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THE MUTAGENICITY AND CARCINOGENICITY OF VINYL CHLORIDE : A HISTORICAL REVIEW AND ASSESSMENT

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5.1 Effects on the Central Nervous System (CNS) (roughly from 1930)

During the early period of the industrial development and use of VC and PVC, the effects of VC on the CNS, at what would now be considered to be very high concentrations, were recognised in experimental animals and man (Patty, 1930). The symptoms include euphoria, headaches, dizziness and loss of consciousness which are manifested in man at concentrations of several thousand ppm. See, for example, Mastromatteo et al (1960), Cordier et al (1966), Berod et al (1972), Lange et al (1974), Moulin et al (1974), Lilis et al (1975), Truhaut et al (1975), Walker (1976) and Delorme et al (1978).

5.2 "Vinyl Chloride Disease" (roughly from 1957)

In the 1950s a variety of other effects became recognised as resulting from chronic exposure to VC at concentrations of (probably) several hundred ppm. Some of them were first described by Filatova (1957) and were later collectively called "vinyl chloride disease". The effects included a sclerotic condition of the connective tissue of the fingers accompanied by a thickening of the dermis, and from fibrosis of the liver tissue and spleen. Another effect is acro-osteolysis, a rare bone-disease resulting in de-calcification of the terminal phalanges of the hand and affecting largely the "autoclave scrapers" (Cordier et al, 1966). Less commonly, osteolytic lesions are observed at other sites in the skeleton.

Acro-osteolysis is frequently preceded by a Raynaud-type phenomenon in which there is a reversible constriction of the arterioles of the fingers leading to numbness, pallor, and cyanosis of the fingers.

5.3 Carcinogenicity (1970 and onwards)

While attempting to reproduce acro-osteolysis in rats exposed to VC by inhalation, Viola (1970) and Viola et al (1971) found an increased incidence of tumours of the skin, lungs and bones. A few years later Maltoni et al (1974) confirmed this, and identified in addition an increased incidence of angiosarcoma of the liver. A most significant finding was also made in the same year when Creech and Johnson (1974) reported that a search of the medical files at a Goodrich plant in the USA had revealed three cases of death from angiosarcoma of the liver (a very rare form of cancer) among the deceased workers. It was recognised that the cause was likely to be inhalation at high levels (probably a few hundred ppm) of VC over long periods.

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This finding, in combination with results from experimental studies, initiated an urgent and radical worldwide revision of measures for protecting the health of groups of people exposed to VC, and simultaneously led to extensive epidemiological and animal studies which are described in the following chapters.

6. EVOLUTION OF OCCUPATIONAL EXPOSURE LIMITS

In parallel with the discovery of the toxic properties of VC, the development of technology to lower the concentration in occupational atmospheres, and improved analytical capability, the various recommended exposure limits were lowered, as summarised in Table 1.

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C. EFFECTS ON HUMAN HEALTH

1. CARCINOGENICITY

This section surveys epidemiological studies of cancer incidence and cancer mortality, in occupationally exposed workers. Certain terms used in reports are not clearly defined or consistent between publications. The following definitions are used in this report and, where necessary for clarity, the terms used by the author have been replaced by the following :

a) Exposure period : the period during which workers were occupationally exposed when employed in a VC or PVC plant.
b) Follow-up period : the period over which the expected morbidity or mortality rate is calculated. It is expressed in person-years.
c) Latency period: the period from the beginning of exposure until the disease becomes apparent or death from the disease occurs.
d) Observation period : the period from the beginning of exposure of an individual to the final date of his follow-up.
e) Study period : the period from the beginning of exposure of the first workers exposed in the cohort to the final date of the study.

1.1 Cohort Studies of Cancer Morbidity and Mortality in VC/PVC Production Plants

Creech and Johnson (1974) first recognised the relationship between exposure to VC and an excess incidence of angiosarcoma of the liver (ASL) in a PVC-production plant at Louisville, Kentucky. Following this, several cohort studies on workers exposed to VC were initiated worldwide. In most studies insufficient attention was paid to the collection of information, the level and duration of exposure, whilst the observation period was insufficient to allow for detection of cancers with a long latency period, especially for other organs than the liver. Each study was examined and judged on the information provided in these areas and on the evidence of a relationship between VC-exposure and cancer mortality. To be objective and if sufficient data are available the observed Standardised Mortality Ratios (SMR's) in different dose groups were tested for homogeneity and trend by the method of Breslow et al (1983).

1.1.1 USA

a) Ott et al (1975) studied a population of PVC-production employees who worked between 1942 and 1960 in areas of potential exposure to VC. Nearly all those who had worked for at least 1 year, and about half of those who had worked for less than 1 year, were traced. A group of 594 people were identified, of whom 72 were omitted because they had also been exposed to arsenic compounds. The mortality of the remaining 522 was studied in relation to their exposure to VC. The 8-hr TWA exposures were :

from 1950-1959, almost certainly below 500 ppm (peak exposures, 4000 ppm);
from 1960-1966, below 250 ppm (peak exposures, 500 ppm);
from 1960 onwards, less than 50 ppm.

The 522 workers were divided into 4 groups with average exposures for at least 1 month to :

- more than 200 ppm (high group);
- 25-200 ppm (intermediate group);
- less than 25 ppm (low group);
- unmeasurable (low group).

There was a total of 286 in the two low groups, of whom 166 had been exposed to VC for less than 1 year. The total number of years of exposure was not given by Ott et al, but is estimated to be 4,000 from Table 8 in their publication. The start and end of the observation and follow-up periods were not stated but were probably 1942 (start) and 1973 (end) for both. The number of person-years of follow-up was not presented by Ott et al but is estimated to be 13,000 based on the expected mortality.

Of the 522 workers exposed to VC the mortality figures were :

Cause of death	Observed	Expected	Statistical Significance (P) ≠
All causes	79	89.1	n.s.
All cancer	13	16.0	n.s.
Respiratory cancer	4	5.2	n.s.
Cancer of digestive organs and peritoneum	5	4.7	n.s.
Cancer of all other sites	4	6.1	n.s.

No liver angiosarcoma were found.

This cohort was also stratified on intensity and duration of exposure and on observation period. Four exposure categories were distinguished on TWA-8 hour levels :

- High level exposure (> 200 ppm)
- Intermediate exposure (>25, <200 ppm)
- Low exposure (< 25 ppm)
- Unmeasured exposure.

The cancer mortality data of these sub-groups are summarised below.

All cancer deaths
stratified on level of exposure

	Observed	Expected	Statistical Significance (P)
High exposure group	9	5.1	n.s.
Remaining groups	4	10.9	0.05

The observed cancer mortality in the remaining exposure groups was significantly lower than expected.

All cancer deaths
high exposure group with observation period > 15 years

	Observed	Expected	Statistical Significance (P)
Exposure duration < 1 year	3	1.3	n.s.
Exposure duration > 1 year	5	1.9	0.05
Total	8	3.2	0.05

≠ Throughout Section C statistical significance testing is based on a one-tailed poisson distribution on the observed number of deaths. A P-value <0.05 is considered as not significant (n.s.).

From the table above a clear influence of the duration of exposure on the observed/expected ratio (2.3 versus 2.6) in the high exposure group is not apparent, but might perhaps not be expected, as the numbers involved are small.

b) Nicholson et al (1975, 1984) carried out a mortality follow-up study of workers in the USA with at least 5 years of exposure to VC in PVC plants. The follow-up period started 10 years after the onset of exposure so that the focus could be on long-term effects. Three cohorts were studied :

i) 256 workers in a plant at Niagara Falls, with a follow-up period from Jan. 1956 to Dec. 1981;
ii) 40 workers at the same plant, with a follow-up period from April 1974 to Dec. 1981;
iii) 195 workers in a plant at South Charleston, with a follow-up period from Dec. 1966 to Dec. 1980.

