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AN EPIDEMIOLOGICAL STUDY OF VINYL CHLORIDE EXPOSED WORKERS IN ITALY

P. A. BERTAZZI[1], A. VILLA[1], V. FOA[1], B. SAIA[2], L. FABBRI[2], C. MAPP[2], C. MARCER[2], M. MANNO[2], M. MARCHI[3], F. MARIANI[3], and F. BOTTASSO[4]

Institute of Occupational Health, University of Milan, Milan, Italy[1], *Institute of Occupational Health, University of Padua, Padua, Italy*[2], *Department of Statistics, Laboratory of Clinical Physiology, C. N. R., Pisa, Italy*[3] *and »B. Ramazzini« Institute for Social Security, Bologna, Italy*[4]

ABSTRACT

During the period 1975–1977 an investigation was carried out in Italy with the aim of identifying and controlling the effects of vinyl chloride monomer (VCM) on workers exposed to this compound in the production of VCM and PVC (polyvinyl chloride). Of the 5441 people for whom exposure was confirmed, 4713 were examined and 64 had died, giving a total number of 4777 traced, i.e., 86.2% of the total. The examined population included workers who were exposed at the time of the investigation, workers exposed in the past but later transferred to other departments, workers exposed in the past and now retired. The investigation was organized by the Italian Federation of Chemical Workers' Unions, with the co-operation of university institutes, regional health services, hospitals, and industrial medical services.

The studies carried out included: a complete medical examination; recording of physiological and pathological anamnesis and occupational history; chest X-ray and sputum cytology; X-ray of the hands; finger plethysmography (basic and after cold test); complete blood count and platelets; SGOT, SGPT, gamma GT, total bilirubin, alkaline phosphatase. Other tests made but not considered here were: fundus oculi, urine analysis and lung function tests.

For evaluation of VCM exposure an individual index was constructed considering homogeneous exposure group, exposure period and length of exposure.

The following are the main results obtained from clinical and laboratory studies in relation to exposure, taking into account the principal confounding and modifying factors:

Twenty-seven cases (0.6%) of osteolysis and 142 cases (3.3%) of suspected osteolysis were observed: a significant association between frequency of alterations and exposure was observed in the total population and in the over 45-years age group. Finger photoplethysmography after cold test was altered in 742 workers (19.2%); the frequencies of the alteration increase with exposure in all age groups and are not significantly associated with smoking habits. There were 339 subjects (7.5%) with under 150 000 platelets; the frequency of thrombocytopenia was related to increasing exposure, except in the younger age stratum. Among the 2 558 correctly performed sputum cytology tests, the most frequent finding (30.6%) was squamous metaplasy and/or typical adenomatous hyperplasy. The frequency of pathological findings increases with increasing exposure in the total population and in the group of older subjects. In 43.2% of the subjects one or more of the liver tests showed abnormalities; the distribution of the abnormalities is significantly related with the duration of exposure. Increases in gamma GT were observed in 28.4% of the workers: the frequency of this alteration is significantly related with increasing duration of exposure in the total population but not in all age strata; a similar increase was observed in heavy drinkers as well. Total bilirubin was altered in 13.3% of the subjects, SGOT in 10.7% and SGPT in 10.3%; AP was elevated in 5.6% of the subjects and the frequency of alterations increased with increasing duration of exposure. Hepatomegaly was observed in 46.2% of the subjects. There was a statistically significant relationship between this finding and the duration of exposure, even when age and alcohol consumption were taken into account.

A mortality study of the exposed subjects started from the commencement of production in Italy. However, due to the lack of adequate records, only indicative data can be furnished. Among the exposed workers traced who had died, a high percentage of tumours as cause of death was observed (48.4% of the total); of these tumours, 30% were of the liver and biliary system, 3 of which were angiosarcomas of the liver: 2 were diagnosed before and 1 during the investigation. In those plants where the deceased subjects were traced more accurately an excess of tumours as cause of death was observed.

Italy is one of the largest producers of VCM and PVC and in 1974 was in fourth place after the USA, Japan and the Federal German Republic. In Italy there are 7 VCM production plants and 8 polymerization plants and there were also 3 pilot plants (Fig. 1): the first plant started operating in 1952. More than 5 000 people were employed in the various plants since the beginning of production until 1975.

When in 1974 the carcinogenicity of VCM was conclusively demonstrated[2,14,19,23,25] and renewed attention directed to the existing toxicity data[1,4,5,7,8,9,10,11,17,22,24,28], the Federation of Italian Chemical Workers' Unions (F.U.L.C.) organized a nationwide survey on the situation in Italy. For this purpose, at the beginning of 1975 two working groups were set up by the F.U.L.C.: one epidemiological on health conditons and causes of death, and the other on plant technology and safety. These two working groups comprised physicians, statisticians, chemists, engineers, and also technicians and workers from the plants involved. The aim of the survey was not to produce confirmation of an already proven pathology but to suggest measures towards an effective prevention and surveillance on the basis of an appraisal of the present conditions both of the workers' health and of the plants. Health measures alone in fact are not sufficient to protect the health of the workers unless they are closely linked with prevention measures focused on the source of risk, i.e. at the plants.

The epidemiological survey took two directions: a cross-sectional study of the health conditions of the workers still living, and a mortality study.

