Incidence of cancer among workers in a Norwegian nitrate fertiliser plant

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Abstract

The incidence of cancer among 2023 male fertiliser workers has been investigated in a historical cohort study. Workers who had been employed for more than one year in work with possible exposure to dust containing nitrate between 1945 and 1979 were included. An individual cumulated exposure to dust expressed in level-years was calculated for each participant. The cohort was followed up from 1953 to the end of 1988, and the incidence of cancer was compared with the national rates. There were 467 deaths *v* 504.8 expected (standardised mortality ratio (SMR) = 0.93), and 185 cases of cancer *v* 195.5 expected (standardised incidence ratio (SIR) = 0.95). Thirty cases of lung cancer were found *v* 27.5 expected (SIR = 1.09). No overall excess of gastric cancer was found (15 cases *v* 17.0 expected; SIR = 0.89). No association was found between cumulated exposure to nitrate and gastric cancer, and there was no association between duration of employment or time since first employment and incidence of gastric cancer.

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Carcinogenic N-nitroso compounds may be formed endogenously in humans. Exogenous nitrate is resorbed in the gastrointestinal tract, and partially secreted into the saliva where some nitrate is reduced to nitrite by bacteria. Nitrite may react with a secondary nitrogen group in substances that occur in food and drugs to form N-nitroso compounds. It has thus been postulated that subjects

ingesting large amounts of nitrate may run an increased risk of gastric cancer.¹ Different epidemiological studies have given inconsistent results, showing association as well as lack of association between exposure to nitrate and gastric cancer.²⁻⁹

In Norway 85% of the population is supplied with surface waters that contain very low nitrate concentrations (about 2 mg NO₃/l), and exposure to nitrate in the general population, estimated to be 31.4 mg/day in 1980, occurs mainly from vegetables and is thus associated with consumption of nitrite scavengers (ascorbate and retinols).¹⁰ Work related exposure to airborne nitrate is without simultaneous consumption of these scavengers, however, and may be prolonged and higher than exposure from food consumption. Exposure to nitrate by inhalation during fertiliser production could thus generate more endogenous nitrosation than nitrates from food. Two cohort studies among British fertiliser workers did not show any excess of gastric cancer,¹¹⁻¹³ and studies in Iceland and Sweden gave comparable results.^{14,15} To further investigate whether exposure to airborne nitrate is associated with increased risk of gastric cancer and lung cancer, we have studied the incidence of cancer in a cohort of fertiliser workers over a long follow up period. These workers have been employed at the largest fertiliser plant in Norway.

Study plants and exposure

The study plants are situated in south east Norway in an industrial complex that also comprises production plants for ammonia, nitric acid, magnesium, and polyvinyl chloride.

The company has produced calcium nitrate fertilisers since 1929 in one plant and complex fertilisers since 1936 in another plant. A second complex fertiliser plant was started in 1967. Complex fertilisers are produced from raw phosphate, nitric acid, ammonia, and potassium compounds. Rasorite, pentahydrate-borax, kieserite, cuprosulphate, and waste copper may be supplied. From 1969 amorphous silica has been used as a conditioner. Kieselguhr and calcium stearate were used before that. Calcium nitrate fertilisers are produced from spill off from the complex fertiliser plants,

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Table 1 Environmental measurements of dust containing nitrate in various plants and departments during the period 1966–87

Plant department	Year	Sampling type	No	Dust (mg/m ³)	
				Mean (range)	
Calcium nitrate fertiliser plant:	1983	Area	> 55	3.2	(0.3–53.2)
	1983	Personal	> 24	2.7	(1.7–4.3)
	1984	Area	10	6.7	(4.3–53.0)
	1987	Area	8	5.2	(0.7–10.1)
Complex fertiliser plant:	1966	Area	36	17.5	(1.1–197.5)
	1967	Personal	2	6.3	(5.7–6.9)
	1974	Area	52	12.3	(0.7–91.8)
	1974	Personal	20	9.8	(0.6–275.0)
Packing department:	1973	Area	12	17.8	(7.0–38.0)
	1974	Area	30	3.8	(0.6–17.0)
	1975	Area	35	12.6	(0.3–57.6)
	1979	Area	19	13.8	(1.0–68.8)

nitric acid, and ammonia. Rasorite or pentahydrate-borax may be added, but no conditioner is used. Calcium nitrate fertilisers were historically produced from local limestone, nitric acid, and ammonia. The nitrate content in complex fertilisers was 25.2% when the plant was restarted after the second world war, in 1945, and was gradually raised to an average of 40.3% in 1988. Calcium nitrate fertilisers have contained 64.0% nitrate since the production was started in 1929.

