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Mortality of nitrate fertiliser workers

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ABSTRACT An epidemiological cohort study was conducted to investigate the mortality patterns among a group of workers engaged in the production of nitrate based fertilisers. This study was designed to test the hypothesis that individuals exposed to high concentrations of nitrates might be at increased risk of developing cancers, particularly gastric cancer. A total of 1327 male workers who had been employed in the production of fertilisers between 1946 and 1981 and who had been occupationally exposed to nitrates for at least one year were followed up until 1 March 1981. In total, 304 deaths were observed in this group and these were compared with expected numbers calculated from mortality rates in the northern region of England, where the factory was located. Analysis was also carried out separately for a subgroup of the cohort who had been heavily exposed to nitrates—that is, working in an environment likely to contain more than 10 mg nitrate/m^3 for a year or longer. In neither the entire cohort nor the subgroup was any significant excess observed for all causes of mortality or for mortality from any of five broad categories of cause or from four specific types of cancer. A small excess of lung cancer was noted more than 20 years after first exposure in men heavily exposed for more than 10 years. That men were exposed to high concentrations of nitrate was confirmed by comparing concentrations of nitrates in the saliva of a sample of currently employed men with control men, employed at the same factory but not in fertiliser production. The men exposed to nitrate had substantially raised concentrations of nitrate in their saliva compared with both controls within the industry and with men in the general population and resident nearby. The results of this study therefore weigh against the idea that exposure to nitrates in the environment leads to the formation in vivo of material amounts of carcinogens.

Environmental exposure to nitrates was not thought to be a potential hazard to health until recently. Now, attitudes have changed, not because of any anxiety about the direct effect of nitrate itself but because of the possible effects of the nitrites that are produced in vivo by enzymatic reduction of nitrates. This chemical reaction is caused by a species of bacteria normally found in the mouth and occasionally in the stomach and bladder.[1] Such nitrate derived nitrite is often the major source of nitrite for most people. Nitrite so produced is capable of causing methaemoglobinaemia in neonates, though this clinical problem has hardly ever occurred in Britain.[2] More importantly, however, nitrate derived nitrite may react with substances that occur in food and drugs to give rise to *N*-nitroso compounds, most of which are strongly carcinogenic to animals.[3] Exposure to unusually high concentrations of nitrates has, therefore, been considered as a possible cause of an increased risk of cancer in man.[4–6]

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The site most commonly regarded as being at risk is the stomach. Gastric acidity favours nitrosation,[7] many *N*-nitroso compounds (particularly the *N*-nitrosamides) cause cancer topically in animal experiments,[6 8] and gastric cancer mortality has been related to high levels of nitrate intake when comparisons have been made between countries.[9] Correlations within countries have, however, given contradictory results and it has not as yet been possible to draw any firm conclusions about the possible role of nitrate intake in human carcinogenesis.[10 11] It seemed, therefore, important to find out whether men who were specifically exposed to high concentrations of nitrates in the course of their work experienced an unusually high risk of cancer and particularly of cancer of the stomach.

PRODUCTION OF NITRATE FERTILISERS

One group which has been exposed in this way consists of men who have been employed in manu-

facturing fertiliser products in the agricultural division of a large chemical company in the north east of England. The company has produced nitrate fertilisers since the 1920s. Two main types have been produced: straight nitrogen fertiliser containing compounds of nitrogen only and compound fertilisers containing compounds of nitrogen, phosphorus, and potassium in different concentrations. These fertilisers have been manufactured in three main plants which, together with the nitric acid plant, constitute the areas where exposure to nitrates is likely to have occurred.

