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Mortality update of workers exposed to acrylonitrile in The Netherlands

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A retrospective cohort study investigating the cause-specific mortality patterns of 2842 workers occupationally exposed to acrylonitrile for at least 6 months before 1 July 1979 was updated. The comparison group consisted of 3961 workers from a nitrogen fixation plant during the same time interval. Industrial hygiene assessments quantified past exposure to acrylonitrile, the use of personal protective equipment, and exposure to other potential carcinogenic agents. All 6803 workers were followed for mortality until 1 January 1996. The follow-up was almost complete (99.6%), and for 99.3% the cause of death was ascertained. Age distribution, follow-up period, and temporal changes in background mortality rates were adjusted for in calculations of standardized mortality ratios for separate causes of death. Cumulative dose-effect relations were determined for 3 exposure categories and 3 latency periods. The results showed that, although cancer mortality fluctuated slightly, no cancer excess seems related to exposure to acrylonitrile.

Key terms carcinogenicity, epidemiology, occupational exposures.

In the late 1970s, following the report of the United States (US) Department of Labor on acrylonitrile carcinogenicity in rats and some excess of lung and large intestine cancer in persons exposed in a US textile fiber plant, the Dutch Association of the Chemical Industry conducted an epidemiologic study of 3935 workers exposed to acrylonitrile (1). The follow-up of the workers was restricted to information that was readily available within the industry, resulting in 25% of the cohort having incomplete follow-up data.

Later, a second attempt was made to conduct a retrospective mortality study of workers exposed to acrylonitrile in The Netherlands (2). In the second attempt the exposed cohort was identified from historical personnel files. For 2 companies the earlier study provided sufficient data for cohort identification. For the other companies the personnel files were searched to identify workers with past exposure to acrylonitrile.

The study presented in the present report provides a further update of the second cohort mortality study conducted in The Netherlands on 2842 workers with past exposure to acrylonitrile and an unexposed reference group of 3961 workers (2).

Cohort selection

In close collaboration with the Dutch Association for the Chemical Industry (VNCI), 9 companies were approached and asked to participate in the study. All 9 companies agreed to participate. However, in 1 company, in which acrylonitrile was only shipped, the exposure turned out to be so low and rare that the company was excluded. It was decided to include an unexposed comparison group in the study. The comparison group comprised the workers of a large nitrogen fixation plant in which mainly fertilizers are produced; the plant was located in the vicinity of the acrylonitrile handling plant contributing most of the exposed workers to the study. No matching procedures were used in selecting the exposed and unexposed workers. However, several eligibility criteria were specified prior to the data collection. First, workers had to be exposed to acrylonitrile for over 6 months or had to be employed in the comparison plant for 6 months or more. Second, the workers had to be men since it was anticipated that the number of exposed female workers would be too small for meaningful analysis. This assumption turned out to be

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correct. During the cohort selection no women were found to have been employed in jobs with exposure to acrylonitrile. Third, the workers had to be Dutch citizens since there are no reference mortality rates for foreigners in The Netherlands and it is difficult to determine the vital status of non-Dutch workers.

The personnel files of the participating companies were screened to identify workers eligible for the study. From the files the necessary data were abstracted for personal identification and occupational job history. Two companies preferred to carry out the screening and data abstraction themselves, for privacy considerations.

Production processes and exposure assessment

Eight chemical companies participated in the study. Acrylonitrile was used for different purposes in each company. A short description of the processes in which acrylonitrile was used is given in table 1.

In the earlier study a substantial effort was made to assess the past exposures to acrylonitrile accurately. For this purpose a short manual was compiled in which the methods for the exposure assessment were described. The actual exposure assessment was carried out by an industrial hygienist (JT), who contacted the company industrial hygienist. This approach guaranteed a uniform procedure for all the companies. For 1 company a different method was followed, since the industrial hygienist of the study was not permitted to visit the industrial facility. In this instance another industrial hygienist (Dr Y Kant) carried out the exposure assessment after consultation with the study industrial hygienist (JT).

