

Excess Lung Cancer Risk in a Synthetic Chemicals Plant

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A standardized mortality ratio of 1.49 for respiratory system cancer (42 observed deaths versus 28.2 expected, $p < 0.01$) was observed among a cohort of 4806 males employed at a synthetic chemicals plant since its startup in 1942. Upon review of pathologic material, the excess was found to be limited to adenocarcinoma and large cell undifferentiated lung cancer. Many of the workers had been exposed to vinyl chloride, as well as to chlorinated solvents, poly(vinyl chloride) (PVC) dust, acrylates and acrylonitrile. To evaluate the association between lung cancer and occupational chemical exposures, detailed work histories for each cohort member were combined with exposure ratings for each of 19 chemicals for each job for each calendar year since 1942. A serially additive expected dose model was then constructed which compared the doses of the chemicals observed for the lung cancer cases to the doses expected based on subcohorts without lung cancer individually matched to the cases. PVC dust appeared to be the most likely etiologic agent ($p = 0.037$). Time trends of PVC dust exposure indicated a potential latent period of 5-16 years before death.

Introduction

Our previously published (1) retrospective cohort mortality study of workers exposed to vinyl chloride monomer (VCM) at a synthetic chemicals plant demonstrated an excess risk of death from respiratory system cancer in addition to the already recognized association between VCM exposure and angiosarcoma of the liver (2-10). Preliminary review of the lung cancer cases indicated they were all adenocarcinomas or large cell undifferentiated tumors—an unusual histologic distribution.

Although lung tumors have been induced experimentally by exposure to VCM (2), the epidemiologic

data are suggestive but equivocal. Two cohort studies found no excess lung cancer risk (4-6). In six other studies, elevated lung cancer risks were found overall or among subcohorts; however, few of these excesses were statistically significant due to moderate excess risks and/or small numbers of cases (7-9, 11-13).

Because of the uncertainty in the literature regarding the association between VCM exposure and lung cancer and because of the diversity of occupational chemical exposures experienced by the lung cancer cases in our previous study (1), we decided to evaluate our cohort further to determine whether or not lung cancer was associated with VCM or with other chemical exposures. Thus, the following research had three objectives: (1) by using a retrospective cohort design, to determine if our previously published excess lung cancer risk among employees exposed to VCM at this synthetic plastics plant also existed for the total plant population (2) by using a case-comparand study, to determine whether an excess lung cancer risk of a particular histologic type was in force at the plant and (3) by using a serially additive expected dose model, to test whether one or more particular

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chemicals used at the plant were associated with either the excess risk of all or of a specific histologic type of lung cancer.

Methods and Results

Retrospective Cohort Study

The population at risk for the retrospective cohort study consisted of the 4806 males ever employed at this plant from its opening in 1942 until December 31, 1973. In the absence of individual data on race, everyone was assumed to be white because the company indicated that less than 2% of the population had been nonwhite. Date of birth and detailed work histories at this plant of all jobs and dates worked by each individual were coded. By follow-up of all study members from the first date hired at the plant through December 31, 1973, it was determined that 4174 were alive and 559 had died. The 73 (1.5%) persons lost to follow-up were considered alive throughout the study. The 16 (3%) deceased persons for whom no death certificates could be located were assumed dead, cause of death unknown. A modified life table analysis (NIOSH) was used to obtain person years at risk of dying by five year age and calendar time periods. United States white male death rates specific for five year age and calendar intervals were used to calculate the expected deaths and standardized mortality ratios (SMR's). SMR's were tested for statistical significance using the Poisson distribution (one-sided).

The cohort was young; by December 31, 1973, only 30% of the cohort, if alive, would have been over 54 years of age. However, 63% of the cohort had been hired before 1954 and thus had the opportunity to achieve 20 years' latency.

Two separate analyses of the cohort were made. Initially, all members were considered at risk from their first date of employment at the plant. This analysis yielded 556 observed and 550 expected deaths (Table 1). Risk of death due to malignant neoplasms of the central nervous system (SMR = 209) and respiratory system (SMR = 149) were both significantly elevated. A second "over ten-year latency" analysis was carried out by beginning person-years at risk only after an individual had achieved the tenth anniversary of his first date of employment at the plant. Results similar to those in the first cohort analysis were found but with slightly higher SMR's. Respiratory system cancer had an SMR of 156 based on 39 observed cases. Because our previously published analysis (1) of just the presumably VCM-exposed workers at this plant

Table 1. Observed and expected deaths among chemical plant worker cohort.