POPULATION AND METHODS

The investigation covered male workers engaged on the production of VCM/PVC since the beginning of operations. Fabricators were excluded with the exception of a small factory producing PVC bags in the Marghera area which was included in the investigation for local reasons. All living or deceased male subjects exposed currently or in the past to VCM/PVC for a period of at least 6 months were admitted to the study; 5 441 subjects satisfied these conditions but it was possible to trace only 4 777 of them, equal to 86.2% of the subjects exposed

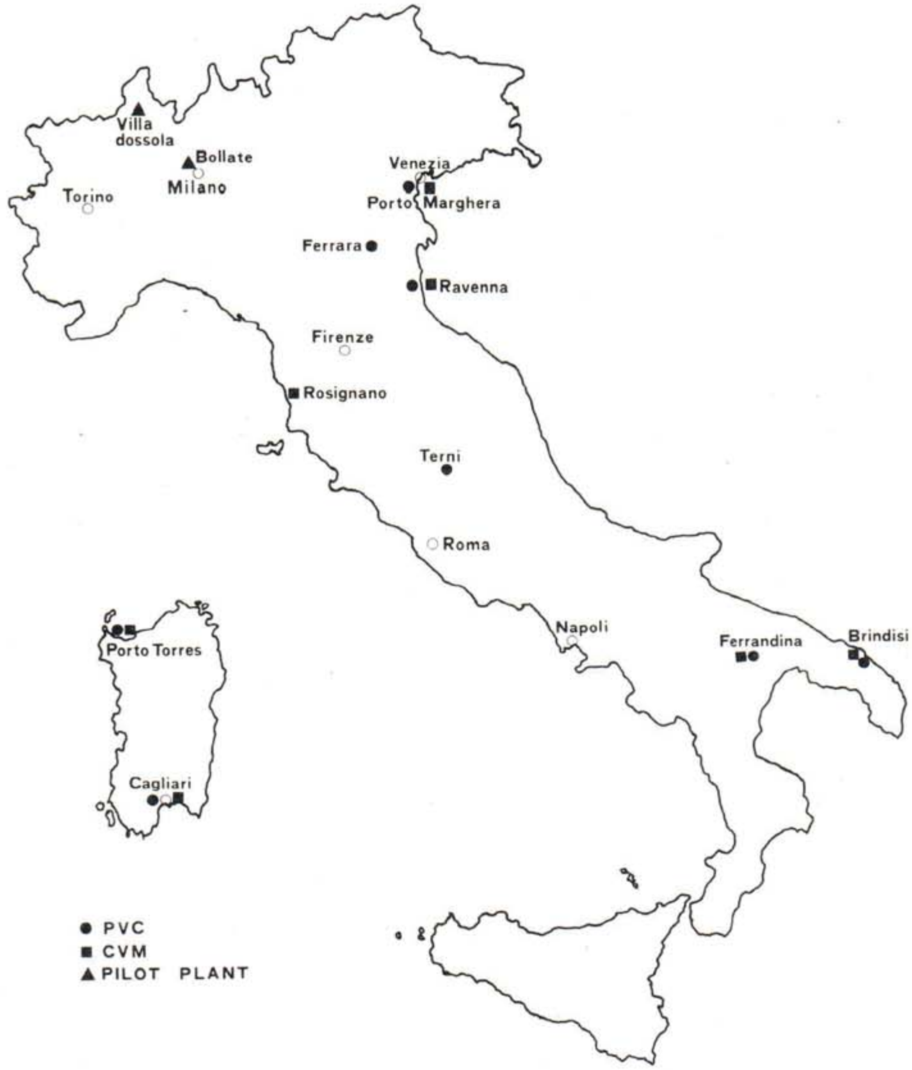

FIG. 1 – VCM/PVC plants' location in Italy.

in the various plants since the beginning of production (1952) until 31 December 1975 (Table 1). The number of workers currently exposed was 3 388 (70.9%) and the number of those exposed only in the past and still working or retired at the time of the investigation was 1 389 (29.1%). Data on the Sardinian plants are presently not available.

For each worker a series of data were collected drawn partly from company records and partly from interviews with the workers themselves. Completion of

TABLE 1
Populations covered by the survey, by plant.

Plant location	Subjects Exposed	Examined		Died	Total traced	
	N	N	%	N	N	%
Ravenna	778	762	97.9	6	768	98.7
Terni	850	514	60.4	2	516	60.7
P. Marghera	1930	1783	92.1	18	1801	93.3
Brindisi	920	779	84.7	9	788	85.6
Bollate	72	56	77.8	–	56	77.8
Villadossola	16	15	93.7	–	15	93.7
Ferrara	322	298	92.5	21	319	99.1
Rosignano	163	129	79.1	2	131	80.4
Ferrandina	490	377	76.9	6	383	78.2
Total	5541	4713		64	4777	86.2

the form and conduction of the interviews were done in most cases by uniformly trained personnel. The data collected included: age, sex, residence, smoking and drinking habits, habitual use of drugs, exposures prior to and following VCM/PVC exposure, main illnesses suffered in the past, hospitalizations. Reconstruction of the VCM/PVC exposure history posed many problems: the investigation was multicentric, the plants varied as regards production and technology, the environmental conditions had changed over the years, and no precise quantitative data were available on past exposure.

The following five components of a tentative exposure index were identified: homogeneous group, period of exposure, degree of exposure, duration of exposure and exposure index.