The three cohorts were combined to one. The total number of person years of follow-up was 7062. The mortality data are presented below :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	80	85.6	n.s.
All cancer	28	19.7	0.05
Lung cancer	4	7.3	n.s.
Brain cancer	1	0.76	n.s.
Lymphoma	3	1.14	n.s.
Liver cancer	10	0.42	0.001

Nine of the ten liver cancer deaths were caused by liver angiosarcomas.

The fact, that the follow-up period in the Nicholson study started 10 years after the onset of exposure must be taken into account when comparing with other studies in which the start of the observation and follow-up periods were much closer. At least 4910 person-years have to be added, to give a total of 11,972 years of observation. The average number of years of observation per worker was 24.3 years, a period long enough to allow for detection of cancers with a long latency period.

At the Niagara Falls plant no detailed data on exposure levels were available before 1972, measurements prior to this being made solely to ensure that the explosive limit of VC in air (greater than 30,000 ppm) was not exceeded in plant operations. Nicholson et al (1975) reported that over 50% of the workers examined had experienced symptoms of dizziness, headache or euphoria during work periods, and 14 had suffered loss of consciousness, suggesting that peak exposures may have exceeded 10,000 ppm.

c) Waxweiler et al (1976) studied a population from 4 PVC plants in the USA which had been operating for more than 15 years and had a sizeable workforce. Only people with at least 5 years exposure to VC, and at least 10 years employment before 31 Dec. 1973, were included in the cohort which comprised 1294 workers of which only 7 were lost to follow-up. The follow-up period (not to be confused with the observation period of at least 10 years) represented 12,720 person-years. Of the cohort of 1294 workers the mortality data are presented below :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	136	126.3	n.s.
All cancer	35	23.5	0.05
Brain cancer	3	0.9	n.s.
Respiratory cancer	12	7.7	n.s.
Lymphatic and haematopoietic system cancer	4	2.5	n.s.
Biliary and liver cancer	7	0.6	0.001

When the cancer mortality of workers with more than 15 years of observation was considered, the statistical significance of the above findings was increased as shown below :

Cancer by site	Observed	Expected	Statistical Significance (P)
All cancer	31	16.9	0.001
Brain cancer	3	0.6	0.05
Respiratory cancer	11	5.7	0.05
Lymphatic and haematopoietic system cancer	3	1.7	n.s.
Biliary and liver cancer	7	0.4	0.001

The statistical significance of the increase of cancer mortality grows with increasing observation period except for cancer of the lymphatic and haematopoietic tissues.

d) Buffler et al (1979) conducted a cohort mortality study of 464 white males employed in a VC production plant in the USA since 1948. The cohort comprised employees who had worked in the VC department for at least 2 consecutive months between 1 Aug. 1948 and 25 Sept. 1975. All of the members of the cohort were traced for follow-up, and the follow-up period represented 5313 person-years. Expected number of deaths for the study population were calculated by applying 1950-59 and 1960-69 age-cause specific death rates for white males in Texas to the observed distribution of person years of observation, categorised into five age groups. The mortality data are summarised below :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	28	31.6	n.s.
All cancer	8	5.19	n.s.
Respiratory cancer	5	1.73	0.05

Four of the 5 who died from respiratory cancer had a history of smoking, but this information was not available for a large proportion (27.6%) of the cohort of 464 workers.

In a subgroup of 314 workers with a minimum observation period of 5 years the mortality data were :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	22	25.18	n.s.
All cancer	6	4.34	n.s.
Respiratory cancer	4	1.49	n.s.

This subgroup was further stratified on level and duration of exposure and on a so-called overall exposure index, based on level and duration together. The mortality data are summarised below for respiratory cancer. A high or low level was not precisely defined.

Subgroups	Respiratory Cancer		
	Observed	Expected	Statistical Significance (P)
Low level exposure	1	0.82	n.s.
High level exposure	3	0.68	0.05
Exposure duration <2.29 year	0	0.45	n.s.
Exposure duration >2.29 year	4	1.05	0.05
Low exposure index	1	0.56	n.s.
High exposure index	3	0.94	n.s.

Both a longer duration and a higher level of exposure during the first five years of observation were associated with a statistical significant excess of respiratory cancer. However, when duration and level of exposure were combined in an overall exposure index the results were not significant.

The authors conclude, that in view of the absence of a significant dose-response relationship, the observed excess in respiratory cancer deaths may not be attributable to exposure to vinyl chloride. However, the fact that excesses were seen in the group with the longer duration of exposure in the initial five years suggests that a relationship may exist.

e) EEH (1978). Equitable Environmental Health Inc. carried out a cohort mortality study for the US Manufacturing Chemists Association on workers employed for at least 1 year, between 1936 and 1972, in 37 VC/PVC production plants in the USA. The cohort included those from the other US studies described in a) - d), above. Of the 10,173 workers, 9,677 (95.1%) were traced for follow-up; 2008 had had 15 or more years exposure, and 1001 more than 20 years. The follow-up period ended on December 31, 1972, and was equivalent to 120,203 person-years. The mortality figures were :

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Cause of death	Observed	Expected	Statistical Significance (P)
All causes	707	795	0.001
All cancer	139	141.4	n.s.
Cancer of the buccal cavity and pharynx	5	5.2	n.s.
Cancer of digestive organs and peritoneum	29	40.8	0.05
Liver angiosarcoma (ASL)	5	0.01	0.001
Liver cancer (including ASL)	10	1.7	0.001
Respiratory cancer	45	44.3	n.s.
Cancer of the genital organs	4	7.2	n.s.
Cancer of the urinary organs	8	6.9	n.s.
Leukaemia and lymphoma	20	17.0	n.s.
Miscellaneous cancers (I.C.D. 190-199 incl. brain)	28	20.2	n.s.
Brain cancer	12	5.9	0.05

The high incidence of liver cancer and liver angiosarcoma reported from the earlier investigations was confirmed.

The authors concluded that their results gave some support to the hypothesis that exposure to VC slightly increases the mortality due to cancer at sites other than the liver. Thus, the incidence of respiratory cancer and those of ICD classification 190-199 (miscellaneous cancers) appeared to be higher in individuals with higher level of exposure or longer periods of exposure. The miscellaneous tumours included 12 brain tumours versus 5.9 expected. The mortality of these was not related to either intensity or duration of exposure. The mortality from respiratory cancer was not significantly related to the total integrated exposure dose.

In addition, the Task Force examined the SMR's for respiratory cancer and leukaemia and lymphoma for homogenicity and trend (by Breslow et al,1983)in subgroups with different levels of exposure or with different integrated doses of exposure. No significant deviations from homogenicity nor any significant trends were found.

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Environmental Health Associates (EHA) (1986) updated this study. Loss of worker identification numbers and non-participation of some plants reduced the cohort to 9,200 workers and of these 725 (7.88%) were not traced. Of the 1,536 deaths, 97 death certificates (6.3% of all deaths) were not available. These deaths were included in the "all death" figure, but not in cause specific death number.

The follow-up period of the update was from January 1, 1973 to December 31, 1982 and contained about 80,000 person years. With the EEH period of follow up (120,203 years) the total follow-up was about 200,000 years; this is not mentioned in the update. The average period of follow-up per worker was thus about 20 years; the average period of employment per worker was reported to be 16 years.

