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May 17, 2007

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Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, D.C. 20460

CONTAIN NO CBI

Dear 8(e) Coordinator:

Acrylonitrile
CAS # 107-13-1

This letter is to inform you of the results of a recently completed epidemiologic study entitled "Mortality Among Workers Exposed to Acrylonitrile in Fiber Production: An Update". This letter supplements a filing made on November 3, 2006, at an earlier analytic phase for this cohort.

The study updates a retrospective cohort study (Wood SM et al., Scand J Work Environ Health 1998; 24 suppl 2:54-62) assessing all-cause and cancer mortality patterns for 2,548 White male employees exposed for at least 6 months to acrylonitrile during fiber production at two plant sites that operated between 1947 and 1991. Since the plants (May Plants I and II in Camden, South Carolina, and one plant in Waynesboro, Virginia) ran identical processes using the same starting materials, all acrylonitrile exposed workers at both sites were combined into a single cohort. This pooling of data increased the statistical power of epidemiologic analyses for a wide-range of mortality categories. Vital status follow-up was extended from December 31, 1991 through December 31, 2002, adding 11 years of mortality results to those reported by Wood et al. (1998). All mortality reports specifying cause of death were ascertained by company registries and were confirmed using the U.S. National Death Index (NDI *Plus*). 839 total deaths have occurred among cohort members through 2002. In our previous letter of November 3, 2006, we described the results of external mortality comparisons assessed by standardized mortality ratios (SMR) using expected rates from both a U.S. population reference and a regional population of White male DuPont workers. These findings have not changed since our initial report.

This letter describes further results from Cox proportional hazards regression that evaluated exposure-response associations between mortality outcomes and quantitative estimates of acrylonitrile exposure. Cox proportional hazards regression models were fitted for all major causes of mortality using both cumulative and mean intensity exposure levels. Relative risk estimates for this update are consistent with those reported in the Wood et al. study.

In our earlier notification, we reported an increase in lung cancer mortality at the highest mean intensity exposure level (Table 1). At that time, proportional hazards regression models considered only the association with exposure metrics and were not adjusted for important potential confounders. Subsequent to this initial finding, our continued analyses have incorporated categorical adjustment terms for birth period and for employment at the South Carolina plant during production start-up from 1950 through 1952.

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As shown in Table 1, 61 lung cancer deaths have occurred among workers in South Carolina, while 27 such deaths have occurred in the group of workers from Virginia. As stated in our previous notification, an important limitation of exposure-response analyses for this cohort is the lack of data concerning individual tobacco use among workers. Since many of the workers at the highest attained level of mean intensity exposure were employed in the 1950s when smoking prevalence was higher for White males, we feel that the increased risk estimate for lung cancer mortality may be due to period and regional differences in respiratory cancer risk factors for workers at the two plant sites.

Relative risk estimates for lung cancer mortality in the highest attained mean intensity exposure category were increased for both crude and adjusted models using a dichotomous indicator for highest attained mean intensity exposure; however, the hazard ratio was not statistically significant after adjustment for birth period and employment at production start-up (Table 1). A limitation to these results is the categorization of mean intensity exposure itself. We did not consider the duration of time spent in the highest attained mean intensity exposure category in proportional hazards analyses. Rather, we restricted categorization to the highest attained mean intensity exposure for each worker based on four categories (low, moderate, high, and very high) which were reduced to two (very high compared to all others) in order to increase statistical power for regression models. The duration of time spent in each subject's mean intensity exposure category was highly variable and was not always consistent throughout employment experience. The very high level of mean intensity exposure was attained more often by workers employed in the 1950s, especially those in the production start-up group. Since these workers are now the oldest members of the cohort, they are also the most likely to experience mortality for a variety of causes including lung cancer.

