Mortality of Workers Exposed to Acrylonitrile

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A retrospective cohort study was carried out in The Netherlands to investigate the potential carcinogenic effects in humans of occupational exposure to acrylonitrile (AN). The total study group consisted of 6803 workers "from eight chemical plants and one control plant" of whom 2842 had been exposed to AN between January 1, 1956 and July 1, 1979 for at least 6 months. All workers were employed by one of eight chemical companies. An extensive review of the available industrial hygiene data was conducted to assess the magnitude of past exposure to AN, occurrence of peak exposures, exposure to recognized potential human carcinogens, and respirator use. The total cohort was observed for mortality until January 1, 1988. In collaboration with the Central Bureau of Statistics, the causes of death were traced for the workers who died before 01-01-1988. In the exposed as well as in the nonexposed cohorts the total mortality was lower than expected, based on national mortality statistics. The observed cancer mortality in the exposed cohort was similar to the expected mortality. Specific analyses were carried out to investigate dose-response relationships and latency for total mortality and lung cancer mortality. Overall, no indications were found for a carcinogenic effect in this cohort of workers exposed to AN.

Acrylonitrile (AN) is a volatile, flammable liquid, mainly used as a raw material for the production of plastics, resins, synthetic rubber, and fibers. AN does not occur as a natural product. Exposure to AN can have several acute health effects, such as headaches and irritation of the eyes, nose and throat.[1] Skin contact with liquid AN can cause dermatitis that can last 3 months. Acute toxic effects among workers exposed to high concentrations of AN have been reported since 1944.[2] In the last decades there has been concern about possible long-term health effects, in particular about a possible carcinogenic effect of exposure to low concentrations of AN.

Carcinogenic effects in animals have been reported on several occasions. Maltoni et al[3] reported the findings of inhalation experiments in rats. The investigators concluded that AN showed borderline oncogenic effects. Inhalation of AN in rats leads to increased incidences of tumors of the central nervous system, Zymbal gland, stomach, and some other sites.[4]

Triggered by these positive animal experiments, a number of epidemiologic studies have been carried out. The findings of a number of these studies are summarized in Table 1. The first epidemiologic study of workers exposed to AN was conducted by O'Berg of the DuPont company in the United States.[5] In this retrospective cohort study of 1345 exposed workers, eight cases of respiratory cancer were observed compared with 4.4 expected. In 1985 the results of an update of this study were reported.[6] The number of lung cancer cases was closer to the expected number than in the previous study (14 observed vs 11.6 expected). The number of prostatic cancer cases was statistically significantly higher than the expected number, but this was not related with dose. Later the findings of what was essentially a 1-

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TABLE 1
Description of Retrospective Cohort Studies of Workers Exposed to Acrylonitrile

	No. of Exposed Workers	No. of Observed Deaths	Findings	Comments
O'Berg[5] (1980)	1345	89	Respiratory cancer SMR* 113 (49–222)† SIR‡ 183 (78–368)	
O'Berg[6] (1985)	1345	155	Lung cancer SMR 121 (66–203) SIR 140 (67–255) Prostate cancer SMR 100 (12–556) SIR 333 (122–722)	5 y update of previous study
Chen[7] (1988)	1329	168	Lung cancer SMR 106 (58–178)	Essentially 1 y update of O'Berg (1985)
Chen[8] (1988)	1329		Lung cancer SIR 106 (51–196) Prostate cancer SIR 222 (81–484)	Essentially 1 y incidence update of O'Berg (1985), using also external rates
Kieselbach[9] (1980)	884	58	Lung cancer SMR 90 (39–195)	
Thiess[10] (1980)	1469	89	Lung cancer SMR 195 (97–348)	Co-exposure to known carcinogens, no dose response
Zack[19] (1980)	352	15	Lung cancer SMR 125 (2–655)	
Werner[11] (1981)	1111	79	Lung cancer SMR 120 (54–225)	
Delzell[12] (1982)	327	74	Lung cancer SMR 150 (70–290)	No dose response
Chen[13] (1987)	1083	92	Lung cancer SMR 60 (21–154) SIR 73 (23–169) Prostate cancer SMR 142 (16–519) SIR 263 (85–614)	
Collins[14] (1989)	1774	145	Lung cancer SMR 100 (47–133) Prostate cancer SMR 149 (17–539)	Smoking habits considered

* SMR = standardized mortality ratio.
† 95% confidence interval ().
‡ SIR = standardized incidence ratio.

year update of incidence and mortality was reported;[7,8] internal as well as external rates were used for comparison. Observed and expected number of incidents and decreased number of lung cancer cases were the same.