The mortality figures were as follows.

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	1536	1705.3	0.001
All cancer	359	341.7	n.s.
Cancer of buccal cavity and pharynx	12	11.6	n.s.
Cancer of digestive organs	99	89.2	n.s.
Liver angiosarcoma (ASL)	15	0.02	0.001
Liver cancer excluding ASL	15	3.1	0.001
Biliary tract cancer	7	2.7	0.05
Respiratory cancer	115	122.3	n.s.
Bone cancer	2	1.8	n.s.
Skin cancer	6	7.4	n.s.
Prostate cancer	5	15.2	n.s.
Bladder cancer	5	8.5	n.s.
Kidney cancer	11	9.1	n.s.
Brain and CNS cancer	23	12.8	0.01
Lymphatic and haematopoietic system cancer	37	36.3	n.s.
Emphysema	41	22.8	0.001

In addition to the effects upon the liver the mortality increase from biliary tract cancer was significant. This is the first report that biliary tract cancer appeared to be related to VC-exposure. No increase of respiratory cancer or of cancer of the lymphatic and haematopoietic tissues was found. The power of the updated study had an 80% chance of detecting a relative risk of 1.24 for respiratory cancer and of 1.45 for cancer of the lymphatic or haematopoietic tissues at the 5% level of significance.

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In the update, no evaluation of the historical exposure level was made, because the authors considered it subjective and not reliable because of lack of enough personal monitoring data.

The cohort was stratified on :

- length of exposure;
- time between start and end of follow-up;
- age of first exposure;
- year of first exposure;
- type of plant (VCM,PVC).

The authors found the SMR's in the various strata to be significantly different from 1 at the 5% level and evaluated the trend from visual inspection of the data.

The SMR for liver cancers increased with increasing duration of exposure, with increasing period of follow-up and with decreasing age and calendar year of first exposure. Only two plants (VC polymerisation), involving 3,533 employees, contributed 14 ASL-cases to a total of 15. The authors felt this might indicate that exposure at these plants was different from that in others.

The SMR for brain cancer was significantly increased only in workers with more than 20 exposure years (6 versus 1.55 expected). However, brain cancer was not related to time of follow-up and the incidence increased with increasing age and year of first exposure, the reverse of what is seen for liver cancer. What this means in terms of human risk remains unclear, according to the authors. Twelve brain cancer deaths came from the same two plants as the 14 ASL-cases.

The SMR for emphysema increased with decreasing length of exposure and with increasing age at first exposure, but did not change in relation to time of follow-up or to calendar year of first exposure. The SMR was higher in PVC-plants than VC-plants.

The overall conclusion of the authors was that the study confirmed that VC workers experienced significant mortality excess from angiosarcomas, cancer of the liver and biliary tracts and cancer of the brain and other central nervous system. The study also showed a significant higher mortality from emphysema but no excess of respiratory or lymphatic or haematopoetic cancer.

This Task Force tested the SMR's for the various strata by the Breslow et al (1983) method. Only liver cancers showed significant trend ($P<0.01$) with length of exposure, time between start and end of follow-up and age at first exposure. No other significant trend was found.

1.1.2 United Kingdom

a) Duck et al (1975) conducted a cohort mortality study on 2,100 workers who had had any exposure to VC between 1948 and 1975 while employed in VC or PVC plants. Only 7 could not be traced for follow-up and the follow-up period comprised 23,052 person-years. Of this cohort, 136 had died (expected, 142.2) and the number of deaths from cancer was 35 (36.4 expected). No case of ASL was found during the study period but 1 occurred just outside it. There was no increase in mortality from the common malignant diseases.

The observation and follow-up period (about 11 years) were too short to draw any conclusions about target organs for cancer in relation to VC-exposure.

b) Fox and Collier (1977) studied the mortality of workers exposed to VC at PVC plants. There was no criterion of exposure for admittance to the cohort. Of the 7561 persons identified as having started work between 1944 and 1974, 85 could not be traced for follow-up and information was lacking for a further 72. The cohort of Duck et al (1975) was included. The number of person-years of follow-up was 75,000. Only 8% of the workers had been employed for more than 20 years.

Analysis of the levels and duration of exposure revealed that of the 7,409 workers included in the follow-up, 385 were constantly, and 486 occasionally, exposed to high and medium levels of VC for more than 10 years (high level TWA >200 ppm, medium level TWA > 25 < 200 ppm). The mortality figures were as follows :

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Cause of death	Observed	Expected	Statistical Significance (P)
All causes	393	521.2	0.001
All cancer	115	126.8	n.s.
Stomach cancer	14	15.3	n.s.
Liver cancer	4	1.64	n.s.
Lung cancer	46	57.2	n.s.
Brain cancer	2	3.66	n.s.
Lymphatic and haematopoietic cancer	9	9.01	n.s.

Two of the 4 liver cancer deaths were due to liver angiosarcoma. There was no indication of excess mortality from other types of cancer. This is not surprising since the average period of follow-up was about 10 years.

This study has been updated by Jones et al (in press) to provide a further 10 years of follow-up. A criterion of 1 year of employment between 1940 and 1974 in a job or jobs with potential exposure to VCM for at least 25% of the working week was introduced, and this had the effect of reducing the male population to 5500, of whom 5498 (98.9%) were traced. As only 105 female employees qualified for inclusion, analysis was restricted to the male employees. The study period has been extended to the end of 1984, follow-up is started one year after commencing employment, and the total number of person-years is 104,000. Expected figures were calculated from male mortality rates for England and Wales. The mortality figures are summarised below :

Cause of Death	Observed	Expected	Statistical Significance (P)
All causes	780	894	0.001
All cancer	235	228.6	n.s.
Stomach cancer	26	23.9	n.s.
Liver cancer (including ASL)	11	1.94	0.001
Liver angiosarcoma	7	0.1	0.001
Respiratory cancer	81	92.1	n.s.
Brain cancer	4	6.2	n.s.
Lymphatic and haematopoietic cancer	16	12.4	n.s.
Skin melanoma	2	1.7	n.s.

As part of this update, each employee's work history was classified into job titles, and these job titles were further categorised into 4 groups, autoclave workers, baggers and driers, craftsmen, and other workers. All 7 cases were autoclave workers (6 from one plant), and the mean latency was 25 years. The

data were analysed by occupation for lung cancer, brain cancer, lymphatic cancer, malignant melanoma and cancer of the thyroid. No evidence was found of any increase in mortality from these causes, that was attributable to VCM exposure. There was no evidence of increased mortality from non-malignant liver disease (5 observed versus 4.9 expected), and the incidence of deaths from respiratory disease was low (78 observed versus 105 expected) and was not affected by PVC dust exposure.

A significant excess of bladder cancer (14 observed versus 8.0 expected, $P < 0.05$) was found in the total cohort. Further analysis showed that this excess could not be considered to be associated with VCM exposure because mortality from genito-urinary cancer was heavily concentrated in the low exposure workers at 3 of the 9 factories.

According to the authors this update confirms the relation between exposure to VC and liver cancer mortality. There was no evidence for other cancer mortalities in relation to VC-exposure.

