ORIGINAL ARTICLE

Mortality study update of acrylamide workers

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Objective: The authors examined the long-term health effects of occupational exposure to acrylamide among production and polymerisation workers.

Methods: An earlier study of 371 acrylamide workers was expanded to include employees hired since 1979. In this updated study, 696 acrylamide workers were followed from 1955 through 2001 to ascertain vital status and cause of death. Exposure to acrylamide was retrospectively assessed based on personal samples from the 1970s onwards and area samples over the whole study period.

Results: Fewer of the acrylamide workers died (n = 141) compared to an expected number of 172.1 (SMR 81.9, 95% CI 69.0 to 96.6). No cause-specific SMR for any of the investigated types of cancer was exposure related. The authors did, however, find more pancreatic cancer deaths than expected (SMR 222.2, 95% CI 72.1 to 518.5). With respect to non-malignant disease, more diabetes deaths were observed than expected (SMR 288.7, 95% CI 138.4 to 531.0). To assess the influence of regional factors, the analysis was repeated with an internal reference population. The elevated SMR for diabetes persisted.

Conclusion: This study provides little evidence for a cancer risk from occupational exposure to acrylamide at production facilities. However, the increased rates of pancreatic cancer in this study and another larger study of acrylamide production workers indicate that caution is needed to rule out a cancer risk. The authors believe that the excess of diabetes mortality in this study is most likely not related to acrylamide exposure, because a larger study of acrylamide workers reported a deficit in this cause of death. The authors conclude that the increased SMR for diabetes mortality is probably not related to regional influences.

Acrylamide is a crystalline solid material used as an intermediate and monomer in the production of polyacrylamides. These water soluble polyacrylamides are primarily used in the mining, wastewater, paper and oil industry or as a feedstock for the production of other materials.

Acrylamide is biotransformed to its epoxide, which has been reported to be genotoxic in several test systems.[11] Oral administration of acrylamide increases tumour rates in rats.[3 7] In 1994, the International Agency for Research on Cancer classified acrylamide as a probable human carcinogen based largely on these animal studies.[6]

Epidemiological data on the potential long-term health aspects of acrylamide are limited. Only two groups of employees involved in acrylamide production and use have been studied. First, Sobel and colleagues conducted a retrospective cohort mortality study of 371 acrylamide employees employed between 1955 and 1979.[15] In these facilities acrylamide monomer was produced since 1955 and polymer since 1965. Personal air samples taken since 1958 ranged from 0.1 to 1 mg/m^3 of monomer, in the form of daily time-weighted averages, and indicated a decrease in exposure over time. After 1970 all air samples taken were below 0.1 mg/m^3. There was also potential for exposure to acrylonitrile in the monomer production area, as acrylonitrile is the raw material for acrylamide production. A part of the cohort was also potentially exposed to organic dyes.

The 371 employees employed at one of the facilities for acrylamide production were identified from personnel census lists. They were followed for mortality until 31 December 1982. Twenty nine employees had died compared to 38.0 expected (standardised mortality ratio (SMR) 76, 95% CI 51 to 110). The SMR for cancer mortality was 139 (95% CI 70 to 249). The authors concluded that the study did not support a cause effect relation between exposure to acrylamide and overall mortality, all cancer mortality or any specific cancers.

The second and larger study of acrylamide workers was done by Collins *et al* and consisted of 8854 employees hired between January 1925 and January 1973 of which 2293 were acrylamide employees.[1] Exposure estimates for all jobs and plants were developed based on industrial hygiene measurements when available. The cohort was followed for mortality from 1950 to 1983. Analysis by exposure levels showed no trend of increased risk of mortality from any cancer sites. The authors concluded that the results did not support the hypothesis that acrylamide is a human carcinogen. Later, this cohort study was updated by Marsh and colleagues, except for the Dutch subcohort.[9] The follow-up period was expanded through 1994 and 1115 deaths and nearly 60 000 person-years of observation were added. Again, the authors concluded that the study found little evidence for a causal association with potential exposure to acrylamide, although they reported a statistically significant excess of pancreatic cancer mortality in employees with over 0.3 mg/m^3 years of cumulative exposure. The excess of pancreatic cancer mortality was thought not to be related to acrylamide exposure. Later, in a letter to the editor it was reported that if the two middle out of four exposure groups were combined a monotonically increase of pancreatic cancer with cumulative exposure emerged.[13]

