Cohort and Case-Control Analyses of Workers Exposed to Vinyl Chloride: An Update

Weiai Wu, PhD; Kyle Steenland, PhD; David Brown, MS; Victoria Wells, PhD; James Jones, BS; Paul Schulte, PhD; and William Halperin, PhD

The mortality in a cohort of workers at a vinyl chloride polymerization plant has been updated, extending the period of observation in the original study from 1974 to 1986. Workers at this plant may have been exposed to vinyl chloride monomer and/or polyvinyl chloride dust, or may have had no exposure to either substance. Seventy-six percent of the work force worked in jobs with potential exposure to vinyl chloride monomer. Among the total cohort, statistically significant excess risks were observed for liver, lung, and brain cancer. For the subcohort of workers exposed to vinyl chloride monomer, the standardized mortality ratio (SMR) for liver cancer was 333 (90% confidence interval (CI) 202 to 521). However, there were no significant excesses of either brain (SMR = 145, 90% CI 78 to 249) or lung cancer (SMR = 115, 90% CI 96 to 141). To investigate dose response, nested case-control studies for liver, brain, and lung cancer were conducted among the total cohort (including the nonexposed). For these studies there were two exposure variables, cumulative dose of vinyl chloride monomer and cumulative dose of polyvinyl chloride dust. Cumulative dose was defined as the product of level and duration of exposure. The only significant association between disease risk and cumulative dose was for liver cancer and cumulative dose of vinyl chloride monomer. Further division of the liver cancers into angiosarcoma (n = 12) and other liver cancers (n = 7), based on review of death certificates and medical records, showed that the dose response existed only for angiosarcomas.

The association between exposure to vinyl chloride monomer (VCM) and development of angiosarcoma of the liver (ASL) has been well documented by epidemiologic and laboratory studies.[1-5] However, the association between VCM and other cancers is unclear.

Not only ASL but also malignant tumors of several organs such as skin, lung, bone, zimbal gland, kidney, and mammary gland have been found in experimental animals exposed to VCM.[4-6] Several epidemiologic studies of VCM-exposed workers have found an excess of cancers other than ASL,[7-10] cancer of the lung and brain being of particular concern. However, more recent studies with longer follow-up have failed to confirm significant associations between VCM and lung cancer, whereas the data have been contradictory for brain cancer.[11-13] Some investigators have also suggested that an excess of lung cancer is associated with exposure to polyvinyl chloride (PVC) dust.[14]

A comprehensive review of the vinyl chloride studies to date has recently been published by Doll.[15] This review concludes that there is little evidence to date for an association between VCM and any malignancy with the exception of liver cancer. Furthermore, the excess of liver cancer appears to be confined to ASL.

The purpose of this study was to further test the hypothesis that exposure to VCM is associated with liver, brain, or lung cancer, by extending the period of observation among a cohort of workers at a large VCM/PVC polymerization plant from 1974 to 1986. In addition to extending the period of observation in a cohort study, we have conducted nested case-control studies of liver, brain, and lung cancer to test for possible associations

From the Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, People's Republic of China (Dr Wu); the Industrywide Studies Branch, Division of Surveillance, Hazard Evaluation and Field Studies, National Institute for Occupational Safety and Health, US Public Health Service, Department of Health & Human Services, Cincinnati, OH 45226 (Dr Steenland, Mr Brown, Dr Wells, Dr Schulte, Dr Halperin); and the Engineering and Control Technology Branch, Division of Physical Science Engineering, National Institute for Occupational Safety and Health, Cincinnati, OH 45226 (Mr Jones).

Address correspondence to NIOSH, Industrywide Studies Branch, Robert A. Taft Laboratories, Cincinnati OH 45226-1998 (Dr Steenland).

0096-1736/89/3106-0518$02.00/0

between cumulative dose and either VCM or PVC dust (defined as duration of exposure times level of exposure). For the case-control studies, each job was assigned a level (0 to 5) of exposure of VCM monomer, and a level of PVC dust. These levels served as an estimate of relative exposure for each job.