1.1.3 Federal Republic of Germany

a) Frentzel-Beyme et al (1978) studied a cohort of 1618 workers exposed to VC while employed in VC or PVC plants. There was no exposure criterion for inclusion in the cohort. Of the German and non-German workers, 95.5 and 60% respectively were traced for follow-up. The 313 non-Germans all had their first exposure after 1960. The follow-up period was from 1952 to December 1975, and the number of person-years was 19,767. Standard mortality rates were estimated from the vital statistics of the population of the Rhinehessia Palatinate over the years 1970-1975. The mortality figures were :

Mortality from	Oberserved	Expected	Statistical Significance (P)
All causes	81	90.8	n.s.
All cancer	18	16.8*	n.s.
Cancer of the digestive organs	12	8.8*	n.s.
Stomach cancer	3	2.4	n.s.
Colon cancer	4	1.1	0.05
Respiratory cancer	6	5.1	n.s.

* estimated figures from tables, not presented by the authors.

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The absence of deaths from ASL may, according to the authors, be due to the relatively low levels of exposure to VC at the plants concerned.

b) Reinl et al (1979) and Greiser et al (1982). A mortality follow-up study was carried out on all workers employed before 31 December 1974 in 11 VC and PVC plants in the FRG. In parallel, a cohort of workers with no exposure to VC and another of workers from PVC-processing plants were studied. The first group comprised 7021 German and Austrian workers whose combined follow-up period represented 73,734 person-years up to 31 December 1974 (882 workers of other nationalities, of whom 6 had died, were omitted from the group). Standard mortality rates were estimated from the vital statistics of the national population from 1969 to 1974 (Reinl et al,1979). The mortality figures were :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	414	434.7	n.s.
All cancer	94	90.6	n.s.
Cancer of the digestive organs	45	32.7	0.05
Stomach cancer	18	14.4	n.s.
Colon cancer	6	5.8	n.s.
Liver cancer	12	0.9	0.001
Respiratory Cancer	24	26.6	n.s.
Bladder cancer	1	2.9	n.s.
Brain cancer	2	1.3	n.s.
Cancer of lymphatic and haematopoietic tissues	15	7.7	0.05

There were cases of ASL among those of liver cancer but the number could not be stated because of a lack of adequate identification in the early years of PVC production. The statistical probability that the increased mortality from liver cancers was due to chance is 3×10^{-10}, providing further evidence for a casual relationship between liver cancer and exposure to VC. Mortality from liver cancers was elevated in the other two cohorts, but to a much lesser extent. The increased mortality from cancer of the lymphatic and haematopoietic tissues is also statistically significant ($P < 0.05$). In the other two cohorts, deaths from this cancer were lower than expected.

Although no information on level of exposure was provided in this study, Marsteller et al (1975) had previously reported that workers in German PVC plants, especially autoclave cleaners, had often suffered pre-narcotic effects due to exposure to VC.

Greiser et al (1982) presented observed and expected mortalities from cancer for subgroups of the VC/PVC-cohort, exposed to VC during <1, 1-5, 5-10 and >10 years. ECETOC tested the SMR's of liver cancer, of respiratory cancer and of cancer of the lymphatic and haematopoietic tissues for homogeneity and trend by the Breslow et al (1983) method. The SMR's did not show any significant deviation from homogeneity nor any significant trend with exposure-duration ($P < 0.05$).

1.1.4 Italy

Bertazzi et al (1979) studied male workers employed in VC and PVC plants since they started operating in 1952. Of the 5441 workers with at least 6 months exposure to VC, 4777 (88%) were traced for follow-up. The follow-up period was from 1952 to 1975 and is estimated by the present authors to represent 23,000 person-years. The mortality figures were :

- total deaths, 62 (141 expected);
- deaths from cancer, 30 (30.9 expected).

Of the deaths from cancer, 8 were from liver cancers. These included 3 from ASL, 2 of which were of workers at a PVC plant and 1 of a worker in a PVC-processing plant (his employment history was uncertain). The average follow-up per worker was 4.2 years, a period too short to allow a study of cancer of other organs. This paper was essentially a discussion of individuals clinical symptoms and the above data were extracted from the narrative.

A partial update of this study was presented by Belli et al (1986). From the VC-PVC plant at Ravenna (started 1959), the VC plant at Rosignano (started 1953), and the PVC plant at Ferrara (started 1953) a cohort of 1263 workers was identified, who had more than 6 months exposure to VC. Seven workers were not traced. The expected mortality was calculated from the statistics for the total Italian population. The follow-up period was from the start of production until December 31, 1983 for the Ravenna plant and until December 31, 1984 for the Ferrara and Rosignano plants. The number of person years of follow-up was 22,395 and so the average period of follow-up per worker was 17.7 years.

There were 83 mortalities (102.6 expected) and initially 36 cancer deaths (26.9 expected). Of these cancer deaths 2 were due to liver cancer (0.4 expected) and 12 to lung cancer (7.6 expected). After careful examination by the authors of

the available clinical and pathological evidence these figures changed to 39 for all cancer deaths, 5 for liver cancer deaths and 13 for lung cancer death. These liver and lung cancer mortalities represent a significant excess at the 5% level. This excess in all and specific cancer deaths arose mainly from the cohort of the PVC-plant at Ferrara, all cancer 26 (14.5 expected), liver cancer 4 (0.1 expected) and lung cancer 10 (4.1 expected).

The careful examination of the clinical and pathological evidence in the study population introduced observer bias since the same evaluation could not be made for the reference population. Further, the lung cancer mortality in the area of Ferrara seems to be higher than in the general Italian population. Finally, the report does not provide information on VC exposure levels, on possible exposure to other carcinogenic compounds or on smoking habits. The study does confirm the relation between liver cancer and VC-exposure.

1.1.5 Sweden

Byren et al (1976) studied a cohort of 771 workers employed in VC/PVC production from the early 1940s to October 1974. There was no exposure criterion for admittance to the cohort. Twenty-one workers with a very short period of employment could not be traced and were omitted. The total time of employment of the remaining 750 workers was 6300 person-years and the follow-up period amounted to 12,000 person-years. The mortality findings were :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	58	Not provided	
All cancer	11	Not provided	
Lung cancer	3	1.78	n.s.
Liver, pancreas cancer	4	0.97	0.05
Brain cancer	2	0.33	0.05

Two of the 4 cases of liver and pancreas cancer were liver angiosarcoma. Only 112 workers in the study group had been exposed for more than 10 years and conclusions about cancer in other target organs than the liver cannot be derived from such a small group.

1.1.6 France

Pierre et al (1979) studied the mortality and cancer incidence in a population of workers in VC and PVC plants in Tavaux. Of the 1,482 workforce, 160 were lost to follow-up and together with the 11 women in the population were excluded from the follow-up analysis. The remaining 1311 workers were followed from 1953 until 31 December 1976. There were 15,458 person-years of follow-up. The number of workers exposed to VC for more than 5 years was 872. They had been heavily exposed (81 for more than 5 years and 44 for more than 15 years). The mortality findings were :

- total deaths 25 (48.7 expected);
- deaths from cancer, 8 (8.63 expected).

There was 1 death (0.0015 estimated expectance) from ASL of an autoclave cleaner with more than 15 years of high exposure. The rather low observed and expected mortality in this cohort is attributed to the low average age of the population, which makes it difficult to draw conclusions from this study.

1.1.7 Canada

Theriault and Allard (1981) performed a cohort mortality study on 451 workers at a PVC plant with more than 5 years exposure to VC between 1 January 1948 and 31 December 1972. The follow-up period ended on 31 December 1977. The average exposure-period of the cohort was 17.4 years and the average observation period 22.6 years. Mortality was as follows :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	59	71.1	n.s.
All cancers	20	16.4	n.s.
Cancer of digestive organs	14	5.4	0.01
Liver cancer (all ASL)	8	0.14	0.001
Respiratory cancer	2	5.80	n.s.
Cancer of bone, skin, and connective tissue	2	0.38	n.s.
Cancer of eye, CNS	0	0.60	n.s.
Leukaemia, lymphoma	1	1.67	n.s.

