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Mortality of industrial workers exposed to acrylonitrile

by Aaron Blair, PhD,[1] Patricia A Stewart, PhD,[1] Dennis D Zaebst, MS,[2] Linda Pottern, PhD,[3] John N Zey, MS,[4] Thomas F Bloom, MS,[5] Barry Miller, MS,[6] Elizabeth Ward, PhD,[5] Jay Lubin, PhD[7]

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Objectives This study was designed to evaluate the relationship between occupational exposure to acrylonitrile and cancer mortality.

Materials and methods Workers (18 079 white men, 4293 white women, 2191 nonwhite men, and 897 nonwhite women) employed in acrylonitrile production or use in the 1950s through 1983 were followed through 1989 for vital status and cause of death. Exposure-response relationships were evaluated from quantitative estimates of historical exposures. Tobacco use was determined for a sample of workers to assess potential confounding. Mortality rates between the exposed and unexposed workers in the cohort were compared using the Poisson regression.

Results Analyses by cumulative, average, peak, intensity, duration, and lagged exposure revealed no elevated risk of cancers of the stomach, brain, breast, prostate or lymphatic and hematopoietic systems. Mortality from lung cancer was elevated for the highest quintile of cumulative exposure. When the decile categories were used, the relative risk did not continue to increase at higher levels. Adjustment for cigarette use reduced the risk for lung cancer only slightly. Separate analyses for wage and salaried workers, long-term and short-term workers, fiber and nonfiber plants, and individual plants revealed no clear exposure-response patterns.

Conclusions The results indicate that exposure to acrylonitrile at the levels studied is not associated with an increased relative risk for most cancers of a priori interest. The excess of lung cancer in the highest quintile of cumulative exposure may indicate carcinogenic activity at the highest levels of exposure, but analyses of exposure-response do not provide strong or consistent evidence for a causal association.

Key terms cancer, cohort study, industrial workers, lung cancer, nested case-control study.

Acrylonitrile is a volatile, colorless liquid with a pungent onion or garlic odor (1). It is an important industrial chemical and is used in the production of acrylic and modacrylic fibers, acrylonitrile-butadiene-styrene, and styrene-acrylonitrile resins, adiponitrile and butadiene-acrylonitrile copolymers, and it has been used as a fumigant in the past. Manufacturing capacity was about 10 billion pounds (4 535 970 metric tons) in 1995. The United States accounts for 30% of the world capacity (2). Acrylic and modacrylic fibers are primarily used in clothing and home furnishings. Acrylonitrile-butadiene-styrene resins are used in pipe fittings, in components of motor vehicles, and in large appliances. Copolymers of acrylonitrile and other monomers are used in the production of beverage containers. Acrylonitrile and carbon tetrachloride mixtures have been used as fumigants on stored tobacco and on flour milling equipment. Acrylonitrile occurs in tobacco smoke (3), but there are few other general environmental exposures. The United States Occupational Safety and Health Administration's permissible limits of 2 parts per million (ppm) for an 8-hour time-weighted average (TWA_{8h}) and 10 ppm as a 15-minute ceiling have been in effect since 1978.

Acrylonitrile has a variety of biological effects (4). It causes sister chromatid exchanges, mutation, and unscheduled DNA (deoxyribonucleic acid) synthesis in

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human cells in vitro; chromosome aberrations, micronuclei, and sister chromatid exchanges in hamster cells; and mutations and DNA strand breaks in rodent cells. Acrylonitrile binds covalently to DNA, and it is mutagenic in bacteria. It causes cancers of the brain, stomach, and Zymbal gland of rodents by oral administration and cancers of the central nervous system, mammary gland, Zymbal gland, and forestomach by inhalation (5). The International Agency for Research on Cancer (IARC) (5) concluded in 1987 that there was sufficient evidence that acrylonitrile causes cancer in animals, but only limited evidence for carcinogenicity in humans.

Epidemiologic studies have recently been reviewed by Ward & Starr (6), Rothman (7) and Blair & Kazerouni (8), and they show no clear evidence of an excess for any cancer. Slightly elevated relative risks have been reported in more than 1 study for cancers of the lung, brain, prostate, and lymphatic and hematopoietic system, but the findings have been too inconsistent to allow definitive conclusions. The previously completed epidemiologic investigations are small [the largest cohort included only 2842 exposed persons (9)], and only 4 provided information on risk by level of exposure.

The National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) assembled a large cohort of workers from 8 acrylonitrile producing and using facilities in the United States to evaluate the potential cancer risk from exposure to acrylonitrile by level of exposure.

Materials and methods

Plant selection

In the early 1980s, the National Cancer Institute received a request from industry representatives to evaluate the opportunity for a high-quality, large-scale epidemiologic study of workers exposed to acrylonitrile. To assess the feasibility of such an investigation, we identified candidate industrial facilities using acrylonitrile assessment documents from the Occupational Safety and Health Administration (10), the Environmental Protection Agency (11), the World Health Organization (12), and the International Agency for Research on Cancer (3); directories of chemical and plastic producers; and a specially prepared NCI document (13). Plants engaged in the production of acrylonitrile monomer, acrylonitrile fibers, and acrylonitrile resins appeared to have the greatest potential for exposure both in terms of level and numbers of exposed workers. These plants were surveyed for the adequacy of personnel records to assemble a cohort and for the availability of industrial-hygiene monitoring data and plant production records to characterize acrylonitrile exposure. The feasibility study indicated that records and exposure information from several plants were sufficient to assemble a large cohort for a mortality investigation.

The plants selected for inclusion in the cohort study included 4 producers of acrylonitrile monomer (table 1). They composed all plants in the United States producing the monomer at the time of the data collection, with the exception of 1 plant that started production too recently to allow for a meaningful evaluation of cancer risks. Three of the 6 plants in the United States that produced acrylic fibers were included (table 1). Two of the excluded plants were the subject of earlier studies (14, 15) and 1 employed only 30 workers. Since the initiation of this investigation, a report describing the mortality experience of workers at 2 participating plants (plants 1 and 6) has also been published (16). At the time of the feasibility study, there were 13 plants producing acrylonitrile resins in the United States. The largest was included in our study. In all, a total of 8 plants was selected, and agreement was reached to provide access to the records and other plant facilities needed for the study.

Cohort identification and follow-up

The cohort was composed of all workers employed at any of the 8 participating plants prior to 1984 and after the start-up of acrylonitrile operations. The personnel records of all the employees were accessed to obtain information on date of birth, race, gender, address, social security number, next-of-kin, and a complete work history at the plant up through the date of abstracting (ie, 1983). The work history included job titles, department names, and

Table 1. Characteristics of the plants selected for study. (TWA_{8h} = 8-hour time-weighted average)

Plant and acrylonitrile process	Year 1st used acrylonitrile	Other exposures	Number of personal samples	Estimates for exposed jobs (TWA_{8h} ppm)	
				Median	Mean
1 - fibers	1958	Methylmethacrylate, sodium thiocyanate, dimethylformamide	1100	0.10	1.88
2 - monomer	1965	Ammonia, propylene, hydrogen cyanide	2300	0.39	2.17
3 - monomer, resins acrylamide	1960	Ammonia, propylene, hydrogen cyanide, methyl acrylate, butadiene	400	3.46	6.13
4 - fibers	1958	Vinyl bromide, methyl acrylate, zinc chloride	2300	0.34	5.30
5 - fibers, adiponitrile	1952	Vinyl acetate, vinyl bromide, hexamethylenediamine	1400	0.42	3.37
6 - monomer, acrylamide	1954	Ammonia, hydrogen cyanide, acetylene, propylene, sulfuric acid	500	0.54	0.63
7 - resins	1959	Butadiene, styrene	1900	0.36	1.34
8 - monomer	1953	Ammonia, hydrogen cyanide, acetylene, propylene	2100	1.90	1.45

dates the jobs were held. Personnel records of wage workers were at the plants, but it was sometimes necessary to obtain records for salaried workers from other company facilities. Teams of abstractors extracted the information from paper records at all except 2 plants, where information was obtained from computer files. For these 2 plants a validation study comparing a sample of records on the computer files with the paper personnel files found a high degree of accuracy. Data abstracted from the other plants were reviewed by field supervisors for completeness, and a 5% sample was reabstracted by another member of the field team to assess the accuracy of the abstraction process and to make any adjustments necessary to insure that the data collected were of high quality. Date of birth, race, and gender were also obtained from the Social Security Administration, and any discrepancies with company records were resolved by a reevaluation of company records.

All or parts of the cohort were linked with the National Death Index, medicare files of the Health Care Financing Administration, social security mortality tapes, the Veterans Administration Beneficiary Identification and Record Locator System, credit bureaus, and company records to determine the vital status of the study subjects. Vital status was determined up to 1 January 1990. Death certificates were sought from state vital record offices for the subjects identified as deceased, and the underlying and contributing causes of death were determined by an experienced nosologist using the rules in effect at the time of death and assigned rubrics according to the 8th revision of the International Classification of Diseases.

Exposure assessment

In this study, a sophisticated procedure was created to develop quantitative estimates of exposure by job, department, and time period. These procedures are briefly described in this report, but a more-detailed description of the methods employed has been presented elsewhere (17).

The visits made to each plant to obtain information consisted of walk-through surveys to observe acrylonitrile-using operations, to collect monitoring data and other records, and to conduct interviews with long-term workers.

Personal monitoring of acrylonitrile exposures was performed in all 8 plants in 1986 by the study investigators using the recommended NIOSH method (18). Four hundred measurements were taken. Seven of the plants conducted their own monitoring (following their regular monitoring protocols) simultaneously with the study monitoring. The company and study monitoring results were compared to identify any systematic differences that might exist between data from the various companies, but no major differences were found.

The 127 000 job lines obtained from personnel records were standardized into 6500 unique job title, department, plant combinations. In some jobs, workers were required to visit several areas of the plant. Names of 200—500 of these workers per plant were sent to the companies and unions to identify how much time was spent in acrylonitrile areas. A custom database program was developed to characterize, store, and document descriptive information (job-exposure profiles) on each of the 6500 unique job, department, plant combinations (19). Each job, department, plant combination was divided into time periods thought to have consistent exposures based on a lack of change in equipment, operation, and other factors that would have affected exposure. The addition of time periods to the job-department-plant titles yielded 18 000 cells requiring estimates.