The plant studied in this report has been the subject of three prior investigations.[7,12,14] In the first two reports, the cohorts were observed only through 1973. In the first report,[7] the cohort was restricted to men who had been exposed to VCM and had at least 15 years since first employment (a subset of those studied here). Statistically significant excesses of mortality from cancer of the respiratory system (9 observed *v* 4.6 expected, SMR = 194), brain and CNS (2 observed *v* 0.5 expected, SMR = 498), and biliary and liver cancer (6 observed *v* 0.4 expected, SMR = 1606) were observed. To further investigate the lung cancer excess observed in this first study, Waxweiler et al[14] again studied this plant. They included all workers at the plant (not just those exposed to VCM), but did not extend the observation period. After assigning each job a dose level for a variety of chemicals (VCM, PVC dust, and others), Waxweiler et al[14] used a nested case-control approach to determine which chemical exposures at the plant were associated with lung cancer. These investigators concluded that the agent most likely associated with the observed excess of lung cancer was PVC dust. Finally, this same plant was included in an industry-wide study (37 plants) of workers exposed to VCM,[12] in which the period of observation extended through 1982 and all workers were required to have a minimum of 1 year exposure. However, in the industry-wide study, the data were not reported for each specific plant. The industry-wide study also did not assign exposure levels to specific jobs and did not conduct a dose-response analysis, with the exception of an analysis by duration of exposure.

Methods

Description of the Plant and Exposure

The PVC polymerization plant under consideration in this study began operations in 1942. This study has been restricted to the workers who were employed at the plant between 1942 and 1974, when records were collected. In 1974, there were 271 persons working in PVC polymerization and about 850 persons employed at the plant in other activities such as synthetic rubber production, compounding and milling operations, managerial and clerical positions, and maintenance work outside PVC polymerization areas.

Prior to 1966, VCM, as well as PVC, was produced at the plant. After 1966, however, all VCM utilized at the plant was shipped by tank car from other facilities, reducing the number of workers exposed to VCM. After 1966, the VCM was unloaded and piped into large polymerization reactors through essentially a closed system. Each reactor received a measured amount of VCM along with appropriate catalysts, stabilizers, emulsifiers, and additives. The mixture was heated under pressure and the polymerization reaction took place. After polymerization, the reactors were opened and cleaned manually, resulting in some exposure to VCM. In the late 1970s, larger reactors were installed which eliminated, almost entirely, the need for manual cleaning.

Exposure to PVC dust occurred primarily during the packing of the dried polymer, which was in the form of a powder. PVC dust exposure occurred in many of the same areas in which exposure to VCM monomer occurred. The plant also had several other product lines, in addition to PVC production. Some workers at the plant were exposed to butadiene during the production of styrene-butadiene rubber. Because animal studies have indicated that butadiene might be a lung or liver carcinogen,[16] we also evaluated its possible effects in our case-control studies.

Quantitative exposure data for VCM for this particular plant was not available. However, some general statements can be made based on the overall history of the industry. Because VCM initially was thought to be harmless, there were no limits on exposure in the 1940s and early 1950s.[1] The first recommendations for limiting exposures to 500 ppm were issued in 1955 in the United States. One estimate is that typical exposures to VCM among the more highly exposed workers at VC/PVC polymerization plants were as high as 1000 ppm prior to 1955, from 300 to 500 ppm during 1955 through 1970, and from 100 to 200 ppm during 1970 to 1974.[17] Following reports in 1974 of VCM carcinogenicity in animals and case reports of liver cancer in humans, the Occupational Safety and Health Administration (OSHA) promulgated a 1 ppm standard. Industrial exposures have been generally below that level since that time.[18,19] We have no data on work history after 1974, when the original records were collected. However, exposure was minimal after 1974, when OSHA limited exposures to 1 ppm.

