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Incidence of cancer among vinyl chloride and polyvinyl chloride workers

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ABSTRACT The results of a follow up study of the incidence of cancer and the mortality in a cohort of 454 male workers producing vinyl chloride and polyvinyl chloride are presented. The study population was restricted to employees with more than one year's work experience in the study plant between 1950 and 1969 and the cohort was followed up from 1953 to the end of 1979. Twenty three new cases of cancer were observed compared with 20·2 expected; one case of liver angiosarcoma was found. Five cases of lung cancer were found (2·8 expected) and four cases of malignant melanoma of the skin were observed (0·8 expected). The possibility of a causal relationship between exposure to vinyl chloride and the development of malignant melanomas is discussed.

Since 1974 when Creech and Johnson presented their report,[1] human exposure to vinyl chloride (VCM) has been associated with the occurrence of angiosarcoma of the liver. Several studies have confirmed these initial results as reviewed by Spirtas and Kaminski.[2] In animal studies where VCM was given to mice, rats, and hamsters by different routes of administration neoplasms have also been induced in other organs.[3]

Whether VCM has the potency to induce cancer in man in organs other than the liver has not yet been confirmed. Lung cancer,[4–7] brain tumours,[4–6] and cancer in the digestive system, primarily angiosarcoma of the liver,[5–8] have been suggested to be in excess in workers producing VCM and polyvinyl chloride (PVC), and the prime purpose of the present investigation was to study the incidence of cancer in workers exposed to VCM, with special emphasis on cancers other than liver tumours.

Material and method

PLANT DESCRIPTION

The study plant is located in the county of Telemark in south east Norway. In addition to VCM and PVC the company produces fertilisers, magnesium, and chlorine in adjacent plant complexes. The production of VCM and PVC was started in 1950. VCM was produced from acetylene in the room where the polymerisation reactors were located. In 1967 the VCM production was partly altered, and cracking of ethylenedichloride (EDC) was introduced as one of two production methods. The production of VCM was discontinued in 1971 after which time the plant was operated as a polymerisation unit. From 1955 onwards VCM and PVC were produced in separate rooms; table 1 shows the volume of VCM and PVC production and the number of employees over time.

STUDY POPULATION

A list containing the names of employees who had started work before the end of 1974 and whose period of employment had exceeded one month was constructed from the personnel register provided by the plant. The health department of the company has kept the health records of all present and previous workers employed from 1940 and onwards. These records also contain some information on the place of work of each employee. By combining these

Table 1 *Annual vinyl chloride and polyvinyl chloride production and number of employees in the study plant*

Work period	*VCM (tons)*	*PVC (tons)*	*No of employees*
1950–55	1000– 2500	1000– 2500	45– 50
1956–60	2500– 5000	2500– 5000	45– 90
1961–70	5000–30000	5000–30000	90–130
>1971	None	30000–60000	120–130

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two sources of information a list of names was constructed which was presumed to be complete. The individual records contained the following information on each worker: full name, date of birth, identity number, last known address, dates for beginning and terminating employment, departments in the plant at which each person had worked, and the duration of work in each department. Data were obtained for 1233 workers.

It was decided to restrict the analyses to male workers who had been employed for at least one year and who had first been employed at the plant before 1970. These limitations reduced the number of subjects to 454.

ESTIMATION OF EXPOSURE

As a consequence of the technical design of the plant and the process operation, the level of exposure to VCM in the past must have been high but no industrial hygiene survey had been performed before 1974. Estimates of the average atmospheric concentration in the past were based on sporadic measurements that had been carried out with an "explosion-meter" which was graded from 0% to 100% of the estimated lower explosion limit; 1%, equivalent to 400 ppm of VCM. Two sources of supplementary information for estimating the VCM concentration were used: interviews with workers, some of whom had been employed in the plant since the start of production, and a suggested odour threshold of about 500 ppm VCM. Based on this information, we have assumed that the VCM concentration was about 2000 ppm from 1950 to 1954, about 1000 ppm from 1955 to 1959, about 500 ppm from 1960 to 1967, and about 100 ppm from 1968 to 1974. During autoclave cleaning the exposure level may have been as high as 3000 ppm.[10] Both emulsion PVC and suspension PVC were produced. The surplus monomer in the PVC leaving the manufacturing plant before 1970 may have contained 500 ppm VCM or even higher concentrations.[11]

The plant was closed for reconstruction in October 1974 and since 1975 the VCM in the working atmosphere has been monitored continuously with automatic measuring devices, including alarm systems that warn the workers during even minor leakages. Since 1975 the VCM exposure level in the production units has been below 1 ppm most of the time.

JOB CLASSIFICATIONS

Jobs considered to have been associated with high VCM exposure include production, autoclave cleaning, maintenance, and tapping. Owing to the great amounts of surplus monomer in the PVC, one may also assume that the exposure level in the packing unit may have been high until 1970. Those working in the development laboratory which contained small autoclaves in small rooms, in the control laboratory, and at processing in the customers' service laboratory, may also have been heavily exposed, but no information about VCM levels in these working places is available. Nine different exposure categories were defined (table 2), a number of the workers having been employed in more than one exposure category. Membership of an exposure category was defined as that category in which the longest time had been spent. If an individual had been a production worker for some years and subsequently spent a greater number of years at a job that clearly entailed minimal exposure, he would by definition belong to a low exposure category.

As the exposure level was high in the early 1950s an attempt was also made to classify the jobs as determined by the exposure level, using the number of "years of 500 ppm" exposure. The procedure was as follows: one year of production work in 1951

Table 2 *Observed (O) and expected (E) deaths from all causes, and all new cases of cancer in the study population except non-melanoma skin cancer*

Exposure categories	No of workers	All deaths			All cancers			Person-years 1953–79
		O	E	O/E	O	E	O/E	
01 Vinyl chloride (acetylene)	17	1	2·41	NC*	0	0·81	NC*	368·5
02 Vinyl chloride (EDC)	8	0	0·50	NC*	1	0·20	NC*	110·0
03 Research laboratory	48	2	4·32	0·46	0	1·69	NC*	912·0
04 Polyvinyl chloride production	117	19	16·42	1·16	9	5·10	1·76	2308·5
05 Autoclave cleaning	17	5	3·04	1·64	2	1·03	1·94	309·5
06 Maintenance	43	4	7·64	0·52	1	2·87	NC*	888·0
07 Packing/drying	95	5	8·44	0·59	5	2·95	1·69	1742·5
08 Customers service laboratory	59	7	8·77	0·80	3	3·06	0·98	1065·5
09 Various jobs	50	7	7·80	0·98	2	2·44	0·82	971·5
Total	454	50	59·34	0·84	23	20·16	1·14	8676·0

*NC = Not calculated.

when the working atmosphere contained about 2000 ppm VCM on average, was classified as four "500 ppm-years." The same type of work in 1961, when the atmosphere was about 500 ppm, would give one 500 ppm-year. This additional categorisation of exposure could be given for VCM production, PVC production, autoclave cleaning, maintenance work, and PVC packing. Owing to the surplus monomer in the resin, one year of packing PVC would give about one 500 ppm-year for each year up to 1970, and it is even possible that this high level continued until 1974. In this way high exposure for short periods in workers categorised by jobs with low exposure level could be accounted for.

All workers were placed in an exposure category before we had any knowledge of their state of health or diagnoses.

FOLLOW UP

The main element of the method is to identify those individuals who meet the criteria for membership of the study population and to compare this population with a constructed Norwegian population whose age distribution was identical with that of the study group. (The method has been described in more detail by Langård *et al.*[12])

Total mortality and cancer incidence from 1953 to the end of 1979 have been determined for the study population. The Cancer Registry in Norway has records of all new cases of cancer since 1953 and has access to information on all causes of death provided by the Central Bureau of Statistics. This study is based on a comparison of observed and expected total mortality and incidence of cancer for the period 1953–79. To estimate the expected number of cases of cancer, the national five year age specific incidence rates were used. According to the data of the Cancer Registry, the rates of cancer incidence in the Telemark county are between 0·90 and 0·95 of the national figures.[13] Consequently, the more robust national rates could be used for reference purposes and the expected number of deaths are based on the national rates.

