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Bruce Whitney, Esq.
Air Products and Chemicals, Inc.
7201 Hamilton Boulevard
Allentown, PA 18195-1501

LAW DEPT.

Dear Bruce:

As discussed with you, Thorne and Andy today, I enclose a copy of the article on vinyl chloride epidemiology. As I told you, after many calls to government offices of NIOSH, CDC, etc., I was able to determine that this article by Sir Richard Doll published in 1988 is the last scientific journal article summarizing mortality and carcinogenic effects from exposure to vinyl chloride in the work place.

I have obtained a copy of a report to the US Department of Health and Human Services dated April 1993 on the Toxicological Profile for Vinyl Chloride which was prepared by Clement International Corp. This is the report I mentioned which says NIOSH continues to do epidemiology updates. That proves not to be true, according to those I was able to contact. However, this document may be of interest to you. It appears to contain a wealth of information that will be useful if the going gets heavy on this matter. So that you can decide, I include copies of the cover page, Contents, Forward, and the Table 2-5 which led me to believe NIOSH was still working on epidemiology. As you will see, the report is about 165 pages long. I'd be happy to send it to you to copy if you wish to do that. I'd like to get it back for my files if you do. Just let me know.

Best wishes,

Dick

Richard Fleming

RF/ta
Enclosures

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Effects of exposure to vinyl chloride

An assessment of the evidence

by Sir Richard Doll, FRS¹

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 summation 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 expo-

sure). 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 reports 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

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

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 So-
cial 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, ob-
served 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 em-
ployment for many years, two-thirds being employed
for 10 years or more and the average duration of em-
ployment being 16 years.

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

The numbers of deaths expected from each of 38
causes or groups of causes were obtained by multi-
plying 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 criti-
cisms, which are unlikely to have had any material
effects on the results. First, the lists of employees were
compiled by company personnel from company re-
cords without any independent check. Second, the as-
sumption 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 uncer-
tainty 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 as-
sumption 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 in-
dustrial 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 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 en-
vironmental and social factors unrelated to the occu-
pation 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 calcu-
lation of the overall mortality by the inclusion of deaths
due to unknown causes. It was not allowed for, how-
ever, 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 un-
published) 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 expo-
sure to VCM for at least 25 % of the work week and
who were first employed in the period 1940-1974. De-
tails of the men were compiled from the personnel
records of nine chemical plants manufacturing or poly-
merizing 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 Classifica-
tion 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

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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 nonmalign-
nant 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 obser-
vation 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 un-
likely to have been large.

Italian study. A study of all men employed in the pro-
duction 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 Ro-
signana) 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 esti-
mated 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 fol-
lowed 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 prin-
cipal analyses. It may be noted, however, that one
death was attributed to liver cancer when 0.1 was ex-
pected.

Other sources. The Norwegian study (22) provided ob-
servations 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 em-
ployed 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 Cen-
tral Bureau of Statistics and the national cancer regis-
try. 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 justi-
fied 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 an-
giosarcoma 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 can-
cers, 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 em-
ployed before 1954 and were therefore capable of con-
tributing person-years at risk more than 20 years after
first employment, when an occupational hazard of can-
cer 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

VCM and PVC, and employees. Byren et al (7) studied when exposed from the persons were excluded from the country after gaining 750 were members of deaths on-years at risk mortality rates for numbers of cancer (during which period nationally) the national age in instances, the 1969. Fifty-eight given for the exposed only for and expected of the liver and members of deaths of cardiovascular angiosarcoma of liver cancer died of after the close

sults of a long-term plant (41) and died in 12 plants that provided obituary notices in selected newspapers. The Tavaux plant had no employees because of lack of occupation because their vital status was undetermined. It was compared against 48.75 and age-specific rates (at risk). One of the liver, in more than 15 years, and cover such things as the plant's value to the men in the addition

ations on 1 100, were exposed in 12 plants, in VCM polymerization (published). Many died at Tavaux. The cohort studied followed for five years. Mortality were common 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 25 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 chlo-

ride 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 deaths² 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*	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	5.25	.	.
Larynx	.	.	4	2.21	.	.	1	0.9
Lung	118	115.87	81	92.12	2	5.78	12	5.1
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	0.7
Kidney	12	3.06	3	4.10	1	1.33	.	.
Other and unspecified urinary	.	.	3	4.29	.	.	.	.
Brain	25	12.76	4	6.18	.	.	.	.
Eye and central nervous system	.	.	.	.	0	0.60	.	.
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

* 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*	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	31.57	19	27.4
Other circulatory disease	157	123.55	105	141	.	.	.	.
Bronchitis ^a	44	22.83	36	44	.	.	.	.
Pneumonia	16	31.94	.	.	6	3.21	3	5.0
Other respiratory disease	15	32.84	40	61	.	.	.	.
Cirrhosis of the liver	37	56.06	5	5	.	.	4	5.2
Other digestive disease	27	39.52	.	.	4 ^c	3.85	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	.	.	.	.	1	0.9
Accidents and other violence	130	173.19	40	50	2	10.58	4	7.7
All nonmalignant causes	1 153	1 363.54	545	565	39	54.76	36	56.4
All causes	1 536	1 705.27	780	894	59	71.07	66	77.5

* See footnote to table 1.