Retrospective Cohort Mortality Study

Of the total number of employees who had worked at the plant prior to data collection, only 5% were female. Although data on race were not available, company estimates were that less than 2% of the work force was nonwhite.[14] For the purpose of this study, all employees were considered white. Cohort analyses were restricted to 4835 men ever employed at the plant between 1942 (when the plant opened) until Dec 31, 1973 (data collection). Among these cohort members, those with work histories indicating they had exposure to VCM at the plant were included in a specific VCM subcohort (75% of entire cohort, 3635 out of 4835). These men may or may not have had exposure to PVC dust.

The vital status of the cohort was determined using standard techniques of follow-up, principally via records of the Social Security Administration, the Internal Revenue Service, and the National Death Index.[20] Follow-up for each worker extended from date of hire until Dec 31, 1986. If the vital status could not be determined,

the worker was assumed to be alive through the study end date. For all those identified as deceased, an attempt was made to obtain the death certificate from the state vital statistics office. If death certificates could not be located, the person was assumed to be deceased, but with an unknown cause of death. The underlying cause of death was coded by a qualified nosologist according to the rules given in the revision of the International Classification of Diseases at the time of death.

A modified life Table Analysis Program[21] was used to obtain person-years at risk (PYAR) by 5 year age and 5 year calendar periods. In the analysis of the subcohort, PYAR did not start accumulating until the worker was employed in a job considered exposed to VCM. The death rates for white men in the United States were used to calculate the expected number of deaths. Standardized mortality ratios (SMR) were calculated by dividing the observed deaths by the expected deaths and were tested for statistical significance assuming the Poisson distribution.[22]

Case-Control Studies

To determine whether a dose-response for VCM or PVC dust existed for any of the cancer sites of interest, case-control studies nested within the original population at risk were conducted for these cancers. For the case-control studies, each job held by each man was ranked by level of exposure (0 to 5, see Table 1) to VCM and to PVC dust. Given that butadiene (a potential lung and liver carcinogen[16]) was also used at the plant, jobs were also ranked by level of exposure to butadiene. The rankings were done by industrial hygienists taking into account the nature of the job and the calendar time in which the exposure occurred. The ranking was originally developed for use in the earlier report by Waxweiler et al.[14]

The dose-response analysis was based on a measure of cumulative dose, which was developed specifically for use in the case-control studies. Three separate cumulative dose variables (for VCM monomer, PVC dust, and butadiene) were created. Cumulative dose was determined by assigning a level of exposure for each chemical in question for each job held by each worker in the case-control study (Table 1), multiplying this level by the duration of the job, and then summing these products across all jobs. A significant positive dose-response was determined to exist if the regression coefficient for cumulative dose was positive and statistically significant.

Case and control subjects were selected from the entire original population at risk (VCM-exposed and nonexposed, women included). Case subjects for the case-control studies were deaths from the cause of interest identified in the cohort study. Case subjects were matched to five control subjects by age, via a National Institute for Occupational Safety and Health control selection computer program described elsewhere.[23] Briefly, for each case subject (failure), a risk set of those who attained the same age as the case subject was created. A random sample of five control subjects was then chosen from the risk set. For each control subject, the work history was truncated at the time the control subject reached the age at which the index case subject died.

Conditional logistic regression was used to analyze the data.[24] The model included variables for sex (dichotomous), year of first employment (continuous), cumulative dose of VCM, cumulative dose of PVC dust, and cumulative dose of butadiene (all continuous). When potential confounders (sex, year of first employment, butadiene) did not confound (or interact) with the exposure variables (VCM, PVC dust), they were dropped from the model.