Cause (ICDA-7 Code)	Observed	Expected	SMR
All causes	556 ^a	550.2	101
All malignant neoplasms (140-205)	109	92.5	118
Digestive system (150-159)	24	25.6	94
Respiratory system (160-164)	42	28.2	149 ^b
Central nervous system (193)	9	4.3	209 ^c
Lymphatic and hematologic (200-205)	9	11.4	79
Other cancers	25	23.0	109

^aFive persons, including three of the original 559 deaths, were not included in the cohort analysis because of missing work histories.

^b $p < 0.01$.

^c $p < 0.05$.

also found an SMR of 156 after 10 years latency, these results indicate an excess lung cancer risk not solely due to VCM exposure.

Case-Comparand Study

The second objective of this study was to determine whether an excess risk existed for a particular histologic type of lung cancer. Because no historical data exist on histology-specific lung cancer incidence or mortality rates and because histologic classification is somewhat variable between pathologists and over time, a case-comparand design was chosen to accomplish the second objective.

Medical records and pathology reports were obtained on all deceased members of the cohort whose death certificates mentioned cancer or respiratory disease. For 45 cohort members, primary or unspecified lung cancer was reported on at least one of these three records. A few persons who died after December 31, 1973, the cohort ending date, were included. Of the 45 cases, 42 were born in Kentucky or an adjacent state. Histologic material was requested. The worker case group consisted of the 27 of the 45 deceased individuals for whom histologic specimens were available.

As a comparison group, the lung cancer cases (comparands) most closely preceding and succeeding the chemical plant worker case in the chronologically ordered hospital pathology logs were selected that matched in age at diagnosis, sex, race, and county of residence. For four cases, only one matched comparand could be found.

Histologic material was reviewed by a panel of pathologists unaware of the employment histories (case versus comparand status) of the deceased. The histologic type distributions, according to the

Environmental Health Perspectives

Veterans' Administration classification scheme (14), were compared between the cases and comparands.

The results of the majority opinion of the pathology panel are listed in Table 2. The panel found a significantly ($p < 0.05$, chi-square) higher percentage of large cell undifferentiated (type 4) cancers among the worker cases than among the community comparands (30% vs. 10%).

By using the SMR for respiratory system cancer of 149 in the retrospective cohort study and the observed and expected histologic distribution of lung cancer deaths based on the case-comparand study, Table 3 demonstrates the calculation of histology specific lung cancer SMR's (column C). If the 27 cases for which histologic specimens were available are considered representative of all 45 lung cancer cases, it appears the excess lung cancer risk appears limited to types 3 and 4, adenocarcinoma and large cell undifferentiated, with the greater risk due to the latter. Approximately 13.5 of the 14.8 excess lung cancers among the plant workers would be due to adenocarcinoma and large cell undifferentiated carcinoma.

It appears that there is a histology-specific excess lung cancer risk among workers at this plant and that this differential distribution of cell types is

not an artifact of the geographic region nor of the pathologist's techniques. The fact that this risk occurs for adenocarcinomas and for large cell undifferentiated lung cancers makes it very unlikely that it is due to cigarette smoking.

Serially Additive Expected Dose Model

The third objective was to test whether any presumed occupational chemical exposures were associated with the excess lung cancer risk at the plant. It was decided to analyze the previously mentioned cohort data in a serially additive expected dose (SAED) model (10), obtaining for each lung cancer case the observed and expected doses of each chemical, conditional on certain characteristics. The purpose of the SAED model is to compare the observed exposure of each case in a study with the exposures of fellow workers close to the case in year of birth, and in age at commencement of work at the company. If the total work force in the plant under study is referred to as the cohort, then each case can be thought of as belonging to a subcohort of workers with approximately the same year of birth and age at commencement of work in the plant. In each year that a case worked at the plant, his exposure can be compared with that of the other members of his subcohort who were working in that year.

