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cc: Copy to R. Wilson + Vinyl Chloride Panel Manager

JAN 06 1992

DOW

The Dow Chemical Company

Midland, Michigan 48640

2030 Dow Center
January 2, 1992

FILE: VINYL CHLORIDE PANEL

Ms. Kathy Rosicca
Chemical Manufacturers Association
2501 M Street, Northwest
Washington, D.C. 20037

~~PATHOLOGY REPORT~~ ON THE BRAINS FROM MICE, HAMSTERS AND RATS EXPOSED TO ~~VINYL CHLORIDE~~ & IBT STUDY 663-03222 - Submitted to Chemical Manufacturers ~~Association on~~ May 14, 1980 by experimental Pathology Laboratories, Inc.

Dear Ms. Rosicca:

Dow has entered into a TSCA 8(e) (Compliance Audit Program) agreement with the EPA. This is a one time voluntary audit program to locate and report any outstanding studies or other information reportable under this section.

We currently have the above-described study in our file and feel it is reportable under section 8(e) of TSCA. We are forwarding a copy to the EPA and wanted to let you know of this submission.

If you have any questions, please do not hesitate to contact me.

Very truly yours,

Karen Lauzon

Karen Lauzon
Legal Department
(517) 636-4879

For Distribution by CMA
CHEMSTAR DIVISION
From H. Shah
Re: Vinyl Chloride
Date 1/27/92

cc: R. L. Hagerman, 1803 Building
J. E. LeBeau, 2030 Dow Center
P. A. Wright, 2030 Dow Center

WSS

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CORPORATE SAFETY
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Originals

Dec. 1991

STUDY LINKS LIVER, BRAIN CANCER TO WORKING MEN EXPOSED TO CHEMICAL

An industrywide study of workers exposed to vinyl chloride found they were significantly more likely to die from cancer of the liver and biliary tract, cancer of the brain and central nervous system, and emphysema and chronic obstructive pulmonary disease.

The study, published in the September *American Journal of Industrial Medicine* (Vol. 20, No. 3), was based on data on 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride before January 1973. The workers were employed at 37 U.S. plants belonging to 17 companies.

The researchers—led by Otto Wong of Applied Health Sciences of San Mateo, Calif.—analyzed length of exposure, latency, age at first exposure, calendar year of first exposure, and type of products to which workers were exposed.

There were 1,536 deaths identified in the study. Mortality from all types of cancer was slightly, but not significantly, higher than the average U.S. experience. But, there were 37 deaths from cancer of the liver and biliary tract—which the researchers referred to simply as liver—compared with only 5.8 expected.

There were 23 deaths for cancer of the brain and other central nervous system, compared with 12.8 expected. No other cancer types showed any statistically significant excess, the study said.

Two Plants

Approximately half the cases of brain cancer came from two plants that were manufacturers of only polyvinyl chloride—as opposed to producing vinyl chloride monomer, both PVC and VCM, or homopolymer and copolymers. The researchers said these two plants produced a "disproportionately large number of deaths" from cancer of the brain and nervous system when compared to other plants in the study.

CURRENT REPORT

Study results also indicated that for the entire cohort, 41 deaths were due to emphysema or other chronic obstructive pulmonary disease, compared with the expected 22.8. The excess came mainly from those with less than 10 years of exposure: in this group there were 25 deaths from emphysema and related illnesses.

The researchers noted that their findings of a statistically significant excess in emphysema mortality have not been reported previously by other investigators.

No Smoking Data

The researchers said because the study did not contain data on smoking history, they were unable to assess its role in increased mortality from emphysema. "However, it must be pointed out that there was no excess in lung cancer, which would imply that the cohort did not have a higher percentage of smokers than the general population," they said.

The major limitation of the study was lack of exposure information, the researchers said. Because of this, "analyses by detailed exposure were not feasible," they said.

Also, the researchers were unable to get vital status follow-up information on a small percentage of the cohort.

And finally, because it was a mortality study, the research lacked in-depth clinical information, the researchers said. In particular, histologic information on the cell type of the liver cancers and brain cancers "would have been useful in interpreting the epidemiologic findings," they said.

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CHEMICAL MANUFACTURERS ASSOCIATION

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November 20, 1991

Dear Vinyl Chloride Research Coordinators:

Otto Wong et. al. recently published the enclosed article entitled, "An Industry-Wide Epidemiologic Study of Vinyl Chloride Workers, 1942-1982." The publication was based on studies that the CMA Vinyl Chloride Panel had sponsored in the past.