Although the average exposure period and the average observation period were much longer than in nearly all other presented studies, there was no evidence of excess mortality from cancers other than of the liver.

The authors suggest the possibility that some of the men who died of liver cancer, might have developed lung cancer had they lived longer. However, the average latency time of the liver cancers was 19.6 years and this seems long enough to allow for the development of cancer in other target organs.

Theriault (1982) presented an update of this study, in which the follow-up ended on January 31, 1981. Eleven men could not be traced. The mortality figures are summarised below :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	73	91.1	0.05
All cancers	23	21.5	n.s.
Cancer of digestive organs	15	0.16	0.01
Liver cancer (all ASL)	8	0.16	0.001
Respiratory cancer	4	7.70	n.s.
Cancer of bone, skin, and connective tissue	2	0.50	n.s.
Cancer of eye, CNS	0	0.57	n.s.
Leukaemia, lymphoma	1	2.07	n.s.

The results of this updated study confirm the association between VC-exposure and liver angiosarcoma incidence, but does not support an association between VC-exposure and the incidence of respiratory or of brain cancer.

1.1.8 Norway

Heldaas et al (1984) studied the overall mortality from all causes and the incidence of cancer in 454 male employees who had worked for more than 1 year between 1950 and 1969 at a VC/PVC plant. The follow-up period was from 1953 to the end of 1979 and involved 8676 person-years.

During this period 50 workers had died (59.3 expected). This difference between observed and expected mortality was not statistically significant. This is the only cohort study, which presents cancer morbidity instead of cancer mortality. The cancer cases are summarised below :

New cases of cancer	Observed	Expected	Statistical Significance (P)
All sites	23	20.2	n.s.
Lung	5	2.8	n.s.
Skin melanoma	4	0.8	0.01
Colon	3	1.44	n.s.
Thyroid gland	2	0.16	0.01
Liver angiosarcoma	1	0.001	0.001

The task force noted that the excess of different cancers was seen in the group with highest estimated exposure level and this observation might suggest an association between vinyl chloride exposure and these types of cancers. However, a significant trend of cancer incidence with level of exposure, years of observation or integrated exposure dose could not be established by ECETOC for any cancer type according to the method of Breslow et al (1983). The absence of a significant trend may be caused by the small cohort and the small observed incidences.

Recently, Heldaas et al (1987) presented an update of this study, in which the follow-up period was extended with the period 1980-1984. The study population in this second period consisted of 430 male workers. A number of 1809 years of follow-up were added to the previous 8183, resulting into a total of 9992 years. The new cases of cancer for the total follow-up period were as follows :

New cases of cancer	Observed	Expected	Statistical Significance (P)
Lung	7	4.0	n.s.
Skin melanoma	6	1.1	0.001
Colon	5	2.1	n.s.
All sites (subgroup)	31	24.0	n.s.

The Task Force tested again the cancer incidences on trend in relation to level of exposure and in relation to the number of years from first employment. A significant trend could not be established.

1.1.9 Japan

a) Masuda (1979) studied a group of 305 workers who had been exposed to VC at a VC/PVC plant for at least 1 year in the period 1949-1975. The author noted that after 1961 the maximum level of exposure of autoclave cleaners was below 250 ppm, but may have been much higher before this. Only 1 person was lost to follow-up, and the number of person-years of follow-up was 4,777. Masuda found :

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- 27 deaths (26.5 expected);
- 8 deaths from cancer (5.8 expected), but no significant increase in any specific type of cancer mortality.

b) Nakamura (1983) conducted a cohort mortality study on male employees who had worked for at least 1 year before 31 December 1964 in one of 25 plants which had begun to produce VC and/or PVC before 1965. The follow-up period was from 1 January 1950 to 31 October 1975. This gave a cohort of 4,524 workers of whom 29 were lost to follow-up. It is not clear whether the Masuda cohort (see above) was included. Nakamura's cohort was divided into PVC-workers (2546) and others, the former group representing about 41,500 person-years of follow-up. Twenty-eight percent of this group was observed for more than 20 years. In the group of PVC-workers the mortality data were as follows :

Cause of death	Observed	Expected	Statistical Significance (P)
All causes	128	147.6	n.s.
All cancers	37	26.9	0.05
Stomach cancer	16	11.9	n.s.
Liver cancer	6	2.54	0.05
Pancreatic cancer	3	1.05	n.s.
Lung cancer	2	2.33	n.s.
Other cancers	10	9.04	n.s.

The SMR of liver cancer rose with increasing duration of exposure, but that of all the remaining types of cancer did not. Of the 6 cases of liver cancer, 1 was diagnosed as ASL and it is highly probable that there was one other. A further case, recorded as death from an unspecified cancer, was also probably one of ASL. There was no correlation between deaths from liver cancer and length of employment as an autoclave cleaner. In the group of non-PVC workers there was no increase in deaths from any specific cause.

1.1.10 Soviet Union

Filatova et al (1982) and Fedotova (1983) reported a retrospective cohort study of all Soviet workers exposed to VC between 1939 and 1977. The cohort of 3,232 was dividied into 3 groups :

- those exposed to more than 115 ppm VC, and often to thousands of ppm. This group probably started work involving exposure to VC between 1939 and 1949;
- those exposed to between 11 and 115 ppm VC, and probably starting work between 1950 and 1959;

- those exposed to less than 11 ppm VC and starting work after 1959.

The authors presented no data on total deaths, deaths from cancer or the number of workers in the groups. SMR's were estimated from the vital statistics of the urban and total population of (probably) the USSR for 1959, 1969 and 1975, but the values in the two papers are not identical. However, the following information was drawn from these publications :

- of the total deaths from cancer, 31.7% were due to cancer of the stomach, 26.9% were due to cancer of the lung and 14.3% to cancer of the lymphatic and haematopoietic tissues;
- in men there was an increase in death from cancer of the lung and the lymphatic and haematopoietic tissues (SMR's 1.5 and 2.4 respectively);
- in women there was an increase in deaths from cancer of the stomach, colon and the lymphatic and haematopoietic tissues. The increases in deaths from cancer seemed to be related to the level but not duration of exposure, this being clear in the first of the above groups with the highest exposure. In the third group, with the lowest exposure the mortality from cancer was comparable to that of the normal population.

The authors stated that

> "liver angiosarcomas were not observed. However, a retrospective analysis of disease cases revealed 71 cases of chronic hepatitis. After these workers had been removed from exposure to VC, the majority was found to be free from changes in the liver" (Filatova et al, 1982).

It is uncertain how this opinion was obtained.

1.2 Studies of Workers in Polyvinyl Chloride Processing

Studies of workers employed in PVC-processing may provide information on the effects on health of exposure to low levels of VC. During the conversion of PVC into fabricated articles some of the residual VC is released from the polymer but the resulting exposure levels will clearly be much lower than those at VC/PVC production plants.

AS1 000019357

1.2.1 USA

a) Chiazze et al (1977) carried out a proportional mortality study on 4,341 workers who had died during the period 1964-1973 among current and former employees at 17 PVC-processing companies with a total of 55 plants. Data on all deaths were obtained because it was not possible to identify those workers who had been exposed to VC only. The total number of employees could not be precisely determined but was estimated to have been between 65,000 and 70,000 by the end of 1973. The deceased employees only included those in the following categories :

- those who died during employment;
- those who died after retiring from the company, with retirement benefits;
- those who died after terminating employment but who were in a company life-insurance plan.