In Western Germany, Kieselbach[9] carried out a cohort study of 884 workers exposed to acrylonitrile. Investigators did not find indications for a cancer risk related to AN exposure in these workers. Thiess[10] carried out a similar study in Germany. Among the 1469 exposed workers under investigation a statistically significant excess mortality from lung cancer was observed. However, the authors stated, that because of combined exposure to other chemicals it could not be concluded that AN was the actual carcinogenic agent.

Werner and Carter[11] studied the mortality patterns of 1111 polymerization workers in Great Britain[11] who had been exposed to AN. Increased mortality rates for lung cancer, stomach cancer, colon cancer, and brain tumors were reported, although they were not statistically significant. The investigators stated "the results are not conclusive and neither add to nor detract from existing suspicions that acrylonitrile is a human carcinogen."

A subgroup of American rubber workers, all 327 potentially exposed to AN was studied for cancer mortality by Delzell and Monson.[12] Nine deaths from lung cancer were observed versus 5.9 expected. A cancer incidence and mortality study among 1083 textile fiber plant workers showed a lower than expected lung cancer incidence (5 vs 5.6) and mortality (5 vs 6.9).[13] The largest retrospective cohort study in terms of the number of deceased workers was conducted by Collins et al.[14] In this study 1774 workers exposed to acrylonitrile were studied. No increased mortality rates for cancer in general or specific sites were observed.

In conclusion, although animal experiments give evidence for carcinogenic properties of AN, the human epidemiologic studies conducted so far do not support this statement.

The epidemiologic study reported here was carried out specifically to evaluate the existence of cancer risks in workers exposed to AN in The Netherlands, in particular respiratory cancer. After publication of the first reports of a possible cancer risk related to AN exposure in the workplace, there was public concern in The Netherlands that this risk could exist in the Dutch chemical industry. Therefore, an attempt was made by representatives of the chemical industry to carry out an industrywide epidemiologic study of workers exposed to AN.[15] In this cohort study, 3935 workers were identified who had been potentially exposed. However, in this study the follow-up was successfully completed for approximately 75% of the workers, which was regarded to be too low. A study group was formed consisting of a principal investigator from the university of Limburg, representatives of the participating companies, and a representative of the Dutch Association of Chemical Industries to conduct the study with improved follow-up. The findings are presented here.

Cohort Selection

Nine companies were requested to participate in the study. All nine agreed to participate, and written agreements were drawn up. During the data collection, it turned out the AN exposure was so rare in one company, which shipped AN on average once a month, it was decided not to include this company in the study. The chemical processes with exposure to AN varied greatly from one plant to another. In one plant AN was produced; in another plant AN was used to produce acrylate paints. Table 2 shows a tabulation of the types of processes in which AN was involved in the eight participating companies.

At the start of the study, it was thought the exposed cohort defined in a previous study could be used. The study had made an inventory of all workers exposed before July 1979. Therefore, this eligibility criterion was used. However, during data collection it turned out this was not possible, and the cohorts had to be assembled from scratch.

The data collection in the personnel files of the companies was largely carried out by two of the authors (G.S. and J.S.). The files were organized in an alphabetical order, separated into current employees and past employees. All files contained information on jobs held and workplaces. However, two companies preferred to extract the data on the exposed workers themselves, for privacy considerations. The general procedure was first to have meetings with key persons in the plant to make a list of departments where AN exposure had occurred. After this list was drawn up, all the personnel files of the company were screened for workers who had worked in the departments and who also met the eligibility criteria. During the meetings with key persons the completeness of the personnel files was queried in great depth. It was ascertained that no files had been destroyed. However, in The Netherlands there is no objective method to check the completeness of the archives of a particular company.

For each worker a job title and the duration of employment in each specific job was written down. Although this procedure was tedious, it was the best assurance that all eligible workers were included in the study and that workers who had not been exposed to AN were excluded from the exposed cohort.

TABLE 2
Types of Processes in which Acrylonitrile (AN) was Involved, Occurring in Eight Participating Companies

Type of process/end product
AN production
Production of latex rubbers
Production of polymers
Production of acrylic fibers
Production of vinylidene/acrylonitril polymers
Production of artificial resins
Production of acrylamide
General chemical purposes
Nonprocess department
Quality control
Maintenance departments

The following eligibility criteria were used for the exposed cohort: the worker must have been exposed for at least half a year before the first of July 1979, the worker must have the Dutch nationality, the worker had to be living in The Netherlands at the time of exposure, and the worker had no history of underground coal mining work.