Recently there has been much controversy about acrylamide in food and its carcinogenic potential. In April 2002, Swedish scientists sounded an alarm after having detected levels of acrylamide in certain cooked foods, particularly in potato chips and French fries.[10 12] The Norwegian Food Agency has estimated the mean daily intake at 38 μg for males and at 29 μg for females.[2] There was concern about the carcinogenic potential, and the World Health Organization advised

Abbreviations: ESS, Epidemiological Surveillance System; SMR, standardised mortality ratio

minimising the consumption of certain foods because of their (albeit low) acrylamide concentrations.

In 2005 Rice reviewed the available human and experimental data on the carcinogenicity of acrylamide and concluded that no statistically significantly exposure-related increased risk for cancer at any organ site was consistently associated with exposure to acrylamide, except that a doubling of the risk for pancreatic cancer was found for employees with highest cumulative exposure in the study conducted by Marsh.[8]

In summary, there is evidence from experimental chronic toxicity studies that acrylamide may have carcinogenic potential, but epidemiology studies to date have reported no increased cancer mortality risks related to acrylamide levels, other than pancreatic cancer. We update an earlier study with additional vital status follow-up and add extra workers to examine the cancer rates among acrylamide workers.[15] The aim of the study is to provide further information on the potential long-term health effects of acrylamide in humans.

MATERIAL AND METHODS

The study presented here is a retrospective cohort mortality study. Cohort identification was done by means of the Epidemiological Surveillance System (ESS). Dow maintains the ESS for all major manufacturing sites in North America. In the ESS data including personal identifiers, job history, vital status and cause of death are stored and periodically updated. It currently contains this information for over 180 000 past and current Dow employees and its most recent vital status update has been done through 2001. We used the ESS to compile the acrylamide cohort. All 371 employees in the initial study by Sobel were included in this update except two, for whom employment in an acrylamide facility was not confirmed by their job history in the ESS. In addition 327 employees were identified whose job history indicated that they had worked in an acrylamide facility between 1955 and 1979, or who were identified as having worked in an acrylamide facility between 1979 and 1997. This new cohort identification process, completely independent of the earlier cohort study, resulted in a cohort of 696 employees with documented employment in an acrylamide facility of at least four days. Employees who have worked for three days or less are not included in the ESS. For each employee a job history and department history was available up to 1997. Exposure after this date could not be taken into account because the job histories of the employees who were still involved in acrylamide production were not yet included in the ESS. This may have led to a marginal underestimation of exposure for a small group of employees. In short, vital status follow-up has been determined by company records and searches of the US National Death Index, Social Security Administration, and the internet. Death certificates were obtained where possible and all coded to the International Classification of Diseases version at the time of death by a trained nosologist or National Death Index.

The basic characteristics of the cohort are given in table 1. Follow-up and ascertainment of the causes of death for deceased workers were routinely done as an integrated part of the ESS and was already available for analysis. End date of follow-up used in this study was 31 December 2001, which adds 19 years of follow-up to the original study.

Table 1 Distribution of basic characteristics of the acrylamide cohort

Characteristic	n (%)
Employees first employed in acrylamide	
1950–9	87 (12.5)
1960–9	190 (27.3)
1970–9	227 (32.6)
1980–9	170 (24.4)
1990 onwards	22 (3.2)
Race and sex distribution	
Males	655 (94.1)
Females	41 (5.9)
White	651 (93.5)
Non-white	45 (6.5)
Duration of employment	
<10 years	99 (14.2)
10–19.9 years	93 (13.4)
20–29.9 years	227 (32.6)
⩾30 years	277 (39.8)
Duration of follow-up since hire date	
<10 years	3 (0.4)
10–19.9 years	36 (5.2)
20–29.9 years	187 (26.9)
30–39.9 years	253 (36.4)
⩾40 years	217 (31.2)
Vital status as of 31 December 2001	
Alive	555 (79.7)
Deceased	141 (20.3)
Lost to follow-up	0 (0)

EXPOSURE CHARACTERISATION

Acrylamide production at Dow Midland began in 1955 at a pilot plant. The monomer was made in a continuous process, from acrylonitrile, which was hydrolysed in the presence of a catalyst. The monomer was used to make poly- acrylamides, including Separan. The Separan plant was closed in 2001.

