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EFFECTS OF EXPOSURE TO VINYL CHLORIDE:

AN ASSESSMENT OF THE EVIDENCE

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SUMMARY

The results are reported of a review of: (i) the possible effects of vinyl chloride (VC) on the personal health of men exposed to it 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 arrhythmias, 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 VC as a pollutant. The possibility that VC 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 reached that no such effects have been demonstrated.

Many groups of workers exposed to VC in the manufacture of vinyl chloride monomer (VCM) or polyvinyl chloride (PVC) have been studied since the carcinogenic potential of VC was first recognized. The results have shown that occupational exposure can cause angiosarcoma of the liver and some have suggested that it may cause several other types of cancer as well. Whether this is so or not can be decided only by examining all the evidence and, in particular, 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 per cent of the employees to have been expected to die.

The results of four studies can be usefully combined in this way: namely, two national studies in the USA and the UK and two studies of employees in one plant in Canada and two plants in Italy. The results of other studies in 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 USA and the UK relate to

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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) study 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 is potentially important for the US study which covered workers in 37 plants, 22 of which were situated in the south 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 standardized mortality ratio (SMR), reflecting the ratio between the numbers of deaths observed and those expected in the absence of an occupational hazard multiplied by 100, has 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 almost exactly 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 they were kept under observation. All the men who developed the disease are likely to have been exposed to concentrations of VC of several hundred ppm or more.

Three other types of cancer, which, it was suggested soon after the discovery of the carcinogenicity of VC, might be caused by VC, are cancers of the lung, brain, and lymphatic and haematopoietic systems. The combined data for the mortality from respiratory cancer fail to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups of men in whom 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 in the most heavily exposed. The combined data show small excesses in the mortality from cancers of the brain and of the lymphatic and haematopoietic systems; but the excesses are 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 haematopoietic 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 is provided by other studies.

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

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

Three non-malignant causes of death have required special examination: cirrhosis of the liver because of the damage to the liver that occurred as part of the 'vinyl chloride illness', non-malignant respiratory disease because of the changes in lung function and x-ray appearance observed in men exposed to PVC dust, and myocardial infarction from analogy with the effect of other halogenated hydrocarbons and because of some observations on Swedish PVC fabricators.

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 (SMRs of 69 based on 46 deaths and of 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 ischaemic heart disease and there is no evidence that either ischaemic heart disease or cardiovascular disease as a whole was unduly common (SMRs of 90 and 92) or related to occupational exposure.

The data for the third category of non-malignant disease (non-malignant 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, however, hides 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 UK study, which was preferentially described as bronchitis, is less than expected (SMR 82) as is the mortality from pneumonia (SMR 30) and other respiratory 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 is an artefact due to nomenclological difficulties in the use of the 7th revision of the International Classification of Diseases.

Review of the massive data now available relating to the long term health of men occupationally exposed to VC 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 has died of the disease and approximately 2% of observed deaths have been attributed to it. In the course of time the numbers of cases of angiosarcoma must be expected to be increased 2 to 3 times. Secondly, the mortality from all other causes has been typical of that in normally healthy industrial workers. If any other 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 VC does produce risks of cancer in sites other than the liver that are small compared to those due to non-occupational causes, but which

might, in total, cause almost as many deaths as angiosarcoma of the liver.

There is too little evidence either to confirm or refute the suggestion that VC might cause melanoma or cancers of the thyroid, brain, and lymphatic and haematopoietic 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 haematopoietic systems in the German study, 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 does not exclude the possibility that there may have been a small occupational hazard of developing the disease, as geographical 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 in other groups, suggests that a small hazard may have existed. The evidence is, however, weak and the existence of a hazard is not proven.

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 VC is a mutagen in laboratory experiments and a proven 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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INTRODUCTION

The inhalation of large amounts of vinyl chloride (VC) has been recognized to be potentially hazardous for many years. Concentrations of the order of 10,000 ppm in 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 acro-osteolysis, 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 by ensuring that exposure never exceeds a few hundred ppm, to which level 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 VC has been shown to act as a mutagen (International Agency for Research on Cancer, 1979) and it cannot be assumed that a threshold exists below which no carcinogenic risk persists. Moreover, the possibility has to be considered that VC may cause some cancers other than angiosarcoma of the liver, partly because laboratory studies have shown that it does this in animal experiments and partly because the initial studies, which demonstrated the production of angiosarcoma of the liver in Man, were inadequate in size to exclude a material increase in the risk of cancer in common sites, such as

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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 acting over a long period may have noxious effects on Man that could not easily be seen 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 the offspring.

In this review I have not examined the possibility that VC acts as a teratogen nor that it causes mutations in germ cells, as there is too little serious evidence to require it. Reviews carried out for sections of the industry by Downes et al. (1977) and by MacMahon (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 (1981), apart from a report that embryos were absorbed and skeletal ossification produced when pregnant rats were exposed to doses appreciably less than those that had been used by other workers without any such effects being observed. The report of absorbed embryos (Mirkova et al., 1978) 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 VC other than on their reproductive capacity, and the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of VC as a pollutant.

