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Acrylamide cohort mortality study

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ABSTRACT The mortality experience of 371 employees assigned to acrylamide monomer and polymerisation operations was examined with particular emphasis on cancers at sites identified from animal studies such as the central nervous system, thyroid gland, other endocrine glands, and mesotheliomas. A total of 29 deaths was observed up until 1982 (38·0 expected). No statistically significant excesses were noted in the total cohort and no deaths were found for the hypothesised sites of cancer. The observed deaths in the total cohort for the all cancers category were somewhat in excess (11 *v* 7·9); however, this was due entirely to excess cancers of the digestive tract and respiratory system in the subgroup with previous exposure to organic dyes. Among those employees not exposed to organic dyes, four deaths were due to malignancies versus 6·5 expected. This study does not support a cause effect relation between exposure to acrylamide at this work site and overall mortality, total malignant neoplasms, or any specific cancers.

Acrylamide is a white crystalline solid which is important as a chemical intermediate and as a monomer used in the production of polyacrylamides. The effects of exposure to acrylamide have been reported to include peeling and redness of the skin of the hands, localised numbness of the legs, excessive sweating of the feet and hands, and both central and peripheral nervous system damage.[1] Epidemiological studies of employees exposed to acrylamide have not been published to date.

The chronic effects of acrylamide in rats have been investigated in a two year toxicity-oncogenicity study.[2] Fischer 344 rats were divided into groups of 90 rats by sex and dose level and given water formulated to provide 0. 0·01, 0·1, 0·5, and 2·0 mg/kg/day of acrylamide. Histopathological examination indicated that in the female rats at the highest dose level there was a statistically significant increase in the number of neoplasms of the mammary gland, nervous system, clitoral gland, uterus, oral cavity, and thyroid gland. Data from male rats indicated an increased incidence of mesothelioma in the scrotal cavity at dosages of 0·5 and 2·0 mg/kg/day. The incidence of benign tumours of the thyroid gland was also statistically increased at doses of 2·0 mg/kg/day. Although not statistically significant, there appeared to be an increased incidence of tumours in the brain and spinal cord at the highest level in the male rats.[2]

Acrylamide has been reported to be capable of acting as a tumour initiator in the skin of the female Sencar Mouse by three exposure routes.[3] In addition, the chemical was found to increase the yield of lung adenomas in the Strain A/S mouse using both the oral and intraperitoneal routes of administration.[3]

The present study examines the mortality experience of employees with past potential exposure to acylamide during its production at the Michigan Division of the Dow Chemical Company. The cohort consists of employees assigned to acrylamide monomer and polymerisation operations. Particular emphasis was given to cancers of those sites observed in the animal studies, specifically, malignant neoplasms of the central nervous system, thyroid gland, other endocrine glands, and mesotheliomas.

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Environmental considerations

The potential for exposure to acrylamide at the Michigan Division derived primarily from the production of the monomer and the polymer. The earliest commercial scale acrylamide monomer process began in the Michigan Division in 1955. Three pilot plants were in operation for short periods during the late 1950s and 1960s and the first polymer plant began operations in 1965. A continuous process was used for the production of acrylamide monomer in which acrylonitrile was hydrolysed with excess water to acrylamide in the presence of catalyst. The acrylamide solution produced was polymerised in one reaction step using various catalysts.

The industrial hygiene air monitoring data for acrylamide were reviewed before conducting the study. A categorisation of exposure was developed based on a review of the job classifications. The personal eight hour time weighted average (TWA) con-

centrations of acrylamide have decreased over time due to several process improvements. Before 1957, the personal TWA exposures to acrylamide in the monomer production areas ranged from 0·1 to 1·0 mg/m^3. The data from 1957 to 1970 indicate exposures between 0·1 and 0·6 mg/m^3, and after 1970 personal TWA exposures to acrylamide were $<0·1$ mg/m^3 for all the job classifications.

Associated with the manufacture and processing of acrylamide and polyacrylamide was the potential for exposure to acrylonitrile in the monomer production area and the potential for exposure to residual acrylamide in polyacrylamide dusts in the polymer production area. The acrylonitrile concentration and job evaluation data showed that before process improvements in 1973 the monomer operator job classification had the greatest potential for acrylonitrile exposure (< 10 ppm TWA). After the process improvements, however, all job classifications had estimated acrylonitrile TWA exposures of < 1 ppm. The possible confounding effect of potential acrylonitrile exposures was not formally assessed in this study; however, in a previous Dow epidemiological study which included Midland acrylonitrile-butadiene-styrene (ABS) and TYRIL,* styrene acrylonitrile resins, production employees found no adverse effects that could be directly related to acrylonitrile under the conditions of exposure.[4]