TABLE 1
Exposure Ratings Used in Case-Control Studies to Classify Jobs According to Exposure to VCM, PVC Dust, and Butadiene*

Rating	Exposure
0	No exposure
1	Minimal exposure to low levels (chemical in building, not handled; low vapor pressure and dust level; probably works on different floor)
2	Moderate exposure (works around the chemical, but exposure is minimal)
3	Works in areas where subject to occasional high excursions (normally exposure is minimal but occasional spills, leaks, or dust exposure may occur)
4	Works in areas where level is high (exposure levels in the area are frequently high, might consider that some risk is involved if chemical is very toxic)
5	Intimate contact, skin or high inhalation (such as poly cleaners in earlier years handling slurry)

* From Waxweiller et al.[14] A separate ranking was made for each job for each worker, for each of the three chemicals.

Results

Cohort Mortality Analyses

Vital status and the distribution of person-years for the whole cohort and the VCM-exposed subcohort are presented in Tables 2 and 3. Most workers had been employed for less than 5 years.

The cause-specific mortality from the whole cohort and the VCM subcohort is displayed in Table 4. The updated cause-specific mortality for the whole cohort revealed excesses for liver cancer (18 observed *v* 6 expected, SMR = 300, 90% confidence interval [CI] 196 to 449), for lung cancer (115 observed *v* 94 expected, SMR = 122, 90% CI 104 to 142) and for brain cancer (15 observed *v* 9 expected, SMR = 166, 90% CI 100 to 250). Among 18 liver cancers found in the whole cohort, 12 cases were diagnosed as ASL, according to information on the death certificates or hospital reports.

In the VCM subcohort, these excess risks persisted, but they were not significant for lung and brain cancer. The SMRs were as follows: liver cancer, 14 observed *v* 4 expected, SMR = 350, 90% CI = 202 to 521; for lung

cancer, 80 observed *v* 68.8 expected, SMR = 116, 90% CI = 96 to 140; and for brain cancer, 10 observed *v* 6.8 expected, SMR = 147, 90% CI = 80 to 249).

The results of further analysis by duration of employment in VCM-exposed jobs for liver, lung, and brain cancer are presented in Table 5. These results indicate that the risk of mortality due to cancer of the liver was consistently elevated for all duration categories after 5 years of exposure. No such increase with duration of exposure was seen for lung cancer and brain cancer. No analyses were done with "lagged" exposures (in which most recent exposures are discounted as unlikely to contribute to cancer development) because exposure histories ended in 1974 (date of date collection). The end of follow-up for most persons was far later, so that, in effect, a lag period already existed for these data.

Case-Control Studies

Table 6 presents the number of workers ever exposed to the three chemicals in question (VCM, PVC dust, butadiene) by case status, for the three case-control studies. As can be seen, there was little difference between case and control subjects for any chemical for any of the three case-control studies. Odds ratios for the three chemicals were not significantly different from 1.00. The majority of case and control subjects were exposed to VCM and to PVC dust, whereas only about 40% had any exposure to butadiene (usually at low levels).

Table 7 shows the average values for cumulative dose for case and control subjects for each of the three chemicals, for the three case-control studies. Coefficients for the cumulative dose coefficients are shown in Table 8. The only statistically significant association was the one between cumulative dose to VCM and liver cancer. For VCM and liver cancer, the estimated odds ratio for having been exposed at the highest level of

TABLE 2
Distribution of Total Cohort and VCM Subcohort by Vital Status

Vital Status	Total Cohort Frequencies (%)	VCM Subcohort Frequencies (%)
Alive	3,620 (75)	2,767 (76)
Dead	1,181 (25)	843 (23.2)
Unknown	34 (1.9)	25 (1)
Total	4,835 (100)	3,635 (100)
Person-years at risk	139,106	103,368

TABLE 3
Distribution of Person-Years at Risk by Duration of Employment for Whole Cohort and VCM Subcohort

Duration of Employment, yr	Total Cohort		VCM Subcohort*	
	Person-yr	%	Person-yr	%
Less than 5	104,334	75	81,946	79
5–10	13,139	9	8,821	9
10–15	6,989	5	4,158	4
15–20	6,060	4	3,893	4
20–25	5,034	4	2,673	3
25–30	2,923	2	1,729	2
Greater than 30	626	1	149	1

* Duration in VCM Subcohort is based on exposure to VCM only.

