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CANCER EPIDEMIOLOGY STUDIES ON VINYL CHLORIDE WORKERS

As per our telephone conversation earlier today, I am sending you a copy of a 1988 publication by Sir Richard Doll which presents an authoritative, interpretive summary of the evidence for a link between vinyl chloride exposure and human cancer. A list of studies published since Doll's review is also attached. I cannot verify the completeness of the list, but it should be sufficient to meet your stated need of "getting started".

Let me know if I can be of further help.

Sincerely yours,

G. Bond/pk

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Attachments

R&S149991

job histories were available for all factories except two. "Typical exposures" to VC in air were estimated as time-weighted averages by industrial hygienists using several sources of variable quality. In most factories, occasional measurements of VC provided the basis for past typical exposures, supplemented by knowledge of exposure conditions, processes, and technological changes over time. Systematic measurements taken since the mid-1970s provided the basis for more recent exposure assessments, and an indication of the variability of exposure levels between job titles.

In terms of agents to which the workers were exposed in VCM, PVC, and VCM/PVC production, VC was the main exposure, and virtually the only exposure in many of these factories. Use of butadiene was rare. In PVC processing (one factory in this study), however, additional exposures could have included PVC dust, asbestos, and other agents. All the job-exposure matrices referred only to VC exposure in air.

Each job-exposure matrix was checked and validated by two independent industrial hygienists, who were able to provide, prior to the statistical analysis, an index for the ranked level of exposure (low: <50 ppm; intermediate: 50—449 ppm; and high: ≥ 500 ppm) in which the classification of the subjects was based on the highest level to which the workers were potentially exposed, specific to their jobs and the years in which they worked, according to levels of VC recorded in the job-exposure matrices.

The same information, that is, job histories and job-exposure matrices, was used to calculate cumulative exposure in parts per million-years (exposure level from the job-exposure matrices multiplied by duration of employment) for the subjects. In some of the analyses for cancer of the liver an estimated job-exposure matrix was used for the four factories in the United Kingdom which were unable to provide their own matrices. The estimated job-exposure matrix was based on the matrices provided for the other factories in the United Kingdom. This matrix was checked with the industrial hygienist from the United Kingdom. In the following text, it is clearly noted if the analyses under discussion include this estimated matrix.

For liver cancer only, the Poisson regression analysis was performed to assess the significance of several variables simultaneously. This analysis used observed deaths and the person-years distribution for cross-classified categories of temporal and exposure variables and performed an internal comparison with the base-line categories (ie, within the cohort only) (17, 18).

Mortality results

Cause-specific mortality for the total cohort is presented in table 3. A statistically significant deficit for all-cause mortality was apparent (1438 deaths observed versus 1636.4 expected, SMR 88, 95 % CI 83—93). The following four main causes of death contributed to this deficit: (i) diseases of the circulatory system, (ii) diseases of the respiratory system, (iii) accidents, poisonings and violence, and (iv) other known causes.

For all malignant neoplasms, the SMR was 104 (95 % CI 95—114), with 445 deaths observed. However, there were two causes of death, both cancers, which showed statistically significant excesses. They were cancer of the liver with 24 observed deaths and 8.4 expected (SMR 286, 95 % CI 183—425) and cancer of an unspecified site with 24 observed deaths and 12.9 expected (SMR 187, 95 % CI 120—278). Increases which were not statistically significant were apparent for bladder cancer (21 deaths observed, SMR 146, 95 % CI 91—224), malignant melanoma (7 deaths observed, SMR 163, 95 % CI 65—335), and lymphosarcoma (7 deaths observed, SMR 170, 95 % CI 69—351).

In this report the results are not given by process. The statistically significant excess of liver cancer evident in the total cohort was mainly due to the excess in VCM/PVC production (19 deaths observed, SMR 311, 95 % CI 187—486).

Twenty-three sites were selected for analysis according to the years since first exposure, and the results for 10 of these sites are presented in table 4. Apart from liver cancer, which will be discussed in detail, there were no noteworthy patterns in risk according to this variable.