NITRIC ACID PLANT

Nitric acid is the main precursor of all manufactured nitrate based fertilisers. It has been produced since the early 1920s in the division by the catalytic oxidation of ammonia which is subsequently oxidised to nitric dioxide and then converted to nitric acid by absorption in water. No nitrate compounds have been produced in the plant apart from small amounts of ammonium and sodium nitrate which are produced along the similar amounts of nitrite as side products. Direct exposure to nitrates is low and no records of the amount in the atmosphere of the plant were kept. There has been, however, considerable exposure to the oxides of nitrogen (NO and NO_2), particularly in the early years of the plant's operation. These oxides of nitrogen can act as direct nitrosating agents both in vivo and in vitro and may be converted to nitrite and nitrate in vivo.[12-14] Men employed in the plant can, therefore, be regarded as having been, in effect, exposed to nitrates and the degree of exposure has been estimated from the results of the in vivo experiments.[12 14]

NITRO-CHALK PLANT

"Nitro-Chalk" is the name given to a simple nitrogen fertiliser compound of ammonium nitrate and calcium carbonate. The plant making the fertiliser operated between 1928 and 1969.

"NITRAM" PLANT

"NITRAM" is the name given to another simple nitrogen fertiliser composed entirely of ammonium nitrate. It is better suited to British farming conditions than Nitro-Chalk and the plant making it came into operation when the Nitro-Chalk plant closed.

COMPLETE COMPOUND FERTILISER (CCF) PLANT

The production of compound fertilisers was started in the division in 1930. The fertilisers were at first a mixture of ammonium sulphate, potassium chloride, and superphosphate, but the last was subsequently replaced by ammonium phosphates. In 1964 the costly and less effective ammonium sulphate was replaced by ammonium nitrate, which was used to make up nitrate based compound fertilisers with a nitrogen content varying between 8% and 27%.

Employees studied

DEFINITION OF COHORT

Records of individuals employed before or during the war, but not subsequently, have not been preserved and it was thus possible for us to study only those who had been in employment on or after 1 January 1946. For the purpose of the study we therefore sought to include all who had been employed for at least one year on work that involved possible exposure to nitrates between 1 January 1946 and 1 March 1981 and to follow them all up to the latter date. This, however, was not simple as the records were kept in different ways and different places, with varying degrees of accessibility.

Detailed records of all employees have been kept on a computer file since 25 September 1972 and from these data it was relatively easy to obtain a complete occupational history of all employees in the agricultural products division and to select those who had exposure to nitrates. Records were also readily available for all employees who had retired on pension or had died at work between 1 January 1946 and 24 September 1972. These records, however, lacked occupational histories before 25 September 1972 and the original employment records had to be sought for all men in these categories who had been employed in the agricultural products division to determine the place and date of work and the nature of their occupations. Lastly, information had to be obtained for employees who were paid off—that is, who had ceased employment in the division without qualifying for a company pension—between 1 January 1946 and 24 September 1972. This was not difficult for men and women paid off before 1 January 1962, for although the records were kept with the records of all other employees of the company in the area, they were kept on cards and it was possible to go through them and to pick out those relating to men and women with possible exposure to nitrates. In was difficult, however, for men and women paid off between 1 January 1962 and 24 September 1972, as their records were available only on the original files and it was laborious and time consuming to search through them for the necessary information. Staff were not available to examine all the files and we therefore limited the study to include only a 35% random sample of this group (which, in itself, took an entire person-year). By these means we identified a cohort of 1448 individuals (1327 men and 121 women) who had been employed for one year or more in one or other of the four plants

in which exposure to nitrates might have occurred.

CLASSIFICATION BY INTENSITY OF EXPOSURE

The degree to which employees were exposed to nitrates depends on the plant in which they worked, the jobs on which they were employed, and the duration and period of their employment in each job. Objective classification of exposure by reference to ambient or biological measurements was not possible, as detailed measurements of the amount of nitrate to which employees were exposed did not begin until the late 1970s. Jobs were, therefore, classified crudely into three levels of exposure by evaluating individually the likelihood of exposure to nitrates that each involved. Jobs with regular contact with nitrates, such as chemical and physical processing, filling and packing, and loading and transporting, were classed as high exposure; jobs with intermittent contact such as maintenance (including engineering crafts), building crafts, and woodworking were classed as intermediate; and jobs in the vicinity of the plant that did not cause direct contact, such as clerical, catering, and security work, were classed as low. Employees of the nitric acid plant were classified similarly, save that these jobs were coded for exposure to nitrogen oxides rather than to nitrates per se.