^a Emphysema in data from the United States.

^b Includes two cases certified as cirrhosis of the liver which proved to be angiosarcoma of the liver.

^c 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 at-

tributed to cancer of the liver (for a total of four), but only one of the four was described as an angiosarcoma (4).

studies (4, 14, 25,

Italy	
O	E
1	0.8
1	0.6
3	3.0
0	1.2
1	0.6
0	0.7
1	0.9
12	6.1
0	0.2
1	0.7
1	0.7
0	0.4
0	0.7
9	4.5
30	21.1

discovered cause.

18). (O = observed

Italy	
O	E
0	0.5
19	27.4
3	5.0
4	5.2
3	2.7
2	7.0
1	0.9
4	7.7
36	56.4
66	77.5

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1 angiosarcoma

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	1547	1844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2441	2747.84	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 = expected 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	1	2, 4
Brain	29	19.54	148	1, 2, 3
Thyroid	2	0.43	2	2
Lymphatic and hematopoietic system	57	50.87	112	1, 2, 3, 4
Other	53	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 ^c	.	.	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	0.15	.	.	.	.	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 Angio-

sarcoma 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*	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	53	53.44	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

* 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 plants³ 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

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.

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

⁴ If the study of Waxweiler et al (50) is regarded as the origin of the hypothesis, 25 deaths are left against 18.94 expected (P one-tailed = 0.07).

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Melanoma. An excess of melanoma was reported for Norwegian workers by Heldaas et al (22), who raised

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	90	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

* 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 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 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

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be expected to be concentrated. The authors of the En-
vironmental 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,² 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 arterio-
sclerotic) heart disease (which may be presumed to in-
clude 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 dis-
ease 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 in-
creased mortality within one month of leaving em-
ployment in the UK study either for all workers (52
deaths, SMR 61) or for the most heavily exposed auto-
clave workers (9 deaths, SMR 42).

A slight increase in ischemic heart disease mortal-
ity was recorded for the exposed workers in the Ger-
man study (49), but it was less than that recorded for

² The deaths attributed to different groups of respiratory dis-
eases and the corresponding SMR values that are cited in
this section for the US study are as given by the Environ-
mental 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.

the unexposed chemical workers and the PVC fabri-
cators (SMR values of 127, 131, and 158 based on 97.2,
125.7, 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 pro-
tection 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 dis-
ease, and the number of cases is reflected in the num-
ber of deaths. Some 50 deaths have occurred among
the 16 740 men who were followed in the four prin-
cipal 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 de-
velop 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 mor-
tality 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 dif-
ficult 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 abso-
lutely almost as large as the risk of developing the nor-
mally 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 diges-
tive 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 avail-
able studies have provided information about them.
There is no good theoretical reason or laboratory evi-
dence to suggest that either should be produced by

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 in-

cidence 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-tenthousandth 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-

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giosarcoma of the liver is different. This disease is nor-
 mally 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 chlo-
 ride 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 thiorast or arsenic and could trace "no contact
 with vinyl chloride," but they made no specific men-
 tion 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 at-
 tributed to any known cause, five of which were in peo-
 ple 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 occur-
 rence 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 pa-
 tients 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 devel-
 oped 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 dis-
 covery of these cases strongly suggests that pollution
 of the environment around plants manufacturing VCM
 or PVC may have caused a minute hazard to the gen-
 eral 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 aver-
 age 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 asso-
 ciated with putting one plant into operation and with

⁶ The figure of $1.4 \cdot 10^{-4}$ cited by Heath et al (21) seems to
 have been a misprint for $1.4 \cdot 10^{-7}$.

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.

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 ex-
 posed when the industry was first developed — uncon-
 sciousness, cardiac arrhythmia, and the characteristic
 "vinyl chloride illness") and (ii) the carcinogenic
 effects that might conceivably be observed in the gen-
 eral population as a result of the widespread distribu-
 tion 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 exam-
 ined, as the little evidence that has been adduced
 relating to such possible effects has been reviewed else-
 where and the conclusion was reached that no such ef-
 fects 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 occu-
 pational 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 evi-
 dence, 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 sup-
 plementary 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 hy-
 potheses.

