years or more of just one of these exposures.

TABLE III. Hepatobiliary Cancer Mortality for all Workers and Long-Term Workers (≥90 Days Employment) by Quartiles of Employment Duration and Vinyl Chloride Exposure Duration

	All workers						Workers employed≥90 days					
Metric[a]	PYAR	OBS	SMR[b]	95% CI	SRR	95% CI	PYAR	OBS	SMR	95% CI	SRR	95% CI
Duration of employment (years)												
<17	50,489	2	0.94	0.11–3.39	1	(referent)	34,423	1	0.67	0.02–3.72	1	(referent)
17–<23	3,801	3	7.97	1.64–23.3	7.51	1.15–48.9	3,801	3	7.97	1.64–23.3	10.66	1.05–108
23–<33	3,974	4	7.21	1.96–18.5	4.48	0.79–25.3	3,974	4	7.21	1.96–18.5	6.68	0.73–61.1
≥33	1,702	2	5.37	0.65–19.4	4.46	0.62–32.0	1,702	2	5.37	0.65–19.4	6.48	0.58–71.7
						$P_{trend} = 0.050$						$P_{trend} = 0.044$
Duration of vinyl chloride exposure (years, lagged 20 years)[c]												
<7.4	54,961	3	1.26	0.26–3.69	1	(referent)	38,895	2	1.15	0.14–4.15	1	(referent)
7.4–<16	3,160	2	3.94	0.48–14.2	1.45	0.21–10.2	3,160	2	3.94	0.48–14.2	1.29	0.15–11.0
≥16	1,846	6	10.9	4.01–23.8	3.92	0.84–18.4	1,846	6	10.9	4.01–23.8	3.88	0.64–23.5
						$P_{trend} = 0.0038$						$P_{trend} = 0.036$
Duration of vinyl chloride exposure in 1974 or earlier (years, lagged 20 years)[c]												
0–<6.8	55,305	3	1.23	0.25–3.60	1	(referent)	39,240	2	1.11	0.13–4.02	1	(referent)
6.8–<16	3,241	2	3.52	0.43–12.7	1.38	0.20–9.64	3,241	2	3.52	0.43–12.7	1.27	0.15–10.4
≥16	1,420	6	13.8	5.07–30.0	4.68	1.02–21.4	1,420	6	13.8	5.07–30.0	4.75	0.82–27.5
						$P_{trend} = 0.041$						$P_{trend} = 0.10$

PYAR, person-years at risk; OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio.
[a]Quartiles defined by distribution of metric among all hepatobiliary cancer decedents.
[b]SMRs are based on US underlying cause of death analysis, 1960–2007.
[c]The third and fourth quartiles were combined since the cutpoints were similar.

Other Outcomes

Eleven deaths occurred in the cohort due to pancreatic cancer (5.79 expected). Nine of these occurred among long-term workers (SMR = 1.85, 95% CI: 0.85–3.52). Among workers considered exposed to vinyl chloride, pancreatic cancer deaths were non-statistically significantly increased compared to the US population (eight deaths observed, SMR = 1.61, 95% CI: 0.69–3.17); and no increase was observed with the internal comparison group of workers not exposed to vinyl chloride (SRR = 0.54, 95% CI: 0.11–2.72). We observed similar results among workers exposed to vinyl chloride in 1974 or earlier (eight deaths observed, SMR = 1.74, 95% CI: 0.75–3.42 and SRR = 0.61, 95% CI: 0.11–3.45). Furthermore, we did not observe significant trends for pancreatic cancer mortality with duration of employment or duration of vinyl chloride exposure (results not shown).

Brain cancer was also an outcome of interest for vinyl chloride exposure; however, no further analyses were conducted since only two deaths occurred (3.93 expected). Other outcomes of interest for shift work—colorectal, prostate and breast cancer—had small numbers of deaths and were not further analyzed. For *o*-toluidine exposure, the *a priori* outcome was bladder cancer mortality; however, with only four observed deaths (2.57 expected), no further analyses were performed.