Homogeneous group

To identify groups with "homogeneous" exposure we relied partly on technological and environmental data but above all on the direct experience and knowledge of the workers, recorded in the course of many meetings at each plant. The definiton "homogeneous group" is wider than "job" and different from "department": it includes similar jobs in similar environmental, hygiene and technological conditions; it may cover only a portion of a department, several departments, etc. In identifying the groups we were assisted by the working group on plant technology, which informed us of the areas with homogeneous environmental features in the production of the monomer and of the polymer. The list of the homogeneous groups which, except for few variations, was used in all the plants was as follows:

Monomer production panel operator

Monomer operator

Monomer storage and recovery operator
Reactor operator and additive make-up
Reactor cleaner
Polymerization panel operator and assistant
Reactor discharge and degassing operator
Drying panel operator
Dryer and vibrating screen operator
Bagging, shipping and warehouse operator
Security officer, foreman, supervisor
Compounding operator
Machine maintenance
Electrical maintenance
Laboratory technician

Period of exposure

Production requirements, technological evolution and other factors produced changes of even considerable degree in the working environment conditions over the years, with consequent change in VCM exposure. The more remote the technological period, the greater the weight attributed to the exposure.

Degree of exposure

An estimated "degree" of exposure was assigned to each combination "homogeneous group – period of exposure" (from <50 ppm to above 800 ppm); the degree of exposure has only an indicative value: it is an indirect estimation, which does not correspond to a precise concentration but allowed us to arrange the exposures on a scale. To each pair "homogeneous group/period of exposure" was assigned an increasing value starting from 1.

Duration of exposure

For each worker the duration of exposure in each homogeneous group in each period was ascertained; a great number of workers had worked in different homogeneous groups at different times and for different periods.

Exposure index

The VCM/PVC exposure history of each worker was thus reconstructed by combining the different degrees of exposure and the duration of each exposure so as to obtain an exposure index (EI) according to the following formula:

$$EI = \frac{\Sigma_i \text{ (Degree of exposure}_i \times \text{Duration of exposure}_i)}{\Sigma_i \text{ (Duration of exposure}_i)}$$

where i may vary from 1 to n and indicates the different exposures of the subject. The index gives an estimation of the degree of exposure, weighted according to the length of exposure; each worker was characterized by a value of this index.

The range of the values obtained was divided into three categories of increasing severity which, for the sake of briefness, will be defined as "low", "medium", and "high".

Exposure was also classified using only the duration calculated as the sum of the different periods of exposure. In this case too the workers were divided into three groups: ⩽5 years, 6–15 years, >15 years. In Table 2 the workers are distributed according to the category and duration of exposure.

TABLE 2
Distribution of workers examined according to exposure category and duration of exposure.

Exposure category	Duration of exposure (years)							
	<5		6–15		>15		Total	
	N	%	N	%	N	%	N	%
Low	463	23.8	556	24.9	69	15.1	1 088	23.4
Medium	1 020	52.3	1 170	52.3	258	56.5	2 448	52.7
High	467	23.9	510	22.8	130	28.4	1 107	23.9
Total	1 950		2 236		457		4 643*	

*For 70 workers (4 713–4 643) information was not sufficient to estimate the exposure.

The cross-sectional morbidity investigation was based on a series of clinical, instrumental and laboratory tests involving the target organs and systems affected by the toxic action of vinyl chloride. For the lung: sputum cytology and chest X-ray were performed; for the hands: X-ray of both hands, photoplethysmography at rest and before work with basic tracing followed by a further tracing after the "cold test" (immersion of the hands in running water at 13–15 °C for 10 minutes); complete urine and sediment analysis plus cytological examination in the case of hematuria; complete blood and platelets count; for the liver: alkaline phosphatase, (AP) bilirubinemia, gamma GT, SGOT, SGPT; complete medical examination. About thirty medical services, including hospitals, university institutes, local health services and plant medical services, participated in carrying out these tests and examinations. This posed serious problems of standardization of methods: each centre was provided with standard instructions for the radiological examinations and a doublereading was done; the photoplethysmographic tracing was always made by the same operators who travelled to the various centres with their instruments; the same analytical methods were advised for the hematochemical tests and laboratory technicians from the Clinica del Lavoro in Milan went to some centres to train the staff of the various laboratories so as to obtain uniform performance; the cytological examinations were read at the local hospitals and a check reading was done at the Institute of Oncology in Bologna. In spite of these general instructions, for various reasons the standard methods were not fully followed at all the centres; hepatomegaly was established only on the basis of an accurate medical examination. When completed, all the results of the examinations were recorded on an *ad hoc* form, punched and stored on magnetic tape.

Not all the workers included in the investigation underwent all the scheduled tests, one of the reasons being the fact that not all the men exposed in the past reported for examination. The variables on which information was collected (age, smoking/drinking habits, previous illnesses, etc.), were controlled by stratification analysis.

The mortality study considered the period from the start of production of each plant up to 31 December 1975. The following data were collected for each worker: year of first exposure, age at first exposure, place and cause of death. The cause of death was obtained from death certificates and, in some cases, from hospital records. Due to the high turnover, the high emigration rate in some regions, and the lack of accurate records, it was impossible to trace all the subjects and obtain the exact number of deceased persons.