OCCUPATIONAL HAZARDS

Many studies of workers exposed to VC in the manufacture of vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) have been undertaken

since it was first found that VC could cause cancer in animals (Viola et al., 1971; Maltoni et al., 1974) and in Man (Creach and Johnson, 1974). These have confirmed that exposure causes a hazard of angiosarcoma of the liver and, in several instances, have shown excess incidence or mortality rates from other diseases, which were conventionally statistically significant. 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. We 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 by examining the overall results, when the data from comparable studies are summed: that is, by adding together the numbers of deaths observed and expected in each study, and comparing the totals. This does not require the assumption that the exposures have been the same in each study, any more than it does for each individual when the results of each study are considered alone. What it does require is that each exposed population should have 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 control 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). This does not introduce any new complexity, as both these conditions 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 these requirements: namely, the two large national surveys reported by Jones (1986) for the UK and by Environmental Health Associates (1986) for the USA, and studies of individual plants in Canada reported by Thériault and Allard (1981) and in Italy reported (as a part of a national study) by Belli et al. (1986). 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 per cent of the total number of employees indicating a long average period at risk. Earlier observations on UK and USA employees reported by Monson et al. (1979), Tebershaw and Gaffey (1974), Duck et al. (1975), Nicholson et al. (1975), Ott et al. (1975), Maxwell et al. (1976), Fox and Collier (1977), Equitable Environmental Health (1978), Buffler et al. (1979), and Cooper (1981) are subsumed in the national surveys and now serve only as sources of hypotheses and to provide some detailed information not included in the national reports. Studies of German workers (Greiser et al., 1982), Norwegian workers (Meldness et al., 1984), Swedish workers (Byren et al., 1976), French workers (Pierre et al., 1979 and Laplanche et al., 1987), Japanese workers (Masuda, 1979 and Nakamura, 1981) and some other Italian workers (Belli et al. 1986) provide some supplementary information but, in general, the periods of observation have not been long enough for useful epidemiological 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 PVC fabricators are not included as the workers will have had much less exposure to VC 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 (1986) on behalf of the US Chemical Manufacturers Association is the largest and most informative. It covers 10,173 men who had worked in 37 plants owned by 17 companies - 1,214 in 11 plants that produced only VCM, 6,848 in 18 plants that produced only PVC, 935 in 3 plants that produced both, and 1,176 in 5 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 in the North eastern or North central parts, and one in the West.

Men were included if they had been exposed to VC 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 VC 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 per cent 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 was 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 (1981) earlier study 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 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 latent 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 were employed for 10 years or more and the average duration of employment was 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 97 (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 quinquennia.

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. Secondly, 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. Thirdly, an element of uncertainty is introduced by the failure to trace as many as 7.3% of employees.

Two other criticisms are more important. First, the expected numbers of deaths have been 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 over-estimation of the expected numbers of deaths, so that the employees

appear to be unusually healthy. This "healthy worker effect" is well known and will be taken into account in the 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 geographical 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 this could have caused any material distortion of the results.

Secondly, causes were not obtained for 97 of the 1,536 deaths. This was allowed for in the calculation of the overall mortality by including 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 (SMRs) to be underestimated by, on average, 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 (1986) on behalf of the UK Health and Safety Executive covers 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 working week and who were first employed in the period 1940-74. Details of the men were compiled from the personnel records of 9 chemical plants manufacturing or polymerising VC and the vital status of the men were 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 were sent to the investigators coded to the 8th ICD revision of the list of causes of death if they occurred before 1979 and to the 9th revision if they occurred later.

Several specific points about the study need to be noted. First, national mortality rates for England and Wales were calculated by five year age groups for quinquennial periods for 66 causes of death and these were used to estimate 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 was, however, experienced in obtaining suitable rates for all causes of death, which could be related to the causes of death coded according to the 8th and 9th revisions of the ICD list, 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 2 categories the earliest available rates were 1960-64, for 1 they were 1965-69, for 24 they were 1970-74, and for 1 they were 1975-79.

Secondly, 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 with advice from the plants concerned, under 12 job titles. 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 groups, exposure to VCM was likely to have been higher if it had begun before 1956.

The study makes an important contribution to the sum of knowledge concerning the long term effects of VC. The use of national rates to

calculate the expected numbers of deaths may be justified on the grounds that the men were employed in 9 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, so that the expected numbers of deaths are more likely to be biased downwards than upwards; but this 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 have 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 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 (e.g. 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 are calculated. Movements from one job to another are 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 be over-estimated.

Canadian Study

The Canadian study (Thériault and Allard, 1961) 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 production workers whose names appeared on the unions' lists or the companies' payrolls of the whole industrial complex including the VC 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 5 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 5 years (451 men), (ii) unexposed to VCM if they had worked similarly for less than 6 months (870 men), and (iii) other men (134 in total). The last were excluded from the study. Follow-up was closed on 31 December 1977. Copies of the death certificates were obtained and the causes coded according to the 8th revision of the ICD list for all who had died (59 exposed and 233 unexposed). 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 were compared after standardization for quinquennium and 5 year age group. Secondly, the mortality of the exposed men was compared with that expected if the men had experienced 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. This showed that all 8 cancers diagnosed as liver cancer (including 2 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 exposed and "unexposed" employees of the same companies as this shows that the low mortality observed for all non-malignant diseases could be attributed to a healthy worker effect and was not due to bias in the recording of exposure (relative risk for all non-malignant causes compared to "unexposed" men 0.93).