Exposure data between 1958 and 1989 were available as personal air samples in the form of 8-hour time-weighted average concentrations (n = 71) and 8-hour time-weighted average area samples (n = 357). These samples were taken primarily via two methods. Before 1981, air samples were collected by pulling air through two fritted absorbers or impingers (in series) containing approximately 15 ml of water. Water samples were then analysed for acrylamide via ultraviolet spectroscopy, or pulse polarography and liquid chromatography. After 1980, air samples were collected by pulling air through 1 g silica gel tubes. Acrylamide was desorbed from the silica gel and then analysed with high performance liquid chromatography with ultraviolet detection. Exposure data after 1989 are more limited, because the acrylamide exposures were regarded as so low that constant monitoring was given less priority compared with other exposures such as acrylonitrile.

Statistical analysis of the samples indicated that there was a downward trend in both area concentrations and exposure concentrations over time. Analysis of the area concentration data showed that there were two distinct exposure periods: before 1970 and after 1970. After 1970, an increased emphasis on controlling air emissions and general housekeeping resulting in a reduction of the area acrylamide air concentrations by approximately 75%.

Exposure profiles were then created for two broad job groupings: Operations and Maintenance/Administration. The Maintenance/Administration jobs were grouped together because there was no statistical difference in their exposures. This was not totally unexpected as the Dow practice is to clear equipment before opening it for maintenance work, so the Maintenance jobs had less chance for exposure than the Operations jobs.

After 1970, the analysis indicated that personal exposures for employees in the Operations profile were about 100% higher than for employees in the Administration/Maintenance profiles. Personal exposures for the time period before 1970 were made by using the area concentration data as a sentinel. The Operations exposure profile was approximately 50% of the area

Table 2 Acrylamide exposure matrix developed to describe the exposure concentrations, changes over time and differences between Operations and Non-Operations

Area	1958–70	1970–89
Operations	0.25 mg/m^3	0.05 mg/m^3
Administration/ Maintenance	0.125 mg/m^3	0.02 mg/m^3

data, and the Maintenance/Administration exposure profile was approximately 15% of the Operations profile.

Based on the available sampling data, a simple exposure matrix was constructed that was thought to accurately describe the trends in exposure conditions for the acrylamide plants (table 2). The exposure matrix formed the basis for the calculation of past cumulative exposure for each individual in the study, necessary to analyse exposure-response relationships. For each employee a cumulative exposure score was calculated by multiplying the appropriate exposure concentration (table 2) with the duration of exposure expressed in months of employment. The resulting unit of cumulative exposure is therefore expressed in mg/m^3 months. The mean cumulative exposure for the whole cohort was 4.6 mg/m^3 months. Mean duration of employment in an acrylamide job was 42 months.

STATISTICAL ANALYSIS

Standardised mortality ratios were calculated using OCMAP.[9] Accumulation of person-years at risk started from the first employment date at an acrylamide facility. SMRs were calculated based on cause-specific US rates, separately for males and females in order to adjust for differences in age, sex, time interval and duration of follow-up. Exact Poisson distribution probabilities were used to calculate the 95% confidence intervals. SMRs were calculated for the total cohort and then stratified for cumulative exposure, duration of follow-up, and a 20-year exposure lag. The cut-off point for the stratified analysis for cumulative exposure was chosen in such a way that the expected number of deaths in the two strata for all cancers combined would be similar.

