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Occupational exposure to hydrazine and subsequent risk of cancer

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ABSTRACT Four hundred and twenty seven men with varying degrees of occupational exposure to hydrazine, a weak animal carcinogen, were studied to see if they provided any evidence of carcinogenicity to man. The observed mortality was close to that expected for lung cancer, other cancers, and all other causes, irrespective of the level of exposure. There were 49 deaths (61·47 expected) from all causes including five deaths from lung cancer (6·65 expected). The results show that no obvious hazards associated with hydrazine exposure have yet appeared but because of the small number of men studied they can only exclude gross hazards.

Hydrazine (N_2H_4) is a colourless, fuming, oily liquid with an ammonia like odour. The estimated total world production in 1981 was 30 000 tons. About 75% of hydrazine is used as a chemical intermediate in the production of pesticides or plastic additives, about 10% is used in fine chemical manufacture (particularly in the production of isoniazid and allopurinol), and the remaining proportion is used as a deoxygenating material for boiler-feed water and as a propellant in rocketry.

Hydrazine has been categorised by the International Agency for Research on Cancer as a weak carcinogen[1] and by the American Conference of Governmental Industrial Hygienists (ACGIH) as an industrial substance suspected of carcinogenic potential for man.[2 3] The evidence is based largely on the administration of hydrazine and its sulphate salts to rodents.

Mice given hydrazine sulphate by mouth at up to 45 mg/kg/day showed a dose related increase in the incidence of hepatoma, mostly "hepatocarcinomas."[4 5] Hydrazine, at doses around 25 mg/kg/day, has also been shown to cause myeloid leukaemia, reticulum cell sarcoma of the mediastinum, and pulmonary adenomas and lymphomas.[6–8] Rats fed 3–4·4 mg/day over a 68 week period showed an increased incidence of lung adenomas and carcinomas, and an increased incidence of liver tumours.[4 9]

Oral administration of hydrazine sulphate to hamsters, however, did not cause a significant excess of cancers, but 1,2-dimethyl hydrazine did cause angiosarcomas of blood vessels and caecal and hepatic tumours.[5 10]

Rats exposed for one year to hydrazine vapour by inhalation in concentrations comparable to occupationally exposed men (0·25–5 ppm), and then kept for their normal lifespan, showed an increased incidence of benign and macroscopically malignant tumours in the nose, the incidence of which was dose dependent. Mice and hamsters similarly exposed showed an increased incidence of lung adenomas and of nasal polyps respectively.[11]

It seemed highly desirable, therefore, to see whether there was any evidence that hydrazine was carcinogenic to man and to see what had happened to men who had been exposed to hydrazine vapour in the course of their work, even if the number available for study was small. A preliminary analysis of men working at a hydrazine plant failed to suggest an excess risk of cancer associated with exposure to hydrazine.[12] The follow up was incomplete, however, and as mortality was not analysed by cause we conducted a fresh study using the same cohort.

The plant

At a factory in the east Midlands between 1945 and 1971 about 700 tons of hydrazine were produced a year. The plant was in an enclosed building and, as hydrazine was not considered to be more hazardous than ammonia, exhaust ventilation was not provided. Hydrazine was kept in open tanks and hydrazine compounds were made from strong hydrazine solutions in open vessels, which were heated to

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enhance evaporation. Packing of hydrazine into small commercial containers was carried out in the same building. Spillages were not necessarily flushed away immediately, and it was the practice of the laboratory workers to pipette hydrazine solutions by mouth.

Unfortunately, no measurements of atmospheric hydrazine were ever carried out at this plant, although the level of hydrazine is likely to have been from 1 to 10 ppm in the general plant area and levels much higher than this (up to 100 ppm) may have occurred close to hydrazine storage vessels. These estimations have been derived by the simulation of spillages and calculations using data on the saturated vapour pressure of hydrazine at 20°C, which suggest that maximum levels of 100 ppm are possible. Other organic chemicals were also manufactured in the same factory.

Method

Factory records showed that 427 men were employed there for at least six months during this period. For each of these men the following information was sought: identifying details, date of birth, date of first employment, date of leaving the company, and an estimate of the extent of hydrazine exposure based on the knowledge of the factory works manager. Each type of employment was classified in one of the following categories, according to the estimated degree of exposure.

Category 1—Exposure associated with the direct manufacture of hydrazine, or of its derivatives, or involving the use of liquid hydrazine as a raw material. Exposure to hydrazine vapour was potentially greatest for men in this category, who may have been exposed to about 1 to 10 ppm in the ambient air.

