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The Mutagenicity and Carcinogenicity of Vinyl Chloride: A Historical Review and Assessment

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

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TABLE OF CONTENTS

	ii-iv
SUMMARY	1.
A. INTRODUCTION AND HISTORICAL REVIEW	4
1. VC and PVC Production Processes	4
1.1 Dispersion Process	5
1.2 Bulk Process	7
2. PVC Conversion Processes	7
3. PVC Packagings for Food and Drink	7
4. Exposure to Vinyl Chloride	7
5. Effects of Vinyl Chloride on Health	8
5.1 Effects on the Central Nervous System (CNS) (roughly from 1930)	9
5.2 "Vinyl Chloride Disease" (roughly from 1957)	9
5.3 Carcinogenicity (1970 and onwards)	6
6. Evolution of Occupational Exposure Limits	10
B. EXPOSURE OF HUMAN BEINGS TO VINYL CHLORIDE	11
1. Odour Threshold	11
2. Occupational Exposure	11
2.1 Locations	11
2.2 Measuring and Monitoring Methods	12
2.3 Levels of Exposure	13
3. Exposure of the General Public	16
3.1 By Inhalation	16
3.2 By Ingestion	19
3.3 Summary and Risk Assessment	23
C. EFFECTS ON HUMAN HEALTH	25
1. Carcinogenicity	25
1.1. Cohort Studies of Cancer Morbidity and Mortality in Vinyl Chloride and Polyvinyl Chloride Production Plants	25
1.2. Studies of Workers in Polyvinyl Chloride Processing	45
1.3 Evaluation of Epidemiological Studies	49
1.4. Register of Angiosarcoma of the Liver (ASL) Cases	54
1.5. Angiosarcoma of the Liver in the General Population	55

1.6. Conclusions 57
2. Clastogenicity and Mutagenicity 57
2.1. Studies 57
2.2. Conclusions 59
3. Other Effects Relevant to Carcinogenicity or Mutagenicity 59
3.1. Non-malignant Liver Diseases 59
3.2. Acro-osteolysis (AOL), Raynaud's Phenomenon and Effects on the Skin 61
3.3. Conclusions 52

D. EXPERIMENTAL TOXICOLOGY 63
1. Carcinogenicity 63
1.1 Exposure by Inhalation 63
1.2 Exposure by Routes other than Inhalation 70
1.3 Special Studies of Vinyl Chloride Carcinogenesis 72
1.4 Comments 77
1.5 Conclusions 80
2. Mutagenicity and Genotoxicity 81
2.1 Mutagenicity and Genotoxicity In Vitro 81
2.2 Mutagenicity and Genotoxicity In Vivo 81
2.3 Mutagenicity of VC-metabolites In Vitro and In Vivo 84
2.4 Conclusions 86
3. Other Toxicological Data Relevant to Carcinogenicity and Mutagenicity 86
3.1 Acute Exposure by Inhalation 87
3.2 Conclusions 87

E. METABOLISM AND RELATED STUDIES 89
1. Animal Studies 89
2. Toxicokinetics of Inhaled Vinyl Chloride in Man 91
2.1 Retention of Inhaled Vinyl Chloride in the Lung 91
2.2 Clearance of Vinyl Chloride from Air by Inhalation 91
2.3 Biological Monitoring 92
2.4 Comparison of the Rate of Uptake of Vinyl Chloride from Air in Man and other Mammals 94

F. CONCLUSIONS 95

BIBLIOGRAPHY 97-106

TABLES 107-136

FIGURES 137-140

APPENDICES

1. Properties of Vinyl Chloride 141
2. Tests for Significance of the Increased Incidence of Melanoma in Maltoni's experiment BT8 142
3. Estimation of the Exposure Concentration of VC Corresponding with 50% of the Maximum Metabolic Conversion Rate in Humans 144
4. Members of Task Force Vinyl Chloride 146
5. Members of the ECETOC Scientific Committee 147

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

SUMMARY

In 1974 the first evidence that occupational exposure to vinyl chloride (VC) could lead to a rare type of liver cancer in man, angiosarcoma, was published. Since then an enormous amount of epidemiological, clinical and toxicological research has been carried out and a large volume of data on occupational exposure and exposure of the general public has been collected. This information is scattered in many types of publications by numerous authors. The purpose of this report is to present under one cover a coherent picture of the most important aspects of the toxicology of VC (with the emphasis on carcinogenicity and mutagenicity), and the risk it poses for human health at current levels of exposure.

A brief Introduction and Historical Review is given in which the processes for producing VC and its polymer (polyvinyl chloride, PVC) are described; the sources and types of exposure to VC are given; the various diseases arising from excessive exposure are noted, and the evolution of exposure limits is summarised.

Human occupational exposure is predominantly via inhalation at plants where VC and PVC are manufactured and at factories where PVC is processed to give various fabricated articles. In practice skin exposure from the liquid phase is negligable. The development of methods for determining VC concentrations in air is briefly noted, and the historical levels of VC at the various types of plants are reviewed. By far the highest levels (hundreds of ppm) were experienced periodically at PVC-production plants, but by mid-1974 they had been reduced to, typically, around 50 ppm. Progress in lowering the levels continued, and since 1978 they have been at a few ppm or lower.

The general public is exposed to very small amounts of VC : i) from inhalation of ambient air in urban areas typically in the order of 5µg/person/day with higher amounts in the vicinity of VC and PVC plants, ii) by ingestion of food and drinks packed in VC-containing polymers as films, cartons or can-linings from which residual VC can migrate into the packed material and iii) by inhalation of tobacco smoke (a few ng/person/day). Since 1978 emissions from VC and PVC producing plants have been reduced considerably. Between mid-1973 and mid-1975 the amount of

residual VC in polymers was also drastically reduced, typically from more than 10 ppm to about 1 ppm, and the concentrations in food and drink fell from around 100 to about 2 ppb over the same time period, and data obtained in 1986 show typical values of 0.1 ppb or less.

The carcinogenic, mutagenic, clastogenic and related effects of VC on humans are reviewed. Twenty-six papers describing epidemiological studies are critically assessed and it is concluded that, apart from the well-established fact that exposure to the high levels of VC experienced in the past can cause angiosarcoma of the liver, there is no convincing evidence that it causes cancer at other sites, nor is there any evidence of teratogenic or heritable mutagenic effects in man. Clastogenicity was only seen at higher occupational exposure levels experienced before the marked reduction in exposure in the mid-1970's.

Various non-carcinogenic effects of chronic occupational exposure to VC have been described under the collective heading "Vinyl Chloride Disease", and these are briefly reviewed. There have been no reports of such effects in workers exposed to VC after the early 1970s when VC levels were lowered to a few ppm.

The experimental studies on the carcinogenicity, mutagenicity and genotoxicity of VC are also reviewed. From the extensive work on carcinogenicity, much of it by Maltoni, it is concluded that VC is a versatile carcinogen in animals when administered by inhalation or orally. In the three species tested (rat, mouse and hamster) it induced hepatic haemagiosarcomas, Zymbal gland tumours, nephroblastoma, pulmonary and mammary gland tumours, and forestomach papillomas. The minimum dose at which compound-related tumours were induced by inhalation was 10 ppm for rats, 50 ppm for mice and 500 ppm for hamsters. When VC in PVC powder was administered orally to rats, the minimum effective dose was 1.7 mg VC/kgbw per day. When it was administered as a solution in water to the same species, the minimum effective dose was 25 ppm.

VC is mutagenic and clastogenic in vivo. It is also mutagenic and clastogenic in vitro but only in the presence of appropriate metabolic activating systems. Chloroethylene oxide appears to be the most potent mutagenic metabolite.

The liver is the primary site of structural damage by VC, and it appears that the effect is due to toxic metabolites whose formation is induced by the mixed function oxidase system. The fact that, in experimental animals, tumours were induced in

organs which were not adversely affected in acute and sub-acute studies, and that tumours developed in the liver at dose levels well below those found to cause hepatotoxicity, is consistent with a genotoxic mechanism of action.

The major pathways in the metabolism of VC have been established. In experimental animals the key metabolic step is its conversion by mixed function oxidase into chloroethylene oxide. Although this process is readily saturable, the ability of chloroethylene oxide to bind covalently to DNA at levels which do not induce saturation probably accounts for the induction of tumours at such low levels. From studies on the clearance rates of inhaled VC in rats, mice and humans it is concluded that rats and mice exposed to VC produce more of the carcinogenic metabolite per kgbw than do humans.

As to the current risks, our conclusions are that although it is not possible to set definitely safe levels of exposure for genotoxic carcinogens, the evidence presented in this report suggests that occupational exposure at current levels, as would be achieved when in compliance with, for example the EEC limit of 3 ppm, does not present any significant risk to health. At the atmospheric levels to which the general public is exposed, in the order of 5 µg/person/day with higher values in the vicinity of VC and PVC plants, and less elsewhere, the risk of adverse health effects is even less. The content of residual VC in PVC and copolymers in food and liquid packaging materials has fallen, typically from more than 10 ppm in the early 1970's to below 1 ppm in subsequent years. There has been a corresponding reduction in the VC content of packed food and drink from about 100 ppb, to below 2 ppb from about 1977 onwards. Conservative estimates have indicated that the current intake of VC from food and drink presents a negligible risk of cancer.

A. INTRODUCTION AND HISTORICAL REVIEW

Since about 1974 vinyl chloride (VC) has become one of the most intensively studied of all industrial chemicals from the point of view of its toxic effects. An enormous amount of clinical and toxicological research has been carried out and a large amount of data relating to occupational exposure and exposure of the general public has been collected. By about 1985 many epidemiological or animal studies had been completed and reported. Most of the information necessary to understand the toxic effects of VC have been obtained. As this information is widely scattered it is difficult to have a coherent view of the results and developments which form the background of control measures currently in force. This is necessary for all who are concerned with the voluntary and regulatory control of VC.

As a consequence ECETOC set up a Task Force composed of experts to assess the carcinogenicity and mutagenicity of VC and their significance for the health of exposed workers and the general public. Emphasis was placed on carcinogenicity and mutagenicity because measures taken to reduce the risk from these effects would automatically minimise, and probably eliminate entirely, the risk of those VC-related diseases and conditions, which develop only after exposure to "high" concentrations. These other VC-related diseases are described briefly for the sake of completeness.

The report is set out as follows. The short historical review which completes this Chapter is followed by an account of human exposure (Chapter B) and the effects of exposure to VC on human health (Chapter C). Experimental studies are then assessed under the headings: experimental toxicology (Chapter D), and metabolism and related studies (Chapter E). Conclusions from the whole review are drawn in Chapter F. It is emphasised that only those publications relevant to the task in hand are considered.

1. VC AND PVC PRODUCTION PROCESSES

Vinyl chloride (VC) is a colourless, inflammable, explosive gas, slightly soluble in water, and soluble in fats and organic solvents (Appendix 1).

It was first synthesised by Regnault in 1835. Research on the polymerization of VC was carried out in Germany to provide a substitute for rubber during the First World War, but it was not until a century after its discovery, i.e. in the 1930s,

that the production of VC and its polymerisation to polyvinyl chloride (PVC) was developed industrially. After the Second World War production expanded considerably and PVC became one of the most important synthetic resins produced by the plastics industry. Worldwide annual production of the polymer in 1985 was about 12 million tons.

Apart from its use in the production of PVC and the manufacture of copolymers with monomers such as vinyl acetate or vinylidene chloride, VC still retains some minor use as a raw material for the manufacture of 1,1,1-trichloroethane and monochloroacetaldehyde. Certain of its less important uses have been abandoned since the early days and are not considered further. eg aerosol propellant and general anaesthesia.

There are two methods for the industrial production of VC. Formerly it was made from acetylene and hydrogen chloride but nowadays ethylene and chlorine are mainly used. They are reacted to give 1,2-dichloroethane, which is thermally cracked to produce VC and hydrogen chloride. There is very little exposure to VC, since production is carried out as a continuous process in plant closed to the outside atmosphere.

Descriptions of VC polymerization processes have been given by Cook et al (1971), Cohan (1975), Barnes (1976), Bonnefoy (1977) and Stafford (1977). There are two main processes : the dispersion process and the bulk process. Because most of the adverse effects of VC on human health occured at plants in which PVC was manufactured by the dispersion process, this is described in some detail below. The bulk process was introduced only in the later 1960s and a much shorter description of this is given.

1.1 Dispersion Process

As VC is a gas at ambient temperatures polymerisation is carried out in autoclaves at 40-70°C. The reaction is exothermic, and the most common method of dissipating the heat is to disperse the monomer in fine droplets in an approximately equal quantity of water. The reaction takes place in a three-phase system; the solid polymer is precipitated in the monomer droplets, which in turn are dispersed in the aqueous phase. Despite more than 30 years of research, no way has yet been found to prevent a film of PVC forming on the inside wall of the reactor. This film interferes with the transfer of heat between the reactor and its contents, and the

process has to be interrupted periodically to allow the reactor to be cleaned. The fact that it is technically impossible to polymerize VC by a continuous process in a permanently-closed system lies at the origin of the occupational pathology of autoclave cleaning personnel.

Over the years, the size of the autoclaves has gradually been increased. Whereas the first had a capacity of only a few cubic metres, those in current use have a volume of several tens of cubic metres, and even larger autoclaves are being designed.

In a typical process, deionized water is first introduced into the autoclave, followed by emulsifiers, catalysts, surfactants, buffers, etc. Air is purged from the reactor, and the liquid VC is then pumped into the sealed autoclave under pressure. The autoclave is heated to between 50 and 60°C in order to initiate polymerisation which then continues exothermically. Once polymerisation has ended, the autoclave charge is emptied into degassing tanks, and the non-polymerized VC is degassed and pumped into a gasometer where it is compressed and then stored under refrigeration in pressurised spheres. The wet PVC is transferred to mixers in which the charges from several reactors are combined in order to make the product uniform. It is then transferred to driers, and the resulting dried powder is sent either to bulk storage silos, or to hoppers for bagging. The autoclave, after being emptied, is opened, rinsed and washed either with solvents or by means of automatic high-pressure water jets.

Nowadays, many precautions are taken to guarantee the best achievable sealing involving the complex system of piping, tanks, pumps and valves in which the VC flows. This even applies to the autoclave which only needs to be opened occasionally. A combination of technologies are used for autoclave cleaning all of which involve washing between individual, or a limited number of batches, thereby reducing the formation of crusts or deposits resulting from polymerisation. In the past, the autoclaves were cleaned manually ; gloves were worn, whilst the inside of the autoclave was scrapped with a spatula, or sometimes a hammer and chisel, to remove the encrusted polymer adhering to the walls of the vessel and the mixing devices. Lumps of polymer often released monomer when broken, resulting in dangerously high concentrations in the autoclave. The usual practice up until about 1970 was not to go into the vessel, in which the atmosphere was still lader with monomer, until an explosimeter had been used to check that the autoclave contained less than about 400 ppm, ie. a safety margin of around two orders of magnitude

below the lower limit of explosivity of VC. Nowadays much more sensitive instruments are used to ensure that entry into autoclaves occurs only when the VC level is at or below 10 ppm.

1.2 Bulk Process

Liquid VC under pressure, plus a free-radical catalyst and other additives, are charged to an autoclave where pre-polymerisation occurs. When 8 to 12% of the monomer has been converted into polymer this "seed" material is passed to the main polymerisation autoclave where further VC, catalyst, etc. are added and the polymerisation is allowed to go substantially to completion. The remaining VC is removed and recovered, and the dry polymer is then screened, and passed to storage.

In the period between its production and use, PVC is stored in warehouses for periods of several days or weeks and can lose significant amounts of its residual monomer by diffusion into the atmosphere.

2. PVC CONVERSION PROCESSES

PVC is converted into a wide range of products by various processes, including dry blending. Most of which involve heating until it softens or melts. It can then be formed into solid articles (by extrusion, thermo-forming, or rotational moulding), or rigid or flexible film (by extrusion or callendering). During the processes, part of the residual VC is expelled from the PVC. The industrial operations described above can lead to occupational exposure to VC.

3. PVC PACKAGINGS FOR FOOD AND DRINK

Exposure of the general public can arise from the packaging of a wide variety of foods and drinks in containers or film made of PVC or VC co-polymers. Residual VC in the polymer may migrate into food or drink and minute amounts can thus be ingested by the consumer.

4. EXPOSURE TO VINYL CHLORIDE

An inventory of the population groups liable to be exposed to VC shows a steeply-decreasing degree of exposure, in the following order (Bonnefoy, 1977):

1. Polymerisation unit workers - the most heavily exposed because of the many manual operations, the frequent opening of equipment and the fact that the installations are often situated inside buildings.
2. Workers in monomer production units - only slightly exposed since the continuous process under pressure necessitates sealed systems, and the installations are situated in the open air.
3. Workers in plants where PVC is converted into manufactured articles. The levels have always been very low, as the only source of VC is traces released from the resin.
4. People living near plants.
5. Consumers of food and drink packed in PVC or VC copolymers containing residual monomer.

More details about the levels of exposure of these groups are given in Chapter B.

The concurrent publication in 1974 of papers on angiosarcoma of the liver in VC exposed experimental animals and man stimulated a major technological effort to reduce the exposure at workplaces. The result was that exposure was markedly reduced and atmospheric concentration limits in the workplace were lowered, e.g. from 500 ppm (ACGIH, 1970) to a "harmonized" long-term Limit Value of 3 ppm as an annual average in the European Communities (EEC, 1978), cf table 1. At the same time there was a sustained effort to lower the amount of residual monomer in PVC, and hence in food and drink packaged in PVC-containing materials. In 1978 the EEC set a limit of 1 ppm of residual VC in PVC polymers, and a migration limit of 10 ppb in food or drink resulting from the packaging (EEC, 1978).

5. EFFECTS OF VINYL CHLORIDE ON HEALTH

There are many reviews of the toxicology of VC, eg. Schottek (1969), Viola (1974), Foa et al (1974), CIRC (1974), Haley (1975), Hublet (1975), Truhaut et al (1975), Szadkowski (1976), Heuse (1978), Binns (1979) and Veltman (1980). In addition Cavigneaux (1975), Heiman et al (1975), Warren et al (1975) and Szadkowski et al (1982), have produced bibliographic inventories.

Our understanding of the toxicology of VC developed in three historical stages as set out below.

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.

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.

B. EXPOSURE OF HUMAN BEINGS TO VINYL CHLORIDE

1. ODOUR THRESHOLD

The odour of VC could be detected in the neighborhood of autoclaves when they were opened and while they were being ventilated prior to cleaning. Various authors have given differing values of the odour threshold. Viola (1974) and Patty (1966), who carried out experiments with human volunteers, put the threshold at 5000 and 4000 ppm respectively. Cook et al (1971) put the lower odour threshold at 400 ppm. Bauer (1974) reported that the range of perceptible concentrations was between 200 and 2000 ppm, while Baretta et al (1969) reported that one of the experimental subjects recognised the odour of VC at 250 ppm, although the sensation faded very quickly. Lefevre, quoted by Hublet (1975), puts the threshold at as low as 150 ppm.

2. OCCUPATIONAL EXPOSURE

2.1 Locations

Occupational exposure to VC by inhalation can occur at three different locations :

- VC production plants,
- VC polymerisation (PVC-production) plants,
- PVC processing areas.

It is important to distinguish between them because, especially in the past, they correspond, to markedly different levels of exposure. VC concentrations and the incidence of various adverse effects on health were undoubtedly highest in PVC-production plants and the measurement/monitoring of exposure levels has consequently been much more extensive at these plants, data from the other locations being scarcer.

Skin exposure to VC in its liquid phase is of no practical consequence in view of the closed manufacturing process.

2.2 Measuring and Monitoring Methods

During the early industrial manufacture and polymerisation of vinyl chloride only limited measurements at workplace atmospheres were carried out by simple grab sample methods based on :

- the halide lamp detector in which the colour change in a flame was observed when it was supplied with air containing VC. Workplace air samples were taken into a syringe or evacuated flask and tested in the laboratory, the limit of detection being around 500ppm, the ACGIH Threshold Limit Value established in 1959. The method is not specific for VC;
- explosimeters were used for the (non-specific) detection of VC in the 1950s and 1960s. Initially, the limit of detection was around 200 ppm, but it was progressively lowered to about 40 ppm.

  Gradually more sophisticated techniques became available, such as :
- colour-indicator test tubes of the Draeger or Gastec type, with a detection limit of down to 1 ppm depending on the measuring range. The tubes are not specific for VC, since other unsaturated or halogenated hydrocarbons interfere;
- GLC or infra-red absorption techniques specific for detecting vinyl chloride in workplace air samples, which were taken into syringes, evacuated vessels or "gas bags". This technique became available in the 1960s. Its limit of detection depends on sample size, but is usually well below 1 ppm; it has been developed for continuous area monitoring.
- various portable direct reading equipment such as infra-red analyzers with absorption at specific frequencies has also been described (Wilkes and Lavery, 1974; Ketterer, 1974; Thain, 1975).
- non-specific direct-reading instruments, e.g. various flame-ionisation detectors, or more recently photo-ionisation detectors, used since the mid-1970s to determine atmospheric VC at the ppm level.