Results

Deaths from all causes and the number of new cases of cancer, excluding non-melanoma skin cancer, are presented in table 2. The number of person-years at risk is also shown together with a tabulation of the nine different exposure categories. Among 454 men there were 50 deaths from all causes (expected 59·3).

During the 27 years of follow up, 23 new cases of cancer were found against 20·2 expected. The nine exposure categories have been combined into three groups reflecting high, medium, and low exposure (table 3); the increased incidence of cancer is accounted for almost entirely by the high exposure group.

There was only one liver angiosarcoma, recruited from exposure category 04, and this case has been included in a previous survey.[4]

Table 3 presents the observed and expected figures for some malignant neoplasms of interest. Five cases of lung cancer were observed in the whole study population compared with 2·8 expected. The mean time between first exposure and the time of diagnosis (latent period) in these five cases was 17·2 years (range 3–26) (not shown in the table). Four of the five cases were in the high exposure group (1·82 expected).

Four malignant melanomas of the skin were identified in the study population whereas only 0·8 was expected; three of the cases were observed in the high exposure group (0·5 expected). The tumours were located as follows: two on the trunk, one in the face-neck area, and one on a foot. After the observation period one more case has been diagnosed in the medium exposure group; this was in the face-neck area. We are aware of one case of incipient malignant melanoma located on the trunk

Table 3 *Broad categories of work indicating exposure level. Observed (O) and expected (E) deaths from all causes, cases of cancer (all sites), colon cancer (ICD 153), bronchial cancer (ICD 162/163), malignant melanoma of the skin (ICD 190), and cancer of the thyroid gland (ICD 194). For work label, see table 2*

*Exposure level**	*No of workers*	*All cancers*			*ICD 153*			*ICD 162/163*			*ICD 190*			*ICD 194*			*Person-years 1953–79*
		O	*E*	*O/E*	*O*	*E*	*O/E*	*O*	*E*	*O/E*	*O*	*E*	*O/E*	*O*	*E*	*O/E*	
Group 1	297	18	12·96	1·4	3	0·92	3·3	4	1·82	2·2	3	0·51	5·9	2	0·11	18·2	5727·0
Group 2	107	3	4·75	0·6	0	0·34	NC*	0	0·67	NC*	1	0·18	NC*	0	0·04	NC*	1977·5
Group 3	50	2	2·44	0·8	0	0·18	NC*	1	0·35	NC*	0	0·10	NC*	0	0·02	NC*	971·5
Total	454	23	20·16	1·1	3	1·44	2·1	5	2·84	1·8	4	0·79	5·1	2	0·16	12·5	8676·0

*Group 1 (high vinyl chloride exposure) = Work labels 01, 02, 04, 05, 06, 07.
Group 2 (medium vinyl chloride exposure) = Work labels 03, 08.
Group 3 (low vinyl chloride exposure) = Work label 09.
NC = Not calculated.

Table 4 *Observed (O) and expected (E) cases of cancer (all sites), lung cancer (ICD 162/163), and malignant melanoma of the skin (ICD 190) in relation to time of first employment in the plant*

Years of first employment	No of workers	All cancers			ICD 162 163			ICD 190			Person-years 1953–79
		O	E	O/E	O	E	O/E	O	E	O/E	
1950–4	105	6	7·21	0·8	2	1·01	2·0	1	0·23	NC*	2619·0
1955–9	128	8	6·51	1·2	2	0·94	2·1	1	0·25	NC*	2717·0
1960–4	123	6	4·33	1·4	0	0·59	NC*	2	0·19	11·1	2093·5
1965–9	98	3	2·12	1·4	1	0·29	NC*	0	0·12	NC*	1246·5
Total	454	23	20·16	0·8	5	2·84	1·8	4	0·79	5·1	8676·0

NC* = Not calculated.

Table 5 *Observed (O) and expected (E) cases of cancer, all sites, of the colon (ICD 153), of the lung (ICD 162/163, malignant melanoma of the skin (ICD 190), and cancer of the thyroid gland (ICD 194), by 500 ppm-year exposure in*

No of 500 ppm-years*	No of workers	All cancers			ICD 153			ICD 162 163			ICD 190			ICD 194			Person-years 1953–79
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	
<1	169	6	7·06	0·8	0	0·51	NC*	2	1·01	2·0	1	0·29	NC*	0	0·06	NC*	3074·0
1–5	124	3	3·10	1·0	1	0·21	NC*	0	0·88	NC*	0	0·16	NC*	0	0·03	NC*	2088·5
>5	161	14	9·95	1·4	2	0·74	2·7	3	1·44	2·1	3	0·33	9·1	2	0·06	33·3	3540·5
Total	454	23	20·16	1·1	3	1·44	2·1	5	2·84	1·8	4	0·79	5·1	2	0·16	12·5	8676·0

NC* = Not calculated.
†For classification of exposure for these cases see material and methods

Table 6 *Distribution of exposure categories among workers in whom cancer has been diagnosed (all cases of cancer). Figures give duration of exposure under different categories in years*

Age when cancer was diagnosed	Time of first employment	Year of diagnosis	ICD No*	Exposure categories†								
				01	02	03	04	05	06	07	08	0
63	1962	1979	151							2		
67	1964	1967	151								3	
62	1956	1972	153					5				
67	1962	1973	153				11					
55	1968	1977	153							6		
56	1950	1971	155				22					
63	1950	1963	162									4
67	1952	1978	162 177				3					5
58	1955	1977	162 194				7			6	10	
54	1958	1977	162					11		10		
56	1968	1971	162							2		9
70	1950	1973	177				2				15	
26	1961	1967	178						18			
45	1952	1979	181				14					
38	1952	1957	190				4					
45‡	1953	1981	190			2						
40	1958	1980	190					4				
41	1961	1974	190								13	
41‡	1961	1977	190								15	
66	1964	1979	190				14					
62	1969	1972	193									3
33	1957	1980	194		11							
55	1955	1966	199					2				

*ICD 151 (stomach cancer), ICD 153 (colon cancer), ICD 155 (cancer of the biliary passages and liver), ICD 162/163 (lung and bron cancer), ICD 177 (cancer of the prostate), ICD 178 (testis cancer), ICD 181 (bladder cancer), ICD 190 (malignant melanoma o skin), ICD 194 (cancer of the thyroid gland).
†Exposure categories corresponding with the numbers in table 2.
‡This case occurred after the end of observation period.
§Incipient case.

and diagnosed in 1977 from the medium exposure group. This case has not been included in the study. The latent period for the four cases occurring during the follow up period was 8·8 years (range 2–28) (not shown in table 3). When the two additional cases were included the latent period was 13·1 years.

Three cases of colonic cancer were observed in the high exposure group against 0·9 expected. Two cases of cancer in the thyroid gland were observed; both were medullary carcinomas.

Table 4 shows the relationship between the date of first employment in the plant and the incidence of all cancers and of some specific tumour sites. We also related the expected chance (risk) of developing cancer to the estimated weighed level of exposure, the 500 ppm-year indicator, and these results are shown in table 5. The highest risk ratios were found among those workers who were characterised by high exposure—that is, those accumulating more than five 500 ppm-years. We have no information about the VCM exposure level for the exposure categories 03 and 08 (table 2), which are classified in table 5 under the "less than one" index and which includes workers with less than one 500 ppm-year. It may be assumed, however, that some of these workers were exposed to VCM levels of about 500 ppm. Therefore, the correct exposure category for one of the two cases of lung cancer under the "less than one" index (table 5) could be the "one to five" index. The same may be true for the one malignant melanoma under the "less than one" index.

The plant employment history of all workers in whom cancer has been diagnosed and the tumour sites, ranked according to ICD code (7th revision), are presented in table 6. The year of first employment and the age when cancer was diagnosed are also included. The previously mentioned latent periods have been calculated from table 6.

Discussion

The present investigation has shown an increased incidence of malignant melanomas of the skin, lung cancer, colonic cancer, and thyroid cancer in VCM/PVC workers. Our observation on lung cancers is in accordance with the results of several other studies but to our knowledge, an increased incidence of malignant melanomas in workers producing VCM/PVC has not been shown before. The present study is one on the incidence of cancer, by contrast with the other investigations which refer to deaths from cancer. If the percentage survival in diagnosed cases of malignant melanoma is high, studies on deaths from cancer may have masked a possible increased incidence of this tumour.