The actual exposure estimation process started with monitoring data (20). Seven of the 8 companies had measurements dating back to 1977—1978, and 1 plant (number 4) started monitoring in 1960. Over 18 000 measurements were available from the companies between 1960 to 1989, and over 12 000 of these were personal samples (table 1). All told, these measurements covered about 300 job, department, plant combinations. Area measurements were also available from plants 2, 3, 4, and 8.

A computer exposure-assessment system documented the data used, the estimation method employed, and the level of confidence associated with the estimate (20). The estimated time-weighted average for an 8-hour period (TWA_{8h}), covering a minimum period of 1 year, served as the primary index of historical exposure developed for this study. Each job, department, plant, time period combination was considered a unique estimation cell and evaluated individually (20). Exposure estimates were made without knowledge of the vital status of the subjects holding the jobs.

Estimates were developed using a hierarchy of methods. These were arithmetic means (21), a TWA procedure (where exposure concentrations in different work locations for the job were weighted by the time spent in each location), a deterministic approach that modified the estimates from more recent years by evaluating the impact of engineering and other changes at the workplace, and professional judgment. For the deterministic method, the following 3 sets of estimates were developed for each change: the best estimate and the minimum and maximum estimates to reflect the range of possible values. Maximum and minimum estimates provided the opportunity to evaluate mortality risks while considering uncertainty in the exposure estimates. The level of confidence in each estimate (developed by study industrial hygienists) was based on the amount of information available about job duties, location within the plant, and other factors affecting exposure.

In addition to TWA_{8h} estimates, other acrylonitrile exposure estimates included the frequency of peaks

(defined as 15-minute exposures that averaged 20 ppm or greater), TWA_{8h} estimates taking into account respirator use, a dermal score to account for skin contact and the total mass inhaled (based on a semi-quantitative estimated level of physical activity associated with the job, the respiratory rate expected to be associated with that level of activity, the average tidal volume, and the estimated air concentration).

A rigorous quality control effort was built into the exposure estimation process. An advisory committee reviewed the protocol and met annually to review the progress of the study and provide guidance. A separate protocol for the exposure estimation procedures was developed. The protocol, plant site visit reports, job standardization lists, job-exposure profiles, and exposure estimates were provided to companies and unions for review and comment. Numerous meetings and telephone conversations were held with management and labor to explain the assessment procedures, to discuss assumptions, to obtain additional information, to correct inaccuracies, and to reach agreement regarding each TWA_{8h} estimate.

A reliability study was conducted to compare the accuracy and precision of the exposure estimates with actual measurement data (22). In this reliability study, a set of estimates that was developed using the TWA and the deterministic methods already described and that was independent of the study was compared with the actual measurement means (ie, reference values) for the same job, department, plant, time-period cell. Relative bias and correlations were used to evaluate the reliability of the estimates. On the average, the estimates from the TWA method tended to underestimate the reference values (average relative bias) by 24%. The exposure estimates derived from the deterministic method were similar to the reference values (average relative bias 1%). The correlation between the reference values and the estimates from these 2 methods was about 0.6. These results compare well with the normal variability observed in measurement data (usually a 3-fold difference) (23) and correlations of current estimates with measurement data (24).

Cohort analytic methods

The standardized mortality ratios and rate ratios (RR) from the Poisson regression were used to evaluate the mortality experience of the cohort (25). Standardized mortality ratios were used to compare the mortality rates in the cohort with that of the general United States population. They were calculated because it is an analytic approach traditionally used in cohort studies, even though the ratios of exposed and unexposed persons may not be strictly comparable if they are heterogeneous within age and calendar-year strata. Person-year accumulation began on the first day of employment at the plant or at the time when a certain level of exposure (depending upon the type of analysis being conducted) was achieved, and it ceased on 31 December 1989, the date of death, or the last date the subject was known to be alive (if earlier than the closing date of the study). The person-years of follow-up of the unexposed persons included all person-years accumulated by workers who never held exposed jobs, plus those occurring prior to first exposure among the workers who first held unexposed jobs but later moved to exposed jobs. The expected numbers for the standardized mortality ratios were developed from 5-year age and calendar-time mortality rates from the general population, considering race and gender as appropriate, using EPICURE software (25).

Rate ratios, based on internal comparisons of exposed and unexposed workers, were estimated by Poisson regression, adjusted for date of birth (in 5-year categories), plant, and calendar time (25). These internal comparisons were used to reduce biases that can arise from the use of the general population as a reference (26). Where appropriate, the rate ratios were also adjusted for race, gender, and wage or salary status. Confidence intervals (95%) were calculated using the usual Wald estimator (25).

To evaluate exposure-response gradients, workers were categorized as unexposed or exposed, and the exposed workers were grouped into quintiles and deciles of cumulative or other exposure according to the observed number of deaths from lung cancer and analyzed in a time-dependent manner. This categorization approach was used to insure that a similar number of deaths from lung cancer occurred in the various exposure categories. Both quintile and decile analyses were performed to ensure an objective categorization of exposure and to evaluate risks at the highest level of exposure possible while maintaining a sufficient number of events in each category for statistical stability.

Subcohort with information on smoking

Information on tobacco use was obtained for a sample of workers using a case-cohort design to allow statistical adjustment of the relative risk for lung cancer from acrylonitrile exposure for potential confounding from smoking. Information was sought for a 10% systematic sample of the cohort. The sample was assembled by selecting every 10th subject abstracted from employment record files beginning with a randomly selected record. Interviews were conducted by telephone from 1988 through 1990. For deceased members of the 10% sample and all lung and brain cancer deaths identified from the first National Death Index search (ie, deaths occurring prior to 1 January 1983), interviews were sought with next-of-kin. Interviews were not sought with surrogates of the workers who died from cancer between 1983 and 1990 because government approval for interviewing expired prior to the completion of the second National Death Index search. The interviews sought information on cigarette use (including age started, number of years smoked, and

amount smoked) and ever use of other tobacco products. Information on tobacco use was also collected from available company medical records. The rate ratios for lung cancer from acrylonitrile exposure in the smoking subcohort were calculated using the PEANUTS module in EPICURE (25). This is a proportional hazards model adapted for case-cohort data, and it includes adjustment for age, age at hire, year of hire, race, gender, and plant.

The cohort included 25 460 workers (18 079 white men, 4293 white women, 2191 nonwhite men, and 897 nonwhite women) (table 2). The numbers of workers by plant ranged from 1545 in plant 3 to 7321 in plant 5. Forty-six percent of the subjects started work at one of the study facilities prior to 1966, and therefore we had a large number of workers with a lengthy follow-up period. Ninety-two percent of the workers were under 30 years of age at entry into the cohort. Approximately 88% of the cohort was alive as of 31 December 1989. Vital status tracing was successful for 96% of the cohort. Tracing was more successful for the men (3% with unknown vital status) than for the women (8% unknown). Of the 2038 subjects believed to be deceased on the basis of one of the tracing sources, death certificates were found for 1919 (94%). Those thought to be deceased, but lacking death certificates, were only included in the all-causes and unknown-cause-of-death categories in the analyses. The consequences of the failure to obtain death certificates for 6% of the decedents indicated that, on the average, the standardized mortality ratios for each specific cause of death would be underestimated by approximately this proportion. Most of the analyses were based, however, on rate ratios based on internal comparisons and were therefore less likely to be biased by failure to obtain death certificates.

The entire cohort generated 545 368 person-years of follow-up. Of the total person-years of follow-up, 348 642

Table 2. Demographic information on the study subjects by plant.

Demographic characteristics	Plant 1	Plant 2	Plant 3	Plant 4	Plant 5	Plant 6	Plant 7	Plant 8	Total
Subjects									
White men	1467	1400	944	1852	5579	1864	1889	3084	18 079
Nonwhite men	111	194	99	441	365	366	213	402	2191
White women	291	333	458	719	1202	370	187	733	4293
Nonwhite women	27	62	44	367	175	53	50	119	897
Total population	1896	1989	1545	3379	7321	2653	2339	4338	25 460
Year of entry									
-1955	3	3	162	1	1132	599	145	1716	3761
1956—1960	400	3	194	359	1149	269	210	691	3275
1961—1965	685	658	137	363	1832	192	414	416	4697
1966—1970	344	338	400	876	1664	286	837	459	5204
1971—1983	464	987	652	1780	1544	1307	733	1056	8523
Age at entry (years)									
<20	116	92	261	595	2191	393	364	279	4291
20—29	1082	1173	815	1744	3727	1486	1464	2432	13923
30—39	474	577	329	707	1073	561	389	1148	5258
40—49	193	129	105	298	290	184	105	379	1683
49>	31	18	35	35	40	29	17	100	305
Year of birth									
-1925	278	84	174	226	767	365	147	1174	3215
1925—1934	429	333	323	532	1294	559	373	1357	5200
1935—1944	702	729	342	857	2551	505	787	841	7314
1945—1954	399	606	500	1276	2120	750	815	669	7135
1954-	88	237	206	488	589	474	217	297	2596
Vital status									
Alive	1700	1859	1358	3063	6559	2340	2037	3522	22 438
Deceased									
With certificate	133	72	102	185	517	229	110	571	1919
Without certificate	14	4	2	16	23	11	9	40	119
Unknown[a]	49(3)	54(3)	83(5)	115(3)	222(3)	73(3)	183(8)	205(5)	984(4)
Person-years[b]									
Unexposed	7534	17995	22 326	11 487	56 054	20 985	9411	50 935	196 727
Exposed	34 123	17 453	7724	48 471	115 751	32 030	36 812	56 278	348 642
< 0.13 ppm-years	9723	5558	567	21 085	40 563	16 533	10 520	16 880	121 534
>0.13 to 0.57 ppm-years	8529	4564	924	6794	19 286	7656	8497	12 874	69 134
>0.57 to 1.5 ppm-years	6112	2547	734	4459	13 432	4404	6115	11 897	49 726
>1.5 to 8.0 ppm-years	6408	2618	1852	8575	20 342	2574	8864	12 249	63 464
>8.0 ppm-years	3352	2166	3648	7557	22 128	763	2816	2376	44 771
Total	41 657	35 448	30 050	59 958	171 805	53 015	46 223	107 212	545 368

[a] Percentage of total in parentheses.