  Reference has also been made to application of paper-tape analyzers (Denberg and Miller, 1974).

Early measurements of Time Weighted Average (TWA) exposures were often calculated on the basis of the time spent in given areas by the worker and the VC content of grab samples of workplace air taken supposedly nearby. By the early 1970s more sophisticated methods had become available and were increasingly used, permitting TWA measurements to be made by personal monitoring in the worker's breathing zone. Air from the breathing zone is drawn by a small light-weight pump through a carbon

absorber at a pre-set rate. The absorbed vinyl chloride is subsequently analysed by GLC after solvent or thermal desorption (NIOSH, 1975; Hill, 1974; Zado and Rasmusson, 1974; Ketterer, 1974; Thain, 1975). Recently, passive sampling devices (Perkin-Elmer, 1980), i.e. with no pump, have been used for this purpose but further experience is necessary before their performance can be fully validated.

In the early 1970's location monitoring predominantly in VC production and polymerisation plants was developed to give continuously-operating, sequential measurements at a number of fixed locations in the workplace, particularly for plants inside a building. These extensive monitoring systems scan the workplace many times during each shift, providing in addition a near-instant review of the workplace concentration of shift, weekly and monthly exposures.

Since the early 1970s, personal exposure concentrations (TWAs) have been measured with portable equipment carried on the worker.

2.3 Levels of Exposure

2.3.1 VC-production plants

There are little or no published data before the mid-1970s. Oelfke (1974) reported that 8-hour TWAs for personal exposure at two VC plants were in the range of 1 to 45 ppm for all employees. The highest exposures were associated with tank-car filling, and levels were subsequently reduced by careful purging of the loading hoses before disconnection and better techniques for warning of the completion of filling. From 1977 onwards the 8-hour TWA was below 8 ppm (Jones, 1981; Rowe, 1985).

In general, exposure levels in VC production plants, in which the process is continuous and the systems closed, are lower than those in PVC-manufacturing plants where the process is discontinuous and parts of the plant (e.g. autoclaves) have to be opened periodically.

2.3.2 VC-polymerisation plants

There are few data on the exposure of workers in polymerisation halls before the carcinogenic role of VC was discovered in 1974. In 1957, Filatova et al (see Kramer et al, 1972) reported workplace atmospheric levels of VC of 20 to 315 ppm. Kramer

et al (1972) quoted average values of 10 ppm and stated that some workers were exposed to more than 300 ppm TWA. Cook et al (1971) found concentrations of 50 to 100 ppm in reactors after ventilation, i.e. when the autoclave cleaner went down into the autoclave, but levels of 600 to 1000 ppm could be detected around the workers' hands during scraping. Lefevre (cf. Hublet et al, 1977) carried out measurements in 1967 which showed that the average exposure of autoclave scrapers at that time was in the region of the TLV, i.e. 500 ppm. In the epidemiological study carried out by Ott et al (1975) (see also section C.1.1.a), very precise exposure profiles were given for workers carrying out different tasks in the polymerisation units of an American company where continuous monitoring of the atmosphere had been carried out from 1959. These values were significantly lower than those reported above.

Several authors estimated average exposure levels prior to the mid-1970s from the rather limited data available (see Baretta et al, 1969; Ott et al, 1975; Siciu et al, 1975; Barnes, 1976; Hansteen et al, 1978). By about 1974 onwards, when accurate personal monitoring became possible, the levels were much lower (Barnhardt et al, 1975; Milby, 1977; Jones, 1981). The various author's estimates are not very different, and there is general agreement that historical VC concentrations in polymerisation plants were broadly as in Table 2 (Dowrick, 1974; Barnes, 1976).

Until the mid-1970s, peak exposures, probably of greater than 1000 ppm, often occurred during autoclave cleaning. The data in Table 2 are reasonably consistent with the following statement by Sittig (1978):

> "Since early occupational health studies often reported acute toxic effects (dizziness, headaches, nausea, etc.), it can be assumed that peak exposure levels of several thousand ppm were experienced at times. Air monitoring data in one group of PVC plants during the period 1950 to 1959 indicate that 8 hour TWA exposures in these facilities were in the range 120 to 385 ppm. This may not be typical of exposure in all PVC plants. Peak exposures probably exceeded 1,000 ppm".

The progress made in lowering the weekly-average VC concentrations in seven polymerisation plants in the UK during 1974 and 1975 can be seen from Table 3.

This trend has continued to the present day, current average concentrations in plants located in EEC member states falling well within the requirements of the

European Communities Directive (EEC, 1978) on the health of workers exposed to VC, i.e. 8 ppm over 1 h, 7 ppm over 8 hs, 6 ppm over 1 week, 5 ppm over 1 month and 3 ppm over 1 year.

2.3.3 PVC-processing plants

Atmospheric VC-concentrations at these workplaces were, even in the early 1970s, generally below 2 ppm (Dowrick, 1974; Becker, 1974), although intermittent personal exposures of 60-120 and 1.5-2.2 ppm at the site of mixing and blending operations at 70-110°C and 46-68°C, respectively, were recorded by Oberg (1974). Magnavita et al (1983) made grab sample measurements at a single PVC-processing plant from 1972 onwards, finding atmospheric concentrations of 50 ppm or more in 1972, falling generally to 1 ppm in 1974 (with occasional peaks at 10 ppm) and to lower levels in subsequent years with the introduction of degassing procedures.

Because the level of residual VC in PVC has fallen to 1 ppm or less in order to comply with regulatory requirements, eg. EEC (1978), there can be little doubt that current levels in the atmospheres of PVC-processing units are correspondingly lower.

2.3.4 Discussion

Although this brief summary is believed to be a true reflection of historical vinyl chloride exposures, it must be remembered that at some factories worse conditions may have existed than in those for which data are given above. In some countries there is a remarkable clustering of cases of angiosarcoma of the liver in a small number of factories, suggesting that working conditions and standards of hygiene varied between factories. Thus, cases of ASL in PVC-production plants were restricted to 1 out of 16 Japanese factories and 9 out of 28 US factories (23 out of 33 cases were in just 2 plants). At a US chemical PVC plant in Midland, USA, the average concentrations were much lower than those given in Table 2 (Rowe, 1975) As a consequence the results of animal studies by Torkelson et al (1961) stricter in-house standards were introduced, and until now there have been no cases of angiosarcoma of the liver at the plant despite the fact that it started operation in 1950 (Bennett, 1985).

It is clearly difficult to quantify exposures retrospectively, particularly where there are no, or only limited, contemporaneous observations. In any investigation

attempting to relate the incidence of disease to exposure, it is essential that the specific exposure data of the study population be used rather than the general data in the above survey.

It can be seen from the foregoing review that, in relation to the occupational exposure of humans, the inhalation toxicology of VC is of interest in the range of up to about 3 ppm (the EEC 1 year average limit) for current exposures, and up to several thousand ppm for exposures prior to the mid-1970s.

3. EXPOSURE OF THE GENERAL PUBLIC

3.1 BY Inhalation

The general public may be exposed to VC present in ambient air not necessarily originating from VC plants.

Lahmann et al (1978) measured the concentrations of VC at 3 sites in Berlin - a residential suburb; at the side of a road with a high density of traffic; and in the middle of an industrial area. Fifty samples were taken at 15-min. intervals at each site from January to July 1977. The average VC concentration at all 3 sites was between 0.11 and 0.15 ppt (0.3 to 0.4 $\mu g/m^3$).

Exposure of the public to VC also arises from smoking tobacco. In the "mainstream" smoke of a typical 85 mm-long cigarette, 12.2 ng of VC per cigarette were found, the analytical data suggesting that the total inorganic chloride content of tobacco determines the amount of VC formed (Hoffmann et al, 1976).

3.1.1 Plant emission levels

The US Environmental Protection Agency (EPA, 1976) reported that the average VC concentration in air around polymerisation plants was 0.017 ppm (44 $\mu g/m^3$). Gordon and Meeks (1977) sampled air at randomly-chosen locations in industrial regions of Houston, Texas, where 40% of the total US vinyl chloride capacity is situated. In 100 grab samples, 82 contained levels of VC below the detection limit (probably 0.001 ppm, 2.6 $\mu g/m^3$). The highest concentration in the remaining 18 samples was 1.2 ppm (3.2×10^3 $\mu g/m^3$).

A survey of atmospheric VC levels at housing areas within 1 km of all six VC-production plants in the UK was performed to assess the levels to which the inhabitants were exposed (Anon, 1978). Preliminary results from one plant showed that 97% of the readings were below 0.034 ppm, and that the highest daily value was 0.12 ppm, compared with the UK occupational exposure standard of 10 ppm TWA at that time. In a follow up study conducted in 1984 when data was obtained from the same factory sites (Turner et al, 1984) lower ambient VC levels were obtained downwind (measured at 100 to 1050 m from source), except during period of minor plant malfunction. For the entire two month sample period details were :

Site No.	Distance from emission point (m)	Overall 24 hr mean, ppm		Highest daily 24 hr reading, ppm	
		1976-78	1984	1976-78	1984
1	670	0.015	<0.005	0.12	0.011
2	570-1000	0.028	<0.005	0.23	0.009
3	680	0.008	<0.005	0.10	0.038
4	100-1050	0.020	0.088	0.17	0.84
5	180-540	0.029	0.020	0.37	0.20

The data for Site 4 are not exactly comparable, production capacity had increased and the only pratical sampling point was close to the plant (100 m).

Dimmick (1981) reported the analyses of samples taken in the vicinity of VC-producing, PVC-producing and PVC-processing plants. The location of sampling is not very clear, but seems to have been on the factory property outside of the plant buildings or area. The findings were as follows:

- VC plants : the arithmetic mean of grab samples taken at more than 1000 m. from the plant (the distance was not better defined in the paper) was 0.0013 ppm (3.4 $\mu g/m^3$). The maximum 24-hour average concentration was 10.4 ppm (27 x 10^3 $\mu g/m^3$), probably in the direct vicinity of the plant.
- PVC production plants : the arithmetic mean of grab samples at more than 1000 m from the plant was 0.044 ppm (11.5 $\mu g/m^3$).
- PVC-processing plants : the highest 24-hour average concentration around the plant was 0.007 ppm (17 $\mu g/m^3$). Out of 313 samples, the 24-hour average concentration of 224 of them was below the limit of detection, ie. 0.0005 ppm (1.3 $\mu g/m^3$).

In recent years despite maintaining capacity, emissions have been lowered, for example the Dutch Ministry of Physical Planning and Environmental Housing quote emission levels of VC in the Netherlands to be :

year	air emission (tons)
1975	4,073
1978	1,340
1981	356

(NL, Ministrie van Volkshuisvesting, Ruimtelijke Ordering en Milieubeheer, 1984).

In the above Dutch Criteria Document an estimate is given of the inhalation exposure of the Dutch population. The average concentration in the Netherlands as a whole calculated from the emission and dispersion data is 0.00001 ppm (0.2 $\mu g/m^3$). The highest concentrations were calculated to be 0.001 ppm (2 $\mu g/m^3$) (annual average). Close to VC and PVC plants calculated average concentration ranges from 0.003 ppm (8 $\mu g/m^3$) at a distance of about 1Km to 0.0005 ppm (1 $\mu g/m^3$) at a distance of 5 Km.

From regional maps and population density data it seems reasonable to assume that 0.01 % of the Dutch population is exposed to average levels of 0.002 ppm (5-6 $\mu g/m^3$), 0.04% to levels of 0.0015 ppm (4-5 $\mu g/m^3$), and 0.05 % to 0.0013 ppm (3-4 $\mu g/m^3$). Calculated daily exposure therefore ranges from 4 μgr per person per day on average to more than 100 μgr for the upper 0.01 % (5-6 $\mu g/m^3$) of the population.

Another example of the reduction measures over recent years can be found on page 31-32 of the Dutch Criteria Document :

Emission of 320 kg VC/hour was dramatically reduced after 1976/77 to 20 kg/hr. This naturally has reduced the surrounding ambient air concentrations, as illustrated below.

Year	Distance from plant	Samples	Concentrations g/m³	Concentrations ppm
1976-77	> 600 m	average concentration	210	0.081
	600 m	maximum concentration	600	0.231
post	0-200 m	average concentration	86	0.033
1976-77	200-500 m	average concentration	55	0.021
	>500 m	average concentration	18	0.007

3.1.2 Legislation regarding inhalation

The Task Force is not aware of official and enforceable regulations on maximum ambient air concentrations for VC in Western Europe.

In The Netherlands an unofficial target concentration of maximum 1 µg/m³ for ambient air is being used. This value is based on an estimation that continuous exposure to 0.001 mg VC/m³ (3.8 ppb) corresponds to an additional cancer mortality risk of 1 in 10^6 per lifetime for the general population (Netherlands Health Council, 1987).

3.2 By Ingestion

Many consumer goods are packaged in various physical forms of PVC or VC-copolymers. The general public is thus potentially exposed to very small amounts of VC when it consumes or uses the goods becauses residual VC in the polymer or copolymer can migrate into the packaged contents.

3.2.1 Sources of ingestion

PVC, and VC copolymers, are widely-used in food packaging in the form of :

- bottles produced by blow-moulding for containing liquid foods, beverages, cooking oils, vinegar, etc.;
- rigid film (either calendered or extruded) which is converted into tubs and shaped containers by subsequent vacuum- or pressure-forming, for the packaging of butter, rye-bread, sweets, biscuits, salads, etc.;
- flexible film, manufactured by blowing or calendering, which is generally applied to wrapping solid foods such as cheese, meat, sandwiches and vegetables and sometimes cheese;
- coatings in metal cans.

Another important use of PVC is in pipes and auxiliaries for the transport of potable water. In a number of countries a considerable part of the water network consists of plastic - mainly PVC - pipes.

Two other sources of potential oral exposure to VC are via PVC-based packaging for pharmaceuticals and toys. In comparison with the other areas of application mentioned above, however, exposure to VC originating from these sources is negligible.

3.2.2 General aspects of ingestion via migration

Migration is the mass transfer of a substance to a medium in contact with it. Potential health hazards exist when substances migrate from a packaging material into food in significant quantities. Because so many different types of food are wrapped in PVC, migration into food and drink has been established by the use of simulants (EEC, 1980, 1981, 1985, FDA, 1986).

Ethyl Corporation Inc, in a series of reports to the FDA dating from 1975 have developed a model of the migration of VC from PVC into food simulants (FDA, 1986).This accurately predicted the extent of migration from bottles containing from 80 to 330 ppm of VC. The FDA later confirmed the accuracy of the model with PVC sheet containing much lower concentrations of VC : sheets containing 0.44 and 0.28 ppm of VC, in contact with 50% aqueous-ethanol,for 19 days at 49°C gave concentrations of 2.4 and 1.6 ppb in the simulant respectively (Diachenko et al, 1977). The model predicts that migration will occur even if the VC level is below 1 ppm, as confirmed by the above figures.

It has been argued that in PVC containing less than 1 ppm of VC the monomer the latter is bound to active sites and will not migrate (Kontominas et al, 1985). The FDA (1986) did not support this hypothesis.

3.2.3 Typical values for VC in PVC articles and in food

Evidence has been produced showing that the VC content of a fabricated article is influenced by each link in the production chain (UK-MAFF, 1978). The initial VC content of the newly-produced polymer used for blending influences the residual VC content since monomer is lost during intermediate storage. The VC present in the powdering blend is influenced by the processing conditions, which in turn affect

the VC content of the fabricated article. The amount of VC detected in food simulants has been shown to be clearly related to the level in the packaging material, the storage time, and the temperature.

A number of investigations on the residual VC content in PVC packaging materials and in food or drink in contact with them have been reported in the literature during the past few years (UK-MAFF, 1974; Fuchs et al, 1975; Rösli et al, 1975; Ehtesham-Ud Din et al, 1977; UK-MAFF, 1978; van Lierop, 1979; Codex Committee, 1984). Because in this report we are concerned with the potential cancer risk from VC in food and drink at current levels, only the more recent data on these are discussed below.

a) Levels of VC in polymers. A significant reduction in these levels has been achieved since 1974. The UK-MAFF (1978, 1984) reported that whereas in 1974 only about 20% of PVC bottles analysed contained less than 10 ppm of residual VC, by early 1977 all contained less than 1 ppm.

   Substantiation of this reduction has been provided by reports from the U.S. Society of the Plastics Industry (SPI, 1987) of VC levels of 10 ppb in PVC bottles and from Union Carbide (1980) on an estimate 100 ppt VC in can coatings.

b) Levels in food and drink. These have also fallen substantially since 1974 as shown by the UK-MAFF (1978, 1984). VC levels in concentrated fruit drink and cooking oil fell from over 100 ppb in 1974 to less than 2 ppb (the limit of detection of the method of analysis) by 1977.

A recent review (Codex Committee, 1984) demonstrated, that in general, residual VC levels in food and drink are well below 10 ppb, a maximum value which is higher than some of the earlier values noted above.

The UK-MAFF (1987) have provided the results of a three laboratory -survey of residual VC levels in food and drink undertaken during 1986. 50 samples were analysed using methods of analysis with limits of detection ranging from 0.1 ppb to 2 ppb. VC was detected in only 5 of these samples, the highest recorded levels being 0.04 ppb (sic) in sunflower oil and 0.74 ppb in orange drink.

Kontominas et al (1985) studied the migration of VC from PVC bottles into selected food simulants; distilled water, 3 % acetic acid, n-heptane and olive oil. Under

exaggerated storage conditions (4 months at 35°C), migration of VC from the bottles containing the highest residual level (121 ppb) resulted in concentrations of 1.8 ppb in n-heptane and 1.7 ppb in olive oil.

3.2.4 Estimated average intake of VC by ingestion

By considering the typical daily consumption of various foods and drinks by human beings, and their VC content, the average daily intake of VC can be estimated. The maximum VC intake/person/day in the UK thus was calculated to be 0.1 µg in 1976 (UK MAFF, 1978) but less than 0.02 µg/d in 1978 (MAFF, 1984). The FDA (1986) arrived at similar values. They calculated the intakes from : oil, liquor and wine bottles; food packed in PVC, or VC-VDC co-polymer, film, and other sources. The upper limits of these were summed to give a total maximum daily intake of 0.025 µg (25 ng).

3.2.5 Evaluation of risk to VC by ingestion

Til et al (1983) have estimated the cancer risk in humans from the oral intake of VC, based on the results of a study in which rats were fed a diet containing VC as residual monomer in PVC. They used a linear model to extrapolate their results to man and estimated that at an oral intake of 0.4 µg of VC per person per day the risk of cancer was 1 in 10^6. They concluded on the basis intake values at 0.1 µg the risk of cancer was further lowered by a factor of 4. They noted that the linear extrapolation model is conservative and concluded that :

> "translated into practical terms this means that the cancer risk of a maximum daily intake of 0.1 µg of VC/person/day is small enough to be practically neglected".

The FDA (1986) also used the results of the animal studies by Til et al (1983), and together with their own estimated daily intake of 0.025 µg/person/day, to calculate an individual lifetime risk of below 1 in 10^7. The linear proportional model used was said by the FDA to exaggerate the risk, and they added that

> "Because of numerous conservatisms in the exposure estimates, lifetime-averaged individual exposure is expected to be substantially less than 25 ng/day".

ECETOC (1982) has expressed its reservations about the validity of mathematical models for estimating the risk of cancer in humans by : extrapolating data from animal experiments. It should be emphasised that linear extrapolation models over-estimate the risk at low dose and this gives more weight to the conclusions of Til et al and the FDA that the cancer risk from consumption of foods and drinks containing VC at present levels is negligible.

3.2.6 Legislation affecting the use of PVC for food packaging

The EEC (1976) has published a General Directive defining health, safety and organoleptic requirements for food packaging materials. In its 1978 Directive the EC established a 1 ppm limit for residual VC in PVC used for food contact applications, and a 10 ppb limit in the food. Further Directives, EEC (1980, 1981) describe the analytical methods for the determination of VC in the polymer and food respectively.

In the United States the Food and Drug Administration (FDA, 1986) has recently published new more stringent regulations on the use of PVC in contact with food. The residual VC content in the polymer should be limited to :

- 5 ppb in VC homo- or co-polymer films and coatings, and plasticised PVC bottles;
- 10 ppb in rigid PVC;
- 50 ppb in water-pipes and vinyl chloride-vinylidene chloride copolymer films.

3.3 Summary and Risk Assessment

The exposure to the general public is primarily from ambient air, 0.2 µg VC/m³ (Lahman et al,1978) up to 18 µg VC/m³ in the immedicate vicinity of VC and PVC plants.

Calculation of daily inhalation rates indicates the amount inhaled ranges from 4 µg/person/day on average to more than 100 µg/person/day for a very small part of the population living immediately adjacent to VC and PVC plants. Less than 50% of the inhaled amount is retained and metabolised.

Exposure from food sources is less than 0.1 µg/d.

Risk assessment should therefore concentrate on inhalation exposure, and reference is therefore made to the report of the Netherlands National Health Council (1987) who estimated that continuous exposure to 0.001 mg VC/m^3 (corresponding to an inhalation dose of 20 µg/person/day) leads to an additional cancer mortality risk of 1 in 10^6 per lifetime for the general population.

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 Significiance (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 onsecutive 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 :

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.

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.

