

# Mortality Patterns among Workers Exposed to Acrylamide

James J. Collins, PhD; Gerard M. H. Swaen, Drs; Gary M. Marsh, PhD;  
H. Michael D. Utidjian, MD; Joseph C. Caporossi, MPH; and Lorraine J. Lucas, PhD

*A cohort of 8854 men, 2293 of whom were exposed to acrylamide, was examined from 1925 to 1983 for mortality. This cohort consisted of four plant populations in two countries: the United States and The Netherlands. No statistically significant excess of all-cause or cause-specific mortality was found among acrylamide workers. Analysis by acrylamide exposure levels showed no trend of increased risk of mortality from several cancer sites. These results do not support the hypothesis that acrylamide is a human carcinogen.*

Although experimental studies have suggested that Acrylamide, a substance widely used in the manufacture of water-soluble polymers used for water treating, paper, mining, and sugar processing, is carcinogenic,<sup>1,2</sup> few epidemiologic studies have been conducted. No excess of cancer deaths was observed when the mortality patterns of 371 persons exposed to acrylamide were examined<sup>3</sup>; however, the study was of such a limited sample size that only large excesses could have been detected. Thus, the present study was undertaken to examine the mortality experience of 8854 persons with potential exposure to acrylamide at four American Cyanamid locations: three US plants (Fortier, LA; Warners, NJ; and Kalamazoo, MI) and a plant in Botlek, The Netherlands.

## Methods

The cohort was defined as all men who were hired at any of the four plants between Jan 1, 1925 and Jan 31, 1973. Person-year accumulation for the cohort began either when a person started employment after plant start-up or upon the person first achieving a specified level of cumulative exposure to acrylamide, depending upon the type of analysis being undertaken. 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) date of death.

A total of 8508 men consisting of 7242 white and 1266 non-white employees at the three US locations were identified from personnel records and examined through Dec 31, 1983 using the Social Security Administration, the National Death Index, credit bureaus, The Veterans Administration, state motor vehicle departments, and company records. Follow-up was complete for 94% of the cohort; 5847 persons (68.7%) were alive at the end of the study, 2148 (25.2%) were dead, and 513 (6.0%) were lost to follow-up. Death certificates were obtained for 94.8% of the decedents. Those employees for whom a death certificate was unavailable (n = 111) were assumed to have died from unknown causes. The underlying cause of death was coded by a trained nosologist according to the eighth revision of the International Classification of Diseases.<sup>4</sup>

Follow-up of the Botlek population was conducted through the national population registries in The Netherlands. Of a total of 346 men identified from personnel and pension fund records, 315 (91.0%) were alive, 11 (3.2%) were dead, and 20 (5.8%) were lost to follow-up. An underlying cause of death was determined for 9 of the 11 deaths (81.8%).

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From American Cyanamid Company, One Cyanamid Plaza, Wayne, NJ 07470 (Dr Collins, Dr Utidjian, Mr Caporossi, Dr Lucas); The University of Limburg, 6200 MD Maastricht, The Netherlands (Dr Swaen); and The University of Pittsburgh, Pittsburgh, PA 15261 (Dr Marsh). Dr Collins is currently Associate Director, Epidemiology, at Monsanto, St Louis, MO 63167.

Address correspondence to: American Cyanamid Company, One Cyanamid Plaza, Chemicals Group, W-3, Wayne, NJ 07470 (Dr Lucas).  
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Exposure estimates for all jobs at each of the four plants over time were developed using extensive monitoring data and by working with plant persons who had knowledge of past jobs and processes. When available, actual measurements were used to indicate a job exposure for the substance under study. Since industrial hygiene monitoring was underway at all plants in 1977, exposure levels in 1977 were considered representative in most cases back to operation start-up. There has been a decline in exposure to acrylamide over time at all plants, as exposure to acrylamide has been regulated to prevent possible neurotoxicity.<sup>5</sup>

Exposure to acrylamide was defined as a cumulative exposure greater than 0.001 mg/m<sup>3</sup>-years, which is approximately equivalent to a one-day average concentration exposure to the current permissible exposure limit of 0.3 mg/m<sup>3</sup>. Cumulative exposure was calculated as the product of the number of days in the job and the estimated average daily exposure, divided by 365.

### Smoking History

Smoking history data were available from medical records for 2992 cohort members (85%), of whom 2285 were smokers and 707 were nonsmokers. If the medical record indicated a person had smoked cigarettes, cigars, or a pipe for 3 months or more, this person was coded as a smoker. This 3-month convention was a company criterion for classifying smokers. When no information was provided in the medical record about smoking, smoking status was coded as unknown. Smoking status was available on 71% (246/346) of Botlek men, 57% (738/1295) of Fortier men, 48% (29/60) of Kalamazoo men, and only 28% (1979/7153) of Warners men. Kalamazoo had the highest percentage of smokers (86%), followed by Warners (79%), Botlek (76%), and Fortier (70%).