The first step of the exposure assessment was to make an inventory of the measurements available for each of the plants. These measurements formed the basis for the exposure assessment, together with temporal information on changes in the production process, task rotation, work procedures, personal hygiene, and total production. Information on the work environment and control measures was obtained through interviews with plant employees.

A job-exposure matrix was constructed for this study. In this matrix, the job history was described in detail, giving information on the job held in a specific period and in a specific workplace. Within each department, exposure job classes were constructed which included all the job titles believed to have had a similar exposure profile based on the exposure assessments.

The results of the 8-hour time-weighted average exposure assessment of all the workers in an exposure class were grouped to determine the average exposure level of that job in that workplace for each calendar year. On the basis of this outcome, it was decided in which exposure range each exposure job class would be placed for that year. The ranges used were ≤0.5, >0.5—1, >1—2, >2—5, and >5 ppm. There were no exposures thought to be greater than a time-weighted average of 5 ppm. For 1 company it was possible to carry out the exposure assessment on an individual worker level rather than by job title, since exposure estimates had been recorded in the medical files of each worker.

The exposure assessment had some limitations. For instance respirator use and the potential for skin exposure, which were not taken into account, may have resulted in a different exposure than the one assessed.

Various other exposure characteristics were studied, such as exposure to peak concentrations and exposure to established carcinogens. Peak exposures were defined as intervals with elevated exposure in the ranges of <10, 10—20, and >20—30 ppm occurring on a regular basis, at least once a week. An assessment of the occurrence of peak exposures could be made for all but 1 of the participating companies. In addition, an inventory was made of exposure to other agents considered to be potential human carcinogens by the International Agency for Research on Cancer.

An example of the job-exposure matrix generated in this manner is given in the appendix. By means of combining the job-exposure matrices and the individual job history, an estimated exposure was constructed for each worker. The cumulative exposure was defined as the sum of the products of the average concentration and the duration (in years) of that exposure. For example, a worker exposed to a concentration of 2 ppm during a 2.5-year period accumulated a dose of 5 ppm-years. The arithmetic mean of each exposure class was used for these calculations. After 1 January 1980, acrylonitrile exposure had been greatly decreased due to the implementation of effective industrial hygiene actions and the systematic use of personal protection in work situations involving possible exposure to acrylonitrile. For the purpose of this project the period after 1 January 1980 was regarded as being without exposure to acrylonitrile, which may have resulted in a slight underestimation of the exposures. Even after 1 January 1980, situations are known to have occurred in which the acrylonitrile could be smelled. The odor threshold for

Table 1. Acrylonitrile (AN) use in each company and the number of exposed workers employed. (ABS = acrylonitrile-butadiene-styrene, STEL = short-term exposure level)

Plant	Number of workers	Start of exposure	Type of plant	Highest STEL	Average exposure range
1	594	1969	AN and ABS plant	20	0.5
2	382	1959	Acrylate plant	20	1-2
3	30	1973	Catalyst experimental plant	20	0.5-1
4	38	1973	Acrylate plant	10	0-1
5	715	1967	ABS plant	20	0.5
6	645	1962	Fiber plant	30	1-5
7	266	1966	ABS plant	30	0-1
8	210	1967	Resin plant	20	0-2

acrylonitrile among the workers has been estimated to be around 22 ppm (3).

During the determination of the exposure assessment, it was found that, in 1 plant, exposure to acrylonitrile occurred only 5% of the time worked. Therefore the workers (N=38) of this plant were excluded from further analyses.

Ascertainment of vital status and causes of death

The procedures that were applied to obtain the vital status and the causes of death were similar to the procedures that were used in the previous study. The municipal population registries were requested to provide information on the whereabouts of the workers included in the study. For workers who had moved from one municipality to another the new municipality was requested to provide vital status information on the workers. This process was repeated after each notification that a person had moved to another municipality. In this way the vital status of 6608 workers, as of 1 January 1996, of the total 6803 workers could be traced. More-detailed results of the follow-up are given in table 2. Next the causes of death were ascertained through the Dutch Central Bureau of Statistics (CBS). The death certificates of persons who died in The Netherlands are all sent from the municipal population registries to the CBS. After the receipt of the death certificates the causes of death are coded by trained nosologists and computerized to accumulate the annual vital statistics, which are presented by cause of death. Because of strict privacy protection laws, the CBS will not provide individual causes of death. However frequency tabulations for groups are given, and scientific researchers are provided an opportunity to analyze the individually linked data set in a CBS office under supervision of CBS personnel. The causes of death are coded soon after the death certificates are received at the CBS without any knowledge of the project.