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 :

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 5560, 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.

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 8 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 :

- 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.

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

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.

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.

	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.

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

(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

frequent X-ray exposures and that the positive results could be attributed to X-rays rather than VC. Both Hansteen et al (1978) and Anderson et al (1980) found a decrease in chromosomal aberrations of circulating lymphocytes to the levels found in control groups (people on-site or off-site not exposed to vinyl chloride) with the improvement of plant hygiene. Fleig and Thiess (1978) failed to demonstrate an increased frequency of chromosomal aberrations in 10 persons classified as "exposed persons showing no symptoms of VC illness". Picciano et al (1977) failed to show an increased prevalence of chromosomal abberations in 209 workers employed for up to 28 years in a VC plant. The average exposure had been to 50 ppm or less since 1959. Two studies reported that there was a small increase in sister chromatid exchange rate (Kucerova et al, 1979; Georgevia and Tsoneva, 1981), whereas two other studies failed to demonstrate such an increase (Hansteen et al, 1978; Anderson et al, 1981).

In the bone marrow cells of VC exposed workers the frequency of chromosomal breakage was higher than that reported for unexposed people (Hansteen et al, 1978). The urine of workers exposed to VC did not induced mutations in the Salmonella typhimurium strain TA100, even in the presence of rat liver homogenates or β-glucuronidase (Matlern et al,1977).

Some other studies on the possible effects of VC on reproduction are also noted here for completeness. Infante et al (1976) compared the outcome of pregnancies in the wives of workers before and after they had been exposed to VC with the outcome in the wives of workers in the PVC-processing and rubber industries. They found an excess of foetal loss in the group of wives whose husbands had been exposed to VC. However, Paddle (1976) and Clemmensen (1982) pointed out some fallacies in the study, and Downs et al (1977) have questioned some of the reported findings on the clastogenic, mutagenic and genotoxic effects of VC, concluding that there was evidence of an association between occupational exposure to VC and chromosomal abberations in the lymphocytes, but none for an association between foetal loss in wives and exposure of the husbands, or between exposure to VC and excess birth defects in communities near PVC-production plants.

Infante et al (1976) reported higher incidences of birth defects (cleft lip and palate, abnormal genital organs, clubfoot, and abnormalities in the CNS) in communities in Ohio where PVC polymerisation plants were located. Edmonds et al (1976) reinvestigated the data and found no correlation between congenital abnormalities of the CNS and exposure to VC. In Canada, Thèriault et al (1983)

found higher incidences of birth defects, among them abnormalities of the CNS, in a community where a PVC polymerisation plant was located. The occupational and residential histories of parents who gave birth to malformed infants and normal infants (controls) did not indicate an association with exposure.

2.2 Conclusions

Exposure to VC causes chromosomal abberations in human beings, but only at the levels existing before the marked reduction in occupational exposure in the mid-1970's. It is uncertain whether it causes changes in the rate of sister chromatid exchange. From the scant evidence available it seems unlikely that VC has caused any adverse effects on human health via its mutagenic potential.

3. OTHER EFFECTS RELEVANT TO CARCINOGENICITY OR MUTAGENICITY

In this section, long-term effects of exposure to VC which are relevant to its carcinogenicity are reviewed. Fortwengler et al (1981) have shown that ASL originates from effects in the endothelial cells and this type of cell may also be involved in the development of acro-osteolysis (AOL) and non-malignant liver diseases related to liver cancers.

3.1 Non-malignant Liver Diseases

Jühe et al (1973) investigated W. German PVC-production workers with symptoms resembling progressive scleroderma. Three of a group of 13 had a history of bleeding from oesophageal varices due to portal hypertension.

Tribukh et al (1949) studied a group of 73 workers at a plant in the Soviet Union at which PVC resins were manufactured and compounded. Twenty-one subjects were found to have "anicteric hepatitis" (hepatitis without jaundice) and the authors reported non-tender hepatomegaly but gave no details.

Suciu et al (1963, 1975) reported that 30% of a group of 168 workers at two Rumanian PVC-production plants had hepatomegaly, and this was associated with splenomegaly in 6%. The VC concentration in the working environment was 880 ppm. Four years later, following a reduction in this concentration to 38 ppm, the prevalence of hepatogegaly was only 11%.

Marsteller et al (1973) found varying degrees of non-cirrhotic portal fibrosis, perisinusoidal fibrosis and subcapsular fibrosis of the liver in all of a group of 20 male PVC-production workers. The prevalence of findings related to liver disease was :

- increased bromsulphthalein (BSP) retention	19/20
- thrombocytopenia	16/20
- hepatic-spleen surface alterations on peritoneoscopy	14/20
- splenomegaly	7/20
- hepatomegaly	6/20
- acroosteolysis	4/20
- oesophageal varices	3/20

The subjects were aged 30-56 years at diagnosis and their exposure time was 1.5-21 years. No information on exposure levels was given but all 20 workers had been engaged in autoclave cleaning, some of them full-time. Barnes (1976) suggested that in the early 1950s autoclave cleaners had been exposed to levels of VC of up to 3000 ppm.

After the first report that exposure to VC was related to ASL (Creech and Johnson, 1974) the performance of liver-function tests on workers exposed to VC was extended and it later appeared that non-cirrhotic portal fibrosis leading to portal hypertension was a more common lesion than was ASL (Lelbach and Marsteller, 1981; Jones and Smith, 1982). Non-cirrhotic portal hypertension and ASL are both rare. Iber (1969) estimated that of all subjects with portal hypertension similar to that encountered in cirrhosis or portal vein blockage, 3 to 5% had normal liver morphology.

Falk et al (1974) reviewed the pathology of liver biopsy specimens from VC exposed workers and with non-malignant liver disease or ASL. They suggested that there was a close histological similarity between these two diseases, both leading to portal fibrosis and sinusoidal changes. The progression of VC-induced hepatic fibrosis to ASL has been described by Smith et al (1976), Lelbach and Marsteller (1981) and Jones and Smith (1982) who suggested that periportal fibrosis and sinusoidal changes were precursors to ASL. Hepatic sinusoidal cells include endothelial cells, and Fortwengler et al (1981) have given evidence that VC-induced ASL has its origin in endothelial cells. They demonstrated an increase in factor VIII, a known marker for endothelial cells, in the tumour cells of ASL cases, suggesting that the endothelial cells were the target. Hepatocytes may not be the target cells for toxic action, which would explain why the standard biochemical liver-function tests

were of limited value for the early detection of non-cirrhotic portal hypertension and ASL in populations at risk (Creek and Makk, 1975; Williams et al, 1976; Lee et al, 1977).

3.2 Acro-osteolysis (AOL), Raynaud's Phenomenon and Effects on the Skin

Filatova and Gronsberg (1957) published one of the earliest papers to record adverse effects from exposure to VC, finding effects similar to Raynaud's phenomenon ("toxic angioneurosis") in exposed workers. A few years later, Smirnova (1961) reported finding destructive bone lesions of the terminal phalanges of the hand in PVC-production workers exposed to VC for between 3 and 9 years. Those affected also had symptoms similar to those of Raynaud's phenomenon, and Smirnova believed that the bone lesions were caused by the exposure to VC. Suciu et al (1963, 1975) found Raynaud's phenomenon in 6% and scleroderma in 3.6%, of the work-force of 168 at two Rumanian PVC-producing plants where the VC concentration in the working atmosphere was 880 ppm. After this had been lowered to 37 ppm, the prevalence of Raynaud's phenomenon fell to 2.9% and that of scleroderma to zero. The authors did not mention finding any bone lesions such as AOL.

Cordier et al (1966) described AOL of the hands in two male autoclave cleaners at a Belgian PVC-production plant. Several months after starting this work they developed the symptoms of Raynaud's phenomenon, eruptions on the skin of the hands, asthma and drowsiness. The most striking sign, however, was radiological evidence of lysis of some terminal phalanges of the hand and, in one case, the feet. In the succeeding years additional cases were reported from France (Chatelian and Motillon, 1967), Great Britain (Harris and Adams, 1967) and the USA (Wilson et al,1967). These last authors found 31 cases among 3,000 employees engaged in VC- and PVC-production. Dinman et al (1971) observed a strong association of AOL with PVC autoclave cleaning (1 case per 72 workers at risk) and the bagging and packing of PVC (1 case per 86 at risk), but found no cases among the 1,257 employees working on the compounding of PVC resins.

The first cases of AOL in W. Germany were observed by Jühe and Lange (1972) among workers at PVC plants. Initially the clinical findings resembled systemic sclerosis and it emerged that some workers, mainly occupied as autoclave cleaners, had a history of bleeding from oesophagal varices due to portal hypertension. Arteriographic evaluation of the vascular tree of the hands showed the presence of vascular lesions confined to the small digital arteries, although there was some

narrowing of the superficial and deep palmar arterial arch (Lange et al, 1974). Arterial irregularities and segmental stenosis were accompanied by retardation of the flow of the contrast medium and peculiar tortuosities of the patent arteries. The results of arteriography correlated well with those of non-invasive methods such as photoplethysmography, neography and thermography.

Ward et al (1976) demonstrated that circulating immune complexes were present in 19 out of 28 patients with "VC disease", ie. Raynaud's phenomenon, AOL, thrombocytopenia, portal fibrosis, and hepatic and pulmonary dysfunction. They suggested that the disease was an immune complex disorder, a suggestion also made by Langauer-Lewowicka et al (1976). Lange et al (1974) had already concluded from their results that there was no convincing evidence that VC disease was an auto-immune disease.

3.3 Conclusions

Vinyl chloride-induced chronic toxicity affects the endothelial lining of the liver sinusoids from which ASL originates. Exposure to VC may also lead to periportal fibrosis and to changes in the distal vasculature of the hands manifested by the development of Raynaud's phenomenon, scleroderma or AOL. It is not clear whether these lesions are caused by VC itself or its metabolites. These effects were seen in workers exposed in the 1950s and 1960s. There have been no reports of such effects in workers whose exposure to VC started in the early 1970s when exposure levels in most countries were lowered to a few ppm.

D. EXPERIMENTAL TOXICOLOGY

1. CARCINOGENICITY

1.1 Exposure by Inhalation

1.1.1 Viola's initial experiment

The first investigation of the long-term effects of VC on animals was carried out in the Institute of General Pathology, Perugia, and was reported by Viola (1970, 1971). It was undertaken in an attempt to produce AOL in experimental animals. A group of 26 3-month old male Wistar rats of the IRE strain were exposed to VC at a concentration of 3% v/v in the inhaled air for 4 h/d, 5 d/wk for 12 months. Twenty-five rats of the same strain served as controls. The animals were slightly sleepy but otherwise appeared to tolerate these high exposures well. Tumours started to appear after the 10th month of treatment and the experiment was terminated after 12 months. Seventeen rats survived beyond the 10th month and epidermoid tumours appeared in the para-auricular region in all of them. Fourteen of these tumours were reported to be epidermoid carcinomas, 2 muco-epidermoid carcinomas and one a papilloma. Five of the 17 animals had osteochondromas and 7 had lung tumours, but no haemangiosarcomas were reported. The epidermoid tumours were reviewed by other pathologists and re-classified as Zymbal gland carcinomas and the lung tumours were metastases from the Zymbal gland carcinomas (Maltoni et al, 1974, 1975). No tumours of these types were observed in the control rats.

1.1.2 Investigations by Maltoni - BT series

Because the Viola study indicated a risk of cancer from occupational and environmental exposure to VC, its carcinogenicity was then thoroughly investigated in laboratory rodents by Maltoni. Maltoni numbered his experiments BT 1, BT 2, etc. and the detailed results of the experiments are tabulated in a book, Maltoni et al (1984). Three earlier papers containing details of the design of the BT series of experiments as well as some important interim and final results are cited in Table 7. As the tumourigenic response in experiments BT 3 and BT 15 was low due to inadequate dosage discussion of these experiments have not been included in this report.

In an extensive series of studies, Maltoni administered VC in air to adult rats, mice and hamsters, and VC dissolved in olive oil, to rats by the oral and parenteral routes. He also exposed pregnant and neonatal rats to VC by inhalation to examine the sensitivity of foetal and newly-born animals.

1.1.2.a Dose-response in Sprague-Dawlay rats exposed by inhalation

In one of these studies (BT 6, Table 8) the Viola experiment was repeated. A group of 30 male and 30 female Sprague-Dawley rats was exposed to 30,000 ppm of VC for 52 weeks and killed at 68 weeks. Zymbal gland carcinomas were observed as in Viola's experiment. In addition a high incidence of angiosarcomas and forestomach tumours but no bone or cartilaginous tumours were induced. It is difficult to account for this discrepancy. The longer period of observation in Maltoni's study may have allowed more time for the development of the hepatic tumours but there appears to be no explanation for the absence of bone lesions. The increase in the incidence of forestomach tumours was not observed in later experiments and appears to be an isolated observation.

The carcinogenicity of VC was convincingly demonstrated in a dose-response study on Sprague-Dawley rats (BT 1, Table 9). Animals of both sexes were exposed to a wide range of concentrations of VC from 50 ppm at the lowest level to 10,000 ppm at the highest for 4 h/d, 5 d/wk over 52 weeks. The experiment was terminated at 135 weeks. There was a clear dose-response relationship for Zymbal gland tumours and hepatic angiosarcomas, but it was less clear for hepatomas, nephroblastomas and brain tumours although the increased incidence of these appeared to be treatment-related. In particular, a haemangiosarcoma, a rare tumour in rats, was observed in a female rat at 50 ppm. Other tumours (mammary gland, forestomach, papillomas and leukaemias) occurred in both test and control groups and were randomly distributed. There was also an indication of a reduction in the latent period of the treatment-related tumours compared with that of the same type of tumours occurring in the control group.

1.1.2.b Other dose-response inhalation experiments in Sprague-Dawley rats

The occurrence of haemangiosarcomas at 50 ppm prompted further dose-response experiments (BT 2 and BT 15, Tables 10 and 11) to explore further the carcinogenicity of VC at relatively low levels of exposure. In one of these experiments (BT 2) a comparatively narrow range of concentrations was investigated,

ie. 100, 150, and 200 ppm, and the number of rats exposed was twice that in the previous experiment (BT 1). The regime of exposure was the same as in BT 1 and exposure was maintained for 52 weeks, the experiment being terminated at 143 weeks. Haemangiosarcomas and nephroblastomas occurred in the treated animals but not in the controls. Zymbal gland carcinomas occurred in the females in the treated groups at all dose levels and also in the controls. The highest incidence of these tumours occurred in males at the 200 ppm dose, but no such tumours were observed in males at the lower dose-levels. A few hepatomas occurred late in the experiment in both sexes at the highest dose and in male control animals. In addition, mammary gland tumours, leukaemias and forestomach papillomas were observed in this experiment, and were randomly distributed in test and control groups. No brain tumours were observed. This experiment confirmed the carcinogenic activity of VC to the Sprague-Dawley rat at exposure levels between 100 and 200 ppm.

In experiment BT 15, 13-week old Sprague-Dawley rats were exposed to 0, 1, 5, 10 and 25 ppm of VC for 52 weeks (Table 11). Treatment was then stopped and the rats allowed to live free of exposure until the termination of the experiment at 147 weeks. Zymbal gland carcinomas occurred in all treated groups and in 2 males in the control group. Angiosarcoma occurred in both sexes at the highest concentration only and predominantly in females. At this concentration one hepatoma was observed in one female and one nephroblastoma in one male. No brain tumours were observed.

In experiment BT 15 the carcinogenic effect of VC at 25 ppm rested principally on the induction of haemangiosarcoma in the female, and reflects the higher incidence of this type of tumour in the exposed females compared with males which was found in other experiments in this series. This sex difference was clearly observed in experiment BT 9 (Table 12) when VC was administered by inhalation to comparatively large groups of rats (5 times the number used in BT 1 experiment) at 50 ppm. In this experiment the incidence of hepatic angiosarcoma in females was 6 times that found in males. Zymbal gland carcinomas and brain tumours were also treatment-related but for these there was virtually no sex difference.

Experiment BT 9 was presumably carried out to explore further the incidence of less frequently observed cancer at a low level of exposure (50 ppm) since the number of VC-related tumours at the same level in experiment BT 1 was very low.

1.1.2.c Inhalation experiments in Wistar strain rats

Maltoni's design of the experiment on Wistar rats (BT 7, Table 13) followed closely that of his original study on Sprague-Dawley rats (BT 1). The concentrations at which VC was administered, the regimen of exposure and duration of treatment were the same. The time of observation was about 30 weeks longer, the experiment being terminated after 165 instead of 135 weeks. For an unknown reason only males were employed in this experiment. The results mirrored closely those obtained in males in experiment BT 1. There was unquestionably a dose-related incidence of hepatic angiosarcoma, while the incidence of Zymbal gland carcinomas, nephroblastomas, hepatomas and brain tumours appeared to be treatment-related but not dose-related. With the exception of hepatic angiosarcoma, the incidence of the tumours was lower than that observed in BT 1, the comparable experiment on Sprague-Dawley rats. Apart from these tumours, a few mammary adenocarcinomas, skin carcinomas and leukaemias were observed, occurring randomly in the test and control groups.

In experiment BT 17 three extra-hepatic angiosarcomas were observed when 120 male Wistar rats were exposed to 1 ppm VC 4h/d, 5d/wk for 52 wks and observed for a further 82 wks (Table 13).

1.1.2.d Inhalation experiments in Swiss albino mice

In Maltoni's experiment BT 4 (Table 14) groups of 30 male and 30 female weanling Swiss Albino mice were exposed to the same levels of VC as were Sprague-Dawley rats in BT 1, and the Wistar rats in BT 7. Double this number were allocated to the control groups. Mortality was low in the control groups, but increased with the increase in exposure level in the treated groups. Despite the lower survival in the treated groups there was a clear increase in the incidence of hepatic haemangiosarcoma, pulmonary adenocarcinoma and mammary gland tumours. A dose-response relationship for the number of cancer observed was not so clearly evident, presumably because of the increased mortality. On the other hand, there was a dose-related shortening of the average latency period, particularly noticeable for pulmonary adenomas and mammary gland tumours. Such a shortening was not particularly conspicuous for the hepatic angiosarcomas.

1.1.2.e Inhalation experiments in golden hamsters

In experiment BT 8 (Table 15) Maltoni exposed groups of 32-35 male Syrian golden hamsters to the same concentrations of VC as the Sprague-Dawley rats in BT 1 and the Wistar rats in BT 7. The animals were exposed 4 h/d, 5 d/wk (as for the other species) for 30 weeks, and then allowed a treatment-free period of 79 weeks. A few haemangiosarcomas, melanomas, Zymbal gland tumours and forestomach papillomas were observed in the treated animals. According to the authors, all tumours were compound-related but there was no dose-response relationship for any of them. Because haemangiosarcomas are unknown in untreated hamsters (Greenblatt, 1982) and acoustic-duct tumours are uncommon in this species, there is little doubt that these were induced by VC. In the case of melanomas it is more difficult to come to this conclusion. These tumours are known to occur naturally in this species and the frequency varies from one strain to the next. Because of the total absence of this tumour in the control group and the occurrence of melanoma in each group of hamsters exposed to VC (except at 500 ppm), it is possible that these melanomas occurred as a result of VC exposure. However, statistical analysis by the Fisher exact-probability test failed to show a significant difference between the treated and control animals, and the analysis for possible trends was also negative (see Appendix 2). This is the only species studied in which melanomas have been reported to result from exposure to VC. They have not been observed in other species, presumably because they lack the perifollicular network of melanocytes from which the hamster melanomas arise (Ghadially and Barker, 1960).

1.1.3 Investigations on VC carcinogenesis by other workers

Several other workers have investigated the carcinogenicity of VC. The results obtained in the earlier investigations were confirmed and some other features of VC carcinogenesis were discovered.

1.1.3.a Inhalation experiments in mice

Keplinger et al (1975) observed a pattern of tumour type and incidence similar to those of previous workers when he exposed groups of 100 CD1 Swiss mice of both sexes to 0, 50, 200 or 2,500 ppm of VC in air for 9 months, and kept them for another 9 months without treatment when the experiment was terminated. Forty-nine of the treated mice died with tumours within 8 months of exposure. The incidence of three types of tumours appeared to be related to treatment; lung adenomas, liver

angiosarcoma and mammary adenocarcinomas. The incidence of these tumours in the control and exposed groups (in ascending order of VC concentration) was 0, 2, 11 and 28 respectively for lung adenomas; 0, 2, 11 and 28 for hepatic angiosarcoma; and 0, 2, 3 and 6 for mammary adenocarcinomas.

Lee et al (1978) also found an increased incidence of lung, liver and mammary gland tumours in mice exposed to VC in air. Groups of 36 male and 36 female 2-month old albino CD mice were exposed to 0, 50, 250 and 1,000 ppm of VC for 6 h/d, 5 d/wk for 52 weeks (Table 16). The exposed animals showed some signs of toxicity from the 6th month onwards, the experiment being terminated at 12 months. Most of the treated animals had died by the 10th month. All dead animals were examined for tumours. Only one pulmonary adenoma was found, in a male of the control group that had died between the 7th and 9th month. None was observed in females. The absence of any other tumours in the control group is probably due to the unusually short duration of the experiment, which nevertheless confirms the earlier findings of Maltoni and demonstrates that in the mouse the three target organs for VC carcinogenesis are the lung, liver and mammary glands.

