Scand J Work Environ Health 14 (1988) 61—78

Effects of exposure to vinyl chloride

An assessment of the evidence

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DOLL R. Effects of exposure to vinyl chloride: An assessment of the evidence. *Scand J Work Environ Health* 14 (1988) 61—78. This paper reviews the possible effects of vinyl chloride on the mortality of occupationally exposed men and the carcinogenic effects that might be observed in the general population as a result of environmental pollution with vinyl chloride. The results of four studies fulfilling the criteria of providing substantial numbers of observations more than 25 years after first exposure and covering a period long enough for more than 10 % of the workers to have been expected to die constitute the basis for the assessment of the occupational hazards. Other studies provide only supplementary information. The data permit two conclusions. First, men occupationally exposed to vinyl chloride have experienced a specific hazard of angiosarcoma of the liver. Second, any other occupational hazards that may have existed have been small. No positive evidence of a hazard of any nonmalignant disease or any type of cancer other than angiosarcoma of the liver has been found except possibly for a small hazard of lung cancer when exposure was heavy. More definite conclusions might be reached if those who have studied exposed employees could present their results in appropriate and comparable ways. A very small risk of angiosarcoma may have occurred as a result of vinyl chloride escaping into the environment around plants handling vinyl chloride in the past, but the evidence indicates that the current risk to the general public (if any) must be negligible.

Key terms: angiosarcoma of the liver, cancer, lung cancer, mortality, polyvinyl chloride, review, vinyl chloride monomer.

For many years the inhalation of large amounts of vinyl chloride has been recognized as potentially hazardous. Concentrations of the order of 10 000 ppm in the air induce unconsciousness and cardiac arrhythmia, while prolonged exposure to concentrations an order of magnitude lower have been liable to cause a specific pathological syndrome. This "vinyl chloride illness" has been characterized by four cardinal signs, namely, enlargement of the liver and spleen with a specific histological appearance, patchy infiltration of the skin resembling scleroderma, bony changes in the tips of the fingers described as acroosteolysis, and peripheral circulatory changes identical with the classical picture of Raynaud's disease. These pathological reactions may occur singly or together and may possibly be accompanied by other less characteristic effects. They can, however, be completely avoided if exposure never exceeds the level of a few hundred parts per million, ie, the level to which exposures were generally reduced in the mid-1960s.

One other serious effect has, however, been observed that may not be avoidable in the same relatively easy way, namely, the production of angiosarcoma of the liver. It must, indeed, be presumed that some risk of developing the disease will persist from exposure to doses that are even lower than the current industrial levels of 5 ppm or less, as vinyl chloride has been shown to act as a mutagen (23), and it cannot be assumed that a threshold exists below which no carcinogenic risk persists. Moreover, the possibility has to be considered that vinyl chloride may cause some cancers other than angiosarcoma of the liver, partly because laboratory studies have shown that it causes other cancers in animal experiments and partly because the initial studies demonstrating the production of angiosarcoma of the liver in humans were inadequate in size to exclude a material increase in the risk of cancer in common sites, such as the lung and large bowel. Since no threshold dose can be postulated, it also follows that some cancers may have been produced in the general public by the small amounts that have escaped into the general environment.

Consideration also needs to be given to the possibility that exposure to vinyl chloride over a long period may have noxious effects on humans that cannot be seen easily in animal experiments (by, for example, producing chronic respiratory disease), and, as it is a mutagen, there is also a possibility that it may act as a teratogen and cause congenital malformations in offspring.

In this review I have not examined the possibility that vinyl chloride acts as a teratogen or that it causes mutations in germ cells, as there is too little serious evidence to justify inclusion. Reviews carried out for sections of the industry by Downs et al (unpublished report to the Society of Plastic Industries Inc in 1977)

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and by MacMahon (unpublished report to the Chemical Manufacturers Association in 1977) concluded that the few reports of positive effects could not be substantiated, and no additional evidence was found in a similar later review by Barr (unpublished report to Air Products and Chemicals Inc in 1981), apart from a report that embryos were absorbed and skeletal ossification was produced when pregnant rats were exposed to doses appreciably lower than those that had been used by other workers without any such effects being observed. The report of absorbed embryos (34) could not be evaluated thoroughly, however, as the experiment was inadequately described. I have, therefore, examined only the possible effects on the personal health of men occupationally exposed to vinyl chloride, other than those related to their reproductive capacity, and the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant.

Occupational hazards

Many studies of workers exposed to vinyl chloride in the manufacture of vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) have been undertaken since it was first found that vinyl chloride could cause cancer in animals (28, 48) and man (10). These investigations have confirmed that exposure causes a hazard of angiosarcoma of the liver and, in several instances, have shown excess incidence or mortality rates that were conventionally statistically significant for other diseases. Conventional tests of statistical significance are, however, designed to help answer single questions defined beforehand, and several findings that might be expected to occur by chance alone once in (say) 20 times must be expected to occur if dozens of rates are examined in each of several sets of independent data. Scientists have, therefore, been faced with the problem of deciding whether the excess rates that have been observed in individual studies are due to occupational hazards or to the vagaries of chance.

This problem can be solved in part with an examination of the results of a sumation of data from comparable studies, that is, by a comparison of the sums of the numbers of deaths observed and expected in each study. This procedure does not require the assumption that the exposures have been the same in each study any more than the same assumption is required for each individual when the results of each study are considered alone. It does require however that each exposed population has been observed over a period when its members were at risk of developing disease (if a genuine hazard existed) and that in each study the reference population from which the expected numbers of deaths were derived was appropriate (that is, at the same risk of developing disease as the exposed population would have been in the absence of exposure). These requirements do not introduce any new complexity, as both are, of course, also required if correct conclusions are to be drawn from the results of the individual studies when they are examined on their own.

Sources of information

Four studies meet the aforementioned requirements, namely, two large national surveys, one reported by Jones (25) for the United Kingdom (UK) and the other by Environmental Health Associates (14) for the United States (US), and studies of individual plants in Canada, reported by Thériault & Allard (46) and in Italy, reported (as a part of a national study) by Belli et al (4). All four include observations on men more than 25 years after their first exposure, and the expected number of deaths is, in each case, greater than 10 % of the total number of employees, a value indicating a long average period at risk. Earlier observations on UK and US employees (6, 9, 12, 16, 20, 36, 39, 40, 45, 50) have been subsumed in the national surveys and now serve only as sources of hypotheses and of some detailed information not included in the national reports. Studies of German (49), Norwegian (22), Swedish (7), French (41, and unpublished report of Laplanche et al), Japanese (33, 37), and some other Italian (4) workers provide some supplementary information, but, in general, the periods of observation have not been long enough for useful epidemiologic data to be obtained about diseases that are unlikely to occur within 20 years of first exposure, or they report only selected results which are difficult to interpret, as only excess rates tend to have been selected.

Studies of makers of PVC products have not been included, as the workers have had much less exposure to vinyl chloride than those employed in the manufacture of VCM or PVC and any occupational hazard to which they may have been exposed is more likely to have been produced by PVC dust.

US study. The study carried out by Environmental Health Associates (14) on behalf of the US Chemical Manufacturers Association is the largest and most informative investigation thus far undertaken. It covered 10 173 men who had worked in 37 plants owned by 17 companies — 1 214 men in 11 plants that produced only VCM, 6 848 men in 18 plants that produced only PVC, 935 men in three plants that produced both, and 1 176 men in five plants that produced homopolymers and copolymers, with or without VCM or PVC.

Twenty-two of the plants were in the southern part of the country, 14 were in the northeastern or north central parts, and one was in the west.

Men were included if they had been exposed to vinyl chloride for at least a year before 31 December 1972 and had been employed in 1942 or subsequently (the first year depending on the date the plant began making

or using vinyl chloride and the earliest date that personnel records were deemed to be complete, whichever was the later). Individuals who met these criteria were identified from company records by company personnel.

Racial characteristics were known only for 686 men, 97 % of whom were white, and it was presumed, for the purpose of estimating the number of expected deaths, that all 10 173 men were white.

Follow-up data were obtained from plant and Social Security Administration records and (for men who died after 1979) from the National Death Index. Five plants did not collaborate in the extension of Cooper's (9) earlier study, which had been subsumed in the present investigation, and the 955 employees in these plants who were known to be alive on 31 December 1972 were not followed any further. For the rest, follow-up was attempted to death or 31 December 1982, whichever was the earlier. On this basis 92.7 % of the men were successfully traced. Those who were untraced were excluded from the last date of contact, which was usually the date when employment ceased.

Almost half of the men (46 %) were first employed before 1955. A large proportion was, therefore, observed more than 25 years after first exposure (and in many cases for more than 30 years) when diseases with a long latency period might be expected to be seen.