[b] Person-years refer to follow-up time, not exposure time. Person-years of the unexposed persons accrue from follow-up time among workers never exposed to acrylonitrile, plus follow-up time prior to exposure among workers who started employment in unexposed jobs. The person-years of the exposed workers is the follow-up time after first exposure or after a certain level of exposure has been achieved.

were assigned to workers after their first exposure to acrylonitrile, and 196 727 person-years were associated with persons never exposed or with the time period prior to first exposure among workers who started employment in unexposed jobs (table 2). Over 44 000 person-years occurred among the workers after their cumulative exposure exceeded 8.0 ppm-years. Exposure to chemicals other than acrylonitrile also occurred. Worker-years of exposure totaled approximately 55 000 for benzene, 8000 for butadiene, 50 000 for formaldehyde, 45 000 for styrene, 10 000 for sulfuric acid, and 54 000 for vinyl chloride.

Results

Cohort analyses

The standardized mortality ratios for the workers exposed and those unexposed to acrylonitrile are shown in table 3. They were all adjusted for age and calendar-time, and the all-workers category was additionally adjusted for race and gender. Mortality from all causes of death for the workers exposed and those unexposed to acrylonitrile combined, as well as deaths from all cancers combined, cerebrovascular disease, ischemic heart disease, nonmalignant respiratory disease, cirrhosis of the liver, and accidents, was generally less than expected based on rates of the general United States population. Many of these deficits were statistically significant. The numbers of deaths observed in the race-gender groups were small except for the white men (the total number of deaths was 1624 for the white men, 166 for the white women, 147 for the nonwhite men, and 12 for the nonwhite women). No statistically significantly elevated standardized mortality ratios were observed for the exposed or unexposed workers in any of the race-gender groups. Among the exposed workers, no individual cancer showed a standardized mortality ratio larger than 1.4 for all the workers combined.

The rate ratios by time since first exposure are shown in table 4. Mortality from all causes and all cancer in each exposure category was slightly lower among the exposed (RR mostly about 0.8 or 0.9). No statistically significant excesses occurred for any cause of death. Nonsignificant excesses occurred for cancers of the esophagus (RR 2.0) and rectum (RR 3.6). The rate ratios were greater than 3.0 for deaths from cancers of the esophagus and rectum ≥20 years after first exposure. The rate ratio for lung cancer was 0.4 within 10 years of first exposure, 1.6 for 10 to 20 years, and 1.3 for ≥20 years after first exposure. Although no statistically significant deficits occurred, mortality was lower among the exposed workers than among the

Table 3. Observed(O) number of deaths, standardized mortality ratios (SMR), based on United States general population rates, and 95% confidence intervals (95% CI) for the workers exposed and those unexposed to acrylonitrile.

Cause of death[a]	All workers[b]			White men			White women			Nonwhite men			Nonwhite women		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
All causes combined															
Unexposed workers	702	0.7	0.7—0.8	522	0.8	0.7—0.8	141	0.8	0.7—1.0	33	0.5	0.4—0.8	6	0.4	0.2—0.8
Exposed workers	1217	0.7	0.6—0.7	1072	0.7	0.7—0.7	25	0.4	0.3—0.6	114	0.5	0.4—0.6	6	0.4	0.2—0.9
All cancers (140—239)															
Unexposed workers	216	0.9	0.8—1.0	145	0.9	0.8—1.1	65	1.0	0.8—1.3	3	0.3	0.1—1.0	3	0.8	0.3—2.6
Exposed workers	326	0.8	0.7—0.9	279	0.8	0.7—0.9	12	0.5	0.3—0.9	32	0.7	0.5—1.0	3	0.9	0.3—2.7
Buccal cavity & pharynx (140—149)															
Unexposed workers	7	1.2	0.6—2.5	5	1.1	0.4—2.6	1	1.3	0.2—9.1	1	2.2	0.3—16	-	0	.
Exposed workers	6	0.5	0.2—1.1	5	0.5	0.2—1.2	-	0	.	1	0.5	0.1—3.5	-	0	.
Esophagus (150)															
Unexposed workers	2	0.4	0.1—1.6	1	0.3	0.1—1.8	-	0	.	1	1.8	0.2—13	-	0	.
Exposed workers	12	1.0	0.6—1.8	9	1.0	0.5—2.0	-	0	.	3	1.1	0.3—3.4	-	0	.
Stomach (151)															
Unexposed workers	5	0.7	0.3—1.6	5	0.9	0.4—2.1	-	0	.	-	0	.	-	0	.
Exposed workers	12	0.8	0.4—1.4	10	0.8	0.4—1.5	-	0	.	1	0.4	0.1—2.9	1	9.4	1.3—67
Colon (153)															
Unexposed workers	19	1.0	0.6—1.5	16	1.2	0.7—1.9	3	0.6	0.2—1.9	-	0	.	-	0	.
Exposed workers	19	0.6	0.4—0.9	19	0.7	0.4—1.0	-	0	.	-	0	.	-	0	.
Rectum (154)															
Unexposed workers	1	0.2	0.1—1.6	1	0.3	0.1—2.1	-	0	.	-	0	.	-	0	.
Exposed workers	9	1.1	0.6—2.1	7	1.0	0.5—2.1	-	0	.	2	2.8	0.7—11	-	0	.
Liver (155—156)															
Unexposed workers	4	0.9	0.3—2.4	3	1.0	0.3—3.1	1	1.0	0.1—6.9	-	0	.	-	0	.
Exposed workers	3	0.4	0.1—1.1	3	0.5	0.2—1.4	-	0	.	-	0	.	-	0	.
Pancreas (157)															
Unexposed workers	13	1.2	0.7—2.1	9	1.1	0.6—2.2	4	1.8	0.7—4.7	-	0	.	-	0	.
Exposed workers	10	0.5	0.3—0.9	9	0.5	0.3—1.0	-	0	.	1	0.5	0.1—3.4	-	0	.
Larynx (161)															
Unexposed workers	3	1.2	0.4—3.6	2	0.9	0.2—3.7	1	5.0	0.7—36	-	0	.	-	0	.
Exposed workers	1	0.2	0.1—1.3	1	0.2	0.1—1.5	-	0	.	-	0	.	-	0	.

(continued)

