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Reevaluation of lung cancer risk in the acrylonitrile cohort study of the National Cancer Institute and the National Institute for Occupational Safety and Health

by Gary M Marsh, PhD¹, Ada O Youk, PhD¹, James J Collins, PhD²

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Objectives The present study provides additional analyses of data obtained earlier on lung cancer risk among workers with acrylonitrile exposure.

Methods The original authors provided the data. For total mortality and the cancer sites of a priori interest (lung, stomach, brain, breast, prostate, and the lymphatic and hematopoietic systems), standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) were computed, the total United States and surrounding counties being used as standard populations. Regional rate-based SMR values were also computed between lung cancer and cumulative acrylonitrile exposure.

Results Except for lung cancer, the external comparisons corroborated the earlier internal comparisons (no increased cancer mortality risk). For lung cancer, the external comparisons revealed death deficits for the unexposed workers (SMR 0.68, 95% CI 0.5–0.9) and all categories of acrylonitrile-exposed workers. The SMR obtained using external rates and the most exposed group (SMR 0.92, 95% CI 0.6–1.4) differed from the corresponding relative risk (RR) of the internal rates (RR 1.5, 95% CI 0.9–2.4).

Conclusions The analysis of the present study provides little evidence that acrylonitrile exposure increases the mortality risk of cancers of a priori interest, including lung cancer. The lung cancer findings of the external comparison differed from the earlier findings of the internal comparisons. Selection bias (as the healthy worker effect) was probably not responsible. Additional follow-up and analyses, especially of the unexposed workers with low lung cancer rates, may help elucidate the internal and external comparison differences. Results from both comparisons should be presented when the relative risks differ markedly, as both have advantages and disadvantages.

Key terms epidemiology, mortality risks, industrial workers.

The carcinogenic potential of acrylonitrile has been studied extensively in experimental animals and exposed workers. Long-term chronic bioassays of rats found astrocytomas in the brain and spinal cord and tumors of the Zymbal gland, forestomach, stomach and mammary gland (1). Epidemiologic studies, reviewed by Ward & Starr (2), Rothman (3), Blair & Kazerouni (4) and Collins & Acquavella (5), show no clear evidence of an excess for any cancer related to acrylonitrile exposure, although elevated relative risks have been reported in more than one study for cancers of the lung, brain, prostate and lymphatic and hematopoietic systems. The United States (US) Environmental Protection Agency (6) classified acrylonitrile as a probable human carcinogen

(sufficient evidence in animals, but limited evidence in humans). Acrylonitrile has been recently reclassified from a “probable” to a “possible” human carcinogen (sufficient evidence in animals, but inadequate evidence in humans) by the International Agency for Research on Cancer (7, 8), largely based on findings from 4 recent epidemiologic studies (9–12).

The largest and most comprehensive epidemiologic study to date was performed by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) (9). With the possible exception of lung cancer, the NCI-NIOSH study revealed no evidence of elevated site-specific cancer risks in relation to several indicators of acrylonitrile exposure.

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For lung cancer mortality, the overall relative risk based on internal comparisons (acrylonitrile exposed to acrylonitrile unexposed workers) was only slightly elevated [rate ratio (RR) 1.2, 95% confidence interval (95% CI) 0.9–1.6], and there was no strong or consistent evidence of a linear exposure-response relationship for any of the acrylonitrile exposure indicators. However, the lung cancer excess was largest in the highest quintile of cumulative acrylonitrile exposure (RR 1.5, 95% CI 0.9–2.4) and for the subgroup of workers at risk ≥ 20 years since their 1st exposure (RR 2.1, 95% CI 1.2–3.8). Several subsequent analyses, including a nested case-cohort study that included smoking histories, failed to elucidate the reasons for the elevated risks for lung cancer. The findings for lung cancer led Blair and his co-workers (9) to conclude that there may be evidence of carcinogenic activity at the highest level of acrylonitrile exposure.

The assessment of the cancer site-specific mortality risks in the NCI-NIOSH study was based almost exclusively on internal study group comparisons. The strengths of internal study group comparison are that they usually reduce the healthy worker effect (13) and allow direct comparison of relative risk across strata. However, internal comparisons can be unstable when the study population is small (producing wider confidence limits), and may be misleading if the workers included in the baseline category (ie, least exposed) have different underlying cancer risks than those in the exposed groups.