Four sites were investigated in detail for relationships with temporal and exposure variables. Of the two sites with excess risk for the total cohort, cancer of an unspecified site was not analyzed further due to the diversity of cancers found in this category; they are however discussed in a descriptive fashion in the text. Liver cancer, lung cancer, brain cancer, and lymphosarcoma were chosen a priori for further analysis. Excesses of bladder cancer in PVC production (in the United Kingdom) and of melanoma (in Norway) were not investigated further for the total cohort since they were confined to one country.

Liver cancer

No liver cancer deaths occurred before 15 years since first exposure, after which the SMR was 483 (95 % CI 208—951) for 15—19 years since first exposure, and it did not vary greatly from this level thereafter, the value always being statistically significant. In table 4, the pattern by years since first exposure is seen in 10-year groups. When only those with 15 years since first exposure or more were included in the analysis (15-year latency), the overall SMR for liver cancer was 445 (95 % CI 285—663).

Table 5 shows the SMR values for liver cancer according to the four exposure variables, without and with a 15-year latency analysis. According to job title, dichotomous as ever autoclave worker (suspected a priori as the highest risk job) versus never an autoclave worker, very high risk was experienced by those who

Table 4. Mortality by time since first exposure for selected sites. (O = observed number of deaths. E = expected number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Cause of death[a]	Years since first exposure																			
	1—9				10—19				20—29				≥30				Total			
	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI
All causes (000—999)	207	313.9	66	57—76	529	582.5	91	83—99	471	502.6	94	85—103	231	237.4	97	85—111	1438	1636.4	88	83—93
All malignant neoplasms (140—207)	56	73.5	76	58—99	173	155.6	111	95—129	151	138.6	109	92—128	65	60.2	108	83—138	445	427.8	104	95—114
Liver and intrahepatic bile ducts (155)	—	1.5	0	0—245	8	3.2	253	109—499	11	2.8	388	194—694	5	0.9	561	182—1310	24	8.4	286	183—425
Trachea, bronchus and lung (162)	16	22.7	71	40—114	50	53.9	93	69—122	60	50.4	119	91—153	18	21.3	84	50—133	144	148.3	97	82—114
Bladder (188)	2	1.8	109	13—395	7	4.8	146	59—301	6	5.1	117	43—255	6	2.6	231	85—504	21	14.3	146	91—224
Brain (191)	2	3.4	59	7—213	6	5.3	113	42—247	2	3.4	59	7—212	4	1.0	407	111—1041	14	13.1	107	59—180
Lympho-sarcoma (200)	3	1.3	225	46—657	4	1.6	258	70—662	—	1.0	0	0—381	—	0.3	0	0—1430	7	4.1	170	69—351
Circulatory system (390—458)	67	108.0	62	48—79	223	246.2	91	79—103	209	236.9	88	77—101	123	121.7	101	84—121	622	712.8	87	81—94
Respiratory system (460—519)	8	19.9	40	17—79	30	45.0	67	45—95	47	47.5	99	73—132	23	28.6	80	51—121	108	140.9	77	63—93
Chronic liver disease, cirrhosis (571)	2	8.4	24	3—87	17	17.0	100	58—160	14	12.2	115	63—193	2	2.1	95	11—342	35	39.7	88	61—123

[a] Code of the International Classification of Diseases (eighth revision) in parentheses.

Table 5. Mortality data for liver cancer according to the exposure variables.[a] (O = observed number of deaths, SMR = standardized mortality ratio, 95 % CI = confidence interval)

Exposure variable	O[a]		SMR	95 % CI	15 years of latency[a]			
					SMR		95 % CI	
Job title								
Ever autoclave worker	11		896	447—1603	1358		678—2430	
Never autoclave worker[b]	13		181	97—130	284		151—485	
Duration of employment (years)								
1—9	4		94	26—239	205		56—525	
10—14	5		327	106—763	602		196—1406	
15—19	4		310	84—794	310		84—794	
20—24	6		714	262—1555	714		262—1555	
≥25	5		1111	361—2593	1111		361—2593	
Ranked level of exposure (ppm)								
Low (<50)	3	(4)	119	25—347	227	(244)	47—664	(67—625)
Intermediate (50—499)	3	(7)	161	33—471	250	(551)	52—731	(222—1136)
High (≥500)	12	(12)	567	293—991	719	(719)	371—1255	(371—1255)
Unknown	6	(1)	317	117—691	486	(125)	182—1079	(3—697)
Cumulative exposure (ppm-years)								
0—1999	4	(9)	99	27—254	191	(348)	52—490	(159—662)
2000—5999	4	(4)	351	96—898	460	(400)	125—1177	(109—1024)
6000—9999	4	(7)	800	218—2048	851	(1429)	232—2179	(574—2943)
≥10 000	3	(3)	1429	295—4175	1667	(1667)	344—4871	(344—4871)
Unknown	9	(1)	357	163—678	536	(100)	245—1017	(2—557)
Total	24		286	183—425	445		285—663	