All codes of the International Classification of Diseases in use during the observation period were converted into a classification consisting of 7 main categories. The main category neoplasms was divided into 27 subcategories based on the organ in which the cancer originated (table 3). Some individual causes of death could not be ascertained, mostly because the person had died outside The Netherlands. These deaths were included in the calculation of the total values for the standardized mortality ratio (SMR), but they were excluded when the cause-specific SMR values were calculated.

Of the 6803 subjects, 6774 could be completely followed (in other words, until the end date of the follow-up, until the person's emigration date, or until death) resulting in a completeness of follow-up of 99.6%.

In the total study population 1273 deaths were observed. Compared with the 706 deaths observed in the earlier study, this number is approximately a doubling of the observed number of deaths. The number of deaths in the exposed group increased from 134 to 290. In either group the observed total mortality was still lower than expected, an indication of the healthy worker effect.

For 9 (0.7%) deceased subjects it was not possible to trace the actual cause of death, either because the person had died abroad or because it was not possible to link the record with the CBS cause-of-death file.

Table 2. Vital status of the study population at the end date of the follow-up.

Vital status	Exposed group		Unexposed group	
	N	%	N	%
Alive on 1 January 1996	2420	85.1	2915	73.6
Deceased	290	10.2	983	24.8
Emigrated before 1996	113	4.0	53	1.3
Lost to follow-up	19	0.7	10	0.3
Total group	2842	100	3961	100
Total number of person-years at risk[a]	65 615		120 976	

[a] After 6 months of employment.

Statistical analysis

The statistical analysis mainly consisted of a person-time analysis, in which adjustments are made for differences in age distribution, length of follow-up, and changes in background mortality rates. Age- and time-interval-specific person-years were generated for specific exposure groups and were multiplied by the consecutive mortality rates of the total male Dutch population to generate expected numbers of cause-specific deaths. These calculations were done using a computer program designed by Peto (4). For this purpose the cause-specific national mortality rates were converted into the same classification used to code the causes of death observed in the study.

Despite the availability of a substantially large unexposed group, an indirect comparison with the general population was preferred over a direct comparison between the exposed and unexposed groups. Some of the causes of death under investigation are so rare that even a group of approximately 4000 unexposed workers followed for an average of 30 years still yielded unstable cause-, age- and interval-specific mortality rates. Therefore it was decided to calculate cause-specific SMR values for both the exposed and unexposed groups.

The exposed group was stratified in several ways, by any peak exposure (<10, 10—20, and >20 ppm), by respirator use, and by exposure to other carcinogens.

The person-years of the total exposed group were also stratified into 3 cumulative dose groups, <1 ppm-year (low), 1—10 ppm-years (medium), and >10 ppm-years