EXPOSURE ESTIMATES

Measurements of dust containing nitrate in the working environment have been carried out from 1967 onwards, and table 1 summarises the results. In the complex fertiliser plants the concentrations of dust containing nitrate in the 1960s and the 1970s were from 6 to 17 mg/m³. The dust concentrations in the packing department were up to 18 mg/m³ during the 1970s. Measurements in the calcium nitrate fertiliser plant in the 1980s showed dust concentrations from 3 to 7 mg/m³.

Based on these measurements and information on changes in production methods as well as interviews with some veterans, a job exposure matrix was constructed for exposure to nitrate (figure). This matrix comprised four levels of dust containing nitrate dust for each department. Based on this matrix individual cumulated exposures to nitrate, expressed in level-years, were calculated by multiplying duration of each employment period with the estimated historical level of exposure and adding up these results for all employment periods for every employee.

SMOKING HABITS

Surveys on smoking habits among the employees from the whole industrial complex were conducted in 1962 and 1980. In 1962 71% of 500 randomly selected employees were daily smokers, and in 1980 49% of all 4307 employees were daily smokers. Corresponding figures for male Norwegians were

63% and 42% in 1962 and 1980 respectively (Løchsen *et al*, unpublished data).

Subjects and methods

One personnel department has served all the plants in the industrial complex since 1929 and one health department since 1938. The records at these two departments were the sources of information about each worker. The individual records at the health department contained name, date of birth, five digit personal number (for employees working after 1960), dates for start and end of employment and a short work history. These records were complete from 1945 onwards for name, date of birth, and dates for start and termination of work for all

Estimated levels (0–3) of exposure to dust containing nitrate in different departments in the period 1945–88. Level 0 none; level 1 little; level 2 moderate, usually < 10 mg/m³; level 3 considerable, often > 10 mg/m³.

Table 2 Distribution of date of first employment and number of years of employment within the study cohort of 2023 nitrate fertiliser workers

Date of first employment	No (%)
1945-9	280 (13.9)
1950-9	763 (37.7)
1960-9	634 (31.3)
1970-9	346 (17.1)
No of years of employment:	
< 2	393 (19.4)
2-4	432 (21.4)
5-9	304 (15.0)
≥ 10	894 (44.2)

employees with more than one year of permanent employment. The records at the personnel department contained name, date of birth, places of work, and dates for commencement and interception for each period of employment in the different plants and departments of the company. This register was incomplete because old records were occasionally discarded in the 1970s. Out of 30 334 previous or present employees registered in these files covering the period 1929 to 1989, 5718 employees lacked work histories in the records of the personnel department. These work histories were reconstructed from information in the medical records and this was successful for 5660 employees.

In this study, all male workers were included who had been employed for the first time between 1 January 1945 and 31 December 1979 and employed for at least one year in the calcium nitrate plant, the complex fertiliser plants, or related departments. The inclusion criteria were met by 2023 employees, and 1990 of these were identified by birth and unique personal numbers given to all Norwegian citizens alive in 1960 or born later. Thirty three men had died or had emigrated before 1960, but all these were identified manually. Thus all employees who met the inclusion criteria were identified and included in the cohort. Table 2 shows the distribution of date of first employment and number of years of employment.

Beyond information on department of work or

area of work, the records at the health department and the personnel department were incomplete for job titles of the individual workers. Therefore, job titles were not used for further characterisation of the cohort.

The occurrence of cancer in the cohort was recorded from 1 January 1953 to 31 December 1988. Each member of the cohort was followed up from 1953 or, if first employed at a later date, from the middle of the year he was first employed, until death, emigration, or the end of 1988. Fifteen employees had emigrated after 1 January 1953 and were followed up to the middle of the year of emigration. The cases of cancer were identified through the Cancer Registry of Norway which has recorded all new cases of cancer in the whole Norwegian population since 1 January 1953. The observed incidences of selected cancers were compared with the age adjusted incidences of cancer in the national male population with the use of five year age specific incidence rates for each year from 1953 to 1988.

Several employees had held jobs in different departments during their employment. Calculations on the incidences of cancer among workers in the different departments were made with each department being viewed as a separate entity. Thus one worker may have contributed an observed cancer case to more than one department, but only once in the total cohort.

On the assumption of a Poisson distribution of the observed cases, 95% confidence intervals (95% CIs) were estimated with a two sided test of significance.

Results

There were 467 deaths from all causes in the cohort *v* 504.8 expected (standardised mortality ratio (SMR) = 0.93) and 185 cases of cancer *v* 195.5 expected (standardised incidence ratio (SIR) = 0.95) (table 3).

