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Exposure to vinyl chloride monomer: results of a cohort study after a seven year follow up

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Abstract

In 1980 a prospective cohort study of exposed and non-exposed subjects was initiated in France by the Institut National de la Santé et de la Recherche Médicale (INSERM U287) in collaboration with occupational physicians from the companies involved. The aim was to evaluate the association between mortality and cancer morbidity and occupational exposure to vinyl chloride monomer (VCM). A total of 1100 subjects exposed to VCM and 1100 non-exposed controls matched for age (to two years), plant, and physician were followed up for seven years (8299 and 8202 person years for exposed subjects and controls respectively) for vital status and health and occupational state. Forty deaths occurred among exposed and 43 among non-exposed subjects (relative risk (RR) = 1·0; 95% confidence interval (95% CI) 0·6–1·5). Forty eight and 32 cases of cancer were reported among exposed and non-exposed subjects, respectively (RR = 1·3; 95% CI 0·8–2·1). Three cases of angiosarcoma of the liver occurred in the exposed group. Eight cases of lung cancer occurred among exposed subjects and six among non-exposed subjects. Fourteen cases of Raynaud's disease were found among exposed and one among non-exposed subjects and the difference was significant. One hundred and twenty three and 93 cases of cardiovascular disease (Raynaud's disease excluded) occurred in the exposed and non-exposed groups respectively (RR = 1·4; 95% CI 1·0–1·8); this difference was mainly due to hypertensi n. The test for an increasing risk with increased exposure was significant. The percentages of diseases of the respiratory system did not differ between the two groups (RR = 1·1; 95% CI 0·7–1·8).

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In 1980, a prospective cohort study of workers exposed to vinyl chloride monomer (VCM) and non-exposed workers was initiated by the Institut National de la Santé et de la Recherche Médicale (INSERM U 287) in collaboration with occupational physicians from the different companies involved in France. The main purpose of this study was to evaluate the association between mortality and morbidity (especially malignant tumours) and occupational exposure to VCM. This paper presents the health characteristics of the cohort after a seven year follow up.

Materials and methods

The design of the study has been described previously.[1] Briefly, the exposed group consisted of 40 to 55 year old employees exposed to VCM at the time of inclusion in 1980–1 or previously. Controls were employees who had never been exposed to VCM. Each control was matched to one exposed subject for age (to two years), plant, and physician. Interviews for initial data collection were conducted by the physician of each plant over a one year period. Data collected comprised the following information: identification, employment history (the entire work history was coded), occupational category, dates of exposure to VCM, and medical history as well as smoking and drinking habits. The subjects were followed up yearly for seven years from the time of inclusion until December 1988 for vital status and health and occupational state. Causes of death as well as pathological findings were coded according to the 9th revision of the International Classification of Diseases (ICD–9). Subjects who had terminated

Table 1 Relation between exposure to vinyl chloride and deaths during the seven year follow up

	Deaths during follow up*		
	Yes (n = 83)	No (n = 2115)	RR† (95% CI)
Non-exposed	43	1056	1·0
Exposed after 1976	4	68	1·04 (0·3–3·2)
Exposed < 10 y before 1976	15	405	0·94 (0·5–1·7)
Exposed ⩾ 10 y before 1976	21	586	0·99 (0·6–1·7)

*Two subjects were lost to follow up.
†Adjusted for initial characteristics defined in **Materials and methods.**

Table 2 Causes of death during the seven year follow up

	Exposed (1099)	Controls (1099)
All causes	40	43
Cancer	20	22
Circulatory system	9	10
Suicides	2	4
Traumas	2	0
Alcohol	1	3
Others	1	0
Unknown	5	4

their employment (resigned, been transferred, or retired) were followed up by each physician by mail.