A half year of exposure was taken as minimal to exclude workers with very short exposure periods, because these were regarded as less informative concerning possible long-term health effects of AN. Only workers with a Dutch citizenship were selected to guarantee comparability between the exposed and nonexposed cohorts and with the general population. In The Netherlands no mortality statistics are available by nationality. The workers had to be living in The Netherlands, because if they lived outside The Netherlands the follow-up of these persons could not be carried out. In addition to the exposed cohort, a nonexposed cohort was selected. The nonexposed cohort consisted of workers of a plant located near the AN processing plant that was thought to contribute most of the exposed workers.

Although methodologically it would have been preferable to select the nonexposed cohort from all participating plants, it was decided not to do so because of the possibility that these cohorts may have been exposed to other human carcinogens. The nonexposed cohort consisted of workers of a nitrogen fixation plant in which no substantial exposure to identified human carcinogens has been reported. In the nitrogen fixation plant artificial fertilizers are manufactured.

Similar eligibility criteria were used for the exposed cohort. However, the comparison plant had been in service much longer than any of the plants where AN exposure occurred. Therefore, the cohort was restricted to workers of the comparison plant who had been employed between 1956 and

1979. Because the nitrogen fixation plant was already in service in 1956, a larger proportion of workers in this cohort was employed in 1956 than in the exposed group. This explains the relatively large number of person-years and the higher crude mortality rate in the nonexposed group. The first year of AN use in industrial setting in The Netherlands was 1956.

In total 2842 workers had previous exposure to AN. The comparison group included 3961 workers and all study subjects met the eligibility criteria stated above. The purpose of including a specific occupational comparison group was twofold. First, this specific comparison group made it possible to assess the magnitude of the healthy worker effect in this study. Second, it provided a check on the completeness of follow-up.

Exposure Assessment

The earlier AN cohort study conducted in The Netherlands was subject to criticism because of lack of accurate exposure data. The only quantitative aspect available in that study was a categorization of the exposed workers into three groups: low exposure (lower than 2 ppm), medium (between 2 and 5 ppm) and high exposure (higher than 5 ppm). The industry stressed the importance of having more detailed exposure information. To meet this demand, an industrial hygienist (J.T.) from one of the companies was requested to coordinate the exposure assessments for each of the participating plants. The most important goal of this exposure assessment was to achieve consistent data from all the participating companies.

A short manual was compiled describing the methods for exposure assessment. If actual exposure measurement results were available, these were used. If no measurement results were available for a particular period, an assessment was made based on the measurements taken at a later date and taking into account changes in the production process, industrial hygiene control measures, and work procedures put into effect over time. Information on the work environment and control measures was obtained through interviews with plant personnel.

Within each department exposure job classes were identified, which included all the job titles believed to have had a similar exposure profile based on the activities and workplaces of the people in those positions.

The 8 hour time-weighted average (TWA) exposure measurement results of all workers in an exposure class were grouped to determine the average exposure level of that exposure job class for each calendar year. Based on this outcome, it was decided in which exposure range each exposure job class was placed for that year. Ranges used were 0 to 0.5 ppm, 0.5 to 1 ppm, 1 to 2 ppm and 2 to 5 ppm. In some situations the exposure information was so limited that a detailed classification was not possible, and only a rough classification in categories 0 to 2 ppm and 2 to 5 ppm could be provided by the company industrial hygienist. For one company the exposure assessment was carried out on an individual basis, based on the evaluation of the exposure results for the 1979 study.

For each exposure group an exposure matrix was drawn up. A matrix model is shown in Table 3.

The exposure assessment described above is frequently used but has some limitations. For instance, respirator use and the potential for skin exposure (which were not taken into account) may result in exposure misclassification. On the other hand, increased risk might be associated with peak exposure rather than continuous low-level exposure and may be confounded by the exposure to other carcinogens in the workplace.