One criticism has to be made: namely, 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 VC and PVC in 9 Italian plants was begun in 1983. All men were included who were employed for at least 6 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 (Belli et al., 1986). Two plants (in Ferrara and Rosignano) began operations in 1953. Four hundred and thirty seven men were employed in the 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 5 year age group and quinquennium. Total expected deaths in each case amounted to more than 10% of the employees (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 operations until 1959. Six hundred and thirty eight men were employed. All but 4 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 workforce) 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 (Meldnes et al., 1984) 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. All were included whose names were recorded on 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. 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 is 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 the 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 per cent of the rate in the country as a whole. One man who had been employed on FVC production developed angiosarcoma of the liver. Observed and expected numbers of cases are given for cancers of the lung, colon, and thyroid, for melanomas, and for all cancers, but no expected numbers are given for other types of cancer. It is evident that several other types of cancer must have been in deficit, as there were 8 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 note 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 (Graiser et al., 1982) included 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 FVC had been produced in the Federal Republic of Germany, (ii) 4,820 men who had been employed in 7 chemical plants without having had any exposure to VC, and (iii) 4,007 men employed in 2 other plants where FVC was processed. Employees were included only if they were of German or Austrian nationality and were regarded as exposed to VC if they were production workers or other skilled workers or labourers assigned regularly to the plants, but not if they were employed in them only occasionally. All men were included from the time of opening of the plants to the end of 1974 and were followed to the end of 1974. Many of the men were, in consequence, 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 so 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.

93.2% of the exposed group were successfully followed up 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 weighting 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 FRC. 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.

Epidemiological studies are more difficult to carry out in Germany than in N. America, the UK, 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 the 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 up (6.8%) and the proportions of deaths for which the cause was not obtained (7.2%) were similar to those in the Environmental Health Associates (1986) study.

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 diagnosed more often and will have underestimated those due to diseases that were becoming less prevalent. Secondly, and more importantly, a large proportion of the men had been first employed less than 10 years before the follow up was ended. It follows that the observations on the few men who had been first exposed long enough before to have had much chance of developing an occupational disease with a long latent period must have been swamped by 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 VC exposed workers against 0.9 expected and that smaller excesses were also observed in the unexposed chemical workers (4 observed against 1.1 expected) and in the FVC process workers (3 deaths against 0.8 expected).

Two Swedish plants have produced VCM and FVC since 1945 and 1971 respectively and employees of the first have been studied by Byren et al. (1976). 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 is given for

the expected number. Detailed figures are 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 dying of liver cancer or pancreatic cancer respectively, and a third man died of the disease 17 months after the follow up closed.

Two French studies provide the results of a long term follow up of men employed in one plant (Pierre et al., 1979) and of a short term follow up of men employed in 12 plants (Laplanche et al., 1987). The first provided observations on 1,311 men exposed to VC in the production of VCM and PVC and in selected ancillary operations from the opening of the Taveux plant in 1953 to the end of 1976 (Pierre et al., 1979). 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 epidemiological value to the results of the other studies, apart from the addition of a further case of angiosarcoma.

The second provides observations on 1100 men aged 40 to 55 years who, in 1980, were exposed or had been exposed to VC in 12 plants, which constituted "most of the French VCM polymerisation plants" (Laplanche et al., 1987). Many of the men were, or had been employed at Taveux and were presumably survivors of the cohort studied by Pierre et al. (1979). The men were followed for 3 years and their morbidity and mortality compared.

with that observed in 1100 men of the same ages (± 2 years) employed in the same plants, but who had never been exposed to VCM. Men in both groups were interviewed personally and information obtained about their smoking and drinking habits which were found to be similar in the two groups. Men in the exposed group had been first exposed on average 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 controls. One of the exposed men but none of the unexposed developed an angiosarcoma of the liver. Data are not given separately for different periods after first employment and it is impossible to assess the significance of the finding that 6 of the exposed men developed lung cancer against 2 of the controls, which may well reflect a chance occurrence of unusually few cases in the control groups as the proportion of all cancers in the control group that arose from the lung (2 out of 15) is unusually low. One exposed man developed a cancer of the lympho-haematopoietic system against none of the controls, but no men in either group were known to have developed melanomas or cancer of the brain or thyroid.

A Japanese study reports the mortality experience of 4524 men employed for at least one year before 1965 in one or other of 25 Japanese plants which began producing vinyl chloride monomer (VCM) or polyvinyl chloride (PVC) between 1949 and 1964 inclusive (Nakamura, 1983). The men were followed to 31.10.75. Twenty eight per cent 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 on which they had been longest employed at the termination of their follow up and data are given separately for 2546 men classed as employed on PVC

production and 1978 others (including 900 classed as VCM production workers).

