

Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases

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ABSTRACT The Association of Plastic Manufacturers in Europe maintains a register of all cases of angiosarcoma of the liver (ASL) resulting from exposure to vinyl chloride monomer (VCM). This register has recorded all known VCM related cases of the disease worldwide that have been histologically confirmed. Although likely to be incomplete, it is the most comprehensive tabulation of such cases available and, by the end of 1984, 118 men had been registered. The information from analysis of the cases currently on the register is used to make an approximate projection of the number of cases to be expected in the future. The conclusion from this projection is that the industry is reaching the halfway stage in the appearance of VCM related ASL.

The idea that vinyl chloride might cause cancer was first suggested by Viola in 1970 as a result of experiments in rats.¹ This was subsequently confirmed by Maltoni in 1973 with his comprehensive series of experiments in rats, mice, and hamsters.² Among the tumours that developed in these animals was the normally rare angiosarcoma of the liver (ASL). It was not, however, until three cases of ASL were observed in men who had been heavily exposed to vinyl chloride in a polyvinyl chloride (PVC) polymerisation plant in the United States that the reality of the hazard was generally accepted.³ ASL is normally so rare that only three or four cases occur each year in the whole of Britain (see below) so that the occurrence of three cases in a small group of industrial employees in the United States was, in itself, sufficient to justify the belief that the chemical caused the disease. If, however, any doubt has persisted it was soon dispelled by the steady accretion of new industrial cases and the finding that angiosarcomas and various other tumours could be produced in rats by levels of exposure that were appreciably less than those that had previously occurred in industry.⁴ Steps were therefore quickly taken in the mid-1970s to reduce the extent to which individuals could be exposed from levels of the order of several hundred ppm to 5 ppm (13×10^6 ngm/m³) or less.⁵ This reduction followed

an earlier lowering of exposure levels in the mid-1960s after concern was expressed about the narcotic effects of vinyl chloride and the risk of it producing acro-osteolysis. Before then exposure to some employees was often in the range of several thousand ppm. The rarity of ASL, even under conditions of heavy exposure, has made it difficult to study its epidemiological characteristics⁶ and it seemed, therefore, that it might be of value to summarise the data that have been recorded in the register of cases that has been maintained by Imperial Chemical Industries plc on behalf of the Association of Plastics Manufacturers in Europe (APME). This tabulates information about all the cases of ASL known to have occurred in men exposed to vinyl chloride that have been reported by individual manufacturing companies, trade associations, and occupational health organisations in Europe, North America, and Japan. The register is, doubtless, incomplete. It includes,

Table 1 Numbers of vinyl chloride related cases of angiosarcoma of the liver by date of death

Period	No of deaths
1955-9	2
1960-4	4
1965-9	9
1970-4	23
1975-9	46
1980-4	31
1955-84	115*

*Three men diagnosed in 1980-4 were still alive at 1 January 1985.

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Table 2 Numbers of vinyl chloride related cases of angiosarcoma of liver by age at diagnosis

Age (years)	No of cases
35-39	11
40-44	24
45-49	17
50-54	18
55-59	20
60-64	17
65-69	8
70-74	3
All ages	118

however, all the cases known to the collaborating organisations and they will probably have been informed, in one way or another, about nearly all cases that have been diagnosed among the relevant groups of employees.

Results

Until the end of 1984, 118 men had been recorded as having vinyl chloride related ASL, of whom three were still alive on 1 January 1985. All the cases had been confirmed histologically: 117 were reported to be hepatoangiosarcomas and one a cholangiosarcoma. No cases were recorded in women, but few women have been employed in manufacturing PVC.

Table 1 shows the breakdown of the cases by date of death. It should be noted that the register was begun in 1974 when vinyl chloride first became firmly established as a risk factor for ASL. Under-reporting is, therefore, less likely to be a problem after this date when special attention began to be paid to the disease. Table 2 gives the age distribution of the 118 men at the time of diagnosis. The mean age at diagnosis is 52. Table 3 gives the number of cases diagnosed and the number of PVC producing factories in each of the 12 countries reporting at least one case of ASL. Some

countries have had cases in most of their factories (France, West Germany); others have had cases clustered in a small number of factories (United States, United Kingdom). Indeed, the United States has had 23 of its 33 cases in just two factories. Other countries that produce PVC but have not reported any cases are shown in table 4.