In an effort to address the shortcomings of the exposure assessment, the use of respirators during tasks with a potential for peak exposure were documented. In addition to the assessment of the 8 hour TWA exposure to AN, an evaluation was made of the occurrence of peak exposures in the past. Peak exposures were defined as intervals with elevated exposure concentrations in ranges 0 to 10, 10 to 20, and 20 to 30 ppm, which occurred regularly on at least a weekly basis. An assessment of the occurrence of peak exposure could be made for all but one of the participating companies. Finally, an inventory was made of exposure to other agents considered to be potential human carcinogens by the International Agency for Research in Cancer.

Employment characteristics of the exposed cohort are given in Table 4. A dose was calculated for each exposed worker. A dose was defined as the sum of the products of the average concentration and the duration (in years) of that exposure. A worker exposed to an average concentration of 2 ppm for 3 years received a dose of 6 ppm-years. The arithmetic mean of

TABLE 3
Dummy Table Used for Exposure Assessment of the AN Study Company: no name
Department: production
Exposure jobclass: reaction operator

Year	Average Exposure to AN (ppm)				
	Based on Measurement	Assessment	Peak Concentrations	Respirator Use during Critical Tasks*	Exposure to Other 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	No	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

* Tasks with increased potential for exposure.

each exposure class was used for the calculation of the dose.

In some instances, an indication of exposure levels can be obtained from health effects that have been observed. No accurate health effects have been observed in the workers enrolled in this study. However, instances are known that AN could be smelled by the workers.

Ascertainment of Vital Status and Causes of Death

The Netherlands possess a system of municipal population registries. Each municipality keeps a card for all inhabitants of that municipality. If a person moves from one municipality to another, this card is forwarded to the new municipality, but a record is kept to indicate the person has moved.

This follow-up has been carried out without making any assumptions. A study subject is regarded as alive at the end of follow-up only if this is certified by the population registry. It is very unlikely that deaths are missed in the follow-up, because of the key role the population registries play. The tax system, the military draft system, and the voting system depend on the information in the files of the population registries. In a proportional mortality ratio study in progress, only 2 of 10,000 deaths could not be confirmed by the population registries.

These end points for the follow-up were defined: being alive at the end date of the follow-up, January 1, 1988; having emigrated to another country before the end date of the follow-up; having died before the end date of the follow-up; and being lost to follow-up in the study.

Table 5 shows a tabulation for the end points of follow-up for cohort members of the exposed and nonexposed cohorts.

If a person dies, a death certificate must be filed before burial or cremation. This death certificate receives an order number in the municipality in which death occurred. The death certificate is sent to the Central Bureau of Statistics (CBS) to enable the compilation of annual cause-specific mortality rates in The Netherlands. The causes of death together with the number of the death certificate given by the municipality are stored on a computer tape by the CBS. After special agreements have been made with the CBS to safeguard the privacy of the deceased and the companies under investigation, it is possible to link the exposure data to the causes of death. The matching criteria for this link were exact date of birth, death certificate number, month and year of death, and municipality in which the death certificate was filed. The CBS only provided the cause of death if all criteria mentioned above match. If not, the study group checked the information provided to the CBS. In some occasions clerical errors were traced. We are confident that the traced causes of death are accurate.

The causes of death were not provided on an individual basis because of legally required protection of privacy. However, access to the individual causes of death was given by the CBS, provided the data remained in the CBS building. The causes of death are not given on an individual level but for groups of 15 or more deaths.

The causes of death stated on the death certificate have been coded by a nosologist of the CBS according to the International Classification of Diseases (ICD) revision that was in use at the time of death. A conversion table was made to recode these to a new classification.

TABLE 4
Employment Characteristics of Cohort Exposed to Acrylonitrile

Variable	Number (Percent)
Duration of exposure (years)	
<1	192 (6.7)
1–5	1241 (43.7)
5–15	1288 (45.3)
≥15	121 (4.3)
Total	2842 (100.0)
Duration of follow-up, after 6 mo exposure (years)	
<5	50 (1.8)
5–10	118 (4.1)
10–20	1935 (68.1)
≥20	739 (26.0)
Total	2842 (100.0)
Cumulative dose (ppm × year)	
<1	488 (17.2)
1–10	1676 (59.0)
≥10	678 (23.8)
Total	2842 (100.0)

TABLE 5
Vital Status of Study Population at End of Follow-up

Vital Status	Exposed Group		Nonexposed Group	
	N	(Percent)	N	(Percent)
Total group	2842	(100.0)	3961	(100.0)
Alive at January 1, 1988	2605	(91.7)	3350	(84.6)
Deceased	134	(4.7)	572	(14.4)
Emigrated before 1988	94	(3.3)	39	(1.0)
Lost to follow-up	9	(0.3)	0	(0.0)
Total number of person years at risk*	47,101.0		98,197.9	

* After 6 months of employment.