Crude estimates of the amount of exposure that, it is thought, these various jobs are likely to have involved in different plants at different periods are shown in table 1, based on current measurements of exposure, changes in machinery and regulations regarding exposure to dust, and the experience of senior employees. For men employed in the nitric acid plant, estimates were made based on the results of the animal experiments referred to above which led to the conclusion that approximately 40% of nitrogen oxides are converted to nitrates—that is, that exposure to 1 ppm of the gases, which is equivalent to 2·58 mg nitrate/m^3 is effectively an exposure of 1 mg nitrate/m^3.

Men who were employed for one year or more in a job that was thought to have involved working regularly in an environment that contained 10 mg/m^3 of nitrate (the recommended threshold limit value for nitrate dust in working environments) or more were classed separately as having been "heavily exposed" from the time of completing the first year's work—that is, men who worked for a year or more in high exposure jobs in the Nitro-Chalk plant at any time, in the CCF plant up to the end of the 1974, and in the nitric acid plant up to the end of 1971. The assumption made about the conversion of nitrogen oxides to nitrates in the nitric acid plant can have had little effect on the observations made on men in this group as only three men in the nitric acid plant qualified for inclusion in it.

A few employees could not be categorised by the methods described above as the early records, and particularly those for workers paid off before 25 September 1972, recorded only exposure to nitrates without specifying the plant and such employees could have worked in any of the four. The type of job was, however, always defined so that it could be classed as involving high, medium, or low exposure. The individuals concerned were, therefore, regarded as having been exposed to the mean level for all four plants for the relevant class of job at each period.

Method

FOLLOW UP

The cohort was followed up to determine the status of its members at 1 March 1981, except that follow up was not continued after individuals reached the age of 85, as the accuracy of death certification after this age tends to be unreliable. Employees who had been paid off by the company and whose status was, therefore, not known were followed up through the National Health Service Central Register at Southport and the National Insurance records at Newcastle. Individuals who were not traced in the NHS register as having died or emigrated or whose National Insurance number was extant and did not indicate death before 1 March 1981 were presumed to be still alive at that

Table 1 *Estimated exposure to nitrates in four plants, 1923–81*

Plant	*Period of exposure*	*Mean level of ambient exposure to NO_3 (mg/m^3) for jobs rated*		
		High exposure	*Medium exposure*	*Low exposure*
Nitro-Chalk	1 Jan 28–1 Jan 69	16	0·8–8·0	<0·80
Complete compound fertiliser (CCF)	1 Jan 64–31 Dec 74	10	0·5–5·0	<0·5
	1 Jan 75–1 Mar 81	5	0·25–2·5	<0·25
NITRAM	1 Jul 69–1 Mar 81	1·2	0·8	<0·6
Nitric acid	1 Jan 23–31 Dec 59	15	1·5–15·0	<1·5
	1 Jan 60–31 Dec 71	10	1·0–10·0	<1·0
	1 Jan 72–31 Dec 77	5	0·5–5·0	<0·5
	1 Jan 78–1 Mar 81	1	0·1–1·0	<0·1

date. Those individuals who could not be successfully traced by these means were followed up until the date of leaving the company.

CALCULATION OF EXPECTED MORTALITY

The number of person-years at risk was calculated from knowledge of the dates that each individual entered or left the cohort—that is, from the completion of one year's employment since 1 January 1946 in one or other of the four plants, irrespective of the number of years employed previously, to 1 March 1981, the age of 85, deaths, emigration, or the date of ceasing employment, if subsequently untraced, whichever occurred first.