A further impediment to complete an accurate analysis was the lack of death rates specific for cause and sex on a regional basis. The official data used are those on death rates according sex and broad age groups and categories of causes on a nation-wide basis relative to the periods 1950–52, 1960–62 and 1968–70. The categories of causes considered are "infectious and parasitic diseases" (I.C.D. codes 000–136, VIII revision), "tumours and leukemias" (codes 140–239), "C.N.S. vascular lesions and circulatory diseases" (codes 390–458), and "other causes" (remaining codes). The age groups considered were 15–49 years, 50–64 years, 65 years and over. In order to obtain the number of expected deaths for the individual categories of deaths in the different age groups in the various plants, the years of risk for each subject were calculated considering the period of experience (for the years up to 1956 the mortality rates from the 1950–52 tables were used, for the years up to 1965 those of the 1960–62 tables, and for the years up to 1975 those of the 1968–70 tables) and the age of the subject, i.e., the age group into which fell a certain year at risk experienced in a given period.

For those subjects included in the investigation for whom one or more of these data were not available, an artificial value was taken on the basis of the average value of the corresponding group.

For subjects exposed but not traced, years at risk were attributed as if they were all alive at the time of the investigation. This meant that the years at risk were probably over-estimated (and consequently also the "expected deaths") since it is very likely that there were some deceased subjects among the untraced.

All the data were processed at the CNR Laboratory of Clinical Physiology, Department of Biostatistics and Epidemiology, Pisa.

RESULTS AND DISCUSSION

Clinical and laboratory findings

Table 3 shows the distribution of the cases of confirmed or suspected acro--osteolysis of at least one finger, according to age and exposure category. Hand X-ray examination was performed on 4329 workers. Altogether 27 cases (0.6%)

TABLE 3
Distribution of certain or suspected acro-osteolysis (AOL) according to exposure category, in each age stratum.

Age (years)		Exposure category						Total	
		Low		Medium		High			
		N	%	N	%	N	%	N	%
< 35	AOL	1	0.3	2	0.2	3	0.9	6	0.4
	AOL suspect	7	2.2	14	1.8	4	1.2	25	1.8
	Examined	316		763		315		1394	
36 – 45	AOL	2	0.4	7	0.7	2	0.4	11	0.6
	AOL suspect	13	3.0	39	3.9	18	4.1	70	3.8
	Examined	424		977		435		1836	
> 45	AOL	1	0.4	4	0.7	5	1.9	9	0.8
	AOL suspect	5	2.0	23	4.1	17	6.5	45	4.2
	Examined	250		550		259		1059	
All ages	AOL	4	0.4	13	0.5	10	1.0	27	0.6
	AOL suspect	25	2.5	76	3.3	39	3.8	140	3.3
	Examined	990		2290		1009		4289	100*

AOL suspect > 45: $\chi^2_t = 6.52$, $p < 0.02$

AOL + AOL suspect > 45: $\chi^2_t = 9.63$, $p < 0.01$

AOL + AOL suspect all ages: $\chi^2_t = 4.96$, $p < 0.05$

Frequency of suspected AOL increases progressively with age ($\chi^2_t = 12.49$, $p < 0.001$)

*For 40 workers, 2 of whom with AOL suspect, exposure category was not determined.

of confirmed acro-osteolysis and 142 (3.3%) suspected cases were observed. The frequency of alterations increases with statistical significance in relation to the category of exposure in the total population and in the > 45 years age stratum. The distribution of cases in relation only to duration of exposure behaves in a similar manner but is not statistically significant in any of the age strata.

Basic photoplethysmographic tracing was done for 3877 workers: 150 tracings (3.9%) were abnormal; 3866 subjects had a tracing after the cold test, which in 742 (19.2%) was abnormal. Table 4 shows the distribution of the abnormal tracings after the cold test in relation to age and exposure. The frequency of alterations shows significant trends in each age stratum and in the total population. No significant relationship was observed in relation to length of

TABLE 4
Abnormal photoplethysmographic tracings according to exposure category, in each age stratum.

Age (years)	Exposure category			Total
	Low	Medium	High	
< 35	13.1% (35/267)	14.5% (90/620)	22.8% (68/298)	16.3% (193/1 185)
36 – 45	14.2% (55/388)	15.5% (129/832)	22.7% (100/441)	17.1% (284/1 661)
> 45	17.9% (39/218)	25.9% (121/468)	32.5% (90/277)	23.0% (250/963)
All ages	14.8% (129/873)	17.7% (340/1 920)	25.4% (258/1 016)	19.1% (727/3 809)*

< 35: $\chi^2_t = 10.16$, $p < 0.01$; 36 – 45: $\chi^2_t = 11.01$, $p < 0.001$; > 45: $\chi^2_t = 13.48$; $p < 0.001$. All ages: $\chi^2_t = 35.56$, $p < 0.001$.

* For 57 subjects exposure category not determined (15 with abnormal tracing).
Frequency of abnormal tracings increases also with age.

exposure alone. The distribution of the abnormal photoplethysmographic tracings in relation to the number of cigarettes smoked showed no statistically significant differences. A combined alteration "photoplethysmographic tracing – – AOL" was observed in 35 subjects; of these, 29 had suspected and six confirmed AOL.