Polyacrylamides contain residual acrylamide of varying concentrations. Inhalation exposures to polyacrylamide have been evaluated in the polymer production plant and have been found to be essentially homogenous in all the job classifications except for the packages and dryer operators. Personal TWA exposures to polyacrylamide dust were greater than 2 mg/m^3 for these two job classifications, whereas for all other job classification exposures were less than 2 mg/m^3. Inhalation of residual acrylamide in the polymer dusts does not appear to be an important route of exposure even assuming as much as 1% residual acrylamide in the dusts. Dermal absorption and inadvertent ingestion of acrylamide from polyacrylamide dusts were also potential sources of exposure; however, the potential ingestion or dermal absorption of the polyacrylamide dusts could not be assessed.

Methods

The employees included in the study were identified from annual and monthly census lists (1955 to 1979) of personnel who worked in the production and pilot plants of interest. Work histories were obtained for all identified employees and the job titles and dates of employment for each job of interest were abstracted.

There was a group of individuals who moved into acrylamide areas when the organic dye processes were discontinued. A previous study of organic dye workers reported some non-statistically significant increases in digestive and respiratory malignancies among individuals who had worked five or more years in these areas.[5] Fourteen individuals in the present study had been exposed to organic dye for five or more years. The mortality experience of the acrylamide cohort was examined both including and excluding this group.

Vital status follow up was undertaken from date of first potential exposure to acrylamide to 31 December 1982. Initial follow up was based on a review of records in company personnel systems and for employees lost to direct company follow up, vital status was ascertained by using Social Security records to 1979. The National Death Index (NDI) was used to update the vital status to 1982. NDI is a national mortality registry of all deaths occurring in the United States since 1979.[6] Death certificates were obtained from individual state vital statistics offices for all decedents. Underlying causes of death were coded by an experienced nosologist according to the revision of the International Classification of Diseases (ICD) in effect at the time of death and converted to the 8th revision for analyses.

Mortality comparisons were made between the cohort and the United States white male mortality experience. Expected numbers of deaths from major cause categories and site specific cancer categories were calculated by applying age and calendar year specific United States white male mortality rates to the person-years of the cohort. The rates used were updated to 1980 and the Monson lifetable program was used.[7] Standardised mortality ratios (SMR), the ratio of observed to expected deaths, were calculated for categories in which at least two deaths were observed. Statistical significance was assessed by calculating 95% confidence limits about the SMR estimates using Fisher's exact method[8] and the programs of Rothman and Boice.[9]

Results

The vital and employment status of the 371 employees is summarised in table 1. The cohort was white and included six women; none of the women had died. On 1 January 1983, 192 individuals were still working for the company, 65 had retired and were living, and 27 were known from company records to have died. Of the 87 individuals who had left employment, two were identified on the basis of Social Security and National Death Index searches as having died.

*Trademark of the Dow Chemical Company.

Table 1 *Vital and employment status of acrylamide employees on 1 January 1983*

Vital and employment status	*Total population*	*Acrylamide employees less those with organic dye exposure**
Total population	371	357
Still working	192	192
Retired	65	60
Dead (company records)	27	18
Left company:		
Dead	2	2
Alive	85†	85

*Individuals with past exposure to organic dyes of at least five years duration are treated separately in the analyses.
†Based on National Death Index follow up.

Duration of employment by date of first employment in acrylamide and polyacrylamide production areas is shown in table 2 for the employees with and without exposure to organic dyes. Approximately 19% of the employees first worked in the production areas before 1960. Among those without organic dye exposure, 46% worked for less than one year, 30% for one to four years, and 23% for more than five years.

Table 3 shows the results of the mortality analyses for the total cohort and the cohort without prior organic dye exposure. The all causes mortality for these two groups compared favourably with the expected. There was a non-significant excess in mortality from malignant neoplasms in the total cohort (11 observed *v* 7·9 expected). When those with prior organic dye exposure were excluded, four deaths due to malignant neoplasms were observed when 6·5 had been expected. No malignancies were observed at any of the hypothesised sites (central nervous system, thyroid gland, other endocrine glands, malignant mesotheliomas). Four malignancies of the digestive tract were observed in the total group (1·9 expected), two of these being among employees without previous organic dye exposures (1·6 expected).

Table 4 summarises the pertinent findings for the 11 cases in which the underlying cause of death was a malignant neoplasm.