The same type of tumour incidence in CD-1 mice exposed to VC was reported in a subsequent publication (Hong et al, 1981). Groups of 8 to 28 2-month-old mice strain were exposed to 0, 50, 250 or 1000 ppm VC, 6 h/d, 5 d/week by inhalation for 1, 3 or 6 months. Each group was allowed to live for a further 12 months after the end of the exposure period. The cumulative tumour incidence is given in Table 17.

In both the Keplinger and the Lee experiments the incidences of tumours were dose-related. Holmberg et al (1976) conducted an experiment on mice and, in contrast to the findings of other workers, reported that haemangiosarcomas developed only in extra-hepatic sites. Two groups, each of 12 male and 12 female NMAI outbred albino mice, were exposed by inhalation to 50 or 500 ppm of VC in air, 6 h/d, 5 d/wk. Control groups of the same numbers were taken for both of these dose levels. Most of the mice, particularly those exposed to 500 ppm, were in poor condition and were killed at 26 weeks, the rest dying progressively over the next 25 weeks. Of the animals exposed to 50 ppm, 6 male and 8 female mice developed haemangiosarcoma in the fatty tissue of the abdominal cavity. One female and 3 male mice also had a tumour of the same type in the subcutaneous region. The first tumour appeared at the 36th week in females and at the 46th week in males. Nine males and 4 females from this group developed pulmonary adenomas, the first tumour in males appearing at 26 weeks and in females at 39 weeks. All of the animals

exposed to 500 ppm developed pulmonary adenomas. In addition, 4 female mice developed mammary adenocarcinoma and 3 male and 5 female mice developed haemangiosarcomas in the abdominal fat, the first tumours appearing in males at week 39 and in females at week 36. One male rat developed an angiosarcoma of the liver as well as an abdominal haemangiosarcoma. Only 3 tumours were observed in control animals: a mammary gland adenocarcinoma, a dysgerminoma of the ovary, and a reticulum cell sarcoma of the spleen.

1.1.3.b Inhalation experiments in rats

Lee et al (1978) reported the development of a dose-related incidence of haemangiosarcoma in male and female CD-1 rats exposed to 0, 50, 250 or 1,000 ppm of VC, 6 h/d, 5 d/wk for 12 months, at which time the experiment was terminated. There was a much higher incidence of hepatic haemangiosarcoma in the females than in the males. A few angiosarcomas occurred in extra-hepatic sites but these were not dose-related and were randomly distributed in treated male and female rats, but not in the control animals. Other tumours which occur normally in this strain of rat were also observed but were randomly distributed in exposed and control animals. The number of animals with hepatic haemangiosarcoma in males was 0 (controls), 0, 2, and 6 out of a group of 36 rats for each dose level, and in females was 0 (controls), 0, 10, 15, out of groups of similar size. The incidence of extra-hepatic haemangiosarcomas was 0 (controls), 1, 2, 0 in males and 0 (controls), 1, 0, 1 in females.

Other tumours were found to be randomly distributed in both test and control rats. No zymbal gland carcinomas, nephroblastomas or brain tumours were reported.

In another experiment on the same strain of rats (Hong et al, 1981) groups of 4-16 rats of each sex were exposed to 0, 50, 250 or 1000 ppm VC by inhalation 6 h/d, 5 d/wk for 1, 3, 6 or 10 months. The rats were allowed to live free of treatment for a further 12 months. The cumulative incidence of tumours is given in Table 18. In addition to haemangiosarcoma, a dose-related incidence was also found in respect of hepatocellular carcinoma, bronchioalveolar tumours and malignant lymphomas. The difference in the pattern of tumour incidence between this experiment and the previous one (Lee et al, 1978) is presumably due to the observation period after exposure which in this experiment allowed tumours to develop in other sites (Table 18).

1.2 Exposure by Routes Other Than Inhalation

1.2.1 Oral administration of VC

Maltoni (1974) conducted 2 experiments (BT 11 and BT 27) in which VC was dissolved in olive oil and administered to rats by gavage. In the first experiment (BT 11, Table 19) dose-levels of 50, 16.6 and 3.33 mg/kgbw were employed, while in the second (BT 27, Table 20) the doses were lower, i.e. 1.0, 0.3 and 0.03 mg/kgbw.

In BT 11, one nephroblastoma and 2 Zymbal gland carcinomas (one each in a male and a female) occurred in the group treated with 50 mg/kgbw. No such tumours were observed at any other dose level. Haemangiosarcomas were found in approximately 25% of the rats of both sexes at the highest dose (50 mg/kgbw) and in 20% of female rats dosed with 16.6 mg/kgbw of VC. Only one male developed haemangiosarcoma at this dose level. No tumours related to VC treatment were observed at the lowest dose in BT 11 but in BT 27, in which twice the number of rats were employed, a hepatic angiosarcoma was found in 1 male and 2 females administered 1.0 mg/kgbw. No other tumours related to VC administration were observed at this dose level. In the remaining 2 dose levels, there were no exposure-related tumours.

From the results of these experiments considered together it is seen that haemangiosarcomas occurred in a dose-related manner, but there were very few Zymbal gland tumours or nephroblastomas and then only at the highest dose in BT 11. No increase in brain tumours were observed in either BT 11 or 27. Other tumours common to the Sprague-Dawley rat were observed but their incidence was comparable to that of the control animals.

Evans et al (1978) administered VC dissolved in drinking water to groups of 54 male and 54 female rats of the Wistar strain, at concentrations of 0, 2.5, 25 or 250 ppm for up to 152 weeks (cf. Table 21). Since VC has a high vapour pressure, a system was devised to ensure that the partial pressure in the container was sufficient to maintain the required concentration in the drinking water. In rats receiving the highest dose there was a significantly higher incidence of hepatocellular carcinoma, haemangiosarcoma and mammary gland tumours. One hepatic and one subcutaneous angiosarcoma were observed in male rats receiving 25 ppm of VC. No increased incidence of tumours occurred at the lowest dose.

1.2.2 Oral administration of VC adsorbed on PVC powder

The carcinogenicity of VC administered by the oral route was investigated by incorporating VC in PVC powder and then mixing the PVC powder with the rat diet (Feron, 1981). This diet was provided for 4 h/d throughout the duration of the experiment. No other food was given during the next 20 hours to ensure that the rats consumed the treated diet. This method of administration was thought to simulate the migration of residual VC from PVC wrappings and containers that come into contract with food. Some of the VC incorporated into the PVC powder was lost by evaporation and some remained adsorbed in it after passing through the gastro-intestinal tract, so that the biologically-available VC was less than the amount originally incorporated. The actual dose which the animals absorbed in the control and the 3 dosed groups was estimated to be 0, 1.7, 5.0 and 14.1 mg/kgbw. As a positive control, VC dissolved in edible oil (300 mg/kgbw) was also administered, by gavage.

Groups of 80 Wistar rats of both sexes were allocated to the untreated and positive control groups and to the highest dose group. Groups of 60 Wistar rats of both sexes were allocated to the intermediate and low dose groups. The experiment was terminated when about 75% of the control rats were dead, this point having been reached at wk 135 for M and 144 for F. The results are summarised in Table 22. The incidence of hepatic angiosarcoma was 0 (controls), 0, 6, 27 and 27 (positive controls) in males, in ascending order of VC dose, and similarly 0, 0, 2, 9 and 29 in females. The incidence of hepatocellular carcinoma was 0 (controls) 1, 2, 8 and 1 (positive controls) in males, and 0 (controls), 0, 4, 19, 29, 0 (positive controls) in females. The only other treatment-related tumour was pulmonary angiosarcoma. There was an increased incidence of abdominal mesothelioma in treated as compared to control-group rats, but there was no dose-response relationship and the difference was statistically-significant only in females at the lowest dose level.

In a second study carried out by Til et al (1983) at the same laboratory and with the same method as the previous one, much lower concentrations of VC in PVC were used, the oral doses absorbed being calculated as 0.014, 0.13, 1.3 mg/kgbw (Table 22). A statistically-significant increase in the incidence of liver nodules (presumed to be hepatomas) was the only neoplastic response to the administration of VC at levels below 1.7 mg/kgbw, but both hepatocellular carcinomas and angiosarcomas were found at the highest dose (1.7 mg/kgbw) although in small

numbers. In the previous study, no haemangiosarcomas of the liver were observed at this dose-level.

1.2.3 Parenteral administration of VC in edible oil

These studies (Maltoni et al, 1977) are included for the sake of completeness although the route of administration is not relevant to human exposure. Two groups (75 M and 75 F) of 21-week old Sprague-Dawley rats were administered 1 ml of a solution of VC in olive oil corresponding to 4.25 mg of VC per animal, as a single subcutaneous injection (BT 13). One nephroblastoma was observed in a male. The experiment was terminated at 145 weeks, but data on survival were not given.

The carcinogenicity of VC was also explored by the intraperitoneal route (BT 12, Maltoni, 1977). A single injection of 4.25 mg of VC in olive oil was administered to each animal in the test group (30 male and 30 female Sprague-Dawley rats), 2, 3 or 4 times in 2 months. One nephroblastoma and one subcutaneous angiosarcoma were found. The experiment was terminated after 144 weeks. These experiments are not relevant for assessing the carcinogenicity of VC because the duration of treatment was inadequate.

1.3 Species Studies of Vinyl Chloride Carcinogenesis

1.3.1 Type of pulmonary tumours induced by VC in mice

Suzuki (1978, 1981, 1983) followed up earlier indications from Maltoni's experiments that the incidence of pulmonary adenomas and adenocarcinomas had been consistently reported to increase in a dose-related manner when mice were exposed to VC by inhalation. In his first experiment (1978) the author exposed weanling CD1 male mice to 2,500 or 6,000 ppm of VC, 5 h/d, 5 d/wk for up to 6 months. Groups of mice from each exposure-level were then killed after a treatment-free period of 6, 8 or 37 days. Pulmonary tumours were found in all exposed animals with the exception of one mouse from the group with the highest exposure. Detailed morphological studies carried out on the tumours showed that macroscopically they were round, whitish in colour and 1 to 5 mm in diameter. Histologically, the neoplastic cells were principally arranged as tubulo-papillary and adenomatous formations. "Pleomorphic and atypical structures" were uncommon, suggesting that the tumours were predominantly benign. Ultrastructurally, the neoplastic cells

contained numerous lamellar bodies, microvilli and tubular lumens, indicating that they originated from Type II pneumocytes.

In a second experiment, Suzuki (1981) exposed male CD-1 mice to much lower concentrations of VC. Groups of 30 mice were exposed to 0.1, 10 and 100 ppm of VC for 4 weeks and then left untreated for a further period of 36 weeks. Groups of 1 to 10 mice were sacrificed at 4 and 12 weeks and the remainder killed at 40 weeks. One spontaneous death occurred during this experiment in each of the treated groups. Pulmonary tumours were found only at the terminal kill. Their incidence was 0/10 (controls), 1/9, 2/9 and 5/9 mice.

In a third investigation, Suzuki (1983) studied the response of the mouse lung to inhalation of VC at a range of concentrations for a short period. The results given in Table 23 show a clear dose-response relationship both in the number of pulmonary tumours induced and in the reduction of the time of their appearance.

1.3.2 Effect of single or repeated exposure to VC on tumour induction

The carcinogenic effect resulting from a single or multiple exposure to VC was investigated in rats and mice by Hehir et al (1981). In the "single exposure" part of the experiment, groups of 90 male and 90 female Fischer 344 rats (15 to 16 weeks old at commencement of experiment) were given a single exposure to VC at a concentration of 50, 500 or 50,000 ppm lasting for one hour. They were then left untreated and interim kills were carried out at 8, 16 and 24 months. No treatment-related tumours were observed.

An experiment on the same lines was conducted on ICR Swiss mice. Firstly, groups of 90 male and 90 female mice were exposed once only to 50, 500, 5,000 or 50,000 ppm of VC for one hour and the animals were then sacrificed at 8 and 18 months. Groups of 50 male and 50 female mice were retained as controls. Results from the 8th and 18th month kills were combined. Secondly, the same number of mice were exposed to 50 or 500 ppm of VC, 1 hour daily for 10 or 100 consecutive days. The experiment was terminated at 20 months. Interim kills were carried out at 8 and 16 months. The results are in accord with other studies in mice. In both experiments, there was a dose-related incidence of pulmonary tumours. Furthermore, there is a suggestion that the same total dose resulting from repeated inhalation is more effective in inducing tumours than when given as a single administration (Tables 24 and 25). With a large single administration, only a small proportion is metabolised to the

active intermediate, whereas in repeated smaller doses the proportion metabolised is very much higher, which results in greater damage to the DNA.

1.3.3 Age of rats and susceptibility to tumour induction by VC

The effect of age on the susceptibility to tumour induction by VC was investigated in adult Sprague-Dawley rats of both sexes by Groth et al (1981). The rats were aged 6, 18, 32 or 52 weeks, the number in each treated age group being 110, 119, 116 and 128 males, and 110, 120, 120 and 128 females. A similar number of rats of both sexes in each age group constituted the controls. The rats were exposed by inhalation to 940 ppm of VC vapour, 7 h/d, 5 d/wk for 24 weeks. Interim kills were carried out at 3, 6 and 9 months. The experiment was terminated at the 43rd week. The combined incidence of haemangiosarcoma in the interim and final (43rd week) kills was 1/83, 2/91, 7/94 and 18/102 for males and 2/88, 7/97, 27/98 and 14/104 for females, in increasing order of age group. The author concluded that the older animals were more susceptible to tumour induction than were the younger ones.

Maltoni investigated the carcinogenic potential of VC in rat foetuses and in newly-born rats (BT 5 and BT 14). To test the susceptibility of the foetus to VC, a group of 60 pregnant Sprague-Dawley rats was exposed to 10,000 or 6,000 ppm of VC, 4 h/d from the 12th to the 18th day of pregnancy. After this exposure there was no further treatment either during the rest of the pregnancy or in postnatal life (BT 5). The pregnancy was allowed to terminate naturally and the pups and dams were killed after 143 weeks. No controls were available in this experiment but there was no increase in any of the types of tumours that were found to be increased on exposure to VC in previous experiments. Thus this experiment provided no evidence that VC could act as a transplacental carcinogen. The study on newly-born rats (BT 14, Table 26) showed, however, that those treated for 5 weeks from the day of birth were susceptible to VC carcinogenesis. Forty-four newly-born rats were exposed to 10,000 ppm, and 42 to 6,000 ppm by inhalation, 4 h/d, 5 d/wk for 5 weeks from the day of birth. They were then left untreated until the experiment was terminated at 124 weeks. The results indicated that whereas the breeders, treated for the same length of time as the newly-born, developed no tumours referrable to exposure to VC, a low incidence of hepatic haemangiosarcoma and hepatoma was found in animals treated during the first 5 weeks of postnatal life (Table 26).

These investigations were supplemented by 2 other experiments in which transplacental exposure was combined with exposure after birth, commencing at the perinatal period and continuing for 15 or 76 weeks (BT 4001 and 4006). In these experiments, control animals unexposed to VC were available. One hundred and fourteen pregnant Sprague-Dawley rats were exposed from the 12th day of pregnancy to 2,500 ppm of VC, 4-7 h/d, 5 d/wk for 76 weeks. A total of 554 newly-born rats was then divided into 2 groups, one group being exposed to 2,500 ppm of VC, 4-7 h/d, 5 d/wk for 76 weeks, and the other similarly, but for 15 weeks only. A high incidence of hepatic haemangiosarcomas and hepatomas occurred in all treated groups (Table 27).

The effect of age and duration of exposure on tumour production by VC was further investigated in rats, mice and hamsters by Drew et al (1983). The exposure concentrations were selected to ensure optimal survival at a dose known from previous authors to produce a high incidence of tumours. Groups of 55 to 143 female F344 weanling rats (approximately 9 weeks) old were exposed for 6, 12, 18 and 24 months to 100 ppm VC 6 h/d, 5 d/wk. Rats were then allowed to live out their life-span and were killed when moribund. Other groups of female rats from this strain were held without treatment for 6 or 12 months and then exposed for 6 or 12 months to VC administered by the same regime. One group was held over for 18 months and then exposed for 6 months (Table 28). The tumours induced by VC consisted of haemangiosarcomas, mammary gland adenocarcinomas and benign and malignant tumours of hepatocellular origin. The highest incidence of all these tumours was observed in weanling animals that were treated continuously for 12 months. Treating rats for longer periods did not increase the tumourigenic response except for a marginal increase in the liver.

There seemed to be a decline in sensitivity to VC carcinogenesis with age since rats held without treatment for 12 months or more, and then exposed to VC for 6 or 12 months, failed to produce a significant increase in VC related neoplasms.

Groups of 48 to 69 female mice (approximately 9 weeks old) of the B6C3F1 and CD-1 strain were exposed to 50 ppm VC by the same regimen as rats (Table 29). In mice exposed for 6 months from the beginning of the experiment there was a significant increase in haemangiosarcomas, pulmonary adenomas (CD-1 mice only) and mammary gland carcinomas. There was very little increase in tumour incidence in animals treated with VC for a further 6 or 12 months. The incidence of tumours in mice held over for 6 or 12 months before beginning treatment was of the same order or less

than that observed in mice treated from the beginning of the experiment (Drew et al, 1983).

Groups of 44 to 143 female golden hamsters (approximately 9 weeks old) were exposed to 200 ppm VC by the same regime as rats (Table 30). The highest incidence of haemangiosarcoms, mammary gland carcinoma and stomach adenoma occurred in hamsters exposed for the first 12 months of the experiment. Exposure commencing after a 6-months holding period resulted in less tumours whereas exposure commencing after a holding period of 12 months did not cause any neoplasms. No melanomas were observed in this experiment. This experiment provides evidence that exposure of animals to VC for the first 12-month period from the beginning of the experiment was adequate to provide a clear carcinogenic response. According to the author, there is no indication that older animals are more sensitive to VC carcinogenesis than are the young mature animals. It is worthy of note that no Zymbal gland tumours were observed in any one of the 3 species tested. Skin tumours but not melanomas were observed for the first time in hamsters exposed to VC, while stomach tumours in this species appear to have originated in the glandular portion in contrast to Maltoni's experiment where stomach tumours originated in the squamous region.

The experiments of Groth and of Maltoni suggest that there is an increased susceptibility to tumour development on exposure to VC in both young and old rats, but the experiment of Drew et al (1983) suggests that further investigations are needed to establish the full sensitivity of adult rats to VC carcinogenesis.

1.3.4 Concurrent administration of ethanol and VC in relation to tumour incidence in rats

The effect of social or environmental factors on the carcinogenic response to VC was studied in rat. Two groups of 80 male Sprague-Dawley rats were exposed to 600 ppm of VC in air 4 h/d, 5 d/wk for 1 year. One of these groups was given a 5% v/v solution of ethanol in water instead of drinking water. Two other groups with the same number of rats served as controls, one being given 5% ethanol in place of drinking water and the other being left untreated. The experiment was terminated at 2.5 years from the first exposure to VC. Haemangiosarcomas were found in 18/80 of the rats treated with VC alone and 40/80 of the rats given both VC and ethanol. No such tumours were observed in the other 2 groups. Hepatocellular carcinomas were found in 35/80 of the rats given VC alone and 48/80 of the rats treated with VC and

ethanol. Of the rats treated with ethanol alone, 8/80 had liver carcinoma while only one such tumour was found in the other control animals (Radike et al, 1981).

Interestingly, no pancreatic endocrine tumours were observed in rats treated with VC alone or in rats that were left untreated, but 14/80 rats treated with ethanol alone and 12/80 rats treated with VC and ethanol developed these tumours.

1.4 Comments

The extensive studies carried out on VC establish beyond reasonable doubt that it is carcinogenic to laboratory rodents. They also reveal a number of interesting features of the carcinogenic response which are worth considering in view of the fact that VC is also a human carcinogen.

1.4.1 Rare and common tumours induced

A summary of the various tumours reported to be induced by VC according to the papers reviewed earlier is given in Table 31.

The principal tumours induced by VC in the rat are haemangiosarcoma of the liver, nephroblastoma of the kidney, and Zymbal gland carcinoma (clearly induced in the Sprague-Dawley rat but not so clearly in the Wistar rat). Haemangiosarcomas of the liver occur very rarely in untreated rats, while the other two tumours, although not so rare, are uncommon (Schauer and Kunze, 1976), this allows an assessment of the tumour incidence and an analysis of the features of the carcinogenic response unencumbered by a high incidence of the same type of tumour in the control animals. Haemangiosarcomas were also found in the liver of mice and hamsters. They are extremely rare tumours in untreated animals of these species (Grasso and Hardy, 1975; Ghadially and Barker, 1960).

Although haemangiosarcomas occurred predominantly in the liver of rats and mice treated with VC, they also frequently developed at extra-hepatic sites in these species. Such tumours rarely occur spontaneously in either rats or mice (Carter, 1973; Stewart, 1979) and the low incidence in untreated control animals is in keeping with these reports. Thus, the haemangiosarcomas found outside the liver are likely to be related to the administration of VC. There was, however, no dose-response relationship in any of the experiments reviewed. In one experiment with mice haemangiosarcomas occured in extra-hepatic sites only and in this case

the incidence was dose-related. The reason for the comparatively low incidence of these tumours compared with those of hepatic origin is not apparent from the experiments reviewed.

