

## Census-based mortality study of fertiliser manufacturers

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**ABSTRACT** This study was designed to investigate whether exposure to nitrate-containing dust during fertiliser manufacture was associated with an excess of deaths from cancer in general or specifically from cancers of the digestive tract, liver, lung, and bladder. It was based on data extracted from census schedules by the Office of Population Censuses and Surveys, occupational characteristics recorded by fertiliser workers at the 1961 and 1971 censuses of England and Wales being related to subsequent mortality ascertained through the National Health Service Central Register. The 1961 cohort, followed up until 1978, showed a "healthy worker effect" and no evidence of excess mortality from cancer at any site. The 1971 cohort also showed below average mortality during 1971-7 for all causes of death and for circulatory diseases, but there were more deaths from cancer than expected, due mainly to an excess of cancers of the lung and digestive tract. The excess of cancer was more pronounced, but not statistically significant, when compared with other employed men. Though the numbers for comparison were small, there was weak evidence of an association between cancer mortality and frequency of exposure to nitrate-containing dust in this cohort. It is difficult to reconcile the excess cancer mortality in the 1971 cohort with the more favourable level in the earlier cohort, since industrial hygiene has improved and the cohorts showed a similar distribution by region and social class. To examine further these conflicting results the 1971 cohort will be followed for a longer period and re-examined when more deaths have accrued.

It is now well established that nitrosamines can be formed *in vivo* from dietary amines and nitrite. In feeding experiments in animals sufficient carcinogenic nitrosamine has been generated to induce tumours of the oesophagus, stomach, liver, lung, and bladder.<sup>1</sup> In man endogenously formed nitrosamines have been identified in gastric juice,<sup>2,3</sup> saliva,<sup>4</sup> urine<sup>5-7</sup> and faeces.<sup>8</sup> Since nitrite is derived mainly from bacterial reduction of dietary nitrate the amount of nitrosamine formed depends in part on the amount of nitrate ingested.<sup>9</sup> Therefore, if endogenously formed nitrosamines are important in human cancer, populations ingesting large amounts of nitrate should have a higher incidence of cancer of the relevant target organ. Epidemiological studies in Chile<sup>10-12</sup> and Colombia<sup>13,14</sup> have provided some evidence of an association between the ingestion of

nitrate and gastric cancer.

We have thought it worth while to pursue the hypothesis that high ingestion of nitrate increases the risk of cancer by studying mortality in industrial workers who have been exposed to nitrate-containing dust in the manufacture of nitrogenous fertilisers. Currently nitrate-containing dust is classified as a "nuisance particulate" by the Health and Safety Executive.<sup>15</sup> This category contains substances with a long-term history of little adverse effect on the lungs and no production of significant organic disease or toxic effect when exposure is kept under reasonable control. A threshold limit value of 10 mg/m<sup>3</sup> over a 40-hour working week is recommended.

The route by which inhaled dust reaches other sites in the body has been the subject of speculation; transport through lymphatics, direct penetration of the pleura, and transfer to extrapulmonary sites by macrophages in the blood have been suggested.<sup>16</sup>

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The explanation most often offered is that dust is coughed up from the lung, swallowed, and absorbed.<sup>17</sup> Discussions with representatives from three major manufacturers of nitrogenous fertilisers in the United Kingdom showed that efforts are being made to keep dust levels below the recommended threshold, but that very dusty conditions prevailed in the past. It seemed reasonable therefore to assume that nitrate would have been ingested after inhalation and swallowing in this dusty atmosphere.

The study was designed to test whether exposure to nitrate-containing dust during fertiliser manufacture was associated with an excess of deaths from cancer in general, or specifically from cancer of the stomach and those other sites where, from laboratory and hospital studies, an excess might be expected—that is, the oesophagus, intestine, rectum, liver, lung, and bladder. Mortality from all causes and from the major causes of death were also examined.

### Methods

The study was based on data extracted by the Office of Population Censuses and Surveys (OPCS). At both the 1961 and 1971 censuses of England and Wales replies to several questions on census schedules were coded only in a 10% sample of all records. Information relating to occupation and industry were among these items, the latter being coded according to the standard industrial classification advocated by the Central Statistical Office.<sup>18 19</sup> Using this coding OPCS is able to identify the records of members of industrial groups within each census sample.

