Occupational exposure to hydrazine and subsequent risk of cancer

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Abstract

Objectives—The aim was to examine the cause specific mortality of men exposed to hydrazine.

Methods—Hydrazine was produced at a factory in the east midlands between 1945 and 1971. The cohort of all 427 men who were employed there for at least six months with varying degrees of occupational exposure to hydrazine were followed up until the end of January 1992.

Results—By the end of July 1982 49 deaths had occurred and the observed mortality was found to be close to that expected at each level of exposure. By the end of January 1992 a further 37 deaths had occurred. Again the observed mortality was close to that expected for all causes and also for lung cancer, cancers of the digestive system, other cancers, and all other causes, irrespective of the level of exposure.

Conclusions—The results weigh against there having been any material hazard of occupational exposure to hydrazine. The small number of men studied means, however, that a relative risk as high as 3.5 for lung cancer cannot confidently be excluded.

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Keywords: occupational exposure; hydrazine; cancer

Hydrazine (N_2H_4) is a colourless, fuming, oily liquid with an ammonia like odour. It is used as a polymerisation catalyst, a blowing agent, a reducing agent, and an oxygen scavenger in treatment of boiler water; in the synthesis of maleic hydrazide; and in the manufacture of drugs. Hydrazine is also used as a rocket propellant. The hydrazine bases are used in the production of salts and hydrazones that are used in surfactants, detergents, plastisers, pharmaceuticals, insecticides, and herbicides.

Both the International Agency for Research on Cancer¹ and the National Institute of Environmental Health Sciences² find that there is sufficient evidence for the carcinogenicity of hydrazine in experimental animals, but inadequate evidence for its carcinogenicity in humans. Oral hydrazine tested in mice and rats produced liver, mammary, and lung tumours in mice and lung and liver tumours in rats.^{3,4} When tested by inhalation in concentrations comparable with occupationally exposed men (0.25-5ppm), it produced

benign and malignant nasal tumours in rats, benign nasal polyps, a few colon tumours and thyroid adenomas in hamsters, and a slight increase in the incidence of lung adenomas in mice.⁵

The only observations available to test the carcinogenicity of hydrazine to humans have been those on 427 men who worked at a hydrazine plant in the east midlands region of the United Kingdom, who were followed up for an average of 20 years.⁶ Mortality from all causes was not increased over that expected, but two lung cancers were found compared with 1.51 expected in men in the highest exposure category. The study had very little power to detect even a large hazard, because the number of deaths observed was so small. It has therefore been extended by following up the men for a further 10 years.

Details of hydrazine production at the factory between 1945 and 1971 have been given previously.⁶ No measurements of atmospheric hydrazine were ever carried out, but the concentration of hydrazine is thought likely to have been 1-10 ppm in the general plant area and much higher than this (≤ 100 ppm) close to the hydrazine storage vessels.

Method

Factory records showed that 427 men were employed there for at least six months during the period of hydrazine production. 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.

HIGH EXPOSURE

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

MODERATE EXPOSURE

Exposure was 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

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have been more than 1 ppm and was probably < 0.5 or 1 ppm for most of their employment.

LOW EXPOSURE

Little or no exposure occurred as men in this category were unlikely to have been exposed to hydrazine more than slightly, and then only infrequently.

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	Men (n)	Man-years (n)
High‡	≥ 2 y	<10	54	508
		≥10	50	878
		≥10	78	350
	<2 y	<10	73	409
		≥10	78	858
		≥10	73	1287
Moderate and low‡	All	<10	375	3365
All	All	≥10	342	6154
		<10	427†	4222
		≥10	389	7441

*All men were exposed for ≥ 6 months.

†Men who at first had low or moderate exposures and who were subsequently highly exposed contributed man-years at risk in the low or moderate categories initially and to the high category 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 ≥ 10 y after first exposure and for durations of exposure of ≥ 2 y also contributed to man-years at risk < 10 y after first exposure and to < 2 y duration of exposure.

‡High = men who may have been exposed to about 1–10 ppm hydrazine vapour in the ambient air; moderate = men unlikely to have been exposed to ≥ 1 ppm and probably < 0.5 ppm hydrazine vapour in the ambient air; low = men unlikely to have been exposed to hydrazine vapour.

Table 2 Numbers of deaths observed (O) and expected (E) 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	Deaths		O/E
				O (n)	E (n)	
Lung cancer	High	≥ 2 y	≥ 10	1	2.11	0.47
			All	3	2.42	0.41
			All	3	2.43	1.23
	Moderate or low	All	≥ 10	5	8.32	0.60
			All	5	9.27	0.54
			≥ 10	8	10.76	0.74
Cancer of digestive system	High	≥ 2 y	≥ 10	0	1.64	0.0
			All	0	1.86	0.0
			≥ 10	0	1.90	0.0
	Moderate or low	All	≥ 10	0	2.16	0.0
			All	8	6.54	1.22
			≥ 10	9	7.29	1.24
Other cancer	High	≥ 2 y	≥ 10	8	8.44	0.95
			All	9	9.45	0.95
			≥ 10	2	1.82	1.10
	Moderate or low	All	≥ 10	2	2.01	0.99
			All	2	2.13	0.94
			≥ 10	2	2.40	0.83
IHD	High	≥ 2 y	≥ 10	5	7.27	0.69
			All	6	8.14	0.74
			≥ 10	7	9.39	0.75
	Moderate or low	All	≥ 10	8	10.54	0.76
			All	7	6.60	1.06
			≥ 10	8	7.39	1.08
Other causes	High	≥ 2 y	≥ 10	7	7.60	0.92
			All	8	8.54	0.94
			≥ 10	16	25.82	0.62
	Moderate or low	All	≥ 10	18	28.46	0.63
			All	23	33.42	0.69
			≥ 10	26	37.00	0.70
All causes	High	≥ 2 y	≥ 10	7	8.34	0.84
			All	7	9.53	0.73
			≥ 10	7	9.35	0.75
	Moderate or low	All	≥ 10	7	10.99	0.64
			All	24	28.54	0.84
			≥ 10	28	34.07	0.82

For category and duration of exposure see footnotes to table 1. IHD = ischaemic heart disease.