Waxweiler *et al* observed 11 deaths from lung cancer, as compared with 5·7 expected, in VCM workers with at least five years' exposure who also had been observed for 15 years or more after first exposure.[9] They also noted an unusual distribution in the histological type of lung cancer. Of the eight histologically confirmed cases, five were classified as large cell undifferentiated. In our study two of the cases of lung cancer were classified as oat cell carcinomas (small cell undifferentiated). Both occurred in the high exposure group, and both patients had started work before 1959. As the numbers are small, no conclusions should be drawn, but in Norway,[14] as in other countries,[15] only about 20% of all histologically classified lung tumours are listed as oat cell or small cell carcinomas. Studies on populations occupationally exposed to arsenic, asbestos, chromium VI, radiation from uranium, and chloromethylether[16] indicate that the proportion of oat cell lung cancers in these groups is much higher than expected, and this suggests that attention should be paid to oat cell lung cancer in epidemiological studies on working populations. Buffler *et al* observed three deaths from lung cancer (0·68 expected) in a subgroup of VCM exposed workers with more than five years' exposure at high exposure level and a long observation period.[7] Fox and Collier, on the other hand, could not show an increased risk of lung cancer in members of a cohort recruited from different plants.[8] They included all exposed workers, laid down no requirements for exposure minimum, and no minimum observation period was accounted for.

In the present study the smoking habits of the members of cohort are not completely known. A smoking questionnaire survey in the plant in 1980 showed that 53% of the workers were smokers, by contrast with 42% in the male population in the whole country in the same year.[14] Consequently, it does not seem likely that smoking as a confounding factor can explain the differences in the incidence of cancer.[16]

Maltoni *et al* have indicated that VCM is a multipotent carcinogen in mice, rats, and golden hamsters.[2] They also showed skin tumours in golden hamsters, some of which were malignant melanomas. In a study of the kinetics and organ distribution of VCM in which rats were exposed to ^{14}C-VCM by inhalation, Duprat *et al* showed "a great deal of labelled molecules probably both VCM and its metabolites" in the skin after three hours.[17] In a similar study Watnabe *et al* confirmed these results.[18] None of these authors discussed the significance of the distribution of VCM to the skin, however.

Malignant melanoma of the skin is believed to be associated with exposure to sunlight[19] and few occu-

pations have been associated with the development of these tumours. Tear gas (o-chloroacetophenone) and polychlorinated biphenyls[28] are chemicals that have been suggested as possible inducers. In our study population one more case of melanoma has been diagnosed after the closure of the study and before the increased incidence of tumour was known to us. This additional case considerably strengthens the association between exposure to VCM and the development of malignant melanomas. As the medical services in the Telemark county have been of a high quality and easily accessible, we do not believe that there has been any bias due to the presence of the occupational health service in the company. In fact, none of the four cases was diagnosed by the occupational physicians. One of the five subjects with skin cancer had survived until June 1982. The incidence of malignant melanomas in the rural areas of Telemark county is slightly higher than the national rate while the incidence in urban areas is fairly equal to the national rate.[29] All subjects with skin cancer had lived in the urban area.

We observed two cancers of the thyroid gland (0·16 expected): both cases occurred in the high exposure group and were of the same histological type. We are not aware of other studies indicating an excess of this type of cancer but as only two cases have been observed, no conclusions can be drawn.

In a Canadian study on workers exposed to VCM for five years or more Theriault and Allard showed an excess of cancer in the digestive system,[9] but the authors concluded that the excess is accounted for exclusively by cancer of the liver. In the present study we found a slight excess of cancer of the colon. Many of the other studies referred to include cancer of the liver in digestive cancers, and they conclude that the excess risk is due to this tumour. There are few reports on occupationally induced cancer of the colon and rectum although it has been indicated that asbestos workers, textile workers, and steel workers have an increased risk from these diseases.[30] Watanabe et al in their kinetic study showed some faecal elimination of ^{14}C after the inhalation of ^{14}C-VCM, but they discuss only urinary and pulmonary elimination in their paper.[31]

The results presented in the present study, considered with other epidemiological studies, seem to support the view that VCM may act as a multicarcinogen in man. This is in accordance with observations from animal studies.[1] Some of our findings differ from those presented by other workers, and will be followed up later. The observation period is short for some of the members of the cohort, and the study group is small. Nevertheless, the fact that the excess of different cancers was seen in the group with the highest estimated exposure level strengthens the suggested association between VCM exposure and these types of cancers, in particular the malignant melanomas.

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inated. (3) In several cases, work histories in the employment records did not provide enough details to pinpoint specific exposures. (4) Historical data on exposure levels were inadequate for the chemicals under investigation. Thus no quantification of exposure was possible. (5) Many of the workers were potentially exposed to a multitude of chemicals, and it was impossible to examine mortality by "pure" exposure. (6) For several conditions, the number of study subjects in some of the subgroups was smaller than desirable, and it was difficult to draw definitive conclusions. (7) Being a mortality study, the investigation not only inherited all the problems associated with death certificates but also suffered from lack of in-depth clinical information. (8) Employment other than that with the existing company was not considered. Nor was it feasible to include smoking history in the analysis. Despite these limitations, the study has identified several potential health problems in the cohort. We recommend that this study be updated in the future. A longer observation period will not only increase the statistical power of the study but also establish any trend in mortality, if one exists, in the cohort.

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Incidence of cancer among vinyl chloride and polyvinyl chloride workers

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ABSTRACT The results of a follow up study of the incidence of cancer and the mortality in a cohort of 454 male workers producing vinyl chloride and polyvinyl chloride are presented. The study population was restricted to employees with more than one year's work experience in the study plant between 1950 and 1969 and the cohort was followed up from 1953 to the end of 1979. Twenty three new cases of cancer were observed compared with 20·2 expected; one case of liver angiosarcoma was found. Five cases of lung cancer were found (2·8 expected) and four cases of malignant melanoma of the skin were observed (0·8 expected). The possibility of a causal relationship between exposure to vinyl chloride and the development of malignant melanomas is discussed.

Since 1974 when Creech and Johnson presented their report,[1] human exposure to vinyl chloride (VCM) has been associated with the occurrence of angiosarcoma of the liver. Several studies have confirmed these initial results as reviewed by Spirtas and Kaminski.[2] In animal studies where VCM was given to mice, rats, and hamsters by different routes of administration neoplasms have also been induced in other organs.[3]

Whether VCM has the potency to induce cancer in man in organs other than the liver has not yet been confirmed. Lung cancer,[4–7] brain tumours,[7–9] and cancer in the digestive system, primarily angiosarcoma of the liver,[8 10] have been suggested to be in excess in workers producing VCM and polyvinyl chloride (PVC), and the prime purpose of the present investigation was to study the incidence of cancer in workers exposed to VCM, with special emphasis on cancers other than liver tumours.

Material and method

PLANT DESCRIPTION

The study plant is located in the county of Telemark in south east Norway. In addition to VCM and PVC the company produces fertilisers, magnesium, and chlorine in adjacent plant complexes. The production of VCM and PVC was started in 1950. VCM was produced from acetylene in the room where the polymerisation reactors were located. In 1967 the VCM production was partly altered, and cracking of ethylenedichloride (EDC) was introduced as one of two production methods. The production of VCM was discontinued in 1971 after which time the plant was operated as a polymerisation unit. From 1955 onwards VCM and PVC were produced in separate rooms; table 1 shows the volume of VCM and PVC production and the number of employees over time.

STUDY POPULATION

A list containing the names of employees who had started work before the end of 1974 and whose period of employment had exceeded one month was constructed from the personnel register provided by the plant. The health department of the company has kept the health records of all present and previous workers employed from 1940 and onwards. These records also contain some information on the place of work of each employee. By combining these

Table 1 *Annual vinyl chloride and polyvinyl chloride production and number of employees in the study plant*

Work period	*VCM (tons)*	*PVC (tons)*	*No of employees*
1950–55	1000– 2500	1000– 2500	45– 50
1956–60	2500– 5000	2500– 5000	45– 90
1961–70	5000–30000	5000–30000	90–140
1971–	None	30000–40000	120–150

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structed which was presumed to be complete. The individual records contained the following information on each worker: full name, date of birth, identity number, last known address, dates for beginning and terminating employment, departments in the plant at which each person had worked, and the duration of work in each department. Data were obtained for 1233 workers.