RESULTS

The total acrylamide cohort consisted of 696 employees. Before the end date of follow-up 141 (20.3%) employees were deceased, compared to an expected number of 172.1 (95% CI 69.0 to 96.6) (table 3). The total number of cancer deaths was also lower than expected. There were 43 cancer deaths, compared to an expected number of 45.4 (SMR 94.8, 95% CI 68.6 to 127.7). Although the observed 17 deaths from cancer of the digestive organs and peritoneum were higher than the expected number of 10.9, this number did not reach statistical significance (SMR 155.5, 95% CI 90.6 to 249.0). There were five observed deaths from pancreatic cancer compared to an expected number of 2.3 (95% CI 72.1 to 518.5). None of the SMRs for specific types of cancer mortality reached statistical significance. For the non-malignant diseases 10 deaths attributed to diabetes mellitus were observed compared to an expected number of 3.5. This number of 10 observed deaths was statistically significantly different from the expected number (SMR 288.7, 95% CI 138.4 to 531.0)

Next we divided the total cohort into two subcohorts based on the individual's cumulative exposure. As the cohort size was limited we preferred to use only two cumulative exposure categories with a similar number of expected deaths in each exposure group (table 4). This analysis did not reveal any statistically significant evidence for an exposure-response relation. Three out of the five deaths from pancreatic cancer occurred in the low exposure group (SMR 319.0, 95% CI 65.8 to 932.2). The SMR for pancreatic cancer in the higher cumulative exposure group was 152.7 (95% CI 18.5 to 551.7). The SMRs for

Table 3 Observed and expected numbers of death in 696 acrylamide employees in the total cohort

Cause of death	Obs	Exp	SMR (95% CI)
All causes	141	172.1	81.9 (69.0–96.6)
All malignant neoplasms	43	45.4	94.8 (68.6–127.7)
Buccal cavity and pharynx	1	1.1	90.1 (2.3–502.2)
Digestive organs and peritoneum	17	10.9	155.5 (90.6–249.0)
Oesophagus	0	1.3	– (0.0–275.8)
Stomach	1	1.4	73.1 (1.8–407.5)
Large intestine	7	3.7	187.5 (75.4–386.3)
Rectum	2	0.8	242.6 (29.4–876.5)
Biliary passages and liver	1	1.1	89.4 (2.2–498.3)
Pancreas	5	2.3	222.2 (72.1–518.5)
All other digestive organs	1	0.3	333.0 (8.3–1855.2)
Respiratory system	12	17.0	70.5 (36.4–123.2)
Bronchus, trachea, lung	12	16.3	73.7 (38.1–128.7)
Prostate	1	3.0	33.7 (0.8–187.8)
Kidney	3	1.2	245.3 (50.6–716.9)
Bladder or other urinary organs	1	1.0	96.5 (2.4–538.0)
Malignant melanoma	1	0.9	114.1 (2.9–635.9)
Central nervous system	0	1.4	– (0.0–264.8)
Thyroid and other endocrine glands	1	0.1	719.4 (18.0–4008.3)
Bone	0	0.1	– (0.0–3293.8)
All lymphatic and haematopoetic	4	4.5	89.8 (24.5–230.0)
Non-malignant diseases			
Diabetes mellitus	10	3.5	288.7 (138.4–531.0)
Cerebrovascular disease	5	7.7	65.3 (21.2–152.30
Heart disease	54	58.9	91.8 (68.9–119.7)
Non-malignant respiratory disease	6	12.2	49.2 (18.1–107.1)
All external causes	10	17.3	57.7 (27.7–106.1)
Unknown causes	2		

Table 4 Observed and expected numbers of death in the low and high cumulative exposure groups of 696 acrylamide employees, with a cut-off point of 1 mg/m^3 months