For the present study data were obtained from OPCS on two cohorts of men aged 35–64 who, at the 1961 or 1971 censuses, were identified as “manufacturers of fertilisers or chemicals for pest control.” The sample was restricted to men aged 35–64 because at both censuses women workers were too few for study and cancer is rare under 35. Since fertiliser workers and manufacturers of pesticides were coded to the same industrial code it was not possible to distinguish between them initially in selecting the records for study.

Most fertilisers manufactured in the United Kingdom are either straight nitrogen fertilisers containing ammonium nitrate or compound fertilisers containing potassium and phosphate in addition to a source of nitrogen. With the help of the Fertiliser Manufacturers' Association, lists of companies primarily manufacturing straight nitrogen or compound fertiliser or both were compiled. The use of trade directories enabled the main products man-

ufactured by some other companies who were not members of the Fertiliser Manufacturers' Association to be ascertained. These lists enabled OPCS to classify the companies that featured on the census schedules into four broad categories according to the type of product manufactured:

- (1) Straight nitrogen and compound fertilisers.
- (2) Compound fertilisers.
- (3) Other fertilisers and manures.
- (4) Pesticides only.

This classification was intended to provide a gradient of potential exposure to nitrate and to distinguish fertiliser workers from those who worked only with pesticides.

The jobs carried out by fertiliser workers were classified according to frequency of exposure to nitrate-containing dust by the occupational hygienist in a major fertiliser manufacturing company. This classification enabled OPCS to code the jobs described on the census schedules according to frequency of exposure—frequent, infrequent, very infrequent, or never.

By examining the National Health Service Central Register (NHSCR), OPCS was able to identify and flag the records of the fertiliser workers included in the study. The cause of death, coded according to the 8th revision of the International Classification of Diseases,<sup>20</sup> could then be ascertained for the fertiliser workers who had died. Appropriate dates were used to calculate person-years-at-risk. From these the expected numbers of deaths by cause, derived from age and calendar period specific male mortality rates for England and Wales, were calculated. The ratios of observed to expected deaths were tested for statistical significance using the tables of Bailar and Ederer<sup>21</sup> based on the Poisson distribution. The mortality data were also examined by product and dust exposure categories for evidence of a dose-response relationship.

Also appearing on census schedules are questions relating to economic position—that is, whether currently employed, out of work, etc. The mortality of those men who were in employment at the time of the 1971 census could be studied by comparing the numbers of observed deaths with those expected on the basis of death rates for employed men made available to us from the OPCS longitudinal study.<sup>22 23</sup> In this way an examination of the healthy worker effect was possible.

The study was conducted in a strictly confidential manner entirely within OPCS. The data were supplied to PF and CC in the form of statistical tables of person-years-at-risk accompanied by observed and expected deaths for the selected causes of death. No information about identified individuals left OPCS at any stage.

Table 1 Mortality in fertiliser manufacturers

Cause of death	1961 Cohort (1961-78)			1971 Cohort (1971-7)		
	Observed deaths (O)	Expected deaths (E)	O/E	Observed deaths (O)	Expected deaths (E)	O/E
All causes	232	282.9	0.82*	43	51.6	0.83
All cancers	63	73.8	0.85	19	14.4	1.32
Oesophageal cancer	1	2.0	0.50	1	0.4	2.50
Gastric cancer	6	8.5	0.71	2	1.5	1.33
Intestinal cancer	6	4.5	1.33	1	0.9	1.11
Rectal cancer	2	3.3	0.61	2	0.6	3.33
Liver cancer	0	—	—	0	—	—
Lung cancer	30	30.2	0.99	9	6.4	1.41
Bladder cancer	3	2.9	1.03	0	—	—
Circulatory diseases	114	135.1	0.84	18	26.2	0.69
Ischaemic heart disease	76	92.6	0.82	14	18.7	0.75
Cerebrovascular disease	23	25.6	0.90	3	3.7	0.81
Bronchitis	23	21.3	1.08	2	2.8	0.71
Accidents	6	8.7	0.69	2	2.1	0.95
Others	26	43.3	0.60*	2	6.0	0.33

\* $p < 0.05$ .