Table 2 *Starting date and duration of employment among acrylamide employees without organic dye exposure. (Those with organic dye exposure in parentheses)*

	Duration of employment (years)			
Starting year	*Total*	*<1*	*1–4*	*≥5*
Total	357(14)	166(1)	108(1)	83(12)
1955–9	60(12)	12	12	36(12)
1960–4	30(1)	17(1)	6	7
1965–9	110(1)	51	44(1)	15
1970–4	78	38	15	25
1975–9	79	48	31	0

Table 3 *Observed and expected deaths and SMRs by cause for the acrylamide exposed cohort with and without prior organic dye exposure 1955–82*

	Total cohort (n = 371) Obs/exp	*SMR**	*95% CI*	*Total cohort less organic dye exposed (n = 357) Obs/exp*	*SMR**	*95% CI*
All causes	29/38·0	76	51–110	20/31·5	63	38–97
All malignancies (140–209)†	11/7·9	139	70–249	4/6·5	61	17–158
Cancer of buccal cavity and pharynx (140–149)	0/0·3	—	—	0/0·2	—	—
Cancer of digestive tract (150–159)	4/1·9	202	57–539	2/1·6	124	15–452
Cancer of respiratory system (160–163)	4/2·9	138	38–353	1/2·4	—	—
Cancer of prostate (185)	1/0·4	—	—	0/0·3	—	—
Cancer of bladder and kidney (188, 189)	0/0·4	—	—	0/0·3	—	—
Cancer of brain and other central nervous system (191, 192)	0/0·3	—	—	0/0·3	—	—
Leukaemia (204–207)	1/0·3	—	—	0/0·3	—	—
Cancer of lymphatic and haematopoietic tissue except leukaemia (200–203, 208, 209)	0/0·5	—	—	0/0·5	—	—
All other sites	1/0·6	—	—	1/0·5	—	—
All circulatory diseases (390–458)	12/17·0	71	37–124	11/13·7	80	40–143
All respiratory diseases (460–519)	0/2·0	—	—	0/1·6	—	—
All digestive diseases (520–577)	0/2·0	—	—	0/1·8	—	—
All external causes (800–999)	3/5·8	52	11–151	3/5·5	55	11–159
All accidents (800–949)	3/3·7	80	17–237	3/3·5	86	18–250
Suicides (950–959)	0/1·3	—	—	0/1·2	—	—

*SMR calculated for those categories in which at least two deaths were observed.
†International Classification of Diseases, 8th revision (ICD 8th).

Table 4 *Case summaries of 11 employees whose deaths were due to malignant neoplasms*

Case No	Date of first exposure to acrylamide, duration of total exposure	Year of death	Age of death	Underlying cause (per death certificate)	Exposure to organic dyes	Smoking history (per medical record)
1	1961 9 m	1974	66	Cancer of bowels	+	Unknown
2	1955 9·3 m	1973	70	Bronchiogenic carcinoma	+	+
3	1958 6·6 y	1982	75	Carcinoma of lung	+	Unknown
4	1955 6·1 y	1975	70	Cancer of prostate	+	+
5	1965 2·8 y	1980	63	Adenocarcinoma of lung	−	+
6	1955 8·1 y	1978	76	Metastic carcinoma unknown site	−	+
7	1966 4 m	1972	50	Sigmoid carcinoma	−	+
8	1961 6 y	1969	45	Cancer of stomach	−	Unknown
9	1955 16 y	1971	51	Acute lymphochytic leukaemia	+	Unknown
10	1958 11 y	1972	60	Adenocarcinoma of colon	+	Unknown
11	1958 11 y	1982	66	Bronchiogenic carcinoma of lungs	+	+

Discussion

The results from a recent chronic toxicity-oncogenicity of acrylamide in rats showed statistically significant increases in tumours of several sites.[2] With particular attention being given to the malignancies identified in this animal study, the present research examined the mortality experience of 371 employees who were assigned to acrylamide monomer and polymer operations. A group of individuals in the acrylamide cohort had previous work experience in organic dye areas. Those individuals who had worked five or more years in organic dye areas were identified and examined separately to eliminate potential confounding.

No statistically significant excesses were noted in the total cohort and no deaths were found for the hypothesised sites of cancers. The observed deaths in the total cohort for the all malignancies category were somewhat in excess (11 *v* 7·9); however, this was due entirely to excess cancers of the digestive tract and respiratory system in the subgroup with previous organic dye exposure. Among those not exposed to organic dyes, four deaths were due to malignancies versus 6·5 expected.

Given the size of the total cohort and the period of observation, a twofold increase in total cancers could have been detected with 80% power. The power to detect small increases in risk among site specific cancers was somewhat lower, but the study did have sufficient power to detect major increases in site specific cancers had they existed. For example, in the category cancers of the brain and central nervous system if three deaths had been observed statistical significance would have been reached.

In summary, this study does not support a cause effect relation between exposure to acrylamide at this work site and either overall mortality, total malignant neoplasms, or any specific cancers.

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