If this study is continued for a further 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 6 deaths in PVC production workers against 2.54 expected from national rates while only 1 such death was observed in the other workers against 1.82 expected. One of the 6 deaths from liver cancer in 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 are given for cancers of the lymphatic and haematopoietic systems, for cancer of the brain or thyroid, or for melanomas. The mortality of 305 Japanese VC workers reported by Masuda (1979) is presumably subsumed in Nakamura's (1983) 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 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 is given in Table 5 for 7 types or classes of cancer that has been obtained from four other less informative studies (the German study reported by Greiser et al., 1982, the Norwegian study reported by Madsen et al., 1984, the Swedish study reported by Byren et al., 1976, and the part of the Italian study relating to the Ravenna plant reported by Balli et al.,

1986).

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 in 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 SMRs 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* attributed to cancers of the liver and gallbladder in the US series are known to have been due to angiosarcoma of the liver (Environmental Health Associates, 1986). In the British series, 7 of the 11 deaths attributed to liver cancer, not specified as secondary, were known to be angiosarcomas and all occurred in autoclave workers against 0.38 expected liver cancers of all types ($P < 10^{-5}$).

*Increased to 39 in Table 1, to take account of the 97 extra deaths of unknown cause.

Jones, 1986). In the Canadian series, histological review showed that 7 of the 8 so called liver cancers were angiosarcomas (1 had been described as an angiosarcoma on the death certificate, 2 as hepatomas and 5 as unspecified liver cancers). One so called liver cancer death was found to have been due to cancer of the sigmoid colon, while 1 death attributed to angiosarcoma of the peritoneum was found to have been due to angiosarcoma of the liver (Thériault and Allard, 1981). In the Italian study, further evidence revealed that 3 further deaths should have been attributed to cancer of the liver (making 4 in all), but only 1 of the 4 was described as an angiosarcoma (Bellì et al., 1986).

Further evidence that the excess mortality from liver cancer (or liver and gallbladder cancer in the US series) can be attributed wholly to the known hazard of angiosarcoma is obtained by comparing the excess deaths with the numbers of deaths from angiosarcoma before the ends of the follow-up period that are recorded in the Register of Liver Angiosarcoma Cases maintained on behalf of the Association of Plastics Manufacturers in Europe by Imperial Chemical Industry PLC (Bennett, 1986). Fifty one excess liver cancers are recorded in the combined data and 49 angiosarcomas are recorded in the Register for the relevant periods for the three countries and the two Italian plants* that are covered by the survey.

None of the 120 cases yet recorded on the Register were in men who were first exposed after 1969 and none of the 43 men affected in North America were first exposed after 1964. All may, therefore, have been exposed to concentrations of several hundred ppm and many may have been

*Twenty nine are registered as occurring in the USA against an estimated excess of 33, 9 are registered in the UK against an excess of 9, 10 in Canada against an excess of 8, and 1 in a man employed in one of the two Italian plants studied against an excess of less than 1. Two of the Canadian cases are recorded in the Register as occurring in men who had been employed for 5 years and it is possible that the actual duration of employment had been slightly less than 5 years, when the men would have been excluded from the study.

exposed to concentrations appreciably higher (Barr, 1981).

Lung Cancer

The idea that exposure to VC might cause cancer of the lung was suggested by Monson et al. in 1974, when they noted 13 cases in a study of proportional mortality against an expected number of 7.9. The combined data that are shown in Table 4 do not provide any support for the hypothesis neither for respiratory cancer as a whole (SMR 97) nor in the specified data for lung cancer in the USA, UK, and Italy (SMR 99). There are, however, consistently higher risks in the subgroups of men in the US and UK series in whom occupational hazards would be more likely to be seen than in other groups. This is seen from Table 6, which shows that the SMRs are slightly higher in men observed 20 years or more after first exposure than in men observed earlier, in men employed before 1936 in the UK than in men first employed after 1935 (when exposure levels are believed to have been lower), in men employed for longer than for a shorter periods in the USA, and in autoclave workers in the UK, in whom the angiosarcoma cases have mostly occurred, than in other workers. The differences are all small or very small, but they are 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. Thirty deaths (or cases) were observed in total and this is raised to 31.5, when allowance is made for the number of deaths due to unidentified causes in the German study, giving an SMR of 103. In the German study the SMR was higher in men who had been exposed for 10 years or more than in men who had been exposed for less (111 against 79) and in the Norwegian study, 4 of the 5 cases observed occurred in men whose occupations were regarded as involving high exposure against 1.82 out 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 SMRs correspondingly underestimated as the mortality from lung cancer had been rising throughout the period of observation.

Brain Cancer

The idea that VC might cause brain cancer was suggested by Monson et al. (1974), when they reported 3 cases against 1.2 expected, in the same paper in which they suggested that VC might cause lung cancer. The combined data that are shown in Table 4 provide some support for this hypothesis. Monson et al.'s cases were, however, observed in US workers and must be presumed to be included in the total reported by Environmental Health Associates (1986), in which case they will have contributed a substantial proportion of the total in Table 4. To test the hypothesis we ought, therefore, to subtract Monson et al.'s data. Their study was not a cohort study and their expected deaths do not correspond exactly to those in Table 4; we can, however, only subtract both the observed and the expected cases from the present totals. This leaves 24 observed against approximately 18.3 expected, a difference which might easily occur by chance (P , one-tailed, = 0.1).*

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

*If we regard Waxweiler et al.'s (1976) study as the origin of the hypothesis we should be left with 26 deaths against 18.94 expected (P , one-tailed, = 0.07).

