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Acrylonitrile and human cancer — an overview

by David Coggon, DM,[1] Philip Cole, MD [2]

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The new data presented in this volume are an important addition to what is known about the potential of acrylonitrile to cause cancer in humans; they approximately double the number of deaths that can be analyzed for exposed workers. It is therefore appropriate to reassess the strength of epidemiologic evidence for or against such carcinogenicity in the light of the new findings. The a priori index of suspicion is high in so far as acrylonitrile is clearly carcinogenic in laboratory animals (1). Furthermore, the fact that it produces brain cancer when inhaled by rats makes it plausible that it could cause cancer at sites remote from the respiratory tract when inhaled by people. However, the mechanism whereby acrylonitrile causes cancer in animals is still uncertain, and it does not necessarily follow that it will pose a similar hazard to humans. For example, the capacity for metabolic activation or detoxification may differ between species.

The meta-analysis by Collins & Acquavella (2) draws on a total of 22 epidemiologic studies, including the new investigations reported in this volume. It has several limitations, in particular the poor quality of some of the earlier studies and the potential for bias in reporting and publication. However, these problems are more likely to have led to an overestimation than an underestimation of risk, and it is reassuring that, when all the exposed workers were considered together, only 1 of the 10 types of tumors examined — bladder cancer — showed a significant excess of deaths. The authors point out that the increased mortality from bladder cancer was restricted to plants that handled aromatic amines, and they suggest that a confounding effect of these chemicals could account for the excess. This is the most credible explanation for the findings as they stand, but it would be helpful to have further information about the potential exposure to aromatic amines in individual cases in the studies which found elevated rates of bladder cancer.

The other major limitation of many of the studies reviewed by Collins & Acquavella is the lack of any quantitative information about exposure to acrylonitrile. Thus an increased risk of cancer among workers with high exposure may have been diluted by having them included with others whose exposure was relatively low. The 3 new studies from the United States (3, 4) and The Netherlands (5) are important not only because their statistical power is much greater than that of earlier investigations, but also because they incorporate estimates of individual exposure. Inevitably, there will be inaccuracies in these estimates. Nevertheless, they allow meaningful analysis for subsets of workers who are likely to have had the highest exposures.

In the absence of indications to the contrary (eg, from metabolic studies), it is reasonable to adopt cumulative exposure as a metric when high exposure is defined. The classification of cumulative exposures in the 3 studies is not identical, but the categories of 8 ppm-years and higher in the National Cancer Institute's (NCI) investigation (3) and of 10 ppm-years and higher in the DuPont (4) and Dutch (5) studies are approximately equivalent. Table 1 summarizes the findings for these "high exposure" subsets in relation to all cancer combined and to 4 specific cancers (lung, prostate, brain and leukemia) that have come under suspicion in earlier studies. Results from the DuPont study are also shown for subjects with cumulative exposures of at least 50 ppm-years, but

1 MRC Environmental Epidemiology Unit, University of Southampton, United Kingdom.
2 Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, United States.

Reprint requests to: Professor David Coggon, MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton S016 6YD, UK.

Table 1. Mortality from cancer among the workers with high cumulative exposure to acrylonitrile. (NCI = National Cancer Institute, SMR = standardized mortality ratio, RR = risk ratio)

Cancer	Dutch study (≥10 ppm-years)			NCI study (≥8 ppm-years)			DuPont study					
							≥10 ppm-years			≥50 ppm-years		
	Observed deaths (N)	Expected deaths (N)	SMR	Observed deaths (N)	Expected deaths[a] (N)	RR	Observed deaths (N)	Expected deaths (N)	SMR	Observed deaths (N)	Expected deaths (N)	SMR
All cancer	38	37.9	1.0	53	58.9	0.9	101	119.5	0.8	67	77.5	0.9
Lung cancer[b]	18	15.2	1.2	26	17.3	1.5	37	43.2	0.9	25	28.0	0.9
Prostate cancer	3	1.9	1.6	1	2.5	0.4	8	10.6	0.8	4	7.9	0.5
Brain cancer	0	1.0	0.0	2	4.0	0.5	.	.	.	.	.	.
Leukemia	4	0.9	4.4	1	2.5	0.4	.	.	.	.	.	.

[a] Expected deaths in the NCI study were calculated by dividing the observed number of deaths by the rate ratio.
[b] Findings from the DuPont study are for all respiratory cancer.

corresponding data are not available from the other 2 analyses.

The findings for all cancers combined and for cancers of the prostate and brain indicate no elevation of risk. There is a small excess of leukemia in the Dutch study, but this finding must be set against a deficit in the NCI investigation. In view of this inconsistency and the overall paucity of cases, there seems little cause for concern, although it would be helpful to carry out an analysis of mortality from leukemia in the high-exposure subset of the DuPont cohort.

The observations that most strongly suggest a carcinogenic hazard for subjects with high exposure are those relating to lung cancer. Mortality from lung cancer was higher than expected in both the Dutch and the NCI studies. Moreover, in the NCI investigation risk was further increased when allowance was made for a 20-year latency from first exposure. On the other hand, no excess of lung cancer was apparent in the DuPont study, even for subjects with exposures of 50 ppm-years or higher, and the overall death rate from lung cancer in exposed workers from the NCI study was lower than in the national population. In all 3 studies combined, there were 81 deaths from lung or respiratory cancer with 75.7 expected.

Assessing occupational associations with lung cancer is complicated by the scope for important confounding by smoking habits. No information about smoking was available in the DuPont and Dutch studies, but the high death rate from respiratory disease in the latter suggests that this cohort may have smoked more than the average. Data on smoking were collected in the NCI study, and the association of lung cancer with high exposure to acrylonitrile persisted when allowance was made for smoking habits in a nested case-cohort analysis. However, the rate ratio (ie, 3.6) of ever cigarette smokers as compared with never smokers was surprisingly low, and this finding makes it harder to dismiss the possibility of residual confounding.

Given the uncertain impact of smoking, particularly in the Dutch study, the lack of an overall association with exposure in the NCI study, and the absence of any association in the DuPont investigation, even at the highest exposures, any suspicions about a hazard of lung cancer from acrylonitrile can only be weak. Thus despite its carcinogenicity in animals, there is little evidence to suggest that the compound causes cancer in humans.

How confident can we be that acrylonitrile is not a human carcinogen? It is very difficult to exclude an agent as a human carcinogen by epidemiologic studies. Nonetheless the weight of the evidence available suggests either that acrylonitrile is not a human carcinogen or that it produces only small increases in cancer risk among humans — at least at the exposure levels that have occurred in North America and Western Europe. To evaluate this assumption further, future epidemiologic research should focus principally on workers with cumulative exposure in excess of 10 ppm-years.

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