Table 2 Mortality in fertiliser manufacturers by frequency of dust exposure

Dust exposure	No exposed*	All causes		All cancers		Circulatory diseases	
		O	O/E	O	O/E	O	O/E
<i>1961 Cohort (1961-78)</i>							
Frequent	371	98	0.75	28	0.82	38	0.61
Infrequent	330	96	0.89	26	0.94	56	1.09
Very infrequent	153	37	0.81	9	0.74	19	0.84
Never							
<i>1971 Cohort (1971-7)</i>							
Frequent	252	16	0.84	9	1.69	6	0.62
Infrequent	303	24	0.99	9	1.31	11	0.90
Very infrequent	94	2	0.24	1	0.42	1	0.25
Never							

\*In the 1961 cohort 12 workers and in the 1971 cohort two could not be classified.

## Results

### 1961 COHORT

In the 10% sample of the 1961 census 1000 men aged 35-64 years were identified as being manufacturers of fertilisers or chemicals for pest control. Of these, 955 were traced in the NHSCR; 866 were fertiliser manufacturers. The remaining 89, employed in companies manufacturing pesticides but not fertilisers, were not studied further. Between the census in 1961 and the end of 1978, 232 deaths had been notified in the fertiliser workers whereas 282.9 would have been expected on the basis of national rates (table 1). This observed (O) to expected (E) ratio of 0.82 represents a significant deficit ( $p < 0.05$ ). There were fewer cancer deaths than expected (O/E: 63/73.8) and a deficit of digestive tract cancers with the exception of intestinal cancer. The ratios of observed to expected deaths for cancers of the lung and bladder were approximately

unity. For the other causes of death shown in table 1 the expected deaths exceeded those observed with the exception of deaths from bronchitis where there were slightly more deaths than expected (O/E: 23/21.3).

In table 2 mortality from all causes, all cancers, and all circulatory diseases has been examined in three dust exposure categories. There is no evidence of a gradient in risk or excess mortality with increasing exposure in these broad disease categories, but there were more deaths than expected from bronchitis in men exposed frequently to dusty conditions (O/E: 18/10.3).

In table 3 the cohort has been subdivided according to the type of product manufactured. Over half the cohort worked in companies manufacturing both straight nitrogen and compound fertilisers and only about 10% of workers were assigned to each of the other two product categories. A further 25% worked for small companies where the type of pro-

Table 3 *Mortality in fertiliser manufacturers by product*

Product	No exposed*	All causes		All cancers		Circulatory diseases	
		O	O/E	O	O/E	O	O/E
<i>1961 Cohort (1961-78)</i>							
Straight nitrogen plus compound fertilisers	476	128	0.78	41	0.95	63	0.80
Compound fertilisers	81	22	1.03	5	0.86	11	1.08
Other fertilisers and manures	91	20	0.73	3	0.41	12	0.92
<i>1971 Cohort (1971-7)</i>							
Straight nitrogen plus compound fertilisers	491	32	0.85	12	1.13	15	0.78
Compound fertilisers	86	5	0.76	3	1.66	1	0.31
Other fertilisers and manures	31	3	0.99	3	3.48	0	—

\*In the 1961 cohort 218 workers and in the 1971 cohort 43 could not be classified.

Table 4 *Mortality in fertiliser manufacturers in employment at census, 1971-5*

Cause of death	Observed deaths (O)	Expected deaths (E)	O/E
All causes	30	24.6	1.22
All cancers	12	7.4	1.62
Circulatory diseases	14	12.7	1.10

duct manufactured could not be ascertained. Evidence of a gradient in risk of cancer is minimal, and there is no evidence of a gradient in risk or excess mortality from all causes or all circulatory diseases with increasing exposure.

The cohort was cross-classified by product and frequency of exposure to nitrate, but there was no evidence of a dose-response relationship.

#### 1971 COHORT

In the 10% sample of the 1971 census 690 male workers aged 35-64 were identified. The records of 676 were traced in the NHSCR, of which 651 were fertiliser manufacturers. In this cohort 43 deaths occurred between the census in 1971 and the end of 1977 whereas 51.6 would have been expected on the basis of the experience of men in England and Wales as a whole (table 1). Deaths from circulatory diseases were fewer than expected (O/E: 18/26.2) but, contrary to the findings in the 1961 cohort, the observed to expected ratio for all cancers showed an excess (O/E: 19/14.4), the major contributors to the excess being cancers of the lung (O/E: 9/6.4) and digestive tract (O/E: 6/3.4). These ratios, however, do not represent a statistically significant departure from the expected level of cancer mortality ( $p > 0.05$ ). There was no suggestion that the excess of digestive tract cancers was particularly due to gastric cancer (O/E: 2/1.5).