Proportional mortality rates (PMRs) for various causes of death were estimated from the vital statistics of the US and adjusted for age, race, sex and year. In the calculation of PMRs the expected number of deaths from specific causes in the study population was obtained from the relative frequencies of these causes by age and by calendar year in a comparison population. Among the 3,248 white males and 601 white female employees who had died there was an excess of deaths from cancer, ie. for men, 666 (562 expected) and for women, 181 (138 expected). The causes of cancer death are presented below :

Cause of death Among Men	Observed	Expected	Statistical Significance (P)
All cancer	666	562	0.001
Cancer of buccal cavity and pharynx	15	16.9	n.s.
Cancer of digestive system	209	162.1	0.001
Stomach cancer	41	31.5	n.s.
Colon cancer	73	52.5	0.01
Rectum cancer	25	19.6	n.s.
Liver cancer	6	4.2	n.s.
Respiratory cancer	205	176.7	0.05
Cancer of bone, skin and connective tissue	24	15.1	0.05
Cancer of genital organs	44	52.8	n.s.
Cancer of urinary organs	36	33.1	n.s.
Brain, CNS cancer	16	13.9	n.s.
Lymphomas	42	32.4	n.s.
Leukaemias	19	23.4	n.s.
Other cancers	56	34.6	0.001

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Cause of death Among Women	Observed	Expected	Statistical Significance (P)
All cancer	181	137.7	0.001
Cancer of buccal cavity and pharynx	3	1.9	n.s.
Cancer of digestive system	53	35.3	0.01
Stomach cancer	8	5.0	n.s.
Colon cancer	24	15.3	0.05
Rectum cancer	8	3.9	0.05
Liver cancer	0	0.63	n.s.
Respiratory cancer	12	11.9	n.s.
Cancer of bone, skin connective tissue	7	3.3	0.05
Breast cancer	44	32.4	0.05
Cancer of genital organs	19	23.3	n.s.
Cancer of urinary organs	11	4.5	0.01
Brain, CNS cancer	4	3.5	n.s.
Lymphomas	9	7.6	n.s.
Leukaemias	1	5.0	0.05
Other cancers	18	9.6	0.01

No case of death from ASL was found.

This PMR study must be interpreted with caution because the "healthy worker" effect which produces a low mortality rate for non-malignant diseases in the population studied could account completely for the increases in the PMRs of death from cancers.

b) Chiazze et al (1980)' made a case-control analysis of the above-mentioned 44 deaths from breast cancer, in comparison with 134 control subjects matched for age and selected from 5 PVC-processing companies. When such variables as extent of exposure, length of employment, continuous versus intermittent employment, marriage status and child-bearing history were compared for the cases and the controls, no statistically-significant increase in relative risk was found. However, given the number of cases and controls, the smallest relative risk which could have been detected was 3.

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1.2.2 Sweden

Molina et al (1981) studied a cohort of 2,073 workers with at least 3 months employment between 1945 and 31 December 1974 in 4 PVC-processing plants. 103 could not be traced to follow-up, the period of which was from 1 January 1961 to 31 December 1976. Standard mortality rates were estimated from the national statistics.

The presentation of the data is rather confusing. Somewhat ambiguous data are presented on a sub-group of 1,771 workers with at least 6 months exposure between 1945 and 1974, excluding those whose exposure ceased before 1961. Of these 1,771 persons, 73 died between 1969 and 1976 (87.7 expected). In a longer follow-up period between 1961 and 1976, there were 51 deaths from cancer in the group (expected, 44.6), of which 11 were from cancers of the digestive organs including 1 liver cancer.

1.2.3 Federal Republic of Germany

Greiser et al (1982) made a cohort mortality study of 4,007 workers at 2 PVC-processing units, employment at which was the only criterion for inclusion in the cohort. 92.1% were traced for follow-up, the follow-up period being from 1944 to 31 December 1974 and representing 52,896 person-years.

The mortality findings are given below and compared with those from Greiser's study of workers in VC/PVC production plants - see section 1.1.3 b), above.

ASI 000019360

	Cohorts of Greiser (1982)					
	PVC-Processing			VC/PVC-Production		
Number of workers	4,007			7,021		
Persons years of follow-up	52,896			73,734		
% follow-up	92.1			93.2		
Cause of death	Obs.	Exp.	Statistical Significance	Obs.	Exp.	Statistical Significance (P)
All causes	360	379.6	n.s.	414	434.7	n.s.
All cancer	62	81.9	0.01	94	90.6	n.s.
Cancer of the digestive organs	15	30.3	0.01	45	32.7	0.01
Stomach cancer	7	13.5	0.05	18	14.4	n.s.
Colon cancer	1	5.3	0.05	6	5.8	n.s.
Liver cancer	3	0.8	0.05	12	0.9	0.001
Respiratory cancer	25	24.4	n.s.	24	26.6	n.s.
Bladder cancer	2	2.8	n.s.	1	2.9	n.s.
Brain cancer	5	1.1	0.01	2	1.3	n.s.
Cancer of the lymphatic and haematopoietic tissues	2	6.3	0.05	15	7.7	0.05

The significant deviations from expected in the PVC-processing cohort are mainly based on less deaths than expected, except the deaths of liver and brain cancer. In contrast, all significant findings in the VC/PVC production cohort are based on more cancer deaths than expected.

1.3 Evaluation of the Epidemiological Studies

In these studies excess mortality from liver cancer was frequently found and an excess of deaths from cancer of the respiratory tract, brain, thyroid and skin (malignant melanoma), and of the lymphatic and haematopoietic tissues was sometimes reported. The relationship between deaths from cancer in the various target organs and exposure to VC is discussed below.

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1.3.1 Liver cancer

Angiosarcoma of the liver is such a rare disease that it proved much easier to establish that there was an excess incidence of it in a study than was the case with the more common cancers.

In 12 of the 20 studies reviewed there was a statistically significant excess of deaths due to liver cancer in workers exposed to VC and the relationship of this form of cancer to exposure to VC is thus well-established. In the updated cohort mortality study (E.H.A., 1986) of all VC- and PVC-workers in the USA VC-exposure appeared to increase cancer mortality from liver angiosarcoma, from other liver cancers and from biliary tract cancer. This last finding is the first and only one relating biliary tract cancer mortality to VC-exposure.

It is of interest to consider why 8 of the studies failed to show an excess of deaths from primary liver cancers. The average latency period for ASL in occupationally-exposed workers is between 20 and 29 years (Forman et al, 1985), and thus the average observation time was clearly too short in the Masuda (1979) and Buffler et al (1979) studies.

The integrated dose of exposure and peak exposure were probably less in the studies by Ott et al (1975), Buffler et al (1979), Chiazze et al (1977, 1980), Frentzel-Beyme et al (1978) and Greiser et al (1982, cohort of PVC-processors). There is no evident explanation for the absence of an excess mortality from liver cancers in the studies by Filatova et al (1982) and Fedotova (1983).

The study by Ott et al is completely-comparable in terms of cohort size, average exposure period, average observation period and type of plant (PVC production), with that of Nicolson et al (1975, 1984) and yet Ott found no excess mortality from liver cancers. This is probably because peak exposure and integrated exposure of the Ott population were clearly less than those of the Nicholson population. This indicates that the likelihood that humans develop ASL falls significantly with decreasing peak and integrated exposure to VC.