Fifteen cases of gastric cancer were observed *v*

Table 3 Observed (O) and expected (E) new cases of cancer at selected sites among 2023 male nitrate fertiliser workers employed for the first time between January 1945 and December 1979

Cancer site (ICD-7)	O	E	SIR	(95% CI)
Oesophagus (150)	1	2.4	0.42	—
Stomach (151)	15	17.0	0.89	0.49-1.45
Colon/rectum (153-154)	23	26.0	0.88	0.56-1.33
Lung (162)	30	27.5	1.09	0.73-1.53
Pleura (163)	0	0.7	—	—
Kidney (180)	9	7.6	1.18	0.54-2.25
Bladder (181)	13	13.5	0.96	0.51-1.64
Pancreas (157)	9	7.3	1.23	0.56-2.34
Malignant melanoma (190)	5	6.4	0.78	0.25-1.83
All cancers (140-207)	185	195.5	0.95	0.81-1.09

ICD-7 = Code of the International Classification of Diseases (7th revision).
Follow up period 1953-88; in total 50 966 observation-years.

Table 4 Observed (O) and (E) expected cases of new cancer among 2023 nitrate fertiliser workers by place of work

Place of work	All cancers (ICD-7 140-207)				Stomach (ICD-7 151)				Lung (ICD-7 162)			
	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)
Calcium nitrate/ manufacturing department	37	31.5	1.17	(0.83-1.62)	2	2.9	0.69	(0.07-2.48)	6	4.4	1.36	(0.50-2.98)
Complex fertiliser manufacturing department	25	27.6	0.91	(0.59-1.34)	4	2.3	1.74	(0.48-4.43)	3	3.9	0.77	(0.39-2.26)
All maintenance departments	15	26.7	0.56	(0.31-0.93)	0	2.2	—	—	2	3.8	0.53	(0.05-1.89)
Packing department	75	77.7	0.97	(0.76-1.21)	6	6.8	0.88	(0.32-1.93)	13	11.0	1.18	(0.63-2.02)
Quay	72	82.4	0.87	(0.68-1.10)	4	7.1	0.56	(0.15-1.44)	11	11.7	0.94	(0.47-1.68)
Storehouse	22	33.7	0.65	(0.41-0.99)	2	3.0	0.67	(0.07-2.40)	2	4.7	0.43	(0.04-1.53)
All management departments	7	7.1	0.99	(0.39-2.03)	0	0.5	—	—	0	1.0	—	—

Table 5 Observed (O) and expected (E) cases of new cancer among 2023 nitrate fertiliser workers by estimated cumulative nitrate exposure

Nitrate index (level-years)	All cancers (ICD-7 140-207)				Stomach (ICD-7 151)				Lung (ICD-7 162)			
	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)
01-19	75	85.0	0.88	(0.72-1.13)	6	7.1	0.85	(0.31-1.85)	14	11.8	1.19	(0.65-1.99)
20-39	45	39.8	1.13	(0.82-1.51)	3	3.6	0.83	(0.17-2.44)	5	5.5	0.91	(0.29-2.13)
4-59	25	30.7	0.81	(0.53-1.21)	3	2.8	1.07	(0.21-3.14)	5	4.3	1.16	(0.37-2.72)
≥ 60	40	40.0	1.00	(0.72-1.36)	3	3.5	0.88	(0.17-2.51)	6	5.9	1.02	(0.37-2.22)

17.0 expected, and 23 cases of colon or rectum cancer *v* 26.0 expected. There were 30 cases of lung cancer *v* 27.5 expected (SIR = 1.09). No pleural mesothelioma was found.

Dividing the cohort by place of work did not show any significant excess of total cancer among workers in any department (table 4). There were significantly less cancers than expected among maintenance workers. Four cases of gastric cancer *v* 2.3 expected were observed among employees in the manufacturing departments of the complex fertiliser plants. There were fewer cases of gastric cancer than expected among workers in the other departments. Six cases of lung cancer were observed *v* 4.4 expected among workers in the manufacturing department of the calcium nitrate fertiliser plant, and 13 cases *v* 11.0 expected among workers in the packing department. Cancer of the colon, rectum, kidney, and bladder were not in excess among workers in any department.

The incidence of total cancers was not increased in groups with the highest cumulated exposure to dust (table 5). Six cases of gastric cancer were observed *v* 7.1 expected in the group with the lowest nitrate index and three cases *v* 3.5 expected in the group with the highest index. Similarly, no

associations between the applied nitrate index and the incidence of cancer of the lung, colon, rectum, kidney, and bladder were found.

Table 6 shows the incidence of selected cancers by duration of employment. The incidence of gastric cancer was not higher for employees with more than 25 years of employment compared with employees with less than five years of employment.

To allow for development time for cancer, analyses were performed according to time since first employment (table 7). After a latency period of more than 20 years there was no excess of gastric cancer (6 observed *v* 10.2 expected) and there were 25 cases of lung cancer *v* 19.3 expected. This difference was not significant.