Table 3. Continued

Cause of death[a]	All workers[b]			White men			White women			Nonwhite men			Nonwhite women		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
Lung (162)															
Unexposed workers	59	0.8	0.6—1.1	44	0.8	0.6—1.0	13	1.2	0.7—2.0	1	0.3	0.1—2.3	1	2.0	0.3—14
Exposed workers	134	0.9	0.8—1.1	119	0.9	0.8—1.1	3	0.73	0.2—2.2	12	0.8	0.5—1.4	-	0	.
Melanoma of skin (172)															
Unexposed workers	7	1.4	0.7—3.0	5	1.4	0.6—3.3	2	1.7	0.4—6.9	-	0	.	-	0	.
Exposed workers	7	0.7	0.3—1.5	7	0.8	0.4—1.6	-	0	.	-	0	.	-	0	.
Breast (174)															
Unexposed workers	19	1.1	0.7—1.7	-	0	.	18	1.2	0.7—1.8	-	0	.	1	1.1	0.1—7.6
Exposed workers	5	0.7	0.3—1.7	-	0	.	4	0.7	0.3—1.9	-	0	.	1	1.0	0.1—7.2
Prostate (185)															
Unexposed workers	10	1.2	0.7—2.3	10	1.3	0.7—2.5	.	0	.	-	0	.	.	0	.
Exposed workers	16	0.9	0.6—1.5	16	1.1	0.7—1.8	.	0	.	-	0	.	.	0	.
Bladder (188)															
Unexposed workers	4	1.0	0.4—2.8	4	1.2	0.5—3.2	-	0	.	-	0	.	-	0	.
Exposed workers	6	0.8	0.4—1.8	5	0.8	0.3—1.8	-	0	.	1	1.7	0.2—12	-	0	.
Kidney (189)															
Unexposed workers	7	1.3	0.6—2.7	6	1.4	0.6—3.1	1	1.1	0.2—7.9	-	0	.	-	0	.
Exposed workers	9	0.8	0.4—1.6	6	0.6	0.3—1.4	1	3.1	0.4—22	2	2.7	0.7—11	-	0	.
Central nervous system (191—192)															
Unexposed workers	11	1.3	0.7—2.3	9	1.4	0.7—2.8	2	1.0	0.2—3.9	-	0	.	-	0	.
Exposed workers	12	0.7	0.4—1.3	11	0.8	0.4—1.4	-	0	.	1	1.4	0.2—10	-	0	.
All lymphatic & hematopoietic (200—209)															
Unexposed workers	18	0.8	0.5—1.2	12	0.7	0.4—1.2	5	0.9	0.4—2.2	-	0	.	1	3.4	0.5—24
Exposed workers	27	0.6	0.4—0.9	23	0.6	0.4—0.9	-	0	.	4	1.1	0.4—3.1	-	0	.
Lymphosarcoma & reticulosarcoma (200)															
Unexposed workers	2	0.6	0.1—2.4	2	0.8	0.2—2.9	-	0	.	-	0	.	-	0	
Exposed workers	1	0.2	0.1—1.0	1	0.2	0.1—1.2	-	0	.	-	0	.	-	0	.
Hodgkin's disease (201)															
Unexposed workers	-	0	.	-	0	.	-	0	.	-	0	.	-	0	.
Exposed workers	3	0.5	0.2—1.6	3	0.6	0.2—1.8	-	0	.	-	0	.	-	0	.
Leukemia (204—209)															
Unexposed workers	8	0.9	0.4—1.7	6	0.9	0.4—2.0	1	0.5	0.1—3.3	-	0	.	1	7.5	1.1—54
Exposed workers	11	0.6	0.4—1.2	10	0.7	0.4—1.2	-	0	.	1	0.8	0.1—5.5	-	0	.
Other lymphatic & hematopoietic cancer[c] (202)															
Unexposed workers	8	1.0	0.5—2.1	4	0.7	0.3—1.9	4	2.2	0.8—5.9	-	0	.	-	0	.
Exposed workers	12	0.8	0.4—1.4	9	0.7	0.4—1.3	-	0	.	3	2.0	0.7—6.4	-	0	.
Diabetes (250)															
Unexposed workers	13	0.9	0.5—1.5	7	0.7	0.3—1.5	4	1.1	0.4—2.8	2	2.0	0.6—8.80	-	0	.
Exposed workers	9	0.3	0.2—0.6	6	0.3	0.1—0.6	-	0	.	3	0.8	0.2—2.3	-	0	.
Cerebrovascular disease (430—438)															
Unexposed workers	23	0.5	0.4—0.8	18	0.6	0.4—1.0	5	0.5	0.2—1.2	-	0	.	-	0	.
Exposed workers	37	0.5	0.4—0.7	31	0.6	0.4—0.8	1	0.3	0.1—2.3	5	0.4	0.2—0.9	-	0	.
Ischemic heart disease (410—414)															
Unexposed workers	186	0.8	0.7—0.9	155	0.8	0.7—0.9	20	0.8	0.5—1.2	9	1.1	0.6—2.2	2	1.3	0.3—5.1
Exposed workers	374	0.8	0.7—0.9	347	0.8	0.7—0.9	2	0.2	0.1—0.9	24	0.6	0.4—0.9	1	0.9	0.1—6.1
Nonmalignant respiratory disease (460—519)															
Unexposed workers	36	0.7	0.5—1.0	31	0.8	0.6—1.2	4	0.4	0.2—1.2	1	0.4	0.1—2.5	-	0	.
Exposed workers	40	0.4	0.3—0.6	33	0.4	0.3—0.6	1	0.3	0.1—2.3	6	0.5	0.2—1.1	-	0	.
Emphysema (492)															
Unexposed workers	6	0.8	0.4—1.7	6	0.9	0.4—2.1	-	0	.	-	0	.	-	0	.
Exposed workers	6	0.4	0.2—1.0	6	0.5	0.2—1.1	-	0	.	-	0	.	-	0	.
Cirrhosis of liver (571)															
Unexposed workers	12	0.4	0.2—0.7	7	0.3	0.1—0.6	5	1.0	0.4—2.3	-	0	.	-	0	.
Exposed workers	18	0.3	0.2—0.4	17	0.3	0.2—0.5	-	0	.	1	0.1	0.1—0.8	-	0	.
Accidents (800—873)															
Unexposed workers	63	0.7	0.5—0.9	45	0.6	0.5—0.9	10	0.9	0.5—1.7	8	1.0	0.5—2.0	-	0	.
Exposed workers	156	0.8	0.6—0.9	137	0.8	0.7—0.9	3	0.8	0.2—2.4	14	0.5	0.3—0.9	2	1.6	0.4—6.5
Motor vehicle accidents (810—873)															
Unexposed workers	39	0.8	0.6—1.1	26	0.7	0.5—1.0	9	1.3	0.7—2.5	4	1.1	0.4—2.9	-	0	.
Exposed workers	92	0.8	0.7—1.0	79	0.8	0.7—1.0	3	1.3	0.4—3.9	8	0.7	0.3—1.4	2	3.1	0.8—12
Suicides (950—959)															
Unexposed workers	34	1.0	0.7—1.4	27	1.0	0.7—1.5	5	0.9	0.4—2.2	2	1.3	0.3—5.3	-	0	.
Exposed workers	57	0.8	0.6—1.0	54	0.8	0.6—1.0	1	0.5	0.1—3.8	2	0.4	0.1—1.8	-	0	.

[a] Code of the International Classification of Diseases in parentheses.
[b] Adjusted for race and gender in addition to age at entry and calendar time.
[c] Composed of 10 deaths from multiple myeloma, 9 from lymphoma, and 1 from other.

unexposed workers for cancers of the buccal cavity and pharynx, colon, biliary passages and liver, pancreas, larynx, breast, kidney, bladder, melanoma, central nervous system, and lymphatic and hematopoietic systems and for such nonneoplastic diseases as rheumatic heart disease, cirrhosis of the liver, and suicides.

The rate ratios (adjusted for age, year at hire, race, gender, and salary or wage status) for selected causes of death by categories are shown in table 5 by quintiles of cumulative exposure to acrylonitrile relative to nonexposure. Cut points for the cumulative exposure categories were positioned to equalize the number of deaths from lung cancer in each exposure category. Cancer of the stomach, prostate, central nervous system, and lymphatic and hematopoietic systems (sites with excesses in experimental or epidemiologic studies) showed no indication of

Table 4. Observed (O) numbers of deaths among the exposed (Ex) and unexposed (Unex) workers, relative risks[a] (RR), and 95% confidence intervals (95% CI) for selected causes of death among the workers exposed to acrylonitrile[b] (compared with the unexposed workers[c]).

Cause of death[d]	Time since first exposure															
	All Workers				<10 years				10—20 years				>20 years			
	O		RR	95% CI	O		RR	95% CI	O		RR	95% CI	O		RR	95% CI
	Ex	Unex			Ex	Unex			Ex	Unex			Ex	Unex		
All causes	1217	702	0.9	0.8—1.0	249	122	0.9	0.7—1.2	380	201	0.9	0.7—1.1	588	379	0.9	0.8—1.0
All cancers (140—239)	326	216	0.8	0.7—1.0	46	34	0.6	0.4—1.0	97	57	1.0	078—1.4	183	125	0.8	0.7—1.1
Buccal cavity & pharynx (140—149)	6	7	0.4	0.1—1.1	1	-	..	.	2	3	0.2	0.1—1.2	3	4	0.3	0.1—1.5
Esophagus (150)	12	2	2.0	0.4—9.0	1	-	..	.	1	1	0.2	0.1—3.7	10	1	3.6	0.4—29.0
Stomach (151)	12	5	1.1	0.4—3.1	3	-	..	.	1	-	..	.	8	5	0.7	0.2—2.3
Colon (153)	19	19	0.5	0.3—1.0	4	3	0.5	0.1—2.4	6	4	0.8	0.2—3.3	9	12	0.4	0.2—0.9
Rectum (154)	9	1	3.6	0.4—29.1	-	-	..	.	2	-	..	.	7	1	3.3	0.4—28.2
Liver (155—156)	3	4	0.4	0.1—2.0	1	1	0.3	0.1—6.3	1	-	..	.	1	3	0.3	0.1—3.1
Pancreas (157)	13	10	0.4	0.2—1.0	1	1	0.6	0.1—10.0	1	7	0.1	0.1—0.8	8	5	0.9	0.3—3.0
Larynx (161)	1	3	0.2	0.1—2.4	-	-	..	.	-	-	..	.	1	3	0.4	0.1—2.5
Lung (162)	134	59	1.2	0.9—1.6	15	13	0.4	0.2—0.9	43	15	1.6	0.8—3.1	1.3	76	31	0.8—2.0
Melanoma of skin (172)	7	7	0.6	0.2—1.7	½		0.2	0.1—2.4	5	3	0.9	0.2—4.4	½		0.4	0.1—5.1
Breast (174)	5	19	0.6	0.2—1.8	-	4	..	.	3	8	1.0	0.2—4.2	2	7	1.4	0.3—7.2
Female genital (180—184)	3	5	1.1	0.2—5.0	2	2	0.8	0.1—6.4	1	-	..	.	-	3	.	.
Prostate (185)	16	10	1.0	0.4—2.3	1	1	0.4	0.1—5.7	3	2	0.9	0.1—6.6	12	7	1.2	0.5—3.3
Bladder (188)	6	4	0.6	02—2.2	-	-	..	.	1	1	0.3	0.1—5.0	5	3	0.7	0.2—3.0
Kidney (189)	9	7	0.7	0.2—1.9	1	1	0.5	0.1—9.1	3	1	1.5	0.1—16.9	5	5	0.5	0.1—1.8
Central nervous system (191—192)	12	11	0.5	0.2—1.2	-	2	..	.	4	4	0.5	0.1—2.2	8	5	0.6	0.2—1.8
All lymphatic & hematopoietic (200—209)	27	18	0.7	0.4—1.4	5	2	1.2	0.2—7.9	8	4	0.6	0.2—2.1	14	12	0.6	0.3—1.5
Non-Hodgkin's lymphoma (200, 202)	5	7	0.5	0.2—1.8	1	-	..	.	3	-	..	.	1	7	0.1	0.1—1.2
Hodgkin's disease (201)	3	0			2	-	..	.	1	-	..	.	-	-	.	.
Leukemia (204—209)	11	8	0.6	0.2—1.6	2	2	0.5	0.1—4.5	3	3	0.3	0.1—1.6	6	3	0.9	0.2—3.7
Multiple myeloma (203)	7	3	1.0	0.2—3.8	-	-	..	.	-	1	..	.	7	2	1.4	0.3—6.8
Cerebrovascular disease (430—438)	37	23	0.9	0.5—1.6	3	3	0.7	0.1—3.8	13	5	1.3	0.4—3.8	21	15	1.0	0.5—1.9
Ischemic heart disease (410—414)	374	186	1.0	0.8—1.2	56	17	1.5	0.8—2.6	122	59	1.0	0.7—1.3	196	110	0.9	0.7—1.2
Bronchitis (491)	2	1	1.0	0.1—11.1	-	-	..	.	1	-	..	.	1	1	0.6	0.1—10.4
Emphysema (492)	6	6	0.6	0.2—1.9	1	-	..	.	3	3	0.5	0.1—2.7	2	3	0.4	0.1—2.8
Cirrhosis of liver (571)	18	12	0.8	0.4—1.7	1	2	0.2	0.1—3.0	7	3	1.4	0.3—5.8	10	7	0.8	0.3—2.2
Accidents (800—949)	156	63	1.1	0.8—1.4	84	32	1.2	0.8—1.8	43	21	0.8	0.4—1.3	29	10	1.3	0.6—2.7
Motor vehicle accidents (810—823)	92	39	1.1	0.7—1.6	57	22	1.2	0.7—2.0	19	10	0.8	0.3—1.7	16	7	0.9	0.4—2.4
Suicides (950—959)	57	34	0.7	0.4—1.1	23	12	0.7	0.4—1.5	22	11	0.8	0.4—1.6	12	11	0.5	0.2—1.2