[a] The values in parentheses were determined in analyses including the estimated job-exposure matrices.
[b] In Norway, the longest-held job was used. In Sweden job rotation was practiced, and no one was classified as an autoclave worker.

Table 8. Cases of liver cancer on the basis of cancer incidence and other information (not included as liver cancer deaths in the mortality analysis). (ICD = International Classification of Diseases)

Subject	Age at hire (years)	Year of hire	Duration of exposure (years)	Length of latency (years)	Year of death	Cause[a]	ICD revision	Site of incidence or other information	Angiosarcoma of the liver	Histological confirmation by pathology	Total cumulative exposure (ppm-years)
1	24	1951	19	19	1970	197 8	8	Cancer incidence: ICD 155.0	Yes	Yes	8 203
2	45	1961	6	8	1970	197 8	8	Death certificate: carcinoma of liver	Unknown	No	..
3	28	1966	8	8	1974	197 8	8	Death certificate: carcinoma of liver, angiosarcoma, hepatic cirrhosis	Yes	Yes	1 749
4	34	1965	10	12	1977	197 8	8	Death certificate: hepatic failure due to liver cancer	Unknown	No	..
5	18	1965	7	?	Emigrated	—	—	Cancer incidence: ICD 155.0	No	Yes	.
6	36	1957	7	7	1964	199.0		Best evidence (clinical): ICD 155.0	Unknown	No	..
7	50	1954	11	11	1965	199.0	8	Best evidence (clinical). ICD 155.0	Unknown	No	
8	54	1969	9	10	1980	199.0	9	Cancer incidence: ICD 155.2	Unknown	No	..
9	29	1941	31	31	1972	157.9	8	Cancer incidence: ICD 155.0	Yes	Yes	28 156
10	32	1953	20	22	1975	159.0	8	Best evidence (pathology): ICD 155.0	Yes	Yes	7 673
11	43	1944	22	28	1972	227.0	8	Death certificate: hemangioendothelioma of liver, natural causes	Yes	Yes	7 114
12	42	1963	8	17	1980	571 5	9	Death certificate: hepatic failure due to hepatic fibrosis	Yes	Yes	2 658

[a] According to the ICD.

liver, age at first exposure and calendar period of exposure did not. Very clear exposure-response relationships were evident between the cumulative exposure to VC and the risk of liver cancer and angiosarcoma of the liver. Finally, an effect of misclassification was demonstrated when the estimated job-exposure matrix was included, although the effect was minimal for the angiosarcoma results.

Lung cancer, brain cancer and lymphosarcoma

The SMR for trachea, bronchus, and lung cancer was 97 (95 % CI 82—114) for the total cohort, on the basis of 144 observed deaths. The SMR values did not show any remarkable association with a particular process, and although no pattern was evident for years since first exposure, there was a statistically significant increase at 25—29 years since first exposure on the basis of 33 observed deaths (SMR 147, 95 % CI 101—207), mainly from an excess in VCM production in this time period (5 deaths observed, SMR 486, 95 % CI 158—1134). Calendar period at exit and at hire did not reveal any consistent pattern.

Fourteen deaths from brain cancer occurred in the cohort, and, although the overall SMR was not increased (SMR 107, 95 % CI 59—180), there was a statistically significant excess at ≥ 30 years since first exposure on the basis of four observed deaths (SMR 407, 95 % CI 111—1041) (table 4). The excess was confined to the calendar period of hire of 1945—1954 and was the most evident for VCM/PVC production. Analyses by calendar period of exit, age at hire, and age at exit did not reveal any patterns of risk for brain cancer mortality.