Discussion

The present results accord with the results of Fraser *et al*¹³ and Al-Dabbagh *et al*,¹¹ which showed no excess of gastric cancer among British fertiliser workers. Workers exposed to an average airborne nitrate concentration of 10 mg/m³ were characterised as heavily exposed by Al-Dabbagh *et al*.¹¹ In the present study the average historical concentration of nitrate in the working atmosphere was

Table 6 Observed (O) and expected (E) cases of new cancer among 2023 nitrate fertiliser workers by years of employment

Years of employment	All cancers (ICD-7 140-207)				Stomach (ICD-7 151)				Lung (ICD-7 162)			
	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)
01-04	54	62.0	0.87	(0.65-1.14)	6	5.3	1.13	(0.42-2.47)	10	8.5	1.18	(0.56-2.16)
05-14	56	58.6	0.96	(0.72-1.24)	4	5.7	0.70	(0.19-1.79)	9	8.0	1.13	(0.46-2.14)
15-24	46	50.6	0.91	(0.67-1.21)	3	4.4	0.68	(0.14-2.00)	4	7.1	0.56	(0.15-1.44)
≥ 25	29	24.8	1.17	(0.78-1.68)	2	1.7	1.18	(0.12-4.24)	7	4.0	1.75	(0.70-3.60)

Table 7 Observed (O) and expected (E) cases of new cancer among 2023 nitrate fertiliser workers by years since first employment

Years since first employment	All cancers (ICD-7 140-207)				Stomach (ICD-7 151)				Lung (ICD-7 162)			
	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)	O	E	SIR	(95% CI)
01-09	13	18.8	0.69	(0.37-1.18)	2	2.2	0.91	(0.09-3.27)	2	2.0	1.00	(0.10-3.60)
10-19	41	45.3	0.91	(0.65-1.23)	7	4.7	1.49	(0.60-3.06)	3	6.2	0.48	(0.10-1.42)
20-29	59	70.5	0.84	(0.64-1.08)	3	5.9	0.51	(0.10-1.49)	12	10.3	1.17	(0.60-2.04)
≥ 30	72	61.4	1.17	(0.92-1.48)	3	4.3	0.70	(0.14-2.04)	13	9.0	1.44	(0.77-2.47)

estimated to be about 10 mg/m³, which is higher than estimated in the study by Hagmar *et al.*¹⁵ Rafnsson *et al.*¹⁴ indicated exposure to higher concentrations of dust containing nitrate than the Swedish study, but there was no excess of gastric cancer in the Icelandic cohort.

The records of the personnel department and the medical department were the sources of information on each worker. The work histories constructed from the available information in the records of the health department were considered to be complete with the exception of shorter periods when some employees may have been hired by other departments.

The health department has existed since 1938 and health examinations before employment in the 1940s and 1950s may have resulted in selection of members to the cohort at its inception, which could have concealed possible positive associations between work related exposure and illness.¹⁶ The impact on the incidence of cancer in general, however, from this possible selection as an aspect of the healthy worker effect is assumed to be limited.¹⁷ Chronic atrophic gastritis may be associated with gastric cancer,¹⁸ but we did not find individual records where gastritis was diagnosed at the pre-employment health examination and used as refusal of employment. To minimise selection through attrition of the population as another aspect of the healthy worker effect, and heterogeneous exposure before inclusion, we chose an inception cohort design as proposed by Weiss.¹⁹

Neither the records at the health department nor those at the personnel department had complete individual data on job titles of each worker, which may have resulted in loss of some small subgroups of workers with higher exposure to dust containing nitrate.

The incidence of cancers of concern in the county where the industrial complex is situated are close to the national rates, and the national rates were used as the reference entity. Age standardised incidence of gastric cancer for men in the period 1970-9 was 20.4 per 100 000 in the county and 20.7 in Norway. The corresponding figures for lung cancer were 22.0 in the county and 25.2 in Norway.

The British studies¹¹⁻¹³ indicated a slight excess of lung cancer in some subgroups. That found in

the present study may be due to chance. A higher prevalence of smoking in the index group compared with the reference population may also contribute to the excess. Interviewed veteran workers considered the exposure to asbestos dust in the study plant to be sporadic or low. Asbestos exposure in other plants in this industrial complex (a magnesium plant and an electrochemical plant) has been prevalent and an increased incidence of lung cancer has been found.^{20,21} Information on exposure to asbestos in these and other plants before or after employment in the fertiliser plants was lacking for workers included in the cohort. The absence of pleural mesotheliomas in the study cohort is in accord with the view that exposure to asbestos may not have contributed much to the occurrence of lung cancers.

In summary, the present results do not support the hypothesis of increased risk of gastric cancer among fertiliser workers exposed to nitrate.

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- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
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