Short-term workers had been excluded from the cohort, and most of the men had continued in employment for many years, two-thirds being employed for 10 years or more and the average duration of employment being 16 years.

Fifteen hundred and thirty-six men were found to have died. In 1 439 cases, the cause of death was obtained from the death certificate, but no cause was obtained for the other 97 persons (6.3 %).

The numbers of deaths expected from each of 38 causes or groups of causes were obtained by multiplying the person-years at risk by the disease-specific national rates for white males, for the corresponding age groups and five-year periods of the study.

This important study is open to three minor criticisms, which are unlikely to have had any material effects on the results. First, the lists of employees were compiled by company personnel from company records without any independent check. Second, the assumption that all the employees were white will have caused the expected deaths to have been very slightly underestimated, as the few black employees are likely to have had higher mortality rates and there is no reason for supposing that the small sample from which the proportion of black employees was estimated was necessarily representative. Third, an element of uncertainty was introduced by the failure to trace as many as 7.3 % of the employees.

Two other criticisms are more important. First, the expected numbers of deaths were calculated on the assumption that the men would have experienced the same mortality rates as the white male population of the whole country at the corresponding dates. The use of national rates is common practice in studies of industrial populations and tends to result in an overestimation of the expected numbers of deaths so that the employees appear to be unusually healthy. This "healthy worker effect" is well known and has been taken into account in my discussion of the results. A more serious objection to the use of national rates is the way mortality varies from one part of the country to another, due to differences in the prevalence of environmental and social factors unrelated to the occupation of interest. It is, therefore, generally preferable to use state (if not county) rates in place of national rates. With 37 plants, however, it might be thought that their geographic distribution would be sufficiently wide to make the use of national rates appropriate. Unfortunately 22 of the plants were located in the south, and a check would have been desirable to see whether their location could have caused any material distortion of the results.

Second, causes were not obtained for 97 of the 1 536 deaths. This deficiency was allowed for in the calculation of the overall mortality by the inclusion of deaths due to unknown causes. It was not allowed for, however, in the calculation of the disease-specific mortality rates and will have caused the standardized mortality ratios to be underestimated by an average of 6.3 %. For the present purpose, therefore, the numbers of deaths attributed to specific diseases have each been multiplied by 1.0674 [100/(1—97/1536)] and rounded off to the nearest integer.

UK study. The study reported by Jones (25 and unpublished) on behalf of the British Health and Safety Executive covered 5 498 men who were employed for at least one year in jobs that involved potential exposure to VCM for at least 25 % of the work week and who were first employed in the period 1940—1974. Details of the men were compiled from the personnel records of nine chemical plants manufacturing or polymerizing vinyl chloride, and the vital status of the men was determined at the end of 1984 from the records of the National Health Service Central Register. Five thousand four hundred and ninety-eight men were traced (98.9 %). Seven hundred and eighty deaths were identified, and copies of the death certificates [coded to the eighth revision of the International Classification of Diseases (ICD) if they occurred before 1979 and to the ninth revision if they occurred later] were sent to the investigators.

Several specific points about the study need to be noted. First, national mortality rates for England and Wales were calculated for five-year age groups over quinquennial periods for 66 causes of death, and these rates were used in the estimation of the numbers of deaths that might have been expected in the cohort by multiplying them by the corresponding numbers of person-years under observation. Some difficulty which could have been related to the causes of death being

coded according to the eighth and ninth revisions of the ICD was, however, experienced in obtaining suitable rates for all causes of death, and rates for a relatively late period had to be used for estimating the numbers of deaths from many diseases that might have been expected to occur in earlier periods. For two categories the earliest available rates were 1960—1964, for one they were 1965—1969, for 24 they were 1970—1974, and for one they were 1975—1979.

Second, an attempt was made to classify men according to whether they had high, intermediate, or low exposure to VCM or PVC dust, and each man's employment history was recorded according to 12 job titles with advice from the plants concerned. The men were then grouped according to whether exposure to VCM was likely to have been high (group A), exposure to PVC dust was likely to have been high with exposure to VCM low (group B), or exposure to VCM and PVC dust was intermediate and intermittent (group C). All other men, who would generally have had low exposure to both VCM and PVC dust, were classed as group D. Within all the groups, exposure to VCM was likely to have been higher if it had begun before 1956.

The study makes an important contribution to the knowledge concerning the long-term effects of vinyl chloride. The use of national rates to calculate the expected numbers of deaths may be justified on the grounds that the men were employed in nine plants, which were presumably distributed about the country, but no details of their location are given. In general, mortality rates tend to be higher in the parts of Britain where heavy industry is located than in other parts of the country so that the expected numbers of deaths are more likely to be biased downwards than upwards; but whether this is so or not needs to be shown.

The use of recent rates to calculate expected numbers of deaths from many specific causes of death was presumably necessary if the diseases were to be studied individually and will have done no harm if the incidence and fatality of the diseases in question remained stable. It would have been desirable, however, for the diseases to have been specified so that the reader would know which were liable to be distorted.

The system used to classify the men into four exposure groups is the sort of system that is commonly used if precise measures of exposure are not available. It creates some difficulties in the statistical analysis if men move from one job to another and are classed (as in this instance) as having had high exposure if they have *ever* had a particular type of employment (eg, ever been employed as an autoclave worker). No evidence is provided to show that the person-years at risk before a man entered the category have been subtracted and added to another exposure group before the numbers of expected deaths were calculated. Movement from one job to another was said to have tended to be out of groups A and B into D, but even so it must be presumed that the expected numbers of deaths in the first two exposure categories are likely to have been overestimated.

Canadian study. The Canadian study (46) was limited to employees of a single plant in Shawinigan, Quebec. The plant, which was situated in an industrial complex, was opened in 1943. VCM and PVC were both made until the late 1960s, when the production of VCM ceased, while the production of PVC continued. An attempt was made to trace all the production workers whose names appeared on the unions' lists or the payrolls of the companies in the whole industrial complex, including the vinyl chloride plant, between 1 January 1948 and 31 December 1972, and contact was made with the worker or his next-of-kin in 1 611 out of 1 659 instances (97.1 %). Detailed occupational and smoking histories were obtained by questionnaire, and 156 men who had been employed by the companies for less than five years were excluded. The remaining men were categorized as (i) exposed to VCM if they had worked on the production of VCM or PVC for at least five years (451 men), (ii) unexposed to VCM if they had worked similarly for less than six months (870 men), and (iii) other men (134 in total). The last group was excluded from the study. Follow-up was closed on 31 December 1977. Copies of the death certificates were obtained, and the causes for all who had died (59 exposed and 233 unexposed) were coded according to the eighth revision of the ICD. Information was also sought for histological or cytological confirmation of all the diagnoses for all the exposed men who had died of cancer.

The results were examined in two ways. First, the mortalities of the exposed and unexposed men were compared after standardization for five-year periods of the study and five-year age groups. Second, the mortality of the exposed men was compared with that expected if the men had had the sex- and age-specific mortality rates recorded in Quebec for the year 1971. In both comparisons the causes of death used were those specified on the death certificate, and the additional pathological information was used later only for interpretation of the results.

Most of the exposed men were exposed for more than 10 years (75 %), the average length of exposure was approximately 17 years, and 44 % were observed more than 25 years after first exposure.

Although small, the study makes a useful contribution to the overall results. The histological review of the cancer cases is particularly helpful. It showed that all eight cancers diagnosed as liver cancer (including two specified as hepatoma and one specified as angiosarcoma) were angiosarcomas of the liver, as well as one that had been diagnosed as angiosarcoma of the peritoneum. Two other cases of angiosarcoma of the liver were found to have been certified as hepatic cirrhosis. It is also helpful to have a comparison between

the exposed and "unexposed" employees of the same companies as it shows that the low mortality observed for all nonmalignant diseases could be attributed to a healthy worker effect and was not due to bias in the recording of exposure (relative risk for all nonmalignant causes compared to that of the "unexposed" men 0.95).

One aspect of the study has to be criticized however, ie, the use of provincial rates for one year (1971) to calculate expected mortality spread over a 30-year period (1948 to 1977 inclusive). Deaths will have tended to bunch up towards the end of the period of observation so that the rates for this particular year may have been fairly representative, but it must have caused some distortion of the expected numbers of deaths, the size (and even the direction) of which is impossible to estimate. For most disease groups the distortion is unlikely to have been large.