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 excep-

tion 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-

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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 data 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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**TOXICOLOGICAL PROFILE FOR
VINYL CHLORIDE**

Prepared by:

Clement International Corporation
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Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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CONTENTS

FOREWORD	v
CONTRIBUTORS	vii
LIST OF FIGURES	xiii
LIST OF TABLES	xv
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT IS VINYL CHLORIDE?	1
1.2 WHAT HAPPENS TO VINYL CHLORIDE WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO VINYL CHLORIDE?	2
1.4 HOW CAN VINYL CHLORIDE ENTER AND LEAVE MY BODY?	3
1.5 HOW CAN VINYL CHLORIDE AFFECT MY HEALTH?	3
1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO VINYL CHLORIDE?	4
1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	5
1.8 WHERE CAN I GET MORE INFORMATION?	6
2. HEALTH EFFECTS	7
2.1 INTRODUCTION	7
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	7
2.2.1 Inhalation Exposure	8
2.2.1.1 Death	8
2.2.1.2 Systemic Effects	8
2.2.1.3 Immunological Effects	26
2.2.1.4 Neurological Effects	27
2.2.1.5 Developmental Effects	28
2.2.1.6 Reproductive Effects	31
2.2.1.7 Genotoxic Effects	32
2.2.1.8 Cancer	33
2.2.2 Oral Exposure	36
2.2.2.1 Death	36
2.2.2.2 Systemic Effects	37
2.2.2.3 Immunological Effects	37
2.2.2.4 Neurological Effects	37
2.2.2.5 Developmental Effects	37
2.2.2.6 Reproductive Effects	37
2.2.2.7 Genotoxic Effects	37
2.2.2.8 Cancer	37
2.2.3 Dermal Exposure	41
2.2.3.1 Death	41
2.2.3.2 Systemic Effects	42
2.2.3.3 Immunological Effects	42
2.2.3.4 Neurological Effects	42
2.2.3.5 Developmental Effects	42

2.2.3.6	Reproductive Effects	42
2.2.3.7	Genotoxic Effects	42
2.2.3.8	Cancer	42
2.3	TOXICOKINETICS	42
2.3.1	Absorption	42
2.3.1.1	Inhalation Exposure	42
2.3.1.2	Oral Exposure	43
2.3.1.3	Dermal Exposure	43
2.3.2	Distribution	43
2.3.2.1	Inhalation Exposure	43
2.3.2.2	Oral Exposure	44
2.3.2.3	Dermal Exposure	44
2.3.3	Metabolism	44
2.3.3.1	Inhalation Exposure	44
2.3.3.2	Oral Exposure	47
2.3.3.3	Dermal Exposure	47
2.3.4	Excretion	47
2.3.4.1	Inhalation Exposure	47
2.3.4.2	Oral Exposure	48
2.3.4.3	Dermal Exposure	49
2.3.4.4	Other Routes of Exposure	49
2.4	RELEVANCE TO PUBLIC HEALTH	49
2.5	BIOMARKERS OF EXPOSURE AND EFFECT	59
2.5.1	Biomarkers Used to Identify or Quantify Exposure to Vinyl Chloride	60
2.5.2	Biomarkers Used to Characterize Effects Caused by Vinyl Chloride	61
2.6	INTERACTIONS WITH OTHER CHEMICALS	62
2.7	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	64
2.8	METHODS FOR REDUCING TOXIC EFFECTS	65
2.8.1	Reducing Peak Absorption Following Exposure	65
2.8.2	Reducing Body Burden	65
2.8.3	Interfering with the Mechanism of Action for Toxic Effects	66
2.9	ADEQUACY OF THE DATABASE	68
2.9.1	Existing Information on Health Effects of Vinyl Chloride	68
2.9.2	Identification of Data Needs	68
2.9.3	On-going Studies	76
3.	CHEMICAL AND PHYSICAL INFORMATION	79
3.1	CHEMICAL IDENTITY	79
3.2	PHYSICAL AND CHEMICAL PROPERTIES	79
4.	PRODUCTION, IMPORT, USE, AND DISPOSAL	83
4.1	PRODUCTION	83
4.2	IMPORT/EXPORT	83
4.3	USE	83
4.4	DISPOSAL	86
5.	POTENTIAL FOR HUMAN EXPOSURE	87
5.1	OVERVIEW	87
5.2	RELEASES TO THE ENVIRONMENT	87
5.2.1	Air	87
5.2.2	Water	89
5.2.3	Soil	89