[a] Based on internal comparisons with adjustment for race, gender, age, calendar time, and salary-wage classification.
[b] Person-years: 348 642 for all workers, 161 721 for <10 years since first exposure, 117 342 for 10—20 years since first exposure, and 69 579 for >20 years since first exposure.
[c] Person-years: 196 727 for all workers, 94 427 for <10 years since first exposure, 61 783 for 10—20 years since first exposure, and 40 515 for >20 years since first exposure.
[d] Code of the International Classification of Diseases in parentheses.

rising risks with increasing level of cumulative exposure. The rate ratio for cancer of the lung was slightly elevated in the next-to-the-lowest (RR 1.3) and the highest (RR 1.5) quintile of cumulative exposure, but showed no monotonic trend (P = 0.65 for trend of the exposed). None of the rate ratios for lung cancer in the individual exposure categories was statistically significant. The rate ratios for cancer of the esophagus and rectum were greater than 1.0 in all the quintile categories, but they were based on 4 or fewer deaths in each cell and showed no evidence of a trend with increasing level of cumulative exposure (P = 0.58 and 0.81 for trend for esophagus and rectum, respectively). Analyses were also conducted which included adjustment for plant. This additional adjustment had little effect on the rate ratios (eg, the rate ratios for lung cancer by quintile of cumulative exposure were 1.1, 1.3, 1.2, 1.0, 1.6), and the results presented did not include plant in the model.

Analyses were also conducted by deciles of cumulative exposure to evaluate lung cancer risks at subcategories within the upper quintile. The rate ratios for lung cancer were 1.2, 0.9, 1.1, 1.5, 1.3, 1.1, 1.0, 1.0, 1.7, and 1.3 from the lowest to the highest decile. None of these rate ratios was statistically significant, and the P for trend equaled 0.84. Analyses of lung cancer by cumulative exposure for individual plants also revealed no clear exposure-response gradients for any of the plants.

The rate ratios for cancer of the lung by cumulative exposure and time since first exposure are shown in table 6. They were 0.4 for all cumulative exposure categories in the <10-year since-first-exposure category and ranged from 0.5 to 2.6 in the 10-to-19-year category. For ≥20 years after first exposure and the highest quintile of cumulative exposure, a rate ratio of 2.1 was observed, which was statistically significant. The P for trend by cumulative exposure in the category ≥20 years after first exposure was 0.11.

We also evaluated the risk of lung cancer mortality using several exposure measures and subgroups (table 7). Most of the indicators of exposure displayed a rate ratio pattern similar to that observed for cumulative exposure (ie, a nonsignificant excess in the upper quintile), and none showed a strong exposure-response gradient or a statistically significant exposure-response trend. We also evaluated the rate ratios by duration of exposure at each level of intensity. No exposure-response patterns were observed at any intensity by duration category (data not shown).

While inspecting the jobs held by workers who died of lung cancer in the upper quintile of cumulative exposure, we noted what appeared to be an unusually large

Table 5. Observed (O) number of deaths among the exposed workers, relative risks[a] (RR), and 95% confidence intervals (95% CI) for selected causes of death by cumulative exposure to acrylonitrile (comparison with the unexposed workers).

Cause of death	Cumulative exposure categories (ppm-years)[b]														
	<0.13			>0.13—0.57			<0.57—1.5			<1.5—8.0			>8.0		
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI
All causes combined	347	1.0	0.9—1.1	236	0.9	0.8—1.1	213	0.8	0.7—0.9	245	0.8	0.7—0.9	176	0.8	0.7—1.0
All cancer	78	0.8	0.6—1.1	63	0.9	0.7—1.2	60	0.8	0.6—1.1	72	0.8	0.6—1.1	53	0.9	0.7—1.3
Buccal cavity & pharynx	2	0.5	0.1—2.7	3	1.1	0.3—4.4	-	..		-	..		1	0.4	0.1—3.2
Esophagus	2	1.6	0.2—11.4	3	2.9	0.5—17.8	2	1.4	0.2—10.2	4	2.7	0.5—15.0	1	1.2	0.1—13.2
Stomach	6	2.0	0.6—6.9	1	0.5	0.1—4.0	1	0.4	0.1—4.0	3	1.2	0.3—5.0	1	0.6	0.1—5.5
Large intestine	3	0.3	0.1—1.1	5	0.7	0.2—1.8	4	0.6	0.2—1.7	6	0.7	0.3—1.8	1	0.2	0.1—1.3
Rectum	1	1.7	0.1—27.9	1	2.1	0.1—33.9	4	7.8	0.8—71.6	2	3.4	0.3—37.5	1	3.2	0.2—52.0
Liver	-	..	.	-	..	.	1	0.7	0.1—6.8	-	..	.	2	1.7	0.3—10.1
Pancreas	1	0.2	0.1—1.5	3	0.7	0.2—2.5	1	0.2	0.1—1.8	2	0.4	0.1—1.6	3	0.9	0.2—3.2
Lung	27	1.1	0.7—1.7	26	1.3	0.8—2.1	28	1.2	0.7—1.9	27	1.0	0.6—1.6	26	1.5	0.9—2.4
Melanoma of skin	1	0.2	0.1—2.1	1	0.4	0.1—3.1	1	0.6	0.1—4.7	4	1.8	0.5—6.9	-	..	.
Breast	3	0.7	0.2—2.8	-	-	.	1	1.1	0.1—8.1	1	0.9	0.1—7.0	-	..	.
Prostate	7	1.9	0.7—5.4	1	0.3	0.1—2.4	2	0.7	0.2—3.3	5	1.5	0.5—4.5	1	0.4	0.1—3.5
Bladder	-	..		2	1.0	0.2—5.6	2	1.1	0.2—6.5	1	0.4	0.1—4.0	1	0.6	0.1—5.8
Kidney	1	0.3	0.1—2.7	1	0.4	0.1—3.6	3	1.1	0.3—4.7	2	0.6	0.1—3.2	2	1.1	0.2—5.6
Central nervous system	3	0.5	0.1—1.8	1	0.2	0.1—1.7	2	0.5	0.1—2.3	4	0.8	0.1—2.4	2	0.5	0.1—2.5
All lymphatic & hematopoietic	6	0.7	0.3—1.8	7	1.1	0.4—2.6	6	0.8	0.3—2.0	5	0.6	0.2—1.7	3	0.6	0.2—1.9
Hodgkin's disease	-	..	.	-[c]	..	.	-[c]	..	.	-[c]	..	.	-	..	.
Non-Hodgkin's lymphoma	2	1.0	0.2—5.2	1	0.6	0.1—5.5	1	0.5	0.1—4.4	1	0.4	0.1—3.4	-	..	.
Leukemia	3	0.6	0.1—2.2	3	0.9	0.2—3.6	2	0.6	0.1—2.7	2	0.6	0.1—2.8	1	0.4	0.1—3.5
Multiple myeloma	1	0.7	0.1—7.4	2	1.5	0.2—9.1	1	0.6	0.1—5.6	1	0.5	0.1—5.3	2	1.8	0.3—11.8
Cerebrovascular disease	10	1.0	0.5—2.3	7	0.9	0.4—2.2	8	1.0	0.4—2.3	6	0.7	0.3—1.7	6	1.1	0.4—2.7
Ischemic heart disease	95	1.1	0.8—1.4	76	1.1	0.8—1.4	66	0.9	0.7—1.2	82	1.0	0.7—1.3	55	0.9	0.7—1.3
Bronchitis, emphysema, asthma	4	1.6	0.5—5.4	-	..	.	3	0.8	0.2—3.0	1	0.2	0.1—1.9	-	..	.
Cirrhosis of liver	7	1.4	0.5—3.7	2	0.5	0.1—2.2	3	0.7	0.2—2.5	5	0.9	0.3—2.8	1	0.2	0.1—2.0
Accidents	58	1.1	0.8—1.6	28	1.0	0.6—1.6	18	0.9	0.5—1.5	33	1.3	0.8—2.0	19	1.0	0.6—1.6
Suicides	27	1.1	0.6—1.8	9	0.6	0.3—1.2	9	0.7	0.3—1.5	5	0.3	0.1—0.8	7	0.5	0.2—1.2

[a] Adjusted for race, gender, age, calendar time, and salary-wage classification.
[b] Person-years of the exposed: 121 430 for the 0.01—0.13 category, 69 122 for the 0.14—0.57 category, 49 800 for the 0.58—1.50 category, 63 483 for the 1.51—8.00 category, and 44 807 for the >8.00 category.
[c] There was 1 exposed and no unexposed workers.

Table 6. Observed(O) number of deaths among the exposed workers, relative risks[a] (RR), and 95% confidence intervals (95% CI) for lung cancer by quintile of cumulative exposure and time since first exposure with the unexposed workers as the comparison.

Cancer and cumulative exposure	Time since first exposure								
	≤10 years ago			11—19 years ago			≥20 years ago		
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI
>0.13 ppm-years	7	0.4	0.2—1.2	9	0.5	0.5—3.2	11	1.1	0.6—2.2
>0.13 to 0.57 ppm-years	3	0.4	0.1—1.4	13	2.6	1.2—5.7	10	1.0	0.5—2.1
>0.57 to 1.5 ppm-years	2	0.4	0.1—1.6	10	2.0	0.9—4.8	16	1.2	0.6—2.2
>1.5 to 8.0 ppm-years	2	0.4	0.1—2.0	7	1.2	0.5—3.1	18	1.2	0.6—2.1
>8.0 ppm-years	1	0.4	0.1—3.1	4	0.9	0.3—1.2	21	2.1	1.2—3.8

[a]Based on internal comparisons adjusted for race, gender, age, calendar time, and salary/wage classification.