in the German study was less than that observed in chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and in workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of Lymphatic and Haematopoietic Tissues

The idea that VC might cause cancer of the lymphatic and haematopoietic tissues - and more specifically the lymphatic tissue - was suggested by Tabershaw and Gaffey (1974) and by Waxweiler et al. (1976) when they found, respectively, in two cohort studies (i) 5 deaths from lymphomas in the most heavily exposed workers against 2.34 expected, and (ii) 4 deaths from cancers of the lymphatic and haematopoietic 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 (Maltoni and Lafemina, 1975). On this basis, the idea that similar exposure might also cause lymphomas in Man needed 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 haematopoietic 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 (using Tabershaw and Gaffey's definition of ICD list numbers, 8th revision, 200-203 and 205) that are shown in Table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered by subtracting the data in Tabershaw and Gaffey's initial report (29 deaths against 23.36 expected, SMR 124).

Some little additional information is provided by the results of the German study, some of which are shown in Table 3. This obtained an SMR of 214 for exposed workers (based on 13 observed deaths, increased to 16.5

when allowance is made for the number of deaths of unknown cause) against SMRs of 77 and 34 for an unexposed group of chemical workers and a group of PVC fabricators and showed that the excess in the exposed workers was present only for men who had been exposed for more than 1 year and was most marked for men who had been exposed for 5 years or more (10.7 deaths after allowance for the number of deaths of unknown cause against 4.0 expected, SMR 268, P one-tailed <0.01).

Melanoma

An excess of melanoma was reported in Norwegian workers by Haldane et al. (1984), who raised the possibility that VC might have produced the disease. Four cases were observed when 0.79 were expected, three of which were in men whose occupations involved the highest exposures (against 0.51 expected). At the time of writing their report one further case had been detected with onset 3 years after the closure of the study. Subsequent studies in other countries have, so far, reported only 2 deaths against 2.0 expected (see Tables 1 and 5).

Thyroid Cancer

An excess of thyroid cancer was also reported in the Norwegian study, in which 2 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 draw no conclusion from their observation. Two of the three major studies that have been reported since the Norwegian observation was made give 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 USA by Henson et al. (1974).

Cancers of Digestive Tract

Suggestions that VC might cause cancers of the digestive tract in general have sometimes been made but they have not taken adequate account

of the contribution that cancers of the liver make 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 63.24 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, and so boosted the number of deaths in this category.

Hazards of non-malignant disease

No previous study has suggested that any non-malignant cause of death other than cirrhosis of the liver would be likely to be increased as a result of exposure to VC, and that is only presumed to be increased because of the liver changes that were observed as part of the 'vinyl chloride illness' (Marsteller *et al.*, 1973 and 1975; Jones and Smith, 1982). Two other possibilities have, however, been raised: namely the production of non-malignant respiratory disease because of the changes in lung function and x-ray appearances that have been recorded for men exposed to FVC dust (Lillis *et al.*, 1976; Haser *et al.*, 1985; Soutar, 1980; Lloyd *et al.*, 1985) and acute cardiac death, from analogy with the effect of other halogenated hydrocarbons (Jones, 1986) and the observation of an increased mortality from myocardial infarction in the few years following the cessation of exposure in the Swedish FVC processing industry (Molan *et al.*, 1981).

Relevant figures for the numbers of deaths from these and other non-malignant causes that are obtainable from the four principal studies were given in Table 2 and are summarized in Table 7.

Cirrhosis of Liver

Three of the four 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 4 deaths from all diseases of the digestive system combined against 3.85 expected and noted that the 4 included 2 that were certified as due to cirrhosis of the liver, but were actually due to angiosarcoma (Theriault and Allard, 1981). In the two supplementary studies in which data are given for this disease, the SMR was 82 in one, based on 15.1 deaths after making allowance for the number with unknown cause (Greiser *et al.*, 1982) and 133 in the other, based on 7 deaths (Nakamura, 1983).

Non-malignant Respiratory Disease

The data for non-malignant 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 SMR of 180 before any allowance is made for deaths of unknown cause). No such excess was found in the UK where 36 deaths from bronchitis gave an SMR of 82. International comparisons of chronic non-malignant 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 USA and chronic bronchitis in the UK. 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. On this basis, we should have to assume 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 VC.

Separate figures are shown, where available, for the mortality observed in men with different durations and intensities of exposure in Table 8. 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 (1986) report were unable to give any explanation for the increased mortality from emphysema and 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 non-malignant respiratory disease (pneumonia 15 deaths,* SMR 47.0; other respiratory disease 14 deaths, SMR 42.6) and the question arises whether the emphysema excess could be a classificatory artefact. Environmental Health Associates (1986) list all the 41 deaths which show that they were coded under ICD List no. 527 which, in the out of date 7th 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 List numbers 500 to 502 and the

*The deaths attributed to different groups of respiratory diseases and the corresponding SMRs that are cited in this section for the US study are as given by Environmental Health Associates (1986) and have not been adjusted to take account of the numbers of deaths of unknown cause. To take account of the deaths the observed deaths and SMRs can both be multiplied by 1.0674.

possibility may be considered that some of the emphysema deaths should have been classified in some category of respiratory disease other than List no. 527. If this were so, it could account for both the excess mortality from emphysema and the grossly deficient mortality from other non-malignant respiratory diseases.