It was decided to restrict the analyses to male workers who had been employed for at least one year and who had first been employed at the plant before 1970. These limitations reduced the number of subjects to 454.

ESTIMATION OF EXPOSURE

As a consequence of the technical design of the plant and the process operation, the level of exposure to VCM in the past must have been high but no industrial hygiene survey had been performed before 1974. Estimates of the average atmospheric concentration in the past were based on sporadic measurements that had been carried out with an "explosion-meter" which was graded from 0% to 100% of the estimated lower explosion limit; 1%, equivalent to 400 ppm of VCM. Two sources of supplementary information for estimating the VCM concentration were used: interviews with workers, some of whom had been employed in the plant since the start of production, and a suggested odour threshold of about 500 ppm VCM. Based on this information, we have assumed that the VCM concentration was about 2000 ppm from 1950 to 1954, about 1000 ppm from 1955 to 1959, about 500 ppm from 1960 to 1967, and about 100 ppm from 1968 to 1974. During autoclave cleaning the exposure level may have been as high as 3000 ppm.[9] Both emulsion PVC and suspension PVC were produced. The surplus monomer in the PVC leaving the manufacturing plant [illegible] 500 ppm VCM or even higher concentrations."

The plant was closed for reconstruction in October 1974 and since 1975 the VCM in the working atmosphere has been monitored continuously with automatic measuring devices, including alarm systems that warn the workers during even minor leakages. Since 1975 the VCM exposure level in the production units has been below 1 ppm most of the time.

JOB CLASSIFICATIONS

Jobs considered to have been associated with high VCM exposure include production, autoclave cleaning, maintenance, and tapping. Owing to the great amounts of surplus monomer in the PVC, one may also assume that the exposure level in the packing unit may have been high until 1970. Those working in the development laboratory which contained small autoclaves in small rooms, in the control laboratory, and at processing in the customers' service laboratory, may also have been heavily exposed, but no information about VCM levels in these working places is available. Nine different exposure categories were defined (table 2), a number of the workers having been employed in more than one exposure category. Membership of an exposure category was defined as that category in which the longest time had been spent. If an individual had been a production worker for some years, and subsequently spent a greater number of years at a job that clearly entailed minimal exposure, he would by definition belong to a low exposure category.

As the exposure level was high in the early 1950s, an attempt was also made to classify the jobs as determined by the exposure level, using the number of "years of 500 ppm" exposure. The procedure was as follows: one year of production work in 1951, 2000 ppm VCM on average, was classified as four "500 ppm-years." The same type of work in 1961, when the atmosphere was about 500 ppm, would give one 500 ppm-year. This additional categorisation of exposure could be given for VCM production, PVC production, autoclave cleaning, maintenance work, and PVC packing. Owing to the surplus monomer in the resin, one year of packing PVC would give about one 500 ppm-year for each year up to 1970, and it is even possible that this high level continued until 1974. In this way high exposure for short periods in workers categorised by jobs with low exposure level could be accounted for.

All workers were placed in an exposure category before we had any knowledge of their state of health or diagnoses.

FOLLOW UP

The main element of the method is to identify those individuals who meet the criteria for membership of the study population and to compare this population with a constructed Norwegian population whose age distribution was identical with that of the study group. (The method has been described in more detail by Langård *et al.*[10])

Total mortality and cancer incidence from 1953 to the end of 1979 have been determined for the study population. The Cancer Registry in Norway has records of all new cases of cancer since 1953 and has access to information on all causes of death provided by the Central Bureau of Statistics. This study is based on a comparison of observed and expected total mortality and incidence of cancer for the period 1953–79. To estimate the expected number of cases of cancer, the national five year age specific incidence rates were used. According to the data of the Cancer Registry, the rates of cancer incidence in the Telemark county are between 0·90 and 0·95 of the national figures.[11] Consequently, the more robust national rates could be used for reference purposes and the expected number of deaths are based on the national rates.

Results

Deaths from all causes and the number of new cases of cancer, excluding non-melanoma skin cancer, are presented in table 2. The number of person-years at risk is also shown together with a tabulation of the nine different exposure categories. Among 454 men there were 50 deaths from all causes (expected 59·3).

During the 27 years of follow up, 23 new cases of cancer were found against 20·2 expected. The nine exposure categories have been combined into three groups reflecting high, medium, and low exposure (table 3); the increased incidence of cancer is accounted for almost entirely by the high exposure group.

There was only one liver angiosarcoma, recruited from exposure category 04, and this case has been included in a previous survey.[4]

Table 3 presents the observed and expected figures for some malignant neoplasms of interest. Five cases of lung cancer were observed in the whole study population compared with 2·8 expected. The mean time between first exposure and the time of diagnosis (latent period) in these five cases was 17·2 years (range 3–26) (not shown in the table). Four of the five cases were in the high exposure group (1·82 expected).

Four malignant melanomas of the skin were identified in the study population whereas only 0·8 was expected; three of the cases were observed in the high exposure group (0·5 expected). The tumours were located as follows: two on the trunk, one in the face-neck area, and one on a foot. After the observation period one more case has been diagnosed in the medium exposure group; this was in the face-neck area. We are aware of one case of incipient malignant melanoma located on the trunk

Table 2 *Observed (O) and expected (E) deaths from all causes, and all new cases of cancer in the study population except non-melanoma skin cancer*

Exposure categories	No of workers	All deaths			All cancers			Person-years 1953–79
		O	E	O/E	O	E	O/E	
01 Vinyl chloride (acetylene)	17	1	2·41	NC	0	0·81	NC	368·5
02 Vinyl chloride (EDC)	8	0	0·58	NC	1	0·20	NC	110·0
03 Research laboratory	48	2	4·32	0·46	0	1·69	NC	912·0
04 Polyvinyl chloride production	117	19	16·42	1·16	9	5·10	1·76	2308·5
05 Autoclave cleaning	17	5	3·04	1·64	2	1·03	1·94	399·5
06 Maintenance	43	4	7·64	0·52	1	2·87	NC*	880·0
07 Packaging/tying	95	5	8·44	0·59	3	3·05	1·69	1742·5
08 Customers service Laboratory	59	7	8·77	0·80	3	3·06	0·98	1065·5
09 Various jobs	50	7	9·80	0·48	2	3·44	0·82	971·5
Total	454	50	59·34	0·84	23	20·16	1·14	8676·0

*Not calculated.

Table 3 *Broad categories of work indicating exposure level. Observed (O) and expected (E) deaths from all causes, cases of cancer (all sites), colon cancer (ICD 153), bronchial cancer (ICD 162/163), malignant melanoma of the skin (ICD 190), and cancer of the thyroid gland (ICD 194). For work label, see table 2*

Exposure level*	No of workers	All cancers			ICD 153			ICD 162/163			ICD 190			ICD 194			Person-years 1953–79
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	
Group 1	297	18	12·96	1·4	3	0·92	3·3	4	1·82	2·2	3	0·51	5·9	2	0·11	18·2	5727·0
Group 2	107	3	4·75	0·6	0	0·34	NC*	0	0·67	NC*	1	0·18	NC*	0	0·04	NC*	1977·5
Group 3	50	2	2·44	0·8	0	0·18	NC*	1	0·35	NC*	0	0·10	NC*	0	0·02	NC*	971·5
Total	454	23	20·16	1·1	3	1·44	2·1	5	2·84	1·8	4	0·79	5·1	2	0·16	12·5	8676·0

*Group 1 (high vinyl chloride exposure) = Work labels 01, 02, 04, 05, 06, 07.
Group 2 (medium vinyl chloride exposure) = Work labels 03, 08.
Group 3 (low vinyl chloride exposure) = Work label 09.
NC* = Not calculated.