Company personnel compiled estimated exposures on a scale of 0 to 5 (5 being the highest exposure) for each of 19 chemicals (Table 4). Each job was assigned an exposure rank for each calendar year of the study (Table 5). These exposure data were then linked with work histories identifying the jobs each worker had in the plant and the calendar time involved. The analytical method is based on estimating exposure dose by multiplying the exposure level by the number of days worked at that level. These "doses" are accumulated over a calendar year for a case to yield the observed dose and for

Table 2. Case and matched comparand histologic distributions.

Histologic type	Veterans Administration classification code	Frequency	
		Worker cases	Community comparand cases
Epidermoid	1	6 (22%)	15 (30%)
Small cell undifferentiated	2	6 (22%)	15 (30%)
Adenocarcinoma	3	7 (26%)	14 (28%)
Large cell undifferentiated	4	8 (30%)	5 (10%)
Other	-	0	1 (2%)
Total		27 (100%)	50 (100%)

Table 3. Histologic specific lung cancer risk among plant personnel.

	Histologic distribution		Histologic specific SMR C = 149 (A/B)	Excess cases among those pathologically reviewed (D) ^a	Total excess cases (E) ^b
	Observed (A)	Expected (B)			
Total	100%	98% ^c	149	8.9 ^c	14.8 ^c
Epidermoid	22.2%	30%	110	0.6	0.9
Small cell	22.2%	30%	110	0.6	0.9
Adenocarcinoma	25.9%	28%	138	1.9	3.2
Large cell	29.6%	10%	441	6.2	10.3

^aD = (27 A) - (27 B × 100/149).

^bE = (45 A) - (45 B × 100/149).

^cSpecific cell types do not add up to total because of "other" type lung cancer among comparands.

his subcohort to yield an expected dose for each year that a case works. The methodology has previously been described in detail elsewhere (10).

In addition to testing the total-dose hypothesis, the SAED analysis facilitates examination of the observed and expected doses for each year of exposure before death. Exposures to 19 chemicals

were assessed; seven of the chemicals were, however, excluded from the formal analysis because so few persons were exposed to them at levels 3, 4 and 5 (Table 6).

The SAED model analysis resulted in the observed minus expected cumulative dose differences per case in Table 7. The differences for PVC dust are striking in comparison with the other exposures. For the large cell undifferentiated cancer and adenocarcinomas combined and for large cell undifferentiated cancer by itself, the differences in exposure to PVC dust are three to four times as large as those estimated for vinylidene chloride, the

Table 4. Exposure ratings used to classify jobs.

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)

Table 5. Chemical exposure ratings specific for job identification number and calendar year for a given chemical.

Chemical #1, job identification number	Exposure ratings					
	1942	1943	1944	1945	1946	1973
1	0	0	0	2	2	2
2	5	5	5	5	5	5
3	2	2	1	1	0	0
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84	4	4	4	1	1	1

Table 6. Frequency of job categories having at least one year of exposure greater than specific exposures levels.^a

	No. at each exposure level				
	1	2	3	4	5
Acrylic acid	13	4	3	0	0
Acrylamides	14	4	4	0	0
Acrylonitrile	35	25	13	6	1
Acetylene	20	17	10	3	1
Acrylates	39	30	21	8	2
Bisphenol A	7	2	0	0	0
Butadiene	23	15	9	5	1
Caprylyl chloride	25	9	6	6	3
Chlorinated solvents	30	18	7	4	4
Chloroethyl vinyl ether	22	6	4	1	0
Diethyl maleate	14	6	0	0	0
Mercuric chloride	15	7	5	3	3
Methanol	30	21	14	2	2
Phenol	2	1	0	0	0
Toluene	2	0	0	0	0
Vinyl chloride	55	40	29	21	4
Vinylidene chloride	20	14	8	5	2
Vinyl acetate	26	18	10	0	0
PVC dust	56	32	19	9	6

^aE.g., for acrylic acid, employees could have worked in 13 different job categories that had exposure levels of one or higher in at least one calendar year between 1942 and 1973.

Table 7. Observed minus expected cumulative dose differences per lung cancer case.