Relative risks (RRs) among exposed compared with non-exposed subjects, are presented for death (all causes), malignant tumour, cardiovascular disease (Raynaud's disease excluded), and pulmonary disease. Subjects with a disease at the beginning of the study were excluded from comparisons concerning that disease. Relative risks were adjusted for age (continuous), duration of activity as a blue collar worker (continuous), foreign origin (yes/no), marital state, (married, single, widowed, divorced), place of residence (urban or rural), paternal or maternal history of cancer, cardiovascular, respiratory, or other disease, smoking habits (non-smoker, current or ex-smoker, number of daily cigarettes, (< or ⩾20) duration (< or ⩾25 years)), subject considered ethylic by the plant physician (yes/no), and weekly alcohol consumption (<14, 14–56, 57–112, >112 glasses). Relative risks were also expressed according to whether the workers were exposed to VCM for 10 or more years before 1976, exposed for less than 10 years before 1976, or exposed after 1976. The data were verified using the PIGAS system[2] and analysed with the GLIM package.[3]

Results

The study population included 1100 exposed and 1100 controls in 12 plants, and has been described elsewhere.[1,4] The follow up of the two groups was similar. In 1990 the number of person years was 8299 and 8202 and the number of subjects lost to follow up were 2% and 1% in the exposed and non-exposed groups respectively.

MORTALITY

During the seven year follow up, 40 and 43 deaths were reported in the exposed and non-exposed groups, respectively (RR = 1·0; 95% CI 0·6–1·5). Table 1 gives the RRs according to the different levels of exposure. None of the risks differed significantly from unity. Table 2 presents the main causes of death.

MORBIDITY

Exposure to VCM increased the risk of malignant tumour (ICD–9 140–208) slightly but not significantly (RR = 1·3; 95% CI 0·8–2·1). Table 3 shows the relation between the different categories of exposure to VCM and the occurrence of malignant tumour. Table 4 presents the distribution of the 70 sites of malignant tumours. Three cases of angiosarcoma of the liver occurred in the exposed group, but no cases of skin melanoma or malignant brain

Table 3 Relation between exposure to vinyl chloride and occurence of malignant tumours (ICD–9 140–208) during the seven year follow up

	Malignant tumours*		
	Yes (n = 70)	No (n = 2119)	RR† (95% CI)
Non-exposed	32	1061	1·0
Exposed after 1976	3	69	1·4 (0·4–4·9)
Exposed < 10 y before 1976	14	404	1·2 (0·6–2·4)
Exposed ⩾ 10 y before 1976	21	585	1·3 (0·7–2·3)

*Nine subjects had a malignant tumour at entry to the study (three among exposed subjects and six among controls).
†See footnote to table 1.

Table 4 Types and numbers of malignant tumours found during the seven year follow up

	Exposed (1099)	Controls (1099)
All sites (ICD–9 140–208)	38	32*
Lip mouth pharynx (140–149)	1	5
Digestive organs (150–159):	15	12
Oesophagus	1	1
Stomach	2	1
Small intestine	1	0
Colon rectum	5	6
Liver angiosarcoma	3	0
Liver	3	0
Pancreas	0	2
Digestive non-specific	0	2
Larynx (161)	2	2
Lung (162)	8	6
Bone (170)	1	1
Connective tissue (171)	1	0
Melanoma of skin (172)	0	1
Other skin (173)	3	1
Testis penis (186–187)	1	1
Bladder kidney (188–189)	2	3
Endocrine (194)	1	0
Lymphohematopoietic (200–208)	1	2
Secondary (196–198)	1	0
Primary site uncertain (199)	1	2

Subjects without malignant tumours at initial examination (No of subjects at risk): exposed 1096, controls 1093.
*The total exceeds 32 as four subjects exhibited two primary cancers.

tumour. Fourteen lung cancer cases were reported, eight in the exposed and six in the non-exposed group. One case of lymphoma was seen in the exposed and two cases in the non-exposed group.

The risk associated with the onset of diseases of the circulatory system (Raynaud's disease excluded) (ICD–9 390–459) was significantly higher than unity (RR = 1·4; 95% CI 1·0–1·8; $p < 0·05$). Moreover, an increased exposure to VCM was significantly ($p = 0·02$) associated with increased incidence of cardiovascular diseases (table 5). One hundred and twenty three and 93 cases of diseases of the circulatory system were noted in the exposed group and controls respectively. Table 6 presents the types of cardiovascular diseases. Fourteen cases of Raynaud's disease were seen in the exposed and one in the non-exposed group ($p < 0·01$).