The men were followed up to the end of January 1992 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 last 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. These dates were all before July 1982 (the cut off date for the previous analysis). Men who were first exposed in the low or moderate categories and who were subsequently exposed in the high category contributed man-years at risk in the low or moderate categories initially and to the high category after their first exposure in that category. Similarly, all men who contributed man-years at risk > 10 years after first exposure and for durations of exposure of two years or more also contributed to man-years at risk < 10 years after first exposure and to less than two years' duration of exposure.

Person-years at risk and death rates were calculated by five-year age groups and time since first exposure (< 10 and ≥ 10 years). The expected number of deaths was calculated from the death rates of men in England and Wales in the same five-year age bands over the same period of time. The overall death rates in the area in which the factory was located were similar to those in England and Wales. The observed and expected numbers of deaths were compared and tested for significance with one sided Poisson tests. The results for the period < 10 years since first exposure have been reported previously and are not reported here.

The death rates in those men who had the greatest exposure (high exposure for more than two years) were also compared to the death rates for all other men with Kaplan-Meier product limit analysis. Cox's proportional hazards regression analysis was not carried out due to the lack of fit of the models.

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. Of the 11664 man-years 18% at risk were in the high exposure category.

Table 2 shows the numbers of deaths observed compared with the numbers expected. The observed mortality is close to that expected for lung cancer, cancers of the digestive system, other cancers, and all other causes. For men in the highest exposure category the upper 95% confidence intervals (95% CIs) for the relative risks were: 3.61 for lung cancer, 1.94 for cancers of the digestive system, 1.90 for ischaemic heart disease, and 1.27 for mortality from all causes.

Log rank test statistics from non-parametric survival analysis showed that men with

Table 3 Kaplan-Meier log rank tests of homogeneity of survival rates of men in the high exposure category for >2 y compared with all other men

Cause of death	χ^2	P value
Lung cancer	0.04	0.85
Cancers of the digestive system	1.36	0.24
All cancer	0.10	0.75
All causes	3.21	0.07

the highest exposure did not seem to have significantly different mortalities for lung cancer, cancers of the digestive system, and all causes, compared with all the other men in the study (table 3).

Discussion

The only categories in which the number of observed deaths exceeded expected deaths (but not significantly) are lung cancer in men in the high exposure category for six months or more (three observed *v* 2.43 expected) and cancers of the digestive system in men in the low or moderate exposure category (eight observed *v* 6.54 expected). Two of the three deaths from lung cancer in men in the high exposure category were in men exposed in that category for less than two years. Only one case, however, occurred in men exposed in the high exposure category for more than two years *v* 2.11 expected. No cancers of the digestive system occurred in men with exposure in the high exposure category. No deaths occurred from nasal cancer.

A similar study in France of 140 men working at a plant producing hydrazine since 1962 reached similar conclusions (personal communication: Cordier S, Grand C, Contassot J-C). No significant excess in incidence of cancer was observed in the cohort of workers in comparison with the numbers expected

from local cancer incidence. As in our study, however, an excess of digestive cancers was found in the low exposure group (three cases observed *v* 0.52 expected; *P* = 0.02). A significant excess of head and neck cancers (ICD-8 140-9) in the high exposure category was also found in the French study (two cases observed *v* 0.27 expected; *P* = 0.03), but no death from these causes was found in our study (0.49 expected). No excess of respiratory cancers was observed in the French study (we found one case *v* 1.29 expected).

Conclusions

The numbers of men exposed to hydrazine in both this and the French study were small. The results obtained are encouraging in that no obvious hazard from lung cancer or any other disease has appeared up to 46 years later. The study can confidently exclude a relative risk of lung cancer of about 3.5 or more, but the power of the study is too limited to exclude lower relative risks.

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- 1 IARC Monogr Eval Carcinog Risks Hum Suppl 1988; 7:223-4.
- 2 National Institute of Environmental Health Sciences. Fifth annual report on carcinogens [summary]. Research Triangle Park, NC: DHHS Public Health Service, 1989. (NTP 89;239:166-8)
- 3 IARC Monogr Eval Carcinog Risks Hum 1976;4:127-36.
- 4 Menon MM, Bhide SV. Perinatal carcinogenicity of isoniazid (INH) in Swiss mice. *J Cancer Res Clin Oncol* 1983;5:1050-64.
- 5 Vernot EH, MacEwan JD, Bruner RH, Haun CC, Kinkade ER, Prentice DE, et al. Long-term inhalation toxicity of hydrazine. *Fundam Appl Toxicol* 1985;5: 258-61.
- 6 Wald N, Boreham J, Doll R, Bonsall J. Occupational exposure to hydrazine and subsequent risk of cancer. *Br J Ind Med* 1984;41:31-4.

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- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology, mechanisms of disease*. Philadelphia: W B Saunders, 1974:451-72.