

# Mortality Patterns among Employees Exposed to Acrylonitrile

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*A cohort of 2671 men, 1774 of whom were exposed to acrylonitrile, was observed from 1951 through 1983 for mortality. No statistically significant excess of all-cause or cause-specific mortality was observed. Analysis of exposure duration to acrylonitrile with respiratory cancer mortality showed no trend. Men exposed to high levels of acrylonitrile had respiratory cancer rates similar to men not exposed in the workplace and to the US general male population. These study results do not support the hypothesis that acrylonitrile is a human carcinogen.*

Several epidemiology studies have examined the morbidity and mortality patterns of workers exposed to acrylonitrile (AN). Statistically significant cancer excesses have been observed in the incidence of respiratory<sup>1</sup> and prostate cancers,<sup>2,3</sup> and mortality from lung cancer,<sup>4-6</sup> lymph cancer,<sup>4</sup> and stomach cancer.<sup>5</sup> No consistent findings have emerged from these studies; other investigations found no significant cancer excesses at any site.<sup>7,8</sup>

Exposure estimates to AN and possible confounding exposures were often not available in these earlier studies. Thus, the present cohort mortality study was undertaken to quantify AN exposure and to determine cigarette smoking history. Only one study attempted to crudely characterize exposure to AN as high, medium, or low,<sup>1</sup> and in only two studies were crude adjustments for smoking attempted.<sup>4,9</sup>

Two plants of the American Cyanamid Company were chosen for the study, one in Fortier, LA, the other in Santa Rosa, FL. The Fortier plant manufactures AN as well as several other materials and the Santa Rosa plant uses large quantities of AN in the manufacture of acrylic fiber. A particular strength of this study is the number of persons exposed to AN.

## Methods

The study population consisted of all men who worked at either plant from start-up (1951 for Fortier and 1957 for Santa Rosa) through Dec 31, 1973 ( $n = 2671$ ). Among 2473 white and 198 nonwhite men, 1302 worked only at the Fortier plant and 1361 worked only at the Santa Rosa plant. Eight men worked at both plants.

The vital status of the entire cohort was observed to the end of 1983 using records of the Social Security Administration and the National Death Index. At the end of the study, 2373 (89%) were alive, 237 (9%) were dead, and 61 (2%) were lost to follow-up. Of the 237 deaths, death certificates were obtained and cause of death was ascertained for 224 (95%). The 15 persons for whom no death certificate could be obtained were assumed to have died from unknown causes. All death certificates obtained were coded for underlying cause of death according to the Eighth Revision of the International Classification of Diseases by an independent nosologist.

## Exposure Estimates

Exposure estimates for all jobs at both plants over time were developed. Industrial hygiene monitoring, which began at both plants in 1977 prior to many major engineering changes, was considered representative of

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exposure levels back to plant start-up. Whenever possible, actual measurements were used to indicate job-specific exposure to AN. Present-day measurements were adjusted for changes in handling practices and installation of engineering controls, with assistance provided by plant personnel. This method for quantifying exposure in an occupational study is similar to methods described elsewhere.<sup>10</sup>

Exposed men were defined as having a cumulative exposure of greater than 0.01 ppm/year. This level was chosen to ensure that only persons with significant exposures were included in the exposed groups. Cumulative exposure was calculated as the time-weighted average for eight hours in parts per million estimated for a particular job in a particular time period, multiplied by the number of days spent in that job. All jobs with AN exposure were summed for a worker and then divided by 365 to produce an estimate of parts per million per years of exposure. Four exposure categories were defined: "none" or <0.01, 0.01 to 0.7, 0.7 to 7.0 and >7.0 ppm/year, to place sufficient numbers for analysis in the highest category.

### Smoking History

Smoking history data was available from medical records for 1541 cohort members (58%). If the medical record indicated a person had ever smoked cigarettes, cigars, or a pipe for 3 months or more, this person was coded as a smoker. If medical records stated that a person was a nonsmoker or had smoked for less than 3 months, that person was coded as a nonsmoker. The 3-month convention was a company criterion for determining smoking status. When no information was provided in the medical record about smoking, a person's smoking status was coded as unknown.

Generally, workers hired in earlier years were more likely to have smoking information. For instance, of the men hired prior to 1955, 64% had smoking information, whereas for men hired in 1955 to 1964 and 1965 to 1973, 54% and 60%, respectively, had smoking information. Nonwhites had more complete smoking information than whites, 75% compared with 56%. However, when plants were compared, no difference was found; both Fortier and Santa Rosa had smoking information on 58% of the men.