Table 9. Maximum likelihood estimates for the final model with cumulative exposure and years since first employment for the deaths from angiosarcoma of the liver (N = 22). (95 % CI = 95 % confidence interval)

Variable	Relative risk	95 % CI
Cumulative exposure (ppm-years)		
< 2000	1.0	.
2000—5999	6 8	1.1—41.7
6000—9999	24.7	4.1—150.1
≥ 10 000	45.4	7.3—281.1
Years since first employment		
0—19	1.0	.
20—24	4.7	1.0—22.8
≥ 25	6.2	1.4—29.0

Table 10. Absolute risk of angiosarcoma of the liver per 100 000.

Years since first employment	Cumulative exposure (ppm-years)			
	< 2000	2000—5999	6000—9999	≥ 10 000
0—19	1 0	6.8	24 4	44 8
20—24	4 7	32 0	115.6	212 5
≥ 25	6 2	42.2	152 3	280.0

A detailed analysis of the seven deaths from lymphosarcoma showed no pattern in the SMR values according to years since first exposure. All seven deaths occurred in VCM/PVC production, and for this process alone there was no excess apparent by calendar period of hire or exit or age at hire or exit.

Cancer of unspecified site

Twenty-four deaths in the cohort were classified as malignant neoplasms of unspecified sites (ICD 199), giving a statistically significant excess (24 deaths observed, SMR 187, 95 % CI 120—278). Additional information, such as cancer incidence data, was available for 20 of the 24 deaths. Three subjects had liver cancer and were therefore included in table 8. It was unknown, however, whether they had angiosarcoma of the liver since no histological information was available. No other clear excess of a particular cancer among those classified as cancer deaths of an unspecified site was apparent.

Cancer incidence results

For the 2643 subjects from the four factories in Norway and Sweden included in the cancer incidence analysis, the total number of cancers observed was 127 (SIR 107, 95 % CI 89—127), and their distribution by site is shown in table 13 (reported for one or more observed deaths). The only statistically significant excess was for liver cancer, on the basis of seven observed cases (SIR 303, 95 % CI 122—623). Suggestive increases were found for stomach cancer (13 cases observed, SIR 150, 95 % CI 80—256), lung cancer (22 cases observed, SIR 152, 95 % CI 95—230), melanoma (8 cases observed, SIR 184, 95 % CI 79—362), and brain cancer (8 cases observed, SIR 159, 95 % CI, 68—312).

Although the lung cancer increase was not statistically significant, it was investigated in more detail as other studies have suggested increased risk for lung cancer. There was no excess according to process type or category of years since first exposure. A slight excess was suggested for <15 years of employment, while the SIR values were close to 100 for 15—19 and ≥ 20 years of employment. For the ranked level of exposure, the risks in the high and low categories were virtually identical. According to cumulative exposure, no exposure-response was apparent (results not presented in tabular form). Without statistical significance and with little apparent relationship to VC exposure, some indication of increased lung cancer risk remained for one PVC-processing plant and one Norwegian VCM/PVC production plant. The national investigator for the PVC-processing plant attributed the excess to exposure to asbestos, which was utilized in the process (7), while the excess remained unexplained in Norway.

Discussion

This collaborative study was carried out with the main purpose of analyzing exposure-response relationships between exposure to VC and liver cancer and investigating whether exposure to VC could increase cancer risk for sites other than the liver.

The results confirmed the association between exposure to VC and liver cancer. The excess of liver cancer mortality was associated with duration of employment, and a clear association with ranked level of exposure was found. The results were strengthened by the regression analyses, which indicated that the risk of liver cancer depended on cumulative exposure and years since first exposure.

Twenty-two subjects had histologically confirmed angiosarcoma of the liver, and the regression analyses demonstrated that the risk was mostly influenced by cumulative exposure to VC. The relative risks were higher at each level of cumulative exposure than those for all liver cancer deaths, but it must be remembered that the same 16 angiosarcoma deaths were included in both analyses. The approximate incidence rate of angiosarcoma of the liver in Norway, for example, based on 1953—1988 data, was 1 in 10 million per year (personal communication from A Andersen, 1989). Others have estimated the annual incidence at 1 to 2 in 10 million (20, 21).