	Below 1 mg/m^3 months		Over 1 mg/m^3 months	
Cause of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	62	86.2 (66.1 to 110.4)	79	78.9 (62.5 to 98.3)
All malignant neoplasms	20	104.5 (63.8 to 161.4)	23	87.7 (55.6 to 131.6)
Digestive organs, peritoneum	9	198.0 (90.5 to 375.8)	8	125.3 (54.1 to 246.9)
Oesophagus	0	to (0.0 to 623.8)	0	to (0.0 to 494.4)
Stomach	0	to (0.0 to 669.9)	1	122.5 (3.1 to 682.3)
Large intestine	3	197.8 (40.8 to 578.1)	4	180.4 (49.2 to 461.9)
Rectum	2	607.8 (73.5 to 2195.6)	0	to (0.0 to 744.9)
Biliary passages and liver	0	to (0.0 to 744.0)	1	160.7 (4.0 to 895.1)
Pancreas	3	319.0 (65.8 to 932.2)	2	152.7 (18.5 to 551.7)
All other digestive organs	1	818.3 (20.5 to 4559.4)	0	to (0.0 to 2071.1)
Respiratory system	5	69.5 (22.6 to 162.2)	7	71.2 (28.6 to 146.7)
Bronchus, trachea, lung	5	72.6 (23.6 to 169.5)	7	74.4 (29.9 to 153.3)
Prostate	0	to (0.0 to 360.5)	1	51.5 (1.3 to 286.7)
Kidney	0	to (0.0 to 692.8)	3	434.6 (89.7 to 1270.0)
Bladder or other urinary organs	0	to (0.0 to 960.0)	1	153.5 (3.8 to 855.3)
Central nervous system	0	to (0.0 to 569.0)	0	to (0.0 to 495.3)
Thyroid and other endocrine glands	1	1625.5 (40.6 to 9057.2)	0	to (0.0 to 4760.6)
Lymphatic and haematopoetic	3	155.2 (32.0 to 453.5)	1	39.7 (1.0 to 221.1)
Non-malignant diseases				
Diabetes mellitus	4	266.2 (72.6 to 681.7)	6	305.9 (112.3 to 665.8)
Cerebrovascular disease	2	72.9 (8.8 to 263.2)	3	61.0 (12.6 to 178.4)
Heart disease	21	92.5 (57.3 to 141.4)	33	91.3 (62.8 to 128.2)
Non-malignant respiratory disease	3	65.9 (13.6 to 192.5)	3	39.3 (8.1 to 114.7)
All external causes	7	76.5 (30.7 to 157.6)	3	36.7 (7.6 to 107.1)

12 mg/m^3 months equal to 1 mg/m^3 years.

diabetes mellitus were comparable in the two cumulative exposure groups.

All person-years of observation and observed deaths were divided by latency since first hire at an AMD facility (table 5). Again, because of the relatively small cohort size only two subcohorts were made—one subcohort with less than 20 years of latency and the other with over 20 years of latency. No differences between the two subcohorts were noted except that the excess of diabetes mellitus mortality was higher in the over 20 years of latency subcohort. In the stratum of over 20 years of latency the SMR for diabetes mortality was 433.1 (95% CI 198.0 to 822.2).

The increased SMR for diabetes mortality was an unexpected finding and, because to our knowledge no association between acrylamide and diabetes has ever been reported before in the scientific literature, we conducted further analyses to better understand the increase. One alternative explanation for the excess of diabetes mortality is a possible difference in coding practices between the in-house nosologists and US nosologists. Diabetes can be mentioned on the death certificate either as

Table 5 Observed and expected numbers of death with less than or more than 20 years of latency since hire at an acrylamide facility