The percentage of persons who had ever smoked was calculated as the number of smokers divided by the sum of smokers and nonsmokers omitting persons with unknown smoking status. Smoker status is a static definition which assumes that smoking status is constant since date of hire. The percentage of smokers increases with increasing cumulative exposure. Among the nonexposed group, 70.8% have ever smoked; in comparison, 72.7%, 74.4%, and 79.3% of exposed persons have ever smoked.

### Analysis

Person-year accumulation for the cohort began at first date of employment and/or upon the employee first

achieving a specified level of exposure, depending upon the type of analysis being undertaken. Workers contributed person-years to each exposure category they passed through, although their deaths were assigned to the exposure interval in which they occur. Person-year accumulation stopped at (1) the study termination date (Dec 31, 1983), (2) the last day worked if the person was lost to follow-up, or (3) the date of death.

Standardized mortality ratios (SMR) and an internally standardized relative risk measure as described by Gilbert and Buchanan<sup>11</sup> were employed to estimate risk. The relative risk measure based on an internal control avoids the biases associated with the use of external controls and adjusts for confounding.<sup>12</sup> The internal standardization technique was adjusted for smoking status, age, time period, latency, and race. Both the standardized mortality ratios and the relative risk measure were calculated by using a program developed by Marsh and Preininger.<sup>13</sup> For the SMR, 95% confidence intervals were calculated using the method of Bailar and Ederer.<sup>14</sup> A  $\chi^2$  test was used to evaluate the statistical significance of the trends based on the method proposed by Mantel.<sup>15</sup> Ninety five percent confidence intervals based on the procedure of Miettinen<sup>16</sup> were calculated for each relative risk measure.

### Results

Table 1 presents the SMRs indirectly standardized for race for selected causes of death for all men hired prior to 1974, by exposure category. Analyses stratified by race and plant were also done but, since they were similar to Table 1, were not presented. Of 1571 men in the no exposure group, 674 persons eventually exceeded the cumulative AN exposure of 0.01 ppm/years; these persons thus contributed person-years to both groups.

For each cause of death category, the observed numbers of deaths were not significantly different than the expected levels for either the no exposure or the exposure categories. No significant excess mortality for any cause of death was observed among 1774 men exposed to AN. Statistically significant mortality deficits were observed among exposed men from all causes of death (SMR = 0.67), ischemic heart disease (SMR = 0.71), all digestive diseases (SMR = 0.30), and all external causes of death (SMR = 0.48). Comparisons with local populations and counties within 20 miles of the plant yielded similar results, which were not presented.

The indirect and internally standardized levels of respiratory cancer mortality are presented by exposure group in Table 2. Eight of the 23 respiratory cancers observed occurred among the nonexposed group and two, four, and nine respiratory cancers were observed in the 0.01 to 0.7, 0.7 to 7.0, and >7.0 ppm/year categories, respectively. No mortality trend is observed and none of the individual AN exposure categories is statistically significant, although the highest exposure category of >7.0 ppm/year has an SMR of 1.41 (Table 2). Analysis by the internal standardization indicated no increased risk of respiratory cancer with increased exposure to AN.

**TABLE 1**  
Standardized Mortality Ratios (SMRs) Indirectly Standardized for Race for Selected Causes of Death in Men Hired Prior to 1974 by Exposure to Acrylonitrile Compared to US Men

Cause of Death (ICD 8 Revision Code)	No Exposure (<0.01 ppm/years)		Exposure (>0.01 ppm/years)	
	Observed	SMR	Observed	SMR
All causes (1-999)	92	.85	145	.67*
All infective and parasitic (1-139)	1	.89	1	.48
All malignant neoplasms (140-209)	22	1.08	43	1.01
Buccal cavity and pharynx (140-149)	1	1.43	3	2.01
Digestive organs and peritoneum (150-159)	7	1.38	8	.77
Large intestine (153)	2	1.26	1	.30
Stomach (151)	1	1.13	3	1.69
Respiratory system (160-163)	8	1.09	15	.95
Lung (162-163)	7	1.01	15	1.00
Prostate (185)	1	1.34	2	1.49
Brain and other CNS (191-192)	1	1.18	1	.56
All lymphopoietic (200-209)	3	1.26	5	1.04
All other cancers (170-174, 180-184, 186-199)	1	.30	9	1.29
Ischemic heart disease (410-413)	28	.86	48	.71*
Vascular lesions of CNS (430-438)	4	.77	4	.41
All respiratory diseases (460-519)	3	.58	7	.69
All digestive diseases (520-577)	3	.47	4	.30*
All genito-urinary diseases (580-609)	1	.81	1	.44
All external causes of death (800-998)	17	.77	19	.48*
Unable to locate death certificate	9		4	
Persons	1,571		1,774	
Person-years	18,745		35,310	

\* Significantly ( $P < .05$ ) less than expected.