Table 3. Observed (O) and expected (E) numbers of deaths for 7 main disease categories and specific cancer sites in the exposed and unexposed study populations. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Causes of death	Exposed group				Unexposed group			
	O	E	SMR	95% CI	O	E	SMR	95% CI
Main categories								
I Infectious diseases	-	1.7	0.0	0.0—217.0	7	6.84	102.3	41.0—210.8
II Neoplasms	97	110.78	87.6	71.0—106.8	332	400.38	82.9	74.2—92.3
III Circulatory system	108	119.03	90.7	74.4—109.5	422	481.31	87.7	79.5—96.5
IV Respiratory system	17	14.03	121.2	70.6—194.1	69	76.2	90.5	70.4—114.6
V Digestive system	6	10.96	54.7	20.0—119.1	24	37.07	64.7	41.5—96.3
VI Others	36	37.05	97.2	68.0—134.5	80	118.57	67.5	53.5—84.0
VII External causes	23	29.51	77.9	49.4—117.0	43	66.33	64.8	46.9—87.3
Unknown	3				6			
Total	290	323.01	89.8	79.7—100.7	983	1186.52	82.8	77.7—88.2
Mouth cancer & pharynx	1	1.85	54.1	0.7—301.2	2	4.93	40.6	4.6—146.6
Esophagus	-	3.07	0.0	0.0—199.4	3	8.81	34.0	6.8—99.5
Stomach & small intestine	2	7.97	25.1	2.8—90.7	33	32.01	103.1	71.0—144.8
Large intestine	9	7.14	126.0	57.5—239.3	20	35.02	79.9	48.8—123.4
Rectum	3	2.73	109.8	22.1—320.7	10	10.49	95.3	45.6—175.4
Liver & biliary passages	2	1.93	103.7	11.7—374.5	3	7.03	42.7	8.6—124.8
Pancreas	2	5.16	38.8	4.4—140.1	17	17.87	95.1	55.4—152.3
Nose	1	0.17	588.2	7.7—3272.9	-	0.58	0.0	0.0—636.0
Larynx	3	1.16	258.0	51.8—753.7	2	3.84	52.1	5.8—187.9
Trachea & lung	47	42.82	109.8	80.6—146.0	124	161.36	76.8	63.9—91.6
Bone	-	0.31	0.0	0.0—1190.0	-	0.96	0.0	0.0—384.3
Connective tissue	-	0.75	0.0	0.0—491.9	4	1.68	238.1	64.1—609.6
Skin	1	2.03	49.3	0.6—274.5	4	4.19	95.5	25.7—244.4
Kidney	1	3.3	30.3	0.4—168.9	8	10.88	73.6	31.7—144.9
Prostate	4	4.8	83.3	22.4—213.2	13	25.62	50.8	27.0—86.8
Genital organs	1	0.82	122.5	1.6—681.8	1	1.99	50.4	0.7—280.2
Bladder	3	3.07	97.9	19.7—285.9	14	13.09	106.9	58.4—179.4
Brain	6	3.45	173.9	63.5—378.4	7	8.16	85.7	34.4—176.7
Thyroid gland	-	0.23	0.0	0.0—1603.9	4	0.87	459.2	123.5—1175.8*
Lymphatic glands & lymphoreticular sarcoma	-	0.52	0.0	0.0—709.4	1	2.1	47.7	0.6—265.3
Hodgkin's disease	-	1.02	0.0	0.0—361.7	1	2.68	37.3	0.5—207.6
Other lymphoma	1	2.58	38.8	0.5—215.7	7	7.11	98.4	39.4—202.8
Multiple myeloma	1	1.52	197.2	39.6—576.3	5	5.58	89.7	28.9—209.3
All leukemia	5	3.0	166.9	53.8—389.6	11	10.0	110.1	54.9—196.9
Benign neoplasms	1	0.38	266.7	3.5—1483.7	2	1.29	154.8	17.4—558.9
Unspecified neoplasms	-	6.54	0.0	0.0—56.4	28	22.28	125.7	83.5—181.6
Others	1	1.7	59.1	0.8—328.6	8	5.9	135.7	58.4—267.3

* $P<0.05$.

(high). The analysis was done in such a way that all the exposed workers started out in the low-exposure group. At the time they exceeded the 1 ppm-year dose they were transferred to the medium-exposure group, and, when they exceeded 10 ppm-years of cumulative exposure, they were transferred into the high-exposure group.

Next the person-years at risk in each of the 3 dose groups were stratified into 3 latency periods (<10 , 10—20, and >20 years of latency). This type of stratified analysis implies that "latency" is defined as time elapsed since the respective dose group was entered.

The accumulation of person-years at risk started 6 months after the day of first exposure, since one of the eligibility criteria of the study was at least 6 months of exposure or 6 months of employment in the comparison plant. In the study reported in 1992 (2) the enumeration of person-years at risk was started on the date of first exposure. Considering the eligibility criteria, the enumeration of person-years at risk should have started after 6 months of exposure.