DISCUSSION

This study found evidence for excess hepatobiliary cancer mortality among workers exposed to vinyl chloride in a chemical manufacturing plant, as well as a trend with 20-year lagged duration of exposure. Our findings support an earlier study that showed an increase in hepatobiliary cancer among plant workers [Nicholson et al., 1975, 1984], and are consistent with other occupational studies of exposure to vinyl chloride [International Agency for Research on Cancer, 2012]. The International Agency for Research on Cancer (IARC) has classified vinyl chloride as a Group 1 carcinogen that causes angiosarcoma of the liver and hepatocellular carcinoma, based on sufficient evidence in humans and sufficient evidence in experimental animals [International Agency for Research on Cancer, 2012]. Approximately 20% of the workers in our cohort were exposed to vinyl chloride in 1974 or earlier for 5 or more years. Surviving workers may still be at increased risk of developing hepatobiliary cancer.

The IARC Working Group that reviewed the evidence of carcinogenicity for vinyl chloride for Monograph 100 did not find strong evidence for associations of exposure to vinyl chloride with cancers of the brain, lymphatic and hematopoietic tissues, or melanoma of the skin. We evaluated the association between non-Hodgkin lymphoma mortality and

TABLE IV. Non-Hodgkin Lymphoma Mortality for All Workers and Long-Term Workers (≥90 Days Employment) by Employment Duration and Shift Work and Vinyl Chloride Exposure Duration

	All workers						Workers employed ≥90 days					
Metric[a]	PYAR	OBS	SMR	95% CI	SRR	95% CI	PYAR	OBS	SMR	95% CI	SRR	95% CI
Duration of employment (years)												
<0.16	10,751	2	3.57	0.43–12.90	1	(referent)	191	0				
0.16–<1.1	16,711	4	4.82	1.31–12.34	3.62	0.59–22.26	11,206	3	5.21	1.07–15.22		
1.1–<15	21,703	2	1.53	0.19–5.54	1.50	0.17–13.51	21,703	2	1.53	0.19–5.54		
≥15	10,800	3	1.55	0.32–4.54	3.85	0.42–35.20	10,800	3	1.55	0.32–4.54		
						$P_{trend} = 0.40$						
Duration of shift-work (years)												
0	13,571	3	2.59	0.53–7.56	1	(referent)	10,232	2	2.02	0.24–7.30	1	(referent)
>0–<1	23,985	3	2.22	0.46–6.48	0.41	0.08–2.08	11,258	1	1.41	0.04–7.83	0.39	0.04–4.33
≥1	22,410	5	2.37	0.77–5.52	0.61	0.14–2.61	22,410	5	2.37	0.77–5.52	0.98	0.19–5.06
						$P_{trend} = 0.93$						$P_{trend} = 0.57$
Duration of vinyl chloride exposure (years)												
0	12,689	3	4.35	0.90–12.7	1	(referent)	6,647	2	4.92	0.60–17.8	1	(referent)
>0–<6	33,326	4	2.14	0.58–5.49	0.48	0.09–2.64	23,303	2	1.49	0.18–5.40	0.48	0.06–3.87
≥6	13,950	4	1.93	0.53–4.95	0.39	0.07–2.19	13,950	4	1.93	0.53–4.95	0.39	0.06–2.50
						$P_{trend} = 0.33$						$P_{trend} = 0.25$
Duration of vinyl chloride exposure in 1974 or earlier (years)												
0	21,433	3	2.95	0.61–8.62	1	(referent)	14,069	2	2.88	0.35–10.4	1	(referent)
>0–<6	27,832	4	2.25	0.61–5.76	0.60	0.10–3.64	19,130	2	1.55	0.19–5.60	0.52	0.06–4.87
≥6	10,701	4	2.19	0.60–5.60	0.47	0.08–2.89	10,701	4	2.19	0.60–5.60	0.48	0.06–3.58
						$P_{trend} = 0.12$						$P_{trend} = 0.38$

PYAR, person-years at risk; OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio.