The expected numbers of deaths were then calculated by dividing the person-years at risk into five year age and calendar period groups, multiplying by the corresponding death rates for the northern region of England* in which the factory was located, and summing over all periods and all age groups (up to age 85). Expected numbers were calculated separately for all causes of death, six broad categories of causes, and five categories of cancer. Region specific data were not, however, available for all the causes that we wished to examine and for these causes (cancers of the oesophagus and bladder) national rates for England and Wales were used instead. A similar calculation was made for the subset of men who had experienced heavy exposure (see above). These men entered the heavy exposure cohort after completion of one year in a high exposure job. Men who were heavily exposed but who had worked initially on jobs that did not involve heavy exposure were classed with all other men from the time they entered the cohort to the time they qualified for inclusion as heavily exposed.

VALIDATION OF EXPOSURE CATEGORIES

No direct measure of the extent to which men classed as heavily exposed was possible, as such men were required to have been exposed to estimated mean concentrations of ambient nitrates of at least 10 mg/m^3 and the highest concentrations to which men were exposed at the time of the study were only 5 mg/m^3 (table 1). It was possible, however, to check that even these current concentrations would materially affect the metabolism of nitrates in the body by measuring the concentration of nitrate in the saliva at the end of a shift in men who were doing different types of job. Salivary samples were used because some 25% of exogenous nitrates is extracted from the circulation and secreted in the saliva and about 20% of this is reduced to nitrite by oral bacteria.[15 16] This nitrite, formed from nitrate, constitutes approximately 80% of the normal total exposure to nitrite,[5] and salivary measures should, therefore, provide a good indication of the amount of nitrite that is available, particularly in the stomach, for the formation of *N*-nitroso compounds in vivo.

An attempt was, therefore, made to collect samples of about 1 ml of saliva in specially prepared glass tubes from three groups of 30 workers subject, respectively, to high exposure (men working on jobs involving regular contact with nitrates in the CCF plant), moderate exposure (men working on similar jobs in the NITRAM plant), and no exposure (men employed by the same company but not in any nitrate or nitric acid plant) and to compare the measurements with those obtained in men resident in a comparable town near to the plants and elsewhere obtained in the course of another study.[10] Men attending morning shifts in the three specified groups were asked to participate over a two week period until the required numbers of 30 in each group were obtained. Almost all those approached agreed to participate. Each individual was asked to provide samples at the start of the shift (usually between 0700 and 0800), two hours later, and at the end of the shift, and to avoid eating or drinking between the first and second samples and, if possible, between the second and third samples, as by this means samples may be obtained that are sufficiently standardised for comparison to be made between different populations.[10] In addition, participants were asked to list all the food and drink consumed since midnight, including time spent on the shift, and to note the times of consumption and the times of providing the samples. The samples were then taken to Oxford under conditions in which no degradation occurs and analysed blind by one of us (SA) using the method of Phizackerley and Al-Dabbagh.[17]

Results

MEASUREMENTS OF BIOLOGICAL EXPOSURE

The extent to which individuals were effectively exposed to nitrates and consequently to nitrites was estimated from the concentrations of nitrates and nitrites in the samples of saliva collected more than two hours after any food or drink had been consumed. Measurements were made preferentially on saliva collected at the end of a shift but if food or drink had been consumed within two hours measurements were made on the second samples collected towards the middle of the shift. None of the samples

*As region specific mortality data are not published in five year age categories, these were calculated by multiplying the England and Wales rates by correction factors. These factors were derived using the formula:

$$\text{Correction factor} = \frac{\text{Deaths (n region)}}{\text{Rate (E\&W} \times \text{popn (n region))}}$$

which was calculated for five year calendar periods and age categories with as narrow groupings as available in the northern region mortality figures.