Given 222 746 person-years at risk accumulated by this cohort, with an annual incidence of angiosarcoma of the liver of 2 per 10 million in the general population, the overall expected figure for the cohort would be 0.045. The rarity of this tumor supports the use of internal comparisons to assess the significance of exposure variables.

Table 13. Cancer incidence, based on data for four factories in Norway and Sweden, by detailed cause. (O = observed number of cases, E = expected number of cases, SIR = standardized incidence ratio, 95 % CI = 95 % confidence interval)

Cancer site[a]	O	E	SIR	95 % CI[b]
Buccal cavity and pharynx (140—148)	5	4 2	119	39—277
Stomach (151)	13	8 7	150	80—256
Intestine, except rectum (152—153)	8	8 9	89	39—176
Rectum (154)	2	5 9	34	4—123
Liver and intrahepatic bile ducts (155)	7	2 3	303	122—623
Pancreas (157)	3	4 3	70	14—203
Larynx (161)	2	1 6	122	15—441
Trachea, bronchus and lung (162)	22	14 5	152	95—230
Melanoma of skin (190)	8	4 4	184	79—362
Prostate (177)	16	18 0	89	51—144
Testis (178)	1	2 2	45	1—252
Bladder (181)	7	7 9	88	36—182
Kidney (180)	4	5 4	74	20—188
Brain (193)	8	5 1	159	68—312
Thyroid (194)	3	0 9	327	67—955
Lymphosarcoma and other lymphoma (200, 202)	1	3 6	28	1—154
Multiple myeloma (203)	1	1 9	53	1—297
Other malignant neoplasms	16	11 9	135	77—219
All malignant neoplasms (140—205)	127	119 0	107	89—127

[a] Code of the International Classification of Diseases in parentheses
[b] Based on a Poisson distribution

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Mortality From Liver Disease Among Italian Vinyl Chloride Monomer/Polyvinyl Chloride Manufacturers

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The possible association in humans between nonangiosarcoma primary liver tumors (PLC-non-A), particularly hepatocellular carcinoma (HCC), and exposure to vinyl chloride monomer (VCM) is supported by both experimental and human data. This article presents a review of the information regarding 253 deaths that occurred in seven plants manufacturing VCM/PVC and one plant extruding PVC. The retrieval of clinical and pathological data, in addition to the information from death certificate, is referred to as "best evidence" (BE). BE has been carried out for 63 deaths. A total of 14 primary liver cancer (PLC) were detected: seven were angiosarcoma (PLC-A), and two of the remaining seven were hepatocellular carcinoma (HCC). In our series of 14 PLC cases, there was no significant difference between PLC-A and PLC-non-A as to length of exposure and latency. There was no noticeable difference in terms of job title between ASL and non-ASL cases. The list of longest held jobs shows the presence of various job titles, different from autoclave cleaner, for primary liver cancer, PLC-A and PLC-non-A. In conclusion, our observations show that VCM may have a broader carcinogenicity action on the liver and that exposure lower than that occurring in autoclave cleaning can cause primary liver cancer, both angiosarcoma and nonangiosarcoma.

Key words: primary liver cancer, VCM/PVC, occupational exposure, angiosarcoma liver (ASL)

INTRODUCTION

Vinyl chloride monomer (VCM) has been shown to be a multipotential carcinogen in rodents, i.e., capable of causing a variety of tumors, among which angiosarcoma of the liver (ASL) [Viola et al., 1971; Popper et al., 1977; IARC, 1987; Maltoni et al., 1984; Doll, 1988; Maltoni and Cotti, 1988].

In humans, a causal relationship has been found between occupational exposure to VCM and ASL. In exposed workers, the association between the chemical and other malignant tumors—namely, brain neoplasms, lung carcinomas, and malignant

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primary liver cancer (PLC) other than angiosarcoma—has been pointed out by some investigations, but it is still debated [IARC, 1987].