Italian study. A study of all men employed in the production of vinyl chloride and PVC in nine Italian plants was begun in 1983. All men were included who were employed for at least six months at any time from the start up of the plant to the end of 1981. The study is still incomplete, but results are now available for men in three plants (4). Two plants (in Ferrara and Rosignana) began operation in 1953. Four hundred and thirty-seven men were employed in one plant and 181 in the other. All but three (from the Ferrara plant) were followed to the end of 1984. Expected deaths were estimated by multiplying the person-years at risk by the corresponding national mortality rates for each five-year age group and each five-year period of the study. The total expected deaths in each case amounted to more than 10 % of the employees in the two plants (12.4 and 12.8 %).

Clinical information was sought about the cause of death of all the 55 employees of the Ferrara plant who had died. Revised diagnoses, which were not used for comparison with the expected deaths, revealed four deaths from cancers of the liver in place of one.

The Ravenna plant did not begin operation until 1959. Six hundred and thirty-eight men were employed. All but four were traced to the end of 1983, and 17 were found to have died. No man could have been followed for more than 24 years, and only 25.1 deaths (3.9 % of the work force) were expected. The data for this plant have not, therefore, been used in the principal analyses. It may be noted, however, that one death was attributed to liver cancer when 0.1 was expected.

Other sources. The Norwegian study (22) provided observations on 454 men who had been employed in a plant in Telemark where VCM had been manufactured from 1950 to 1971 and PVC from 1950 to the end of the study period. Every man was included whose name was recorded in the company's personnel register and health department records who had ever been employed from the start of production to the end of 1969 and had worked for at least one year. The men were followed from 1953 to 1979 inclusive. Deaths and cases of cancer were identified from the records of the Central Bureau of Statistics and the national cancer registry. No reference was made to any men being lost to follow-up, but it can be assumed that the number (if not zero) was small, as all citizens have an identity number which is used by both employers and central agencies. Fifty men were found to have died against 59.34 expected if the sex-, age-, and quinquennium-specific national mortality rates had operated. Twenty-one men were found to have developed 23 cancers against 20.16 cancers expected from the comparable national incidence rates, the use of which was justified by the finding that the incidence in the county in which the plant was situated was between 90 and 95 % of the rate of the country as a whole. One man who had been employed in PVC production developed angiosarcoma of the liver. The observed and expected numbers of cases were given for cancers of the lung, colon, and thyroid, for melanomas, and for all cancers, but no expected numbers were given for other types of cancer. It is evident that several other types of cancer must have been in deficit, as there were eight cases in all against 14.93 expected, and it is difficult to know what weight to give the excesses observed for the reported types of cancer, as they seem likely to have been reported specifically because the numbers were in excess of those expected. The authors noted that one further case of melanoma had occurred after the closure of the study and that one "incipient case" was also known to them.

The German study (49) included the following three groups: (i) 7 021 men who had been exposed to VC in the course of their employment in any of the 11 plants in which VC and PVC had been produced in the Federal Republic of Germany, (ii) 4 820 men who had been employed in seven chemical plants without having had any exposure to vinyl chloride, and (iii) 4 007 men employed in two other plants where PVC was processed. Employees were included only if they were of German or Austrian nationality, and they were regarded as exposed to vinyl chloride if they were production workers or other skilled workers or laborers assigned regularly to the plants, but not if they were employed in them only occasionally. All the men were included from the time of opening of the plants to the end of 1974, and they were followed to the end of 1974. Many of the men were therefore observed for only a few years after first employment, and only 14, 36, and 19 %, respectively, of the three groups were first employed before 1954 and were therefore capable of contributing person-years at risk more than 20 years after first employment, when an occupational hazard of cancer could be expected to be observed.

Of the exposed group 93.2 % were successfully followed, and causes of death were discovered for 92.8 % of the 414 men discovered to have died. The proportions for the other two groups were respectively 89.8 and 88.7 % for the unexposed and 92.1 and 86.9 % for the PVC process workers. The failure to obtain causes of death for all the men who had died was allowed for in the subsequent analysis by the weighting of the numbers attributed to each cause by a system which took account of the age group and calendar period in which death with an unknown cause occurred. The expected numbers of deaths from each cause was calculated by multiplying the person-years at risk by the sex-, age-, and cause-specific mortality rates for the Federal Republic of Germany. National data before 1968 used an idiosyncratic classification system, and the 1968 rates had to be used to multiply all the person-years at risk up to the end of 1968. For subsequent years (1969 to 1974) the person-years at risk were multiplied by the corresponding rates for the same calendar year.

Epidemiologic studies are more difficult to carry out in the Federal Republic of Germany than in North America, the United Kingdom, or Scandinavia because the medical cause of death is not recorded publicly, and there is no central system which can be used for checking whether an individual is alive or dead. In these circumstances, the German authors have made valiant efforts to obtain reliable data, and the proportions of men in the exposed groups who were not successfully followed (6.8 %) and the proportions of deaths for which the cause was not obtained (7.2 %) were similar to those in the study of the Environmental Health Associates (14).

Two defects, however, make the data less useful. First, no national mortality rates were available before 1968, and the use of the 1968 rates to estimate the numbers of deaths in and before 1968 will have overestimated the numbers attributable to diseases that were becoming more prevalent or were being diagnosed more often and underestimated those due to diseases that were becoming less prevalent. Second, and more importantly, a large proportion of the men had been first employed less than 10 years before the follow-up ended. Therefore the useful observations on the few men who had been exposed long enough to have had much chance of developing an occupational disease with a long latency period must have been swamped by a mass of other observations that had little to contribute. The expected deaths amounted to only 6.2 % of the exposed men, and there is, therefore, little to be gained, and something to be lost, by including the German data in the overview. It may be noted, however, that 12 deaths were attributed to cancer of the liver among the workers exposed to vinyl chloride against 0.9 expected and that smaller excesses were also observed among the unexposed chemical workers (4 observed against 1.1 expected) and the PVC process workers (3 deaths against 0.8 expected).

Two Swedish plants have produced VCM and PVC, one since 1945 and the other since 1971, and employees of the first plant have been studied by Byren et al (7). All persons who had ever been employed when exposure to VCM could occur were listed from the personnel files of the factory. Twenty-one were excluded because they were foreigners who left the country after a short period of employment. The remaining 750 were followed to October 1974. Expected numbers of deaths were estimated by multiplying the person-years at risk by the corresponding age-specific mortality rates for the whole country, and the expected numbers of cancer cases from 1958 to 1971 inclusive (during which period all cancer cases had been registered nationally) were estimated by multiplying by the national age-specific cancer incidence rates. In both instances, the rates used were those recorded in 1969. Fifty-eight deaths were found, but no figure was given for the expected number. Detailed figures were given only for the numbers of deaths and cases observed and expected for cancer of the lung and for cancers of the liver and pancreas combined and for the numbers of deaths from brain cancer and three categories of cardiovascular disease. Two men known to have angiosarcoma of the liver were certified as having died of liver cancer or pancreatic cancer, and a third man died of angiosarcoma of the liver 17 months after the close of the follow-up.

Two French studies provide the results of a long-term follow-up of men employed in one plant (41) and of a short-term follow-up of men employed in 12 plants (Laplanche et al, unpublished). The first provided observations on 1 311 men exposed to vinyl chloride in the production of VCM and PVC and in selected ancillary operations from the opening of the Tavaux plant in 1953 to the end of 1976 (41). Six other employees were excluded from the study because of lack of occupational histories and 160 men because their vital status at the end of the study period was undetermined. Twenty-five men were found to have died against 48.75 expected from contemporaneous sex- and age-specific national mortality rates (3.7 % of the men at risk). One death was attributed to angiosarcoma of the liver, in a man who had been exposed for more than 15 years. The reported data are so incomplete and cover such a relatively short period from the opening of the plant that they add nothing of epidemiologic value to the results of the other studies, apart from the addition of a further case of angiosarcoma.

The second study provided observations on 1 100 men aged 40 to 55 years who, in 1980, were exposed or had been exposed to vinyl chloride in 12 plants, which constituted "most of the French VCM polymerisation plants" (Laplanche et al, unpublished). Many of the men were, or had been, employed at Tavaux and were presumably survivors of the cohort studied by Pierre et al (41). The men were followed for five years, and their morbidity and mortality were compared with those observed for 1 100 men of the same

ages (±2 years) who were employed in the same plants but who had never been exposed to VCM. The men in both groups were interviewed personally, and information was obtained about their smoking and drinking habits, which were found to be similar in the two groups. The men in the exposed group had been first exposed for an average of about 14 years and had first been employed in the plant about 18 years previously. Morbidity and mortality data were recorded annually by the plant physician, who successfully traced 98 % of the exposed men and 96 % of the referents. One of the exposed men, but none of those unexposed, developed an angiosarcoma of the liver. Data were not given separately for different periods after first employment, and it is impossible to assess the significance of the finding that six of the exposed men developed lung cancer against two of the referents, which may well reflect a chance occurrence of unusually few cases in the reference group, as the proportion of all lung cancers in that group (2 out of 15) was unusually low. One exposed man developed a cancer of the lymphohematopoietic system against none of the referents, but none of the men in either group were known to have developed melanomas or cancer of the brain or thyroid.