Table 4 *Observed (O) and expected (E) cases of cancer (all sites), lung cancer (ICD 162/163), and malignant melanoma of the skin (ICD 190) in relation to time of first employment in the plant*

Years of first employment	No of workers	All cancers			ICD 162/163			ICD 190			Person-years 1953–79
		O	E	O/E	O	E	O/E	O	E	O/E	
1950–4	105	6	7·21	0·8	2	1·01	2·0	1	0·23	NC	2619·0
1955–9	128	8	6·51	1·2	2	0·94	2·1	1	0·35	NC	3093·5
1960–4	121	6	4·33	1·4	0	0·59	NC	2	0·19	11·1	2993·5
1965–9	98	3	2·12	1·4	1	0·29	NC	0	0·12	NC	1246·5
Total	454	23	20·16	0·8	5	2·84	1·8	4	0·79	5·1	8676·0

NC = Not calculated.

Table 5 *Observed (O) and expected (E) cases of cancer, all sites, of the colon (ICD 153), of the lung (ICD 162/163), malignant melanoma of the skin (ICD 190), and cancer of the thyroid gland (ICD 194), by 500 ppm-year exposure index*

No of 500 ppm-years*	No of workers	All cancers			ICD 153			ICD 162/163			ICD 190			ICD 194			Person-years 1953–79
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	
<1	169	6	7·06	0·8	0	0·51	NC	2	1·01	2·0	1	0·29	NC	0	0·06	NC	3074·0
1–5	124	3	3·10	1·0	1	0·21	NC	0	0·40	NC	0	0·16	NC	0	0·03	NC	2088·5
>5	161	14	9·95	1·4	2	0·74	2·7	3	1·44	2·1	3	0·33	9·1	2	0·06	33·3	3540·5
Total	454	23	20·16	1·1	3	1·44	2·1	5	2·84	1·8	4	0·79	5·1	2	0·16	12·5	8676·0

NC = Not calculated.
*For classification of exposure for these cases see material and methods

Table 6 *Distribution of exposure categories among workers in whom cancer has been diagnosed (all cases of cancer). Figures give duration of exposure under different categories in years*

Age when cancer was diagnosed	Time of first employment	Year of diagnosis	ICD No*	Exposure categories†								
				01	02	03	04	05	06	07	08	09
61	1962	1979	151							2		3
67	1964	1967	151					5				
62	1956	1972	153				11					
67	1962	1973	153							6		
55	1968	1979	153				22	1				
56	1950	1971	155									4
61	1950	1963	162				3					5
67	1952	1978	162/173				7			6	10	
55	1955	1977	162/194					11		10		
54	1958	1977	162							2		9
56	1968	1981	162				2				15	
70	1950	1973	173						18			
26	1961	1962	178				14					
45	1952	1979	181				4					
35	1952	1957	190			2						
35	1953	1981	190					4				
30	1958	1960	190								13	
[illegible]	1971	1974	190								15	
[illegible]	[illegible]	[illegible]	190				13					
[illegible]	[illegible]	[illegible]	193									3
[illegible]	[illegible]	[illegible]	193					1				
[illegible]	[illegible]	1969	193		11							
[illegible]	[illegible]	1968	193					2				

*ICD 151 (cancer of the stomach), ICD 153 (colonic cancer), ICD 155 (cancer of the biliary passages and liver), ICD 162/163 (lung and bronchial cancer), ICD 173 (cancer of the prostate), ICD 178 (cervix cancer), ICD 181 (bladder cancer), ICD 190 (malignant melanoma of the skin), ICD 194 (cancer of the thyroid gland).
†Exposure categories corresponding with the numbers in table 2.
‡One case omitted after the end of observation period.
§Suspect case.

and diagnosed in 1977 from the medium exposure group. This case has not been included in the study. The latent period for the four cases occurring during the follow up period was 8·8 years (range 2–28) (not shown in table 3). When the two additional cases were included the latent period was 13·1 years.

Three cases of colonic cancer were observed in the high exposure group against 0·9 expected. Two cases of cancer in the thyroid gland were observed; both were medullary carcinomas.

Table 4 shows the relationship between the date of first employment in the plant and the incidence of all cancers and of some specific tumour sites. We also related the expected chance (risk) of developing cancer to the estimated weighed level of exposure, the 500 ppm-year indicator, and these results are shown in table 5. The highest risk ratios were found among those workers who were characterised by high exposure—that is, those accumulating more than five 500 ppm-years. We have no information about the VCM exposure level for the exposure categories 03 and 08 (table 2), which are classified in table 5 under the "less than one" index and which includes workers with less than one 500 ppm-year. It may be assumed, however, that some of these workers were exposed to VCM levels of about 500 ppm. Therefore, the correct exposure category for one of the two cases of lung cancer under the "less than one" index (table 5) could be the "one to five" index. The same may be true for the one malignant melanoma under the "less than one" index.

The plant employment history of all workers in whom cancer has been diagnosed and the tumour sites, ranked according to ICD code (7th revision), are presented in table 6. The year of first employment and the age when cancer was diagnosed are also included. The previously mentioned latent periods have been calculated from table 6.

Discussion

The present investigation has shown an increased incidence of malignant melanomas of the skin, lung cancer, colonic cancer, and thyroid cancer in VCM/PVC workers. Our observation on lung cancers is in accordance with the results of several other studies but to our knowledge, an increased incidence of malignant melanomas in workers producing VCM/PVC has not been shown before. The present study is one on the incidence of cancer, by contrast with the other investigations which refer to deaths from cancer. If the percentage survival in diagnosed cases of malignant melanoma is high, studies on deaths from cancer may have masked a possible increased incidence of this tumour.

Waxweiler *et al* observed 11 deaths from lung cancer, as compared with 5·7 expected, in VCM workers with at least five years' exposure who also had been observed for 15 years or more after first exposure.[6] They also noted an unusual distribution in the histological type of lung cancer. Of the eight histologically confirmed cases, five were classified as large cell undifferentiated. In our study two of the cases of lung cancer were classified as oat cell carcinomas (small cell undifferentiated). Both occurred in the high exposure group, and both patients had started work before 1959. As the numbers are small, no conclusions should be drawn, but in Norway,[14] as in other countries,[15] only about 20% of all histologically classified lung tumours are listed as oat cell or small cell carcinomas. Studies on populations occupationally exposed to arsenic, asbestos, chromium VI, radiation from uranium, and chloromethylether[16] indicate that the proportion of oat cell lung cancers in these groups is much higher than expected, and this suggests that attention should be paid to oat cell lung cancer in epidemiological studies on working populations. Buffler *et al* observed three deaths from lung cancer (0·68 expected) in a subgroup of VCM exposed workers with more than five years' exposure at high exposure level and a long observation period.[7] Fox and Collier, on the other hand, could not show an increased risk of lung cancer in members of a cohort recruited from different plants.[8] They included all exposed workers, laid down no requirements for exposure minimum, and no minimum observation period was accounted for.

In the present study the smoking habits of the members of cohort are not completely known. A smoking questionnaire survey in the plant in 1980 showed that 53% of the workers were smokers, by contrast with 42% in the male population in the whole country in the same year.[14] Consequently, it does not seem likely that smoking as a confounding factor can explain the differences in the incidence of cancer.[14]

Maltoni *et al* have indicated that VCM is a multipotent carcinogen in mice, rats, and golden hamsters.[5] They also showed skin tumours in golden hamsters, some of which were malignant melanomas. In a study of the kinetics and organ distribution of VCM in which rats were exposed to ^{14}C-VCM by inhalation, Duprat *et al* showed "a great deal of labelled molecules probably both VCM and its metabolites" in the skin after three hours.[17] In a similar study Watnabe *et al* confirmed these results.[18] None of these authors discussed the significance of the distribution of VCM to the skin, however.

Malignant melanoma of the skin is believed to be associated with exposure to sunlight[19] and few occu-

patients have been associated with the development of these tumours. Tear gas (α-chloroacetophenone) and polychlorinated biphenyls[16] are chemicals that have been suggested as possible inducers. In our study population one more case of melanoma has been diagnosed after the closure of the study and before the increased incidence of tumour was known to us. This additional case considerably strengthens the association between exposure to VCM and the development of malignant melanomas. As the medical services in the Telemark county have been of a high quality and easily accessible, we do not believe that there has been any bias due to the presence of the occupational health service in the company. In fact, none of the four cases was diagnosed by the occupational physicians. One of the five subjects with skin cancer had survived until June 1982. The incidence of malignant melanomas in the rural areas of Telemark county is slightly higher than the national rate, while the incidence in urban areas is fairly equal to the national rate.[13] All subjects with skin cancer had lived in the urban area.