Table 2 *Concentrations of salivary nitrate and nitrite (n.moles/ml) in three groups of employees by class of exposure and residents in four parts of Britain: men only*

Exposure group	*No of men*	*Concentration in saliva**	
		Nitrate	*Nitrite*
Company employees with:			
High exposure	28	212·3 (160·6–280·6)	129·0 (95·2–174·8)
Moderate exposure	24	206·8 (149·9–285·2)	96·4 (69·9–133·0)
No exposure	28	102·7 (87·7–120·2)	88·9 (65·0–121·6)
Residents in:			
North east England	25	63·8 (38·2–106·7)	67·9 (51·3–89·9)
North Wales	26	111·5 (79·4–156·7)	51·9 (39·0–69·2)
Central England	53	161·0 (120·8–214·6)	115·1 (96·0–138·0)
South east England	30	154·3 (118·5–200·8)	92·5 (68·8–124·4)

*Geometric mean and 95% confidence limits.

collected at the start of the shift could be used as insufficient numbers of samples had been provided more than two hours after eating or drinking. Only 80 samples were suitable for comparison and the numbers in each exposure group were, therefore, somewhat less than the desired number of 30. The proportion of usable samples collected by the end of the shift was in each group over 70% but was slightly higher in the high exposure group (86%) than in the moderate exposure group (71%). In the unexposed control group it was 100%. The proportions of usable samples between the three groups varied due to differing shift patterns, those in the moderate exposure group being more likely to have an opportunity to eat or drink before the saliva sample.

The geometric means and the 95% confidence limits of the concentrations of nitrate and nitrite in the salivary samples in the three exposure groups are shown in table 2 and compared with comparable samples obtained a year before in four parts of Britain, one of which (north east England) included the area in which the plants were located. Both nitrate and nitrite concentrations were higher in men exposed to high concentrations of nitrates than in men exposed to moderate concentrations and the concentrations in the latter were higher than in control men in the same company without exposure. Moreover, the nitrate concentrations in the high and moderate exposure groups were statistically significantly greater than in the control group with no exposure ($p < 0{\cdot}0001$, and $p < 0{\cdot}001$, respectively). In neither case, however, was this so for the differences in nitrite concentrations.

Comparison with the geometric means of the concentrations observed previously in different parts of Britain[10 18] showed that the nitrate concentrations in the men with high or moderate exposure were higher than those obtained in any of the four areas, whereas the concentrations in the control men were higher than those observed in the same geographic area but lower than those observed elsewhere. Nitrite concentrations were generally less disparate, but the concentrations in the men with high exposure were again higher than any of those observed elsewhere.

FOLLOW UP

The results of the follow up are shown in table 3 separately for men and women who were identified in the 35% random sample of employees who were "paid off" between 1 January 1962 and 24 September 1972 (group A) and all others (group B). The proportions of employees in group A and, in particular, of those in group A who had died are relatively so small (6·1% and 1·3% respectively) that the failure to have

Table 3 *Status of cohort of nitrate fertiliser workers at 1 March 1981*

Status	*Group A**		*Group B‡*		*Whole cohort*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Alive at 85, follow up ceased	0	0	13	0	13	0
Alive under 85	61	15	930	98	991	113
Emigrated	8	0	9	0	17	0
Died	4†	0	300	8	304	8
Untraced	0	0	2	0	2	0
All categories	73	15	1,254	106	1,327	121

*Thirty five per cent random sample of men and women paid off between 1 January 1962 and 24 September 1972.
†The four deaths in the 35% random sample were attributed to cancers of the lung (1), stomach (1), bladder (1), and ischaemic heart disease (1).
‡All others.