On the other hand, external comparisons based on regional rates have the strengths of being able to adjust for geographic variability in social, cultural, and economic factors in relation to disease (14) and of being generally very stable. The disadvantages of external comparison groups are the inability to adjust for the healthy worker effect and difficulty in comparing standardized mortality ratios (SMR) between groups when their confounder distributions differ (15). We report here our analysis of the relationship between cumulative acrylonitrile exposure and mortality from the cancer sites of a priori interest, particularly lung cancer, using external comparisons (SMR values) and compare our findings to those of Blair et al (9) who relied mostly on internal comparisons for their interpretation.

Subjects and methods

We obtained a copy of the NCI-NIOSH acrylonitrile study data from the authors. This file included individual demographic, work history, and acrylonitrile exposure data for 25 460 workers employed in 1 or more of 8 plants that produced or used acrylonitrile from 1952

through 1983 in 1 or more of 8 plants in the United States. The study group was followed through 1989 for vital status and cause of death. Further details about the NCI-NIOSH study have been provided in Blair et al (9).

Due to the summary nature of the NCI work history and acrylonitrile exposure data, we first reconstructed a cohort analysis file that was compatible with the more-detailed input format of the OCMAP-Plus cohort analysis program (16). Because of the many assumptions required to reformat the NCI cohort file, we performed an extensive cross-check to establish the comparability of the NCI data and our cohort data. The appendix provides details of the study file reformatting and validation process.

We computed the standardized mortality ratios and 95% confidence intervals for all causes of death combined and the cancer sites of a priori interest for workers exposed and unexposed to acrylonitrile. Standardized mortality ratios were also computed for the categories (quintiles) of cumulative acrylonitrile exposure and time since 1st acrylonitrile exposure reported in the NCI-NIOSH study. We focused on lung cancer mortality and computed standardized mortality ratios and 95% confidence intervals by overall and cumulative acrylonitrile exposure for workers in each of the 8 study plants.

All the standardized mortality ratios were adjusted for race, sex, age group, and time period. The cumulative acrylonitrile exposure measure incorporated the 5/7 multiplier used in the NCI-NIOSH study to discount nonwork time. As in the NCI-NIOSH study, person-year counts in the unexposed or lowest exposure baseline categories include the observation time of workers before their 1st acrylonitrile exposure.

Standardized mortality ratios were computed using both the total US and plant-specific regional mortality rates. Regional rates were based on an aggregate of individual counties or parishes from which at least 80% of the workforce of each plant resided. The plant code, the counties or parishes comprising the regional rate, the 1980 total populations (N) of the regional areas, and the total US population in 1980 are as follows: plant 1: Santa Rosa and Escambia, Florida (N=291 813); plant 2: Brazoria, Galveston and Harris, Texas (N=2 805 142); plant 3: Allen, Auglaize, Hardin, Hancock, Mercer, Putnam and Van Wert, Ohio, (N=354 340); plant 4: Hampton City, Newport News City and James City, Virginia (N=291 483); plant 5: Morgan, Lawrence, Limestone, Cullman and Madison, Alabama (N=425 877); plant 6: Jefferson, Orleans and St Charles Parishes, Louisiana (N=456 072); plant 7: Hamilton, Ohio and Dearborn and Ripley, Indiana (N=932 154); plant 8: Galveston and Brazoria, Texas (N=367 858); total US (N=227 052 306).

Our interpretation of the external rates focused on the regional rates as we believe they usually provide the

Table 1. Observed deaths, internal rate-based rate ratios (RR) and standardized mortality ratios (SMR), using US and regional rates, for all causes of death combined and cancer site by NCI-NIOSH cumulative acrylonitrile exposure category.^a (ppm = parts per million, NCI = National Cancer Institute, NIOSH = National Institute for Occupational Safety and Health)