Table 5 shows the numbers of cases by time since first exposure and maximum exposure time possible. It seems that the incidence of ASL reaches a peak 20-29 years after first exposure but substantial numbers of cases may still occur after more than 30 years. The table also gives hypothetical numbers for expected new cases based on the distribution of cases in men who could have experienced the maximum latency period. These calculations show that the occurrence of vinyl chloride related ASL is not yet at the halfway stage and one might reasonably expect another 150 cases or so with an unknown number of further cases occurring 35 years or more after first exposure. Table 6 shows the principal occupations of the 118 affected men. At least 43% of the men (51/118) had been employed as autoclave cleaners, an occupation that has been thought to have necessitated the highest exposure to vinyl chloride monomer.

Discussion

The reassuring feature of these results is that the number of cases on the register is so small, and, in particular, that only 80 new cases have been diagnosed since 1975, despite the large size of the industry.

In the decade 1975-84, 19 cases were registered from the United States and seven from the United Kingdom. In men aged over 15 about 3300 deaths a year are attributed to all types of liver cancer in the United States and about 550 a year in the United Kingdom. Many of these cancers are probably sec-

Table 3 Distribution of vinyl chloride related cases of angiosarcoma of liver by country. (Number of factories with three or more cases in parentheses)

Country	No of cases	No of factories reporting cases	Total No of factories making PVC		Capacity* in 1972
			Pre-1974	Pre-1964	
United States	35	10 (3)	44	28	2090
W Germany	26	6 (3)	9	7	1155
France	18	5 (3)	7	5	627
Canada	10	1 (1)	4	3	88
United Kingdom	9	2 (1)	7	4	502
Sweden	5	1 (1)	2	1	105
Italy	4	4 (-)	11	7	778
Yugoslavia	4	1 (1)	3	2	60
Czechoslovakia	2	1 (-)	1	1	48
Japan	2	1 (-)	31	16	1699
Belgium	2	1 (-)	2	1	195
Norway	1	1 (-)	1	1	65
All countries reporting cases	118	34 (13)	122	76	9462

*Capacity in kilotonnes pvc production a year (Information supplied by ICI and by recipients of the register).

Table 4 Countries with PVC factories operational before 1974 with no cases reported to register

Country	Total No of factories	
	Pre-1974	Pre-1964
<i>Western Europe</i>		
Austria	1	1
Finland	1	—
Greece	1	—
Holland	2	1
Portugal	1	1
Spain	4	3
Switzerland	1	1
<i>Eastern Europe</i>		
Bulgaria	1	—
East Germany	2	2
Hungary	1	1
Poland	2	1
Rumania	5	4
USSR	3	1
<i>South America</i>		
Argentina	3	3
Brazil	2	2
Chile	1	—
Colombia	2	—
Mexico	5	2
Peru	1	—

Source: Information supplied by ICI and by recipients of the register.

ondary liver cancers originating in other organs, particularly in men over 60, but if this is ignored it appears that only about 0.06% of liver cancers in adult men in the United States ($19/3300 \times 10$) are attributable to vinyl chloride and about 0.13% in Britain ($7/550 \times 10$).

Two pieces of evidence suggest that an extremely high exposure to vinyl chloride may be needed to induce ASL. Firstly, the fact that so many of the cases were among men working as autoclave cleaners in which the highest exposures are thought to have occurred: it was in these jobs that employees some-

times became faint and unconscious before the 1960s, when the main concern about vinyl chloride was its narcotic effect. Secondly, in some countries there is a remarkable clustering of cases into a small number of factories. This suggests that the working conditions and hygiene standards varied in different factories. Fifteen of the 16 Japanese and 19 of the 28 United States factories operating before 1964 have reported no cases, and it would be helpful if it could be shown that the exposures in these factories was appreciably less—unless, of course, the number of employees in these factories were all very small.

It is the rarity of this tumour that has enabled its rapid identification as an effect of exposure to vinyl chloride. Baxter *et al* have calculated that the background incidence of ASL in the United Kingdom is between two and seven cases a year—that is, cases unattributable to exposure to vinyl chloride or to thorostrast, the other established aetiological agent. That being so then the seven industrial cases in the decade 1975–84 represent an increase in the national figures of between 10% and 35%.