TABLE 5
Cancer Risk by Duration of Employment in VCM-Exposed Jobs for the Subcohort with Greater than 15 Years Since First Exposure

Years of Duration, yr	Liver Cancer*			Lung Cancer			Brain Cancer		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
<5	2	2.40	83	54	42.92	126	6	3.58	168
5–10	1	0.22	455	1	3.59	28	0	0.29	–
10–15	2	0.14	1429	4	2.21	181	0	0.16	–
15–20	3	0.39	1000	6	4.56	132	1	0.37	270
20–25	3	0.25	1200	5	4.26	117	1	0.32	313
25	2	0.24	833	3	4.39	68	0	0.28	–
Total	**13**	**3.50**	**371**	**73**	**61.93**	**118**	**8**	**5.00**	**160**

* Liver cancer includes primary liver, gall bladder, biliary passages, and liver not specified.

TABLE 4
Cause-Specific Mortality for Total Cohort and VCM Subcohort

Causes of Death (9th ICD)	Total Cohort			VCM Subcohort		
	Obs.	Exp.	SMR (90% CI)*	Obs.	Exp.	SMR (90% CI)
All deaths	1181	1246.2	94 (90–99)	843	885.7	95 (90–101)
All cancers (140–208)	274	270.5	101 (91–112)	190	195.0	97 (86–110)
Digestive system (150–159)	56	70.4	79 (63–99)	42	50.0	84 (64–109)
Liver (155–156)	18	6.0	300 (196–449)	14	4.2	333 (202–521)
Respiratory system (160–165)	123	99.6	123 (106–143)	85	72.9	116 (97–140)
Larynx (161)	7	4.0	177 (83.2–332)	5	2.9	223 (69–368)
Lung (trachea, bronchus (162)	115	94.5	123 (104–142)	80	69.2	115 (95–139)
Brain (191–192)	15	9.2	162 (100–250)	10	6.8	145 (79–248)
Hematopoietic (200–208)	23	26.3	87 (60–124)	15	19.2	78 (48–121)
Diseases of heart (primarily 410–414)	424	493.5	85 (79–93)	302	348.1	86 (79–95)
Diseases of the circulatory system (primarily 430–438)	88	97.1	90 (75–108)	66	66.6	100 (81–123)
Diseases of respiratory system (460–519)	64	71.2	89 (72–111)	44	49.4	89 (68–115)
Cirrhosis of liver (571)	30	37.0	80 (58–110)	22	27.6	79 (54–114)

* The inclusion or exclusion of an SMR of 100 in a 90% confidence interval corresponds to a one-sided test of significance at the .05 level, given the a priori hypotheses for liver, brain, and lung cancer.

TABLE 6
Case and Control Subjects Chosen from Total Cohort, Ever Exposed to VCM, PVC Dust, and Butadiene in Case-Control Studies of Liver, Brain, and Lung Cancer

	Number (%) Exposed to VCM	Number (%) Exposed to PVC Dust	Number (%) Exposed to Butadiene
Liver cancer study			
Case subjects	16 (84%)	16 (84%)	7 (37%)
Control subjects	74 (78%)	81 (85%)	34 (36%)
Brain cancer study			
Case subjects	13 (87%)	13 (87%)	4 (26%)
Control subjects	63 (84%)	62 (83%)	34 (45%)
Lung cancer study			
Case subjects	96 (84%)	98 (86%)	47 (41%)
Control subjects	475 (83%)	456 (80%)	227 (40%)

TABLE 7
Average Values of Cumulative Exposure (Years of Exposure × Exposure Level)* for Case-Control Studies of Liver, Brain, and Lung Cancer