A Japanese study has reported the mortality experience of 4 524 men employed for at least one year before 1965 in 25 Japanese plants which began producing VCM or PVC between 1949 and 1964 inclusive (37). The men were followed to 31 October 1975. Twenty-eight percent of the men were observed more than 20 years after first employment, but none was observed more than 26 years. Only 0.6 % of the men were untraced, and copies of the death certificates were obtained for all the 209 men who had died (4.6 % of the initial cohort). Individuals were classified according to the job in which they had been longest employed at the termination of their follow-up, and data were given separately for the 2 546 men classed as employed in PVC production and 1 978 others (including 900 classed as VCM production workers).

If this study is continued for another 10 years, it should provide useful additional information, but the present data include too few observations on men more than 20 years after first exposure to be of any material use. They confirm the evidence of a hazard of liver cancer with six deaths among the PVC production workers against 2.54 expected from national rates, while only one such death was observed among the other workers against 1.82 expected. One of the six deaths from liver cancer among the PVC production workers was certified as due to angiosarcoma of the liver, and at least one of the other liver cancer deaths was due to the same cause. Lung cancer deaths were not in excess (2 observed in PVC workers against 2.33 expected). No data were given for cancers of the lymphatic and hematopoietic systems, for cancer of the brain or thyroid, or for melanomas. The mortality reported by Masuda (33) for 305 Japanese vinyl chloride workers has presumably been subsumed in Nakamura's (37) later and larger study.

Hazards of cancer

The results of the four most useful studies are listed individually in tables 1 and 2. The overall results for all causes, liver cancer, and three broad groups of conditions are shown in table 3, and those for 10 types, or classes, of cancer are presented in table 4. Data have not been reported for each type of cancer in each study, and the sources of the data are, therefore, specified separately for each type. Additional information obtained from four other less informative studies (4, 7, 22, 49) is given in table 5 for seven types or classes of cancer.

Table 3 shows that, apart from cancer of the liver, the overall mortality is what would be anticipated for an industry without any major hazard of accident or disease. In particular the standardized mortality ratio (SMR) of 84 for diseases other than cancer is typical of the ratios that are commonly observed for groups of employed men. A low SMR of this order reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the least healthy members of the population from industrial employment. This effect does not, however, normally affect the mortality from cancer beyond that observed in the first few years after the start of employment, and an SMR of 102 for cancers other than cancer of the liver is compatible both with the absence of hazard and with SMR values of 84 for other diseases and 77 for accidents, poisonings, and violence.

Angiosarcoma. Death certificates are an unreliable source of information about the histology of cancers that cause death, but there is no reason to suppose that the excess mortality attributed to liver cancer (or, in the US series, liver and gallbladder cancer) is not entirely accounted for by the known hazard of angiosarcoma. Fifteen of the 37 deaths[2] attributed to cancers of the liver and gallbladder in the US series are known to have been due to angiosarcoma of the liver (14). In the UK series, seven of the 11 deaths attributed to liver cancer, not specified as secondary, were known to be angiosarcomas, and they all occurred in autoclave workers against 0.38 expected liver cancers of all types ($P < 10^{-5}$) (25). In the Canadian series, histological review showed that seven of the eight so-called liver cancers were angiosarcomas (one had been described as an angiosarcoma on the death certificate, two as hepatomas, and five as unspecified liver cancers). One so-called liver cancer death was found to have been due to cancer of the sigmoid colon, while one death attributed to angiosarcoma of the perito-

[2] Increased to 39 in table 1 to take account of the 97 extra deaths from an unknown cause.

Table 1. Observed and expected numbers of deaths from different cancers reported in the four principal studies (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths)

Type or class of cancer	United States		United Kingdom		Canada		Italy	
	O[a]	E	O	E	O	E	O	E
Buccal cavity and pharynx	13	11.55	4	3.58	0	0.64	1	0.8
Esophagus	7	8.07	6	14.34	.	.	1	0.6
Stomach	11	16.01	26	23.91	.	.	3	3.0
Large intestine	21	28.79	9	13.94	.	.	0	1.2
Rectum	.	.	11	10.49	.	.	.	.
Liver	.	.	11	1.94	8	0.14	1	0.6
Liver and gallbladder	39	5.77	.	.	.	.	.	.
Pancreas	17	18.40	7	9.88	.	.	0	0.7
Other digestive	.	.	.	.	6	5.26	.	.
Larynx	.	.	4	2.21	.		1	0.9
Lung	118	115.87	81	92.12	2	5.78	12	6.1
Other respiratory	5	6.38	.	.			.	.
Bone	2	1.81	.	.	.	.	.	.
Skin (nonmelanoma	6	7.36	.	.	.	.	.	.
Melanoma	.	.	2	1.74	.	.	0	0.2
Prostate	16	15.20	12	9.59	.	.	1	0.7
Testis	.	.	2	1.38			.	.
Bladder	5	8.46	14	8.00	1	1.33	1	0.7
Kidney	12	9.06	3	4.10			.	.
Other and unspecified urinary	.	.	3	4.29			.	.
Brain	25	12.76	4	6.18	0	0.60	.	.
Eye and central nervous system	.	.	.	.			.	.
Thyroid	.	.	2	0.43	.	.	.	.
Lympho- and reticulosarcoma	12	7.98	4	2.35			.	.
Hodgkin's disease	3	5.45	3	2.50			0	0.4
Leukemia	14	13.94	7	5.16	1	1.67	0	0.7
Multiple myeloma	11	8.37	2	2.35			.	.
Other lymphatic			.	.			.	.
Other	46	40.50	18	8.12	2	0.95	9	4.5
All cancers	383	341.73	235	228.60	20	16.37	30	21.1

[a] Observed deaths multiplied by 1.0674 and rounded off to the nearest integer to allow for deaths without discovered cause.

Table 2. Numbers of deaths from nonmalignant and all causes reported in the four principal studies (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths)

Cause of death	United States		United Kingdom		Canada		Italy	
	O[a]	E	O	E	O	E	O	E
Benign and other unspecified tumors	4	5.08	.	.	.	.	0	0.5
Cerebrovascular disease	75	91.93	.	.			.	.
Ischemic heart disease	521	597.73	276	288	25	31.67	19	27.4
Other circulatory disease	157	123.55	105	141				
Bronchitis[b]	44	22.83	36	44	6	3.21	3	5.0
Pneumonia	16	31.94	40	61				
Other respiratory disease	15	32.84						
Cirrhosis of the liver	37	56.06	5	5	4[c]	3.85	4	5.2
Other digestive disease	27	39.52	.	.			3	2.7
Disease of the genitourinary system	11	20.41	.	.	.	.	.	.
Other diseases	67	115.68	43	76	2[d]	5.40	2	7.0
Suicide	49	52.78	40	50	2	10.58	1	0.9
Accidents and other violence	130	173.19					4	7.7
All nonmalignant causes	1 153	1 363.54	545	665	39	54.76	36	56.4
All causes	1 536	1 705.27	780	894	59	71.07	66	77.5

[a] See footnote to table 1.
[b] Emphysema in data from the United States.
[c] Includes two cases certified as cirrhosis of the liver which proved to be angiosarcoma of the liver.
[d] Includes one case with cause unknown.

neum was found to have been due to angiosarcoma of the liver (46). In the Italian study, further evidence revealed that three further deaths should have been attributed to cancer of the liver (for a total of four), but only one of the four was described as an angiosarcoma (4).

Table 3. Mortality from cancer of the liver and other causes among vinyl chloride workers in 49 plants in the four principal studies combined (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Cause of death	O	E	SMR
Cancer of the liver[a]	59	8.45	698
Cancer of other sites	609	599.35	102
Other diseases	1 547	1 844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2 441	2 747.84	89

[a] Including cancers of the gallbladder in the series from the United States.

Table 4. Mortality from various cancers among vinyl chloride workers in 49 plants in the four principal studies combined. (O = observed number of deaths, E = exposed number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	O	E	SMR	Source of information[a]
Mouth and pharynx	18	16.57	109	1, 2, 3, 4
Digestive system (other than liver)	125	154.59	81	1, 2, 3, 4
Respiratory system	223	229.36	97	1, 2, 3, 4
Lung	211	214.09	99	1, 2, 4
Genitourinary system	70	62.81	111	1, 2, 3, 4
Melanoma	2	1.94	.	2, 4
Brain	29	19.54	148	1, 2, 3
Thyroid	2	0.43	.	2
Lymphatic and hematopoietic system	57	50.87	112	1, 2, 3, 4
Other	83	63.24	131	1, 2, 3, 4
All other than of the liver	609	599.35	102	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).