The occurrence of diseases of the respiratory system (ICD–9 460–519) did not differ between the two groups (RR = 1·1; 95% CI 0·7–1·8). None of the risks significantly differed from unity when different degrees of exposure were considered (table 7).

Table 6 Type of cardiovascular disease (Raynaud's disease excluded) found during the seven year follow up

	Exposed (1099)	Controls (1099)
No of subjects at risk*	933	955
Circulatory system (390–459)	123†	93†
Hypertension (401–405)	55	34
Coronary insufficiency (410–414)	30	28
Myocardial infarction (410)	21	16
Cerebral vascular disorders (430–438)	8	10
Arteriosclerosis of limbs (4476, 4479, 4402)	9	11
Other circulatory disorders	27	15

*Subjects without a circulatory disease at the initial examination.
†The total exceeds 123 and 93 as some subjects exhibited two or more circulatory diseases.

Discussion

In our study, no relation was found for the occurrence of malignant tumour or respiratory diseases and exposure, whereas an increased risk of cardiovascular diseases was seen in the group exposed to VCM compared with the non-exposed group.

With respect to cancer, the risk of angiosarcoma of the liver has been well documented since 1974. This was confirmed in our study although only three cases were found. During the same period 14 cases of angiosarcoma of the liver were registered in France. This discrepancy can be explained by the limited size of our cohort as well as the selection of the plants and exposed group.

Our results showing a lack of relation between exposure to VCM and other cancers agree with others.[5–8] The IARC study,[3] which pooled data from Great Britain, Italy, Norway and Sweden totalling 222 746 person years, did not show any positive evidence that a particular malignant disease was a hazard either.

Our findings for the control group are in agreement with French statistics of incidence of cancer[9] in the same age groups, as 32 cases of malignant tumours were observed, corresponding to an annual incidence rate of 390 per 100 000.

Table 5 Relation between exposure to vinyl chloride and occurrence of cardiovascular disease (except Raynaud's disease) (ICD-9 390–459) during the seven year follow up

	Cardiovascular diseases*		
	Yes (n = 216)	No (n = 1672)	RR† (95% CI)
Non-exposed	93	862	1·0
Exposed after 1976	7	63	0·8 (0·4–1·9)
Exposed < 10 y before 1976	46	327	1·3 (0·9–1·9)
Exposed ⩾ 10 y before 1976	70	420	1·5 (1·1–2·1)

*Three hundred and ten subjects had a cardiovascular disease at entry in the study (166 among exposed and 144 among controls).
†See footnote to table 1.

Table 7 Relation between exposure to vinyl chloride and occurrence of pulmonary disease (ICD-9 460–519) during the seven year follow up period

	Pulmonary diseases*		**
	Yes (n = 82)	No (n = 1918)	RR† (95% CI)
Non-exposed	37	952	1·0
Exposed after 1976	8	61	1·3 (0·5–3·5)
Exposed < 10 y before 1976	18	381	1·2 (0·6–2·1)
Exposed ⩾ 10 y before 1976	19	524	1·0 (0·6–1·9)

*One hundred and ninety eight subjects had a pulmonary disease at entry to the study (88 among exposed and 110 among controls).
†See footnote to table 1.

An increased occurrence of non-malignant respiratory disease as a result of exposure to VCM and polyvinyl chloride dust has been cited. In our study, morbidity from non-malignant respiratory disease was not different among the exposed and non-exposed group. Also the incidence of death from non-malignant respiratory disease was not affected by exposure to VCM in two other recent studies.[6,7]

By analogy with the effect of other halogenated hydrocarbons, an increased risk of myocardial infarction has been suspected[8] with, however, little published evidence. One study[10] showed a slight increase in mortality due to ischaemic heart disease. In our study, although a linear increase in risk of cardiovascular diseases with increased exposure was noticed, no association with myocardial infarction was apparent. The increase in cardiovascular abnormalities is mainly due to hypertension but also to a variety of other circulatory problems including venous disorders, arythmia, and valvopathy. This lack of precision makes it difficult to provide an explanation for our positive result. The excess hypertension could be explained by the shift work,[11] but this relation has never been found, not even in a study that included 15 000 workers.[12] With respect to Raynaud's disease, 14 cases were seen among the exposed workers (0·2%); this rate is lower than that estimated for the general population—namely, 4%.[13] The difference can be explained because (1) the disease affects women more than men, (2) a healthy worker effect may exist, and (3) the cases of Raynaud's phenomenon have perhaps been included in the estimation for the general population.