	Less than 20 years latency		Over 20 years latency	
Cause of death	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
All causes	55	67.3 (50.7 to 87.6)	86	95.1 (76.1 to 117.5)
All malignant neoplasms	16	83.6 (47.8 to 135.8)	27	102.9 (67.8 to 149.8)
Digestive organs, peritoneum	8	172.9 (74.6 to 340.7)	9	142.7 (65.3 to 271.0)
Oesophagus	0	to (0.0 to 696.7)	0	to (0.0 to 456.6)
Stomach	1	152.1 (3.8 to 847.7)	0	to (0.0 to 519.6)
Large intestine	3	194.8 (40.2 to 569.3)	4	182.3 (49.7 to 466.8)
Rectum	2	513.2 (62.1 to 1854.0)	0	to (0.0 to 848.7)
Biliary passages and liver	0	to (0.0 to 879.5)	1	143.1 (3.6 to 797.3)
Pancreas	2	210.2 (25.4 to 759.3)	3	231.0 (47.7 to 675.1)
All other digestive organs	0	to (0.0 to 2640.1)	1	622.7 (15.6 to 3469.5)
Respiratory system	4	56.5 (15.4 to 144.7)	8	80.4 (34.7 to 158.5)
Bronchus, trachea, lung	4	59.4 (16.2 to 152.0)	8	83.7 (36.2 to 165.0)
Prostate	1	115.1 (2.9 to 641.2)	0	to (0.0 to 175.9)
Kidney	0	to (0.0 to 712.7)	3	425.4 (87.8 to 1243.2)
Bladder or other urinary organs	1	261.9 (6.5 to 1459.5)	0	to (0.0 to 564.1)
Central nervous system	0	to (0.0 to 517.7)	0	to (0.0 to 542.0)
Thyroid and other endocrine glands	0	to (0.0 to 5398.0)	1	1414.8 (35.4 to 7883.4)
Lymphatic and haematopoetic	1	50.1 (1.3 to 279.2)	3	122.1 (25.2 to 356.7)
Non-malignant diseases				
Diabetes mellitus	1	72.2 (1.8 to 402.1)	9	433.1 (198.0 to 822.2)
Cerebrovascular disease	2	59.7 (7.2 to 215.5)	3	69.7 (14.4 to 203.6)
Heart disease	20	73.0 (44.6 to 112.7)	34	108.1 (74.9 to 151.1)
Non-malignant respiratory disease	2	45.3 (5.5 to 163.6)	4	51.4 (14.0 to 131.7)
All external causes	7	55.7 (22.4 to 114.8)	3	62.9 (13.0 to 183.8)

underlying cause or contributory cause. Coding practices prescribe that if the underlying cause is a likely complication of diabetes—for example, heart disease or renal failure—the death certificate must be coded as a diabetes death. Differences in coding practices would not confound an internal comparison. Another alternative explanation is related to lifestyle with regional patterns. As obesity, lack of physical activity and smoking are risk factors for diabetes, it is conceivable that the acrylamide coworkers may share lifestyle-related risk factors. The internal comparison group consisted of all Midland Operations employees employed between 1 January 1955 and 31 December 1997, excluding employees of Company Headquarters and employees already included in the acrylamide cohort. These restriction criteria resulted in an internal comparison cohort of 35 004 employees. The Maentel–Haenszel procedure was used to compare age, sex and time specific diabetes mortality rates between the internal comparison group and the acrylamide cohort. This analysis resulted in a relative risk of 5.01 (95% CI 2.77 to 9.03) indicating that the excess was not likely to be a result of regional differences. As data on known risk factors for diabetes, such as smoking, diet, obesity and low physical exercise, were unavailable it was not possible to adjust for these factors.

DISCUSSION

Acrylamide in experimental studies is genotoxic and increases tumours in several sites. These properties of acrylamide warrant extensive investigation of potential effects in humans involved in its production. So far, there are only two epidemiological studies that have evaluated the potential long-term health effects of acrylamide in humans involved in its production.

We have updated and expanded the earlier study conducted by Sobel *et al*.[15] Although the sample size of the study was expanded from 371 to 696 subjects, the statistical power of the study still remains small and the findings should be interpreted in the light of this. The results of this study on 696 acrylamide employees confirm earlier results by Sobel and from other studies that there is no excess in terms of all-cause mortality, or site-specific cancer mortality in employees involved in acrylamide production. Our study and the larger study by Marsh *et al* found no increase in cancer related to acrylamide exposure. However, both the Marsh study and our study found increased rates of pancreatic cancer in the study groups overall, although not related to acrylamide exposure level. In our study, five deaths from pancreatic cancer were observed versus two expected. This excess in the SMR was less prominent in the higher cumulative exposure group and no exposure-response gradient was found. Additionally, there was no relation with latency. The study of Marsh *et al* also reported an increased SMR for pancreatic cancer, based on 14 observed and 7.8 expected deaths. As in our study, this finding was not related to acrylamide exposure level.