	Cumulative exposure to VCM	Cumulative exposure to PVC	Cumulative exposure to butadiene
Liver cancer study			
Case subjects	42.8	16.2	1.9
Angiosarcomas (n = 12)	61.1		
Other (n = 7)	11.5		
Control subjects	9.6	9.7	5.0
Brain cancer study			
Case subjects	14.2	19.0	3.6
Control subjects	14.0	13.5	8.8
Lung cancer study			
Case subjects	10.8	10.0	4.6
Control subjects	12.2	11.5	6.1

* Exposure levels varied from 0 (nonexposed) to 5 (heavy exposure), as described in Table 1. For each job the time in the job (years) was multiplied by the exposure level, and these values were summed across all jobs.

TABLE 8
Coefficients and *P* Values for Cumulative Dose (Duration × Exposure Level) for VCM, PVC, and Butadiene in Three Case-Control Studies*

	Coefficient	*P*
Liver cancer study		
VCM	.083	.002
PVC	−.071	.194
Butadiene	−.050	.227
Brain cancer study		
VCM	−.002	.906
PVC	.024	.113
Butadiene	−.063	.150
Lung cancer study		
VCM	.000	.987
PVC	−.001	.897
Butadiene	−.006	.509

* These models included only the three exposure variables. There was no confounding effect of sex or date of first employment, nor any interaction between date of first employment and any exposure varaible. Analyses were done via conditional logistic regression. Case and control subjects were matched on age. Odds ratios for any given level of cumulative dose (level of exposure times duration) are determined by exponentiating the product of the regression coefficient and cumulative dose.

exposure (level 5) for 5 years *v* no exposure was 7.96 (2.17 to 29.2, $P = .002$).

After a review of medical records and death certificates, we divided the liver cancer cases between angiosarcomas (n = 12) and other liver cancers (n = 7). The positive dose response was found to exist only for the angiosarcomas ($P = .03$). Using the data set restricted to the angiosarcoma case subjects and their control subjects, the estimated odds ratio for exposure to VCM for 5 years at level 5 was 109.9.

These results were unchanged when we controlled for the effects of year of first employment. There was no indication of either confounding by year of first employment, nor of interaction between exposure and year of first employment.

Discussion

Results from the cohort mortality study indicate a strong association between exposure to VCM and liver cancer. The cohort mortality study compared an exposed group with the US population. In the nested case-control study, in which the effect of different levels of exposure to VCM on disease risk was evaluated, a strong dose response was seen between VCM exposure and liver cancer. These data confirm the well-known association between VCM and liver cancer. When we divided the liver cancer between angiosarcomas of the liver (n = 12) and other liver cancer (n = 7), we found that the positive dose-response relation held only for the angiosarcomas.

On the other hand, our data do not support the hypothesis that the excess risk of lung cancer and brain cancer which had been observed at this plant is associated with exposure to either VCM or PVC dust. In the VCM subcohort, there were excesses of lung and brain cancer, but these excesses fell short of significance at the .05 level even in a 1-sided test of significance (appropriate given the a priori hypothesis). Statistical power was relatively weak for detecting excess brain cancer, but was good for detecting excess lung cancer. For brain cancer we had an 80% power to detect an SMR of 2.20, whereas for lung cancer we had an 80% power to detect an SMR of 1.33. The lack of significant findings in the cohort analyses for these two cancers was further supported by the lack of a dose response in the case-control studies for exposure to either VCM or PVC dust.

Although Waxweiler et al[14] reported that PVC dust appeared to be associated with an excess risk of lung cancer in this PVC polymerization plant, we did not find such an association. The difference between the two studies may be due to the 13 years of additional observation in our study, resulting in more lung cancer deaths (115 *v* 42) for analysis.

It should be noted that we did not update the work history information from the original study of this plant. Therefore, we could not consider exposures at the plant after Dec 31, 1973. However, after 1974 and the intro-

duction of the 1 ppm OSHA standard, VCM exposures were probably reduced enough that there is minimal effect on the analysis.