Table 2 shows mortality in the 1971 cohort by frequency of dust exposure. There is no clear gradient between the frequency of dust exposure and mortality from all causes of death or from circulatory diseases, but there appears to be a dose-response relationship for cancer deaths. No single cancer features, cancers of both the lung and digestive tract contributing to the ratios of 1.69 and 1.31. The trend is not statistically significant ( $p > 0.05$ ), however, and a dose-response relationship is not supported by the analysis of mortality by product category (table 3), since there is no evidence of a gradient with increasing exposure to nitrate. In this cohort it was possible to assign 93% of the workers to a product category.

Of the fertiliser workers in the 1971 cohort 96% were in employment the week before the census. When death rates from 1971 to 1975 for employed men in the OPCS longitudinal study were used as the basis for calculating the expected deaths in this period, the fertiliser workers' mortality experience for all causes (O/E: 30/24.6) and all circulatory diseases (O/E: 14/12.7) was no longer favourable (table 4). The excess of cancer was more pronounced than in the comparison with national death rates, but was not statistically significant (O/E: 12/7.4;  $0.1 < p < 0.2$ ). There were seven cancers of the lung, three of the digestive tract, one of connective tissue, and one brain tumour. The deaths from cancer occurred in the two categories most often exposed to dust but were not associated with the manufacture of any particular type of fertiliser.

#### Discussion

This investigation is among the first census-based studies to be carried out with OPCS in which occupational characteristics recorded at census are related to subsequent mortality. This approach to

the study of cause of death in relation to exposure to nitrate was undertaken because no suitable records were available for study within the fertiliser manufacturing industry, and a detailed industry-based study was impracticable. In these circumstances use of the census to identify an exposed population and the NHSCR to ascertain their causes of death provides a means whereby the mortality pattern in an industrial group can be examined relatively quickly and cheaply.<sup>24</sup>

A difficulty in interpreting the results of this type of study lies in the choice of death rates used to calculate the numbers of expected deaths. On the basis of national rates overall mortality in both cohorts of fertiliser workers appears more favourable than in men in general. This mortality pattern reflects a selection effect; members of these cohorts were able to report an occupation at census. The permanently sick and men otherwise out of work who did not report an occupation at census were not eligible for selection for the study. The chronic sick and unemployed (with the exception of students) have higher death rates than employed men.<sup>22</sup> They are included, however, in national mortality statistics. Thus in using national rates the number of deaths from all causes expected in the fertiliser workers is likely to have been over-estimated, leading to the healthy worker effect created by selection for work in the study population.

A more appropriate measure of mortality was obtained for the 1971 cohort by using death rates among employed men in the OPCS longitudinal study as the basis for calculating the expected deaths. This comparison with the observed deaths leads to the conclusion that all cause mortality in the fertiliser workers does not differ significantly from that of other employed men. Similar rates are not available before 1971 so it was not possible to correct for the healthy worker effect in the earlier cohort. The observed to expected ratios by year of death in the 1961 cohort, however, show a pattern similar to that reported in the longitudinal study during the first five years of follow-up—low death rates initially rising progressively in subsequent years as the healthy worker effect wears off.<sup>25</sup>

Whereas the pattern of mortality from circulatory diseases is similar to that for mortality from all causes in both cohorts, the cohorts differ with respect to mortality from all cancers, although the difference falls short of the 5% level of statistical significance ( $0.05 < p < 0.1$ ). There are fewer deaths than expected in the 1961 cohort but an apparent excess in the 1971 cohort, which becomes larger when compared with cancer mortality in other employed men. The gradient in cancer mortality with increasing frequency of exposure to nitrate-

containing dust in the more recent cohort could have arisen by chance, because the period of follow-up so far is short, resulting in small numbers of deaths in each dust exposure category. Examination of data from the early years of follow-up of the 1961 cohort did not show any evidence of a similar dose-response relationship.

The quality of the data and some other aspects of the study design warrant consideration in interpreting these results. Statements on census schedules about occupation, industry and socioeconomic group were among the items checked in the post-enumeration surveys that followed up both the 1961 and 1971 censuses. There was generally close agreement between the results of the post-enumeration surveys and the original enumeration.<sup>26 27</sup>

The underlying cause of death was ascertained from death certificates. Several studies have shown that there may be inaccuracies in the diagnostic information available at the time of death,<sup>28</sup> but confusion between the broad diagnostic categories used in this study is unlikely. The tracing rate was satisfactory, the records of 96% and 98% respectively being located in the NHSCR. Fewer than 1% of the study population were lost to follow-up through emigration.