The mean induction period (time from first exposure to initial diagnosis) for the 118 cases is 22.6 years. Most cases have occurred 15 to 29 years after first exposure as is common with occupationally induced cancers. There are also, however, substantial numbers of cases occurring after longer time intervals, 18 having been diagnosed 30 or more years after first exposure. This means that new cases are likely to be diagnosed well into the 1990s even if it is assumed that exposures were significantly reduced in the mid-1960s when the first major improvements in standards of hygiene were made. The mean induction period of the cases currently on the register (22.6 years) must there-

Table 5 Cases of vinyl chloride related angiosarcoma of liver tabulated by years from first exposure to vinyl chloride to diagnosis and years to 31 December 1984 (maximum possible latent period). (Number of cases expected to occur shown in parentheses*)

Years from first exposure to 31 December 1984	Years from first exposure to date of diagnosis							Total within 35 years	35 or more
	5–	10–	15–	20–	25–	30–34			
≥35	—	2	1	10	12	7	32	8	
30–34	—	1	4	12	7	3 (+4)	27 (+4)	?	
25–29	—	3	10	8	4 (+9)	0 (+10)	25 (+19)	?	
20–24	—	4	15	2 (+25)	0 (+29)	0 (+22)	21 (+76)	?	
15–19	1	2	2 (+7)	0 (+17)	0 (+18)	0 (+14)	5 (+56)	?	
0–14	—	—	—	—	—	—	0 (+?)†	?	
Total	1	12	32 (+7)	32 (+42)	23 (+56)	10 (+50)	110 (+155)	8 (+?)‡	

*Number of cases expected to occur calculated by comparing proportion of cases in relevant years since first exposure category for previous time periods with proportion in other categories—for example, for 25–29 years since first exposure and 25–29 years maximum latency expected:

$$\frac{(3+10+8)}{(2+1+10+1+4+12)} \times (12+7) = \frac{21}{30} \times 19 = 13.3$$

As four cases have already been diagnosed, another nine may be expected.

†Number of new cases to be expected among workers who had less than 15 years since first exposure at 31 December 1984 will be dependent on whether the hazard of vinyl chloride was eliminated in the late 1960s or in the mid-1970s. In the former instance no cases would be expected, in the latter a number approaching the 61 cases projected for those with 15–19 years since first exposure by the end of 1984.

‡It is virtually impossible to estimate the number of expected new cases 35 or more years after first exposure.

Table 6 Recorded occupations among ASL cases on register

	No*
Production worker/operator	69
Autoclave cleaner	51
General maintenance/fitter	3
Other jobs	11
Unknown	17
	156

*As several employees have more than one job recorded for them, these numbers do not add up to 118.

fore be expected to be materially increased with the passage of time.

Any method to assess the number of expected new cases is likely to be imprecise. Our method simply looks at the proportions of cases with different latent periods and makes projections based on the distribution of cases that have occurred within different periods of maximum possible latency. In the absence of any information about the numbers of exposed employees it is all that can be done. The results suggest that another 155 cases are likely to be diagnosed within 35 years after first exposure. Compared with the 110 cases in this category diagnosed so far, this means that the industry is approaching the halfway stage in the appearance of ASL. The calculation of 155 more cases within 35 years of first exposure assumes that the hazard was essentially eliminated in the late 1960s. If it was not a further 50 or 60 cases (something slightly less than the number expected to have been induced in men who could have been observed for only 15 to 19 years by the end of 1984) must be added to the total.

Further cases must also be expected to occur 35 or more years after first exposure but it is, as yet, virtually impossible to estimate the number to be expected with any precision. It could, however, easily be around 50. We suggest, therefore, that it should be assumed that there will be another 200–250 deaths from vinyl chloride related ASL over the next 30 years. This estimate is in pronounced contrast with that calculated by Nicholson *et al* who suggest that "within a factor of 2 or 3" there will eventually be a total of 350 deaths from vinyl chloride related ASL in the United States and 1200 in Western Europe alone.⁸ Nicholson *et al* used a complex model to deduce these figures based on the assumption that the incidence of

ASL at any point in time increases in proportion to (i) the first power of the product of the population at risk and the degree of exposure and (ii) a higher power (most probably the third) of the time since exposure first occurred.⁸ Knowledge of the distribution of cases recorded by the National Institute of Occupational Health and Hygiene (1982) by year of first exposure and year of occurrence, the amount of vinyl chloride produced, estimated average exposures at work at different periods from before 1950 to 1970–4, and normal national mortality rates allowed them to make approximate estimates of the variables in these equations and hence to calculate the number of cases that might be expected to occur in the future.

Only time will show which of the two methods will give the better estimate of the number of cases that will eventually be observed. We are encouraged, however, to think that the lower estimate may be the nearer as the method of Nicholson *et al* predicted an increase in the annual number of cases after 1979, whereas the number recorded to date has declined from an average of 9.2 in 1975–9 to an average of 6.8 in 1980–4. The latter figures will, however, almost certainly, be revised upwards in the course of the next few years owing to delayed reporting.