Chemical	All lung cancers	Pathologically reviewed cases	Adenocarcinoma and large cell	Large cell
Acrylonitrile	-652	-402	-446	-128
Acetylene	-353	-289	291	-167
Acrylates	-322	-251	-83	-339
Butadiene	-330	-207	-406	-622
Caprylyl chloride	-547	-258	-270	-1139
Chlorinated solvents	-868	-672	-150	749
Mercuric chloride	-507	-425	-211	-62
Methanol	-430	-618	-456	-1078
Vinyl chloride monomer	-1428	-795	26	907
Vinylidene chloride	-341	210	804	1525
Vinyl acetate	-707	-480	-217	328
PVC dust	763	2448	3225	4526

next most evident chemical. The significance levels of the larger of these differences are found in Table 8 for the total cumulative doses and also for cumulative doses until 10 years before death. Statistical significance was observed only for exposure to PVC dust.

Latency analysis for PVC dust (Fig. 1) shows a peak for the difference between observed minus expected dose during the period 5 to 16 years before death. As the diagnosis of the disease of interest becomes more narrowly defined as a pathologically homogeneous entity, the dose difference per case increases, yet the implied latent period stays constant.

Discussion

The first objective of this study was to determine if the excess lung cancer risk among employees exposed to VCM also existed for the total plant population, including those persons not exposed to VCM. The retrospective cohort mortality study showed that respiratory system cancers occurred approximately 50% more frequently among the employees of the entire plant than would have been expected based on age, sex, race, and calendar year specific United States death rates. A similar excess had been previously shown to exist among the subcohort of employees exposed to VCM (1). Thus, the excess lung cancer risk at the plant appeared to be independent of VCM exposure unless one hypothesized that it was due to extremely low levels

of VCM that could have permeated throughout the plant.

Potentially confounding variables are age, sex, calendar year, race/ethnicity, migration, urban residence, cigarette smoking and socioeconomic status (SES). In the retrospective cohort study, age and calendar year cannot confound because they are adjusted in the results. All persons in the study are male and 98% are presumed white. White male specific rates were used for comparison to control those potential confounders by subject category restriction. Ethnicity and migration (both inter- and intracountry) effects are considered minimal for all three study designs because 42 of the 45 cases were born in Kentucky or an adjacent state. Urban residence is mainly associated with an excess of epidermoid and small cell undifferentiated lung cancer (15) rather than the histologic types of lung cancer found in excess in this study. Excess lung cancer risk is associated with low socioeconomic status (16, 17), measured either by education (relative risk of 1.2 for persons with fewer than eight years of school) or by occupation (relative risk of 1.3 for laborers). Since the cohort consists of a mixture of socioeconomic status levels, there is probably insignificant confounding due to SES at the plant considered as a whole. Furthermore, recent infor-

Table 8. Probability value of paired *t*-tests of cumulative differences between observed and expected doses for lung cancer cases.

	Total (all years) ^a	10 or more years before death
All cases (N = 45)		
PVC dust	0.185	0.253
All pathologically reviewed cases (N = 27)		
PVC dust	0.026 ^b	0.047 ^b
Adenocarcinoma and large cell (N = 15)		
PVC dust	0.037 ^b	0.061
Vinylidene chloride	0.267	0.333
Large cell (N = 8)		
PVC dust	0.068	0.177
Chlorinated solvents	0.360	0.435
Vinylidene chloride	0.201	0.322

^aTwelve chemicals were tested for each lung cancer group, thus, under an assumption of independence of tests, one would expect one test to be significant at the 0.08 level.

^b*p* < 0.05.