No excess mortality from "bronchitis, emphysema, and asthma" was observed in the German study (Graiser *et al.*, 1982; SMR 44 with 6.3 deaths observed after making allowance for the number of deaths of unknown cause).

Cardiovascular Disease

Data for ischaemic (or arteriosclerotic) heart disease (which may be presumed to include the vast majority of all deaths certified as due to acute cardiac disease) are given only by the two big national studies and they provide no evidence of an increased mortality. The SMR of 90 for this group of diseases and of 91 for all cardiovascular disease recorded in the four principal studies are typical of the SMRs that are recorded in 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 ischaemic heart disease mortality was recorded for the exposed workers in the German study (Graiser *et al.*, 1982), but it was less than that recorded for the unexposed chemical workers and the PVC fabricators (SMRs of 127, 131, and 158 based on 97.2, 126.7, and 109.7 deaths after allowing for the number of deaths of unknown cause).

Discussion

The information that has now been obtained about the long term health

of men occupationally exposed to vinyl chloride is massive and compares favourably 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 latent 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 we can be certain about the extent of the protection provided by the reduction in exposure in the 1960s and the further reduction that followed the recognition of the hazard in 1974. 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 in the 16,740 men who have been followed up in the four principal studies that have been reviewed in this report, so that approximately 1 in 335 men have been affected, while 2% of the deaths have been due to this one cause. Eventually many more men must be expected to develop the disease. One estimate (Nicholson et al., 1984) suggests that the total may be increased 10 times, but a more realistic estimate is 2 to 3 times (Forman et al., 1985).

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 VC does produce a risk of developing cancer, other than angiosarcoma of the liver, which might be small compared to the risks produced by non-occupational causes, but yet

absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards that have been suggested can be dismissed, as there is no evidence to support it: namely, the idea that VC causes 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 VC and, on 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 has been 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 may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and of brain cancer) were suggested by the early results of some of the American studies. That VC might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many studies that have now been undertaken (see Maltoni and Lafemina, 1984) do not suggest that lymphoma or any other cancer of the haematopoietic system is liable to be produced. There is, however, some evidence that brain tumours can be produced in rats (see Maltoni and Lafemina, 1984). The hypotheses that lymphomas and brain cancers might be produced by VC 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 are small and not statistically significant and the hypotheses remain unproven. The small excess of brain cancer is particularly difficult to evaluate as mortality rates from this disease have changed rapidly over time in company with improved methods of diagnosis 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 USA 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 haematopoietic cancers are more impressive, particularly as the excess was most marked for men who had been employed for at least 5 years. In these circumstances, we must still suspend judgment until the data for each study are analysed for each specific type of cancer, by intensity and duration of exposure, and time since exposure began.

There remains the suggestion that VC might cause lung cancer. At first sight, this 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 mortality from angiosarcoma of the liver might easily be overlooked (95% confidence limit of the SMR, 85-112). The incidence of the disease is moreover very variable within a country and there must be doubts whether the national experience provides a suitable control for men employed in plants that are not evenly distributed about the country. In these circumstances we cannot exclude an occupational hazard unless it can be shown that the mortality within 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 VC produces a small hazard of lung cancer. Taken in conjunction with the knowledge that lung tumours have been produced in several species of animals exposed to VC by inhalation (see Maltoni and Lafemina, 1984) 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 in men who had been employed for many years at a time when exposures of several hundred ppm 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 would 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 VC 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 VC, even within a kilometre of VC handling

plants, used to be (in or around 1975) of the order of 10 to 40 ppb (Environmental Protection Agency, 1975; Air Products and Chemicals Inc., 1976; Baxter et al., 1977) and this 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 VC other than a risk of angiosarcoma of the liver, as it has proved so difficult to detect any other risk in men who were exposed occupationally. The position with regard to angiosarcoma of the liver is different. This disease is normally so rare that, in the absence of specific exposure to one or other of the known causes (VC, thorium dioxide, and arsenic in pesticides and medicines), the annual incidence is of the order of $1-2 \times 10^{-7}$ (Byron and Helmsberg, 1975; Brady et al., 1977).^a In these circumstances the discovery of even one case in a man living close to a factory in which VC 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 see if any such cases have occurred. Saric et al. (1976) and Elinder and Pershagen (1978) sought for cases in the vicinity of plants handling VC in Yugoslavia and Sweden and found none. Balderup et al. (1976) found 8 confirmed cases in Holland 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. (1977) found 14 confirmed cases in Great Britain over a 12 year period, one of which was in a man who had lived half a kilometre from a PVC manufacturing plant, and Brady et al. (1977) found 19 cases in New York State over an 18 year period that could not be

^aThe figure of 1.4×10^{-8} cited by Heath et al. (1985) seems to have been a misprint for 1.4×10^{-7} .

attributed to any known cause, 5 of which were in people living within a mile of plants manufacturing or using VC. The overall incidence rates in these last two studies are not unduly high, but the occurrence of as many as 6 cases in people living so close to manufacturing plants is surprising. Brady and his colleagues, moreover, compared their series of patients with matched controls and found that none of the control subjects lived equally close to a plant. Two of these 6 neighbourhood cases (1 in England and 5 in New York State) cannot be attributed to environmental pollution with VC, as the men who developed the disease had lived near the plants for 6 and 8 years respectively before developing the disease and this is too short a time to allow for the necessary latent period. The other 4 cases, however, all occurred after 15 or more years local residence and the discovery of these cases strongly suggests that pollution of the environment round plants manufacturing VCM or PVC may have caused a minute hazard to the general public.