5.3	ENVIRONMENTAL FATE	89
5.3.1	Transport and Partitioning	89
5.3.2	Transformation and Degradation	93
5.3.2.1	Air	93
5.3.2.2	Water	93
5.3.2.3	Soil	94
5.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	94
5.4.1	Air	94
5.4.2	Water	95
5.4.3	Soil	95
5.4.4	Other Environmental Media	95
5.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	96
5.6	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	96
5.7	ADEQUACY OF THE DATABASE	97
5.7.1	Identification of Data Needs	97
5.7.2	On-going Studies	98
6.	ANALYTICAL METHODS	101
6.1	BIOLOGICAL MATERIALS	101
6.2	ENVIRONMENTAL SAMPLES	104
6.3	ADEQUACY OF THE DATABASE	109
6.3.1	Identification of Data Needs	109
6.3.2	On-going Studies	110
7.	REGULATIONS AND ADVISORIES	111
8.	REFERENCES	119
9.	GLOSSARY	155
APPENDICES		
A.	USER'S GUIDE	A-1
B.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS	B-1
C.	PEER REVIEW	C-1

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

- (A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

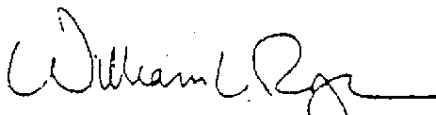
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

2. HEALTH EFFECTS

TABLE 2-5. On-going Studies on Vinyl Chloride*

Investigator	Affiliation	Research description	Sponsor
<i>David</i> D. Brown <i>ATSDR Atlanta</i>	NIOSH, Cincinnati, Ohio	Updating epidemiologic studies on vinyl chloride	NIOSH
M. Humayun	University of Medicine and Dentistry of New Jersey	Mechanisms of mutagenesis by cyclic DNA adducts in rabbits	NCI
H. Jiang	University of Maryland	Effects of vinyl chloride on pregnancy, parturition and fetal development among female workers	NA
B. Singer	University of California, Lawrence Berkeley Lab	Biochemical mechanisms of vinyl chloride carcinogenesis	NCI
J. Taylor	NIEHS	Molecular epidemiology of cancer susceptibility and oncogene activation	NIEHS
R. Thurman	University of North Carolina at Chapel Hill	Mechanisms of hepatotoxicity by environmental pollutants	NIEHS

*Sources: FEDRIP (1990); SCISearch (1990)

DNA = deoxyribonucleic acid; NA = not available; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Science; NIOSH = National Institute for Occupational Safety and Health

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Bruce Whitney

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Bruce-

Here is the article on epidemiology that appeared in the Well St. Journal on Jan 3, that I mentioned during our dinner that evening. It gives an interesting view of the accuracy, and the utility, of epidemiologic data. This may have some relevance as the arguments for the vinyl chloride case develop. Please give copies to Thomas and Andy.

PAGE 1 of 2

Best wishes

Dick

Cancer Risks for 'Thee, but Not for Me

WSS 1/3/75

Mr. Taylor is director of natural resource studies at the Cato Institute in Washington.

Well, Dr. Fama, the future is now.

Should it be an attractive prospect into behaving the way they think we

denise, will be in a position to blackmail us

activists, using dubious scientific ev-

"we could reach a situation where health

Sunday Telegraph a few years back that

James Le Fanu warned in London's

ally reduces the risk of lung cancer.

being exposed to secondhand smoke actu-

fact, showed negative correlations—that

from the above example. Some studies, in

and seldom did risk ratios differ much

hand smoke included 40 or fewer subjects

of the epidemiological studies on second-

nothing. Now consider that more than half

shows up on top of the nickel 197 more of

between heads and tails. If Jefferson

likely that the results will be evenly split

ness. If one flips a coin 50 times, it's im-

(for epidemiologists) of sheer random-

And then there is the messy problem

live children.

in Germany; the other, the number of

represents the number of mating storks

sets of data must be related. Yet one time

The students invariably say yes, the two

The two lines almost completely match.

representing data from 1950 to the present

his students a graph with two lines rep-

California at Berkeley is fond of showing

chemist Bruce Ames of the University of

relation three times more significant than

that of secondhand smoke. Similarly, but

increase in the risk of lung cancer, a cor-

ing birds correlates with a sevenfold in-

published in London that found that keep-

istics. Consider an epidemiological study

sation, no matter how impressive the sta-

Correlation simply does not equal cau-

we may be studying a confounder.

gory of a causative factor when in reality

mental error by placing ETS in the cate-

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