Cancer site	Observed deaths (N)	NCI-NIOSH internal rate analysis		Our external rate analysis			
		RR ^b	95% CI	US rates		Regional rates	
				SMR ^c	95% CI	SMR ^c	95% CI
All causes of death							
Unexposed ^d	702	1.0	.	0.75	0.7 —0.8	0.73	0.7 —0.8
Exposed	1217	0.9	0.8—1.0	0.66	0.6 —0.7	0.64	0.6 —0.7
>0 —0.13	347	1.0	0.9—1.1	0.70	0.6 —0.8	0.68	0.6 —0.8
0.13—0.57	236	0.9	0.8—1.1	0.66	0.6 —0.7	0.64	0.6 —0.7
0.57—1.50	213	0.8	0.7—0.9	0.62	0.5 —0.7	0.60	0.5 —0.7
1.50—8.00	245	0.8	0.7—0.9	0.62	0.5 —0.7	0.60	0.5 —0.7
≥8.00	176	0.8	0.7—1.0	0.67	0.6 —0.8	0.65	0.6 —0.8
Lung cancer							
Unexposed ^d	59	1.0	.	0.81	0.6 —1.0	0.68	0.5 —0.9
Exposed	134	1.2	0.9—1.6	0.90	0.8 —1.1	0.74	0.6 —0.9
>0 —0.13	27	1.1	0.7—1.7	0.79	0.5 —1.1	0.64	0.4 —0.9
0.13—0.57	26	1.3	0.8—2.1	0.92	0.6 —1.4	0.76	0.5 —1.1
0.57—1.50	28	1.2	0.7—1.9	0.97	0.6 —1.4	0.79	0.5 —1.1
1.50—8.00	27	1.0	0.6—1.6	0.79	0.5 —1.1	0.64	0.4 —0.9
≥8.00	26	1.5	0.9—2.4	1.13	0.7 —1.6	0.92	0.6 —1.4
Stomach							
Unexposed ^d	5	1.0	.	0.65	0.2 —1.5	0.70	0.2 —1.6
Exposed	12	1.1	0.4—3.1	0.79	0.4 —1.4	0.85	0.4 —1.5
>0 —0.13	6	2.0	0.6—6.9	1.64	0.6 —3.6	1.75	0.6 —3.8
0.13—0.57	1	0.5	0.1—4.0	0.33	0.01—1.9	0.36	0.01—2.0
0.57—1.50	1	0.4	0.1—4.0	0.32	0.01—1.8	0.33	0.01—1.8
1.50—8.00	3	1.2	0.3—5.0	0.91	0.2 —2.7	0.97	0.2 —2.8
≥8.00	1	0.6	0.1—5.5	0.48	0.01—2.6	0.56	0.01—3.1
Breast							
Unexposed ^d	19	1.0	.	1.11	0.7 —1.7	1.14	0.7 —1.8
Exposed	5	0.6	0.2—1.8	0.70	0.2 —1.6	0.71	0.2 —1.6
>0 —0.13	3	0.7	0.2—2.8	1.08	0.2 —3.2	1.02	0.2 —3.0
0.13—0.57	—	..	..	..	0.0 —2.6	..	0.0 —2.7
0.57—1.50	1	1.1	0.1—8.1	0.88	0.02—4.9	0.94	0.02—5.2
1.50—8.00	1	0.9	0.1—7.0	0.76	0.02—4.2	0.80	0.02—4.4
≥8.00	—	..	..	..	0.0 —7.7	..	0.0 —8.6
Prostate							
Unexposed ^d	10	1.0	.	1.22	0.6 —2.2	1.29	0.6 —2.4
Exposed	16	1.0	0.4—2.3	0.92	0.5 —1.5	0.95	0.5 —1.5
>0 —0.13	7	1.9	0.7—5.4	1.92	0.8 —4.0	1.97	0.8 —4.1
0.13—0.57	1	0.3	0.1—2.4	0.30	0.01—1.7	0.32	0.01—1.8
0.57—1.50	2	0.7	0.2—3.3	0.46	0.01—1.7	0.49	0.01—1.8
1.50—8.00	5	1.5	0.5—4.5	1.26	0.4 —2.9	1.28	0.4 —3.0
≥8.00	1	0.4	0.1—3.5	0.46	0.01—2.5	0.45	0.01—2.5
Central nervous system							
Unexposed ^d	11	1.0	.	1.29	0.6 —2.3	1.21	0.6 —2.2
Exposed	12	0.5	0.2—1.2	0.74	0.4 —1.3	0.69	0.4 —1.2
>0 —0.13	3	0.5	0.1—1.8	0.69	0.1 —2.0	0.65	0.1 —1.9
0.13—0.57	1	0.2	0.1—1.7	0.32	0.01—1.8	0.30	0.1 —1.7
0.57—1.50	2	0.5	0.1—2.3	0.74	0.01—2.7	0.70	0.1 —2.5
1.50—8.00	4	0.8	0.1—2.4	1.15	0.3 —2.9	1.05	0.3 —2.7
≥8.00	2	0.5	0.1—2.5	0.80	0.01—2.9	0.72	0.1 —2.6
Lymphatic & hematopoietic system							
Unexposed ^d	18	1.0	.	0.75	0.4 —1.2	0.78	0.5 —1.2
Exposed	27	0.7	0.4—1.4	0.60	0.4 —0.9	0.64	0.4 —0.9
>0 —0.13	6	0.7	0.3—1.8	0.49	0.2 —1.1	0.53	0.2 —1.1
0.13—0.57	7	1.1	0.4—2.6	0.80	0.3 —1.7	0.85	0.3 —1.8
0.57—1.50	6	0.8	0.3—2.0	0.76	0.3 —1.7	0.80	0.3 —1.7
1.50—8.00	5	0.6	0.2—1.7	0.52	0.2 —1.2	0.56	0.2 —1.3
≥8.00	3	0.6	0.2—1.9	0.46	0.01—1.4	0.49	0.1 —1.4