The possible association in humans between nonangiosarcoma liver tumors (PLC-non-A), particularly hepatocellular carcinoma (HCC), and exposure to VCM is supported by three orders of data, dealing with: 1) the experimental results of long-term carcinogenicity bioassays in rats [Maltoni et al., 1984]; 2) the analogies between VCM and Thorotrast carcinogenesis [Popper et al., 1977]; and 3) the observation of cases of HCC among workers exposed to VCM [Gokel et al., 1976; Koischwitz et al., 1981; Evans et al., 1983; Dietz et al., 1985].

In an experimental study, pregnant female rats were exposed by inhalation to 2,500 ppm VCM for 76 weeks (group I). Concurrently, one group of male and female offspring was exposed in the same way for 76 weeks (group II) and another for 15 weeks (group III). Adequate control groups of breeders (group IV) and offspring (group V) were available. The incidence of ASL and HCC in the five groups was, respectively, as follows: 50.9% and 9.4% in group I; 65.1% and 56.5% in group II; 44.4% and 72.6% in group III, 0 and 0 in group IV; 0 and 0.3% in group V. No sharp differences were found in the incidence of these two neoplasms between male and female offspring [Maltoni et al., 1984].

Both VCM and Thorotrast have been shown to induce ASL and HCC in experimental rodents and ASL in humans; moreover, Thorotrast exposure has been documented in a variety of liver neoplasms other than ASL in humans [Keplinger et al., 1975; Maltoni and Lefemine, 1975; Maltoni, 1977; Maltoni et al., 1984; Commission of the European Communities, 1984; Maltoni and Cotti, 1988]. In a comprehensive epidemiological investigation on 5,000 Thorotrast-injected patients and on 5,000 controls, a total of 152 PLC occurred among the exposed, whereas no cases were detected in controls. These neoplasms included both ASL and HCC [Commission of the European Communities, 1984].

In addition, steroids have been suggested as causative agents of both hepatocellular carcinoma and liver angiosarcoma. Women taking oral contraceptive steroids have a small increased risk for developing hepatocellular carcinoma [Klatsin, 1977]. The use of androgenic anabolic steroids has been implicated in the development of hepatocellular carcinoma [Johnson et al., 1972] and angiosarcoma [Falk et al., 1979]. In both ASL and HCC, the common accompanying precursor stage is a lesion consisting of varying degrees of mixed hyperplasia of hepatocytes and sinusoidal cells and sinusoidal dilatation [Popper et al., 1977].

Few cases of HCC in workers exposed to VCM have been reported in the literature [Gokel et al., 1976; Koinschwitz et al., 1981; Evans et al., 1983; Dietz et al., 1985]. In the Federal Republic of Germany, Dietz et al. [1985] reported three cases of HCC in VCM-exposed workers with no history of exposure to other known liver carcinogens (such as Thorotrast and alcohol) and no signs of hepatitis B infection.

The present article analyzes data on the mortality from various liver diseases and provides some preliminary observations that strengthens the evidence that VCM can cause HCC in humans.

MATERIALS AND METHODS

We reviewed information regarding 253 deaths occurring in seven plants manufacturing VCM/PVC and one plant extruding PVC. The seven plants represent all

TABLE I. Description of "Best Evidence" Data and Agreement With Death Certificate Information for Workers in Three Plants in Italy Manufacturing VCM/PVC

City	Plant #	No. of deaths	Best evidence data			Degree of agreements DC/BE
			Total	Clinical data	Pathological data	
Ravenna	1	17	10	10	7	80% (8/10)
Rosignano	2	11	8	8	3	100% (8/8)
Ferrara	3	56	45	45	25	71% (32/45)

Italian production facilities, with the exception of two industries in Sardinia, where the investigation is still ongoing. The results of the study, in terms of standardized mortality ratios, have been published for three cohorts [Belli et al., 1987] and is ongoing in the remaining six plants.

Causes of death, noted on death certificates and from hospital records (when available), age at death, duration of exposure, latency, and occupational history are reported for each death.

Retrieval of clinical and pathological data, in addition to information from the death certificate, is referred to as "best evidence" (BE). BE was compiled for deaths that occurred in three of the seven plants. The type of additional data and its frequency are given in Table I.