Some causes of death could not be traced (see Table 6). These were included in the study for the calculation of the standard mortality ratio (SMR) for total mortality. However, for the calculation of cause-specific SMRs these were not included in the observed mortality, but the accumulated person-years were included for the calculation of the expected numbers of death. Most of the deaths for which no cause of death was available occurred outside The Netherlands, most likely during vacation. In this group, acute causes of death (such as automobile accidents, cardiac failure) are quite common.

If a person dies in another municipality than he/she has lived in, it is reported to the population registry in which the event occurred. This population registry will inform the population registry in which the person is registered.

Statistical Analysis

The first statistical analysis consisted of a person-time analysis. The person-years of observation were calculated of each cohort or subcohort specifically for age groups and calendar periods. These age- and period-specific person-years were multiplied by the background cause-specific mortality rates of the total Dutch male population. A summation of these using the PETO-program[16] gave an expected number of deaths by cause. Because one of the eligibility criteria of the study was a minimal duration of employment of a half year, the first 6 months after start of employment was not regarded as person-years *at risk*. However, the AN dose experienced in this half year was included in the calculation of the total AN dose and in the investigation of dose-response relationships. No direct standardizations were carried out between the exposed and nonexposed cohorts. It was preferred to use an indirect method of standardization by generating expected numbers of death for the exposed cohort as well as for the nonexposed cohort by applying the national cause-specific mortality rates to the age-specific person-years of follow-up generated by each cohort. This method was preferred over a direct method of standardization because the age-cause and period-specific mortality rates in the nonexposed group are less stable than those of the total male Dutch population.

No direct comparisons have been made between the exposed and nonexposed group. This was intentionally avoided because the age, calendar time, and cause-specific mortality rates of a cohort of 4000 persons are quite unstable and will have many empty cells. The difference in age distribution cannot have affected the results, because no direct comparisons between the exposed and nonexposed group have been made.

It can be argued that the test for trend proposed by Breslow and Day[17] is not appropriate. However, the data in each exposure group speak for themselves. There is no dose-effect relationship. We are confident that another test for trend will confirm this observation.

The SMR were calculated by dividing the observed number by the expected number and multiplying this ratio by 100. Confidence intervals of 95% were calculated according to the method proposed by Breslow and Day.[17] In the case of zero observed deaths, the Fisher exact test was applied.[18] These analyses were carried out for the total exposed and nonexposed groups. Next, several specific analyses were carried out. The exposed cohort was divided into several subgroups according to peak exposures, ever respirator use, and exposure to other carcinogens, respectively. Finally, a subanalysis was carried out to investigate the existence of dose-response relationship taking into account a specific latency period. Analysis of trends in SMRs was done according to the method proposed by Breslow and Day.[17]

Latency was defined as the period between entering a specific dose category to an observed event in terms of a mortality rate.

Results

The total mortality in the exposed as well as in the nonexposed cohorts was lower than expected. In the exposed group, 134 deaths were observed versus an expected number of

TABLE 6
Observed and Expected Numbers of Death for Seven Main Disease Categories, in Exposed and Nonexposed Study Population

Main Categories	Deaths in Group Exposed to AN*				Deaths in Group not Exposed to AN			
	Observed	Expected	SMR†	(95% CI‡)	Observed	Expected	SMR	(95% CI)
I. Infectious diseases	0	0.99	0	(0–373)	4	6.40	62	(20–160)
II. Neoplasms	42	50.82	83	(60–112)	176	230.48	76	(66–89)
III. Circulatory system	59	64.19	92	(70–119)	266	305.85	87	(77–98)
IV. Respiratory system	3	6.80	44	(11–129)	32	43.37	74	(51–99)
V. Digestive system	1	5.93	17	(0–94)	12	24.06	50	(27–85)
VI. Others	6	19.70	30	(13–663)	34	73.62	46	(23–63)
VII. External causes	15	24.36	62	(36–102)	34	56.70	60	(29–83)
Unknown	8				14			
Total	134	172.66	78	(65–92)	572	740.19	77	(71–84)

* AN = acrylonitrile.
† SMR = standardized mortality ratio.
‡ CI = confidence interval.