Altogether, 339 cases of thrombocytopenia below 150 000 were observed in the 4 503 subjects examined (7.5%); 66 (1.5%) were < 100 000 and 10 (0.2%)

TABLE 5
Distribution of thrombocytopenia according to exposure category, in each age stratum.

Age (years)	Exposure category			Total
	Low	Medium	High	
< 35	3.8% (12/318)	5.2% (40/769)	6.3% (20/318)	5.1% (72/1 405)
36 – 45	3.4% (15/442)	6.5% (65/999)	8.2% (37/451)	6.2% (117/1 892)
> 45	8.0% (22/276)	12.2% (72/592)	13.8% (40/290)	11.6% (134/1 158)
All ages	4.7% (49/1 036)	7.5% (177/2 360)	9.1% (97/1 059)	7.3% (323/4 455)*

< 35: $\chi^2_t = 2.07$, p = n.s., 36 – 45: $\chi^2_t = 8.88$, $p < 0.01$; > 45: $\chi^2_t = 4.63$, $p < 0.05$; all ages: $\chi^2_t = 15.24$, $p < 0.001$.

* 48 subjects not included due to lack of exposure information (16 with thrombocytopenia). Alterations are also associated with age.

< 50 000. Table 5 gives the distribution of thrombocytopenia in relation to exposure category. There is a clear association between prevalence of thrombocytopenia and increasing exposure in the total population and in the age strata 35 – 45 and > 45 years. Distribution according to duration of exposure showed a significant trend only when considering all ages together: < 5 years 125/1 912 (6.5%); 6 – 15 years 160/2 150 (7.4%); > 15 years 53/438 (12.1%); $\chi_t^2 = 11.5$, $p < 0.001$.

Table 6 gives the classification of 2 558 sputum cytology tests: the table also includes workers who had a cytology test but are not covered by the present survey (e.g., workers at the Sardinian plants). Findings other than "normal" (codes 04-08) relative to the workers covered by the survey on the whole increase

TABLE 6
Sputum cytology results.

Class	Description	Frequency	
		N	%
01 – 02 – 03	"Normal"	1 500	58.7
04	Grade +++ squamous metaplasia Typical adenomatous hyperplasia	784	30.6
05	Initial dystypical adenomatous hyperplasia Initial squamous dysplasia	212	8.2
06	As 05, more represented	20	0.8
07	Definite dystypical adenomatous hyperplasia Definite squamous dysplasia	35	1.4
08	Hyperplasia and severe dysplasia	7	0.3
09	Cells suspect of adenocarcinoma, epidermoid carcinoma, undifferentiated carcinoma	0	—
10	Cells indicative of epidermoid carcinoma, adenocarcinoma, undifferentiated carcinoma	0	—
Total		2 558	100

with increased exposure (Table 7); the trend was statistically significant also in the > 45 age stratum as well. It is interesting to note that the frequency of findings other than "normal" are not associated with age. No significant association was observed between frequency of abnormal findings and smoking habits.

Altogether 4 713 workers underwent liver tests but 114 underwent only some of them. The following analysis refers only to the 4 599 subjects who underwent at least four of the scheduled tests. However, for each test the total is subject to variations.

In 1 986 of the 4 599 subjects examined the liver tests showed an abnormality (43.2%), 1 140 (24.8%) had one or two abnormal tests and 846 (18.4%) had more than two abnormal tests simultaneously. The frequency of

TABLE 7
Distribution of abnormal sputum cytology results according to exposure category, in each age stratum.

Age (years)	Exposure category			Total
	Low	Medium	High	
< 35	35.9% (50/139)	45.9% (147/320)	42.5% (79/186)	42.7% (276/645)
36 – 45	36.5% (80/219)	40.2% (199/495)	44.0% (121/275)	40.4% (400/989)
> 45	27.3% (30/110)	37.7% (106/282)	46.2%* (61/132)	37.5% (197/524)
All ages	34.1% (160/468)	41.2% (452/1 097)	44.0%** (261/593)	40.4% (873/2 158)***

* $\chi^2_1 = 9.13$, $p < 0.01$
** $\chi^2_1 = 10.02$, $p < 0.01$

*** 400 missing (compared to table 7) are workers of Sardinian plants or workers for whom exposure data were not available. Frequency of abnormal results does not increase with age.

subjects with abnormal liver tests increases according to duration of exposure (Table 8), but no association was observed with the category of exposure. Table 9 gives the distribution of each abnormal test and hepatomegaly according to duration of exposure. The most frequent alterations were: hepatomegaly in 46.2% of the subjects [in 229 (5.0%) the liver enlargement was greater than 3 cm]; elevated gamma GT (28.4%); total bilirubin increased in 13.3%. Transaminases were elevated in about 10% of the subjects (SGOT = 10.7%; SGPT = 10.3%); slight alterations in alkaline phosphatase (AP) were observed (5.6%). Frequency of hepatomegaly, high gamma GT and AP increased significantly in relation to

TABLE 8
Number of abnormal liver test according to duration of exposure.

Test	Duration of exposure (years)			Total
	5	6 – 15	15	
1 or 2 abnormal	24.7% (485/1 966)	24.5% (535/2 185)	26.8% (120/448)	24.8% (1 140/4 599)
3 or more abnormal	16.0% (3 4/1 966)	19.9% (435/2 185)	21.6%* (97/448)	18.4% (846/4 599)
Total (at least one abnormal)	40.6% (799/1 966)	44.4% (970/2 185)	48.4%** (217/448)	43.2% (1 986/4 599)

* $\chi^2_1 = 13.49$ $p < 0.001$

** $\chi^2_1 = 11.52$ $p < 0.001$

TABLE 9

Frequency of abnormal liver tests and liver enlargement according to duration of exposure.