Dr. Wong did not send a draft manuscript to CMA for review and comments prior to the publication. Drs. Bob Hinderer and J.R. Drumwright have expressed concerns regarding the interpretation of our data by Dr. Wong et. al. The enclosed letters from Drs. Hinderer and Drumwright describe their concerns.

I would like to schedule a conference call during the week of December 1, 1991, to discuss the enclosed publication and the concerns expressed by Drs. Hinderer and Drumwright, and to decide on a course of action. Please complete the enclosed survey form concerning your availability and return it to me as soon as possible. You may fax your availability survey to me at (202) 887-1237. I have asked Dr. Bill Gaffey, who is very familiar with the studies we sponsored, to be available for the conference call. We may want to consider hiring him to prepare our response to Dr. Wong's publication.

Sincerely,

Has Shah

Hasmukh C. Shah
Manager, Vinyl Chloride Panel

cc: J.R. Drumwright
William Gaffey
James Barter
Eugene Skiest

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2501 M Street, NW, Washington, DC 20037 202-887-1100 Panafax 202-887-1237 Telex 89617 (CMA WSH)

CHEMICAL MANFUCTURERS ASSOCIATION

Vinyl Chloride Research
Coordinators

November 20, 1991

Availability Survey

Please circle the day(s) and the time(s) that you are available for a conference call.

I am available for a conference call on:

a) Monday, December 2, 1991 (Morning/Afternoon)

b) Tuesday, December 3, 1991 (Morning/Afternoon)

c) Wednesday, December 4, 1991 (Morning/Afternoon)

d) Thursday, December 5, 1991 (Morning/Afternoon)

e) Friday, December 6, 1991 (Morning/Afternoon)

NAME: _____
COMPANY: _____

ADDRESS: _____
_____
_____

PHONE: _____
FAX: _____

PLEASE RETURN VIA FAX TO:

Hasmukh Shah
CMA
FAX: (202) 887-1237

American Journal of Industrial Medicine 20:317–334 (1991)

An Industry-Wide Epidemiologic Study Of Vinyl Chloride Workers, 1942–1982

Otto Wong, ScD, M. Donald Whorton, MD, Donna E. Foliart, MD, and David Ragland, PhD

The cohort consisted of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to 1 January 1973. These men were employed at 37 plants in the U.S. belonging to 17 companies. Observation of the mortality experience of the cohort was updated from 31 December 1972 to 31 December 1982 (the study now covering 1942–1982). A total of 1,536 cohort members were identified as having died. The observed mortality, by cause, was compared with the expected based on U.S. mortality rates, standardized for age, race, and calendar time. Analyses by length of exposure, latency, age at first exposure, calendar year of first exposure, and type of products were performed. The study confirmed that the vinyl chloride workers experience a significant mortality excesses in angiosarcoma (15 deaths), cancer of the liver and biliary tract (SMR = 641), and cancer of the brain and other central nervous system (SMR = 180). In addition, the study also found a significant mortality excess in emphysema/chronic obstructive pulmonary disease (COPD) (SMR = 179). On the other hand, the study did not find any excess in either respiratory cancer or lymphatic and hematopoietic cancer. This study also found an increase in biliary tract cancers, independent from liver cancer.

Key words: angiosarcoma, liver cancer, brain cancer, chronic obstructive pulmonary disease

BACKGROUND

In 1974, three cases of angiosarcoma of the liver were reported among workers employed at a vinyl chloride (VC) polymerization plant in the U.S. [Creech and Johnson, 1974]. About the same time, similar cancerous hepatic effects were reported in laboratory animals exposed to vinyl chloride [Maltoni et al., 1981]. Since then, a number of epidemiologic studies have confirmed the association between angiosarcoma of the liver and occupational exposure to vinyl chloride [Tabershaw and Gaffey, 1974; Cooper, 1981; Fox and Collier, 1977; Waxweiler et al., 1976; Jones et al., 1988]. In addition to angiosarcoma of the liver a number of other cancer sites have also been implicated, including the overall digestive system [Thériault and Allard, 1981; Chiazze et al., 1977; Smulevich et al., 1988], the respiratory system [Monson

Applied Health Sciences, San Mateo, CA (O.W.).
ENSR Health Sciences, Alameda, CA (M.D.W., D.E.F., D.R.).
Address reprint requests to Dr. Otto Wong, Applied Health Sciences, 181 Second Avenue, Suite 628, P.O. Box 2078, San Mateo, CA 94401.
Accepted for publication December 31, 1990.

additional years of observation). This report summarizes the conduct, statistical results, and epidemiologic interpretation of the updated CMA study.