Table 5. Mortality[a] from various cancers among vinyl chloride workers: Supplementary evidence (4, 7, 22, 49). (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	Federal Republic of Germany (11 plants)		Norway (1 plant)		Sweden (1 plant)		Italy (1 plant)		Four countries combined (14 plants)		
	O	E	O	E	O	E	O	E	O	E	SMR
Digestive system (excluding the liver)	35.0	31.8	3[b]	1.44[b]	.	.	1	1.2	39.0	34.44	113
Lung	23.5	24.6	5	2.84	3	1.78	0	1.5	31.5	30.72	103
Melanoma	.	.	4	0.79	.	.	0	0.1	4.0	0.89	.
Brain	2.1	1.3	.	.	2	0.33	.	.	4.1	1.63	.
Thyroid	.	.	2	0.16	.	.	.	.	2.0	0.16	.
Lymphatic and hematopoietic system	16.5	7.7	.	.	.	.	0	0.7	16.5	8.4	196
Other (excluding the liver)	10.7	24.3	8	14.93	.	.	4	2.0	22.7	41.43	55
All excluding the liver	87.8	89.7	22	20.16	5[c]	2.11[c]	5	5.7	119.8	117.67	102

[a] Incidence and cases in the Norwegian study.
[b] Cancer of the intestine only.
[c] Cancer of the lung and brain only.

Further evidence that the excess mortality from liver cancer (or liver and gallbladder cancer in the US series) can be attributed principally if not wholly to the known hazard of angiosarcoma is obtained in a comparison of the excess deaths with the numbers of deaths from angiosarcomas recorded in the Register of Liver Angiosarcoma Cases (maintained on behalf of the Association of Plastics Manufacturers in Europe by the Imperial Chemical Industry PLC) before the end of the follow-up period (Bennett, unpublished). Fifty-one excess liver cancers are recorded in the combined data, and 49 angiosarcoma are recorded in the Register for

Table 6. Mortality from lung cancer in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[a]	Category 1			Category 2		
	O[b]	E	SMR	O[b]	E	SMR
Observed 20 years or more after first employment (1), others (2)	114	113.96	100	85	93.83	91
Employed 10 years or more in the US (1), others in the US (2)	55	52.45	105	63	63.44	99
Employed before 1956 in the UK (1), others in the UK (2)	52	51.39	101	29	40.50	72
Ever employed as autoclave worker in the UK (1), others in the UK (2)	16	17.08	94	65	74.82	87

[a] The numbers in parentheses designate the category.
[b] See footnote to table 1 for observed deaths in the US.

the relevant periods for the three countries and the two Italian plants[3] that are covered by the survey.

None of the 120 cases yet recorded in the Register were in men who were first exposed after 1969, and none of the 45 men affected in North America were first exposed after 1964. All may, therefore, have been exposed to concentrations of several hundred parts per million, and many may have been exposed to concentrations appreciably higher (unpublished report by Barr to Air Products and Chemicals Inc in 1981).

Lung cancer. The idea that exposure to vinyl chloride might cause cancer of the lung was suggested by Monson et al in 1974 (36), when they noted 13 cases against an expected number of 7.9 in a study of proportional mortality. The combined data shown in table 4 do not provide any support for the hypothesis, either for respiratory cancer as a whole (SMR 97) or for the specified data for lung cancer in the US, the UK, and Italy (SMR 99). There are, however, consistently higher risks in the subgroups of men in the US and UK series, in which occupational hazards would be more likely to be seen than in other groups. This circumstance is illustrated by table 6, which shows that the SMR values are slightly higher for men observed 20 years or more after first exposure than for men observed earlier, for men employed before 1956 in the UK than for men first employed after 1955 (when exposure levels are believed to have been lower), for men employed for longer than for shorter periods in the US, and for autoclave workers in the UK (among whom the angiosarcoma cases have mostly occurred) than for other workers. The differences are all small or very small. They are, however, all in the same direction, and the probability that the rates should all be higher in the groups in which an occupational hazard is more likely to be seen in each of the four pairs of groups is 1 in 16.

Additional information from other sources is given in table 5. A total of 30 deaths (or cases) was observed, and this figure increases to 31.5 when allowance is made for the number of deaths due to unidentified causes in the German study (SMR becoming 103). In the German study the SMR was higher for the men who had been exposed for 10 years or more than for those who had been exposed for shorter periods (111 against 79), and, in the Norwegian study, four of the five cases observed occurred in men whose occupations were regarded as involving high exposure against 1.82 of the 2.84 expected. Both the German and the Swedish studies derived the expected numbers of deaths from national mortality rates for a single year towards the end of the study period. The expected numbers of deaths are likely, therefore, to have been overestimated and the SMR values correspondingly underestimated as the mortality from lung cancer had been rising throughout the period of observation.

Brain cancer. The idea that vinyl chloride might cause brain cancer was also suggested by Monson et al (36) when they reported five cases against 1.2 expected. The combined data that are shown in table 4 provide some support for this hypothesis. The cases of Monson et al (36) were, however, observed in US workers and must be presumed to be included in the total reported by Environmental Health Associates (14); therefore they will have contributed a substantial proportion of the total in table 4. As a test of the hypothesis the data of Monson et al ought, therefore, to be subtracted from those in the table. Their investigation was not a cohort study, and their expected deaths do not correspond exactly to those in table 4. If, however, the observed and the expected cases are both subtracted from the totals, twenty-four observed deaths remain against approximately 18.3 expected, a difference which might easily occur by chance (P one-tailed = 0.1).[4]

[3] Twenty-nine were registered as occurring in the United States against an excess of 33; only 20, however, were identifiable in both series. Inquiry has, as yet, failed to reveal information about the histology of the remaining 13 in the cohort study and the origin of the nine extra deaths in the register. Nine deaths were registered as occurring in the United Kingdom against an excess of nine, but one of the registered cases was certified as due to a benign hemangioma and not related to the liver (code 227 in the eighth revision of the International Classification of Diseases). Ten cases were registered as occurring in Canada against an excess of eight; two were recorded as being in men who had been employed for five years, and it is possible that the actual duration had been slightly less than five years with consequent exclusion from the Canadian cohort. One case was registered as occurring in one of the two Italian plants against an excess of less than one.

[4] If the study of Waxweiler et al (50) is regarded as the origin of the hypothesis, 26 deaths are left against 18.94 expected (P one-tailed = 0.07).

Additional information from two other sources is given in table 5. The small excess reported provides little further evidence of an occupational hazard, as one of the two deaths observed in the Swedish study occurred in a young man who had been employed for less than a year when the diagnosis was made, while the excess death rate for brain cancer observed in the German study was less than that observed among chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and among workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of lymphatic and hematopoietic tissues. The idea that vinyl chloride might cause cancer of the lymphatic and hematopoietic tissues — more specifically the lymphatic tissue — was suggested by Tabershaw & Gaffey (45) and by Waxweiler et al (50) in two cohort studies, when they found, respectively, five deaths from lymphomas in the most heavily exposed workers against 2.54 expected and four deaths from cancers of the lymphatic and hematopoietic tissues against 2.5 expected. These small excesses might have been ignored if the laboratory findings had not been interpreted as suggesting that lymphomas were produced experimentally in animals exposed to vinyl chloride by inhalation (29). The idea that similar exposure might also cause lymphomas in humans, therefore, merits serious consideration. The data from the four principal studies that are summarized in table 4 provide little support for the hypothesis when all cancers of the lymphatic and hematopoietic tissues are considered together (57 deaths against 50.87 expected, SMR 112) and very little more is obtained from the separate data for cancers of the lymphatic system (Tabershaw & Gaffey's definition of ICD list numbers, eighth revision, 200—203 and 205 being used) that are shown in table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered if the data in Tabershaw & Gaffey's initial report are subtracted (29 deaths against 23.36 expected, SMR 124).

Little additional information is provided by the results of the German study (49). (See table 5.) This study obtained an SMR of 214 for exposed workers (based on 15 observed deaths, increased to 16.5 when allowance is made for the number of deaths from unknown causes) against SMR values of 77 and 34 for an unexposed group of chemical workers and a group of PVC fabricators. It showed that the excess of the exposed workers was present only for men who had been exposed for more than one year and that this excess was most marked for men who had been exposed for five years or more (10.7 deaths after allowance for the number of deaths from unknown causes against 4.0 expected, SMR 268, P one-tailed <0.01).