In order to further quantitatively assess acrylonitrile exposure duration, risk estimates for lung cancer mortality were calculated using cumulative exposure metrics (Table 1). Cumulative exposure is generally considered to be a more biologically meaningful exposure metric as it incorporates both exposure concentration and employment duration for each worker (Checkoway, Pearce, and Kriebel, 2004). There were no exposure-response trends observed for lung cancer mortality with increasing cumulative exposure; therefore, we feel that the unadjusted lung cancer mortality results associated with highest attained mean intensity may be spurious.

Finally, our revised models did result in a single marginally significant finding for increased mortality due to non-neoplastic chronic liver diseases (ICD-9 codes 571 through 573) based on 18 deaths among the cohort members. For an increase of 100 parts per million-years (ppm-years) of cumulative acrylonitrile exposure, the adjusted hazard ratio was 1.58 (95% confidence interval: 0.99, 2.54, p-value = 0.054). Limitations for interpreting this finding include the relatively rare occurrence of this cause of death (2.2% of all deaths among cohort members) and a lack of data detailing individual alcohol usage - a well-known risk factor for chronic liver diseases. To our knowledge, no published epidemiologic study has reported an association between acrylonitrile exposure and chronic liver disease mortality. Furthermore, this outcome was one of 20 major causes of death that we analyzed. Therefore, we feel that the marginal significance of this finding may be a result of multiple comparisons within the cohort.

In summary, no cause-specific mortality outcome, including lung cancer, was found to be significantly associated with increasing acrylonitrile exposure. At the present time, we have completed all analyses and are drafting a manuscript for submission to a peer-reviewed journal. A copy of the accepted manuscript will be sent to the Agency when available.

Sincerely,

A. Michael Kaplan

A. Michael Kaplan, Ph.D.
Director – Regulatory Affairs and Occupational Health

AMK/JMS: clp
(302) 366-5260

REFERENCES

Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology, 2nd edition. Oxford University Press, Oxford, United Kingdom: 2004.

Wood SM, Buffler PA, Burau K, Krivanek N. Mortality and morbidity of workers exposed to acrylonitrile in fiber production. Scand J Work Environ Health 1998; 24 suppl 2:54-62.

Table 1. Hazard ratio estimates for lung cancer mortality through December 31, 2002, by exposure level for the DuPont fiber production cohort.

	SOUTH CAROLINA		**VIRGINIA**		**COMBINED COHORT**	
	Workers n (%)	**Lung Cancer Deaths, n**	**Workers n (%)**	**Lung Cancer Deaths, n**	**Workers n (%)**	**Lung Cancer Deaths, n**
Total	1,416 (56)	61	1,132 (44)	27	2,548 (100)	88
Exposure Metric						
Mean Intensity (ppm)					**Hazard Ratio [a] (95% CI) *p-value***	**Hazard Ratio [b] (95% CI) *p-value***
Low to High (0.11 to 11)	932 (66)	25	973 (86)	22	REF [c]	REF [c]
Very High (30)	484 (34)	36	159 (14)	5	1.9 (1.3, 3.0) *0.002*	1.5 (0.9, 2.4) *0.12*
Cumulative Exposure (ppm-years)						
Low (< 10)	256 (18)	5	372 (32)	3	REF [c]	REF [c]
Moderate (≥ 10, < 50)	542 (38)	21	378 (33)	10	1.4 (0.7, 2.7) *0.31*	1.1 (0.5, 2.5) *0.73*
High (≥ 50, < 100)	225 (16)	9	154 (14)	3	1.1 (0.5, 2.4) *0.80*	0.9 (0.4, 2.3) *0.89*
Very High (≥ 100)	393 (28)	26	228 (20)	11	1.6 (0.8, 3.0) *0.17*	1.1 (0.5, 2.6) *0.75*

[a] Crude hazard ratio model with exposure terms only as reported in November 3, 2006, filing.
[b] Adjusted hazard ratio model with exposure terms, birth period indicator, and indicator for employment at South Carolina plant during start-up phase, 1950 through 1952.
[c] Lowest exposure category serves as referent group for model, hazard ratio is 1.0 by definition.