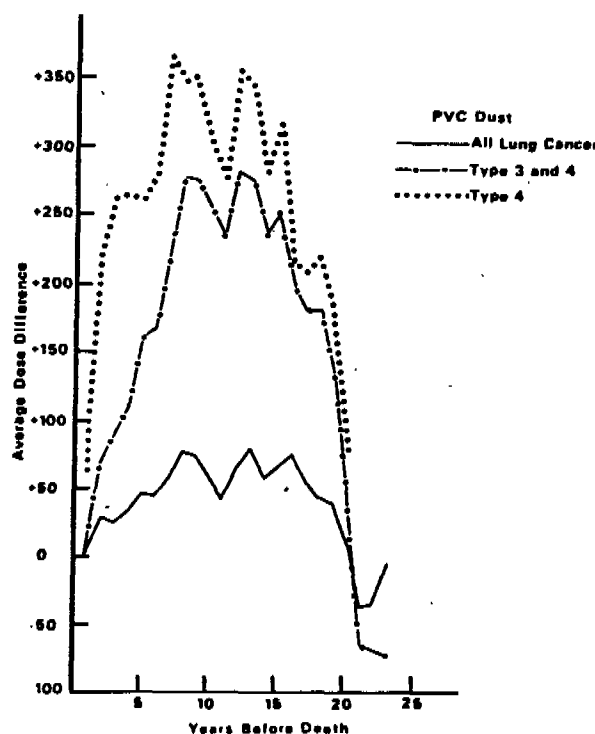


FIGURE 1. Observed minus expected dose differences per case among lung cancer cases for PVC dust.

mation indicates that these risk gradients may be partially due to smoking patterns (18, 19), which would affect epidermoid and small cell undifferentiated lung cancers.

The second objective of this research was to determine whether an excess lung cancer risk of a particular histologic type existed. The case-comparand study showed that there was an excess of adenocarcinomas and large cell undifferentiated lung cancers among the cases occurring among plant employees compared to other lung cancer cases from the same community. Because the pathologists reviewed both sets of slides without knowing which were those of plant employees, it is unlikely diagnostic biases occurred.

Histologic specimens were more difficult to find among the cases which died earlier and which were older on the date of death. However, community comparands were matched with the cases on age and date of diagnosis and had to have specimens available themselves; hence a biased ascertainment by histology between cases and comparands would be unlikely. The choice of community comparands makes it unlikely that a community wide pollutant was responsible for the excess risk at the plant for types 3 and 4 lung cancer. Consequently, it can be inferred from Table 3 that the excess lung cancer risk in the cohort was limited to adenocarcinoma and large cell undifferentiated cancer. Adenocarcinomas, accounting for a minor proportion of this excess risk, have been shown to be weakly, if at all, related to cigarette smoking (14, 20-22).

Large cell undifferentiated carcinoma of the lung is the only major histologic type that has appeared to be unrelated to cigarette smoking. Thus, cigarette smoking was probably not a major confounding variable. However, the role of smoking as a promoter or cocarcinogen cannot be ruled out. Nevertheless, the conclusion of this phase of the investigation was that an excess risk occurred among plant employees for types 3 and 4 lung cancer, especially type 4.

The third objective was to test whether one or more particular chemicals used at the plant were responsible for either the excess risk of all lung cancer or of the types 3 and 4 or just type 4 lung cancer. The SAED model was specifically developed for this objective.

The major hypothesis was tested for each chemical in the SAED model by using the one-sided *t*-test of the observed minus expected cumulative doses over all years before death and ten or more years before death (Table 8). PVC dust was the only chemical that was statistically significant. These results suggest that an excess of types 3 and 4 lung

cancer exists at this plant and is related to PVC dust exposure.

The suggestion of PVC dust being a lung carcinogen is biologically plausible. Almost all PVC particles produced by the emulsion system, one of the systems at this plant, are in the respirable range (23). These particles could settle in the lungs and conceivably by themselves cause lung cancer. In fact, one case of supposedly PVC dust-induced pneumoconiosis has been found in a worker (24), and pulmonary granulomas (25, 26) have been induced in animals exposed to PVC dust. In a large proportional mortality study of 4341 deaths that occurred among PVC fabricators, persons expected to be exposed to VCM and PVC dust demonstrated a slight (PMR = 117) excess lung cancer risk (27).

VCM gas is easily inhaled, and possibly would be in contact with tissue only a short time before being either exhaled or absorbed into the bloodstream. However, VCM becomes entrapped in the PVC dust and can be released slowly over time. Thus, PVC dust particles in the lung may slowly release VCM to small adjacent areas of the tissue, prolonging the contact time of that chemical to tissue. If this latter hypothesis is true, then it begs the question of why almost all of the liver angiosarcoma cases occurred among polymer reactor cleaners who received extremely high VCM doses while the lung cancer cases occurred frequently among the less heavily exposed workers. In fact, there was no relationship between VCM and lung cancer in this analysis; yet, one would expect the lung to be the major route of entry for VCM regardless of the cancer site.

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