Exact confidence intervals for the SMR values were calculated (5). The analysis of trends for the SMR values was done according to the method proposed by Breslow & Day (6).

Results

Total mortality in the exposed group, as well as in the unexposed group, was lower than expected (table 3). The

SMR for total mortality in the exposed group was 89.8, which is not significantly lower than expected. The SMR for total mortality in the unexposed group was 82.8, which is also significantly lower than expected. The SMR values for the 7 main categories of causes of death in the exposed group were all within the range of normal variation, as were the SMR values for specific cancer types.

The exposed group was stratified in several ways. A stratification was made according to year of employment, being before 1965, between 1965 and 1969, and after 1969. This analysis revealed no significant trends. Five out of the 6 brain tumor deaths occurred in the group that was employed after 1969 (expected number 1.71). In table 4 the SMR values for total mortality and cancer mortality are presented by exposure group and latency. Similar data for lung cancer, prostate cancer, brain cancer, and leukemia mortality are given in table 5.

The results of the stratified analyses by peak exposures, respirator use, and exposure to other carcinogens are presented in table 6. Again these analyses do not provide indications for elevated site-specific cancer risks in any of the subgroups. Apart from the stratified analyses already presented, a stratification was made on the basis of dose and latency. For each worker in the exposed group a dose was calculated by multiplying the concentration with the duration, giving a dose in terms of ppm-years. The person-years of observation of the workers in the exposed group were stratified into the 3 dose groups of <1, 1—10, and >10 ppm-years. Within each of the 3 dose groups substratifications were made by latency. The person-years were subdivided into a latency of <10, 10—20, and >20 years of follow-up. The SMR values for total mortality, cancer mortality, and lung cancer, prostate cancer, brain cancer and leukemia mortality for all 9 specific subgroups are given in table 5. Four out of the 5 deaths from leukemia occurred however in the high exposure group (SMR

Table 4. Total mortality, cancer mortality, and lung cancer mortality of the workers exposed to acrylonitrile, by 3 cumulative exposure categories and latency periods.[a] (O = observed number of deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Dose[b]	Total mortality			Cancer mortality		
	O	SMR	95% CI	O	SMR	95% CI
Low (<1 ppm-year)						
<10 years' latency	7	43.1	17.3—88.8	-	0.0	0.0—90.0
10—20 years' latency	20	108.3	66.1—167.3	7	108.3	43.4—223.2
>20 years' latency	12	128.2	66.2—224.0	2	56.7	6.4—204.8
Total[c]	39	88.5	62.9—121.0	9	64.0	29.2—121.5
Moderate (1 to 10 ppm-year)						
<10 years' latency	35	71.7	50.0—99.8	8	56.3	25.7—107.0
10—20 years' latency	71	91.5	71.4—115.4	30	108.7	73.3—155.1
>20 years' latency	42	87.2	62.8—117.9	12	66.5	34.3—116.3
Total[d]	148	84.8	71.7—111.5	50	84.6	62.8—111.5
High (>10 ppm-year)						
<10 years' latency	35	119.8	83.5—166.7	9	80.9	36.9—153.6
10—20 years' latency	47	94.6	69.5—125.8	21	107.8	71.7—177.2
>20 years' latency	21	76.8	47.5—117.4	8	92.0	39.6—181.4
Total[e]	103	97.0	79.1—117.6	38	100.2	70.9—137.5

[a] Latency was defined as time since the particular dose group was entered.
[b] The trend in cumulative dose (calculated only if observed was > 0) for the 3 dose groups of mortality combined was 0.44 for total mortality and 0.20 for cancer mortality.
[c] The trend in cumulative dose (calculated only if observed was > 0) was 0.02 for total mortality.
[d] The trend in cumulative dose (calculated only if observed was > 0) was 0.45 for total mortality and 0.81 for cancer mortality.
[e] The trend in cumulative dose (calculated only if observed was > 0) was 0.10 for total mortality and 0.76 for cancer mortality.