^a ppm-years, NCI-NIOSH cutpoints, RR estimates taken from Blair et al (9).

^b RR values adjusted for race, gender, age, calendar time and salary-wage classification.

^c SMR values adjusted for race, gender, age and calendar time.

^d Baseline category for RR values.

most valid external comparison by helping to adjust for the social, cultural, and economic factors related to disease. The large size of the regional populations used assures the stability of the associated death rates. We provide the comparison with US rates as Blair et al (9) did the same in some of their analyses. Standard mortality rates adjusted to the 8th revision of the International Classification of Diseases (ICD-8) were obtained from the Mortality and Population Data System (17). The same US rates were also used by Blair et al (9) in the NCI-NIOSH study.

In the Blair et al study (9), internal rate ratios (RR), based on internal comparisons of exposed and unexposed workers, were estimated by Poisson regression, adjusted for race, gender, age, calendar time, and salary or wage classification. Confidence intervals (95%) were calculated using the Wald estimator (9). Rate ratios and standardized mortality ratios were shown for workers categorized as unexposed (baseline category for the rate ratios) and exposed to acrylonitrile. Rate ratios only were shown for exposed workers grouped into

approximate quintiles of cumulative acrylonitrile exposure according to the observed number of deaths from cancer of the bronchus, trachea, and lung (lung cancer). The Blair et al (9) study also included a nested case-cohort study in which tobacco smoking data were collected for a 10% sample of the workers to assess potential confounding.

Results

Table 1 (on page 7) shows the rate ratios reported by Blair et al (9) and the US and regional external rate-based SMR values using the same data for all causes of death combined and the cancer sites of a priori interest. The SMR values for all causes of death combined, based on US and regional rates, were less than 1.0 for all the categories of exposed workers. For both external comparisons, we observed the largest SMR values for workers who were unexposed or in the lower exposure cate-

Table 2. Observed deaths, internal rate based rate-ratios (RR) and standardized mortality ratios (SMR), using regional rates, for lung cancer by NCI-NIOSH cumulative acrylonitrile exposure category and time since first exposure.^a (ppm = parts per million, NCI = National Cancer Institute, NIOSH = National Institute for Occupational Safety and Health)

Cumulative exposure to acrylonitrile	Time since first exposure ^b														
	<10 years					10–19 years					≥20 years				
	Observed deaths	RR	95%CI ^c for RR	SMR	95%CI ^d for SMR	Observed deaths	RR	95%CI ^c for RR	SMR	95%CI ^d for SMR	Observed deaths	RR	95%CI ^c for RR	SMR	95%CI ^d for SMR
>0–0.13	7	0.4	0.2–1.2	0.72	0.3–1.5	9	0.5	0.5–3.2	0.71	0.3–1.4	11	1.1	0.6–2.2	0.56	0.3–1.0
0.13–0.57	3	0.4	0.1–1.4	0.63	0.1–1.8	12 ^e	2.6	1.2–5.7	1.18	0.6–2.1	11 ^f	1.0	0.5–2.1	0.57	0.3–1.0
0.57–1.50	2	0.4	0.01–1.6	0.70	0.1–2.5	10	2.0	0.9–4.8	1.01	0.5–1.8	16	1.2	0.6–2.2	0.71	0.4–1.2
1.50–8.00	2	0.4	0.1–2.0	0.87	0.1–3.1	7	1.2	0.5–3.1	0.66	0.3–1.4	18	1.2	0.6–2.1	0.61	0.4–1.0
≥8.00	1	0.4	0.1–3.1	0.81	0.02–4.5	4	0.9	0.3–1.2	0.54	0.2–1.4	21	2.1	1.2–3.8	1.07	0.7–1.6

^a ppm-years, NCI-NIOSH cutpoints, RR estimates taken from Blair et al (9).