In estimating exposure the jobs described at census were classified according to the likely frequency of exposure to nitrate-containing dust. It did not prove possible to classify jobs consistently according to the concentration of nitrate-containing dust to which workers were likely to have been exposed, and direct measurements of the dust concentration were not available. The classification of companies according to type of product manufactured was intended to provide an additional aspect of potential exposure, but 25% of subjects in the 1961 cohort and 7% in the 1971 cohort could not be categorised in this way.

Implicit in this method of investigation is the assumption that subjects have remained in the industry long enough to have been at risk. An obvious disadvantage of this method of investigation is that it is not possible to measure duration of employment within the industry directly, by contrast with studies in which personal contact is maintained with the participants. Although no information was available for individual workers in the study, some data on labour turnover and duration of service were obtained from a large fertiliser manufacturing company (G Paddle, personal communication). Total labour turnover averaged 12% a year over the period 1961–73. The duration of service distribution for a single year (1974) indicated that 66% of the workforce had a duration of service of 10 years or

more and 85% five years or more. Among those who left the company voluntarily in 1963 nearly half had worked for under one year. Thus the 12% average annual turnover must be predominantly among short-service employees. Some leavers may have moved within the fertiliser manufacturing industry, such movements being more likely in skilled occupations.

Examination of the occupation recorded at death also provided some evidence of prolonged exposure to risk. Overall nearly 80% of the fertiliser workers who had died were in jobs compatible with fertiliser manufacture at death or retirement. Fertiliser manufacture was explicitly mentioned on 14% of death certificates; in the 1961 cohort these deaths were spread evenly over the 18 years following the census, but in the 1971 cohort death certificates mentioning fertiliser manufacture all related to men dying before normal retirement age and were clustered in the early years after the census. Chemical manufacture was mentioned on a further 21% of death certificates. In another 44% of deaths the occupation recorded at death appeared among the jobs listed on the census schedules, although many of these jobs were non-specific and could be equally applicable to other industries. Only 19% of the study population had definitely moved out of the fertiliser manufacturing industry before death or retirement. In 2% the occupation at death was not recorded on the death certificate.

Since conditions in the industry with respect to dust exposure have improved over time it is difficult to reconcile the excess cancer mortality in the 1971 cohort with the more favourable level of mortality in the earlier cohort. Table 2 provides some evidence in support of an improvement in industrial hygiene. In the earlier cohort 43% of workers who could be categorised according to dust exposure were in jobs where exposure to dusty conditions was frequent, compared with 39% in the more recent cohort. The trend in deaths from bronchitis, a disease exacerbated by dusty conditions,<sup>29</sup> is also consistent with an improvement in industrial hygiene, though the number of deaths from this cause in the 1971 cohort is small.

The fertiliser manufacturing industry is concentrated in the three northern regions of England, 47% of the fertiliser workers in the 1961 cohort being resident in these regions compared with 59% in the 1971 cohort. The regional distribution of the fertiliser workers in the two cohorts differs slightly, but in the north and north-west regions, where male cancer mortality is the highest in England and Wales,<sup>30</sup> the percentage of fertiliser workers is similar in the two cohorts (31% and 34% respectively). Although on this basis both cohorts might be

expected to have higher cancer mortality than men in general, the discrepancy between them cannot be attributed to differences in the regional distribution of the industry in 1961 and 1971.

The social class distribution of fertiliser workers is shifted towards the lower social classes, which generally experience higher cancer death rates.<sup>31</sup> The similarity, however, in the distribution of workers by status within the relevant occupation units at both censuses<sup>32,33</sup> makes social class differences an unlikely explanation of the dissimilar levels of cancer mortality in the two cohorts. Smoking habits are strongly related to social class<sup>31</sup>; the cohorts could not be compared directly with respect to cigarette consumption because smoking habits are not recorded at census.

To examine further the conflicting results in the two cohorts it will be necessary to follow the 1971 cohort for a longer period. Having been flagged in the NHSCR, follow-up will proceed automatically so that the mortality experience of the fertiliser workers can be re-examined when more deaths have accrued.

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