MATERIALS AND METHOD

Original Study

The cohort consisted of 10,173 workers from 37 plants belonging to 17 companies. (Since the original study has been completed, the ownership of several plants has changed.) There were 11 plants with 1,214 workers which produced only vinyl chloride monomer (VCM), 18 plant with 6,848 workers which produced only polyvinyl chloride (PVC), 3 plants with 935 workers which produced both, and 5 plants with 1,176 workers which produced homopolymers and copolymers. Twenty-two of the 37 plants are located in the South, with eight in the Northeast, six in the North Central, and one in the West.

To be eligible for the cohort, male employees at the 37 participating plants must satisfy the following criteria:

- exposure to VC for at least 1 year prior to 12/31/1972; and
- employed during or after 1942.

In the original study, the designation of jobs involving exposure to VC was made by staff members at individual plants or by corporate industrial hygienists. In approximately two-thirds of the study population, employment records of all employees at the plants were microfilmed by the original investigation team, and exposed individuals were identified through these records [Cooper, 1981]. In the remaining portion of the population, detailed employment information on exposed individuals was provided by plant personnel on special forms. A small portion of these individuals were identified in the study only by a study number, and no personal identifiers were available to the investigators.

The period of time in which the employees of a plant were included in the study depended on the date it began making or using VC and also on the earliest date when personnel records were complete for all employees, whichever was later. This was done to eliminate periods when there was differential record retention of workers terminated, deceased, or retired, since such differential record retention might result in a potentially biased cohort. The end of observation in the original study was 31 December 1972.

In an attempt to characterize historical exposures, individual jobs and job locations indicated by company personnel exposed to VC were graded by company personnel in terms of probable exposure on a scale of "high," "medium," and "low." These terms were used to describe relative exposures within each plant. The original investigators acknowledged in their report of the study that this approach failed to reconcile differences among plant exposures [Tabershaw and Gaffey, 1974]. In some plants it was likely that a "high" grading might have meant average exposures in excess of 200 ppm, while in others, a "high" might have indicated average exposures of about 50 ppm. Actual levels were not known.

Study Update

The vital status of this cohort as determined by the original study investigators included 8,970 (92.7%) alive, 707 (7.3%) dead, and 496 (4.9%) unknown. These

TABLE I. Distribution of Vital Status of Current PVC Study Cohort Members

	No.	%
Subject to update		
Alive (as of 12/31/89)	6939	75.42
Dead (as of 12/31/89)	1536	16.70
Identified in original study (707)		
Identified in update (829)		
Unknown (as of 12/31/89)	725	7.88
Total (with updated vital status)	9200	100
Not subject to update		
Alive (as of 12/31/1972)	955	98.15
Unknown (as of 12/31/1972)	18	1.85
Total (not subject to update)	973	100

The vital status of the cohort as of 31 December 1982 is given in Table I. As of the end of the study period, 6,939 among those with updated vital status were still alive. A total of 1,536 individuals were identified as having died during the study period. Among these, death certificates were obtained for all except 97 deaths (6.3 of all deaths). Of the 1,536 deaths, 707 were identified in the original study and 829 in the update. A total of 973 individuals were not subject to follow-up in the update, either due to the lack of personal identifiers (the identification codes of 170 were lost) or non-participation of the plants (803). Among those with updated follow-up, the vital status (as of 31 December 1982) of 725 individuals (7.88%) remained unknown. Of the 973 individuals not subjected to a follow-up in the update, 955 were known to be alive on 31 December 1972, the end day in the original study. As such, person-years up to 31 December 1972 for these individuals were counted in the analysis.

Cause-Specific Mortality Analysis

As mentioned earlier, race was not available for all individuals from the previous study. However, there were very few known non-whites (3%) among the employees at the participating plants. For the analysis, the entire cohort was assumed to be white.

In the study, a total of 1,536 deaths were identified. Death certificates were obtained for 1,439 (94%) decedents. The 97 deaths without death certificates, but with dates of death, were coded as cause unknown. These deaths were included in the calculation of overall SMRs, but not in any cause-specific SMRs.

The observed and expected deaths by cause, SMRs and their 95% confidence limits for the total cohort are presented in Table II. The 1,536 deaths observed produced an overall SMR of 90.07, which was significantly low ($p < 0.01$) in comparison with the U.S. national mortality experience.

Mortality from cancer of all sites combined was slightly, but not significantly, higher than the U.S. experience (359 observed vs. 341.73 expected, SMR = 105.1). The excess came primarily from the following sites: cancer of the liver and biliary tract (hereafter referred to as "liver") and cancer of the brain and other central nervous system (CNS). For cancer of the liver, 37 deaths were observed, compared

There was a significant deficit in mortality from all diseases of the circulatory system. The number of observed deaths was 635, compared with 721.28 expected (SMR = 88.0, $p < 0.01$). The deficit came primarily from arteriosclerotic heart disease (SMR = 81.6, $p < 0.01$).