We observed two cancers of the thyroid gland (0·16 expected); both cases occurred in the high exposure group and were of the same histological type. We are not aware of other studies indicating an excess of this type of cancer but as only two cases have been observed, no conclusions can be drawn.

In a Canadian study on workers exposed to VCM for five years or more Theriault and Allard showed an excess of cancer in the digestive system,[9] but the authors concluded that the excess is accounted for exclusively by cancer of the liver. In the present study we found a slight excess of cancer of the colon. Many of the other studies referred to include cancer of the liver in digestive cancers, and they conclude that the excess risk is due to this tumour. There are few reports on occupationally induced cancer of the colon and rectum although it has been indicated that asbestos workers, textile workers, and steel workers have an increased risk from these diseases.[11] Watanabe *et al* in their kinetic study showed some faecal elimination of ^{14}C after the inhalation of ^{14}C-VCM, but they discuss only urinary and pulmonary elimination in their paper.[18]

The results presented in the present study, considered with other epidemiological studies, seem to support the view that VCM may act as a multicarcinogen in man. This is in accordance with observations from animal studies.[2] Some of our findings differ from those presented by other workers, and will be followed up later. The observation period is short for some of the members of the cohort, and the study group is small. Nevertheless, the fact that the excess of different cancers was seen in the group with the highest estimated exposure level strengthens the suggested association between VCM exposure and these types of cancers, in particular the malignant melanomas.

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Occupational exposure to hydrazine and subsequent risk of cancer

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

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

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

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

Oral administration of hydrazine sulphate to hamsters, however, did not cause a significant excess of cancers, but 1,2-dimethyl hydrazine did cause angiosarcomas of blood vessels and caecal and hepatic tumours.[3 6]

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

It seemed highly desirable, therefore, to see whether there was any evidence that hydrazine was carcinogenic to man and to see what had happened to men who had been exposed to hydrazine vapour in the course of their work, even if the number available for study was small. A preliminary analysis of men working at a hydrazine plant failed to suggest an excess risk of cancer associated with exposure to hydrazine.[11] The follow up was incomplete, however, and as mortality was not analysed by cause we conducted a fresh study using the same cohort.

The plant

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

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Epidemiological study of the lung function of workers at a factory manufacturing polyvinylchloride

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ABSTRACT A preliminary epidemiological study has been carried out to investigate a report that some men working in a factory manufacturing polyvinylchloride (PVC) had abnormally low values of the single breath diffusing capacity for carbon monoxide (T_LCO). All 265 present and past employees of the PVC factory were studied, together with 219 men from the workforce of a nearby foundry. Each man's T_LCO was measured and a smoking history and detailed occupational history obtained. The distribution of standardised T_LCO results from all persons examined was symmetrical and did not indicate an unexpectedly high proportion of men with clinically important impairment of T_LCO. The results of a case-control study showed that, having allowed for age, height, weight, and smoking habit, T_LCO was associated with a history of working in the PVC factory before 1975 (when levels of vinylchloride monomers (VCM) were much higher than subsequently), and slightly associated with working in jobs where exposure to VCM was likely to have been highest. The men with low T_LCO also tended to have smoked more heavily than controls. The relative importance of occupational factors and smoking in relation to low T_LCO is not clear, but the results give some support to the hypothesis that work in the PVC factory before 1975 entailed exposure to a substance that caused impairment of lung function in a small number of men.

The management and occupational physician of a factory making polyvinylchloride (PVC) had become concerned over an apparent excess in their workforce of men with impairment of the single breath transfer factor for carbon monoxide (T_LCO). The present study was planned to determine whether there was such an excess of men with low values of T_LCO in the workforce, and to make a preliminary assessment of whether low T_LCO might be related to occupational factors.

The factory had been in operation since 1969 and produced PVC powder from vinylchloride monomer gas (VCM). All men who had worked at the factory, whether or not they were currently employed there, were invited to participate in the study. A sample of men working in a nearby foundry were also invited to participate; they had been exposed to the same environmental conditions outside the workplace and were included in order to augment the number of men in the study who had not been exposed to possible hazards in the PVC factory.

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Methods

SELECTION OF SURVEY POPULATION

All 177 men currently employed at the PVC factory were invited to take part and attempts were made to trace and invite all the 263 former employees. At the foundry, the study was confined to 285 men selected randomly from the 1085 current male employees. The number of men at the foundry aged under 25 was limited to 15 to take account of a disproportionately large number of young men in the foundry population compared with the PVC workers and to provide a group of similar size to the 13 PVC workers of this age. Apart from this, selection did not take account of age.

MEDICAL SURVEY

The medical survey team visited the factories and recorded a full occupational history since leaving school for each man. Trained personnel using a questionnaire which was a modified version of the Medical Research Council questionnaire of respiratory symptoms[1] recorded details of each man's smoking history. Additional questions were related to age of starting smoking and the number of

cigarettes smoked during a man's maximum smoking period.

Measurements of single breath gas transfer factor for carbon monoxide were carried out on all men using the breathholding method[2] based on the modified Krogh technique (transfer test B; P K Morgan Ltd, Chatham, Kent). The mean of two measurements was used in the subsequent analysis. All PVC factory employees had forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measured using an electronic dry rolling seal spirometer (Ohio 800). The best of three technically satisfactory measurements was used for the analysis. Approval was not obtained for FEV_1 and FVC measurements in the foundry workers.

METHODS OF ANALYSIS

Analysis of data from the total survey population

The data were studied initially by summary descriptive statistics and by multiple linear regression analysis of lung function taking into account age, height, weight, and smoking habit. Men were assigned to one of three smoking categories; lifelong non-smoker, current smoker, and ex-smoker. The two smoking groups included smokers of pipes, cigars, and hand-rolled cigarettes but the majority smoked manufactured cigarettes.

In the regression model used for both T_LCO and FEV_1 different intercepts and age slopes were allowed for the three smoking groups, non-smokers, current smokers, and ex-smokers. This means that the estimated effects of age were not constrained to be the same necessarily in the three smoking habit groups.

The relation between a man's observed and predicted lung function values was expressed as a standardised residual (SR). This is defined by the equation:

$$SR = \frac{\text{(observed value—value predicted from fitted equation)}}{\text{(estimated standard deviation of the prediction)}}$$

The distribution of FEV_1 and T_LCO SR values of the whole population was examined.

Case-control study

For each lung function variable, those men with the largest negative SR value were chosen as cases. Two groups of controls were selected randomly, firstly, from those men whose SRs were clustered around zero ("average" controls) and, secondly, from those with largest positive SRs ("healthiest" controls). The groups were chosen because men with average values may have included some whose lung function had been slightly affected by noxious influences, whereas those with very high values were least likely to have been affected by noxious influences but might include men who were highly resistant to these influences.

Table 1 *Classification of all jobs at PVC factory into six broad occupational groups.*

Broad occupational group	*Jobs included in group*
1	All men working in reactors 1 and 2*
2	Dryer room B operators†
3	Dryer room Lead, A and A/B operators
4	Warehousemen, maintenance staff, laboratory staff, and drivers‡
5	General staff who visit plant, such as shift supervisors and foremen
6	Management and office staff

*Men most likely to have been exposed to high concentrations of VCM in the past.
†Men engaged in the bagging of PVC and probably exposed to higher concentrations of dust than other workers in the dryer buildings.
‡Men potentially exposed to all raw materials and products.

Cases were initially compared with the rest of the survey population in order to identify any systematic differences in age, smoking habit, and employment status. Then the occupational and smoking histories of cases and controls were examined and compared. Smoking histories were classified as they were for the total population, but additional information about the number of cigarettes smoked and the age of starting smoking was analysed in the case-control study. Broad occupational categories were defined for the PVC factory (table 1) and for the foundry, and the total number of years spent by cases and controls in each occupational category was calculated. Additional information was available for PVC employees in relation to exposure to emulsion polymer (which has a smaller particle size than suspension polymer and which was manufactured at the factory between 1971 and 1974) and employment in the factory before 1975 when levels of VCM were much higher than the currently permitted levels. From the full occupational history the number of years spent in potentially "noxious" industries (such as coal, steel, chemicals, and a miscellaneous group of industries in which exposure to noxious compounds might have occurred) was recorded.