Test	Duration of exposure (years)			Total
	<5	6–15	>15	
Liver enlargement	41.4% (806/1 947)	48.2% (1 046/2 168)	58.1%* (244/420)	46.2% (2 096/4 535)
Gamma GT	26.3% (512/1947)	28.6% (620/2 168)	37.1%** (161/434)	28.4% (1 293/4 549)
Bilirubin	12.7% (247/1 945)	13.5% (293/2 173)	14.7% (65/442)	13.3% (6 05/4 560)
SGOT	9.5% (182/1 915)	12.2% (257/2 100)	8.2% (36/440)	10.7% (475/4 455)
SGPT	9.8% (187/1 908)	10.9% (230/2 110)	9.3% (41/439)	10.3% (458/4 457)
AP	4.8% (93/1 944)	5.9% (128/2 169)	7.8%*** (34/435)	5.6% (255/4 548)

* $\chi^2_1 = 44.87$, $p < 0.001$

** $\chi^2_1 = 16.36$, $p < 0.001$

*** $\chi^2_1 = 6.60$, $p < 0.02$

Subjects missing from the total 4 599 either did not have the test or their exposure was not determined.

duration of exposure; analysis of frequencies against categories of exposure revealed a greater prevalence of alterations in the medium and high categories, but without statistical significance. Table 10 shows the distribution of liver tests according to the extent of alterations.

Table 11 gives the distribution of hepatomegaly in relation to duration of exposure in each age stratum. There was a positive trend also in the 36–45 and > 45 age strata as well as in the total population. For the other liver tests no trend was observed in relation to exposure in any of the age strata.

The influence of alcohol consumption on hepatomegaly and gamma GT (the most frequent abnormalities) was also evaluated. From Table 12 it can be seen that at the same consumption of alcohol, hepatomegaly increases with duration of exposure; the increase is particularly evident in the group of teetotallers and average drinkers. In heavy drinkers exposure and alcohol seem to act synergically. Liver enlargement also increases with alcohol consumption; however, this was not observed in the group of workers exposed for more than 15 years. Gamma GT abnormalities (Table 13) increase in frequency with increasing alcohol consumption. With the same alcohol consumption, the frequency of abnormalities increases with growing duration of exposure in heavy and average drinkers; this trend is significant only in heavy drinkers.

The results of the other examinations performed will not be commented on here. We should only like to draw attention to data already published relative to a plant under study. Out of 258 polymerization workers, 30 cases of pulmonary fibrosis were detected[16].

TABLE 10
Liver test results.

Test		Value	N	%
Gamma G.T. (U.I./l) N = 4 555*	Normal	≤ 28	3 262	71.6
	Elevated	29 – 50	782	17.2
		51 – 100	331	7.3
		> 100	180	3.9
Bilirubin (mg/100 ml) N = 4 564	Normal	≤ 1.0	3 957	86.7
	Elevated	1.1 – 1.5	523	11.5
		> 1.5	84	1.8
SGOT (U.I./l) N = 4 486	Normal	≤ 19	4 005	89.3
	Elevated	20 – 50	459	10.2
		> 50	22	0.5
SGPT (U.I./l) N = 4 488	Normal	≤ 17	4 026	89.7
	Elevated	18 – 50	428	9.5
		> 50	34	0.8
AP (U.I./l) N = 4 571	Normal	≤ 48	4 315	94.4
	Elevated	49 – 80	239	5.2
		> 80	17	0.4

*Subjects missing from the total of 4 599 did not have the test.

TABLE 11
Distribution of liver enlargement according to duration of exposure, in each age stratum.

Age (years)	Duration of exposure (years)			Total
	< 5	6 – 15	> 15	
< 35	37.8% (366/968)	39.0% (182/467)	66.7% (4/6)	38.3% (552/1 441)
36 – 45	42.7% (269/630)	48.7% (546/1 121)	48.8%* (84/172)	46.7% (899/1 923)
> 45	49.0% (171/349)	54.8% (318/580)	64.5%** (156/242)	55.1% (645/1 171)
All ages	41.4% (806/1 947)	48.2% (1 046/2 168)	58.1%*** (244/420)	46.2% (2 096/4 535)

* $\chi^2_1 = 4.91$, $p < 0.05$ ** $\chi^2_1 = 13.42$, $p < 0.001$ *** $\chi^2_1 = 16.36$, $p < 0.001$
Frequency increases significantly also with age.

TABLE 12
Distribution of liver enlargement according to duration of exposure and alcohol consumption.

Alcohol consumption	Duration of exposure (years)			Total
	< 5	6 – 15	> 15	
Non-drinkers	36.4% (36/99)	47.8% (55/115)	78.6%* (22/28)	46.7% (113/242)
Average drinkers	40.0% (447/1 116)	49.1% (641/1 304)	55.4%** (129/233)	45.9% (1 217/2 653)
Heavy drinkers	52.6% (282/536)	55.7% (322/578)	63.6%*** (89/140)	52.3% (693/1 254)

* $\chi^2_1 = 13.88$, $p < 0.001$

** $\chi^2_1 = 28,93$, $p < 0.001$

*** $\chi^2_1 = 4.90$, $p < 0.05$

Subjects missing either did not declare alcohol consumption or did not have the test.