Current concentrations round VC handling plants are certainly much lower than those reported previously by the EPA. Recent British measurements made within a few hundred metres 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 (Turner, Payne, Bushby, 1984) though substantially higher values were recorded on two occasions associated with commissioning of one plant and an accident at the other. On any reasonable criterion the hazard to the general public (if there is any at all) must be negligible (Royal Society, 1983).

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

CONCLUSION

Occupational exposure to concentrations of VC of the order of 1,000 ppm has caused the classical 'vinyl chloride illness'. Exposure to such levels, or perhaps lower levels of the order of several hundred ppm, has caused angiosarcoma of the liver after a latent period that is seldom less than 15 years.

The evidence now available from following up many thousands of men occupationally exposed to vinyl chloride suggests that a small risk of lung cancer may also have been produced, which must, however, have been substantially less (in absolute terms) than the risk of angiosarcoma of the liver. The balance of evidence does not support the idea that VC has caused cancer in any other organ, but it is impossible to state categorically that it has not. Clearer evidence, one way or the other, could be obtained if the various investigators would present their results in comparable forms that would allow them to be combined and subjected to the standard tests for an occupational hazard.

There is no evidence that exposure to VC has caused any other disease.

Suggestive evidence has been obtained that past levels of environmental pollution with vinyl chloride may have caused a few cases of cancer in the general public.

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Table 1
 NUMBERS OF DEATHS FROM DIFFERENT CANCERS
 OBSERVED AND EXPECTED: FOUR STUDIES

Cause of death	USA	UK	Canada	Italy
	Obs*/Exp	Obs/Exp	Obs/Exp	Obs/Exp
Cancer of				
buccal cavity & pharynx	13/11.55	4/3.58	0/0.64	1/0.8
oesophagus	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 & gallbladder	39/5.77	-	-	-
pancreas	17/18.40	7/9.88	-	0/0.7
other digestive	-	-	6/5.26	-
larynx	-	4/2.21	2/5.78	1/0.9
lung	118/115.87	81/92.12		12/6.1
other respiratory	5/6.38	-	-	-
bone	2/1.81	-	-	-
skin (non-melanoma)	6/7.36	-	-	-
melanoma	-	2/1.74	-	0/0.2
prostate	16/15.20	12/9.59	-	1/0.7
testis	-	2/1.38	1/1.33	-
bladder	5/8.46	14/8.00		1/0.7
kidney	12/9.06	3/4.10	-	-
other & unspecified urinary	-	3/4.29	-	-
brain	25/12.76	4/6.18	0/0.60	-
eye & CNS	-	-		-
thyroid	-	2/0.43	-	-
lympho- & reticulosarcoma	12/7.98	4/2.35	-	-
Hodgkin's disease	3/5.45	3/2.50	1/1.67	0/0.4
leukaemia	14/13.94	7/5.16		0/0.7
multiple myeloma	)	2/2.35	-	-
other lymphatic		-	-	-
other cancers	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

*Observed deaths multiplied by 1.0674 and rounded off to nearest integer to allow for deaths without discovered cause.

Table 2
NUMBERS OF DEATHS FROM NON-MALIGNANT AND ALL CAUSES:
FOUR STUDIES

Cause of death	USA	UK	Canada	Italy
	Obs*/Exp	Obs/Exp	Obs/Exp	Obs/Exp
Benign & other unspecified tumours	4/5.08	-	-	0/0.5
Cerebrovascular disease	75/91.93	-	-	-
Ischaemic heart disease	521/597.73	276/288	25/31.67	19/27.4
Other circulatory disease	157/123.55	105/141		
Bronchitis**	44/22.83	36/44	6/3.21	3/5.0
Pneumonia	16/31.94	40/61		
Other respiratory disease	15/32.84	-	+4/3.85	4/5.2
Cirrhosis of liver	37/36.06	5/3		
Other digestive disease	27/39.52	-	++2/5.40	3/2.7
Disease of genito-urinary system	11/20.41	-		
Other diseases	67/115.68	43/76	2/10.58	2/7.0
Suicide	49/52.78	40/50		
Accidents & other violence	130/173.19	-	-	4/7.7
All non-malignant causes	1153/1363.54	545/665	39/54.76	36/56.4
All causes	1536/1705.27	780/894	39/71.07	66/77.5

* See footnote to Table 1

**Emphysema in US data

+ Includes 2 certified as cirrhosis of the liver which proved to be angiosarcoma of liver

++ Includes 1 cause unknown

Table 3
MORTALITY FROM CANCER OF THE LIVER AND OTHER CAUSES IN
VINYL CHLORIDE WORKERS IN 49 PLANTS IN 4 STUDIES

Cause of death	No. of deaths		Standardized mortality ratio (SMR)
	Observed	Expected	
Cancer of liver*	59	8.45	698
" of other sites	609	599.35	102
Other diseases	1547	1844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2441	2747.84	89