Apart from these rare tumours, VC also induced some other tumours which occur commonly in untreated animals. In the rat, VC induced hepatocellular adenocarcinomas; in the mouse, mammary gland tumours, pulmonary adenomas and carcinomas; and in the hamster, forestomach papillomas and possibly melanomas. The hepatocellular carcinomas were uncommon in rats treated with highest dose of VC but became relatively more frequent at the mid-dose level, particularly in experiments where it was given by the oral route. The clearest indication of this apparent change in the histogenic origin of the tumours induced by VC is seen in the experiment where VC adsorbed on to PVC powder was administered to rats.

The background incidence of melanomas in the hamster is in the range of 3-5% and such tumours are readily induced in this species by some chemical carcinogens (Pour et al, 1979; Ghadially, 1982). Since the cell from which melanomas are derived occurs only in hamsters, this type of tumour has been described only in this species (Ghadially and Barker, 1960).

1.4.2 Dose-response relationships

The principal feature of the induction of the tumours mentioned in the preceding paragraphs (except the extra-hepatic angiosarcoma) is the clear increase in incidence with increasing amount of VC administered. Furthermore, these tumours appeared over a dose-range of at least three orders of magnitude. This type of dose-response, typical of genotoxic carcinogens, is in sharp contrast to that produced by "non-genetoxic" carcinogens where the tumourigenic response is limited to a narrow range of extremely high doses which often produce an additional toxic effect (ECETOC, 1982; Grasso and Hardy, 1975).

1.4.3 Tumours induced after a limited exposure

Another important feature of the above results is that the tumours were induced after only a limited period of exposure (52 weeks) and then mostly by exposure regimes of 4, rather than 6 or 8, h/d. In the case of the liver there is no indication that the tumours were due to a progressive pathological lesion, such as cirrhosis, which eventually could lead to hepatoma (ECETOC, 1982). Hepatic damage

was reported by Viola (1970) who described "torbid degeneration", necrosis and nuclear enlargement and polymorphism in the hepatic cell but apparently found no cirrhosis even though the dose administered was very high indeed. The hepatic tumours induced by VC are therefore most likely to be the result of an irreversible molecular lesion such as an interaction with DNA. It is presumed that a similar mechanism could account for the kidney and Zymbal gland tumours, particularly since no evidence of serious damage has been recorded in these organs.

1.4.4 Tumours induced in a limited number of organs

VC has induced tumours in all the species that have so far been exposed to it experimentally, and consequently it belongs to the class of "versatile" carcinogens such as the nitrosamines (Grasso, 1981). Despite its species versatility, however, VC induced a dose-related incidence of tumours in only a limited number of organs (3 or 4) in any one species, the incidence in other organs being similar to that of the control animals. This would suggest that in carcinogenicity studies of unknown compounds, attention should be given to a dose-related incidence of tumours at specific sites (target organs) rather than to an increase in the total number of tumours.

1.4.5 Time-to-tumour development

The time that elapsed from the intial treatment with VC to the appearance of tumours, estimated as the average latency period or time to first tumour, clearly reveals a dose-related shortening of the latency period. Although this parameter is in disfavour with some statisticians who prefer instead an estimation of the age-related incidence of tumours, the concept of latency is important to the experimentalist interested in studying events leading to the appearance of tumours. The markedly short latency period observed in the VC experiments, particularly at the higher dose-levels, is in contrast to the long latency period observed in the induction of hepato-cellular carcinoma by non-genotoxic agents (ECETOC, 1982).

1.4.6 Sex-difference

With the exception of hepatic angiosarcoma there was little difference in the incidence of the rare tumours induced by VC between males and females. Hepatic angiosarcoma occurred at a higher incidence in female rats and mice than in the males. In contrast, the hepatocellular tumours occurred at a higher incidence in

males. In the mouse, mammary adencarcinomas occurred at a higher incidence in the female.

1.4.7 Other observations

Maltoni's studies suggest that, apart from the tumours considered above, VC may increase the incidence of mammary gland and brain tumours in the Sprague-Dawley rat. This suggestion is difficult to verify. The background incidence of mammary gland tumours in control animals is high and variable so that a statistically-significant difference in any one experiment may be due to chance (see Maltoni et al, 1984). The brain tumour incidence, on the other hand, is low in control animals but it is also low in the exposed groups. Furthermore, the incidence in the Maltoni experiments taken overall was comparable in exposed and control animals and there appears to be little or no consistency in the incidence of brain tumours in the various experiments. This apparent lack of consistency may be due to the limited number of brain sections taken at necropsy so that microscopic tumours may have been missed. Nevertheless, on the evidence available there does not appear to be a causal connection between brain tumours and exposure to VC.

On the other hand, a high incidence of mammary and pulmonary tumours has consistently been reported following the administration of VC to mice. The induction of mammary and pulmonary tumours in mice has been seriously questioned as a reliable index of carcinogenicity because of the genetic, hormonal and viral factors involved in their production (Grasso and Crampton, 1972). Although the increased incidence of such tumours following the administration of VC does not alter the fact that their value in assessing carcinogenic hazard to man is questionable, it does indicate that induction of these tumours by compounds of previously unknown activity requires further and careful investigation.

1.5 Conclusions

VC is a versatile carcinogen in animals. When administered by inhalation it irduced hepatic haemangiosarcomas in rats, mice and hamsters; Zymbal gland tumours in rats and hamsters; nephroblastomas in rats; and pulmonary and mammary gland tumours in mice. In hamsters, forestomach papillomas and melanomas were observed in the treated, but not control, animals. The incidence of forestomach tumours was clearly dose-related, whereas that of the melanomas was not. Furthermore, for melanomas there was no statistically-significant difference between the exposed and control

animals, and no positive trend, so that a causal connection between these tumours and administration of VC is equivocal.

When VC was administered orally to rats the same spectrum of tumours was observed, with the exception of one experiment by the oral route in which the predominant neoplastic lesion was pulmonary haemangiosarcoma which was not the case when VC administered by inhalation.

Tumours were observed over a wide range of dose-levels. The minimum dose at which the compound-related tumours were observed when VC was given by inhalation was as follows: in rats 10 ppm, in mice 50 ppm and in hamsters 500 ppm. When VC adsorbed onto PVC powder was given orally, the minimum effective dose was 1.7 mg/kgbw (equivalent to 25 ppm in the diet), and when administered in solution in water the minimum effect dose was 25 ppm. The tumour incidence increased with dose in the case of most of the neoplastic lesions that were clearly treatment-related. Because multiple tumours were induced by this compound it was not possible to observe a classical dose-response relationship for all of them.

2. MUTAGENICITY AND GENOTOXICITY

The mutagenicity and genotoxicity of VC and its known metabolites have been examined in in vitro and in vivo test systems.

2.1 Mutagenicity and Genotoxicity In Vitro (Table 32)

Mutagenic effects have been detected in numerous in vitro systems. Gaseous VC induced point mutations in Salmonella typhimurium strains (reverse mutations of the base-pair substitution type). The effects were detectable in the presence of, and to a minor extent in the absence of, metabolic activation systems derived from different species, ie. liver preparations from rats (Bartsch et al, 1975; Rannug et al, 1974; Malaveille et al, 1975; Garro et al, 1976; Andrews et al, 1976) and human liver biopsies (Bartsch et al, 1975; Mallaveille et al, 1975). A persistent feature of the findings is that the mutagenicity of VC is highly dependent upon its metabolic conversion into one or more reactive metabolites. Also, it is strongly increased by the addition of activating enzymes of the mixed function oxidase (MFO*) type, NADPH** (supernatant from cytochrome P450-induced rat liver) and NADPH-generating systems (Rannug et al, 1974; Bartsch et al, 1975, 1979; McCann et

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* mixed function oxidase

** nicotinamide adenine dinucleotide phosphate

al, 1975; Andrews et al, 1976). However, Garro et al (1976) found no requirement for NADPH and MFO in contradiction to all other studies. This brings into question the validity of the Garro et al experiments since they also found no stimulation of mutagenesis by liver preparations from rats pretreated with Aroclor 1254, a result which contrasts with the findings of Jaeger et al (1974), who found acute hepatoxicity after pretreatment with phenobarbital or PCB.
VC itself is comparatively weakly mutagenic in systems with little metabolising capacity, and exposure to high concentrations is needed for the induction of mutations in S. typhimurium strains; for example, Bartsch et al (1975) used concentrations of 20%, and Andrews et al (1976) used 0.4-15.4%, in air. It is possible that under such test conditions a different type of genotoxic event is produced.

In aqueous solution VC was not mutagenic to S. typhimurium under the test conditions employed by Bartsch et al (1975) and Rannug et al (1974). Whether this would also be true for more refined tests such as those with pre-incubation procedures cannot be stated. In other aqueous systems, however, VC was mutagenic; for example reverse mutations in E. Coli were obtained upon metabolic activation with 9000 x supernatant from mouse liver (Greim et al, 1975). These authors observed that mutagenicity was a function of metabolic chloro-oxirane formation.

Schizosaccharomyces pombe and Saccharomyces cerevisiae were similarly mutated after metabolic activation in a host-mediated assay in which mice were treated with an oral dose of 700 mg/kg of VC (Loprieno et al, 1976, 1977). Mutagenicity was not detectable in Neurospora crassa exposed to VC vapour or to an ethanolic solution of VC in the presence or absence of metabolic activation (Drozdowicz and Huang, 1977).

Drevon et al (1978, 1979) found that exposure to VC vapour induced mutations in V79 Chinese hamster cells after metabolic activation by an S15 postmitochondrial fraction plus co-factors, inducing forward mutations resistant to 20 µg/ml 8-azaguanine or 1 mM ouabain.

Covalent binding of VC to DNA and RNA in vitro has been demonstrated in the presence of rat liver microsomes, NADPH and oxygen (Kappus et al, 1975; Laib and Ottenwälder, 1978).

2.2 Mutagenicity and Genotoxicity In Vivo (Table 33)

The exposure of Drosophila melanogaster to VC in air gave positive results in the recessive lethal test, i.e. there were significant increases of recessive lethals both in the first and second generation after treatment (Magnusson and Ramel, 1976, 1978). The results were, however, negative in the test for dominant lethals, translocations and sex-chromosome loss after exposure to 30,000 ppm of VC for 2 days (Verburgt and Vogel, 1977). The lowest effective concentration for recessive lethals was 850 ppm for a 2 day and 30 ppm for a 17 day exposure. Exposure to 200 ppm of VC for 2 days was not effective. The mutation frequency increased with concentration and reached a plateau at 10,000 ppm indicating a saturation of metabolism which may also have accounted for the negative findings with the other end-points (Verburgt and Vogel, 1977).

An increase in chromosomal aberrations and elevated sister chromatid exchanges were observed in hamster bone-marrow cells after exposure by inhalation to 25,000 and 50,000 ppm of VC for 6, 12 or 24 h (Basler and Röhrborn, 1980).

In a dominant lethal assay in mice in which post-implantation foetal death, pre-implantational egg losses and reduction in fertility were scored, a negative result was obtained at exposure levels of 3000, 10,000 or 30,000 ppm, 6 h/d for 5 days (Anderson et al, 1976, 1977). The sensitivity of this test, however, is not particularly high and hence this negative result is of little significance. Similarly, dominant lethal and somatic mutations were not detected in the mammalian spot test on the offspring of mice exposed to 4,600 ppm of VC for 5 h at day 10 of gestation (Peter and Ungváry, 1980). However, small amounts of hydroxyethyl-histidines were found in the testes of mice after exposure by inhalation (Ostermann-Golkar et al, 1977), demonstrating that VC can reach the testes and may possibly cause point mutations.

An increase in DNA-single-strand breaks was obtained in various organs of mice after the inhalation of 500 ppm of VC for 6 h/d, 5 d/wk, for 1 to 8 weeks. The target organs investigated were liver, kidney, spleen, brain and lung. The frequency of single-strand breaks increased with the time of exposure in the liver, kidney, lung and (slightly) spleen, reaching a plateau for the kidney and lung after 80 and 120 hours of exposure. No increase of single-strand breaks was detected in the brain (Wallis and Holmberg, 1984). In order to study the dose dependency of the genotoxic effects, the induction of hepatocellular ATPase deficient foci was studied after

several subchronic inhalation exposure regimes (2.5 - 2000 ppm; 8h/d). A straight line linear dose relationship was obtained (Laib et al, 1985).

Alkylation of liver DNA was observed in rats after the oral uptake of VC from drinking water (Green and Hathway, 1978), after exposure by inhalation (Laib et al, 1981) and similarly in mice after exposure by inhalation (Ostermann-Golkar et al, 1977). Metabolic incorporation of ^{14}C-VC fragments into liver DNA after intraperitoneal injection of VC into mice was insignificant.

Various cyclic and straight-chain base adducts, such as 3, N^4-ethenocytidine in the kidney and 1, N^6-ethenoadenosine and 1, N^6-ethenoadenine in the kidney and liver were recovered during in vivo studies on DNA binding (Bergmann, 1982; Green and Hathway, 1978). Laib et al (1981) found primarily 7-N-(2-oxoethyl)guanine which could be transformed into 7-N-(2-hydroxyethyl)guanine. The alkylated DNA sites are prone to mispairing (Zajdela et al, 1980; Scherer et al, 1981) and to increased lability of the glycosidic bond in vivo, leading to fragmentation. It is difficult to decide which is the most mutation-prone DNA-lesion resulting from exposure to VC since, depending on the method of hydrolysing DNA and isolating the bases after in vivo exposure, some of the alkylated DNA-bases may not have been recovered at the end the procedure. The major stable VC-DNA adduct, 7-(2)oxoethyl-guanine, was recently found not to show miscoding properties (Barbin et al, 1985). Similarly, alkylation of RNA occurs leading to formation of 1-N^6-ethenoadenosine (Laib and Bolt, 1977) and 3-N^4-ethenocytidene moiety (Laib and Bolt, 1978).

2.3 Mutagenicity of VC-metabolites In Vitro and In Vivo

Since it was known that metabolic activation is highly important for the genotoxic action of VC, single VC metabolites, especially those with electrophilic potential, were tested for mutagenicity. The following have been investigated: chloroethyleneoxide, chloroacetaldehyde, chlorcethanol and chloroacetic acid (Malaveille et al, 1975; Rannug et al, 1976).

a) Chloroethyleneoxide. Rannug et al (1974) suggested that chloro-oxirane (chloroethyleneoxide) was formed in the course of metabolic toxification, and that it was responsible for the DNA-alkylation and genotoxicity.The formation of this metabolite, as postulated by Rannug et al (1974), was proved by trapping it with 4-(4-nitrobenzyl)pyridine after the oxidation of VC by mouse liver microsomes (Bartsch et al, 1979). This highly-electrophilic compound proved to be

by far the strongest mutagen of all the metabolites tested, being 500 to 1000 times more potent than chloroacetaldehyde when the exposure time was taken into account (Hussain and Ostermann-Golkar, 1976). It was mutagenic in the Ames test (Bartsch, 1975; Rannug, 1976; Elmore et al, 1976), induced gene mutations and gene conversions in Schizosaccharomyces pombe and Saccharomyces cerevisiae (Loprieno et al, 1977) and alkylated DNA bases to give covalent adducts (Laib et al, 1981; Barbin et al, 1975; Bergman, 1982; Green and Hathway, 1978). In subcutaneous injection and dermal initiation-promotion experiments in mice it was found to be strongly carcinogenic (Zajdela et al, 1980).

b) Chloroacetaldehyde. Chloroacetaldehyde was weakly mutagenic in Salmonella typhimurium , E. coli and E. subtilis (Hussain and Ostermann-Golkar, 1976; Laumbach et al, 1977; Malaveille et al, 1975; Rannug et al, 1976 and Elmore et al, 1976) and was of low activity in producing ouabain-resistant mutants in V79 hamster cells (Hubermann et al, 1975). It did not cause forward mutatations or gene conversions in yeast (Loprieno et al, 1977). A chemical reaction with adenosine and cytidine was demonstrated in vitro by Barrio et al (1972). The low response of chloroacetaldehyde in mutation assays may be due to its pronounced cytotoxicity which prevents the expression of significant mutagenicity. In subtoxic doses the mutagenicity of chloroacetaldehyde is either absent or undetectable, and the dose at which mutations are first detected is close to the toxic dose. However, despite the above results, it cannot be ruled out that chloroacetaldehyde may make an important contribution to the carcinogenicity of VC. It could be continuously generated in the target cell and may cause cell necrosis, mitosis and a reduction in the efficiency of DNA repair leading to the fixation of genotoxic lesions (see ECETOC, 1982). Therefore, this metabolite may facilitate the production of tumours by VC.

c) Chloroethanol. 2-Chloroethanol was found to be negative in a number of mutagenicity tests using mammalian cells, yeast and Drosophila (Rannug et al, 1976; Bartsch et al, 1975; Elmore et al, 1976; Loprieno et al, 1977). It did not induce DNA strand breaks in the liver in vivo and was negative in two year dermal carcinogenicity assays in rats and mice (NTP, 1985).

d) Chloroacetic acid. Chloroacetic acid had no mutagenic effect at all in bacterial test systems (Bartsch et al, 1975; Rannug et al, 1976; Elmore et al, 1976).

e) 1,2-Dichloroethane. This possible contaminant of VC was mutagenic to Salmonella typhimurium with or without metabolic activation (McCann et al, 1975; Rannug and Ramel, 1977). It is known to be endogeneously converted into a toxic metabolite by glutathione conjugation.

2.4 Conclusions

The results show that VC is mutagenic and genotoxic only in the presence of appropriate metabolic activating systems. As was suggested by Van Duuren (1975), the most potent mutagenic metabolite is chloroethyleneoxide. This is supported by the appearence of 7-(2-oxoethyl)guanine in the rat liver DNA after vinyl chloride exposure (Laib, 1986). Chloroacetaldehyde is a metabolite of low mutagenic activity but is highly cytotoxic, and the possibility that it contributes to the carcinogenicity of VC cannot be completely dismissed. Other metabolites have no or marginal genotoxic action and are not likely to be involved in the carcinogenic action of VC.

3. OTHER TOXICOLOGICAL DATA RELEVANT TO CARCINOGENICITY AND MUTAGENICITY

Both neoplastic and toxic lesions can be induced in the same organ by carcinogenic chemicals. Whereas toxic lesions usually appear after a few hours or days of administration, cancer may develop only after several months of treatment. Study of the toxic effects of carcinogens may throw light on the nature of the pathological lesions at both the light-microscope and sub-cellular levels and may assist in the quest for the reactive intermediates. Information of this sort often provides some basis for understanding the mechanism involved and for making an assessment of the risk to man.

Vinyl chloride produces acute effects in liver, lung and the CNS in rats. Tumours have been produced in only one of these three organs - the liver. There is no convincing evidence that either lung or brain tumours were induced. On the other hand, VC induced tumours in the kidney and Zymbal gland of rats, as well as in the liver, but there is no evidence of a clear toxic effect on the first two of these organs in shorter term tests.

3.1 Acute Exposure by Inhalation

When mice and rats were exposed to VC at atmospheric concentrations of 10,000, 20,0000 or 30,000 ppm for 30 minutes the principal effect was narcosis. Some deaths occurred at the higher levels. Following a 2-week observation period, the pathological lesions detected were congestion, oedema and haemorrhages of the lungs, and congestion of the liver and kidney (Prodan et al, 1975).

Groups of rats exposed to atmospheres containing 0, 0.5, 5 and 10% of VC for 6 hrs, with and without pretreatment with phenobarbitone, showed centrilobular hepatocellular vacuolisation at the 10% exposure level in the absence of pretreatment, and at both the 10 and 5% levels following pretreatment with phenobarbitone. Some hepatocellular necrosis was also observed at the 10% level (Jaegar et al, 1974; Reynolds et al, 1975).

When Sprague-Dawley rats were exposed to atmospheric concentrations of 15,000 and 28,000 ppm of VC, 2 to 8 h/d , 5 d/wk over 1 to 6 weeks, they showed a reduced weight gain. Conventional histology revealed no signs of hepatocellular damage, though the rough and smooth endoplasmic reticulum were dilated. There was a decrease in glucose-6-phosphate dehydrogenase and glutathione reductase after 103 hours. Following 6 weeks exposure to 28,000 ppm of VC there were significant increases in the non-protein sulphydryl content and the glutathione aldehyde transferase and glutathione S-epoxide transferase levels, and a significant decrease in cytochrome P-450 levels, all indicating early liver injury (Jaeger et al, 1974; Reynolds et al, 1975).

3.2 Conclusions

These studies reveal that the liver is the primary site of structural damage by VC. The toxic effects in rats appeared at lower levels when they were pre-treated with phenobarbitone, suggesting that the toxic intermediates are formed by the mixed function oxidase system induced by phenobarbitone. Studies of this sort led to the metabolic studies which identified chloroethylene oxide as the most important reactive metabolite, probably accounting for the mutagenic and possibly the carcinogenic effects of VC. It is notable that tumours developed in organs which were not adversely affected in acute and sub-acute studies. Also, in the liver, which was the site for the development of both toxic and neoplastic lesions, tumours

developed at dose levels well below those which showed evidence of hepatotoxicity. This is consistent with the effects of genotoxic compounds. (ECETOC, 1982).