In the analysis Fisher's exact test, the chi-squared test for 2 × 2 contingency tables, and the chi-squared test for linear trend were used where appropriate.

Results

A total of 488 men was seen, consisting of 165 current PVC factory employees (93% of those who were asked to participate), 102 PVC former employees (39% of those invited), and 221 foundry employees (78% of those invited). Four men (two PVC and two foundry) were excluded from the

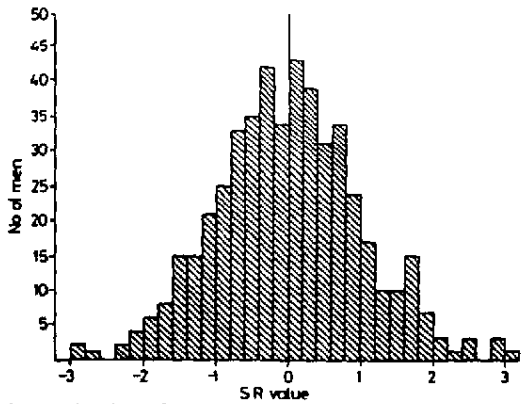

Fig 1 *Number of men by ranges of T_LCO standardised residuals.*

T_LCO analysis because of incomplete data, and to the final analysis was based on 484 men. As FEV_1 and FVC measurements were not obtained from three PVC factory workers and all 221 foundrymen this analysis was based on 264 men.

The distributions of standardised residual values of T_LCO and FEV_1 for the total survey population after allowing for age, height, weight, and smoking habit were fairly symmetrical and conformed approximately to Normal distributions (figs 1 and 2), although for FEV_1 there were slightly more extreme negative values than extreme positive values.

SELECTION OF CASES AND CONTROLS

A threshold SR value for T_LCO of $-1{\cdot}5$ supplied 31 men, a number that was considered large enough to form a study group. A control group of 31 men was selected randomly from those men with SR values between $-0{\cdot}25$ and $+0{\cdot}75$ inclusive (T_LCO average controls). A second control group of 31 "extra healthy" men was selected randomly from those with SR values in excess of $+0{\cdot}75$ (T_LCO healthiest controls). Similarly, 30 men with an FEV_1 SR value of less than $-1{\cdot}1$ were selected as FEV_1 cases and two groups of controls (FEV_1 average controls and FEV_1 healthiest controls) were chosen from those men with SR value between $-0{\cdot}25$ and $+0{\cdot}75$ and in excess of $+0{\cdot}75$ respectively.

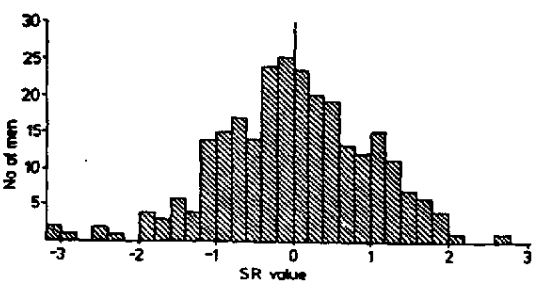

Fig 2 *Number of men by ranges of FEV_1 standardised residuals.*

Table 2 *Features of T_LCO cases, controls, and total survey population. Mean (and standard deviations) of age, height, weight and T_LCO*

No of men	*T_LCO groups*			*Total survey population (484)*
	Cases (31)	*Controls (average) (31)*	*Controls (healthiest) (31)*	
Age (y):				
Mean	41·8	42·3	40·3	42·2
(SD)	(10·2)	(12·5)	(11·3)	(11·9)
Height (cm):				
Mean	176·1	174·0	173·9	173·8
(SD)	(7·1)	(6·6)	(5·6)	(7·0)
Weight (kg):				
Mean	82·7	84·9	79·2	80·2
(SD)	(13·3)	(18·5)	(9·5)	(12·6)
T_LCO (ml/min mm Hg):				
Mean	22·2	31·8	37·3	30·5
(SD)	(4·1)	(2·9)	(4·3)	(5·9)

CLINICAL FEATURES OF CASES, CONTROLS, AND THE TOTAL POPULATION

The general features of T_LCO and FEV_1 cases, controls, and the total population are shown in tables 2 and 3. The mean age of the T_LCO case and control groups were similar.

Observed T_LCO and FEV_1 values of the cases were also expressed as a percentage of values predicted on the basis of Cotes' regression equation.[3] Fifteen of the 31 T_LCO cases had T_LCO values below 70% of their predicted values; four were below 60%. Twelve of these 15 men were PVC workers and three were foundrymen. Nineteen of the 31 cases were from the PVC factory and four of these had evidence of airflow obstruction ($FEV_1 <$ 80% and $FEV_1/FVC <$ 70%); examination of forced expiratory flow-volume loops suggested that a further seven might have mild airflow obstruction. In the remaining eight the low T_LCO appeared to be an isolated abnormality.

Of the 30 FEV_1 cases, 13 had observed FEV_1 values below 80% of their predicted values and 10 of these men had FEV_1/FVC ratios below 70% suggesting airflow obstruction. Seven of the FEV_1 cases also qualified for inclusion as T_LCO cases.

OCCUPATIONAL HISTORIES

Analysis of employment status showed that 19 of the T_LCO cases worked or had worked at the PVC factory and 12 were foundrymen, but this difference could easily have arisen by chance. Most workers

Table 3 *Features of FEV_1 cases, controls, and total survey population. Mean (and standard deviations) of age, height, weight, T_LCO, FEV_1 and FVC*

No of men	*T_LCO groups*			*Total survey population (264)*
	Cases (30)	*Controls (average) (30)*	*Controls (healthiest) (30)*	
Age (y):				
Mean	43·3	41·3	42·1	42·2
(SD)	(11·0)	(12·5)	(12·0)	(11·8)
Height (cm):				
Mean	176·0	174·5	175·9	174·3
(SD)	(7·4)	(6·6)	(8·0)	(7·1)
Weight (kg):				
Mean	82·2	78·4	80·4	80·4
(SD)	(13·3)	(10·1)	(11·5)	(12·3)
FEV_1 (l):				
Mean	2·7	3·9	4·5	3·7
(SD)	(0·7)	(0·7)	(0·8)	(0·9)
FVC (l):				
Mean	4·1	5·1	5·9	4·9
(SD)	(0·9)	(0·8)	(0·9)	(1·0)
T_LCO (ml/min mm Hg):				
Mean	29·1*	32·3	31·3	30·5†
(SD)	(6·8)*	(6·0)	(6·5)	(6·1)†

*Value based on 29 observations.
†Value based on 262 observations.

had worked in more than one type of job and in more than one broad occupational category during their employment with the companies. More cases than controls had worked in jobs in category 1 (on or near the reactors) at the PVC factory; 11 of 31 cases (35%) had worked in this category compared with 10 of 62 controls (16%) and this disproportion is significant at the 7% level (table 4). No suggestive differences were seen in the pattern of employment of FEV_1 cases and controls.

More cases than controls had worked at the PVC factory before 1 January 1975, when levels of vinylchloride were much higher than at present. Seventeen of the 19 T_LCO cases who had worked at the PVC factory had been employed before 1975 whereas only five of the 15 healthiest controls and 11 of the 13 average controls had been. The difference between cases and healthiest controls was significant ($p < 0·002$), and the increase in the proportion of men with pre-1975 employment in the PVC factory for the three groups over healthiest controls, average controls, and cases was also statistically significant ($p < 0·001$). Analysis of the duration of employment of men within different age groups showed that pre-1975 working was seen in both younger and older men. A similar analysis of FEV_1 cases and controls and foundry T_LCO cases failed to show any significant differences in relation to working before 1975. These findings suggest that some factor or factors associated with working at the PVC factory before 1975 had caused impairment of T_LCO in some men.