Table 4 *Mortality of male nitrate fertiliser workers 1 January 1946 to 28 February 1981 by cause and by degree of exposure: observed numbers and numbers expected at northern region rates*

Cause of death	No of deaths in					
	Men heavily exposed (n = 537)		All other men (n = 790)		Total cohort (n = 1327)	
	Obs	Exp	Obs	Exp	Obs	Exp
Cancer of:						
Oesophagus†	3	1·26	2	0·88	5	2·14
Stomach	7	7·22	5	4·84	12	12·06
Lung	25	21·04	10	14·73	35	35·77
Bladder†	2	1·93	0	1·27	2	3·20
Other sites‡	22	19·91	15	13·75	37	33·66
All malignant neoplasms	59	51·36	32	35·47	91	86·83
All respiratory diseases	21	30·97	15	20·07	36*	51·04
Ischaemic heart disease	56	67·74	36	45·98	92*	113·72
Other circulatory disease	35	41·81	18	26·64	53	68·45
All other diseases	15	19·42	5*	13·14	20*	32·56
Accidents and violence	7	8·48	5	7·03	12	15·51
All causes	193	219·78	111**	148·33	304***	368·11

*p < 0·05 (two sided); **p < 0·01 (two sided); ***p < 0·001 (two sided).
†Expected numbers derived from national rates.
‡Expected numbers derived from subtraction.

included all employees who were paid off can have made little difference to the results. The number of women in the cohort is also so small that no useful results could be expected from analysing their experience* and our analyses are therefore limited to the total cohort of male employees, including those in groups A and B.

Of the 1327 men studies in the total cohort, two (0·2%) were untraced at 1 March 1981, 304 (22·9%) were known to have died under age 85, and the rest were either still alive, had reached 85 and ceased to be followed up, or had emigrated. Out of the 304 deaths, details of the cause of death were available for 302 men, the other two having unknown cause.

MORTALITY

The total numbers of deaths observed and the numbers attributed to 11 categories of causes are shown in table 4 for the whole cohort and separately for the 537 men who had been heavily exposed (as defined previously) for at least one year and for the 790 other men who had not. For comparison with the numbers of observed deaths, table 4 also shows the numbers expected on the basis of the northern region mortality rates over the same period, apart from the numbers expected from cancers of the oesophagus and bladder which could be calculated only from the relevant rates for England and Wales as a whole, and the numbers expected from cancers of other sites that were obtained by subtraction.

*The eight deaths in women were attributed to cancer of the breast (1), colon (1), ovary (2), cerebrovascular disease (1), ischaemic heart disease (1), bronchopneumonia (1), and stomach ulcer (1).

The total number of deaths was less than that expected (relative risk [RR] 0·83) and it was also less than expected for each exposure group (heavily exposed, RR 0·88; all other men, RR 0·75). The numbers of deaths were also less than expected for each exposure group for each of the five broad categories of causes (all respiratory diseases, ischaemic heart disease, other circulatory diseases, all other diseases, and accidents and violence). For the remaining category—all malignant neoplasms—the numbers of deaths were slightly greater than expected for the entire cohort (RR 1·05) and for the heavily exposed group (RR 1·15) but not for all other men (RR 0·90). Several of these differences were statistically significant, highly so (two-sided $p < 0·001$) for all causes in the whole cohort and for all causes in the men not heavily exposed, and marginally so for all respiratory diseases and ischaemic heart disease in the whole cohort (p respectively 0·04 and 0·05) and for all other diseases in the whole cohort and in the men not heavily exposed (p respectively 0·04 and 0·03). In each case the fertiliser workers had experienced a lower mortality than that expected from the experience of the region in which the works were located.