^b First time since first-exposure cutpoint differs slightly from that of Blair et al (9), who used ≤10 years.

^c RR values adjusted for race, gender, age, calendar time, and salary-wage classification in comparison with those of the unexposed workers.

^d SMR values adjusted for race, gender, age and calendar time.

^e Blair et al (9) showed 13 observed deaths for this cell.

^f Blair et al (9) showed 10 observed deaths for this cell.

Table 3. Observed deaths and standardized mortality ratios^a (SMR) and their 95% confidence intervals (95%CI) for lung cancer by the Institute, NIOSH = National Institute for Occupational Safety and Health)

Exposure category	Study plant 1			Study plant 2			Study plant 3			Study plant 4		
	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI
Unexposed	1	0.26	0.01–1.4	5	1.21	0.4–2.8	7	0.82	0.3–1.7	2	0.58	0.01–2.1
Exposed	8	0.36	0.2–0.7	1	0.15	0.01–0.8	4	1.60	0.4–4.1	23	1.39	0.9–2.1
>0–0.13	–	..	0–1.3	–	..	0–1.6	–	..	0–44.1	9	1.87	0.8–3.5
0.13–0.57	1	0.27	0.01–1.5	–	..	0–2.2	–	..	0–21.2	1	0.51	0.01–2.8
0.57–1.50	5	0.91	0.3–2.1	1	1.05	0.03–5.8	–	..	0–17.5	2	1.06	0.1–3.8
1.50–8.00	1	0.17	0.01–0.9	–	..	0–3.9	–	..	0–6.6	1	0.24	0.01–1.4
≥8.00	1	0.25	0.01–1.4	–	..	0–3.7	4	2.70	0.7–6.9	10	2.68	1.3–4.9

^a SMR values adjusted for race, gender, age and calendar time.

^b ppm-years, NCI-NIOSH cutpoints.

gories. The SMR pattern was consistent with the corresponding pattern of the internal rate ratios presented by Blair et al (9) using internal rate comparisons for exposed workers in which all the rate ratios were less than 1.0 and decreased slightly with increasing acrylonitrile exposure.

Table 1 (on page 7) also shows that the SMR values for lung cancer were uniformly much lower when based on regional mortality rates than when based on US rates. The regional rate-based SMR values were all less than 1.0, ranging from 0.92 to 0.64. In contrast, the findings based on the internal rate ratios indicated an increased risk of lung cancer mortality in 4 of the 5 acrylonitrile exposure categories, with the largest excess (RR 1.5, 95% CI 0.9–2.4) observed in the highest exposure category. The RR of 1.5 for the highest exposure category, compared with the baseline, was approximately equal to the ratio of the corresponding SMR values (ie, $1.13/0.81=1.40$ and $0.92/0.68=1.35$ for the US and regional comparisons, respectively). No evidence of a linear exposure-response relationship for lung cancer was observed with either the internal or the external comparison groups.

For each of the remaining cancer sites shown in table 1 (on page 7), the general pattern of findings was essentially similar between the US and regional rate-based SMR values and between the SMR and rate ratio analyses. Only a few of the SMR values or rate ratios were greater than 1.0 for the remaining sites, and there was little or no evidence of an exposure-response relationship for any of these cancer sites. In most cases, the SMR values and the internal rate ratios tended to be larger in the lower acrylonitrile exposure categories and smaller among more highly exposed workers.