There was no difference in the numbers of T_LCO or FEV_1 cases and controls who had been exposed

Table 5 *Smoking habits of T_LCO cases, controls, and total survey population. Number of men in each smoking category with percentages in parentheses*

	Non-smoker	*Current smoker*	*Ex-smoker*	*Total*
Cases	3 (9·7)	20 (64·5)	8 (25·8)	31
Controls (average)	4 (12·9)	15 (48·4)	12 (38·7)	31
Controls (healthiest)	7 (22·6)	15 (48·4)	9 (29·0)	31
Total survey population	109 (22·5)	234 (48·4)	141 (29·1)	484

Table 4 *Numbers of men who had spent some time in each occupational group. (Mean time (years) spent in each occupational group)*

	No of men	*Occupational groups*												
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Cases:														
PVC workers	19	11 (2·7)	11 (0·6)	4 (7·6)	4 (9·0)	2 (9·7)	—	1 (7·0)	—	—	5 (5·6)	—	1 (1·4)	—
Foundrymen	12							4 (7·3)	2 (3·0)	5 (12·3)	7 (4·0)	2 (3·2)	2 (11·4)	1 (1·0)
Average controls:														
PVC workers	13	4 (7·0)	7 (0·7)	1 (6·8)	5 (6·0)	1 (12·3)	—	—	—	—	—	—	—	—
Foundrymen	18							3 (4·6)	5 (16·1)	1 (30·4)	9 (9·4)	1 (7·4)	5 (10·6)	1 (2·5)
Healthiest controls:														
PVC workers	15	6 (3·0)	11 (1·0)	1 (10·8)	2 (7·3)	2 (3·3)	1 (1·7)	—	—	—	2 (4·0)	1 (0·5)	—	—
Foundrymen	16							5 (13·4)	3 (4·5)	3 (12·7)	8 (12·5)	— —	6 (11·6)	— —

Note: Occupational groups 1–6 refer to PVC factory (see table 1) and 7–13 jobs at the foundry—that is, 7 work on or near the furnaces; 8 sand work and shot-blasting; 9 grinding and welding; 10 general jobs; 11 painting and dipping; 12 casting work; 13 fettling.

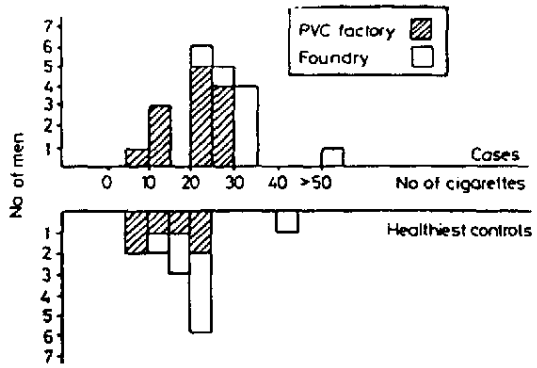

Fig 3 *Number of cigarettes smoked a day at weekends among current smoking T_LCO cases and healthiest controls.*

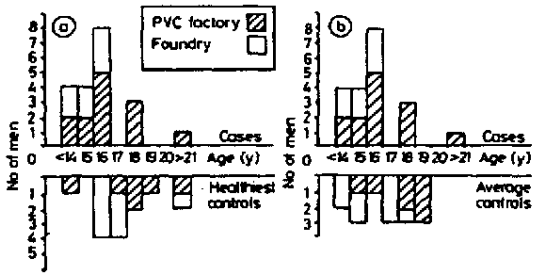

Fig 4 *(a) Age at start of cigarette smoking among T_LCO cases and healthiest controls who were current smokers. (b) Age at start of cigarette smoking among T_LCO cases and average controls who were current smokers.*

to emulsion polymer at the PVC factory.

No evidence was obtained that the observed difference between cases and controls could be explained on the basis of previous employment in industries other than the PVC factory or foundry.

SMOKING HABITS OF CASES AND CONTROLS

Whereas the procedure for selection of cases and controls had taken account of whether a man smoked, it was found that the T_LCO cases had tended to smoke more than controls. A slightly higher proportion of T_LCO cases (65%) were current cigarette smokers than either group of controls (on average 48%) (table 5), and more of these cases smoked 25 cigarettes or more at the weekend than the healthiest controls (fig 3). Weekday smoking followed a similar but statistically insignificant pattern. The T_LCO cases tended to have started smoking at an earlier age than controls (fig 4).

Discussion

Whereas exposure to PVC dust has been shown to be related to a mild reduction of lung function and chest *x* ray abnormalities,[4 5] less is known about the pulmonary effects of exposure to VCM. There have been some case reports of men exposed to VCM who had impairment of lung function, particularly T_LCO,[6 7] and changes in lung histology have been reported.[6 8]

The present study was designed as a preliminary examination of whether an undue number of men at this PVC factory had impaired T_LCO, and whether such impairment was likely to be related to their occupation. We have found no evidence of a substantial excess of men with impairment of the T_LCO, although low T_LCO values were found in a few men, as might be expected in any large population of workers. After allowing for other factors, however, those men with the lowest T_LCO tended to have worked more often than would be expected at the PVC factory before 1975, a date before which concentrations of VCM were known to have been much higher than subsequently; these men also tended slightly to have worked in the jobs where the highest concentrations of VCM were found.

This evidence gives some support to the hypothesis that work in the PVC factory entailed exposure to one or more substances that caused impairment of lung function in a small number of men. The most likely substance is VCM, on which suspicion has previously been cast by case reports of vinylchloride workers with impairment of gas transfer factor, but in which proof of association has been lacking.[6 7] It is also possible that exposure to respirable PVC dust may have contributed to the low gas transfer factors although there was little positive evidence for this in our study. PVC dust has been shown in other studies to be associated with impairment of other aspects of lung function (though not the gas transfer factor) and slight chest *x* ray abnormalities.[4 5]

There was little evidence to support, as an alternative hypothesis, the suggestion that the workforce recruited in the early years of production included an excess of men with poor respiratory health at the time of entry to the factory. The FEV_1, a more sensitive indication of the common types of chronic respiratory illness, was not found to be particularly adversely affected in men working in the factory before 1975.

The selection of cases took into account whether a man smoked, but even after allowing for this, the cases with low T_LCO tended to have smoked slightly more than the controls, and notably the age at which a man started to smoke appeared to be related to low T_LCO. The relative contributions towards impairment of T_LCO of smoking and of occupational factors are not clear from this study, but it is possible

that both were important. The men with the lowest T_LCO values selected as cases were not all necessarily suffering from lung disease but among them were 15 men whose T_LCO was less than 70% of the value predicted by published normal values, a level which probably indicates the presence of disease. In eight of the 19 cases who had worked at the PVC factory the low T_LCO was an isolated abnormality, a pattern unlikely to be the result of damage from smoking and which is usually associated with interstitial lung disease or disturbance of pulmonary perfusion.

Reports of both animal and clinical studies give further support to the suggestion that exposure to VCM might have been an important causative factor. Animal studies have shown that exposure to high levels of VCM leads to pulmonary fibrosis, the changes being most severe in the animals which had been exposed for the longest time.[8] There have been isolated case reports of individuals with interstitial lung disease who had been employed in the manufacture of PVC and who had, therefore, been exposed to VCM.[8 10] Hunter *et al* described six such workers, three of whom had died from liver disease related to VCM exposure[8]; none of the six had respiratory symptoms, three had abnormal chest *x* ray films, and one an abnormal T_LCO, but the lung histology from all six men showed a similar picture with the presence of an inflammatory interstitial infiltrate.

Diligent attempts were made to contact all men who had worked at the PVC factory but response was low (39%). If the men not examined had included either an excess or deficiency of men with impaired gas transfer factor compared with the population examined then the analysis of the distribution of values among the population seen would be unrepresentative to that extent.

We conclude that this preliminary study has shown no evidence that current working conditions in either factory have caused impairment of lung function but it does give some support to the hypothesis that work in the PVC factory before 1975 entailed exposure to a substance that caused impairment of lung function in a small number of men. Further work including clinical studies of affected men would be necessary to characterise this impairment and to explore more fully the relations with occupational and other factors.

This study was carried out with the full cooperation of the management and workforce of Vinatex Limited to whom we are grateful for financial support. We thank the management and employees of the foundry for their generous cooperation in the study and the medical officers at Vinatex and British Steel for their help. We also thank Dr A Seaton and Dr M Jacobson for their advice. Further details of the results of the work are recorded in Institute of Occupational Medicine report TM/82/4.

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