Although mortality from all non-malignant respiratory diseases showed a slight nonsignificant deficit, the deficit from pneumonia was statistically significant (15 observed, 31.94 expected, SMR = 47.0). On the other hand, emphysema/chronic obstructive pulmonary disease (COPD) showed a statistically significant excess. The number of observed deaths from emphysema/COPD was 41, compared with 22.83 expected (SMR = 179.6, $p < 0.01$).

A number of statistically significant deficits were observed in the following causes of deaths. For all diseases of the digestive system, 60 were observed, compared with 95.58 expected (SMR = 62.8, $p < 0.01$). The deficit came mainly from cirrhosis of the liver (35 observed, 56.06 expected, SMR = 62.4). Mortality from diseases of the genitourinary system was significantly low (SMR = 44.1, $p < 0.05$). A statistically significant deficit was also observed in the category of all external causes of death. For this cause of death, 168 deaths were observed, compared with 225.97 expected (SMR = 74.3, $p < 0.01$). The deficit for external causes of death came mainly from the deficit in all accidents (108 observed, 150.16 expected, SMR = 71.9).

Analysis by Length of Exposure

We analyzed SMRs for the entire cohort by length of vinyl chloride exposure by these categories: less than 10 years, 10–20 years, and greater than 20 years (Table III). No obvious increasing trends by length of exposure were identified for any cause of death, except for cancer of the liver and perhaps cancer of the brain and other CNS. For employees with less than 10 years of exposure, 6 deaths were due to cancer of the liver, with 3.30 expected (SMR = 182.1, not significant). However, for those with 10 to 20 years of exposure, there were 20 observed deaths due to cancer of the liver, with only 1.62 expected (SMR = 1235.6, $p < 0.01$). For those employees with more than 20 years exposure, 11 deaths were due to cancer of the liver, compared with only 0.86 expected (SMR = 1284.9 $p < 0.01$).

For cancer of the brain and other CNS, among those employees with less than 10 years exposure, 13 deaths were observed and 7.90 expected (SMR = 164.7, not significant). Among those with 10 to 20 years exposure, 4 deaths were due to cancer of the brain and other CNS, compared with 3.31 expected (SMR = 120.8, not significant). However, for those employees with 20 or more years of exposure, there were 6 deaths, compared with only 1.55 expected (SMR = 385.9, $p < 0.05$).

For emphysema/COPD, among those employees with less than 10 years of exposure there were 25 observed deaths, while 11.97 were expected (SMR = 208.9, $p < 0.01$). For those with 10 to 20 years of exposure, there were 11 deaths due to emphysema and COPD compared with 6.59 expected (SMR = 166.8, not significant). For the group with more than 20 years of exposure, the number of emphysema and COPD deaths was 5, with 4.27 expected (SMR = 117.1, not significant).

Analysis by Latency

Long latent periods are usually required for chronic diseases to develop. In many situations, it is more appropriate to examine mortality experience only after a

TABLE IV. Observed Deaths by Cause and SMRs for All Cohort Members by Latency Since First Exposure to Vinyl Chloride