"Liver disease" cases comprised 39 of 253 deaths. Deaths from liver disease were defined on the basis of either death certificate (coded according to the International Classification of Disease, ICD) or BE-ICD (i.e., ICD after considering the BE), when available. Two categories were identified:

1. Primary liver cancer: ICD or BE-ICD = 155.0, which includes ASL and non-ASL cases (VIII and IX ICD Revision).

2. Liver cirrhosis and other chronic liver disease: ICD or BE-ICD 570 = acute and subacute necrosis of the liver; 571.5 = cirrhosis of the liver without mention of alcohol; 571.9 = unspecified chronic liver disease without mention of alcohol; 573.0 = chronic passive congestion of the liver (VIII and IX ICD Revision).

The seven ascertained Italian cases of ASL in VCM/PVC manufacturers have been reported previously in the literature [Maltoni, 1974; Maltoni and Rondinella, 1980; Chiappino et al., 1982; Maltoni et al., 1984; Brugnami et al., 1988; Chiozzini et al., 1988], and six are included in the Register of ASL cases maintained by the Imperial Chemical Industries. Two cases occurred in PVC extruders, four in polymerization workers, one in a monomer worker. All seven cases are included in the present contribution.

RESULTS

Table II describes the 39 liver-disease deaths in terms of cause of death (ICD and BE-ICD), age at death, duration of exposure, latency, and longest-held job. The letter *A* labels histologically confirmed angiosarcoma cases.

We detected a total of 14 primary liver cancers (PLC): seven were angiosarcoma (PLC-A), two of the remaining seven were HCC; for five subjects, histological data were not available, but their clinical history was not compatible with the diagnosis of

TABLE II. Occupations in Deaths Due to "Liver Disease" in the Italian V.C. Study*

Case #	Age at death	Duration of exposure	Years since first exposure	Prevalent job	ICD	Best evidence
1	62	11	11	PVC loader	571.9	
2	42	20	20	PVC loader	199.1	155.0
3	55	5	5	PVC bagger	571.9	
4	74	16	29	Control	571.5	
5	48	2	19	Autoclave cleaner	571.9	
6	55	1	14	Dryer area helper	571.9	
7	60	3	4	Reactor area operator	156.0	157.9
8	62	11	11	Dryer area operator	199.0	155.0
9	62	28	31	Maintenance	155.0	
10	68	9	25	Dryer area helper	426.0	573.0
11	46	23	23	Reactor area helper	571.9	
12	44	11	7	PVC bagger	199.0	155.0
13	61	21	22	Autoclave operator	250.0	571.9
14	55	22	22	Autoclave cleaner	159.0	155.0 A
15	55	29	32	Autoclave cleaner	196.9	155.0
16	47	17	18	Autoclave operator	155.0	
17	48	11	23	Autoclave cleaner	571.9	
18	68	19	28	Autoclave operator	571.5	
19	52	19	23	Maintenance	571.9	
20	66	25	25	Clerk	571.9	
21	45	6	7	Compounds	571.5	
22	43	14	15	Maintenance	155.0	155.0A
23	50	4	22	Compounds	571.5	
24	50	20	21	Maintenance	571.5	
25	50	25	26	Autoclave operator	571.5	155.0 A
26	46	4	16	PVC Extruder		155.0 A
27	37	2	2	PVC Extruder		155.0 A
28	44	22	22	Reactor area operator	155.0	155.0 A
29	41	18	19	Reactor area operator	571.0	
30	59	11	26	Reactor area helper	571.9	
31	49	11	12	Autoclave operator	571.9	
32	65	10	15	Monomer operator	573.0	
33	50	9	23	Autoclave operator	571.9	
34	43	9	9	Reactor area helper	571 9	
35	55	14	19	PVC bagger	571.9	
36	61	22	28	PVC bagger		155.0 A
37	56	1	21	PVC bagger	571.9	
38	61	3	19	Autoclave operator	571.9	
39	62	9	20	PVC bagger	155.0	

*A = Liver angiosarcoma.

ASL. Twenty of 39 "liver disease deaths" were coded as liver cirrhosis, and the remaining five were unspecified chronic liver disease without mention of alcohol (ICD 571.9) and other disorders of the liver (ICD 573.0). The characteristics of the 14 primary liver cancer cases are presented in Table III.