Standardized mortality ratios (SMRs) and an internally standardized relative risk measure as described by Gilbert and Buchanan<sup>6</sup> were employed to estimate risk. The relative risk measure based upon an internal control avoids the biases associated with the use of external controls,<sup>7</sup> and adjusts for characteristics such as smoking status, latency, and race. The SMRs were calculated by using a program developed by Marsh and Preininger<sup>8</sup> and the relative risk measures by using a program developed by Marsh et al.<sup>9</sup> For the SMR, 95% confidence intervals were calculated using the method of Bailar and Ederer,<sup>10</sup> and a  $\chi^2$  test was used to evaluate statistical significance of the trends.<sup>11</sup> For the relative risk measure, 95% confidence intervals were based on the procedure of Miettinen<sup>12</sup> and the test for the significance of trend is based on the method developed by Mantel.<sup>13</sup>

### Results

Table 1 presents the observed number of deaths, SMRs, number of persons, and person-years by plant. Each plant had a lower than expected mortality rate, with Fortier (.71) and Warners (.91) having statistically significant deficits that were largely attributable to mortality from all circulatory diseases. Statistically significant deficits were also observed for all respiratory diseases at Warners (.75), all diseases of the digestive system at Fortier (.34), and all external causes of death at both Fortier (.45) and Warners (.71).

The SMRs indirectly standardized for race and plant for all causes of death and for selected cancer sites are presented in Table 2 for employees by exposure category. The all-causes SMR of 0.81 for employees exposed to acrylamide ( $n = 2293$ ) was statistically significant ( $P < .05$ ). No other significant deficits or excesses were observed among men exposed to acrylamide.

TABLE 1  
Standardized Mortality Ratios (SMRs) for All Men for Several Cause of Death Classifications at Each of the Four Plants

Cause of Death (ICD-8 Code)	Plants							
	Botlek*		Fortier†		Kalamazoo‡		Warners‡	
	Obs‡	SMR	Obs	SMR	Obs	SMR	Obs	SMR
All causes (1-999)	11	.83	136	.71§	14	.74	1998	.91§
All malignant neoplasms (140-209)	3	.83	39	1.03	2	.55	448	1.09
All circulatory diseases (390-458)	4	.87	59	.71§	8	.80	938	.88§
All respiratory disease (460-519)	1	2.26	7	.75	1	.85	96	.75§
All diseases of digestive system (520-577)	0		4	.34§	1	1.15	94	.84
All external causes of death (800-899)	1	.43	15	.45§	0		179	.71§
Death certificates not obtained	2		8		0		103	
Persons	346		1,295		60		7,153	
Person-years	4,665.6		28,617.6		1,449.1		195,115.5	

\* Expected number of deaths based upon men of The Netherlands 1950 to 1982 indirectly adjusted for age groups and calendar time.

† Expected number of deaths based upon men of the United States 1925 to 1980 indirectly adjusted for race (white and nonwhite), age group, and calendar time.

‡ Observed number of deaths.

§  $P < .05$ .

**TABLE 2**  
Standardized Mortality Ratios (SMRs) Indirectly Standardized for Race and Plant for Men By Exposure Category

Cause of Death (ICD-8 Code)	Cumulative Exposure, mg/m <sup>3</sup> -years			
	<0.001		≥0.001	
	Observed	SMR	Observed	SMR
All causes (1-999)	1,860	.91*	299	.81*
All malignant neoplasms (140-209)	420	1.09	72	.98
Buccal cavity and pharynx (140-149)	13	.99	0	
Digestive organs and peritoneum (150-159)†	118	1.07	22	1.16
Esophagus (150)	13	1.13	3	1.48
Stomach (151)	29	1.26	4	1.09
Large intestine (153)	34	1.04	4	.66
Rectum (154)	15	1.26	2	.97
Liver (155-156)	5	.63	0	
Pancreas (157)	19	.91	8	2.03
Respiratory system (160-163)	169	1.31*	30	1.14
Larynx (161)	8	1.32	0	
Lung (162-163)	161	1.32*	30	1.20
Bone (170)	2	.95	1	2.70
Skin (173)	3	.47	1	.72
Prostate (185)	26	1.05	1	.26
Testis (186-187)	0		0	
Bladder (188)†	11	1.03	2	1.10
Kidney (189)†	10	1.09	2	1.13
Eye (190)†	0		0	
Brain, and other CNS (191-192)	5	.45	1	.42
Thyroid (193)	2	2.80	0	
All Lymphoproliferative (200-209)	33	.90	6	.85
Lymphosarcoma and reticulosarcoma (200)	4	.53	2	1.31
Hodgkin's disease (201)	8	1.59	5	1.29
Leukemia and aleukemia (204-207)	12	.82	2	.70
Other lymphatic tissue (202-203) (208)	9	1.01	2	1.12
Benign neoplasms (210-239)	6	1.08	1	.31
Death certificate not obtained	107		6	
Persons	8,094		2,293	
Person-years	187,951.1		41,896.7	

\*  $P < .05$ .