Cause of death (7th ICDA)	Latency since first exposure: < 20 years Observed	< 20 years SMR	20–30 years Observed	20–30 years SMR	30 + years Observed	30 + years SMR
All causes (1–999)	644	80.7[a]	355	103.5	337	90.8
All cancers (140–205)	130	93.2	133	113.4	96	113.0
Cancer of buccal cavity and pharynx (140–148)	6	126.5	4	95.8	2	75.9
Cancer of digestive system (150–159)	31	85.3	32	105.1	36	160.8[b]
Cancer of esophagus (150–150)	2	66.5	2	67.3	3	143.5
Cancer of stomach (151–151)	4	54.7	4	77.9	2	56.1
Cancer of large intestine (153–153)	8	72.7	3	30.2[b]	9	114.5
Cancer of liver and biliary tract (155–156)	10	385.7[a]	11	590.1[a]	16	1218.3[a]
Cancer of pancreas (157–157)	5	70.0	7	107.6	4	84.2
Cancer of respiratory system (160–164)	45	100.0	47	104.1	23	71.6
Cancer of lung (162–163)	44	103.8	45	105.0	22	71.8
Cancer of bone (196–196)	0	—	1	197.4	1	342.3
Cancer of skin (190–190)	2	49.4	2	92.4	2	173.5
Cancer of prostate (177–177)	1	27.5	6	113.8	8	127.1
Cancer of bladder (181–181)	1	36.2	2	67.5	2	73.3
Cancer of kidney (180–180)	5	131.8	2	62.5	4	193.9
Cancer of brain and CNS (193–193)	13	183.8	6	158.3	4	210.7
Lymphatic and hematopoietic cancer (200–205)	16	87.4	14	129.8	7	97.2
Lymphosarcoma and reticulosarcoma (200–200)	7	170.2	3	121.2	1	72.1
Hodgkin's Disease (201–201)	2	51.5	1	90.9	0	—
Leukemia and aleukemia (204–204)	5	71.0	6	148.1	2	70.4
Other lymphatic tissue cancer (202–203)(205–205)	2	69.7	4	134.8	4	176.6
Benign neoplasms (210–239)	2	71.8	2	142.4	0	—
Diabetes mellitus (260–260)	12	113.5	7	94.1	3	54.4
Diseases of blood (290–299)	1	50.7	1	97.1	0	—
Vascular lesions of CNS (330–334)	23	66.1[b]	20	66.1	27	100.4
Diseases of circulatory system (400–468)	250	83.7[a]	251	101.7	134	76.2[a]
Arteriosclerotic heart disease (420–420)	201	83.9[b]	200	95.7	87	58.4[a]
Nonmalignant respiratory disease (470–527)	20	62.4[b]	26	88.2	24	92.0
Pneumonia (490–493)	5	35.6[b]	5	50.7	5	62.3
Emphysema, including C.O.P.D. (527–527)	11	157.5	17	198.0[b]	13	179.0
Diseases of digestive system (530–587)	27	54.6[a]	15	49.3[a]	18	114.6
Cirrhosis of liver (581–581)	14	48.5[a]	9	48.0[b]	12	142.1
Diseases of genitourinary system (590–639)	1	8.9[a]	6	116.3	2	50.5
Accidents, poisonings, and violence (800–998)	123	74.3[a]	37	84.7	8	47.5[b]
Accidents (800–962)	82	73.2[a]	18	66.0	8	74.0
Motor vehicle accidents (810–835)	42	73.8[b]	7	61.9	3	77.9
Suicide (963–963)(970–979)	29	79.6	17	143.3	0	—

[a]Significant at 1% level.
[b]Significant at 5% level.

For cancer of the brain and other CNS, the trend by latency was not at all obvious. The brain cancer SMRs were 183.8, 158.3, and 210.7, respectively, for those employees with less than 20, 20 to 30, and 30 or more years of latency. Furthermore, none of the three SMRs by latency was statistically significant.

The analysis by latency for emphysema/COPD also did not show any obvious

TABLE V. Observed Deaths by Cause and SMRs for All Cohort Members by Age at First Exposure to Vinyl Chloride

Cause of death (7th ICDA)	Age at first exposure: < 25 years Observed	< 25 years SMR	25–34 years Observed	25–34 years SMR	35 + years Observed	35 + years SMR
All causes (1–999)	249	90.4	547	86.1[a]	740	93.1
All cancers (140–205)	45	94.7	151	117.5	163	98.4
Cancer of buccal cavity and pharynx (140–148)	1	66.2	5	111.6	6	107.9
Cancer of digestive system (150–159)	12	113.2	44	137.5	43	92.3
Cancer of esophagus (150–150)	1	104.4	4	132.1	2	48.9
Cancer of stomach (151–151)	0	—	3	54.6	7	80.1
Cancer of large intestine (153–153)	0	—	8	77.1	12	80.7
Cancer of liver and biliary tract (155–156)	10	1611.0[a]	16	813.2[a]	11	345.7[a]
Cancer of pancreas (157–157)	1	44.7	6	88.0	9	96.4
Cancer of respiratory system (160–164)	15	93.5	53	111.5	47	80.1
Cancer of lung (162–163)	14	91.8	50	110.8	47	84.7
Cancer of bone (196–196)	0	—	2	298.3	0	—
Cancer of skin (190–190)	2	118.5	4	129.7	0	—
Cancer of prostate (177–177)	1	124.2	2	49.7	12	115.7
Cancer of bladder (181–181)	1	142.8	1	37.3	3	59.1
Cancer of kidney (180–180)	0	—	6	169.0	5	119.0
Cancer of brain and CNS (193–193)	3	110.8	9	164.8	11	239.5[b]
Lymphatic and hematopoietic cancer (200–209)	7	99.7	15	105.4	15	99.9
Lymphosarcoma and reticulosarcoma (200–200)	3	207.6	3	94.2	5	149.4
Hodgkin's Disease (201–201)	0	—	1	43.6	2	130.3
Leukemia and aleukemia (204–204)	3	113.0	6	113.2	4	66.8
Other lymphatic tissue cancer (202–203)(205–209)	1	81.0	5	153.8	4	102.8
Benign neoplasms (210–239)	0	—	3	145.3	1	49.0
Diabetes mellitus (260–260)	3	83.9	9	104.5	10	88.2
Diseases of blood (290–299)	0	—	0	—	2	114.8
Vascular lesions of CNS (330–334)	1	10.8[a]	23	80.8	46	84.8
Diseases of circulatory system (400–468)	86	98.1	198	76.0[a]	351	94.1
Arteriosclerotic heart disease (420–420)	67	93.0	149	68.4[a]	272	88.3[b]
Nonmalignant respiratory disease (470–527)	7	69.2	19	63.0[b]	44	93.0
Pneumonia (490–493)	5	113.9	2	18.1[a]	8	48.6[b]
Emphysema, including C.O.P.D. (527–527)	2	106.5	12	160.0	27	200.7[a]
Diseases of digestive system (530–587)	14	81.7	22	55.9[a]	24	61.4[b]
Cirrhosis of liver (581–581)	10	91.0	12	49.1[a]	13	63.0
Diseases of genitourinary system (590–639)	2	63.7	1	14.2[b]	6	58.5
Accidents, poisonings, and violence (800–998)	57	73.4[b]	67	71.3[a]	44	81.0
Accidents (800–962)	33	62.5[a]	47	76.4	28	78.3
Motor vehicle accidents (810–835)	17	59.5[b]	21	72.6	14	96.4
Suicide (963–963)(970–979)	16	101.1	17	75.3	13	90.3