[a]For duration of employment, quartiles were defined by the distribution of employment duration among all non-Hodgkin lymphoma decedents; for duration of shift work, since the lowest quartile was 0, three groups were defined as no shift work, less than 1 year of shift work (median among exposed decedents was 1.1 years), and 1 year or more of shift work; and for duration of vinyl chloride exposure, since the lowest quartile was 0, three groups were defined as no vinyl chloride exposure, less than 6 years of vinyl chloride exposure (median among exposed decedents was 6.6 years), and 6 years or more of vinyl chloride exposure.

duration of exposure to vinyl chloride, but did not see an association with either metric (duration of vinyl chloride exposure or duration of vinyl chloride exposure in 1974 or earlier). Since a weak association between vinyl chloride exposure and pancreatic cancer has been reported [Ojajarvi et al., 2001], we decided to explore this association *a posteriori* in our study. We found no evidence of an association with pancreatic cancer mortality, using both duration of exposure metrics and different cutoff points of duration of employment and duration of exposure.

Shift work, defined as any work that is done outside of normal daytime working hours, has been linked to cancer [Costa et al., 2010] and heart disease [Mosendane and Raal, 2008; Frost et al., 2009; Vyas et al., 2012], but the data are not conclusive. The exact mechanisms by which shift work could cause chronic disease are still not completely understood. For cancer, one hypothesis suggests that light at night suppresses secretion of endogenous melatonin, which may affect the risk of cancer through a number of pathways [Wang et al., 2011]. Other factors related to shift work being considered in the development of cancer include circadian rhythm disruption, long-term sleep disruption and deprivation, immune supression, and desynchronization of clock genes [Costa et al., 2010].

Compared to the US population, this cohort had an increased risk of mortality due to non-Hodgkin lymphoma. This increase does not appear to be associated with HIV-related disease, as mortality from tuberculosis and HIV-related diseases was not elevated among long-term workers, whereas non-Hodgkin lymphoma mortality was. In internal analyses, associations of non-Hodgkin lymphoma mortality with shift work duration were not observed. Lahti et al. [2008] evaluated the effect of nighttime shift work in a retrospective cohort study of 1,666,272 people in Finland. Using a cumulative index of nighttime work (lagged by 10 years), they reported non-Hodgkin lymphoma risk ratios among men of 1.1 (95% CI: 1.03–1.19) for ever nighttime shift work and 1.28 (95% CI: 1.03–1.59) for long-term (21 or more years) nighttime shift work compared to those unexposed to nighttime shift work. A recent case-control study also

TABLE V. Coronary Artery Disease Mortality for All Workers and Long-Term Workers (≥90 Days Employment) by Employment Duration and in Groups Defined by Exposure to Carbon Disulfide and Shift Work

	All workers						Workers employed ≥90 days					
Metric	**PYAR**	**OBS**	**SMR**	**95% CI**	**SRR**	**95% CI**	**PYAR**	**OBS**	**SMR**	**95% CI**	**SRR**	**95% CI**
Duration of employment (years)												
<8y	42,755	52	1.35	1.01–1.77	1	(referent)	26,689	26	1.04	0.68–1.52	1	(referent)
8–<18y	8,478	27	1.27	0.84–1.85	1.25	0.69–2.28	8,478	27	1.27	0.84–1.85	1.73	0.92–3.25
18–<26y	4,421	24	1.16	0.74–1.72	1.13	0.51–2.55	4,421	24	1.16	0.74–1.72	1.59	0.74–3.38
26y+	4,312	27	1.13	0.74–1.64	0.88	0.48–1.61	4,312	27	1.13	0.74–1.64	1.38	0.70–2.70
						$P_{trend} = 0.45$						$P_{trend} = 0.37$
Shift work, carbon disulfide exposure group[a]												
SW:<90d, CS_2:<90d	20,496	37	1.68	1.18–2.32	1	(reference)	4,431	11	1.31	0.65–2.34	1	(reference)
SW:<90d, CS_2:90d+	7,580	18	0.88	0.52–1.40	0.51	0.27–0.97	7,580	18	0.88	0.52–1.40	0.60	0.25–1.43
SW:90d+, CS_2:<90d	12,709	17	0.87	0.50–1.39	0.68	0.37–1.26	12,709	17	0.87	0.50–1.39	0.78	0.33–1.84
SW:90d+, CS_2:90d+	19,181	58	1.36	1.03–1.76	1.03	0.66–1.63	19,181	58	1.36	1.03–1.76	1.09	0.52–2.31
Shift work, carbon disulfide exposure group[b]												
SW:<4y, CS_2:<4y	41,124	56	1.31	0.99–1.70	1	(reference)	25,059	30	1.03	0.69–1.47	1	(reference)
SW:<4y, CS_2:4y+	5,346	23	1.01	0.64–1.52	0.78	0.43–1.40	5,346	23	1.01	0.64–1.52	1.10	0.57–2.10
SW:4y+, CS_2:<4y	6,244	21	1.22	0.75–1.86	1.05	0.61–1.82	6,244	21	1.22	0.75–1.86	1.41	0.77–2.60
SW:4y+, CS_2:4y +	7,252	30	1.37	0.93–1.96	1.97	0.84–4.65	7,252	30	1.37	0.93–1.96	2.70	1.05–6.93