E. METABOLISM AND RELATED STUDIES

Reviews on the metabolism of VC have been published by Pflugge and Safe (1977) and IARC (1979).

1. ANIMAL STUDIES

The metabolism and kinetics of VC have been extensively studied in vitro and in vivo (Antweiler, 1976; Bonse and Henschler, 1976; Green and Hathway, 1975; Greim et al, 1975; Hefner et al, 1975a, 1975b; Malaveille et al, 1975; Müller and Norpoth, 1975; Muller et al, 1978; Watanabe et al, 1976a, 1976b; Watanabe and Gehring, 1976). The quantitative studies of metabolism in the SD rat by Watanabe et al (1978) and Gehring et al (1978) at 9 different concentrations of VC, administered orally and by inhalation, are of especial importance since the results help to link between animal and epidemiological studies, and provide an understanding of the dose-response relationships in VC carcinogenicity and so help the evaluation of evaluation of risk to human beings exposed to VC.

Figure 4 illustrates the major pathways of VC metabolism. VC is absorbed from the lungs and the intestinal tract, distributed in the body and metabolised at several sites. The systemic uptake of VC is determined by its oxidative biotransformation and the amount of VC absorbed is limited by the amount metabolised. The biotransformation pathway has limited capacity (i.e. is readily saturable) and this limits the systemic uptake. VC which is not metabolised is not absorbed but is mainly exhaled and is thus toxicologically irrelevant.

Strong inhibitors of oxidation processes which depend on microsomal cytochrome P450 (mixed function oxidase) markedly reduce the systemic uptake of VC, as shown by Bolt et al (1976) in inhalation studies with rats exposed to 100 ppm of VC in air. Inducers of mixed function oxidase such as phenobarbital or PCB increased the metabolism of VC and its systemic uptake. The combination of exposure to VC at high levels (about 10,000 ppm of VC in air) and inducers of MFO can lead to acute hepatotoxicity in rats (Jaeger et al, 1974).

When radio-labelled (^{14}C) VC was administered (orally or by inhalation) to rats, radioactivity accumulated in the liver, skin, thymus, urinary system and the salivary and lachrymatory glands (Duprat et al, 1977; Watanabe et al, 1976a, 1976b). It is now widely accepted that the first step in the metabolism of VC is its

NADPH-dependent epoxidation to chloro-oxirane (chloroethyleneoxide). The reaction is limited in capacity since the oxidative microsomal enzyme (mixed function oxidase) becomes saturated at low dose levels (Kappus et al, 1975, 1976; Gehring et al, 1978; Guengerich and Watanabe, 1978) at which point the rate of epoxidation and systemic uptake switch from first-order to pseudo-zero-order kinetics.

Chloroethyleoxide is the predominant mutagenic metabolite of VC (see above). Its subsequent metabolism involves :

- spontaneous rearrangement to chloroacetaldehyde, a metabolite of high cytotoxicity and some mutagenic potential;

and - hydrolysis by epoxyhydratase to 1-chloroethane-1,2-diol;

or - conversion into a glutathione adduct by the action of glutathione transferase. Watanabe et al (1976c) observed a depletion of glutathione during the metabolism of VC.

The last two reactions lead to detoxification but although the capacity of the two enzymes is not the limiting factor they have a low affinity for their substrates ; they do not therefore sufficiently protect the cells against DNA damage by the chloro-oxirane. This was demonstrated by Watanabe et al (1978) who found a linear relationship between the amount of radioactivity covalently bound to cellular constituents and the level of exposure to radio-labelled VC even at low levels. This explains why the types of tumour caused by exposure to VC occur even at very low doses in animal experiments. At low levels of exposure by inhalation in animals, the carcinogenic activity of VC is also linearly related to dose (Maltoni and Lefemine, 1975) but at somewhat higher levels the maximal tumour incidence is reached. At this level there is no further increase in the incidence of angiosarcoma or related lesions and the slope of the dose-response curve approaches zero (Maltoni et al, 1975). This reflects saturation of the capacity for microsomal oxidation of VC by mixed function oxidase responsible for generating chloro-oxirane, and the change in the kinetics described above. As the exposure level increases there is an increased incidence of an additional type of tumour, Zymbal gland carcinoma, in rats, these may result from a different kind of genotoxic lesion (Table 2, BT-1).

The kinetic constants of VC metabolism in the rat were determined by Gehring et al (1978) who exposed the animals by inhalation to 9 concentrations of VC ranging from 1.4 to 4600 ppm. They estimated the amount of VC metabolised and bound to liver protein, from which were calculated the Michaelis constant, K_M, and a V_{max} of 8560

µg of VC metabolised per rat in 6 hours of exposure. For a rat weighing 250 g this is equivalent to a K_M of about 336 ppm and a V_{max} of 5.7 mg of VC metabolised per hour per kg (Gehring et al, 1978; Andersen, 1981). The latter author calculated K_M by regression analysis of the dose-response relationship for the incidence of angiosarcoma in rats and obtained a value of about 565 ppm, that is similar to that from the metabolic data.

In conclusion, in animals the key step in the metabolism of VC is readily saturable. Nevertheless, covalent binding to DNA occurs at levels well below the saturation limit. This may explain the induction of tumours at low exposure levels.

2. TOXICOKINETICS OF INHALED VC IN MAN

2.1 Retention of Inhalated VC in the Lung

Krajewski et al (1980) exposed 5 volunteers to 3, 6, 12 and 23 ppm of VC, and found that the average retention in the lung remained constant at 42% in the period 0.5 to 6 hrs after exposure. The mean concentration in exhaled air during the first 30 minutes after cessation of exposure to the three higher concentrations was about 4.2% of the inhaled concentration.

Buchter et al (1978) exposed two volunteers to 2.5 ppm of VC for 15 and 30 minutes. The average retention appeared to be 27%. Five minutes after cessation of exposure, the VC-level in expired air dropped from 1.5 to 0.15 ppm. A half-life of VC in exhaled air of only 1.5 minutes can be derived from these results on the assumption that a fast exchange with the blood compartment occurs, indicating that there is a very short half-life in blood as well.

2.2 Clearance of VC from Air by Inhalation

The work described in the previous section was in open systems. Buchter et al (1978, 1980) estimated the rate of clearance of VC from the air in a closed system. Two volunteers inhaled the air for 30 minutes while the consumed oxygen was automatically supplemented. From the decay in the concentration (10 ppm at the beginning to 0.25-0.50 ppm after 30 minutes) the clearance rate of VC was determined, and averaged for the open and closed systems. The average for open and closed systems was 2.46 l/min or 2 l/h/kgbw.

2.3 Biological Monitoring

2.3.1 VC in exhaled air

Baretta et al (1969) tried to establish a method for the biomonitoring of VC by analysing the exhaled air of humans exposed to it. They exposed 6 volunteers to 48 ppm, 4 volunteers to 248 ppm and 4 volunteers to 459 ppm of VC. The concentrations were expressed as time-weighted-averages (TWAs), based on a total exposure time of 7.5 hours, which included a 0.5 hour lunch period in an uncontaminated area. The concentration of VC in exhaled air was measured directly every hour until 20 hours after cessation of exposure. The retention of VC in the lung, based on the VC concentration in the first exhaled air sample, was not presented. The authors carried out a multiple regression analysis of the data on the decrease in VC-concentrations in exhaled air with time (separately for every exposure concentration) which resulted in smooth decay curves. Such curves, adjusted to 500, 250 and 50 ppm TWA, plus an interpolated curve for 100 ppm, were presented. In the same way, curves for VC in breath were constructed for 10 workers occupationally exposed to a range of VC concentrations from 50 to 250 ppm (8 h TWA). The decay curves were very similar to those of the exposed volunteers and the authors thus considered their approach as a good one for biomonitoring.

From the smooth decay curves of the volunteer experiments the following data were estimated by the Task Force.

Time after cessation of exposure (hours)	VC-concentration in exhaled air (ppm) after 7.5 hours exposure to (TWA-ppm)			
	500	250	100	50
1	20	8.8	2.7	1.1
2	13	5.7	1.8	0.74
4	6.5	3.0	1.0	0.43
8	2.9	1.4	0.5	0.22
20	0.74	0.4	0.16	0.07

Comparison of the exhaled air concentrations after one hour and the exposure concentrations provides evidence for saturation of the metabolic pathways. ECETOC made the assumption that the decay was following Michaelis-Menten kinetics and estimated the exposure concentration of VC at which the metabolic conversion rate

was half of its maximum value (see appendix 3). This concentration was estimated to be 435 ppm, a value close to that found for the rat (330 ppm) by Gehring et al (1978).

The studies of Buchter et al (1978) and Baretta et al (1969) taken together enable three phases of VC elimination from exhaled air to be discerned :

- a fast one with a half-life of 1.5 minutes;
- a moderately fast one with a half-life of about 100 minutes;
- a slow one with a half-life of about 400 minutes.

2.3.2 VC in blood

Hasegawa et al (1979) determined the VC-concentration in the blood of workers exposed to VC. Measurements were made immediately and 8, 16, 24 and 48 hours after the end of the night shift. The exposure concentration was less than 2 ppm. No more information was given about the exposure conditions. VC-concentrations between 0 and 16 ppb were detected in most blood samples but on one occasion, 48 hours after cessation of exposure, about 30 ppb were found.

2.3.3 VC metabolites in urine

Chen et al (1983) determined thiodiglycolic acid (TdGA), a metabolite of VC, in the urine of workers exposed to VC. Average VC-exposure concentrations were presented without any indication of the duration of exposure or TWA. The results are summarised in the table below.

Average VC exposure level (ppm)	Number of workers	Average TdGA level (#g/1)	Standard deviation
0	78	.83	.56
<10	9	1.25	.58
30	23	2.84	1.68
>100	32	3.73	4.02

Müller et al (1978) and Heger et al (1982) studied the TdGA concentration in urine by personal monitoring over 2-h periods of 18 and 15 workers exposed to VC. The concentration increased after a few hours of exposure (TdGA appeared to occur

naturally in the urine). The concentration increased significantly on exposure to 1.5 ppm or higher (Müller, 1978). For exposures over the range 0.14-7 ppm of VC, the TdGA concentrations in urine varied from 0.3 to 4 µg/l.

In the opinion of ECETOC, the measurement of TdGA in urine is probably not a good method of establishing exposure to VC at current levels because the results fluctuate widely and the sensitivity of the measurement is low.

2.4 Comparison of the Rate of Uptake of VC from Air in Man and Other Mammals

Buchter et al (1978, 1980) compared the rate of uptake of VC from air by man and experimental animals. Eleven mice, 3 rats, 4 gerbils and 1 rabbit were placed in a 10.3 l closed system (each species separately) and exposed to VC at a starting concentration of 50 ppm. A 4 kg rhesus monkey was placed in a 200 l closed system and exposed to starting concentrations of VC varying between 20 and 600 ppm. The decay in the VC-concentration with time and the oxygen consumed was recorded by means of a spirograph. For the monkey, the kinetics of the decay in VC concentration was first-order and the clearance rate was linearly related to the concentration at starting concentrations of less than 200 ppm. At above 300 ppm the relationship was no longer linear and showed characteristics of saturation. From the VC decay curves of all of the above animals exposed at below the saturation level, clearance rates were estimated and compared with that of man as below :

Species	Clearance rate of VC from air (l/h/kgbw)
Man	2.02
Rabbit	2.74
Monkey	3.55
Rat	11.0
Gerbil	12.5
Mouse	25.6

As the carcinogenicity of VC is due to the action of its metabolites it can be concluded from the above-noted differences in clearance rates that rats and mice exposed to VC produce more carcinogenic metabolite per kgbw than does man. Thus, if the results of carcinogenicity studies on these species are used to predict quantitatively the carcinogenic response in the human being, appropriate correction factors should be employed.

F. CONCLUSIONS

1. VC has caused primary liver cancer in occupationally-exposed human beings, and a variety of tumours in three species of experimental animals (rat, mouse and hamster).

   In man, a causal relationship between exposure to VC in workplace air and the development of angiosarcoma of the liver is well established, but there is insufficient evidence that such exposure is causally-related to the development of tumours at other sites than the liver. There is some evidence that other primary liver tumours were caused by VC.

   In animals, the liver is the primary target organ for the toxic and carcinogenic effects of VC, but VC also induces tumours at other sites, for instance the Zymbal gland, the kidney, connective tissue, mammary gland, lung and fore-stomach.

2. VC is mutagenic in vivo and in vitro various assays in the presence of appropriate metabolic activity agents. Its most potent mutagenic metabolite is chloroethylene oxide which has been shown to alkylate DNA and is probably responsible for the mutagenicity and possibly for the carcinogenicity of VC. From the scant evidence available it seems unlikely that VC has caused any mutagenic disease in man.

3. Exposure to VC causes chromosomal aberrations in human beings, but only at the levels existing before the marked reduction in occupational exposure in the mid-1970s. It is uncertain whether it alters in the rate of sister chromatid exchange.

4. Occupational exposure to VC has led to periportal fibrosis and to changes in the distal vascular tree of the hands followed by the development of Raynaud's phenomenon, scleroderma or acro-osteolysis. There have been no reports of such effects in workers whose exposure to VC started subsequent to the early 1970s when exposure levels in most countries were lowered to a few ppm.

5. Occupational exposure to VC (by inhalation) has fallen from several hundred ppm, with peaks at several thousand, before the early 1970s, to levels of around 1 ppm subsequently. Although it is not possible to set definitely safe levels of

exposure for genotoxic carcinogens, the evidence presented in this report does not suggest that occupational exposure at current levels in compliance with the EEC limit of 3 ppm presents any significant risk to health.

At the atmospheric levels to which the general public is exposed (up to 5 ppb, annual average at 1 km, in the vicinity of VC and PVC plants, and less elsewhere), the risk of adverse health effects is even less.

6. The content of residual VC in PVC and co-polymers used for packaging food and drink has fallen, typically, from about 50 ppm in the early 1970s to below 1 ppm in subsequent years. There has been a corresponding reduction in the VC-content of the food and drink from about 100 ppb, to below 2 ppb from about 1977 onwards. Conservative risk estimates have indicated that the intake of VC from food and drink presents a negligible risk of cancer at current VC levels.

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TABLE 1

Historical Evolution of Occupational Exposure Limits in Europe and the USA

Year	Authority	Limit (ppm)
1954	ACGIH	500
1962	ACGIH	500
1971	OSHA	500
1972	ACGIH	200
1973	UK - HSE	25 (TWA-8h), 50 max.
1974 (April)	OSHA	50, temporary emergency standard over an 8 h period
1974	OSHA	proposed "not-detectable" level
1975 (April)	OSHA	1, averaged over 8 h period with a max. of 5 for 15 min.
1976	UK - HSE	10 (TWA-8h), 30 max.
1978	EEC	3, technical long-term (1yr) limit, with 7 as TWA-8h and 8 TWA-1h
1980	ACGIH	5

TABLE 2

Estimated Typical VC Concentrations in Atmospheres of Polymerisation Plants

Year	Concentration (ppm)
1945-1955	1000
1955-1960	400-500
1960-1970	300-400
mid-1973	150
mid-1974	50

TABLE 3

Weekly-average VC Concentrations (ppm) in the Atmospheres of 7 Polymerisation Plants (Barnes, 1975)

Plant	Mid 1974	Late 1974	Spring 1975
A	25	15	12
B	10	5	3
C	10	5	4
D	25	13	5
E	20	14	4
F	40	12	5
G	30	13	7

TABLE 4

Number of VC-related Cases of Angiosarcoma of the Liver by Date of Death

Period	No. of deaths
1955 - 9	2
1960 - 4	4
1965 - 9	9
1970 - 4	23
1975 - 9	46
1980 - 6	33
1955 - 1986	117*

* 3 individuals diagnosed during 1980-1986 and still alive on 01.01.86 gives a total of 120 cases.

TABLE 5

Number of VC-related Cases of Angiosarcomas of the Liver by Age at Diagnosis

Age (Years)	No. of cases
35 - 39	11
40 - 44	24
45 - 49	18
50 - 54	18
55 - 59	21
60 - 64	17
65 - 69	8
70 - 74	3
All ages	120

TABLE 6

Recorded Occupations among ASL Cases on Register

	No.*
Production worker/operator	69
Autoclave cleaner	51
General maintenance/Fitter	8
Other jobs	11
Unknown	17
TOTAL	156

* As several employees have more than one recorded job, these numbers do not add up to 120.

TABLE 7

Important Publications by Maltoni Containing the Design and Results of the BT Series of Experiments on the Carcinogenicity of VC

Publication	Experimental Design	Interim Result	Final Result
1	BT 1 to BT 15	BT 2 to BT 8	BT 1
2	BT 1 to BT 15, BT 17 BT 27	BT 7, BT 9, BT 10 BT 11, BT 14, BT 15 BT 27	BT 1, BT 2 BT 3, BT 4 BT 5, BT 6, BT 8
3	BT 1 to BT 3 BT 5 to BT 7 BT 9 to BT 15 BT 17 and BT 27		BT 1, BT 2, BT 6, BT 9 BT 11, BT 15, BT 27
4	BT 1 to BT 15, BT 17 BT 27, BT 4001, BT 4006		BT 1 to BT 15, BT 17 BT 27, BT 4001, BT 4006

NB : BT 16 and BT 18 to BT 26 do not appear in any of the publications consulted.

1) Maltoni C. and Lefemine G.(1975).

2) Maltoni C.(1977).

3) Maltoni C., Lefemine G., Ciliberti A., Cotti G. and Carretti D.(1980).

4) Maltoni C., Lefemine G., Ciliberti A., Cotti G. and Carretti D.(1984).

TABLE 8 - MALTONI EXPERIMENT - BT 6

Incidence of Tumours in Sprague-Dawley * Rats Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survival at 24 weeks***		Zymbal gland tumour		Angiosarcoma				Hepatomas		Forestomach		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
30,000	30	30	17 (43)	18 (60)	5 (52)	13 (64)	0	1 (47)	0	1 (47)	5 (46)	6 (56)	1	0

* 17 weeks old at commencement of treatment.

** 4 hours/day, 5 days/week, 52 weeks; experiment terminated at 68 weeks.

*** Appearance of first tumour : zymbal gland tumour.

Numbers in brackets indicate average latency (weeks).

Other comments : there were no controls
no kidney tumours were reported.

TABLE 9 - MALTONI's EXPERIMENT - BT 1

Incidence of Tumours in Sprague-Dawley* Rats Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survial at 22 weeks***		Zymbal gland Tumour		Angiosarcoma				Hepatomas		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
10,000	30	30	10 (52)	6 (50)	3 (59)	4 (72)	2 (61)	1 (51)	1 (60)	0	3 (54)	2 (67)	2 (52)	5 (54)
6,000	29	30	3 (67)	4 (59)	3 (68)	10 (71)	1 (34)	2 (62)	0	1 (84)	4 (67)	1 (59)	2 (62)	1 (50)
2,500	30	30	1 (41)	1 (26)	6 (77)	7 (77)	2 (58)	1 (70)	0	2 (98)	5 (69)	1 (99)	2 (76)	2 (84)
500	30	30	3 (74)	1 (97)	0	6 (84)	0	1 (73)	0	5 (96)	2 (82)	4 (83)	0	0
250	29	30	0	0	1 (116)	2 (56)	1 (101)	1 (82)	1 (90)	0	1 (70)	4 (80)	0	0
50	30	30	0	0	0	1 (135)	1 (135)	0	0	0	0	1 (135)	0	0
0	29	29	0	0	0	0	0	0	0	0	0	0	0	0

* 13 weeks old at commencement of treatment.

** 4 hours/day, 5 days/week, 52 weeks : experiment terminated at 135 weeks.

*** Appearance of first tumour : subcutaneous angiosarcoma.

Numbers in brackets indicate average latency (weeks).

TABLE 10 - MALTONI's EXPERIMENT - BT 2

Incidence of Tumours in Sprague-Dwaley* Rats Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survial at 12 weeks***		Zymbal gland Tumour		Angiosarcoma				Hepatomas		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
200	60	60	3 (73)	1 (72)	7 (92)	5 (94)	1 (89)	0	1 (126)	2 (107)	5 (85)	2 (69)	0	0
150	60	60	0	4 (91)	1 (100)	5 (87)	0	0	0	0	8 (83)	3 (83)	0	0
100	60	60	0	1 (80)	0	1 (85)	0	0	0	0	8 (83)	2 (69)	0	0
0	65	100	0	2 (76)	0	0	2 (67)	0 (73)	2 (67)	0	0	0	0	0

* 13 weeks old at commencement of treatment.

** 4 hours/day, 5 days/week, 52 weeks : an experiment terminated at 143 weeks.

*** Appearance of first tumour : mammary adenocarcinoma.

Numbers in brackets indicate average latency (weeks).

Other comments : 2 forestomach tumours observed in exposed animals.