**TABLE 2**  
Characteristics of Exposure Groups and Indirect and Internal Standardization for Respiratory Cancer by Cumulative Exposure

	AN Exposure, ppm/years				Trend Test	
	None (<0.01)	0.01-0.7	0.7-7.0	7.0+	$\chi^2$	P
Number of Respiratory Cancers	8	2	4	9		
Person-years	18,745	11,856	15,279	8,212		
% Ever smoked*	70.8	72.7	74.4	79.3		
% Smoking status known	56.2	62.6	72.4	89.1		
Indirect standardization (SMR)	1.09	0.63	0.64	1.41	1.015	0.337
Internal standardization adjusted for smoking, race, latency, age, and time period†	1.11	0.72	0.71	1.22	0.301	0.606

\* Calculated by dividing number of smokers in category by the number of smokers and nonsmokers in that category.

† Adjustment made for smoking (smoker, nonsmoker, unknown), race (white, nonwhite), latency (<10, 10-19, 20+ yr), age (<45, 45-54, 55-64, >65 yr), and time period (<1965, 1965+).

## Discussion

A particular strength of this study was the ability to have detected an excess of respiratory cancer (ie, 80%) due to its large sample size and person-years of observation. To date, this study is the largest conducted on persons exposed to AN and provides the most detailed exposure estimate ever in a study on AN. These estimates have allowed testing for a linear dose-response function for lung cancer risk and AN exposure. More than 50% of the men exposed to AN have latency periods exceeding 20 years, thus providing a vehicle for estimating the long-term impact of AN exposure.

No mortality trend is observed and none of the individual categories is statistically significant, although the highest exposure category has an SMR of 1.41. Analysis by internal standardization indicated a much flatter dose-response function than the SMR, and reduced the magnitude of differences between the exposure groups. Although the number of respiratory cancer

deaths is small, there does not appear to be an increased risk of respiratory cancer with increased exposure to AN.

These results differ from four investigations of reported significant excesses of respiratory cancer among various groups of workers.<sup>1,4-6</sup> O'Berg<sup>1</sup> found respiratory cancer cases significantly elevated among wage workers, with medium to high exposures (6 observed, 2.3 expected) but not among salaried workers with similarly classified exposures. Thiess et al<sup>4</sup> observed a lung cancer mortality excess among workers at one plant (4 observed, 0.4 expected) of 12 plants in their study. When all plants are combined the excess is not significant although the SMR is 1.86. Werner and Carter<sup>5</sup> observed a lung cancer mortality excess among persons aged 15 to 44 years (3 observed, 0.7 expected), but no excess among older age groups and all age groups combined. Delzell and Monson<sup>6</sup> observed a significant mortality excess among persons working 5 to 14 years (5 observed, 1.5 expected), but no excess among persons

working 15 or more years, and overall no excess when all durations are combined. Thus, in each study where a significant excess of respiratory cancer was observed, the risk has been small and has usually been limited to a specific subgroup of the cohort. The small relative risk of respiratory cancer among part of the cohorts may be attributed to smoking and not to exposure to AN. None of the previous studies examined smoking history in detail, although in two cases crude post hoc adjustments for smoking were attempted.<sup>4,9</sup> In our study, when smoking information, albeit limited, was included, there was a small decrease in the respiratory cancer risk among the highest exposure group, indicating that some confounding between smoking and exposure appears to be present.

## Conclusion

The present study, the largest ever done on persons exposed to AN, utilized detailed exposure estimates and smoking status data on most of the population. There was no excess all-cause or cause-specific mortality among the men studied. Dose-response analysis of AN with respiratory cancer showed no mortality trend. Men exposed to high levels of AN had respiratory cancer rates similar to men not exposed at the two plants, and to the general US male population. There is some evidence in this study of a confounding association between smoking status and cumulative exposure to AN. In summary, these study results do not support the hypothesis that acrylonitrile is a human carcinogen.

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