American Journal of Industrial Medicine 17:155–161 (1990)



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

R. Pirastu, MSc, P. Comba, DSc, A. Reggiani, MD, V. Foa, MD, A. Masina, MD, and C. Maltoni, MD

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

University of Rome, "La Sapienza" Department of Animal and Human Biology (R.P.), and Istituto Superiore di Sanita (P.C., A.R.), Rome, Italy
Institute of Occupational Health "L. Devoto," University of Milan (V.F.), Milan, Italy
Institute of Oncology F. Addarii Bologna, Bologna, Italy (A.M., C.M.)
Address reprint requests to Dr. Comba, Istituto Superiore di Sanita', Viale Regina Elena 299, 00161 Rome, Italy.
Accepted for publication August 4, 1989.

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<br>Autoclave operator | Autoclave cleaner<br>Reactor area helper |
| Case no. 2 | Maintenance | Maintenance |
| Case no. 3 | Autoclave operator<br>Controller | Autoclave operator<br>Maintenance |
| Case no. 4 | PVC extruder | PVC loader |
| Case no. 5 | PVC extruder | Dryer area operator |
| Case no. 6 | Reactor area operator<br>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.

## REFERENCES


Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Masina A, Pirastu R, Reggiani A, Vigotti MA (1987): A cohort mortality study on vinyl chloride manufacturers in Italy: study design and preliminary results. Cancer Lett 35:253–261.

Brugnami G, Abbritti G, Morelli A, Maltoni C, Solinas A, Pelliccioli G (1988): Liver angiosarcoma in a vinyl chloride polymerization plant worker. Report of the seventh Italian case. Med Lavoro 79:34–41.

Chiappino G, Bertazzi PA, Baroni M, Masini T (1982): Hepatic angiosarcoma from vinyl chloride report of a new Italian case. Med Lavoro 6:555–563.

Chiozzini G, Saggioro A, Pallini P, Valsecchi M, Magarotto GC, Scattolin A, Nardin M, Polacco A, Oliboni E (1988): Angiosarcoma epatico da cloruro di vinile. Med Lavoro 79:24–33.

Commission of the European Communities (CEC) (1984): "The German Thorotrast Study." Directorate General Science, Research and Development. EUR 9504 EN.

Dietz A, Langbein G, Permatter W (1985): Das Vinychloride-induzierte hepatocellulare karzinom. Klin Wochenschr 63:325–331.

Doll R (1988): Effects of exposure to vinyl chloride. An assessment of the evidence. Scand J Work Environ Health 14:61–78.

Evans DMD, Jones WW, Kung ITM (1983): Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers. Histopathology 7:377–388.

Falk H, Thomas LB, Popper H, Ishak KG (1979): Hepatic angiosarcoma associated with androgenic-anabolic steroids Lancet 2:1120–1123.

Forman D, Bennet B, Stafford J, Doll R (1985): Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases. Br J Ind Med 42:750–753.

Gokel JM, Liebezeit E, Eder M (1976): Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl chloride exposure: A report of two cases. Virchows Arch [A] 372:195–203.

IARC (1987): "Monographs on the Evaluation of Carcinogenic Risks to Humans." Suppl. 7. Lyon.

Johnson FL, Lerner KG, Siegal M (1972): Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 2:1273–1276.

Kepliner ML, Goode JW, Gordon DE, Calandra JC (1975): Interim results of exposure of rats, hamsters and mice to vinyl chloride. Ann NY Acad Sci 246:219–224.

Klatsin G (1977): Hepatic tumors: possible relationship to use of oral contraceptives. Gastroenterology 73:386–394.

Koischwitz VD, Lelbach WK, Lackner K, Hermanuntz D (1981): Das vinylchloridinduzierte Leberangiosarkom und hepatozellulare karzinom. Fortschr Rontgenstr 134:283–290.

Maltoni C (1974): Angiosarcoma epatico in operai esposti a cloruro di vinile in Italia. Med Lav 65:11–12.

Maltoni C (1977): Vinyl chloride carcinogenicity: An experimental model for carcinogenesis studies. In Hiatt HW, Watson JD, Winstar JA (eds): "Origins of Human Cancer." Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp 119–146.

Maltoni C, Cotti G (1988): Carcinogenicity of vinyl chloride. Ann NY Acad Sci 534:146–159.

Maltoni C, Lefemine G (1975): Carcinogenicity bioassays of vinyl chloride: Current results. Ann NY Acad Sci 246:195–217.

Maltoni C, Rondinella R (1980): Angiosarcoma epatico in lavoratori esposti a cloruro di vinile in Italia. Acta Oncol 1:35–49.

Maltoni C, Clini C, Vicini F, Masina A (1984): Two cases of liver angiosarcoma among polyvinyl chloride extruders of an Italian factory producing PVC bags and other containers. Am J Ind Med 5:297–302.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D (1984): Experimental research on vinyl chloride carcinogenesis. In: "Archives of Research on Industrial Carcinogenesis," vol II. Princeton, NJ: Princeton Scientific Publishers.

Popper H (1974): Hepatic angiosarcoma in man and rodents following prolonged exposure to vinyl chloride Gastroenterology 67:794.

Popper H, Selikoff IJ, Maltoni C, Squire RA, Thomas LB (1977): Comparison of neoplastic hepatic lesions in man and experimental animals. In Hiatt HW, Watson JD, Winstar JA (eds): "Origin of Human Cancer." Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp 1359–1382.

Viola PL, Bigotti A, Caputo A (1971): Oncogenic response of rat skin, lungs and bones to vinyl chloride. Cancer Res 32:516–522.

Wong O, Whorton MD, Ragland D, Klassen C, Samuels D, Claxton K (1986). "An Update of An Epidemiologic Study of Vinyl Chloride Workers 1942–1982. Oakland, CA. Environmental Health Associates, Inc.