TABLE 13
Distribution of gamma GT elevated according to duration of exposure and alcohol consumption.

Alcohol consumption	Duration of exposure (years)			Total
	< 5	6 – 15	> 15	
Non-drinkers	8.2% (8/98)	15.2% (17/112)	12.9% (4/31)	12.0% (29/241)
Average drinkers	22.4% (258/1 149)	23.6% (314/1 331)	27.1% (67/247)	23.4% (639/2 727)
Heavy drinkers	37.8% (208/550)	41.8% (254/607)	57.8%* (85/147)	41.9% (547/1 304)

* $\chi^2_1 = 15.21$, $p < 0.001$

Subjects missing either did not declare alcohol consumption or did not have the test.

Mortality

Table 14 gives the results of the mortality study in the 6 plants where it could be carried out. It will be noticed that expected mortality is, on the whole, definitely higher than observed mortality. This might be due to: an over-estimation of the expected values (as explained above), to a failure to establish whether the untraced subjects were alive or dead and to the known "selection" effect whereby workers engaged for employment are in a significantly different state of health with respect to the general population of the same age and sex, with a consequently lower mortality. Study of the data in the table will show that there is an excess of deaths due to "tumours and leukemias" at the plants in Brindisi, Ferrandina, Ferrara. It should be noted that the highest mortality both in an absolute sense and in relation to tumours was observed at the Ferrara plant,

TABLE 14
Cause-specific mortality in VCM/PVC exposed workers in Italy.

Plant	Age (years)	Causes of death											
		Tumours			Cardiovascular diseases CNS vascular lesions			Other			All causes		
		O	E	SMR	O	E	SMR	O	E	SMR	O	E	SMR
P. Marghera	< 50	6	7.4	81.1	3	8.0	37.5	1	22.8	4.4	10	38.2	26.2
	50–65	2	3.5	57.1	3	4.4	68.2	2	4.2	47.6	7	12.1	57.9
	> 65	—	0.4	—	1	1.5	66.7	—	0.8	—	1	2.7	37.0
	Total	8	11.3	70.8	7	13.9	50.4	3	27.8	10.8	18	53.0	34.0
Brindisi	< 50	4	3.3	121.2	—	3.6	—	5**	10.1	49.5	9	17.0	52.9
	50–65	—	1.4	—	—	1.7	—	—	1.7	—	—	4.8	—
	> 65	—	—	—	—	—	—	—	—	—	—	—	—
	Total	4	4.7	85.1	—	5.3	—	5	11.8	42.4	9	21.8	41.3
Ferrandina	< 50	2	1.4	142.9	2	1.5	133.3	—	4.3	—	4	7.2	55.6
	50–65	—	0.6	—	—	0.8	—	2	0.8	250.0	2	2.2	90.9
	> 65	—	—	—	—	—	—	—	—	—	—	—	—
	Total	2	2.0	100.0	2	2.3	87.0	2	5.1	39.2	6	9.4	63.8
Ferrara	< 50	3	1.3	230.8*	2	1.4	142.9	2***	4.2	47.6	7	6.9	101.4
	50–65	8	3.8	210.5*	5	4.9	102.0	—	4.8	—	13	13.5	96.3
	> 65	1	1.1	90.9	—	3.4	—	—	2.0	—	1	6.5	15.4
	Total	12	6.2	193.5*	7	9.7	72.2	2	11.0	18.2	21	26.9	78.1
Ravenna	< 50	2	2.6	76.9	1	2.8	35.7	1**	7.9	12.7	4	13.3	30.1
	50–65	—	1.8	—	2	2.3	87.0	—	2.2	—	2	6.3	31.7
	> 65	—	0.1	—	—	0.4	—	—	0.2	—	—	0.7	—
	Total	2	4.5	44.4	3	5.5	54.5	1	10.3	9.7	6	20.3	29.6
Rosignano	< 50	—	0.5	—	—	0.5	—	—	1.7	—	—	2.7	—
	50–65	1	1.4	71.4	—	1.8	—	—	1.4	—	1	4.6	21.7
	> 65	1	0.3	333.3	—	1.0	—	—	0.6	—	1	1.9	52.6
	Total	2	2.2	90.9	—	3.3	—	—	3.7	—	2	9.2	21.7

* $p < 0.05$
** 1 case of chronic liver disease
*** 2 cases of chronic liver disease
O = observed; E = estimated; SMR = standard mortality rate

which was one of the first to start production, and where nearly all of the people were traced. A slight excess of heart and circulatory diseases as causes of death was also observed in the younger age groups at the Ferrandina and Ferrara plants.

TABLE 15
Tumours as percentage of all causes of death.

Plant location	Expected (%)	Observed (%)
P. Marghera	21.3	44.4
Brindisi	21.6	44.4
Ferrandina	21.3	33.3
Ferrara	23.0	57.1
Ravenna	22.2	33.3
Rosignano	23.9	100.0
Total	22.0	48.4

Table 15 compares the expected proportion with the observed proportion of deaths from tumours; the comparison has a limited value but draws attention to the different relative weight of mortality from tumours, partly neutralizing the effect of inadequate tracing of cases.