For four types of cancer there was some a priori evidence to suggest that they might be produced by conditions that favoured increased formation of nitrosamines and nitrosamides in vivo—namely, cancers of the stomach (see above), oesophagus,[19 20] liver,[21] and urinary bladder.[22] The numbers of deaths attributed to these four types of cancer were, therefore, examined separately along with the numbers attributed to cancer of the lung, which deserved separate examination because the disease is so common

Table 5 *Mortality of nitrate fertiliser workers from cancers by type and by degree and duration of exposure and time since first exposure*

Cause of death	*No of deaths in*							
	Men heavily exposed				*Other men*			
	Exposed 10 y or more, observed 20 y or more after first heavy exposure		*Others*		*Exposed 10 years or more, observed 20 y or more after first exposure*			
	Obs	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*
Cancer of:								
Oesophagus*	0	0·52	3	0·74	1	0·28	1	0·60
Stomach	3	2·91	4	4·31	3	1·50	2	3·34
Bladder*	1	0·86	1	1·07	0	0·44	0	0·83
Cancer of:								
Suspect sites	4	4·29	8	6·12	4	2·22	3	4·77
Lung	13	8·11	12	12·93	4	4·50	6	10·23
Other sites†	6	7·90	16	12·01	3	4·12	12	9·63
All malignant neoplasms	23	20·30	36	31·06	11	10·84	21	24·63

*Expected numbers derived from national rates.
†Expected numbers derived from subtraction.

and has so often been found to be caused by occupational hazards, and those attributed to cancers of all other sites combined. Only one death was attributed to cancer of the liver* and this disease was, therefore, excluded from further consideration, the observed and expected numbers being included in the category of "all other sites."

For two of the five causes of death the mortality was slightly higher than expected for the whole cohort (cancer of the oesophagus, RR 2·34; cancers of other sites, RR 1·10) and for both exposure groups (heavily exposed, cancer of the oesophagus, RR 2·38, and cancers of other sites, RR 1·10; other men, cancer of oesophagus, RR 2·27, and cancers of other sites, RR 1·09). For one category (cancer of the lung) the mortality was raised only in the heavily exposed group (RR 1·19). None of these differences, however, approached statistical significance (p, two tailed always $>0·1$).

The number of deaths attributed to each type of cancer are too few to allow any detailed subdivision. We may, however, examine deaths from the groups of cancers which it had been expected might be caused by exposure to nitrates and from cancer of the lung according to whether they occurred disproportionately often in men who would be most likely to show the effect of an occupational hazard of cancer if one had existed—namely, men who had been exposed for 10 years or more and were observed 20 years or more after first exposure. Table 5 shows the results of dividing the deaths in this way. This provides no evidence to suggest that cancers of the oesophagus, stomach, and bladder were produced by occupational exposure but it does suggest that the small excess of lung cancer observed in heavily exposed men might be. The excess of lung cancer in men who had been heavily exposed for 10 years or more and were observed 20 years or more after first heavy exposure is relatively greater than that observed in any of the other three groups of men whose mortaility experience is shown in table 5. The excess could well be due to chance (p, two tailed, $>0·1$) but it is also compatible with a relative risk of 2·74 (upper 95% confidence limit of observed relative risk of 1·60).

*This occurred in a man who was never in a high exposure job but who had more than 20 years of exposure to nitrate and who died aged 80. Death was certified as due to "primary carcinoma liver" with cirrhosis of liver and portal splenomegaly given as contributory conditions.

Discussion

The choice of a suitable control group to serve for comparison with a cohort of men employed in a particular factory is a constantly recurring problem in occupational medicine. We have chosen men resident in the northern region of Britain, because the region contained the fertiliser works in which we were interested and was the smallest unit for which sex, age, and

Table 6 *Comparison of mortality from cancer in Teesside with that in the northern region of England and in all England and Wales*

Type of cancer	*Standardised mortality ratio**	
	Teeside 1968–78	*Northern region 1973*
Oesophagus	128	110
Stomach	136	119
Lung	133	114
Bladder	109	—
Other sites	113	—
All malignant neoplasms	116	111

*England and Wales SMR = 100.