Table 7. Observed (O) number of deaths among the exposed workers, relative risks[a] (RR) for lung cancer, and 95% confidence intervals (95% CI) for selected causes of death by various indicators of exposure to acrylonitrile (comparison with the unexposed workers).

Exposure indicator	Quintile of exposure														
	1 (lowest)			2			3			4			5 (highest)		
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI
Cumulative[b]	27	1.1	0.7—1.7	26	1.3	0.8—2.1	28	1.2	0.8—1.9	27	1.0	0.6—1.6	26	1.5	0.9—2.4
Cumulative using minimum job estimates[c]	28	1.1	0.7—1.8	26	1.3	0.8—2.1	27	1.1	0.7—1.8	26	1.1	0.7—1.7	27	1.4	0.9—2.3
Cumulative using maximum job estimates[d]	27	1.1	0.7—1.8	27	1.3	0.8—2.1	27	1.2	0.7—1.9	27	1.1	0.7—1.7	26	1.3	0.8—2.2
Duration[e]	26	1.2	0.5—2.5	27	0.8	0.4—1.5	28	1.1	0.5—2.5	29	2.0	0.8—5.1	24	1.1	0.5—2.1
Frequency of peaks exposures[f]	82	1.2	0.8—1.6	13	1.3	0.7—2.4	13	1.0	0.5—1.8	13	1.4	0.8—2.7	13	1.4	0.8—2.6
Cumulative for wage only[b]	22	1.3	0.8—2.3	16	1.3	0.7—2.3	20	1.1	0.6—2.0	23	1.1	0.7—1.9	18	1.2	0.7—2.2
Cumulative for ever salaried[b]	5	0.6	0.2—1.6	10	1.3	0.6—2.9	8	1.4	0.6—3.5	4	0.6	0.2—2.0	8	2.4	1.0—5.8
Cumulative lagged 5 years[g]	27	1.2	0.8—1.9	26	1.2	0.8—2.0	25	1.1	0.7—1.9	26	1.0	0.6—1.6	26	1.4	0.9—2.3
Cumulative lagged 15 years[h]	20	1.0	0.6—1.7	20	1.3	0.8—2.1	21	0.8	0.5—1.4	21	1.0	0.6—1.7	20	1.3	0.8—2.2
Cumulative lagged 20 years[i]	16	1.0	0.6—1.8	16	1.0	0.5—1.6	16	0.9	0.5—1.5	16	1.0	0.6—1.7	15	1.4	0.8—2.5
Cumulative considering dermal exposure[j]	24	1.3	0.8—2.1	24	1.1	0.7—1.8	25	0.9	0.6—1.4	24	1.1	0.7—1.8	23	1.3	0.8—2.1
Cumulative with respirator use considered[b]	27	1.0	0.6—1.7	26	1.3	0.8—2.0	27	1.1	0.7—1.8	27	1.0	0.6—1.6	26	1.5	0.9—2.4
Cumulative considering physical activity[k]	26	0.9	0.6—1.5	27	1.4	0.9—2.2	26	1.1	0.7—1.8	27	1.2	0.8—2.0	27	1.3	0.8—2.1
Cumulative based on jobs with high confidence[l]	25	1.1	0.6—1.7	24	1.4	0.8—2.2	25	1.2	0.8—2.0	25	1.0	0.6—1.6	25	1.5	0.9—2.5
Intensity (highest job held)[m]	27	0.9	0.6—1.5	27	1.2	0.8—1.9	27	1.3	0.8—2.1	26	1.4	0.9—2.3	27	1.0	0.6—1.6
Average[n]	26	1.1	0.7—1.7	29	1.4	0.8—2.1	28	1.0	0.6—1.5	24	1.1	0.6—1.7	27	1.3	0.8—2.2
Cumulative for workers employed < 1 year[b]	11	1.6	0.6—4.4	-[o]	..	.	4	4.9	1.4—17.4	-[o]	..	.	-[o]	..	.
Cumulative for workers employed ≥1 years[b]	16	0.9	0.5—1.5	26	1.4	0.9—2.3	24	1.0	0.6—1.7	27	1.0	0.6—1.7	26	1.5	0.9—2.5
Cumulative for workers never holding maintenance or mechanic jobs[b]	21	0.9	0.5—1.5	25	1.3	0.8—2.1	27	1.2	0.7—1.9	27	1.1	0.7—1.7	21	1.3	0.8—2.2

[a] Adjusted for race, gender, age, calendar time, and salary-wage classification where appropriate.
[b] Quintile cut points at 0.13 ppm-years, 0.57 ppm-years, 1.50 ppm-years, and 8.00 ppm-years.
[c] Quintile cut points at 0.13 ppm-years, 0.55 ppm-years, 1.50 ppm-years, and 6.50 ppm-years.
[d] Quintile cut points at 0.13 ppm-years, 0.61 ppm-years, 1.64 ppm-years, and 8.00 ppm-years.
[e] Quintile cut points at 1.5 years, 6.1 years, 12.1 years, and 17 years.
[f] Lowest category equals no peaks, and for the 4 higher categories the cut points were 1, 5, and 14.
[g] Quintile cut points at 0.11 ppm-years, 0.55 ppm-years, 1.43 ppm-years, and 7.00 ppm-years.
[h] Quintile cut points at 0.10 ppm-years, 0.36 ppm-years, 1.35 ppm-years, and 6.00 ppm-years.
[i] Quintile cut points at 0.08, 0.36, 1.30, and 6.00 ppm-years.
[j] Quintile cut points at 0.02 ppm-years, 0.10 ppm-years, 1.00 ppm-years, and 4.90 ppm-years.
[k] Quintile cut points at 2.6, 11.6, 32.0, and 130 total milligrams inhaled.
[l] Quintile cut points at 0.13 ppm-years, 0.55 ppm-years, 1.40 ppm-years, and 8.00 ppm-years.
[m] Quintile cut points at 0.40 ppm, 1.75 ppm, 2.00 ppm, and 7.00 ppm.
[n] Quintile cut points at 0.03 ppm, 0.07 ppm, 0.24 ppm, 1.00 ppm.
[o] No deaths among the exposed workers.

number of maintenance and mechanics jobs. This observation raised the possibility of confounding from asbestos exposure, since asbestos was used as insulating material in these plants. In analyses excluding maintenance workers and mechanics, the excess rate ratio was reduced in the upper quintile (RR 1.3) when compared with that from the entire cohort (RR 1.5), but was not entirely eliminated. In addition, no death from asbestosis or mesothelioma occurred in the cohort.

Table 8 provides results from analyses designed to explore the statistically significant excess of lung cancer in the upper quintile of cumulative exposure ≥20 years after first exposure (RR 2.1). This excess occurred in several subgroups of the cohort, including wage and salaried workers and long-term workers (employed ≥1 years), in fiber and nonfiber plants, and for cumulative exposure excluding maintenance and mechanics, but not by highest exposed job held or among workers first employed after 1960. None of the tests for trend by cumulative exposure for these analyses was statistically significant. The rate ratios by decile for ≥20 years after first exposure were 1.3, 0.9, 0.5, 1.7, 1.2, 1.1, 1.2, 1.1, 2.5, and 1.8, respectively (P for trend 0.16). The excess in the upper quintile for ≥20 years after first exposure was restricted to those first employed before 1960 (RR 2.2), but the test for trend across the cumulative exposure categories for workers employed before 1960 was not statistically significant (P = 0.19).

We also evaluated the rate ratio of lung cancer by cumulative exposure cut into 11 categories to assess the influence of cut points on risk estimates. The rate ratios from the lowest to the highest cumulative exposure category for ≥20 years after first exposure were 1.4, 1.2, 0.2, 1.4, 1.7, 1.1, 1.3, 1.2, 1.2, 2.1, and 2.0. None was statistically significant, and the P for trend was 0.095.

Case-cohort analyses

Interviews with subjects or proxies were completed with 1890 (71%) of the 2655 persons in the 10% sample selected to obtain information on tobacco use. An additional 71 interviews were conducted with the next-of-kin of the subjects who died of cancer of the lung (N=64) or brain (N=7)

Subjects who ever smoked cigarettes constituted 66% of the sample selected to evaluate tobacco use, and 3% reported using pipes or cigars, but not cigarettes. Among the cigarette smokers, 788 (69%) smoked 1—20 cigarettes per day, 303 (26%) smoked 21—40 cigarettes per day, and 53 (5%) smoked ≥40 cigarettes per day. The proportions reporting duration of cigarette smoking were 52% for <21 years, 38% for 21—40 years, and 9% for ≥40 years. Among the workers never exposed to acrylonitrile, 56% were ever cigarette smokers, while among the exposed workers 68% were ever cigarette smokers. The percentage of subjects who were ever cigarette smokers increased by quintile of cumulative exposure to

Table 8. Observed (O) number of deaths among the exposed workers, relative risks[a] (RR) for lung cancer, and 95% confidence intervals (95% CI) for selected causes of death by various indicators of exposure to acrylonitrile (comparison with the unexposed workers) for ≥20 years after the first exposure stratum.