1.3.2 Respiratory cancer

The mortality from this was significantly increased in the studies of Buffler et al (1979), Heldaas et al (1984), Waxweiler et al (1976), Filatova et al (1982) and

Fedotova (1983). The level of exposure, as deduced from the rates of mortality from ASL, was moderate for the populations of Buffler et al and Heldaas et al, and high for that of Waxweiler et al . Of three cohorts which had experienced high exposure to VC, those of Nicolson et al (1975, 1984) and Theriault and Allard (1981) showed a decrease in mortality from cancer of the respiratory tract, while in the study of Greiser et al (1982) it was normal. Beaumont and Breslow (1981) considered the statistical power of 8 for the epidemiological studies to detect an increased relative risk of respiratory cancer of 1.5 in workers exposed to VC. The only 2 studies of high statistical power (EEH, 1978 and Fox and Collier, 1977) failed to show an increase in relative risk.

In addition, in the updated studies of VC-workers in the United States and the United Kingdom (Environmental Health Associates 1986, and Jones 1986) the power to detect a relative risk of respectively 1.24 and 1.27 at a significance level of 5% was 80%. However, in the US-VC-workers there were 115 respiratory cancer deaths (122.5 expected) a relative risk 0.94, and in the UK-VC-workers 85 respiratory cancer deaths (94.3 expected) a relative risk 0.90. Taken overall, these findings do not suggest that there is a causal relationship between exposure to VC and death from respiratory cancer. Some of the excess mortality found may be due to smoking.

1.3.3 Brain cancer

An increase in death from brain cancer was found in the cohorts of EEH (1978), Byren et al (1976) and Waxweiler et al (1976). Beaumont and Breslow (1981) calculated the statistical power to detect an increase in the relative risk of brain cancer for 5 of the epidemiological studies. Those of Waxweiler (1976) and EEH (1978) had sufficient power to detect a relative risk of 2-3, and an increase in brain cancer was found in these studies and also in that of Byren et al (1976). Beaumont and Breslow concluded that therefore the most reasonable interpretation is, that the data are consistent with an aetiological hypothesis for vinyl chloride and cancer of the brain. However, in the EEH study the increase in this type of cancer was not related to the level or duration of exposure and, in addition, no such increase was found by Nicholson et al (1975, 1984), Greiser et al (1982) or Theriault et al (1981) in whose studies the exposure levels were very high.

In the update of the EEH study (Environmental Health Associates, 1986) 23 deaths from brain cancers were found against 12.76 expected. Although this is considered as highly significant by the authors, this task force could not establish by the

method of Breslow et al (1983) a significant trend of the SMR with length of exposure, with the length of the period of follow-up or with age of first exposure, as was found for deaths from liver cancer. In the updated study of VC-workers in the UK (Jones, 1986) the power to detect a relative risk of brain cancer of 2.2 at the 5% level was 80%. Only 4 brain cancer deaths were found against 6.18 expected (relative risk 0.65).

It should also be noted that statistics on brain cancer for the general population are of doubtful reliability because of the limited number of brain post-mortem examinations. Therefore comparison between observed and expected cases is of limited validity. There is thus a serious doubt about a possible relationship between exposure to VC and death resulting from brain cancer.

1.3.4 Cancer of the lymphatic and haematopoietic tissues

Increased deaths from these types of cancer were reported by Waxweiler et al (1976), Greiser et al (1982), Filatova et al (1982)/Fedotova (1983; same study) and Nicolson et al (1984). The most significant increase was in the VC/PVC-production cohort of Greiser et al (15 found against 7.7 expected) but there may be some doubt about the expected figure as the German statistics for the single year 1968 had to be used for the period 1944-1968. It is possible that reliable figures were not available prior to 1968 because of the influence of the Second World War on German demographic parameters. Greiser et al (1982) stratified the VC/PVC production cohort on the basis of duration of exposure. ECETOC tested the trend of the SMR's in the subgroups in relation to duration of exposure by the method of Breslow et al (1983). A significant trend could not be established.

In the EEH population, 20 deaths from cancer of the lymphatic or haematopoietic tissues were found against 17.0 expected and there was no relationship between mortality and the level of exposure or integrated dose of VC. In the update (Environmental Health Associates, 1986) 37 deaths from lymphatic or haematopoietic cancer were observed against 36.28 expected. The power to detect a relative risk of 1.45 at 5% significance was 80%. A significant trend of the SMR with length of exposure, length of period of follow-up or with age of first exposure could not be established by ECETOC by the method of Breslow et al (1983). In the updated study of VC-workers in the UK the power to detect a relative risk of lymphatic and haematopoietic cancer of 1.8 was 80%. 16 deaths from this type of cancer were observed against 12.36 expected (relative risk 1.3). Information about exposure

conditions was not sufficient to trace a relation between VC-exposure with this type of cancer mortality.

Nicholson et al (1980) and Waxweiler et al (1976) found, respectively, 3 deaths (1.14 expected) and 4 deaths (2.5 expected) from such cancers but did not relate them to exposure. Filatova et al (1982) observed a significant increase in the SMR (=12) for this type of cancer in female workers, a finding which is difficult to assess because the authors give no absolute or expected values of cancer deaths. In the remaining studies no increase was noted.

Overall, there is equivocal evidence, that a relationship exists between exposure to VC and death from cancer of the lymphatic and haematopoietic tissues.

1.3.5 Malignant melanoma

The cohort, cancer incidence study by Heldaas et al (1984), in which an increased incidence of this type of skin cancer was found, is not directly comparable to the other studies which were of cancer mortality. In the updated EEH-study (Environmental Health Associates, 1986) 6 skin melanoma deaths were observed against 7.36 expected. The power of this study to detect a relative risk of skin melanoma deaths of 2.1 at a 5% significance level was 80%.

There are numerous examples in the literature of the finding of an excess incidence of malignant melanomas in studies of occupational cohorts in a variety of industries and countries, as exemplified below for workers not exposed to VC. An increase in melanoma morbidity or mortality has been observed :

- in Norwegian workers exposed to asbestos, 3 melanoma cases (0.6 expected) (Hilt et al,1983);
- in Swedish rubber workers, 21 melanoma cases (9.1 expected) (Holmberg et al,1983);
- in Swedish workers in the telecommunications industry, 12 melanoma cases (4.6 expected) (Vagero et al,1985);
- in Swedish electrical engineers, 3 melanoma deaths (0.9 expected) (Olin et al,1985);
- in English semiconductor workers, 3 melanoma cases (0.68 expected)(Sorahan et al,1985);
- in workers at 8 UK oil refineries, 14 melanoma deaths (6.48 expected) (Alderson and Rushton, 1982);
- In employees of the Lawrence Livermore National Laboratory, a high energy physics research facility in California, where there were 7 melanoma cases in females (1.43 expected), and 22 in males (6.80 expected) (Reynolds et al,1985).

In all these cohort studies, no specific chemical is implicated as the causal agent of malignant melanoma of the skin and it seems that this can arise in a study as a purely coincidental finding.

There seems to be no doubt that solar radiation is a causal factor in the development of malignant melanoma (Magnus, 1981). Scandinavian people have a higher risk of developing melanoma (Amstrong, 1984); it is suggested that infrequent but intense exposure to sunlight contributes more to the risk of melanoma of the fair-skinned Scandinavians that does continuous exposure of people in the more southern countries. This could explain the results of Heldaas et al if PVC-workers had relatively more exposure to sunshine than did the general population. However, the 4 workers with malignant melanoma did not have any excessive exposure to sunshine nor were other skin tumours known to be related to sunshine found (Heldaas, personal communication). Therefore, the finding of Heldaas et al deserves more attention in future studies.