PYAR, person-years at risk; OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio; CS_2, carbon disulfide; SW, shift work; y, years; d, days.

[a]Cutpoint based on long-term employment (90+ days) among coronary artery disease decedents.

[b]Cutpoint based on median exposure duration among long-term coronary artery disease decedents.

reported an excess risk of non-Hodgkin lymphoma associated with night work among men [Parent et al., 2012]. Studies with greater power than ours are needed to confirm these findings.

Cardiovascular disease mortality is usually lower in occupational cohorts because of the healthy worker effect, a bias due to preferential selection of relatively healthy persons for employment [Li and Sung, 1999]. Nevertheless, in this study, we found overall excess mortality for coronary artery disease among all workers, and in particular among short-term workers. Steenland and Stayner [1991] have indicated that short-term workers usually have higher mortality rates in cohort studies, because most of their contributed person-years occur after they have terminated employment in the plant under study. Kolstad and Olsen [1999] reported that shorter durations of employment are associated with more preemployment hospitalizations for alcohol use, accidents, and the effects of violence. For this reason, we conducted analyses for all workers and then excluding short-term workers (<90 days of employment). Our trend analyses were generally similar when short-term workers were excluded, although some loss of power was observed.

We found statistically significantly increased coronary artery disease mortality among workers exposed to shift work and carbon disulfide. In internal comparisons, long-term workers exposed to carbon disulfide and shift work for 4 years or more had a near threefold increase in coronary artery disease mortality, compared to workers exposed less than 4 years. The previous mortality study conducted in this cohort [Prince et al., 2000] reported excess ischemic heart disease mortality among workers in the Rubber Chemicals department. In this study, we further expanded the exposure definitions by classifying workers into categories of carbon disulfide and shift work exposure, based not only on department, but also on job title and year. While the results are not directly comparable, they confirm the earlier finding of excess cardiovascular disease mortality in the plant and affirm the need for further investigation into the causes of the observed excess.

Increased mortality among workers occupationally exposed to carbon disulfide has been reported [Swaen et al., 1994; Pepllonska et al., 2001]. The effect of carbon disulfide exposure on cardiovascular disease incidence has also been investigated, but the results are inconsistent [Tan et al., 2002]. Concurrent exposure to other chemicals, such as hydrogen sulfide, as well as failure to control for other cardiovascular disease risk factors is a limitation of these studies [Sulsky et al., 2002]. To our knowledge, ours is the first study to evaluate the effect of concurrent exposure to carbon disulfide and shift work.

Shift work has been hypothesized to contribute to the development of cardiovascular disease and other metabolic

disorders through pathways that include disturbed circadian rhythms, changes in biomarkers of atherosclerosis, lifestyle changes, job strain, and stress and social stress [Puttonen et al., 2010; Wang et al., 2011]. However, there is still no consistent evidence that shift work increases the risk of cardiovascular disease [Boggild and Knutsson, 1999; Frost et al., 2009; Puttonen et al., 2010]. In a systematic review of epidemiologic studies, Frost et al. [2009] showed a stronger association between shift work and coronary heart disease morbidity than mortality and suggested that selection out of shift work could explain the weaker association with mortality. The authors could not rule out methodological problems such as exposure misclassification, selection bias, and inadequate control of confounding in the interpretation of the results of these studies.