TABLE 11 - MALTONI's EXPERIMENT - BT 15

Incidence of Tumours in Sprague-Dawley* Rats Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survial at 12 weeks***		Zymbal gland Tumour		Angiosarcoma				Hepatomas		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
25	60	60	3 (78)	1 (58)	1 (122)	4 (81)	0	0	0	1 (82)	1 (100)	0	0	0
10	59	60	1 (66)	1 (64)	0	1 (79)	2 (105)	0	0	0	0	0	0	0
5	59	60	0	1 (64)	0	0	0	0	0	0	0	0	1	0
1	58	60	1 (82)	0	0	0	0	0	0	0	0	0	1	0
0	60	60	2 (98)	0	0	0	0	0	0	0	0	0	2	3

* 13 weeks old at commencement of treatment.

** 4 hours/day, 5 days/week, 52 weeks : experiment terminated at 147 weeks.

*** Appearance of first tumour : subcutaneous fibrosarcoma.

Numbers in brackets indicate average latency (weeks).

Other comments : angiosarcomas (?)

TABLE 12 - MALTONI's EXPERIMENT - BT 9

Incidence of Tumours in Sprague-Dawley Rats* Exposed ** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survial at 28 weeks***		Zymbal gland Tumour		Angiosarcoma				Hepatomas		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
50	144	150	4 (60)	5 (71)	2 (90)	12 (96)	3 (74)	6 (84)	0	0	0	1 (112)	2	2
0	48	50	0	0	0	0	0	0	0	0	0	0	0	0

* 13 weeks old at commencement of experiment.

** 4 hours/day, 5 days/wekk, 52 weeks : experiment terminated at 142 weeks.

*** Appearance of first tumour : mammary gland tumour.

Numbers in brackets indicate average latency (weeks).

Other comments : epithelial forestomach tumours found, 1 in exposed and 1 in control animals.

incidence of mammary gland tumours, 78% in exposed female rats, 54% in control female rats.

TABLE 13 - MALTONI's EXPERIMENT - BT 7 and 17

Incidence of Tumours in Male Wistar Rats* Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survival at 39 weeks ***	Zymbal Gland Tumour	Angiosarcoma		Hepatoma	Nephroblastoma	Brain Tumour
			Liver	Other Sites			
BT 7							
10,000	27	2 (64)	8 (73)	0	0	1 (60)	4 (71)
6,000	26	2 (76)	3 (80)	1 (73)	2 (83)	2 (71)	4 (73)
2,500	25	0	3 (89)	1 (70)	1 (50)	0	1 (58)
500	27	0	3 (84)	0	0	2 (84)	0
250	28	0	1 (43)	1 (73)	0	0	0
50	28	0	0	0	0	1 (99)	0
0	38	0	0	1 (116)	0	0	0
BT 17	Survival at 36 weeks+						
1	99	2	0	3	1	0	0
0	94	3	0	0	0	0	0

* 11 weeks old at commencement of treatment.

** 4 hours/day, 5 days/week, 52 weeks : experiment terminated at 165 weeks (BT 7) and 134 weeks (BT 17).

*** Appearance of first tumour : intestinal angioama.

\+ Appearance of first tumour : zymbal gland tumour.

Numbers in brackets indicate average latency (weeks).

Other comments : BT 7, groups of 30 in each exposed group, and 40 in control group at start of experiment.

TABLE 14 - MALTONI's EXPERIMENT - BT 4

Incidence of Tumours in Swiss Albino Mice * Exposed ** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survial at 1 week***		Pulmonary Adenoma		Angiosarcoma				Hepatoma		Adenocarcinomas (kidney)		Mammary Gland Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
10,000	26	30	20 (29)	26 (37)	1 (38)	9 (41)	0	1 (39)	0	0	0	0	0	14 (32)
6,000	30	30	23 (32)	24 (38)	2 (42)	11 (40)	0	1 (50)	0	2 (40)	1 (32)	0	0	9 (34)
2,500	29	30	18 (38)	22 (40)	6 (49)	10 (41)	4 (47)	4 (41)	1 (41)	0	0	0	0	9 (36)
500	30	30	24 (34)	26 (46)	6 (41)	8 (40)	2 (42)	5 (50)	0	0	0	0	1 (42)	10 (44)
250	30	30	24 (45)	17 (40)	9 (46)	9 (46)	2 (44)	1 (56)	0	2 (43)	0	0	0	12 (38)
50	30	30	3 (46)	3 (65)	1 (54)	0	1 (43)	0	0	0	0	0	0	12 (44)
0	80	70	8 (62)	7 (63)	0	0	0	1 (81)	0	0	0	0	0	1 (64)

* 11 weeks old at commencement of experiment.

** 4 hours/day, 5 days/week, 30 weeks : experiment terminated at 81 weeks.

*** Appearance of first tumour : a leukaemia.

Numbers in brackets indicate average latency (weeks).

Other comments : groups of 30 male and 30 female rats allocated to each dose level, and twice that number to the control group.

TABLE 15 - MALTONI's EXPERIMENT - BT 8

Incidence of Tumours in Male Golden Hamsters* Exposed** to Vinyl Chloride by Inhalation

VC Conc. (ppm)	Survival at 12 weeks ***	Zymbal gland Tumour	Liver			Melanoma
			Angiosar-coma	Angioma	Hepatoma	
10,000	30	1 (60)	0	1 (42)	0	1 (50)
6,000	30	2 (59)	1 (80)	1 (75)	1 (80)	2 (37)
2,500	30	1 (59)	0	2 (70)	0	1 (54)
500	30	3 (72)	2 (45)	0	0	0
250	30	0	0	0	0	1 (80)
50	30	0	0	0	0	1 (38)
0	60	0	0	0	0	0

* 11 weeks old at commencement of experiment. Initially there were 32 - 35 animals per exposure level and 64 in the control group.

** 4 hours/day, 5 days/week, 30 weeks : experiment terminated at 109 weeks.

*** Appearance of first tumour : a leukaemia.

Numbers in brackets indicate average latency (weeks). No angiosarcomas at sites other than the liver were observed.

Other comments : all tumours reported in this table appeared after 36th week of experiment.

TABLE 16

Incidence of Tumours in CD-1 Mice Exposed * to Vinyl Chloride by Inhalation

Lee et al (1978)

VC Conc. (ppm)	Effective No. of Mice **		Pulmonary Adenoma		Haemangiosarcoma				Mammary Gland Tumour	
					Hepatic		Other Sites			
	M	F	M	F	M	F	M	F	M	F
1,000	33	36	22	26	13	18	0	9	0	13
250	29	34	10	12	7	16	2	3	0	3
50	29	34	8	4	3	0	5	1	0	9
0	26	36	1	0	0	0	0	0	0	0

* 6 hours/day, 5 days/week, 12 months : experiment terminated after 12 months.

** Appearance of first tumour : pulmonary adenoma (appearing at month 2).

TABLE 17

Cummulative Incidence of Tumours in CD-1 Mice Exposed to Vinyl Chloride by Inhalation for 1, 3, or 6 Months (Hong et al, 1981)

VC Conc. (ppm)	Effective No. of Mice		Bronchioalveolar+ Tumours		Haemangiosarcoma				Mammary Gland Tumours	
					Hepatic		Other Sites			
	M	F	M	F	M	F	M	F	M	F
1000	38	38	27	23(6)**	6	12	0	2	0	6
250	44	40	29(2)**	23	8	5	2	4	0	13
50	40	40	12	6(4)**	1	1	1	1	0	10
0	60	60	8	8	0	1	0	0	0	4

+ = Lung

**(No.) = Metastasising Adenocarcinoma

TABLE 18

Cummulative Incidence of Tumours in CD Rats Exposed to Vinyl Chloride 6 hours/day, 5 days/week for 1, 3, 6 or 10 months (Hong et al, 1981)

VC Dose (ppm)	Effective No. of Rats		Angiosarcoma				Hepatocellular Carcinoma		Bronchioalveolar+ Tumours	Lymphoma		
			Liver		Lung							
			M	F	M	F	M	F	F	M	M	F
1000	36	36	5	9	3	4	4	3	3	1	3	1
250	36	32	1	4	0	2	1	1	1	1	1	0
50	30	36	0	0	0	0	0	0	0	0	0	0
0	36	36	0	0	0	0	1	0	0	0	0	0

+ = Lung

TABLE 19 - MALTONI's EXPERIMENT - BT 11

Incidence of Tumours in Sprague-Dawley Rats Administered * Vinyl Chloride in Olive Oil

VC Dose (mg/kgbw)	Animals per group		Zymbal Gland Tumour**		Angiosarcoma** Liver		Angiosarcoma** Other Sites		Hepatoma		Nephroblastoma**		Brain*** Tumour	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
50	40	40	1 (82)	0	8 (83)	9 (75)	0	2 (71)	0	0	1 (76)	1 (97)	0	1
16.6	40	40	1 (116)	1 (54)	4 (64)	6 (89)	0	0	0	0	2 (88)	1 (75)	1	0
3.33	40	40	0	0	0	0	0	2 (93)	0	0	0	0	1	0
0	40	40	0	1 (104)	0	0	0	0	0	0	0	0	1	0

* once daily, 4-5 days/week, 52 weeks : experiment terminated at 136 weeks.

** Appearance of first tumour : 2 weeks from beginning of treatment : forestomach acanthoma.
Numbers in brackets indicate average latency (weeks)

*** Other comments : no average latency figures given.

TABLE 20 - MALTONI's EXPERIMENT - BT 27

Incidence of Tumours in Sprague-Dawley Rats* Administered** Vinyl Chloride in Olive Oil

VC Dose (mg/kgbw)	Survival at 28 weeks ***		Zymbal Gland Tumour****		Angiosarcoma****				Hepatoma****		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1.0	74	75	2 (96)	3 (103)	1 (129)	2 (96)	0	1 (91)	1 (91)	0	0	0	2	1
0.3	75	73	0	0	0	1 (101)	0	0	1 (103)	0	0	0	4	2
0.03	75	75	0	0	0	0	0	0	0	0	0	0	0	2
0	75	75	0	1 (90)	0	0	0	0	0	0	0	0	2	4

* 10 weeks old at start of experiment.

** 1.0, 0.3, 0.03 mg/kgbw, once daily, 4-5 days/week, 59 weeks.
Experiment terminated at 136 weeks.

*** Appearance of first tumour : mammary carcinoma.

**** Numbers in brackets indicate average latency (weeks).

TABLE 21

Incidence of Tumours in Wistar Rats Treated With Vinyl Chloride in Drinking Water

(Evans et al, 1978)

VC Conc. (ppm)	No. of Animals Examined		Mammary Gland Tumour		Angiosarcomas				Hepatomas		Kidney*		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
250	50	49	0	17	8	8	1	0	3	3	1	0	1	0
25	47	48	0	12	1	0	1	0	0	0	2	0	2	0
2.5	50	52	0	7	0	0	0	0	0	0	1	0	0	0
0	50	52	0	5	0	0	0	0	0	0	0	0	0	0

* The tumour in the highest dose was an adenocarcinoma, the others were mesenchymal tumours.

TABLE 22

Incidence of Neoplasms in Wistar Rats Administered (Orally) Vinyl Chloride Adsorbed on PVC

First Experiment (Feron et al (1981))

VC Dose (mg/kgbw/d)	No. of Animals Examined		Zymbal Gland Tumour		Angiosarcoma				Hepato-cellular carcinoma		Hepatic		Angiosarcoma	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
300	55	54	1	1	27	29	1	1	1	0	0	0	19	23
14.1	59	57	0	0	27	9	0	2	8	29	1	0	19	5
5.0	56	59	2	0	6	2	0	0	2	19	0	0	4	1
1.7	58	58	0	0	0	0	1	0	1	4	0	0	0	0
0	55	57	0	0	0	0	1	0	0	0	1	0	0	0
Second Experiment : Lower Dose-levels (Til et al (1983))														
1.7	49	49	0	0	1	2	0	1	3	3	3	9	data not given	
0.17	99	96	1	0	0	0	2	1	0	1	1	1		
0.017	99	100	0	0	0	0	1	2	0	0	0	1		
0	99	98	1	0	0	0	0	2	0	1	1	0		
0	100	99	0	0	0	0	0	3	0	0	0	0		

TABLE 23

Induction of Pulmonary Tumours in CD1 Male Mice Exposed[+] to Vinly Chloride By Inhalation For 4 Weeks

Suzuki (1983)

VC Conc. (ppm)	No. of mice at start	Sacrificed at							
		4 weeks		12 weeks		12 - 40 weeks		40 weeks	
		An*	Tu*	An	Tu	An	Tu	An	Tu
600	40	10	0	10	9	4	4	7	6
300	30	10	0	9	6	3	2	7	5
100	30	10	0	6	0	1	0	9	6
10	30	10	0	10	0	1	0	9	3
0	60	20	0	18	0	1	0	17	3

* An = Animals; Tu = Tumours.

[+] 6 hrs/day, 5 days/week/4 weeks.

TABLE 24

Incidence of Pulmonary Tumours in ICR Swiss Mice Exposed to VC By Inhalation

Hehir et al (1981)

Single Exposure (1h)

VC Conc. (ppm)	Effective No.* Mice		Pulmonary Tumours			
			Adenoma		Carcinoma	
	M	F	M	F	M	F
0	50	70	4	8	0	0
50	71	68	8	6	0	0
500	66	73	8	10	0	1
5,000	65	78	14	10	1	0
50,000	61	76	31	14	1	2

* Number of animals includes spontaneous deaths, and interim and final kills after 8 and 18 months.

TABLE 25

Incidence of Pulmonary Tumours in ICR Swiss Mice Exposed to Vinly Chloride by Inhalation
Hehir et al (1981)

Multiple Exposure

VC Conc. (ppm)	Number of Days *	Effective No. of Animals**		Pulmonary Tumours			
				Adenoma		Carcinoma	
		M	F	M	F	M	F
0	10	39	45	11	18	2	0
50	10	77	81	27	38	3	4
0	100	43	47	15	16	0	3
500	100	90	76	56	68	12	10

* Exposure for one hour each day.

** Number of animals include spontaneous deaths, and interim and final kills.

TABLE 26 - MALTONI's EXPERIMENT BT 14

Incidence of Tumours in Newly-Born Sprague-Dawley Rats Exposed* to Vinyl Chloride by Inhalation

VC Conc. (ppm)	No. of animals when first tumours appeared**		Zymbal Gland Tumour		Angiosarcoma				Hepatoma		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
10,000	24	20	1 (104)	0	6 (87)	9 (93)	6 (87)	9 (93)	13 (89)	7 (95)	0	0	0	0
6,000	18	24	1 (70)	1 (76)	5 (94)	12 (80)	5 (94)	12 (80)	9 (93)	11 (77)	0	0	0	0

* 4 hours/day, 5 day/week from birth to 5 weeks : experiment terminated at 124 weeks.

** Appearance of first tumour : angiosarcoma and hepatoma, at 35 weeks.

Other comments : Dams treated for 5 weeks with same concentration did not develop tumours referrable to VC exposure.

TABLE 27 - MALTONI's EXPERIMENT - BT 4001 and 4006

Incidence of Tumours in Sprague-Dawley Rats Exposed* to Vinyl Chloride by Inhalation During and After Pregnancy

BT 4001 Transplacental and Post-Natal Exposure

Duration of Exposure (wks)	No. of Animals		Zymbal Gland Tumour		Angiosarcoma				Hepatoma		Nephroblastoma		Brain Tumour	
					Liver		Other Sites							
15	60	60	7 (67)	2 (58)	24 (78)	28 (73)	0	1 (45)	42 (84)	43 (81)	0	1 (32)	0	0
75	63	64	9 (47)	6 (57)	36 (52)	46 (50)	0	0	27 (53)	38 (51)	0	1 (41)	0	0
Controls	158	149	2 (96)	0	0	0	1 (126)	0	1 (102)		0	1 (118)	0	0

BT 4006 Dams (Exposed for 76 weeks from day 12 of pregnancy)

Treated	-	54	-	8 (61)	-	27 (60)	-	0	-	5 (63)	-	0	0	0
Controls	-	60	-	1 (46)	-	0	-	0	-	0	1	1	0	0

* exposed to 2500 ppm VC, starting at 12th day of pregnancy and continuing for either 15 weeks (BT 4001) or 76 weeks (BT 4006).

TABLE 28

Incidence % of Tumours in Female F344 Rats[+]
Treated with 100 ppm Vinyl Chloride
6 hours/day/5 days/week (Drew et al, 1983)

Exposure Period (months)	Group Size	TUMOURS					
		Haemangiosarcomas		Mammary Gland		Hepatocellular	
		Liver	All Sites	Benign	Malignant	Benign	Malignant
0	112	0.9	1.8	21.4	4.5	3.6	0.9
0 - 6	76	5.3*	5.3	36.8*	7.9	20.0*	4.0
0 - 12	56	20.0*	21.4*	50.0*	19.6*	35.7*	7.1*
0 - 18	55	23.6	27.3*	43.6*	16.4*	13.0*	14.8*
0 - 24	55	34.7*	43.6*	47.3*	9.1*	10.9*	16.4*
6 - 12	53	3.8	3.8	43.4**	3.8	19.2*	11.5*
12 - 18	51 - 53	0	0	32.1	5.7	3.9*	0
18 - 24	53	0	0	37.7**	3.8	7.5	1.9
6 - 18	54	9.3	9.1	29.1*	7.3	7.4	1.9
12 - 24	50	4.1	4.0	30.0	0	8.2	0

\+ = Approximately 9 weeks old
* = P<0.01
** = P<0.05

NB : The first figures in Column 1 indicate the time from the beginning of the experiment that animals were without treatment.

TABLE 29

Incidence % of Tumours in Female B6C3F1 and CD-1 Mice[++] Treated with 50 ppm VC by INhalation 6 hours/day/5 days/week (Drew et al, 1983)

Exposure Period (months)	Group Size	TUMOURS				
		Haemangiosarcoma[+]		Mammary Gland Ca.		Lung Carcinoma
		B6C3F1	CD-1	B6C3F1	CD-1	CD-1
0	69 - 71	5.8	1.4	4.3	2.8	12.7
0 - 6	65 - 67	68.7*	43.3*	43.2*	49.3*	27.7*
0 - 12	47 - 90	76.7*	63.8*	41.1*	46.8*	31.9*
0 - 18	45	-	44.4*	-	48.9*	24.4*
6 - 12	42 - 49	64.3*	22.4*	31.0*	26.5*	26.5**
12 - 18	51 - 53	58.8*	9.4*	7.8*	3.8*	13.2
6 - 18	46 - 48	62.5*	37.0*	18.8*	17.8*	19.6**
12 - 24	48 - 50	60.4*	6.0	8.3*	0	6.0

\+ = All sites, primarily peritoneal

++ = Approximately 9 weeks old

* = P<0.01

** = P<0.05

NB : The first figures in Column 1 indicate the time from the beginning of the experiment that animals were without treatment.

TABLE 30

Incidence % of Tumours in Female Golden Hamsters[++]
Exposed to 200 ppm Vinyl Chloride
6 hours/day/5 days/week (Drew et al, 1983)

Exposure Period (months)	Group Size	TUMOURS			
		Haemangiosarcoma (all sites)+	Mammary Gland Carcinoma	Stomach Adenoma	Skin Carcinoma
0	143	0	0	3.6	0
0 - 6	80 - 88	14.8*	32.2*	26.1*	2.5
0 - 12	48 - 52	7.7*	59.6*	6.0**	18.8*
0 - 18	90 - 103	1.9	46.1*	19.8*	3.3
6 - 12	49 - 53	5.7**	3.8**	28.3*	0.
12 - 18	46 - 50	0	0	12.2**	0
18 - 24	52	0	1.9	0	0
6 - 18	38 - 44	2.3	13.6	22.7*	0
12 - 24	30 - 43	0	0	7.3	0

\+ = Spleen, liver and skin

++ = Approximately 9 weeks old

* = P<0.01

** = P<0.05

NB : The first figures in Column 1 indicate the time from the beginning of the experiment that animals were without treatment.