Although we failed to find associations between lung cancer or brain cancer and exposure to either VCM or PVC dust in this study, there were at least 19 other potentially carcinogenic or toxic chemicals used or produced at the plant. Some of these chemicals, or differing smoking habits, may have contributed to the observed excess cancer risks observed in the analysis of the total cohort.

References

1. Dannaher CL, Tamburro CH, Yan LT: Occupational carcinogenesis: The Louisville experience with vinyl chloride-associated hepatic angiosarcoma. *Am J Med* 1981;72:279–287.
2. Forman D, Bennett B, Stafford J, et al: Exposure to vinyl chloride and angiosarcoma of the liver: A report of the register of cases. *Br J Ind Med* 1985;42:750–753.
3. Creech JL, Johnson MN: Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 1974;16:150–151.
4. Maltoni C, Lefemine C: Carcinogenicity bioassays of vinyl chloride: current results. *Ann NY Acad Sci* 1975;246:195–218.
5. Maltoni C, Lefemine C, Ciliberti A, et al: Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. *Environ Health Perspect* 1981;41:3–29.
6. Viola PL, Bigotti A, Compute A: Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res* 1971;31:516–522.
7. Waxweiler RJ, Stringer W, Wagoner JK, et al: Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 1976;271:40–48.
8. Tabershaw IR, Gaffey WR: Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 1974;16:509–518.
9. Monson RR, Peters JM, Johnson MN: Proportional mortality among vinyl chloride workers. *Lancet* 1974;2:397–398.
10. Buffler PA, Wood S, Enfler C, et al: Mortality experience of workers in a vinyl chloride monomer production plant. *J Occup Med* 1979;21:195–202.
11. Jones R, Smith D, Thomas P: A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940–1974. *Scand J Work Environ Health* 1988;14:153–160.
12. Wong O, Whorton D, Ragland D, et al: An update of an epidemiologic study of vinyl chloride workers 1942–1982, Final report to Chemical Manufacturers Association, Oakland, CA: Environmental Health Associates, 1986.
13. Dahar W, Bond G, McLaren E, et al: Update to vinyl chloride mortality study. *J Occup Med* 1988;30:648–649.
14. Waxweiler RJ, Smith AH, Falk H, et al: Excess lung cancer risk in a synthetic chemicals plant. *Environ Health Perspect* 1981;41:159–165.
15. Doll, R. Effects of Exposure to Vinyl Chloride, *Scand J Work Environ Health* 1988;14:61–78.
16. NIOSH, 1,3-Butadiene. Current Intelligence Bulletin 41. DHHS Publication No. 84-105, February 9, 1984, Cincinnati, Ohio.
17. Nicholson WJ, Henneberger PK, Seidman H: Occupational hazards in the VC-PVC industry. *Prog Clin Biol Res* 1984;141:155–175.
18. Jones JH: Worker exposure to vinyl chloride and poly(vinyl chloride). *Environ Health Perspect* 1981;41:129–136.
19. U.S. Department of Labor, Occupational Safety and Health Administration, Standard for Exposure to Vinyl Chloride. *Federal Register* 1974;29(Oct 4):35890.
20. Halperin WE, Beaumont J, Brown DP, et al: The cohort study, in Karvonen M, and Mikheev MI (eds) Epidemiology of Occupational Health, European Series no 20. WHO Regional Publications, 1986.
21. Waxweiler RJ, Beaumont JJ, Henry JA, et al: A modified life-table analysis system for cohort studies. *J Occup Med* 1983;25:115–124.
22. Armitage P: *Statistical Methods in Medical Research.* Oxford: Blackwell Scientific Publications, 1971.
23. Steenland K, Beaumont J, Hornung R: The use of regression analyses in a cohort/mortality study of welders. *J Chronic Dis* 1986;39:287–294.
24. SAS, PROC PHGLM, Supplemental User's Guide, Version 5, SAS Institute, Car, NC, 1986.