Category 2—Exposure associated with an incidental presence in an area of the plant concerned with the manufacture of hydrazine or its derivatives (fitters and engineers, for example). Exposure in this category was unlikely to have been more than 1 ppm and probably less than 0·5 or 1 ppm for most of their employment.

Category 3—Little or no exposure. Men in this category were unlikely to have been exposed to hydrazine more than slightly and then only infrequently.

The men were followed up to the end of July 1982 through the cooperation of the Office of Population Censuses and Surveys by flagging their National Health Service records in the National Health Service Central Register at Southport.

It was possible to trace 406 (95%) of the 427 men. The 21 untraced men were excluded from the study from the latest date they were known to have been living at their last known address, or, in the case of four men for whom this date was missing, from the last date of their employment in the factory. Men who changed from one category of exposure to another were considered to have been at risk in relation to the highest category to which they had previously been exposed (see footnote to table 1).

Results

Table 1 shows the number of man-years under observation according to the category of exposure, duration of exposure, and the number of years since first exposure. Nineteen per cent of the 8351 man-years at risk followed exposure in category 1.

Table 2 shows the numbers of deaths observed

Table 1 *Numbers of men exposed and man-years at risk by category of exposure, duration of exposure, and years since first exposure*

Category	*Durations of exposure*	*Years since first exposure*	*No of men*	*No of man-years*
1	6 months to 2 years	<10	78	350
		≥10	73	198
	2 years or more	<10	54	508
		≥10	50	509
	6 months or more	all	78	1565
2 or 3	6 months or more	all	375	6786
All	All	All	427*	8351

*Men who were first exposed in categories 2 or 3 and who were subsequently exposed in category 1 contributed man-years at risk in categories 2 or 3 initially and to category 1 after their first exposure in that category. The numbers of men in each category, therefore, add up to more than 427 in all, as some men contributed to more than one category. Similarly, all men who contributed man-years at risk more than 10 years after first exposure and for durations of exposure of two years or more also contributed to man-years at risk less than 10 years after first exposure and to less than two years' duration of exposure.

Table 2 *Numbers of deaths observed and expected by category of exposure, duration of exposure, years since first exposure, and cause*

Cause of death	*Category of exposure*	*Duration of exposure*	*Years since first exposure*	*No of deaths Observed*	*Expected*
Lung cancer	1	6 months to 2 years	< 10	0	0·05
			⩾ 10	1	0·10
		2 years or more	< 10	0	0·31
			⩾ 10	1	1·15
		6 months or more	All	2	1·61
	2 or 3	6 months or more	All	3	5·03
	All	6 months or more	All	5	6·65
Other cancer	1	6 months to 2 years	< 10	0	0·12
			⩾ 10	0	0·16
		2 years or more	< 10	0	0·42
			⩾ 10	0	1·48
		6 months or more	All	0	2·18
	2 or 3	6 months or more	All	7	7·10
	All	6 months or more	All	7	9·27
Other causes	1	6 months to 2 years	< 10	0	0·60
			⩾ 10	0	0·70
		2 years or more	< 10	1	2·00
			⩾ 10	7	7·39
		6 months or more	All	8	10·69
	2 or 3	6 months or more	All	29	34·86
	All	6 months or more	All	37	45·55
All causes	All	6 months or more	All	49	61·47

compared with the numbers that would have been expected if the men had experienced the same death rate as those of men in the same ages in the same years in England and Wales as a whole, subdivided similarly (five year age groups and five year calendar periods). The observed mortality is close to that expected for lung cancer, other cancers, and all other causes, irrespective of the category of exposure. No deaths occurred from nasal cancer. Two men with the heaviest exposure died of lung cancer against 1·61 expected. Both had first been exposed more than 10 years before they developed the disease. One had been exposed for two months, the other for 16 years.

Discussion

The number of men exposed to hydrazine in this study is small. Only 78 men have had substantial exposure (category 1) estimated at between 1 and 10 ppm hydrazine vapour in air, and observations were made on only 707 man-years at risk for 10 years or more (up to a maximum of 36 years) after first exposure. The results obtained are encouraging in that no obvious hazard has yet appeared. They exclude, however, only gross hazards, and a note of caution is introduced by the observation of two deaths from lung cancer in men who had been first exposed in the heaviest category more than 10 years previously against 1·61 expected.

Production at this plant ceased in 1971 and the site was cleared by 1973. Some of the men were transferred to a hydrazine plant in Cheshire. This plant is completely open to the general atmosphere, and exposure levels have been low, typically 0·1 ppm. The highest recorded level has been 3 ppm, during a spillage, and such occurrences are rare. It is proposed to follow this cohort for further years.

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