TABLE 31

Summary of Tumours Induced Experimentally by Vinly Chloride
(as evaluated by the authors - see final column)

Administration (Route) (Species)	Zymbal Gland	Haemangiosarcoma		Hepatoma	Nephro-blastoma	Lung	Melanoma	Mammary gland	Forestomach	Author
		Hepatic	Extrahepatic							
INHALATION Sprague-Dawley Rat	x	x	x	x	x				x	Maltoni (1985)
INHALATION Wistar Rat	x	x		x	x					Maltoni (1985)
ORAL Wistar Rat	x	x		x		x				Feron & Til (1981,1983)
ORAL Sprague-Dawley Rat	x	x	x		x					Maltoni (1985)
INHALATION Sprague-Dawley Newley-born Rat	x	x	x	x						Maltoni (1985)
INHALATION Swiss Albino Mouse		x	x			x		x		Maltoni (1985)
INHALATION CD-1 Mouse		x				x		x		Lee et al. (1978)
INHALATION CD-1 Mouse (Male)						x				Susuki (1983)
INHALATION ICR Swiss Mice						x				Hehir et al (1981)
INHALATION Golden Hamster (Male)	x	x					x			Maltoni (1985)

TABLE 32

Mutagenicity and Other Short-Term Tests on Vinyl Chloride

In Vitro

Physical State	Test System	Activating System (AS)	Results	Comments	References
Vapour	Salmonella typhimurium	none	+	High exposure levels	Bartsch et al., 1975 McCann et al.,1975 Andrews et al.,1976
Vapour	Salmonella typhimurium	9000 x g supernatant from rat or mouse liver	+	AS potentiates the mutagenic response	Rannug et al., 1974/76 Bartsch et al.,1975 McCann et al.,1975 Andrews et al.,1976 Garro et al.,1976 Malaveille et al.,1975
Vapour	Salmonella typhimurium	9000 x g supernatant from human liver biopsies	+	AS potentiates the mutagenic response	Bartsch et al.,1975 Malaveille et al.,1975 Bartsch et al.,1979
Solution	Salmonella typhimurium	none	-		Rannug et al.,1974 Bartsch et al.,1979
Solution	Salmonella typhimurium	9000 x g supernatant from rat liver	-		Rannug et al.,1974 Bartsch et al.,1975
Solution	Escherichia coli K12	9000 x g supernatant from mouse liver	+		Greim et al.,1975
Solution	Schizosaccharomyces pombe	9000 x g supernant from mouse liver	+		Greim et al., 1975
Solution	Schizosaccharomyces pombe	Host-mediated assay	+		Loprieno et al., 1976, 1977
Vapour	Neurospora crassa	none	-		Drozdowicz and Huang, 1977
Ethanol solution	Neurospora crassa	purified from un-induced from Buffalo rats	-		
Vapour	V79 Chinese hamster cells	15,000 x g supernatant from phenobarbital-pretreated rat liver	-		Drevon et al., 1978 Drevon and Kuroki, 1979

TABLE 33

Mutagenicity and Other Short-Term Tests on Vinly Chloride

In Vivo

Physical state	Test System	Exposure Level	Results	References
Vapour	Drosophila melanogaster a) recessive lethal test	30 - 3000 ppm, 2 - 17 days	+	Magnusson and Ramel, 1976/78
	b) dominant lethal test, sex chromosome loss	30,000 ppm 2 days	+	Verburgt and Vogel, 1977
Vapour	Alkylation of liver DNA - rats - mice		+ +	Laib et al.,1981 Ostermann-Golkar et al.,1977
Vapour	CD-1 male mice (dominant-lethal test)	30,000; 10,000; 3000 ppm, 6 h/d/5 days	-	Anderson et al.,1976/77
Vapour	Offspring of C57-BL6 JHan X T stock; dominant lethal and somatic	4600 ppm, on the 10th of pregnancy	-	Peter and Ungvary, 1980
Vapour	Chinese hamsters, chromosomal aberrations and SCE in bone marrow	50,000, 25,000 ppm. 6, 12, 24 h	+	Basler and Röhrborn, 1980
Vapour	Mice, single strand breaks	500 ppm, 1 - 8 weeks	+	Wallis and Holmberg, 1984
Drinking water	Rat, in vivo DNA binding	250 ppm, 2 years	+	Green and Hathway, 1978
Vapour	Mouse, in vivo DNA binding	100 - 300 ppm	+	Ostermann-Golkar et al., 1977
Vapour	Rat, in vivo DNA binding	< 100 ppm	+	Bolt et al.,1976

FIGURE 1

Weekly Average Level of Vinyl Chloride in Plant Atmosphere (Barnes, 1975)

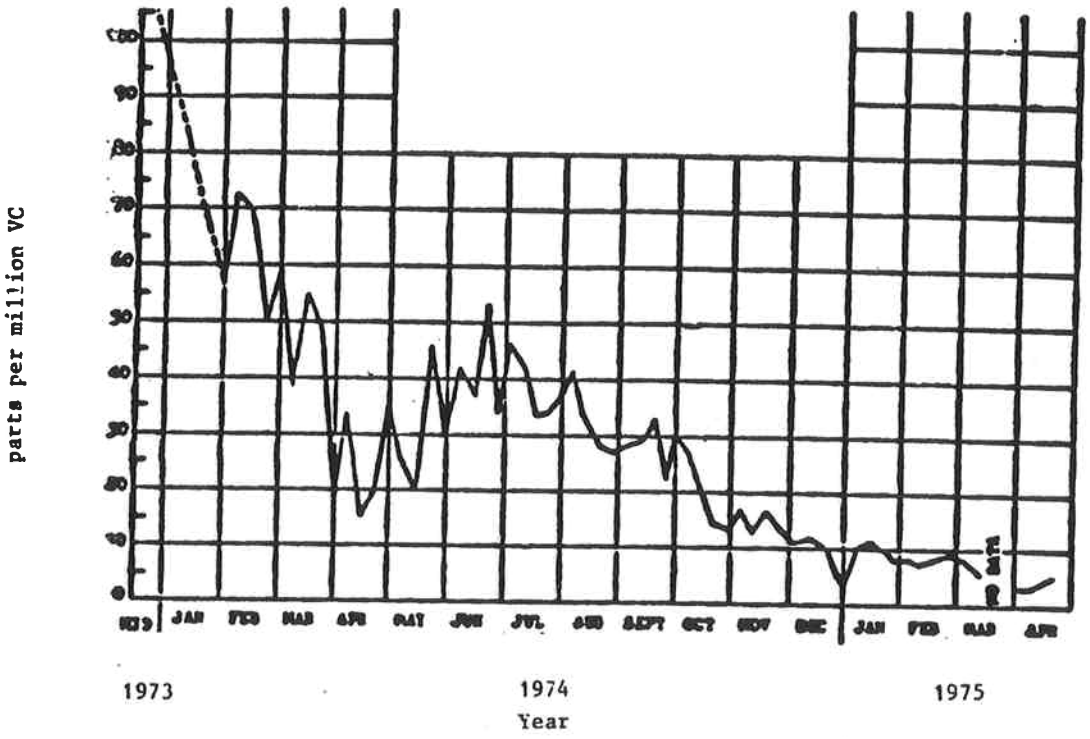
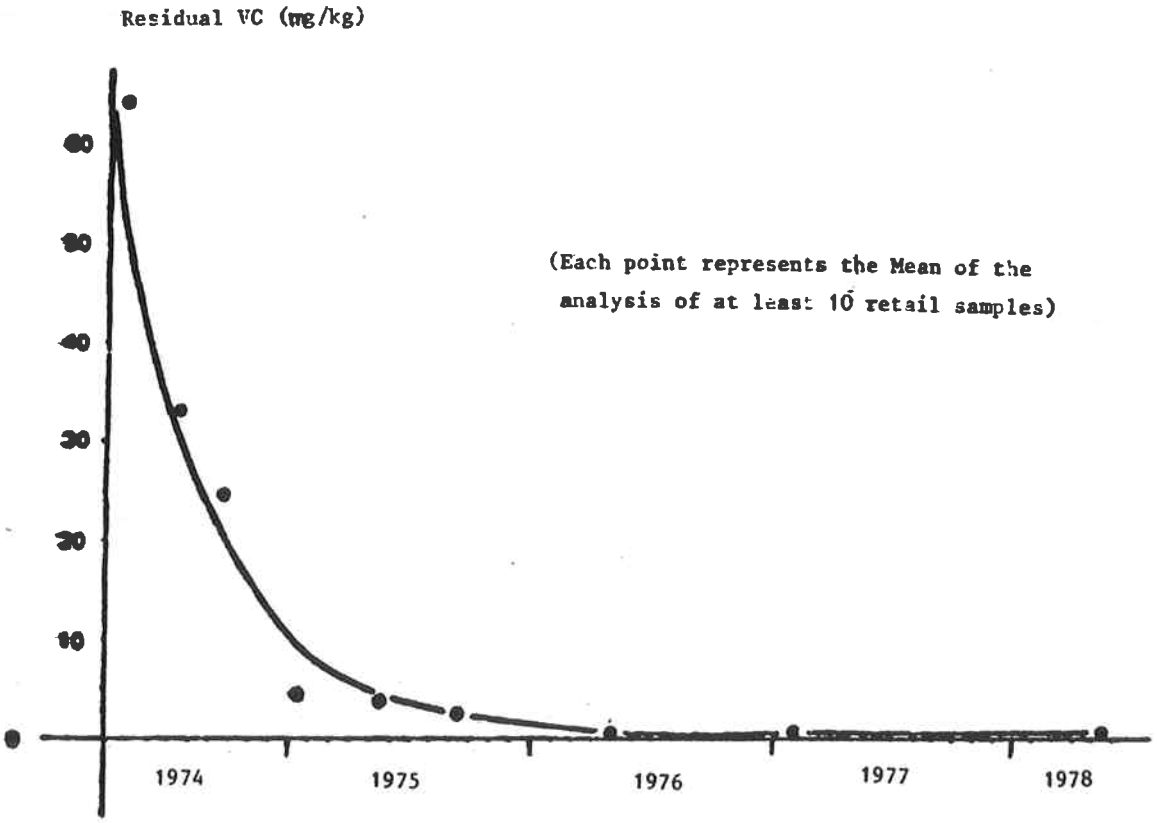
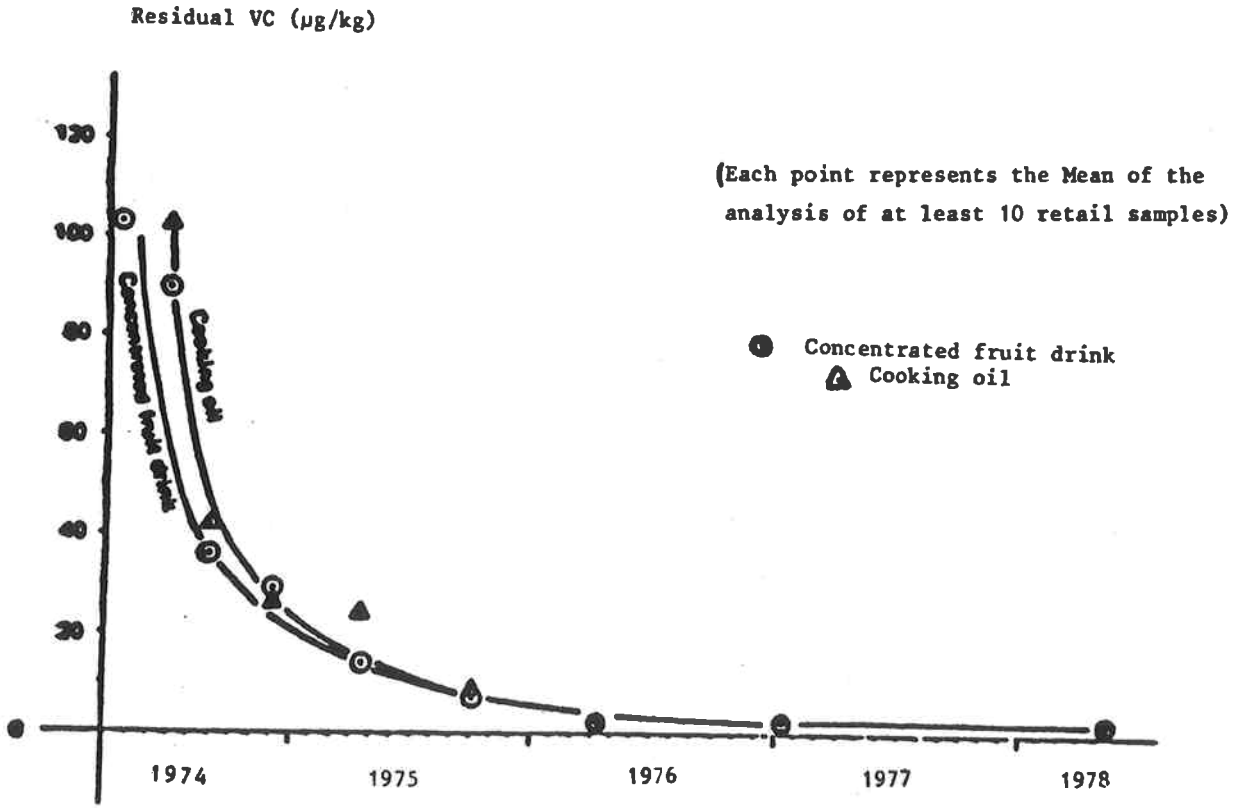


FIGURE 2



Levels of residual vinyl chloride (VC) in PVC bottles

FIGURE 3

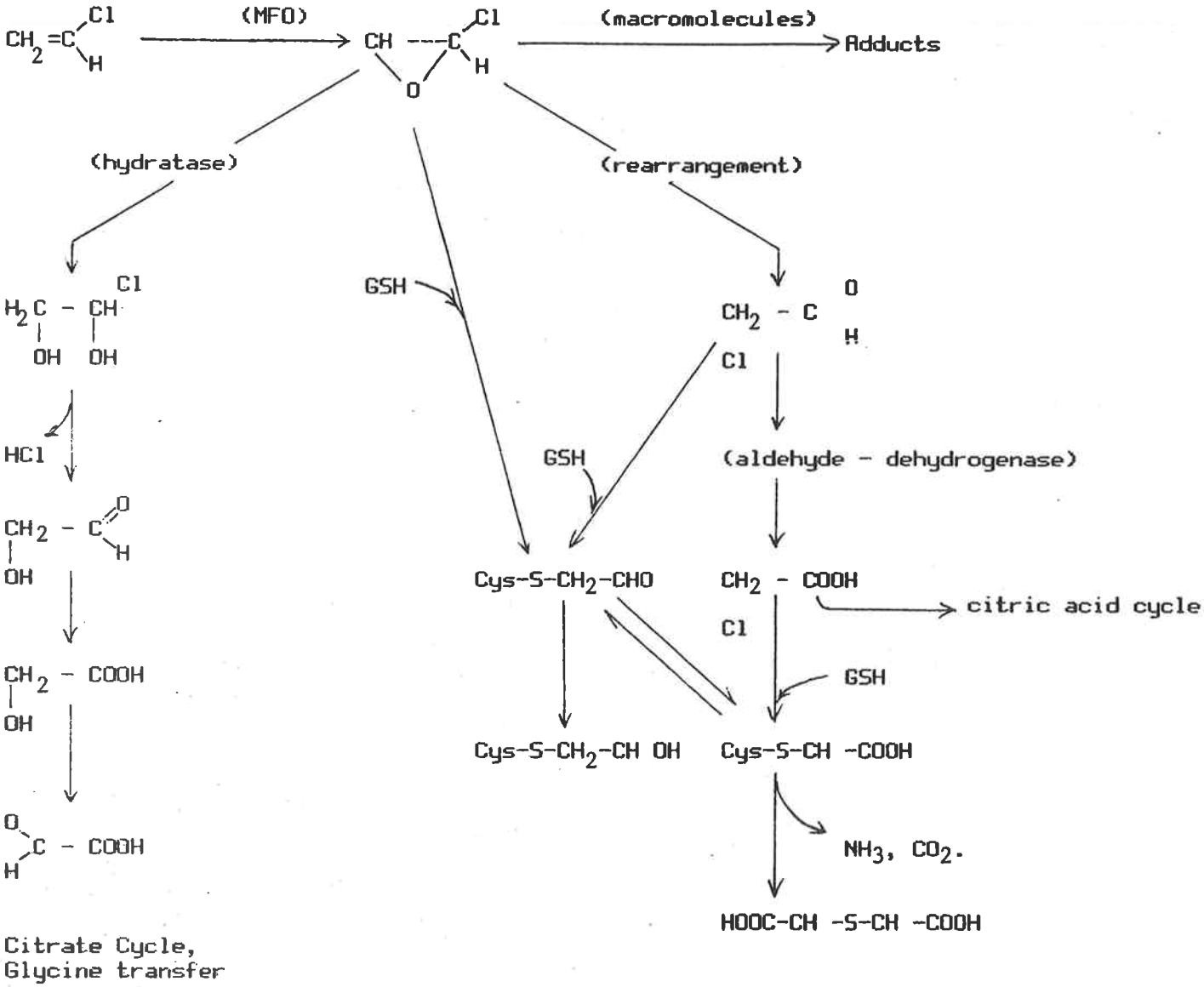


Levels of residual vinyl chloride (VC) in concentrated fruit drink and cooking

FIGURE 4

Major Pathways in Metabolism of VC

(adapted from L. Fishbein, "Industrial Carcinogens", Elsevier, 1979)



APPENDICES

Appendix 1 : Properties of Vinyl Chloride

Synonyms		VC, Vinyl Chloride Monomer, VCM, Monochloroethylene, Monochloroethane
Chemical Formula		$CH_2 = CHCl$
Properties		
General		Vinyl chloride is a colourless gas at ambient temperature and pressure with a sweetish odour at high concentrations. It is normally stored and handled under pressure as a colourless liquid.
Physical	Molecular Weight	62.5
	Boiling Point	-13.9°C
	Freezing Point	-153.7°C
	Flash Point	-78°C (open cup)
	Upper Explosive Limit	26% volume/volume
	Lower Explosive Limit	3.6% volume/volume
	Liquid Density	0.983 (at 20°C)
	Vapour Density	2.15 (relative to air at 20°C)
	Solubility	Readily soluble in most organic solvents but only sparingly in water
Chemical		Vinyl chloride will polymerise exothermically under the influence of light, air, oxygen and initiators such as benzoyl peroxide. Pure vinyl chloride is termally stable to quite high temperatures, however, peroxides formed by slow reaction with oxygen in air may initiate polymerisation. Stablisers, such as benzoquinone or p-methoxyphenol, and storage in an oxygen free atmosphere inhibit adventitious polymerisation.

Appendix 2 : Test For Significance Of Increased Incidence In Skin Melanoma In Maltoni's Experiment BT8

In his experiment BT8, Maltoni et al found an increased incidence of melanoma in male golden hamsters exposed to VC by inhalation. This could be taken as supporting evidence that the excess of malignant skin melanomas found in humans by Heldaas et al (1984) was indeed causally related to exposure to VC. It is therefore of importance to analyse statistically the significance of Maltoni's findings, and this has been done by the reviewers.

The basic data are as follows :

VC Concentration ppm	No. of Animals in Group	No. with Melanoma
10,000	30	1
6,000	30	2
2,500	30	1
500	30	0
250	30	1
50	30	1
0 (controls)	60	0

This gives the following totals :

	Animals	
	With melanoma	Without melanoma
Exposed	6	174
Controls	0	60

When the Fisher exact probability test (Siegel, 1956) was applied to these figures, a value of $P = 0.174$ was obtained, indicating that the increase in melanoma in the exposed animals when compared with the controls is not significant. There was no significantly positive trend for the incidence to increase with dose, as tested by the method of Peto et al (1980).

By contrast, the increased incidences of ASL and Zymbal gland carcinomas in the Maltoni et al experiment BT 1, in which Sprague-Dawley rats were exposed to VC by inhalation, are clearly significant when similarly analysed statistically ($P = 0.0011$ for ASL and 0.011 for Zymbal gland carcinomas by the Fisher test; and $P = 0.0017$ and 2.35×10^{-12}, respectively, in the Peto test for positive trends).

Appendix 3: Estimation of the Exposure Concentration of VC Corresponding with 50% of the Maximum Metabolic Conversion Rate in Humans

The present reviewers estimated the concentration of VC in air at which the metabolic conversion rate was at half of its maximum value in humans. This estimate was based on the decay curves of the VC-concentration in exhaled air after cessation of exposure, determined by Baretta et al (1969). The figures found one hour after cessation of exposure were used as it is assumed that the concentration in exhaled air one hour after cessation of exposure is linearly related to the equilibrium concentration in exhaled air during exposure.

Exposure concentration (ppm)	Concentration in exhaled air one hour after cessation of exposure (ppm)
500	20
250	8.8
100	2.7
50	1.1

The metabolic conversion rate (dCe/dt) may be described by :

$$\frac{dCe}{dt} = V.Ci - k.Ce \qquad (1)$$

V = factor related to respiratory minute volume
k = metabolic conversion rate constant
Ci = inhaled air concentration
Ce = exhaled air concentration

At equilibrium dCe/dt is zero, and the following equation applies :

$$k = \frac{V.Co}{Ce} \qquad (2)$$

Thus, in equation (2) the concentration of VC in exhaled air one hour after cessation of exposure may be substituted for Ce.

Exposure concentration (ppm)	500	250	100	50
Metabolic conversion rate constant (k)	25 V	28.4 V	37.0 V	45.5 V
$\frac{k(500ppm)}{k(50\ ppm)}$	0.625	0.815	1.000	

If the metabolic conversion rate constant is decreasing with increasing exposure concentration, the conversion is becoming saturated and is following probably Michaelis-Menten kinetics. In case of a saturated mechanism the metabolic conversion rate constant may be represented by : $k = \frac{Vmax}{km+C}$ and the conversion rate by kC, where :

Vmax = maximum conversion rate.
km = exposure concentration at which the conversion rate is one-half of its maximum value.
C = exposure concentration.

The parameter km was deduced from the exposure concentrations and the relative conversion rate constants using the method of iterative non-linear least-squares regression analysis (Snedecor and Cochran, 1980). km was estimated to be 435 ppm (standard deviation 143 ppm) which is the exposure concentration corresponding to 50% of the maximum metabolic conversion rate.

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