Table 5. Mortality from lung, prostate, and brain cancer and leukemia for the workers exposed to acrylonitrile, by 3 cumulative exposure categories and latency periods.[a] (O = observed number of deaths, SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Dose[b]	Lung cancer			Prostate cancer			Brain cancer			Leukemia		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
Low (<1 ppm-year)												
<10 years' latency	-	0.0	0.0—283.8	-	0	0.0—4611.3	-	0.0	0.0—1941.6	-	0.0	0.0—1756.7
10—20 years' latency	3	120.6	24.2—352.5	1	427.4	5.6—2377.7	3	1229.5	247.1—3592.4*	-	0.0	0.0—2049.4
>20 years' latency	2	146.6	16.5—529.4	-	0	0.0—709.4	-	0.0	0.0—4611.3	-	0.0	0.0—5270.0
Total	5	97.3	31.4—227.1	1	194.2	2.5—1080.4	3	583.7	117.3—1705.3*	-	0.0	0.0—802.0
Moderate (1 to 10 ppm-years)												
<10 years' latency	1	21.4	0.3—118.8	-	0	0.0—167.8	1	163.1	2.1—907.6	-	0.0	0.0—625.3
10—20 years' latency	16	148.2	84.6—240.6	-	0	0.0—320.8	2	215.7	24.2—779.0	1	140.6	1.8—782.5
>20 years' latency	7	99.7	39.9—205.4	-	0	0.0—361.7	-	0.0	0.0—878.3	-	0.0	0.0—1024.7
Total[c]	24	106.6	68.3—158.7	-	0	0.0—154.4	3	153.1	30.8—448.1	1	60.1	0.8—334.6
High (>10 ppm-years)												
<10 years' latency	4	89.5	24.1—229.1	1	469.5	6.1—2612.1	-	0.0	0.0—1152.8	1	467.3	6.1—2599.9
10—20 years' latency	11	150.2	74.9—268.8	2	212.3	23.8—766.6	-	0.0	0.0—784.9	2	487.8	54.8—176.2
>20 years' latency	3	87.0	17.5—254.2	-	0	0.0—498.5	-	0.0	0.0—1756.7	1	354.6	4.6—1973.0
Total[d]	18	118.1	69.9—186.6	3	158.4	31.8—462.8	-	0.0	0.0—368.9	4	441.5	118.8—1130.3*

[a] Latency was defined as the time since the particular dose group was entered.
[b] The trend in cumulative dose for the 3 dose groups of lung cancer combined was 0.66.
[c] The trend in cumulative dose (calculated only if observed was > 0) was 0.32 for lung cancer.
[d] The trend in cumulative dose (calculated only if observed was > 0) was 0.95 for lung cancer and 0.83 for leukemia.

Table 6. Total mortality, cancer mortality, and lung cancer mortality by exposure to peaks, respirator use, and exposure to other carcinogens. (O = observed number of deaths, SMR = standardixed mortality ratio, 95% CI = 95% confidence interval)

Dose	Total mortality			Cancer mortality			Lung cancer mortality			Prostate			Brain			Leukemia		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
Peaks																		
None	76	78.5	61.9—98.3	32	97.4	66.6—137.5	15	118.0	66.0—194.6	1	63.5	0.8—353.0	1	104.4	1.4—580.8	2	226.5	25.4—817.8
<10 ppm	111	95.0	78.1—114.4	40	99.7	71.2—135.8	20	129.7	79.2—200.4	2	120.3	13.5—434.2	4	305.6	82.2—782.3	2	183.2	20.6—661.3
10—20 ppm	83	92.7	73.8—114.9	20	64.2	39.2—99.1	8	65.4	28.2—128.8	-	0	0.0—281.6	1	105.7	1.4—588.1	1	120.6	1.6—671.2
>20 ppm	20	100.9	61.6—155.9	5	75.6	24.3—176.3	4	162.9	43.8—417.0	1	393.7	5.1—2190.5	-	0	0.0—1537.1	-	0	0.0—1941.6
Respirator use																		
Yes	256	87.1	65.8—113.1	18	79.7	47.2—126.0	9	101.9	46.5—193.4	1	105.9	1.4 —589.4	0	0	0.0—527.0	0	0	0.0—625.3
No	34	90.4	79.2—102.8	79	89.6	70.9—111.6	38	111.8	79.1—153.5	3	77.7	15.6—227.1	6	218.1	79.6—474.7	5	207.6	66.9—484.4
Exposure to other carcinogens																		
Yes	137	92.9	78.0—109.9	42	82.3	59.3—111.3	19	95.1	57.2—148.6	2	82.9	9.3—299.4	3	200.4	40.3—585.5	3	224.7	45.2—656.6
No	153	87.1	73.9—102.1	55	92.0	69.3—119.8	28	122.5	81.4—177.1	2	83.6	9.4—302.0	3	153.5	30.9—448.6	2	120.5	13.5—435.0