[a]Significant at 1% level.
[b]Significant at 5% level.

pected (SMR = 219.5, not significant). For the cohort of PVC employees, 16 deaths were due to brain cancer and other CNS, when only 9.47 were expected. The corresponding SMR was 169.0, $p < 0.05$. Only one emphysema/COPD death was observed among the VCM employees. On the other hand, a total of 29 deaths were due to emphysema/COPD among the PVC employees, compared with 17.75 expected (SMR = 163.4, $p < 0.05$).

TABLE VII. Observed Deaths by Cause and SMRs for All Cohort Members by Type of Plant

Cause of death (7th ICDA)	Type of plant: VCM Observed	VCM SMR	PVC Observed	PVC SMR
All causes (1–999)	76	71.8[b]	1150	88.5[a]
All cancers (140–205)	24	113.9	272	104.6
Cancer of buccal cavity and pharynx (140–148)	3	424.5	6	68.5
Cancer of digestive system (150–159)	4	77.8	78	113.8
Cancer of esophagus (150–150)	1	206.8	6	97.6
Cancer of stomach (151–151)	0	—	7	56.4
Cancer of large intestine (153–153)	0	—	16	72.4
Cancer of liver and biliary tract (155–156)	1	325.8	31	693.3
Cancer of pancreas (157–157)	1	91.0	11	78.3
Cancer of respiratory system (160–164)	12	155.7	85	91.8
Cancer of lung (162–163)	11	150.1	82	93.5
Cancer of bone (196–196)	0	—	1	72.8
Cancer of skin (190–190)	0	—	6	110.6
Cancer of prostate (177–177)	1	144.2	12	98.6
Cancer of bladder (181–181)	0	—	5	75.6
Cancer of kidney (180–180)	1	172.7	8	116.9
Cancer of brain and CNS (193–193)	2	219.5	16	169.0
Lymphatic and hematopoietic cancer (200–209)	0	—	31	113.6
Lymphosarcoma and reticulosarcoma (200–200)	0	—	10	167.4
Hodgkin's Disease (201–201)	0	—	3	74.3
Leukemia and aleukemia (204–204)	0	—	11	104.3
Other lymphatic tissue cancer (202–203)(205–209)	0	—	7	110.8
Benign neoplasms (210–239)	0	—	3	78.0
Diabetes mellitus (260–260)	0	—	14	77.9
Diseases of blood (290–299)	0	—	1	34.2
Vascular lesions of CNS (330–334)	3	62.6	60	83.3
Diseases of circulatory system (400–468)	26	62.0[b]	463	83.6[a]
Arteriosclerotic heart disease (420–420)	18	51.1[a]	357	78.0[a]
Nonmalignant respiratory disease (470–527)	1	20.4	54	79.5
Pneumonia (490–493)	0	—	11	44.3[a]
Emphysema, including C.O.P.D. (527–527)	1	82.6	29	163.4[b]
Diseases of digestive system (530–587)	4	61.9	46	64.2[a]
Cirrhosis of liver (581–581)	3	72.6	26	62.9[b]
Diseases of genitourinary system (590–639)	0	—	6	37.4[a]
Accidents, poisoning, and violence (800–998)	14	77.5	125	75.6[a]
Accidents (800–962)	10	85.9	80	72.4[a]
Motor vehicle accidents (810–835)	4	68.8	36	68.6[b]
Suicide (963–963)(970–979)	4	95.0	34	88.2