Mean age at death was 48 years for angiosarcoma (PLC-A), 53 years for primary nonangiosarcoma liver cancer (PLC-non-A), and 60 for liver cirrhosis and other chronic liver diseases. Mean duration of exposure was 16 years for PLC-A, 18 years for PLC-non-A, and 12 years for the other pathological entities. Mean latency was, respectively, 19, 20, and 20 years.

TABLE III. Demographics and Job Titles Among Primary Liver Cancer Cases in the Mortality Study of Italian Manufacturers of VCM/PVC

	Liver angiosarcoma	Primary liver cancer
No. of cases	7	7
Mean duration of exposure (years)	16	18
Mean latency (years)	19	20
Mean age at first exposure	29.9	33.6
Mean age at death	48	53
Job titles		
Case no. 1	Autoclave cleaner Autoclave operator	Autoclave cleaner Reactor area helper
Case no. 2	Maintenance	Maintenance
Case no. 3	Autoclave operator Controller	Autoclave operator Maintenance
Case no. 4	PVC extruder	PVC loader
Case no. 5	PVC extruder	Dryer area operator
Case no. 6	Reactor area operator Warehouse and transport	PVC bagger
Case no. 7	PVC bagger	PVC bagger

The list of longest held jobs in Table III shows the presence of job titles such as PVC loader, dryer operator, and maintenance worker for primary liver cancer both PLC-A and PLC-non-A.

DISCUSSION

Experimental and epidemiological data from the international literature suggest that VCM is a multipotential carcinogen; the analogies between Thorotrast and VCM carcinogenesis, case reports of HCC in VCM exposed workers, and our present results strongly suggest that VCM can cause PLC-non-A, particularly HCC.

In Italy, only mortality data are available on a routine basis; for the entire country, there are only four tumor registries presenting incidence data with the details of the histotype. As a consequence, it is not possible to carry out a proportional mortality analysis or any other measure of the expected number of PLC and HCC cases. In the present study, the histotype was ascertained for 64% of primary liver cancer (PLC) cases; in the four tumor registries named above, the percentages were 8%, 12%, 23%, and 50%. Therefore, in the present investigation, the histotype of PLC was ascertained in greater detail than in any tumor registry. The percentages of hepatocellular carcinoma (of all PLC) were 14% in this study and 2%, 8%, 14%, and 26%, respectively, in the tumor registries. There is no sound reason to establish a differential and biased histologic ascertainment for ASL and HCC.

In our study, ASL appeared to occur at younger age: mean age at death was 48 years for PLC-A cases and 53 for PLC-non-A. These results are comparable with U.S. data [Wong et al., 1986] reporting 54 years and 61 years as mean age at death, respectively, for PLC-A and PLC-non-A. A report on the Register of ASL cases among VCM-exposed workers, notified to the Imperial Chemical Industries since

1974, gives 53 years as the mean age at death for the 138 ASL cases recorded worldwide [Forman et al., 1985]. Mean age at first exposure was 29.9 for PLC-A and 33.6 for PLC-non-A. The same observation of younger age at first exposure for PLC-A was made in the last U.S. study: 27.2 and 36.6 [Wong et al., 1986]. The lower age at death for ASL cases both in the U.S. and Italian series is in agreement with the hypothesis of an earlier occurrence of ASL in the frame of liver carcinogenesis, but it may also be due to an early age at the time of exposure.

In our series of 14 PLC cases, there was no significant difference in length of exposure and latency between PLC-A and PLC-non-A. There was no noticeable difference in terms of job title between ASL and non-ASL cases.

Vinyl chloride has been shown to induce ASL at very high exposure levels, as shown by the fact that most ASL cases worldwide occurred among autoclave cleaners. In the present study, the job title of the cases of both PLC-A and PLC-non-A show that these tumors may develop in VCM-exposed workers with jobs other than autoclave cleaner.

In conclusion, our observations indicate that VCM may have a broader carcinogenicity spectrum on the liver than known before and that exposure lower than that occurring in autoclave cleaning can cause primary liver cancer, both angiosarcoma and nonangiosarcoma.

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