Table 2 shows the observed numbers of deaths, the internal rate ratios reported by Blair et al (9), and the regional rate-based SMR values for lung cancer by the cumulative acrylonitrile exposure quintile and the time since 1st acrylonitrile exposure. Possibly because of the

estimation process involved in reformatting the study data, we could not replicate exactly the cell-specific observed counts reported by Blair et al (9). Our counts for the 2nd cumulative exposure quintile and 2nd and 3rd categories of time since 1st acrylonitrile exposure differed by 1. The SMR values in table 2 are less than 1.0 for all but 3 cells. This finding contrasts with the internal rate ratios, which were greater than 1.0 or 2.0 in many of the cumulative acrylonitrile exposure categories for workers followed ≥ 10 years since 1st exposure. For workers with the highest cumulative exposure and followed the longest time since 1st exposure, the internal rate ratio of 2.1 contrasts with an SMR of 1.07. No evidence of a linear exposure-response relationship for lung cancer was observed in any of the examined categories of time since 1st exposure.

Table 3 shows plant-specific observed numbers of deaths, regional rate-based SMR values and 95% confidence intervals for lung cancer by acrylonitrile cumulative exposure quintile. Corresponding internal rate ratios were discussed but not explicitly reported by Blair et al (9). While not shown in our report, the US rate-based SMR values were higher than those based on regional rates for all plants except plant 3, for which the regional SMR values were only slightly larger. For the workers in the unexposed baseline category, table 3 shows that deficits in lung cancer deaths, ranging from an SMR of 0.26 (95% CI 0.0–1.4) for plant 1 to 0.88 (95% CI 0.4–1.7) for plant 6. Only unexposed workers in plant 2 have an SMR greater than expected (SMR 1.21, 95% CI 0.4–2.8).

For only 2 plants did we observe an excess among the combined acrylonitrile-exposed workers when they were compared with the unexposed (plant 3, SMR 1.60 and plant 4, SMR 1.39). The plant 3 finding was reported earlier as part of a cohort study of only this plant (18). The 2 largest SMR values shown in table 3 were observed in the highest acrylonitrile exposure category (≥ 8.00 ppm-years) for plant 3 (SMR 2.70, 95% CI

NCI-NIOSH cumulative acrylonitrile exposure category — local comparisons, our cohort file. (ppm = parts per million, NCI = National Cancer

Study plant 5			Study plant 6			Study plant 7			Study plant 8		
Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI
15	0.79	0.4 —1.3	9	0.88	0.4—1.7	2	0.60	0.1 —2.2	18	0.53	0.3—0.8
24	0.50	0.3 —0.7	20	0.89	0.5—1.4	8	0.65	0.3 —1.3	46	0.90	0.6—1.2
2	0.21	0.03—0.7	4	0.46	0.1—1.2	0	..	0 —1.6	12	1.04	0.5—1.8
6	0.75	0.3 —1.6	6	1.14	0.4—2.5	3	1.19	0.2 —3.5	9	0.82	0.4—1.6
4	0.62	0.2 —1.6	7	1.27	0.5—2.6	2	0.92	0.1 —3.3	7	0.55	0.2—1.1
6	0.56	0.2 —1.2	2	0.87	0.1—3.1	2	0.52	0.1 —1.9	15	1.09	0.6—1.8
6	0.44	0.2 —1.0	1	1.38	0.1—7.7	1	0.69	0.02—3.8	3	1.26	0.3—3.7

0.7–6.9) and plant 4 (SMR 2.68, 95% CI 1.3–4.9). We observed several other elevated SMR values greater than 1.0 for lung cancer among the exposed workers across the 8 plants; however, the pattern of these excesses revealed little evidence of a linear exposure-response relationship. SMR trends are difficult to discern in table 3, however, due to the small number of observed deaths involved in most of the plant-specific exposure categories.

Discussion

With the exception of lung cancer, our analysis of the *a priori* cancer sites using external regional comparisons corroborate the corresponding findings based on the internal comparisons reported by Blair *et al* (9). In other words, exposure to acrylonitrile at the levels studied was not associated with an increased cancer mortality risk, there was no linear increase of risk with exposure, and there was no increased risk in the highest exposure category. For lung cancer, however, contrasting relative risks were reported, depending upon whether internal or external comparison groups were used, and the largest differences in risks occurred in the highest exposure category.

When we used external comparisons of the surrounding regional populations, we consistently observed deficits in lung cancer deaths that were generally largest among the unexposed but still present for highly exposed workers. These findings based on external comparisons revealed that the lung cancer excess, produced from internal rates, among the highly exposed workers was essentially created by taking the ratio of a small deficit in deaths to a large deficit in deaths.