Moreover, cardiovascular disease has a multicausal etiology that includes smoking, diabetes, hypertension, high blood cholesterol, and family history of cardiovascular disease. Other factors, such as behavioral, social, and psychological factors also explain some but not all the variance in cardiovascular disease. It is also possible that a combination of two or more risk factors greatly increases the risk, and therefore carbon disulfide and shift work may be cofactors in the presence of other risk factors. Smoking, in particular, has been reported to be more common among shift workers than day workers [Boggild and Knutsson, 1999]. In this study, we used an indirect method of adjustment to account for the effect of smoking, which had a modest effect on the risk estimates: a 7% increase in coronary artery disease mortality among workers exposed to both shift-work and carbon disulfide (using the 90-day threshold) compared to the US population. Thus, smoking differences between exposed workers and the US population could explain some of the observed coronary artery disease mortality elevation, and since the adjusted result was not statistically significant, it could be due to chance. We were not able to account for some of the other confounding factors; however, studies of shift work and ischemic heart disease have found no strong indication that alcohol consumption or exercise differ between shift workers and day-only workers [Frost et al., 2009].

There is also indication that overtime work can increase blood pressure and lead to increased heart disease [Virtanen et al., 2010]. We were informed that plant employees sometimes worked overtime hours, but we did not know the extent of the overtime work.

For *o*-toluidine exposure, the outcome of interest was bladder cancer. Four bladder cancer deaths occurred in the cohort, but the increased overall risk was not statistically significant. Bladder cancer mortality may not be a good indicator of risk, since the relative 5-year survival is approximately 80% [Silverman et al., 2006]. We have evaluated the effect of *o*-toluidine exposure on the risk of bladder cancer incidence among workers in the updated cohort, and identified 50-bladder cancer cases and a near threefold excess when compared with the New York State population [Carreón et al., 2013].

Our study data were limited to personnel records and some industrial hygiene data. Our classifications for exposure to vinyl chloride, carbon disulfide and shift work were based on department, job title, and year, and there was the possibility of misclassification. Particularly since carbon disulfide was used in only one manufacturing process, it is possible that some unexposed workers were considered exposed. We have no reason to believe that there is differential exposure misclassification in this study. Non-differential misclassification biases the risk estimate usually, although not always, towards the null value of 1.0 [Checkoway et al., 2004]. Except for gender, race and age, and a limited number of smoking histories that we used to develop an indirect measure of control of confounding by smoking, we had no information on lifestyle choices and other confounders that affect cancer and coronary artery disease. In addition, our study size may not be large enough to detect some of the associations. Workers in this study have a relatively short duration of employment (median 1.6 years) which could limit our ability to detect an association, if one exists.

In conclusion, we found evidence for excess mortality from hepatobiliary cancers among workers exposed to vinyl chloride. Moreover, we found that hepatobiliary cancer mortality risk increased with duration of vinyl chloride exposure, but did not find associations between vinyl chloride and non-Hodgkin lymphoma or pancreatic cancer. No differences were observed in separate analyses considering exposures to vinyl chloride occurring prior to January 1, 1975. No association was observed between shift work and non-Hodgkin lymphoma. Coronary artery disease mortality was elevated among long-term workers exposed to both carbon disulfide and shift work for 4 years or more compared to workers with less exposure. Due to small numbers, we were unable to evaluate the effect of shift work on the risk of colorectal, prostate or breast cancer mortality, the effect of vinyl chloride exposure on the risk of brain cancer mortality, or the effect of *o*-toluidine exposure on the risk of bladder cancer mortality.

A bladder cancer surveillance program is currently in effect at the plant for current and retired employees of the Rubber Chemicals department. Exposure to vinyl chloride has ceased at the plant. However, medical care for workers, currently employed, and retired, who ever worked in the PVC, Vinyl department should include monitoring for hepatobiliary cancer. In previous studies, NIOSH investigators recommended that the labor-management health and safety committee consider a plant-based intervention program to monitor and reduce cardiovascular risk factors [Prince et al., 2000]. We continue to support this recommendation.

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