† This category does not include the Botlek plant because data were not available on comparison population.

Of 8094 men in the non-exposed group, 1533 were eventually exposed to acrylamide (ie, >0.001 mg/m<sup>3</sup>-years) in their careers and thus appear both in the unexposed and exposed group. The observed number of deaths from all causes was significantly lower than expected (1860 observed v 2043.0 expected; SMR = 0.91 among the non-exposed group). A significant excess in respiratory cancer (SMR = 1.31), due largely to an excess in lung cancer (SMR = 1.32), was observed at the Warners facility. Detailed analysis (not presented) indicated that the respiratory cancer excess was confined to two groups, among men who worked in the now defunct Muriatic Acid Department (n = 11 deaths) and among men hired between 1940 and 1949 who had worked for less than 1 year in a variety of departments (n = 52 deaths).

The risk of mortality by cumulative exposure to acrylamide is shown in Table 3 for selected causes of death. Classifications of cancer were chosen for trend analysis if 25 or more deaths were observed in the cohort, or if the site was elevated in an animal study (ie, brain and other central nervous system).<sup>1</sup>

Four categories of cumulative exposure were defined, "none" (less than .001), .001 to 0.030, 0.030 to 3.0, and

greater than 3.0 mg/m<sup>3</sup>-years, to reflect current and proposed regulated levels of exposure.

## Discussion

In general, each plant had mortality patterns similar to other working populations.<sup>14</sup> No significant excess mortality was observed in the 26 cancer sites examined among the exposed group. Seventy-two cancer deaths occurred among the 2293 persons exposed to acrylamide, v 73.4 cancer deaths expected. Of interest were the sites elevated in an animal study, namely the central nervous system and the reproductive organs.<sup>1</sup> No excesses were observed at these sites among men exposed to acrylamide.

Analyses of trends by cumulative exposure and duration of exposure indicated no increased risk of mortality with increased level of exposure. These analyses took into account smoking status as far as data were available, and plant. Likewise, the test for linear trend based upon internal standardization indicated no significant trend for any category of death.

A particular strength of this study was the ability to

**TABLE 3**  
Observed (Obs) and Expected (Exp) Deaths for Selected Causes by Exposure to Acrylamide using Internal Comparisons

Cause of Death Category (ICD-8 Code)	Cumulative Exposure, mg/m <sup>3</sup> -years				P*	
	None (<0.001)	0.001- 0.03	0.03- 0.30	0.30+	Among Groups	Trend
	Obs/Exp	Obs/Exp	Obs/Exp	Obs/Exp		
All causes (1-999)	1860/1860.1	33/44.3	97/96.9	169/157.9	.844	.423
All cancer (140-129)	420/420.4	11/9.5	22/22.5	39/39.6	.999	.576
Digestive organs and peritoneum (150-159)	118/120.3	2/2.5	8/6.3	12/10.9	.918	.486
Stomach (151)	29/29.5	0/6	2/1.2	2/1.8	.961	.457
Large intestine (153)	34/32.0	0/8	3/2.0	1/3.2	.679	.503
Pancreas (157)	19/21.0	1/7	2/1.8	5/3.8	.583	.461
Respiratory system (160-163)	169/167.7	4/4.0	12/9.6	14/17.7	.914	.734
Lung (162-163)	161/160.8	4/3.8	12/9.3	14/17.1	.931	.873
Prostate (185)	26/24.5	0/2	0/6	1/1.6	.744	.384
Brain and other central nervous system (191-192)	5/4.5	1/3	0/6	0/6	.799	.230
All lymphopoietic (200-209)	33/34.0	2/1.0	1/1.7	3/2.3	.894	.957

\* Probability of no difference after stratification for smoking status (smoker, nonsmoker, unknown status), age in years (<45, 45-54, 55-64, 65+), latency in years (<10, 10-19, 20+), race (white, nonwhite), and time period (<1950, 1950+).

have detected among acrylamide workers a 25% increase in total cancers, a 50% increase in respiratory cancers, and a 3-fold increase of brain and other central nervous system cancers based on a two-tailed 5% significance level with a power of 80%.

In summary, no statistically significant all-cause or cause-specific mortality was found among acrylamide workers. In addition, all tests for trends, adjusting for possible confounding factors, showed no increased risk of mortality with increased exposure to acrylamide. These study results do not support the notion that acrylamide is a human carcinogen.

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