*Including cancers of the gallbladder in the US series

Table 4
MORTALITY FROM VARIOUS CANCERS IN VINYL CHLORIDE WORKERS
IN 49 PLANTS IN 4 STUDIES

Source of Information	Type of cancer	No. of deaths		SMR
		Observed	Expected	
1,2,3,4	Cancer of 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
1,2,4	" " lung	211	214.09	99
1,2,3,4	" " genito-urinary system	70	62.81	111
2,4	Melanoma	2	1.94	-
1,2,3	Cancer of brain	29	19.54	148
2	" " thyroid	2	0.43	-
1,2,3,4	" " lymphatic and haemato- poietic system	57	50.87	112
1,2,3,4	Other cancers	83	63.24	131
1,2,3,4	All cancers other than liver	609	599.35	102

- 1 US study
- 2 UK study
- 3 Canadian study
- 4 Italian study

Table 5

MORTALITY* FROM VARIOUS CANCERS IN VINYL CHLORIDE WORKERS: SUPPLEMENTARY EVIDENCE

Type of cancer	No. of deaths* in studies in:										SMR
	FPC (11 plants)		Norway ^a (1 plant)		Sweden (1 plant)		Italy (1 plant)		Four countries (14 plants)		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	
Cancer of digestive system (other than liver)	35.0	31.8	3 ⁺	1.44 ⁺	-	-	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	-
Cancer of brain	2.1	1.3	-	-	2	0.33	-	-	4.1	1.63	-
" " thyroid	-	-	2	0.16	-	-	-	-	2.0	0.16	-
" " lymphatic and haemato- poietic system	16.5	7.7	-	-	-	-	0	0.7	16.5	8.4	196
Other cancers (other than liver)	10.7	24.3	8	14.93	-	-	4	2.0	22.7	41.43	55
All cancers other than liver	87.8	89.7	22	20.16	5 ⁺⁺	2.11 ⁺⁺	5	5.7	119.8	117.67	102

* Incidence and cases in Norwegian study

⁺ Cancer of intestine only⁺⁺ Cancer of lung and brain only

Table 6
MORTALITY FROM LUNG CANCER IN THE US AND UK SERIES
BY CHARACTERISTICS RELEVANT TO AN OCCUPATIONAL HAZARD

Data characteristic	No. of deaths in category				SMR category	
	1		2		1	2
	Obs.	Exp.	Obs.	Exp.		
Observed 20 yrs or more after first employment (1), others (2)	114	113.96	85	93.83	100	91
Employed 10 yrs or more in USA (1), others in USA (2)	55	52.45	63	63.44	105	99
Employed before 1956 in UK (1), others in UK (2)	52	51.39	29	40.50	101	72
Ever employed as autoclave worker in UK (1), others in UK (2)	16	17.08	65	74.82	94	87

*See footnote to Table 1 for observed deaths in USA.

Table 7
MORTALITY FROM SELECTED NON-MALIGNANT CAUSES AND ALL CAUSES
IN FOUR PRINCIPAL STUDIES COMBINED

Source of Information	Type of cancer	No. of deaths		SMR
		Observed	Expected	
1,2	⁺ Bronchitis, emphysema	80	66.83	120
1,2	Other respiratory disease	71	125.78	56
1,2,3,4	All respiratory disease	160	200.82	80
1,2	Ischaemic heart disease	797	885.73	90
1,2	⁺⁺ Other circulatory	252	264.55	95
1,2,3,4	⁺⁺ All circulatory disease	1103	1209.35	91
1,2,4	Cirrhosis of liver	46	66.26	69
1,2,3,4	Other disease	238	368.07	65
1,2,3,4	All non-malignant disease	1547	1844.50	84
1,2,3,4	All external causes	226	295.15	77
1,2,3,4	All non-malignant causes	1773	2139.65	85
1,2,3,4	All causes	2441	2747.85	89

* 1 US study 2 UK study 3 Canadian study 4 Italian study

⁺ Bronchitis in UK study, emphysema in US study

⁺⁺ Includes cerebrovascular disease in UK and Italian studies

Table 8
MORTALITY FROM CHRONIC OBSTRUCTIVE LUNG DISEASE*
BY CHARACTERISTICS RELEVANT TO AN OCCUPATIONAL HAZARD

Data characteristic	No. of deaths in category				SMR category	
	1		2		1	2
	Obs.	Exp.	Obs.	Exp.		
Observed 20 yrs or more after first employment in USA (1), others in USA (2)	30	15.8	11	7.0	190	157
Employed 10 years or more in USA (1), others in USA (2)	16	10.9	25	12.0	147	208
Employed before 1956 in UK (1), others in UK (2)	26	30.17	10	13.60	86	74
+ Ever employed as autoclave worker in UK (1), others in UK (2)	3	6.55	33	37.22	46	89

*Described as emphysema in US study and bronchitis in UK study.

+ Men ever employed as a bagger or drier, which would have caused the greatest occupational exposure to PVC dust, experienced 1 death from 'bronchitis' against 4.98 expected.