Exposure indicator	Quintile of exposure by ≥20 years after first exposure														
	1 (lowest)			2			3			4			5 (highest)		
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI
Cumulative[b]	11	1.1	0.6—2.2	10	1.0	0.5—2.1	16	1.2	0.6—2.2	18	1.2	0.6—2.1)	21	2.1	1.2—3.8
Cumulative for wage only[b]	8	1.4	0.6—3.3	6	1.1	0.4—2.8	11	1.2	0.6—2.5	15	1.3	0.7—2.6	15	2.0	1.0—4.0
Cumulative for ever salaried[b]	3	0.7	0.7—2.5	4	0.9	0.3—2.8	5	1.3	0.4—4.1	3	0.8	0.2—2.7	6	2.5	0.9—7.1
Intensity (highest job held)[c]	10	0.8	0.4—1.7	16	1.4	0.7—2.5	14	1.1	0.6—2.5	17	1.9	1.0—3.5	19	1.3	0.7—2.4
Cumulative excluding mechanics and maintenance workers[b]	10	1.0	0.5—2.2	10	1.0	0.5—2.2	16	1.2	0.6—2.2	18	1.2	0.6—2.2	16	1.7	0.9—3.2
Cumulative for fiber plants 1,4, & 5[b]	3	0.9	0.2—3.6	3	0.8	0.2—3.1	5	1.4	0.4—4.5	4	0.6	0.2—2.0	15	2.1	0.8—5.5
Cumulative for nonfiber plants 2,3,6,7, & 8[b]	8	1.2	0.5—2.7	7	1.1	0.5—2.7	11	1.3	0.6—2.8	14	1.7	0.9—3.4	6	2.8	1.1—6.9
Cumulative for workers employed < 1 year[b]	3	1.6	0.3—8.1	-	..	.	3	12.9	2.6—65.2	-	..	.	-	..	.
Cumulative for workers employed ≥1 years[b]	8	1.0	0.5—2.3	10	1.0	0.5—2.1	13	1.0	0.5—2.0	18	1.2	0.6—2.1	21	2.1	1.2—3.8
Cumulative for workers first employed before 1960[b]	15	1.3	0.7—2.4	18	1.7	0.9—3.0	20	1.4	0.8—2.5	22	1.4	0.8—2.4	20	2.2	1.2—3.9
Cumulative for workers first employed between 1960 and 1969[b]	8	1.1	0.5—2.8	7	1.1	0.4—2.9	6	1.1	0.4—3.1	4	0.6	0.2—1.9	5	0.8	0.2—2.3

[a] Adjusted for race, gender, age, calendar time, and salary-wage classification, where appropriate.
[b] Quintile cut points at 0.13 ppm-years, 0.57 ppm-years, 1.50 ppm-years, and 8.00 ppm-years.
[c] Quintile cut points at 0.40 ppm, 1.75 ppm, 2.00 ppm, and 7.00 ppm.

Table 9. Observed (O) number of deaths among the exposed workers, relative risks[a] (RR), and 95% confidence intervals (95% CI) for lung cancer by quintiles of cumulative exposure to acrylonitrile (comparison with the unexposed workers) for the full cohort and smoking subcohort.

Factor and subgroup analyzed	Quintile of exposure[b]															
	1 (lowest)			2			3			4			5 (highest)			
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	P for trend
Without consideration of time since first exposure																
Cumulative exposure for full cohort	27	1.1	0.7—1.7	26	1.3	0.8—2.1	28	1.2	0.7—1.9	27	1.0	0.6—1.6	26	1.5	0.9—2.4	0.65
Cumulative exposure for full smoking subcohort (not adjusted for smoking)	27	0.8	0.5—1.3	26	1.1	0.7—1.8	28	1.0	0.7—1.7	27	0.9	0.6—1.5	26	1.5	1.0—2.4	0.7
Cumulative exposure for smoking subcohort with information on cigarette use (not adjusted for smoking)	5	0.3	0.1—1.0	6	0.9	0.4—2.0	7	1.0	0.4—2.3	13	1.0	0.5—2.1	9	1.7	0.8—3.6	0.8
Cumulative exposure for smoking subcohort adjusted for ever cigarette use	5	0.3	0.1—1.0	6	0.8	0.3—1.8	7	1.0	0.4—2.4	13	0.9	0.4—1.9	9	1.6	0.7—3.3	0.99
Cumulative exposure for smoking subcohort adjusted for number of cigarettes per day	5	0.3	0.1—0.9	8	0.7	0.3—1.7	7	1.1	0.5—2.6	13	1.0	0.4—2.1	9	1.7	0.8—3.6	0.96
Full cohort with RR values adjusted for smoking[c]	-	1.1	.	-	1.0	.	-	1.1	.	-	0.9	.	-	1.4	.	.
≥20 years after first exposure																
Cumulative exposure for full cohort	11	1.1	0.6—2.2	10	1.0	0.5—2.1	16	1.2	0.6—2.2	18	1.2	0.6—2.1	21	2.1	1.2—3.8	0.11
Cumulative exposure for full smoking subcohort (not adjusted for smoking)	11	0.8	0.4—1.5	9	0.8	0.4—1.6	16	0.9	0.5—1.7	18	0.9	0.5—1.5	16	1.8	1.1—2.9	0.4
Cumulative exposure for smoking subcohort with information on cigarette use (not adjusted for smoking)	2	0.6	0.1—2.4	3	0.8	0.2—2.7	4	1.1	0.4—3.0	10	1.5	0.7—3.2	5	2.0	0.9—4.6	0.81
Cumulative exposure for smoking subcohort adjusted for ever cigarette use	2	0.5	0.1—2.1	3	0.7	0.2—2.4	4	1.2	0.4—3.2	10	1.3	0.6—2.8	5	1.8	0.8—4.1	0.97
Cumulative exposure for smoking subcohort adjusted for number of cigarettes per day	2	0.3	0.1—1.9	3	0.5	0.1—2.2	4	1.3	0.5—3.3	10	1.5	0.7—3.3	5	1.8	0.8—4.1	0.92
Full cohort with RR values adjusted for smoking[c]	-	0.4	.	-	0.6	.	-	1.3	.	-	1.2	.	-	1.9	.	.

[a] All RR values adjusted for age, calendar time, gender, and race.
[b] Ever smoked cigarettes: 62% of the 1st exposure quintile, 64% of the 2nd exposure quintile, 68% of the 3rd quintile, 72% of the 4th exposure quintile, and 75% of the 5th exposure quintile.
[c] RR values for the full cohort modified according to proportional changes observed between smoking unadjusted RR values and RR values adjusted for number of cigarettes used per day.

acrylonitrile (table 9). There was an excess of smokers in the upper 2 quintiles of cumulative exposure even after adjustment of smoking prevalence for age (ie, the age-adjusted smoking prevalences were 56% for nonsmokers and 65%, 64%, 63%, 71%, and 75% for the 5 cumulative exposure quintiles). The rate ratio for lung cancer among ever cigarette smokers compared with never smokers was 3.6 [95% confidence interval (95% CI) 1.6 — 8.2]. The information on tobacco use for the 1035 persons in the subcohort obtained from company medical records agreed with the interview information on use of cigarettes 86% of the time.

The rate ratios for lung cancer by quintile of cumulative exposure for the full cohort and the smoking information subcohort are shown in table 9. The results from the analyses of the subcohort were similar to those in the full cohort (ie, with rate ratios for lung cancer of near 1.0 for the 4 lower quintiles of cumulative exposure and about

1.5 for the upper quintile). None showed a significant exposure-response trend. There was little change in the rate ratios from adjustment by ever or never use of cigarettes or by the number of cigarettes used per day. If the same proportional changes in the rate ratios observed for the subcohort from adjustment for ever or never cigarette use are applied to the full cohort, the predicted rate ratios by quintile in the full cohort would be 1.1, 1.2, 1.1, 0.9, and 1.4 from the lowest to the highest quintile.

We also performed analyses for lung cancer risk ≥20 years after first exposure in the subcohort with smoking information. Although the number of deaths from lung cancer among the workers in this category was small (a total of 24), the pattern was similar to that of the entire smoking subcohort (ie, adjustment for cigarette use resulted in a slight reduction in the rate ratio in the upper quintile but a nonsignificant excess remained after the adjustment). No statistically significant trend by cumulative exposure was observed. It was not possible to analyze lung cancer by acrylonitrile exposure for the nonsmokers because only 6 lung cancer deaths occurred in this subgroup.

Discussion

This large cohort of workers in the acrylonitrile industry (25 460 subjects and 2038 deaths) with over 500 000 person-years of follow-up had a more favorable mortality experience than did the general United States population. This is a common occurrence in occupational investigations and can often be attributed to the healthy-worker effect (26). It is interesting to note that division of the standardized mortality ratio of the exposed workers by that of the unexposed workers yielded relative risks similar to those of the internal comparisons. We relied, however, primarily upon the internal comparisons of the exposed and unexposed workers to diminish the healthy-worker problem, and these analyses did not reveal statistically significant excesses for any cause of death among the exposed workers. Most of the cancers of a priori interest (ie, stomach, brain, breast, prostate, and lymphatic and hematopoietic system) because of experimental (4) or previous epidemiologic (7, 8) findings showed no evidence of an association with acrylonitrile in any of our analyses. The power to detect a moderate excess was, however, small for these sites because of the small numbers of exposed deaths (ie, 12 for cancer of the stomach, 12 for cancer of the brain, 5 for cancer of the breast, 16 for cancer of the prostate, and 27 for cancer of the lymphatic or hematopoietic system).

Mortality from cancers of the esophagus and rectum was unexpectedly elevated in this cohort. Excesses for these tumors have not been observed in experimental studies (5), and most previous epidemiologic studies did not mention esophageal cancer (7, 8, 14, 16, 27—32). Swaen et al (9) observed no deaths from esophageal cancer versus 0.79 expected, and Siemiatycki (33) reported a slight deficit [odds ratio (OR) 0.6](based on only 2 deaths) for persons who worked with acrylic fiber. Although Siemiatycki (33) found a significant excess of rectal cancer (OR 3.5) among workers classified as having substantial exposure to acrylic fibers, other studies of acrylonitrile workers did not (7—9, 15, 31). The relative risks for esophageal and rectal cancer in our study did not show any evidence of an exposure-response gradient. In fact, the rate ratios for cancers of the esophagus and rectum were typically lower at higher exposure levels than at lower levels. With little or no previous experimental or epidemiologic evidence and the absence of an exposure-response gradient, it seems unlikely that these excesses are related to acrylonitrile exposure.

Of more interest is the small excess of lung cancer, a site of a priori interest. The overall rate ratio of 1.2 for the exposed compared with the unexposed workers was not statistically significant. The excess was, however, larger in the upper quintile of cumulative exposure (RR 1.5), particularly for the subgroup ≥20 years after first exposure, for which the rate ratio equaled 2.1 (which was statistically significant). There were no significant exposure-response trends. Excesses were not consistently observed in the individual plants (although in several plants the numbers were small). The excess in the upper quintile of cumulative exposure could indicate that high levels of cumulative exposure to acrylonitrile are necessary before lung cancer risks are increased, or it could be due to confounding, exposure misclassification, or chance.