The findings of increased SMRs for pancreatic cancer in both studies could have several causes. Firstly, this could be a chance finding—although an increased rate in both studies makes this somewhat less likely. Secondly, pancreatic cancer rates have been related to quality and conventions of medical care and high autopsy rates. The increased rates in both studies could be a result of diagnostic bias because employed workers might have better diagnostics than the general population. Thirdly, the increased rates could be a result of acrylamide exposure. The lack of an exposure-response relation with cumulative exposure to acrylamide argues against this possibility. Only an extensive exposure misclassification could have resulted in the finding of no exposure-response relation had there been a real exposure response association and, at least in our study, this seems unlikely. A fourth possible explanation for the excess of pancreatic cancer could be the observed excess of diabetes mellitus mortality. Other studies have found an approximately twofold risk for pancreatic cancer in diabetics.[5] The excess of diabetes mellitus in the acrylamide cohort could therefore have contributed to the pancreatic cancer excess. Given the lack of control for smoking, the possible influence of the increased diabetes mortality and the uncertainty resulting from the small numbers of cases, the SMR for pancreatic cancer remains difficult to interpret.

The SMR for diabetes mortality of 288.7 was an unexpected finding. We conducted additional analyses in which the mortality rates for diabetes in the acrylamide cohort were compared to other workers at the same site who did not have acrylamide exposures. Using an internal comparison group, the increased rates of diabetes mortality persisted, indicating that differences in coding practices and regional lifestyles are unlikely causes for this finding. In the earlier acrylamide cohort study conducted in this facility, no death from diabetes was found but the expected numbers were small.[15] The Marsh *et al* study did report SMRs specific for diabetes mortality on the total cohort 8508 employees of which 2004 employees were regarded as exposed to acrylamide.[8] The SMR for diabetes for the total cohort and the 1925–94 time period was 66 (95% CI 47 to 89, based on 41 observed deaths). No SMRs for diabetes mortality were given in the publication for the exposed group of 2004 employees only. It is therefore not possible to directly compare the results of the study described here with the results of the only other epidemiology study on acrylamide employees. However, given the low rates of diabetes mortality in the whole study group of Marsh *et al*,[8] it is unlikely that an excess for diabetes mortality in the acrylamide exposed group would occur. The internal analysis provided the opportunity to compare the observed increase in diabetes mortality in the acrylamide cohort with a large worker cohort not involved in acrylamide production, from the same geographical area and also employed by Dow, in the same timeframe as the acrylamide cohort. In this internal analysis the excess of diabetes mortality persisted. Unfortunately data were unavailable on other risk factors for diabetes such as body mass index, physical activity and smoking and therefore it remains difficult to assess the potentially confounding effect of these factors on the study findings. A high prevalence of smoking in the acrylamide cohort is not likely, given the observed deficits in lung cancer mortality and non-malignant respiratory disease mortality.

Diabetes mellitus is a group of metabolic diseases with the common feature of elevated blood glucose levels resulting from defects in insulin secretion.[14] Type II diabetes is the predominant form, accounting for 90%–95% of all cases. Obesity and physical activity and to a lesser extent smoking have been found to be substantial risk factors for diabetes. A body mass index of 35 kg/m^2 or greater, for instance, was reported to have a relative risk of 38.8 for diabetes.[4] Physical activity and smoking have also been consistently found to be risk factors for diabetes, but not as strong as obesity and it was concluded that a healthy diet, regular physical activity, maintenance of a healthy weight, moderate alcohol consumption and smoking could nearly eliminate Type II diabetes.[14] Given these rather prevalent risk factors it is possible that small differences in the distribution of these factors between the acrylamide cohort and the reference group could readily explain the noted increase in diabetes mortality. Together with the lack of an excess in the other acrylamide cohort we believe that it is unlikely that the statistically significantly elevated SMR for diabetes mortality is related to acrylamide exposure, because there was no exposure-response relationship with cumulative acrylamide exposure.

In summary we conclude that this updated cohort mortality study of acrylamide employees does not indicate that these

Main messages

- This expanded update of 696 acrylamide production workers does not show an association with cancer mortality.
- The excess of diabetes mortality is thought not to be related to acrylamide but to some non-occupational related factors.

Policy implications

- Updating historical cohort mortality studies is an important tool in the assessment of long-term health effects from chemicals.

employees are at an increased risk for cancer mortality or death from other diseases resulting from exposure to acrylamide.

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