[a]Significant at 1% level.
[b]Significant at 5% level.

opment of lung cancer, as well as lymphatic and hematopoietic cancer. The update extended the observation period from the end of 1972 to the end of 1982. In addition to the 707 deaths identified in the original study, 829 deaths were identified in the update, 1973–1982, bringing the total number of deaths in the entire study to 1,536. With these newly identified deaths, we now can answer some of the questions that were raised in previous studies.

The cohort as a whole continued to experience a favorable general mortality

the biliary system). Excluding the 15 angiosarcomas, there were 22 cases of liver and biliary tract cancers with only 5.7 expected, for an SMR of 386.0 ($p < 0.02$).

The above cited liver cancer diagnoses based on death certificates probably included cases of angiosarcoma which were not properly diagnosed. In an effort to validate the death certificate diagnosis of the 37 cases of liver/biliary tract cancer, requests for medical records were made to hospitals and attending physicians. Because of the lack of consent from the families, records were obtained for only 17 cases.

In 14 of the 17 cases, actual pathology reports were available. Among these 14 cases, based on the death certificate diagnosis, there were 8 cases of primary liver/biliary tract cancer, 5 cases of angiosarcoma, and 1 case of secondary liver cancer metastatic from another organ. In the same 14 cases, based on pathology records, there were 5 cases of primary liver/biliary tract cancer, 7 cases of angiosarcoma, and 2 cases of secondary liver cancer. Therefore, in 5/8, or 63% of the subset of 14 cases, the death certificate diagnosis of primary cancer of liver/biliary tract agreed with the pathology records.

Among the total 37 cases of liver and biliary tract cancer, 22 were listed on death certificates as dying of primary liver/biliary tract cancer. It is likely that cases of angiosarcoma and metastatic cancer of the liver were included among these 22. As indicated by our review of 14 pathology reports, the agreement rate between death certificates and pathology records for the diagnosis of primary cancer of the liver/biliary tract was 63%. We can estimate that the correct number of primary liver/biliary tract cancers is therefore 22 × 63%, or 13.9. With the expected number of liver cancer deaths of 5.7, the corrected liver cancer SMR is 243 ($p < 0.01$). Thus, after adjusting for the over-reporting of primary liver/biliary tract cancer, there remains a significant excess of primary cancer of the liver/biliary tract among this cohort of vinyl chloride workers.

Another approach was to check the 37 cases of liver/biliary tract cancer against the list of angiosarcomas maintained by ICI. According to the ICI list, there were 21 angiosarcomas among these 37 cases, leaving 16 cases of liver/biliary tract cancer. The corresponding SMR for liver/biliary tract cancer would become 281 ($p < 0.01$).

While angiosarcoma of the liver was the main concern as the primary cancer associated with vinyl chloride exposure, there was also an excess of cancer of the biliary tract (including gall bladder) among this cohort. The excess persisted even after adjustments for misdiagnosis based on death certificates were made. According to the Third National Cancer Survey incidence data, 52% of all hepatobiliary cancers are liver, while 48% arise from the biliary tract. According to these figures, in our study 2.7 cases (non-age adjusted) would be expected to be from the biliary tract, whereas 7 cases were reported for an observed/expected ratio (in %) of 259 ($p < 0.05$). This increase in biliary tract cancer (independent of liver cancer) in vinyl chloride workers has not been previously noted or reported. These results are shown in Table VIII.

This update confirms the excess in cancer of the brain and CNS. In the entire study, 23 deaths were due to brain cancer, compared with 12.76 expected. The corresponding SMR of 180.2, statistically significant at the 0.05 level, was very similar to the SMR of 203 previously reported for the same cohort by Cooper and the combined relative risk for overall brain cancer of 1.74 estimated by Beaumont and

COPD excess. In particular, we do not have information on smoking history of the cohort members. Therefore, cigarette smoking could not be assessed as an explanation for the excess. However, it must be pointed out that there was no excess in lung cancer, which would imply that the cohort did not have a higher percentage of smokers than the general population.