To study the effect of the degree of exposure to VCM, we decided to take into account exposure before and after 1976. This was the year when exposure to VCM was reduced due to the implementation of the 1975 French legislation.[14] Measurements of exposure on workers, or in the workshops themselves, were not available and doses of exposure before 1976 were extremely high compared with doses after 1976.[15] For these reasons, the duration of exposure to VCM was only considered before this date and periods of less or more than 10 years before 1976 were taken as thresholds of low or high exposure.

In conclusion, angiosarcoma of the liver and Raynaud's phenomenon seem to be the major hazards related to the exposure to VCM. Apart from these diseases, the evidence indicates that the risks associated with exposure to VCM, in terms of both mortality and as morbidity, are probably negligible.

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1 Laplanche A, Clavel F, Contassot JC, Lanouzière C. Exposure to vinyl chloride monomer: report on a cohort study. *Br J Ind Med* 1987;44:711–5.
2 Wartelle M, Kramar A, Jan P, *et al.* PIGAS: an interactive statistical database management system. In: *Proceeding of the second international workshop on statistical database management.* Los Altos, CA:1983;124–32.
3 Baker RJ, Nelder JA. *The GLIM system, release 3.77.* Oxford: Numerical Algorithm Group press, 1985.
4 Clavel F, Laplanche A, Contassot JP, Lanouziere C. Exposure to vinyl chloride monomer: Report on a 7-year follow-up cohort study. In: *23rd International Congress on Occupational Health.* Montreal, Canada: M Cusson, 22–28 September 1990. (abstract 278.)
5 Simonato L, L'Abbé KA, Andersen A, *et al.* A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scand J Work Environ Health* 1991;17:159–69.
6 Doll R. Effects of exposure to vinyl chloride. An assessment of evidence. *Scand J Work Environ Health* 1988;14:61–78.
7 Jones R, Smith D, Thomas P. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940–1974. *Scand J Work Environ Health* 1988;14:153–60.
8 Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P, *et al.* Cohort and case-control analyses of workers exposed to vinyl chloride: an update. *J Occup Med* 1989;31:518–23.
9 Benhamou E, Laplanche A, Wartelle M, Faivre J, Gignoux M, Ménegoz F, Robillard J, Schaffer P, Schraub S, Flamant R. *Incidence des cancers en France, 1978–1982.* Paris: éditions INSERM, 1990.
10 Greiser E, Reml W, Weber H. Vinylchlorid-exposition und mortalitat deutscher chemiearbeiter im vergleich zur mortalitat nichtexponierter chemiearbeiter und PVC-verarbeiter. *Prophylaxe und Ergonomie* 1982;32:44–62.
11 De Gaudemaris R, Monzie A, Battistella P, Siche JP, Mallion JM. Pression arterielle et activites de travail poste. *Archives des Maladies Professionnelles* 1988;49:5–9.
12 Perroud D. *Travail posté, tension arterielle, corpulence et tabagisme.* Lyon: thèse de Médecine, 1983.
13 Bayle O, Consoli SM, Baudin M, Vayssairat M, Fiessinger JN, Housset E. Phénomene de Raynaud idiopathique et secondaire. *La Presse Médicale* 1990;19:741–5.
14 Réglement d'administration publique relatif aux mesures de protection des travailleurs contre les risques présentes par le chlorure de vinyle monomere. Journal Officiel, Décret n 80–203 du 12 mars 1980.
15 Contassot JC. *Chlorure de vinyle.* Paris: Encyclopedie Médico-Chirurgicale, 9–1990.

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