Up until now the total evidence from all the studies does not indicate a causal relationship between exposure to VC and the incidence of, or mortality from, malignant melanoma.

1.3.6 Cancer of the thyroid

The increased incidence of this type of cancer found by Heldaas et al (1984) was not paralleled by an increase in mortality in the studies by Nicholson et al (1976) and Greiser et al (1982) in which there were high exposures to VC and long periods of observation and follow-up. Thus the evidence for a causal relationship between exposure to VC and cancer of the thyroid is weak, especially since Heldaas et al found only 2 cancers of that type.

1.4 The Register of Angiosarcoma of the Liver (ASL) Cases

Since 1974, ICI Plc has maintained, on behalf of the Association of Plastics Manufacturers in Europe, a worldwide register of histologically confirmed ASL cases resulting from exposure to VC (Forman et al, 1985). The register is doubtless incomplete, although the collaborating organisations believe that they have been informed about nearly all of the cases. By January 1986, 120 men, of whom three were still alive on 1 January, 1986, had been recorded as having VC-related ASL. Of the 120 cases, 119 were reported to be hepatoangiosarcomas and one a

cholangiosarcoma. No cases were recorded in women but few women have been employed in manufacturing PVC. Table 4 shows the breakdown of the cases by date of death.

It should be noted that the register was begun in 1974 when exposure to VC first became firmly established as a cause of ASL. Under-reporting is therefore less likely to be a problem after this date, when special attention began to be paid to the disease.

In Table 5 the age-distribution of the 120 men at the time of diagnosis is given. The mean age at diagnosis was 52. It seems that the incidence of ASL reached a peak 20 - 29 years after first exposure, but 18 cases occurred after more than 30 years. The average latency period for the ASL cases was 22.5 years, and the average length of exposure 18.3 years. The majority of cases occurred 15 to 29 years after first exposure, as is common with occupationally-induced cancers. There has been no case of ASL recorded in any individual who has been exposed since the levels of VC in the atmosphere were drastically reduced in 1974.

In Table 6 are shown the principal occupations of the 120 affected men. At least 43% of the men (53/120) had been employed as autoclave cleaners, an occupation which was almost certainly associated with the highest exposure to VC. Only 82 new cases have been diagnosed since 1975 despite the large number of workers in the industry.

Forman et al (1985) have estimated the number of future cases of VC-related ASL by analysing the 110 cases diagnosed at the time, in terms of latency, and assuming that the hazard was eliminated in the late 1960's. They estimate that a further 155 cases might occur for latencies of less than 35 years, and in the absence of data for latencies greater than 35 years, they suggest that there might be around 50 cases for these extended latency periods. Thus the total estimate for future cases is in the range 200-250, or about twice as many as have already been reported.

1.5 Angiosarcoma of the Liver in the General Population

The incidence of angiosarcoma of the liver is difficult to estimate as it is a rare condition. Apart form VC, thorium dioxide (in the x-ray contrast medium Thorotrast) and arsenic can induce ASL (Roth, 1955; Tesluk et al, 1955). Edmonson (1958) found only one case in 52,000 autopsies (0.002%), Rein and Huth (1975) report on 6 cases (0.02%) of primary vascular liver tumours in 30,079 autopsies, while Brady et al

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(1977) give 0.25 per million as the annual morbidity incidence rate for histologically confirmed angiosarcoma of the liver among residents of New York State (excluding New York City) for the years 1970 to 1975. In a later and more extensive study of the same geographical area Vianna et al (1981) conclude to an average annual incidence of 0.26 per million. Baxter et al (1977) report that between 1963-1973 an average of four cases per year of ASL were recorded in the UK, while a panel agreed with these diagnoses only in a third of the reported cases.

In their case-control study over the period 1958 to 1975, Brady et al (1977) report on 27 cases with confirmed ASL. One case was excluded because histologic assessment could not confirm ASL. Seven of the patients had documented exposure to VC (all chemical operators), Thorium dioxide (Thorotrast) or arsenical pesticides (Bradey et al, 1977). Of the other 19 patients, 5 lived in highly industrialised areas no more than 1350 m from VC fabrication or polymerisation factories. Neither residential history nor ambient air concentration data were obtained for the remaining 14 patients and statistical analysis for a geopgraphical factor was not carried out. The authors conclude that the geographical factor might be important in the etiology of this disorder but it must be considered unresolved at present. Vianna et al studied the same area and expanded the study by 4 more years (1958 to 1979) including the New York City cases from 1973 through 1979. A total of 43 patients diagnosed with ASL were reported. For five females residing within one mile of plastic producing factories for a period ranging from 8-62 years (medium 26.8 years), VC is mentioned as posssible cause. Furthermore, it is noted that 19 of the 43 patients resided in four urban counties which contain the greatest number of VC polymerisation and fabrication factories. Dalderup et al (1976) investigated all cases diagnosed as ASL in The Netherlands in the period 1950-1975. In that period the population increased from about 10 to 14 millions. From the 27 cases reported by the pathologists only 9 cases were proven angiosarcoma. None of the 27 cases had any traceable contact with vinyl chloride and a geographical factor was not found. One of the cases was probably induced by chronic use of arsenic drugs. Thorotrast induced cases were not included in this series.

Saric et al (1976) studied the incidence of malignant primary tumours of the lung, bronchus and liver in 1968-1971 in a city in Yugoslavia with several factories including a PVC industry. There was no causal relationship between the liver tumours recorded and the area of residence and there were no haemangiosarcomas.

Of the 14 cases of ASL in the periods 1963-1973 in England and Wales, and 1965-1973 in Scotland, which were confirmed by a panel, one case had occupational exposure to VCM. One other case was a man who had lived for 6-7 years before his death in 1970 within half a mile of the PVC plant in which the occupationally exposed person had worked. For the other 12 cases there was no geographical factor (Baxter et al, 1977).

1.6 Conclusions

Occupational exposure to high levels of VC, (probably hundreds of ppm during several years) causes mortality due to angiosarcoma and possibly other primary liver cancers. There is insufficient evidence to establish any relationship between exposure to VC and an increased incidence of cancer of the brain, lung, thyroid, lymphatic or haematopoietic tissues, and skin (malignant melanoma).

The annual incidence of angiosarcoma of the liver in the general population has been reported to be in the order of 0.25 per million, but may even be lower when stringent pathological criteria are used. In addition to VC, arsenic and Thorotrast may cause ASL, but for many of the ASL cases studied no plausible cause could be found. Theoretically exposure from the ambient air, in particular near VC or PVC plants, could present a cancer risk, but the results from the few studies done do not indicate such a possibility or are inconclusive.

2. CLASTOGENICITY AND MUTAGENICITY

2.1 Studies

The finding of carcinogenic and clastogenic effects in workers exposed to VC led to studies on its possible mutagenic effects.

A number of cytogenetic studies have demonstrated that exposure to VC is associated with an increased frequency of chromosomal aberrations in the peripheral lymphocytes of exposed workers (Funes-Cravioto et al (1975). Ducatman et al (1975), Szentezi et al (1976), Purchase et al (1976), Fomenko et al (1976), Purchase et al (1978), Hansteen et al (1978), Kucerova et al (1979), Anderson et al (1980) and Anderson et al (1981). Chromosomal aberrations induced by VC were described as dicentrics, fragments, rings and translocations. Léonard et al (1977) described such aberrations amongst VC exposed workers but underlined that they had received

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