TABLE 16
Causes of death among 62 subjects.

Tumours (N = 30)	Airways: Trachea	1
	Lung	6
	Brain	1
	Lacrimal sac	1
	G.I. tract: Esophagus	2
	Stomach	1
	Peritoneal carcinosis	1
	Liver: Hepatomas	4
	Angiosarcomas	3
	Cholecystic adenocarcinomas	1
	Bladder	3
	Cutaneous melanosarcoma	1
	Seminoma of testicle	1
	Leukemia	2
	Hodgkin's disease	2
Cardiovascular diseases and CNS vascular lesions (N = 19)	Myocardial infarction	9
	Other cardiopathies	1
	Vascular encephalopathies	6
	Other	3
Other causes (N = 13)	Chronic liver disease	5
	Renal insufficiency	3
	Other	5

Table 16 gives the individual causes of ascertained deaths. It can be observed that tumours represent 48.4% of the causes against an expected mean proportion of 22.0%. Of the 30 cases of tumours, 7 (23%) were of the respiratory tract, 4 (13%) of the G. I. tract, and 8 (26%) of the liver and gall bladder. Of the 3 cases of angiosarcoma, 2 occurred in workers employed on polymerization, and 1 in a fabricator engaged on extrusion operations[15]. Vascular lesions of the CNS and circulatory diseases accounted for 30.6% (28.4 expected) of all death causes. Among the remaining causes of death are to be noted 5 cases of "chronic liver disease" not further specified.

An analysis of mortality in relation to exposure (category and/or duration) was not possible since for many deceased subjects exposure data were not available.

DISCUSSION

The type and frequency of alterations in VCM/PVC production workers in Italy are similar to those observed in studies carried out so far in other countries. The incidence of osteolytic alterations (0.6%) was half as frequent as that found in large exposed populations, where 31 cases (1.0%) were observed among 3 000 workers[28] and 25 cases (0.4%) among 5011 exposed subjects[4]; the frequency of suspected acro-osteolytic lesions was higher: 3.3% as against the 0.3% reported in the same study[4]. No scleroderma-like skin lesions were observed.

Peripheral circulation studies with photoplethysmography gave alteration frequencies which could not be compared with a suitable reference population. A partial comparison of the frequencies obtained can be made with the frequency of Raynaud's syndrome found by Suciu[22] (6% of 168 exposed subjects) and Lilis[12]. In the latter study, Raynaud's syndrome was observed in 5.6% of the cases, and abnormalities of the Allen test in 26.6%; the latter percentage is slightly higher than that observed in the tracings after the "cold test", which in our study was 19.2%.

Thrombocytopenia was not observed as frequently as in another study carried out with a smaller and more selected group of people[17,18] but it was much higher than that found by Lilis[12].

An important fact is that the frequency of the three alterations (acro--osteolysis, peripheral circulation, thrombocytopenia) was found to be significantly related to exposure, except in the younger age groups for AOL and thrombocytopenia. It should be borne in mind that at the time of the survey (1976 – 77) the exposure conditions had decidedly improved in the preceding few years and that subjects with potentially reversible alterations such as those considered could have recovered in the meantime.

The frequency of cytological "abnormalities" of the sputum revealed an association with exposure in the total population and in ages > 45. According to data obtained by Maltoni (unpublished data), the frequency of squamous metaplasy and typical adenomatous hyperplasia (code 04) is similar in VCM/PVC-exposed workers and in other groups of workers in the plastics and petrochemical industries, but is much higher than in the metallurgical/engineering industries; the frequency of codes 04 to 08 alterations in VCM/PVC-exposed subjects is lower than that in chromium pigment workers but higher than in other workers of the chemical and metallurgical/engineering industries. Lastly, the frequency of adenomatous hyperplasia (code 04) was much higher than Maltoni found in a large group of smokers.

The frequency of liver alterations observed is rather high, as has been reported in previous cross-sectional studies of exposed populations[3,12,13,18,22,26]; the frequency of alterations in alkaline phosphatase was lower, however. The relationship between frequency of alterations and duration of exposure is quite clear. Alcohol consumption influences the results but does not explain the differences observed in gamma GT and hepatomegaly frequencies. The two factors – alcohol and exposure – appear to act synergically, and particularly after prolonged exposure a clear effect due to exposure is detectable.

A mortality study, admittedly with the limitations already mentioned, revealed an excess of tumours of every type as cause of death in the population under study precisely at those plants where the deceased subjects could be traced more accurately. As a proportion, the number of tumours was clearly higher than expected[19,21] and the sites most frequently involved were the liver, lung and gastro–intestinal tract, as has been found in other studies[6,19,20,23,27].

CONCLUSIONS

The survey is now continuing in two directions: further search for deceased subjects in an attempt to identify all of them and further analysis of the data by means of the multi-variate statistical method with the purpose of discovering possible relationships presently not detectable.

Nevertheless, the survey has already produced results as regards the situation in Italy by adequately demonstrating the present risk for people exposed to VCM/PVC in our country and the fact that, although important measures to improve the environmental conditions in the plants have already been taken, an accurate longitudinal monitoring of exposed workers must be continued.

The results of this health survey and of the plant technology and safety survey will be made known in detail to the workers concerned: this will be a further guarantee that the survey will bring about further improvements in the existing working conditons.

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