Melanoma. An excess of melanoma was reported for Norwegian workers by Heldaas et al (22), who raised the possibility that vinyl chloride might have produced the disease. Four cases were observed when 0.79 were expected, and three of the four were in men whose occupations involved the highest exposures (against 0.51 expected). At the time of the writing of their report, one further case had been detected with onset three years after the closure of the study. Subsequent studies in other countries have, so far, reported only two deaths against 2.0 expected. (See tables 1 and 5.)

Thyroid cancer. An excess of thyroid cancer was also reported in the Norwegian study (22), in which two cases were observed against 0.16 expected. The investigators were not aware of any other studies indicating an excess of this type of cancer, and they drew no conclusion from their observation. Two of the three major studies that have been reported since the Norwegian observation was made gave no data for thyroid cancer; the third reported two deaths against 0.43 expected. (See table 1.) One death from thyroid cancer, it may be noted, was reported in the US by Monson et al (36).

Cancers of the digestive tract. Suggestions that vinyl chloride might cause cancers of the digestive tract in general have sometimes been made, but they have not taken adequate account of the contribution of cancers of the liver to the total number of cancers of the digestive system, particularly when it is borne in mind that some liver cancers are likely to be misdiagnosed as cancers of other organs. The combined data from the four principal studies shown in table 4 weigh heavily against the idea that any such effect has been produced.

Other cancers. One of the remaining types, or classes, of cancer listed in table 4 shows a statistically significant excess, namely, the heterogeneous group of "other cancers" (83 observed deaths against 65.24 expected, P two-sided <0.05). This excess is only marginally significant and may be a chance observation. The most likely explanation is, however, that a few angiosarcomas of the liver were not recognized and were diagnosed as secondary liver cancer or carcinomatosis, site unknown, the number of deaths in this category therefore being increased.

Hazards of nonmalignant disease

No previous study has suggested that any nonmalignant cause of death other than cirrhosis of the liver would be likely to be increased as a result of exposure to vinyl chloride, and cirrhosis of the liver is presumed to be increased only because of the liver changes that were observed as part of the "vinyl chloride illness" (24, 31, 33). Two other possibilities have, however, been raised, namely, the production of nonmalignant respiratory disease, because of the changes in lung function and radiographic appearances that have been

Table 7. Mortality from selected nonmalignant causes and all causes in the four principal studies combined. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type of disease	O	E	SMR	Source of information[a]
Bronchitis, emphysema[b]	80	66.83	120	1, 2
Other respiratory disease	71	125.78	56	1, 2
All respiratory disease	160	200.82	80	1, 2, 3, 4
Ischemic heart disease	797	885.73	90	1,2
Other circulatory disease[c]	252	264.55	95	1,2
All circulatory disease[c]	1 103	1 209.35	91	1, 2, 3, 4
Cirrhosis of the liver	46	66.26	69	1, 2, 4
Other disease	238	368.07	65	1, 2, 3, 4
All nonmalignant disease	1 547	1 844.50	84	1, 2, 3, 4
All external causes	226	295.15	77	1, 2, 3, 4
All nonmalignant causes	1 773	2 139.65	85	1, 2, 3, 4
All causes	2 441	2 747.85	89	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).
[b] Bronchitis in the United Kingdom study, emphysema in the United States study.
[c] Includes cerebrovascular disease in the United Kingdom and Italian studies.

Table 8. Mortality from chronic obstructive lung disease[a] in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[b]	Category 1			Category 2		
	O	E	SMR	O	E	SMR
Observed 20 years or more after first employment in the US (1), others in the US (2)	30	15.8	190	11	7.0	157
Employed 10 years or more in the US (1), others in the US (2)	16	10.9	147	25	12.0	208
Employed before 1956 in the UK (1), others in the UK (2)	26	30.17	86	10	13.60	74
Ever employed as an autoclave worker in the UK (1), others in the UK (2)[c]	3	6.55	46	33	37.22	89

[a] Described as emphysema in the US study and as bronchitis in the United Kingdom study.
[b] The numbers in parentheses designate the category.
[c] Men ever employed as a bagger or drier, occupations which would have caused the greatest occupational exposure to polyvinyl chloride dust, experienced one death from bronchitis against 4.98 expected.

recorded for men exposed to PVC dust (2, 26, 27, 44), and acute cardiac death, from analogy with the effect of other halogenated hydrocarbons (25) and the observation of an increased mortality from myocardial infarction in the few years following the cessation of exposure in the Swedish PVC processing industry (35). Relevant figures for the numbers of deaths from these and other nonmalignant causes that are obtainable from the four principal studies were given in table 2, and they have been summarized in table 7.

Cirrhosis of the liver. Three of the four principal studies gave separate figures for cirrhosis of the liver, none of which showed an increased mortality (table 2); in combination they gave an SMR of 69 based on 46 deaths. The fourth study, which did not give separate data for cirrhosis of the liver, reported four deaths from all diseases of the digestive system combined against 3.85 expected and noted that the four included two that were certified as due to cirrhosis of the liver, but actually due to angiosarcoma (46). In the two supplementary studies in which data were given for this disease, the SMR was 82 in one, based on 15.1 deaths after allowance for the number with unknown causes (49), and 133 in the other, based on seven deaths (37).

Nonmalignant respiratory disease. The data for nonmalignant respiratory disease are confusing in that the total SMR from the combined data for the four principal studies is 80 and is the sort of figure that is commonly found in healthy industrial populations, yet the US study recorded a substantially increased mortality from emphysema (41 deaths and an SMR of 180 before any allowance was made for deaths from unknown causes). No such excess was found in the UK, where 36 deaths from bronchitis gave an SMR of 82. International comparisons of chronic nonmalignant respiratory disease are complicated by the usage of different terms to describe what it is now agreed is best called chronic obstructive lung (or pulmonary) disease, but which in the past tended to be called emphysema in the US and chronic bronchitis in the United Kingdom. It must, therefore, be presumed that the two categories of "emphysema" and "bronchitis" used respectively in the two large national studies were meant to describe the same thing. One must assume, therefore, that the experiences in the two countries were very different, despite the fact that both related to cohorts that had very similar experiences of angiosarcoma of the liver and so, presumably, fairly similar exposures to vinyl chloride.

Separate figures are shown in table 8, where available, for the mortality observed among men with different durations and intensities of exposure. Unlike the data for cancer of the lung that were shown in table 6, they provide no consistent evidence of a greater risk in the groups in which an occupational hazard would

be expected to be concentrated. The authors of the Environmental Health Associates report (14) were unable to give any explanation for the increased mortality from emphysema, and they point out that it could hardly be due to excess cigarette smoking, as there was no overall excess for cancer of the lung. It is striking, however, that the excess is more than compensated for by deficiencies in the other categories of nonmalignant respiratory disease (pneumonia 15 deaths,[5] SMR 47.0; other respiratory disease 14 deaths, SMR 42.6), and the question arises whether the emphysema excess could be a classificatory artifact. Environmental Health Associates (14) list all the 41 deaths which show that they were coded under ICD number 527 which, in the out-of-date seventh revision that was used for the coding of all deaths in the study, was the code for "other respiratory disease not otherwise classified" and included emphysema. Under that revision, however, emphysema that was associated with bronchitis should be classified with bronchitis under ICD numbers 500 to 502, and the possibility may be considered that some of the emphysema deaths should have been classified in some category of respiratory disease other than ICD number 527. If this were the situation, it could account for both the excess mortality from emphysema and the grossly deficient mortality from other nonmalignant respiratory diseases.

No excess mortality from "bronchitis, emphysema, and asthma" was observed in the German study (SMR 44 with 6.3 deaths observed after allowance for the number of deaths from an unknown cause) (49).

Cardiovascular disease. Data for ischemic (or arteriosclerotic) heart disease (which may be presumed to include the vast majority of all deaths certified as due to acute cardiac disease) were given only by the two big national studies, and they provide no evidence of an increased mortality. The SMR values of 90 for this group of diseases and of 91 for all cardiovascular disease recorded in the four principal studies are typical of the SMR values of healthy industrial populations, and there is no suggestion of any occupational hazard in the subsidiary analyses provided by the two national studies. In particular, there is no evidence of an increased mortality within one month of leaving employment in the UK study either for all workers (52 deaths, SMR 61) or for the most heavily exposed autoclave workers (9 deaths, SMR 42).

A slight increase in ischemic heart disease mortality was recorded for the exposed workers in the German study (49), but it was less than that recorded for the unexposed chemical workers and the PVC fabricators (SMR values of 127, 131, and 158 based on 97.2, 126.7, and 109.7 deaths, respectively, after allowance for the number of deaths from unknown causes).