Several analyses were performed to evaluate the possibilities. Analyses by deciles of cumulative exposure were performed to divide the exposures in the upper quintile. Several deciles showed slightly elevated rate ratios and some elevation occurred in lower deciles. A lower rate ratio in the highest decile (RR 1.3) than in the ninth decile (RR 1.7) did not support a consistent upturn in risk at the highest levels of exposure. We evaluated rate ratios for lung cancer by 11 categories of cumulative exposure to see if different cut points affected the risk estimates. The pattern for 11 categories was similar to that for 10 categories. We also lagged exposures 5, 15, and 20 years because very recent exposures are seldom important in cancer development and because lagging often sharpens exposure-response gradients (34). The relative risks from lagged exposures were essentially identical to the unlagged ones and therefore did not support a causal association. Finally, short-term workers often have elevated risks for some diseases, possibly due to life-style factors, and such elevated risks could create spurious findings (35). The lung cancer excess in the upper quintile occurred, however, among the workers employed for ≥1 years and

therefore indicated that it was not simply a pattern associated with short-term employment.

Analyses of lung cancer restricted to the time period ≥20 years after first exposure showed somewhat larger relative risks than the shorter latencies did. In this subgroup, the rate ratio in the upper quintile was typically ≥2.0 and sometimes statistically significant, although the tests for trend were not. The excess in the upper quintile for the 20-year latency group occurred for wage and salaried workers and for workers from both fiber and nonfiber plants. It also persisted when maintenance workers and mechanics were excluded, although at a lower level. This latter finding is important because there was some indication that the lung cancer excess in the entire cohort might be concentrated among workers employed as maintenance workers, for whom exposure to asbestos was possible. No deaths from asbestosis or mesothelioma had occurred in the cohort, however, and confounding by asbestos cannot entirely explain the excess because the workers in the upper quintile never holding maintenance or mechanic jobs experienced a 70% excess of lung cancer ≥20 years after first exposure. An important lead may be the concentration of the excess in the upper quintile among workers first employed prior to 1960. This may simply be a chance finding, but it may also indicate that the excess is due to high ambient-air levels or other exposures during that time period. The small numbers of lung cancer deaths among the workers first exposed prior to 1960 prevented any evaluation of risks at the highest exposures. Further follow-up of the cohort would, however, provide additional events in this category and greater power to evaluate rate ratios than is currently possible.

The availability of work histories only through 1983 is a possible limitation because exposure from subsequent years could not be considered. This should not be a serious problem, however, because our analyses showed that the excess rate ratio for lung cancer was associated with earlier, rather than recent exposures. We know that exposures since 1983 have been much lower than in earlier times; thus contributions to cumulative exposure after 1983 should be proportionally smaller than for exposures prior to 1983. It is also important to note that the cohort was relatively young (ie, about 10% of the subjects were deceased). Since many of the workers in this follow-up have not yet reached ages at which cancer becomes common, we have not fully evaluated risks at the peak cancer ages.

We were able to address the potential for confounding from tobacco use. The proportion of cigarette smokers was slightly larger among the workers exposed to acrylonitrile (68%) than among the unexposed workers (56%), and a greater proportion of smokers occurred in the upper cumulative exposure quintiles than in the lower quintiles (ie, 62% in the lowest quintile and 75% in the highest). Adjustment for cigarette use did not have much of an effect, however, on the rate ratio for lung cancer from acrylonitrile exposure. The rate ratios for lung cancer after adjustment for smoking in the subcohort surveyed for tobacco use were similar to those without such adjustment, (eg, in the upper quintile the rate ratio changed from 1.5 to 1.4). This finding might seem somewhat surprising given the rising prevalence of smoking with increasing exposure to acrylonitrile. The correlation between cigarette smoking and acrylonitrile levels was, however, small (correlation coefficient of 0.08); therefore major confounding was not possible. Some residual confounding from smoking could still have occurred because we were not able to obtain information on the full subcohort and because some interviews were conducted with proxies. A major effect, however, is unlikely for several reasons. First, we found no evidence of excess risks for other smoking-related causes of death among the exposed subjects, and there was no reason to expect that confounding by smoking would affect only lung cancer. Second, if there had been serious confounding by smoking, we would have expected to see more of a change in the rate ratio from adjustment when the available smoking data were used. We can think of no reason why the smoking information we had would indicate little confounding, while the smoking information we lacked would not.

The purpose of obtaining smoking information on the subcohort was to see if we might reasonably expect the rate ratios of the full cohort to change if information on tobacco use had been available for everyone, an approach that has been used previously (36). If information on smoking had been available for the full cohort and we had assumed smoking adjustment would yield the same proportional effect in the full cohort as that in the subcohort, the adjusted rate ratio for the upper quintile would be 1.4, while the adjusted rate ratios for the 4 lower quintiles would be 1.1, 1.0, 1.1, and 0.9, respectively. Similar adjustments of rate ratio by quintile ≥20 years after first exposure would also predict little change from the unadjusted values.

Estimating historical exposures is a complex, but crucial, component of investigations such as ours. A sophisticated and carefully documented exposure assessment effort was undertaken to develop high-quality exposure estimates and to provide the necessary data for exposure-response evaluations (19, 20). In spite of this detailed and careful effort, exposure misclassification undoubtedly occurred, and it is important to consider its effects on the calculated relative risks. Differential misclassification can bias relative risks toward or away from the null, depending upon the nature of the misclassification. Because the assessment of exposures was by job instead of by study subject and because it was carried out without knowledge of the mortality status of persons in the study, differential misclassification is unlikely. Nondifferential misclassification is another matter, however. In a validation study,

we found that the correlation between estimates of acrylonitrile exposure and the actual measurements was 0.6. Although this is an excellent reliability for historical estimates, it still leaves considerable opportunity for nondifferential exposure misclassification. Since nondifferential misclassification would tend to diminish relative risk estimates and dilute exposure-response gradients (37), it could result in an underestimation of the rate ratios if an association truly existed. It is unlikely, however, to cause a spurious excess.

The weight of evidence from previous epidemiologic studies does not suggest a relationship between acrylonitrile exposure and lung cancer. The rate ratios for lung cancer from 9 investigations ranged from 0.77 to 1.96 (9, 14—16, 27—32). A simple summation of observed and expected numbers in these 9 studies yields an overall rate ratio of 1.04, indicating no overall association. Four of the previous studies presented rate ratios by duration or cumulative exposure (9, 14, 16, 30), but they did not show striking excesses in the upper category of exposure. Of the previous reports, only the study by Collins et al (16) included information on tobacco use. They abstracted smoking information from the medical records at the plant (plants 1 and 6 in our investigation) and found that the rate ratio in the highest exposure category decreased slightly after adjustment for smoking. A vital status follow-up of several previously completed investigations has been extended, and the results from these efforts will help the evaluation of cancer and acrylonitrile exposure.

The exposure estimation procedure we employed allowed evaluation of disease risk by several exposure types, including duration, intensity, cumulative, and peak exposures; it also allowed consideration of the potential dose-modifying effects of respirator use, dermal exposure, and the level of physical activity associated with the job. The opportunity to evaluate disease risk by different exposure metrics is particularly valuable in studies such as ours, where no clear exposure-response relationship was observed. Although acrylonitrile is an animal carcinogen [the metabolite 2-cyanoethylene oxide is believed to be the ultimate carcinogen (38, 39)] and it can form DNA adducts, many details regarding the mechanism of action in humans are not well understood. When it is not clear which exposure measure is the best surrogate for delivered dose, the ability to evaluate risks by different exposure types increases confidence that an association has not been missed simply due a reliance on an inappropriate surrogate. The value of using several exposure measures is underscored by the finding that different exposure metrics often classify workers differently. This finding has been reported in other studies (40, 41), and it occurs in this investigation of acrylonitrile. The correlation coefficients between different exposure measures in this study ranged from 0.1 to almost 1.0. Some were highly correlated (eg, cumulative exposure and lagged exposures where the correlation coefficients were greater than 0.9). Over half of the correlations were, however, less than 0.5; this result indicates that the measures would distribute the workers differently across exposure quintiles. Although analysis by several different measures of exposure diminishes the chances of missing an association, it increases the opportunity for chance excesses because of the larger number of comparisons. We found that most measures of exposure showed similar patterns (ie, small increases in the rate ratios for lung cancer in the highest exposure quintile, but no clear exposure-response gradient). The duration and intensity of exposure did not, however, display much of an excess in the upper quintile.

The cohort included 5242 women and therefore provided the opportunity to assess mortality risks among a group of workers often excluded from occupational investigations (42). This possibility is especially important for studies of acrylonitrile because, in bioassays, rodents developed mammary tumors (5). Mortality from breast cancer was not linked to acrylonitrile exposure in this study. Information was not available, however, on important reproductive risk factors for breast cancer (43). This limitation, plus the small number of deaths from breast cancer (N=24 with only 5 deaths among the exposed workers) and the high survival rate for this tumor (44), tempers any interpretation based entirely on our data.

In summary, the results from this study do not provide evidence that exposure to acrylonitrile increases the risk of death from most cancers of a priori interest (ie, stomach, brain, breast, prostate, or lymphatic and hematopoietic system). A rate ratio of 1.5 for lung cancer, also a cancer of a priori interest, in the upper quintile of exposure and of 2.1 for the category ≥20 years after first exposure may indicate carcinogenic activity at the highest levels of exposure. The lung cancer association with acrylonitrile exposure may not be causal because the rate ratio in the upper quintile was small and generally within the bounds of random statistical variation, the rate ratios did not continue to increase in subcategories of the upper quintile of exposure, and no significant exposure-response relationship occurred for any of the many exposure measures evaluated. Additional follow-up at some time in the future would provide additional power to evaluate the risk of lung cancer in this cohort.

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