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TABLE II—MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C. EXPOSURE EXCLUDING PREGNANCIES OF WOMEN WITH ≥ 3 FETAL DEATHS

	"Controls"	Primary V.C.M. exposure†
<i>Prior to husband's exposure:</i>		
Mean paternal age at conception (yr.)	23.0	26.3
Number of fetal deaths among wives	11	9
Number of pregnancies	159	141
Age-adjusted fetal deaths/100 preg.‡	6.9	3.1
<i>Subsequent to husband's exposure:</i>		
Mean paternal age at conception (yr.)	30.2	30.8
Number of fetal deaths among wives	18	14
Number of pregnancies	265	120
Age-adjusted fetal deaths/100 preg.‡	6.8	10.8

* Rubber and P.V.C. fabrication workers.

† Polymerisation workers.

‡ Rate age-adjusted to "control" paternal age distribution.

husbands less than 30 years of age, fetal mortality was 14/70 (20.0%) for the primary V.C.M. exposure group compared with 7/131 (5.3%) for the control group (these data are not shown in tables.)

Furthermore, intragroup comparisons indicated an increase in age-adjusted rates for the primary V.C.M. exposure group from 6.1% before exposure to 15.8% subsequent to the husband's exposure. This difference also was significant, $P < 0.02$ ($\chi^2 = 5.51$, $df = 1$).¹² Similar comparison for rates in the control group, 6.9% versus 5.8%, indicated no significant difference.

To determine whether women who had chronically experienced abortions might have weighted the results in favour of a higher fetal death-rate in the primary V.C.M. group subsequent to husband's exposure, pregnancies of women who had more than two abortions were eliminated from the analyses and the data were recalculated to determine whether or not the trend was maintained. The decision to exclude all pregnancies among families associated with more than two abortions was made without prior knowledge of how these families were distributed among the exposure categories. The data in table II show that the trend was maintained. Prior to exposure, the fetal death-rates in the control and primary V.C.M. exposure groups were 6.9% and 3.1% (age-adjusted), respectively, whereas, after exposure, the rates were 6.8% and 10.8%, respectively. Subsequently, data were eliminated for pregnancies of women who had experienced, firstly, more than one abortion, and, secondly, more than three abortions, and each time the trend was maintained. No changes in rates for controls were observed, whereas a 2–3-fold increase was observed in the primary V.C.M. group subsequent to exposure.

To determine whether differences in fetal loss might have been the result of one or two interviewers weighting the results, the data were analysed by individual interviewer. The results demonstrated a general trend for each interviewer to report a higher ascertainment among V.C.M. polymerisation workers than among the control group.

Further, the possibility was entertained that the interval between the date of interview and the date of fetal loss might have influenced the results through dif-

ferences in recall. The interval, however, was estimated to have been about two years less for controls, suggesting that, if a bias did exist, it would have been towards a greater ascertainment in the control group. In some cases, the worker failed to indicate the ages of his children and in other cases he was unable to recall the approximate time of his wife's abortion; therefore, the data were analysed to determine the distribution of fetal death-rates among the respondents in each occupational group who did not complete the interview properly. The difference in fetal death-rates between groups was very slight.

Finally, the workers may have been subject to bias resulting from prior knowledge of known hazards of vinyl chloride. However, the workers themselves did not always know into which of our employment categories they were being allocated. For example, several P.V.C. fabrication workers who were included in the control group thought that they had a primary V.C.M. exposure as a fabrication worker. In addition, the questions regarding pregnancy outcome were contained in a much larger interview-questionnaire, the results of which demonstrated very few significant differences with no consistent bias for the parameters ascertained between the workers with a primary V.C.M. exposure, and the other groups. This observation as well as several others presented above tend to support the validity of the study.

In summary, a significant excess of fetal loss was observed among wives of workers following exposure to V.C.M. The excess did not appear to be the result of bias from interviewers or respondents, nor from women who experienced chronic abortions weighting the results. Several mechanisms by which such fetal loss may arise are suggested. Either fetal or maternal toxicity or germ-cell mutagenesis in the mother through indirect V.C.M. exposure from the father might be considered, although these mechanisms seem highly unlikely in view of the highly volatile nature of V.C.M.¹³ When the findings of the present study are taken in conjunction with the prior demonstration of a mutagenic response via microbial test systems and observations of significant excesses of chromosomal aberrations among workers exposed to V.C.M., the leading possibility is germ-cell damage in the father through direct V.C.M. exposure. The increased fetal mortality among wives of workers subsequent to V.C.M. exposure now raises serious scientific and public-health concern for the possible genetic risks of vinyl chloride to man.

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