cause specific mortality rates were available for most of the period during which the fertiliser workers were under observation. Two of the sets of rates that we required were not, however, available for the northern region and for these (the rates for cancer of the oesophagus and bladder) we had to use the national rates for England and Wales instead. It might have been better to have used the data for Teesside, the conurbation in which the works were actually situated, but they were not available in sufficient detail over a long enough period to provide sufficient information for our purpose. They were, however, available for 1968–78, based on the population recorded at the 1971 census,[23] and we have been able to use these to compare the rates in Teesside for the five groups of cancers examined in table 5 with the rates in the northern region in 1973 and in England and Wales in 1971. The results, which are given in table 6, show that we have, in each case, probably underestimated the number of deaths to be expected in the fertiliser workers in the absence of any specific occupational hazard. Teesside is, however, a highly industrialised area with many chemical works, and the rates in the area are possibly inflated to some extent by various hazards (recognised and unrecognised) so that the best comparison might produce expected numbers of deaths midway between those for Teesside and those we actually used.

The relatively low mortality from all causes, respiratory diseases, circulatory diseases, and all other diseases other than malignant neoplasms and violence observed in the fertiliser workers is characteristic of industrial cohorts that include a high proportion of long service employees, so long as they are not exposed to any major occupational hazard. The results relating to these broad groups of diseases are therefore not surprising, as no occupational hazard from diseases other than cancer had been suspected, and the group of 1327 men included none with less than a year's employment and over 67% with more than 10 years' employment.

In such circumstances the mortality from malignant neoplasms is commonly close to that generally observed in the same part of the country in men of similar socioeconomic status. The finding that the mortality from cancer was not similarly decreased but was 5% above that expected from the contemporary experience of men living in the same region is, therefore, also unremarkable. Indeed it would not have been remarkable if it had been somewhat higher, as the mortality from cancer increases with decreasing socioeconomic status and the proportion of men in socioeconomic groups 1 and 2 was less than in the northern region as a whole (1·6% against 16·8% averaged over the 1961 and 1971 censuses) whereas the proportion in socioeconomic groups 4 and 5 was greater (71·4% against 30·5%).[18]

The lack of any increased mortality from gastric cancer or of any evidence of an increased mortality from four types of cancer that it was thought might be associated with exposure to nitrates in those men who would be most likely to show evidence of an occupational hazard—that is, those who were heavily exposed for 10 years or more and were observed 20 years or more after first heavy exposure—weighs against the idea that exposure to nitrates in the environment leads to the formation in vivo of material amounts of carcinogens. The numbers of deaths attributable to cancers of the oesophagus, stomach, bladder, and liver are small, and our finding is compatible with the existence of a real hazard causing about twice the normal risk, but the failure to find any evidence of such a hazard in men who have been exposed to substantial amounts of nitrate in the environment, not confounded with possibly anticarcinogenic agents, as may be the case with people who absorb large amounts of nitrate through the consumption of a large amount of vegetables, accords with the absence of a relation in other studies.[10 24] The amount of nitrate to which people in England and Wales have been exposed is possibly insufficient to produce a detectable effect and much larger amounts may be needed. Interestingly, the fertiliser workers that we have studied were more heavily exposed in the past than they are now and they are still exposed to sufficient amounts to double the concentration of nitrate in their saliva.

One other study of fertiliser workers[25] has been based on a 10% sample of all such workers recorded at the 1961 and 1971 censuses and followed up to 1978 and 1977 respectively. In keeping with our results they failed to find any increase of gastric cancer or appreciable increase for any causes of death in either cohort. In the latter cohort they found a weak relation between mortality from all cancers and nitrate containing dust and a non-significant rise in lung cancer mortality (9 deaths against 6·4 expected). In our study the small increase in the mortality from lung cancer in heavily exposed men who had been employed for 10 or more years and were observed 20 or more years after first exposure also suggested the possibility that nitrates in the ambient atmosphere might increase the risk of lung cancer. This increase was not, however, postulated before the study began and, although consistent with the previous study,[25] could easily be attributed to chance or to our inability to adjust for the possible effects of smoking. At present, the finding may be regarded only as the basis for a hypothesis to be tested by further observation.

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