441.5, 95% confidence interval 118.8—1130.3). The 4 leukemia deaths in the highest exposure group consisted of 1 lymphatic leukemia and 3 myeloid leukemias.

In addition an attempt was made to link the study population with existing cancer registers in The Netherlands. These regional cancer registers are thought to be complete since 1989, and they are frequently used to conduct epidemiologic studies. This linkage provided information on 8 incident cases of brain cancer in the study population (which may have included some of those in the mortality study). There was only 1 case of brain cancer in the exposed cohort, which was an invasive anaplastic astrocytoma. The other 7 cases occurred in the unexposed population.

Discussion

In conclusion, while this study finds small fluctuations in cancer mortality among acrylonitrile workers, there does not appear to be any cancer excess related to acrylonitrile exposure. The cancer mortality of the exposed group was lower than expected. For any specific cancer type no consistent and significant excess was noted in the exposed group. Some additional remarks should be made, however. The small excess of brain cancer mortality was not reflected in the dose-effect analysis. Four of the 5 deaths from leukemia occurred in the high-exposure group.

Because of an elevated brain tumor incidence in animal experiments, there has been some concern that acrylonitrile may be a risk factor for malignancies of the brain. In the exposed group 6 deaths from brain cancer were observed compared with an expected number of 4, resulting in an SMR of 150, not statistically significantly different from unity. In the high-dose group no brain tumor death was noted; this finding argues against any etiologic role of acrylonitrile.

The dose-effect analysis did yield an unexpected result, namely, an excess of leukemia mortality in the high-dose group. Four deaths from leukemia were observed versus 0.9 expected, which was statistically significant. However, this finding is not consistent with the results of previous studies of acrylonitrile workers. In addition, there are deficits of leukemia mortality in the lower exposure categories that argue against an exposure-effect trend. This result is probably a chance finding.

This study of a large group of workers exposed to significant levels of acrylonitrile in several types of industrial settings had a detailed exposure evaluation for acrylonitrile levels. The mortality levels for the acrylonitrile workers were favorable when compared with those of both the Dutch population and the unexposed workers.

There were some limitations for this study however. First, some potential confounders were not evaluated in this study. While we evaluated other potential occupational carcinogens in the workplace, we were unable to evaluate smoking, which is especially important for evaluating lung cancer. In addition, because we relied on death certificates, we were unable to determine cell types for cancers. This lack limited our evaluation of the leukemia mortality.

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Appendix

Dummy table used for exposure assessment in the acrylonitrile study

Company: no name
Department: production
Exposure job class: reaction operator

Year	Average exposure to acrylonitrile (ppm)				
	Based on measurement	Assessment	Peak concentrations	Respirator use during critical tasks[a]	Exposure to other potential carcinogens
1972		1—2	20—30	No	Yes
1973		1—2	10—20	No	Yes
1974		1—2	10—20	No	Yes
1975		1—2	10—20	Yes	Yes
1976		0.5—1	<10	Yes	Yes
1977		0.5—1	<10	Yes	No
1978	0.5—1		<10	Yes	No
1979	0.5—1		<10	Yes	No

[a]Tasks with increased potential for exposure.