Discussion

The information that has now been obtained about the long-term health of men occupationally exposed to vinyl chloride is massive and compares favorably with that available for any other occupational group. Two facts are outstanding. First, the men have experienced a specific hazard of a type of cancer that is normally extremely rare, namely, angiosarcoma of the liver. The rarity of this disease under other conditions made the detection of the hazard easy; but the long latency period before the disease appears after first exposure (almost always more than 10 years and usually more than 15 years) meant that a large number of men had been exposed before the hazard was detected and that it will still be many years before the extent of the protection provided by the reduction in exposure in the 1960s and that of the further reduction that followed the recognition of the hazard in 1974 are known. There is, unfortunately, no effective treatment for the disease, and the number of cases is reflected in the number of deaths. Some 50 deaths have occurred among the 16 740 men who were followed in the four principal studies that have been reviewed in this report, so that approximately 1 in 335 men have been affected, 2 % of the deaths having been due to this one cause. Eventually many more men must be expected to develop the disease. One estimate (38) suggests that the total may be increased 10 times, but a more realistic estimate is two to three times (19).

The second outstanding observation is that the mortality of the exposed men, other than that due to angiosarcoma of the liver, is typical of the normally healthy industrial worker — that is not to say that no other hazard exists, but that the effect of any other hazard is small.

The massive data that are now available provide no reason for thinking that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces a risk of developing cancer other than angiosarcoma of the liver which might be small compared to the risks produced by nonoccupational causes, but yet absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards suggested can be dismissed, as there is no evidence to support it, namely, that of vinyl chloride as a cause of any cancer of the digestive tract other than angiosarcoma of the liver. Two hazards (of melanoma and cancer of the thyroid) have been suggested only very recently, and few of the available studies have provided information about them. There is no good theoretical reason or laboratory evidence to suggest that either should be produced by

[5] The deaths attributed to different groups of respiratory diseases and the corresponding SMR values that are cited in this section for the US study are as given by the Environmental Health Associates (14) and have not been adjusted to account for the number of deaths from an unknown cause. To take account of these deaths, the observed deaths and SMR values can both be multiplied by 1.0674.

vinyl chloride, and, in light of present evidence, the simplest explanation is that the reported excesses are the chance effects that must be expected when many different types of cancer are studied in several different populations. So far as melanoma is concerned, it has to be remembered that the disease has become much more common in recent years in Scandinavia (where the excess was reported) due, it is believed, to the popularity of sunbathing and the increased opportunities for Scandinavians to travel to the warmer parts of Southern Europe and North Africa. The extent to which this change may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and brain cancer) were suggested by the early results of some of the US studies. That vinyl chloride might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many investigations that have been undertaken (see reference 29) do not suggest that lymphoma or any other cancer of the hematopoietic system is liable to be produced. There is, however, some evidence that brain tumors can be produced in rats (29). The hypotheses that lymphomas and brain cancers might be produced by vinyl chloride have been supported by the observation that both these types of cancer have caused death more often than might be expected from national mortality rates, but the excesses observed in the combined data from the four principal studies in this review are small and not statistically significant, and the hypotheses remain unproved. The small excess of brain cancer is particularly difficult to evaluate, as mortality rates from this disease have changed rapidly over time as methods of diagnosis have improved and the suspicion of an occupational hazard (which was raised in 1975) could have influenced the findings. What excess has occurred has been limited to the US and Germany, and the German findings carry little weight, as the excess was found in each of the three occupational groups studied, irrespective of the chemicals to which they were exposed. The supplementary data from the German study showing an increased mortality from lymphatic and hematopoietic cancers are more impressive, particularly as the excess was the most marked for men who had been employed for at least five years. In these circumstances, judgment must still be suspended until the data for each study are analyzed for each specific type of cancer, by intensity and duration of exposure, and by time since exposure began.

There remains the suggestion that vinyl chloride might cause lung cancer. At first sight, this possibility is ruled out by the SMR of 97 for the combined data for respiratory cancer for the four principal studies. Lung cancer is, however, normally so common (accounting for about 8 % of the expected deaths) that an increase in mortality that was half as important (numerically) as the increase in mortality from angiosarcoma of the liver might easily be overlooked (95 % confidence limits of the SMR 85—112). The incidence of the disease varies moreover within a country, and there must be doubts as to whether the national experience provides a suitable reference for men employed in plants that are not evenly distributed about the country. In these circumstances one cannot exclude an occupational hazard unless it can be shown that the mortality of the exposed men is independent of the factors that might be expected to influence it if some of it were occupational in origin, namely, the intensity and duration of exposure and the time since exposure began. It is not possible to examine these relationships in detail, as the reports do not provide all the necessary information. Such information as they do provide, which was summarized in table 6, supports the idea that exposure to vinyl chloride involves a small hazard of lung cancer. Taken in conjunction with the knowledge that lung tumors have been produced in several species of animals exposed to vinyl chloride by inhalation (29), it would seem that a small hazard of lung cancer probably did occur. The evidence is not, however, strong enough to conclude that it definitely did. If it did, the hazard was evident only for men who had been employed for many years at a time when exposures of several hundred parts per million or more were common, and any persisting risk can be only minute and incapable of detection.

The questions that have been left unanswered by this discussion might well be answered definitely if (i) all the exposed men could be followed to (say) the end of 1984, (ii) the investigators could present their data in comparable ways, taking account of duration of employment and time since first employment and presenting data separately for men first employed before (say) 1965 and between 1965 and 1974, and (iii) estimates could be made of the effect of correcting the results for each group of employees for the locality in which they lived and worked.

Hazards to the general population

As vinyl chloride has been proved to cause cancer in man and is a mutagen in laboratory experiments, it must be presumed that even the minute doses that escaped into the general environment from production plants or (in the early days of manufacture) from PVC materials will have caused some risk of cancer to the general public. These risks must, however, have been very small, as air concentrations of vinyl chloride, even within a kilometer of plants handling vinyl chloride, used to be (in or around 1975) of the order of 10 to 40 ppb (1, 3, 15), and this level is about one-ten thousandth of the concentration that has caused an occupational hazard. It is obvious, therefore, that it would be impossible to detect the risk of any cancer that might be produced by vinyl chloride other than a risk of angiosarcoma of the liver, as it has proved so difficult to detect any other risk among men who were exposed occupationally. The position with regard to an-

giosarcoma of the liver is different. This disease is normally so rare that, in the absence of specific exposure to one of the known causes (vinyl chloride, thorium dioxide, and arsenic in pesticides and medicines), the annual incidence is on the order of $1—2 \cdot 10^{-7}$ (5, 8).[6] In these circumstances the discovery of even one case in a man living close to a factory in which vinyl chloride was used in the days before exposure was tightly controlled may be regarded as presumptive evidence of the effect of environmental pollution.

Several surveys have been undertaken to determine whether any such cases have occurred. Saric et al (43) and Elinder & Pershagen (13) sought for cases in the vicinity of plants handling vinyl chloride in Yugoslavia and Sweden and found none. In Holland Dalderup et al (11) found eight confirmed cases not attributable to thorotrast or arsenic and could trace "no contact with vinyl chloride," but they made no specific mention of the patient's place of residence. Baxter et al (3) found 14 confirmed cases in Great Britain over a 12-year period, one of which was in a man who had lived half a kilometer from a PVC manufacturing plant, and, in New York State over an 18-year period, Brady et al (5) found 19 cases that could not be attributed to any known cause, five of which were in people living within a mile of plants manufacturing or using vinyl chloride. The overall incidence rates in these last two studies were not unduly high, but the occurrence of as many as six cases among people living so close to manufacturing plants is surprising. Brady and his colleagues, moreover, compared their series of patients with matched referents and found that none of the referents lived equally close to a plant. Two of these six neighborhood cases (one in England and one in New York State) cannot be attributed to environmental pollution with vinyl chloride, as the men who developed the disease had lived near the plants for six and eight years, respectively, before developing the disease, and this period is too short to allow for the necessary latency. The other four cases, however, all occurred after 15 or more years of local residence, and the discovery of these cases strongly suggests that pollution of the environment around plants manufacturing VCM or PVC may have caused a minute hazard to the general public.

Current concentrations around plants handling vinyl chloride are certainly much lower than those reported previously by the US Environmental Protection Agency. Recent British measurements made within a few hundred meters of the VCM areas have given average values below the daily limit of detection (5 ppb) for three of five plants, the readings at the two others being 20 ppb (100 m outside the boundary fence) and 88 ppb (just inside it) (47), although substantially higher values were recorded on two occasions associated with putting one plant into operation and with an accident at the other. According to any reasonable criterion the hazard to the general public (if there is any at all) must be negligible (42).