There are at least 2 possible explanations for the large differences in the lung cancer relative risks in this study population when internal or external comparison rates are used. First, internal comparisons produce more valid results because selection bias stemming from the healthy worker effect can reduce the putative effect of high exposure to acrylonitrile when external comparison rates are used (19). The healthy worker effect is evident in this population by the low relative risks for all causes of death for exposed (SMR 0.64, 95% CI 0.6–0.7) and unexposed (SMR 0.73, 95% CI 0.7–0.8) workers. However, the selection for workers who are healthy at the time of hire is usually more relevant for cardiovascular and nonmalignant respiratory diseases than for lung cancer, which has a relatively sudden onset, short survival time, and high case-fatality rate (20).

A 2nd explanation is that the external comparisons produce more valid results because the unexposed group has a different underlying lung cancer risk than the ex-

posed group. The risk in the highest exposure category when internal comparisons were used may be the result of an unusually low lung cancer death rate among workers in the unexposed baseline category (SMR 0.68, 95% CI 0.5–0.9). In fact, had the death rates for lung cancer among the unexposed workers been closer to or equal to those of the general regional populations from which the 8 plant work forces were drawn, the internal rate ratios calculated for quintiles of acrylonitrile exposure across the total cohort would probably have been uniformly less than 1.0.

The low SMR values for lung cancer, especially among the unexposed workers, are puzzling given that we used regional standard population rates. As regional rates can help adjust for social, cultural, and economic factors related to diseases, such as lung cancer, and even help to adjust for geographic variability in tobacco use (14), it is difficult to postulate what nonoccupational factors may have had such a profound influence on the lung cancer mortality experience of this cohort. Given that the proportion of ever cigarette smokers in the general US population in 1988 (and presumably regional standard populations) is similar to the proportion of ever cigarette smokers in the NCI-NIOSH survey in 1988–1990 (ie, 52% for the US versus 56% for the unexposed workers), negative confounding by tobacco use is not a viable explanation for the lung cancer deficits observed for the unexposed workers in this study (21).

Chance alone does not appear to be an explanation for the lung cancer deficits observed for the unexposed workers in this study. As shown in table 1, the US and regional rate-based SMR values (and RR values) for all categories of cumulative acrylonitrile exposure were based on at least 26 observed deaths and thus provided stable estimates. Moreover, the deficits are consistent across the acrylonitrile exposure categories considered (all but 1 of the SMR values for lung cancer being <1.00). In addition, the quality of the follow-up and cause of death ascertainment in this study also ruled out underascertainment of lung cancer deaths as a reason for the deficits.

Given the absence of a viable explanation derived from the available study data, what remains is the possibility that some heretofore unknown selection factors for a low incidence of lung cancer were operating on members of this cohort or that some type of protective effect for lung cancer arose from a particular exposure or combination of exposures encountered at the plants under study. Clearly, without further formal investigation of the NCI-NIOSH cohort, the reason(s) for the marked deficits in lung cancer will remain unknown.

The results of our reanalysis demonstrate the importance of using both internal and external mortality comparisons when examining the exposure-response relationship for a suspect agent such as acrylonitrile. While

internal rate comparisons can, for some causes of death, help to reduce certain worker selection biases, such as the healthy worker effect, they may also produce misleading results if the mortality risk of the unexposed workers differs greatly from the underlying risk of the exposed workers in the absence of the examined exposure.

In summary, our reanalysis of the cancer mortality experience of the NCI-NIOSH cohort provides little evidence that exposure to acrylonitrile increases the risk of death from the cancers of a priori interest, including cancer of the lung. Our lung cancer findings based on external comparisons using regional rates produced risks very different than when internal rates were used. We conclude that selection bias in the form of the healthy worker effect is unlikely to produce this difference. Further follow-up and analysis of the NCI-NIOSH cohort may help to explain the reasons for the differences between the internal and external relative risks.