One of the unresolved epidemiologic issues is the relationship between occupational exposure to vinyl chloride and respiratory cancer. Previous studies have provided conflicting results on the issue of whether employees exposed to vinyl chloride experienced a higher risk of respiratory cancer. Many of the previous studies, which did not find an excess in lung cancer, have been criticized for lack of statistical power. Our study, being one of the largest studies of vinyl chloride workers, did not indicate any excess in respiratory cancer. Overall, our study had 80% power to detect an increased risk as small as 24%.

Some of the previous studies have also shown an increased risk of cancer of the lymphatic and hematopoietic system among vinyl chloride workers, while others did not find such an excess. In our study, the corresponding SMR was 102.0. Thus, we did not detect any excess of these types of cancer. Overall, our study had 80% power to detect an increased risk in lymphatic and hematopoietic cancer as small as 45%.

It should be pointed out that there are several limitations in this study, most of which are typical of an historical mortality study of industrial populations. The major limitation of this study is the lack of exposure information for the cohort members. As such, analyses by detailed exposure were not feasible.

Another limitation of the study was that a small percentage of the cohort was lost to vital status follow-up. Among those who participated in the update, the vital status of 7.88% cohort members remained unknown as of December 31, 1982. In addition, among those who did not participate in the update, the vital status of 1.85% cohort workers remain unknown as of December 31, 1972, the end of the observation in the original study. A related limitation was that for 6% of all deaths identified in the study, no death certificate was available. Therefore, it was possible (but not very likely) that the missing information in vital status or cause of death could have modified the results of this study.

In the study, the entire cohort was assumed to be white, even though some might be non-white. Among those with race information, only 3% were non-white. However, if the actual number of non-white was larger, some of the results of this study might have been modified.

Finally, being a mortality study, this investigation not only inherited all the problems associated with death certificates (for example, diagnostic accuracy), but also suffered from the lack of in-depth clinical information. In particular, histologic information on the cell type of the liver cancers and brain cancers would have been useful in interpreting the epidemiologic findings.

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NOV 12 '91

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FYI
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November 8, 1991

J.R. Drumwright, M.D.
Manager-Medical

Roy T. Gottesman
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Dear Roy:

Bob Hinderer and I have discussed the Wong et al 1991 study entitled "An Industry-wide Epidemiology Study of Vinyl Chloride Workers, 1942-1982".

I first heard about the updated report while attending the Denver meeting of the VCSA. The BNA report had addressed some of Wong's conclusions as they were reported in the American Journal of Industrial Medicine.

My comments essentially agree with those already presented to you by Bob Hinderer. Namely, the use of the ICD-7 classification lumps all brain and other CNS cancers together; death certificate data without adequate histopathological diagnosis/review and assumptions established without specific cause/effect, consistency in latency period, etc.

Bob's recognition that the authors had apparently failed to have the CMA Panel review the report prior to publication by Wong led to his discussing this with Dr. Shah. It is my understanding that CMA will be addressing this with Dr. Wong.

In any event, the study has been published and we must be cognizant of this when new litigation appears. Hopefully, clarification by Wong et al will receive adequate publication as well.

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I plan to keep in contact with Bob and will keep you posted as well on any events dealing with this issue.

Sincerely,

J. R. Drumwright, M.D., FACOM

JRD/sjl

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October 21, 1991

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Dear Roy:

In response to your request, you should note that there are two main problems with the study by Wong et al. 1991, entitled "An Industry-wide Epidemiology Study of Vinyl Chloride Workers, 1942-1982". First, the authors use the 7th rather than the 9th revision of the International Classification of Disease. The effect here is to lump all brain cancers together. Secondly, the authors leave the question of whether there is a relationship between VCM and brain cancer hanging without providing some logical comments and assessments.

While they reference Doll's earlier review paper in the introduction, they fail to mention what is important from that paper. Specifically, they fail to note that for brain cancer, and in fact all cancers except liver, there is no consistency across studies which is an important consideration in assessing causal relationships in epidemiology studies. Furthermore, the effect of other potential biasing/confounding factors (eg. other exposures) are not addressed.

When I obtained a copy of this publication, I quickly realized that this was the work that was sponsored by the CMA VCM Panel. Unfortunately, the authors failed to send a draft to the Panel for review prior to publication. When I discussed this with Dr. Shah at CMA, he indicated that CMA would notify them that they have violated their contract.

The next step will be for the whole Panel to consider what corrective actions are necessary and/or appropriate. Hopefully, the authors will be agreeable to add some clarifying comments in a letter to the editor.

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At present, I view this as a CMA project. However, I will keep you posted as things progress.

Best regards,

THE BFGOODRICH COMPANY

Robert K. Hinderer,Ph.D.
Manager, Health and Toxicology
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1021-4/jp

cc: Dr. Drumwright
Dr. Shah - CMA