No other hazard to the general population, other than a hazard of cancer, can reasonably be postulated.

[6] The figure of $1.4 \cdot 10^{-8}$ cited by Heath et al (21) seems to have been a misprint for $1.4 \cdot 10^{-7}$.

Summary

This paper reviews (i) the possible effects of vinyl chloride on the personal health of men exposed by virtue of their occupation (other than the early effects of the very high concentrations to which men were exposed when the industry was first developed — unconsciousness, cardiac arrhythmia, and the characteristic "vinyl chloride illness") and (ii) the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant. The possibility that vinyl chloride might act as a teratogen or might cause mutations in the germ cells has not been examined, as the little evidence that has been adduced relating to such possible effects has been reviewed elsewhere and the conclusion was reached that no such effects have been demonstrated.

Many groups of workers exposed to vinyl chloride in the manufacture of VCM or PVC have been studied since the carcinogenic potential of vinyl chloride was first recognized. Some results have shown that occupational exposure can cause angiosarcoma of the liver, and others have suggested that it may cause several other types of cancer as well. The actual situation can be determined only in an examination of all the evidence, especially the combined results of those studies that include a substantial proportion of observations on men more than 25 years after their first exposure and cover a long enough period for more than 10 % of the employees to have been expected to die.

The results of four studies can be usefully combined for this purpose. They are two national studies, one from the US and the other from the UK, and two studies of employees in one plant in Canada and two plants in Italy. The results of other studies from the Federal Republic of Germany, Norway, Sweden, Italy, France, and Japan can be used only to provide supplementary information. The many earlier reports of exposed workers in the US and the UK concern men covered more completely in the two recent national studies, and their results serve only as sources of hypotheses.

Minor criticisms can be made of three of the four most useful studies. They do not seriously affect the value of the results, except that allowance has to be made for the failure to determine the cause of 6.3 % of the deaths recorded in the US study. Three of the studies use national rates to estimate the numbers of deaths that might have been expected to occur in the absence of any special occupational hazard, and the fourth (Canadian) uses rates for the province in which

the plant was situated. It must, therefore, be kept in mind that the rates used may not have been wholly appropriate for the localities in which the plants were situated. This circumstance is potentially important for the US study, which covered workers in 37 plants, 22 of which were situated in the southern part of the country. The other less informative studies are, for the most part, open to more serious criticism, and the value of each set of results needs to be assessed separately in relation to each disease.

The combined results of the four principal studies show that the SMR values, reflecting the ratios between the numbers of deaths observed and those expected in the absence of an occupational hazard multiplied by 100, have been (i) 77 for accidents and other violence, (ii) 84 for diseases other than cancer, and (iii) 102 for cancers other than cancer of the liver. All these results are what might be anticipated for an industry devoid of any specific occupational hazard. The low ratio for diseases other than cancer reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the less healthy members of the population from industrial employment and is compatible with a higher ratio for cancer, as the mortality from cancer is not normally subject to such an effect, apart from the first two or three years immediately following the start of employment.

The mortality from cancer of the liver was nearly seven times that expected. Most of the 51 excess deaths were known to be due to angiosarcoma, even though this diagnosis was not recorded on the death certificate. The excess corresponds closely with the 49 deaths due to angiosarcoma reported to the International Register of Angiosarcoma Cases as occurring in employees of the plants concerned during the periods under observation. All the men who developed the disease were likely to have been exposed to concentrations of vinyl chloride of several hundred parts per million or more.

Three other types of cancer which have been suggested to occur as a result of exposure to vinyl chloride are cancers of the lung, brain, and lymphatic and hematopoietic systems. The combined data for the mortality from respiratory cancer fail, at first sight, to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups in which the effect of an occupational hazard would be most likely to be seen (that is, men employed for more than 10 years, exposed to higher than average concentrations, or observed more than 20 years after first exposure). In two of the supplementary studies it was also noted that the mortality from lung cancer was specifically increased among the most heavily exposed workers. The combined data show small excesses in the mortality from cancers of the brain and of the lymphatic and hematopoietic systems. The excesses are, however, not statistically significant, and there is nothing to suggest that they are occupational in origin. An exception is the observation of an increased mortality from cancers of the lymphatic and hematopoietic systems in the supplementary study from the Federal Republic of Germany.

Two types of cancer were reported to be in excess in the Norwegian study, namely, thyroid cancer and melanoma. The significance of this finding is difficult to assess because very little information about these cancers has been provided by other studies.

Suggestions that vinyl chloride might cause cancers of the digestive tract have failed to account for the contribution of angiosarcoma of the liver. When this disease is excluded, the mortality from digestive tract cancer decreases to below the average (SMR 82 for the four principal studies).

A small excess mortality from the heterogeneous group of "other cancers" in the combined results of the four principal studies was statistically marginally significant (83 deaths against 65.25 expected, $P<0.05$). Some of the excess was likely to have been due to the misclassification of angiosarcomas as secondary cancers of the liver or carcinomatosis, site unknown.

The following three nonmalignant causes of death have required special examination: cirrhosis of the liver because of damage to the liver in "vinyl chloride illness, " myocardial infarction (from analogy with the effect of other halogenated hydrocarbons and because of some observations from Swedish PVC fabricators), and nonmalignant respiratory disease because of changes in lung function and the radiographic appearance of the lungs observed in men exposed to PVC dust. Far from being raised, the mortality from cirrhosis of the liver was less than expected in the three principal studies and in one of the two supplementary studies which gave separate figures for the disease (SMR values of 69, based on 46 deaths, and 82, based on 15 deaths), while in the other supplementary study the increase was trivial.

Data for myocardial infarction have not been reported separately. But myocardial infarction accounts for most of the deaths attributed to ischemic heart disease, and there is no evidence that either ischemic heart disease or cardiovascular disease as a whole was unduly common (SMR values of 90 and 92, respectively) or related to occupational exposure.

The data for the third category of nonmalignant disease (nonmalignant respiratory disease) are confusing, because the two large national studies give conflicting results. The combined data for the four principal studies show the low mortality that is commonly found in healthy industrial populations (SMR 80). This figure hides, however, an increased mortality from chronic obstructive lung disease (SMR 120), which includes emphysema and is due to a grossly increased mortality attributed to emphysema in the US study (SMR 193). The corresponding mortality in the British study, which was preferentially described as due to bronchitis, was less than expected (SMR 82), as was the mortality from pneumonia (SMR 50) and other res-

piratory diseases (SMR 46) in the US study. There is no consistent evidence that the mortality from emphysema or bronchitis was specifically occupational, and it seems possible that the reported excess in the US study was an artifact due to nosological difficulties with the use of the seventh revision of the ICD.

Review of the massive data now available on the long-term health of men occupationally exposed to vinyl chloride leads to two clear conclusions. First the men have experienced a specific hazard of the normally extremely rare angiosarcoma of the liver. Approximately 1 in 335 of the men exposed in the 49 plants studied died of the disease, and approximately 2 % of the observed deaths were attributed to it. In the course of time the numbers of cases of angiosarcoma must be expected to increase two to three times. Second, the mortality from all other causes has been typical of that of normally healthy industrial workers. If any hazard has existed, its effect has been small.

The data provide no reason to think that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deaths as angiosarcoma of the liver.

There is too little evidence either to confirm or refute the suggestion that vinyl chloride might cause melanoma or cancers of the thyroid, brain, and lymphatic and hematopoietic systems. None of the small excesses that have been recorded point specifically to an occupational hazard, apart from that attributable to cancers of the lymphatic and hematopoietic systems in the German study reviewed, and most are likely to be the sort of chance effect that is certain to be observed when many types of cancer are examined in many different studies.

The lack of any increased mortality from lung cancer in the combined results of the four principal studies reviewed does not exclude the possibility that there may have been a small occupational hazard of developing the disease, as geographic variations in the incidence of the disease throw doubt on the validity of using national rates for estimating the expected numbers of deaths. The greater mortality in groups of workers who would be more likely to show an occupational hazard than other groups suggests that a small hazard may have existed. The evidence is, however, weak, and the existence of a hazard has not been proved.

Clearer answers to some of the questions that have been posed in this review might be obtained if the various groups of investigators could present their results in more appropriate and comparable ways.

As vinyl chloride is a mutagen in laboratory experiments and a proved human carcinogen, the minute doses that have escaped into the general environment as pollutants must be presumed to have caused comparably minute risks to the general public. No such risk could possibly be detected, other than one of angiosarcoma of the liver which is normally an extremely rare disease. Several surveys have sought evidence of the existence of such an effect, and suggestive evidence that such an effect may have occurred at a time when environmental pollution was much greater than it is now has been found in one.

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Received for publication: 16 February 1988