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Appendix

Details of reformatting and validating the National Cancer Institute cohort data file

Reformatting

OCMAP-Plus (16) requires that work histories be expressed as individual job entries (ie, for each job, start date, stop date, job code, and average acrylonitrile exposure level must be specified). Because the NCI work history and acrylonitrile exposure data were provided in a highly summarized form (work histories expressed as annual estimates of time exposed and cumulative acrylonitrile exposure level) reformatting was necessary. This conversion required 2 key assumptions about the calendar time distribution of the summary work history data, which was not specified on the NCI cohort file:

1. For exposure time that did not span a full year, the exposed portion of the annual work history occurred at the beginning of the year. The remainder of the annual work history was filled with a dummy unexposed job.
2. Because only annual estimates of exposure and number of days exposed per year were available, individual jobs did not span more than 1 full year.

Specifically, for each worker, individual work histories were recreated from the NCI cohort file date of hire, date of termination, stop date for person-years, date of 1st exposed job, and end date of last exposed job. To meet the specifications of OCMAP-Plus, the job start date of the n th job on the work history was set to the job stop date of the $(n-1)$ th job. The process of reconstruction was as follows. If the 1st job was not exposed, then:

1. The job start date of the 1st job on the work history was set as the date of hire.
2. The job stop date of the 1st job was set as the date of 1st exposure (if the date of hire was equal to the date of 1st exposure, then the date of 1st exposure became the job start date of the 1st job on the work history).
3. The job start date of the 2nd job on the work history was set as the date of 1st exposure.
4. The job stop date of the 2nd job was set as the date of 1st exposure plus the number of days exposed during that year of exposure. Because only the start date of 1st exposure and the end date of the last exposure were available from the NCI cohort file, jobs with partial years of exposure were given a start date of 1 January of that exposure year. The associated job stop date was set as 1 January of that year plus the number of days exposed in that year. The remainder of that exposed year was filled with a dummy unexposed job. If there were no days exposed in a given year, then the associated job was given a start date of 1 January of that year and a stop date of 1 January of the following year. Subsequent jobs in the work history were created in a similar manner.
5. The job stop date of the last job on the work history was set as the date of termination (if the date of termination was equal to the end date of last exposure, then the stop date of the last job was set as the end date of the last exposure).

Table 1. Comparability of the NCI-NIOSH cohort files and our cohort files. (NCI = National Cancer Institute, NIOSH = National Institute for Occupational Safety and Health)

	NCI-NIOSH (N)	Our file (N)	Absolute difference ^a	Relative difference ^b
Total study population	25 460	25 460	–	–
Person-years				
All	54 5368	545 342	26	0.00005
By exposure category ^c				
Unexposed	196 727	196 920	-193	-0.001
Exposed (total)	348 642	348 422	220	0.001
>0–0.13	121 534	124 220	-2686	-0.022
0.13–0.57	69 134	68 723	411	0.006
0.57–1.50	49 726	49 205	521	0.010
1.50–8.00	63 464	62 550	914	0.014
≥8.00	44 771	43 724	1047	0.023

^a Our file minus NCI-NIOSH.

^b Our file minus NCI-NIOSH / NCI-NIOSH.

^c Categories reported by Blair et al (1).

If the 1st job was exposed, then start at step 3 and treat as the 1st job.

To satisfy OCMAP-Plus job-exposure formatting requirements, we computed daily average acrylonitrile-exposure estimates by dividing the NCI annual cumulative acrylonitrile exposure estimates by the number of days exposed in the corresponding year. The NCI cohort file contained acrylonitrile exposure estimates accumulated across individual years beginning in 1942 and ending in 1983, along with the associated number of days exposed during the individual years. The documentation of the NCI cohort file noted that the cumulative acrylonitrile exposure estimates were weighted by a factor of 5/7, presumably to adjust for time off work.

Validation

To validate the reformatting process prior to our statistical analysis, we attempted to replicate selected results of the NCI-NIOSH study (1). Table 1 shows the absolute and relative differences in person-year counts and persons at risk between the NCI and our cohort files

using the cumulative acrylonitrile quintiles reported by NCI-NIOSH. The total number of persons was identical between the 2 analyses and the total number of accumulated person-years differed by only 26 person-years, a relative difference of only 0.005%.

The exposed and unexposed person-year counts showed absolute relative differences of 0.1% for each category. These relative differences become about an order of magnitude larger when the exposed category is divided into Blair et al (1) quintiles. The absolute relative differences ranged from 1.0% to 2.2%. We considered the differences in person-year counts noted between the 2 cohort files to be unimportant for our reevaluation of cancer mortality risks. While not shown here, our file and the NCI-NIOSH files yielded identical distributions of total and cancer site-specific observed deaths.

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