172.7 (SMR = 78, 95% CI: 65–92). This deficit in all cause-mortality is frequently observed in retrospective cohort studies and has been called the healthy worker effect (HWE). The HWE was observed in the exposed group as well as in the nonexposed group. In retrospective cohort studies the HWE can be artificially created because of an underascertainment of deaths. Underascertainment of deaths will occur if persons who have died are thought to be alive at the end date of follow-up. It is very unlikely to have happened in this study because the source of the follow-up (the population registries) is very accurate. The SMR for total mortality in the nonexposed group was 77 (95% CI: 71–84).

The lower mortality rates were observed for all seven main categories individually (see Table 6). In the scope of the results of previous epidemiologic mortality studies special attention was given to the investigation of lung cancer mortality in the exposed cohort. As can be seen in Table 6, the total cancer mortality in the AN exposed cohort was lower than expected. Forty two cancer deaths occurred in this cohort, compared with an expected number of 50.8, giving an SMR of 83 (95% CI: 60–112). In Table 7 the cancer mortality in the study population is presented according to the localization of the tumor. No significant differences were observed between the observed and expected numbers, for the exposed as well as for the nonexposed cohorts. In fact, the number of observed deaths from lung cancer in the cohort of AN exposed workers was lower than expected. In this cohort, 16 workers had died from lung cancer, compared with an expected number of 19.5 (SMR = 82, 95% CI: 47–133). Some caution should be taken in comparing SMRs from the exposed and nonexposed cohorts because the age-distributions are different.

As reported earlier, extensive exposure assessments were carried out for each specific exposure group in each specific department. These assessments were based on actual exposure measurements from the late 1970s. For earlier years, exposure was extrapolated and estimated in the form of a range. The midpoint of the range was used for the calculation of the dose.

For each exposed worker a dose was calculated by multiplying the concentration with the duration of the exposure giving a dose in terms of ppm-

TABLE 7
Cancer Mortality by Type in AN* Exposed and Nonexposed Cohorts

Cancer Type	AN Exposed Cohort				Nonexposed Cohort			
	Observed	Expected	SMR†	(95% CI‡)	Observed	Expected	SMR	(95% CI)
Mouth and pharynx	1	0.63	159	(0–884)	1	2.45	41	(0–227)
Esophagus	0	0.79	0	(0–467)	2	3.53	57	(6–205)
Stomach and small intestine	2	4.36	46	(5–166)	19	23.87	80	(48–124)
Large intestine	4	2.83	141	(38–362)	9	12.44	72	(33–137)
Rectum	2	1.43	140	(16–505)	9	7.03	128	(58–243)
Liver and biliary passages	1	0.96	104	(0–580)	1	4.32	23	(0–129)
Pancreas	2	2.38	84	(10–304)	8	10.46	76	(33–151)
Nose carcinoma	1	0.07	1429	(0–7959)	0	0.35	0	(0–1054)
Larynx	1	0.48	208	(0–1161)	1	2.11	47	(0–264)
Trachea and lung	16	19.50	82	(47–133)	67	93.31	72	(56–91)
Bone	0	0.27	0	(0–1366)	0	1.04	0	(0–355)
Connective tissue	0	0.31	0	(0–1190)	2	0.85	235	(26–849)
Skin	1	0.84	119	(0–662)	2	2.17	92	(10–333)
Kidney	1	1.47	68	(0–379)	7	5.83	120	(48–247)
Prostate	2	1.22	164	(18–592)	6	10.09	59	(22–129)
Genital organs	1	0.79	127	(0–705)	0	1.78	0	(0–207)
Bladder	0	1.25	0	(0–295)	7	6.97	100	(40–207)
Brain	3	1.71	175	(35–513)	6	5.17	116	(42–253)
Thyroid gland	0	0.16	0	(0–2306)	2	0.55	364	(41–1313)
Lymphatic glands	0	0.00	0		0	0.03	0	(0–12296)
Lymphoreticular sarcoma	0	0.73	0	(0–505)	1	2.51	40	(0–222)
Hodgkin's disease	0	1.05	0	(0–351)	0	2.72	0	(0–136)
Other lymphoma	0	0.60	0	(0–615)	1	1.91	52	(0–291)
Multiple myeloma	1	0.64	156	(0–871)	2	3.01	66	(7–240)
Leukemia	1	1.87	53	(0–298)	7	7.00	100	(40–206)
Benign neoplasms	1	0.31	323	(0–1797)	2	1.13	177	(20–639)
Not specified neoplasms	1	2.33	43	(0–239)	12	10.04	119	(62–209)
Others	0	0.83	0	(0–444)	2	3.04	66	(7–237)
Total neoplasms	42	50.82	83	(60–112)	176	230.48	76	(65–88)

* AN = acrylonitrile.
† SMR = standardized mortality ratio.
‡ CI = confidence interval.

years. The person-years of observation of the exposed workers were divided over three dose groups; below 1 ppm-year, between 1 and 10 ppm-years, and over 10 ppm-years. Next, each exposure group was divided into three groups according to the latency period. Three latency periods were used, less than 10 years, between 10 and 20 years, and 20 years or more. For each separate dose group, expected numbers of death were calculated and compared with the observed frequencies. These figures are given in Table 8.

There appears to be a statistically nonsignificant increase in lung cancer mortality with increasing dose and with increasing latency in the highest dose group. However, the SMR for lung cancer in the highest groups are not significantly different from 100 or even from the total SMR of 77. This is supported by the fact that the same trend is seen in total mortality. Therefore, it is more likely this increase in lung cancer mortality is an effect of the fading out of the HWE than of an actual increased risk for lung cancer.

Next, the exposed-workers data were divided according to the maximum peak exposures ever experienced. The SMRs for total mortality and lung cancer mortality are displayed in Table 9. Both SMRs do not vary significantly from 100 in any of the specific peak exposure groups.

In addition to estimates regarding the magnitude of exposure, data were

TABLE 8
Total Mortality and Mortality from Lung Cancer in Workers Exposed to Acrylonitrile in Three Dose Groups and Three Latency Periods

Dose	Total Mortality					Lung Cancer Mortality				
	Observed	Expected	SMR*	(95% CI†)	P‡	Observed	Expected	SMR	(95% CI)	P
Low (<1 ppm/year)										
<10	7	17.1	41	(16–84)		1	1.3	77	(1–428)	
10 to 20	10	8.1	123	(59–227)		0	1.0	0	(0–370)	
≥20	0	0.3	0	(0–1230)		0	0.1	0	(0–3689)	
Total	17	25.5	67	(39–107)		1	2.4	42	(0–232)	
Moderate (1 to 10 ppm/year)										
<10	33	51.8	64	(44–89)		0	4.7	0	(0–78)	
10 to 20	32	35.7	90	(61–126)		7	4.5	156	(62–320)	
≥20	7	5.2	135	(54–277)	.04	0	0.8	0	(0–461)	
Total	72	92.7	78	(61–98)		7	10.0	70	(28–144)	
High (10^+ ppm/year)										
<10	20	28.2	71	(43–109)		3	3.4	88	(18–258)	
10 to 20	21	22.7	93	(57–141)		4	3.2	125	(34–320)	
≥20	4	3.6	111	(30–284)	.30	1	0.6	167	(2–927)	.54
Total	45	54.5	83	(60–110)	.47§	8	7.2	111	(48–219)	.25§

* SMR = standardized mortality ratio.
† CI = confidence interval.
‡ *P* = trend in latency period. (*P* for trend calculated only if observed >0).
§ *P* = trend in cumulative dose.

TABLE 9
Total Mortality and Lung Cancer Mortality by Past Exposure to Peaks of Acrylonitrile, Respirator Use, and Exposure to Other Carcinogens

Subgroups	Number of Workers	Total Mortality				Lung Cancer Mortality			
		Observed	Expected	SMR*	(95% CI†)	Observed	Expected	SMR	(95% CI)
No peaks	745	46	52.6	87	(64–117)	7	6.0	116	(47–240)
Peaks <10 ppm	1144	41	61.1	67	(48–91)	4	6.7	59	(16–153)
Peaks >10, <20 ppm	731	36	48.6	74	(52–103)	4	5.7	70	(19–180)
Peaks 20^+ ppm	222	11	10.2	108	(54–193)	1	1.0	98	(1–545)
Respirator use									
Yes	566	24	32.3	74	(48–111)	1	3.7	27	(0–150)
No	2276	110	140.5	78	(64–94)	15	15.7	95	(53–158)
Exposure to other carcinogens									
Yes	1208	60	77.1	78	(59–100)	7	9.2	76	(30–157)
No	1634	74	95.6	77	(61–97)	9	10.3	87	(40–166)

* SMR = standardized mortality ratio.
† CI = confidence interval.