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159

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Vinyl Chloride-Associated Disease

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1	Introduction	2
2	Technological Details	4
2.1	Vinyl Chloride Monomer (VCM)	4
2.1.1	History	4
2.1.2	Production of VCM	5
2.2	Production of Polyvinyl Chloride (PVC)	6
2.2.1	Technology of Polymerization	6
2.2.2	Methods of Polymerization	7
2.2.3	Compounding	8
2.2.4	Sources of Exposure to VCM in PVC Production	8
2.2.5	The Explosion Hazard	9
2.2.6	The Odour Threshold	10
2.2.7	VCM as an Anaesthetic Agent	10
2.2.8	Effects of Acute Overexposure in Man	11
2.2.9	Monitoring VCM Concentrations in Working Areas	13
2.2.10	Exposure to VCM in PVC-Processing (-Fabricating) Plants	15
2.2.11	National Standards for the Control of Exposure	17
2.2.12	Exposure to VCM Outside the Working Area	18
3	Toxicology of VCM	21
3.1	Acute Toxicity	21
3.2	Chronic Toxicity	21
3.3	Oncogenic Properties	22
3.4	Toxicodynamics	24
3.4.1	Uptake and Distribution	25
3.4.2	Metabolism	26
3.4.2.1	Relation between Chemical Structure, Reactivity and Mutagenic or Carcinogenic Effect	26
3.4.2.2	Metabolic Pathways	26
4	Clinical Spectrum	29
4.1	The Triad: Raynaud's Phenomenon, Pseudoscleroderma and Acroosteolysis	31
4.1.1	Familial and Idiopathic Acroosteolysis	34
4.1.2	Epidemiology of Occupational Acroosteolysis	34
4.1.3	Clinical and Roentgenological Features	36
4.1.3.1	Occupational Acroosteolysis	36
4.1.3.2	Pseudoscleroderma	38
4.1.4	Histology	39
4.1.4.1	Cutaneous Lesions	39
4.1.4.2	Bone Lesions	39
4.1.5	Arteriography, Capillaroscopy, Infrared Thermography	40
4.1.6	Immunological Studies	42

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UCC
044219

4.1.7 Pathogenetic Considerations	44
4.2 Non-malignant Liver Disease in Vinyl Chloride/Polyvinyl Chloride Production Workers	44
4.2.1 Clinical Manifestations of Non-malignant Liver Disease	48
4.2.2 Laboratory Findings	49
4.2.3 Gross Inspection of the Liver and Spleen	50
4.2.4 Histology	51
4.2.4.1 Hepatic Fibrosis	51
4.2.4.2 Sinusoidal Lining Cells	54
4.2.4.3 Hepatocytes	54
4.2.4.4 Histology of the Spleen	54
4.2.5 Pathophysiology of Portal Hypertension	55
4.2.6 Follow-up of Non-malignant VCM-induced Liver Disease	57
4.3 Angiosarcoma of the Liver	57
4.3.1 Epidemiology	57
4.3.2 Clinical Manifestations	74
4.3.3 Pentoneoscopy	76
4.3.4 Gross and Histological Morphology	78
4.3.5 Therapy	80
4.3.6 Risk Assessment	80
4.3.7 Mortality and Cancer Morbidity Studies	81
4.4 Miscellaneous Aspects	82
4.4.1 Thrombocytopenia and Platelet Function Tests	82
4.4.2 Central and Peripheral Nervous System	84
4.4.3 Pulmonary Changes	85
4.4.4 Genetic Effects of VCM	87
5 Conclusion and Outlook	88
References	89

Key words: *Acroosteolysis - Angiosarcoma of the Liver - Portal Fibrosis and Portal Hypertension - Pseudoscleroderma - Raynaud's Phenomenon - Vinyl Chloride*

1 Introduction

The history of vinyl chloride-associated disease, its recognition and prophylaxis is a classic example of shutting the stable door after the horse has bolted. It should help to emphasize the need to shift our attention to preventing exposure from occurring rather than to reparative measures. In view of the large number of new and potentially hazardous chemicals introduced each year into the workplace and the environment, this account should again alert us to the necessity of pretesting chemicals adequately for their potential health effects, even at the risk that technological progress will develop at a more modest rate.

Large-scale production of the synthetic resin polyvinyl chloride (PVC), a thermoplastic material suitable for the most widely diversified industrial use, was begun around 1930 in the United States and in Germany. The monomer, vinyl chloride (VCM), a rather simple aliphatic compound, was believed until the early 1960s to be

one of the least harmful. It was later turned out, had its evaluation of acute effects to reveal its carcinogenicity might have continued in place, considering that it is in the vapour phase under ambient conditions, a reactive double-bond.

Today vinyl chloride formation and data on its carcinogenicity are precisely a quarter of a century old. It is attributable to this new era with the shocking disclosure that workers heavily exposed to the monomer in the 1940s did not alert the public until the 1970s. It was published in 1949 (*Tribuki*).

Ultimately, it was determined that workers exposed to vinyl chloride developed a causal relationship: (1) pseudoscleroderma; (2) liver. Particularly, the discovery of a causal relationship among a comparison of the alarming experience with vinyl chloride and a connection between the lungs or the gastrointestinal tract and the prolonged latency of sarcoma of the liver, to these two fatal consequences, the conclusion that vinyl chloride meeting in Houston to VCM was a very serious matter.

It should be stressed that precise, an intermediate step, mainly in the mammalian polymerization products (PVC) are released from the polymer they contain unreacted PVC (thermal decomposition toxicity of pyrolysis products mainly due to the release of HCl). (*Abbar 1969; Dyer and E* and only very small or rarely (*O'Mara et al. 1971 cite*

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one of the least harmful chlorinated hydrocarbons. Early animal experiments, as it later turned out, had indeed been carried out with dosages sufficiently high for the evaluation of acute effects, but chronic exposure had not been of sufficient duration to reveal its carcinogenic properties. On purely theoretical grounds, however, one might have continued to feel uneasy with this compound as a pollutant of the workplace, considering that it is (1) a halogenated hydrocarbon which (2) exists in its vapour phase under ambient conditions (inhalative exposure) and (3) contains a highly reactive double bond.

Today vinyl chloride-associated pathology is well documented. A large body of information and data on this topic has been accumulated, notably since 1974, but precisely a quarter of a century had to pass before the full range of symptomatology attributable to this new occupational health hazard became recognized in January 1974 with the shocking discovery that haemangiosarcoma of the liver occurred in production workers heavily exposed to PVC. Early and not easily accessible reports suggesting that the monomer might be an environmental risk for workers handling this compound did not alert the experts sufficiently. The earliest indication of adverse effects in workers engaged in the production and processing of PVC, a Russian study published in 1949 (Tribukh et al. 1949), received little attention.

Ultimately, it was the exceptional character of the three major lesions which occurred in workers exposed to VCM that contributed most to the final appreciation of a causal relationship: (1) the syndrome of acroosteolysis, Raynaud's phenomenon and pseudoscleroderma; (2) non-cirrhotic portal hypertension; and (3) angiosarcoma of the liver. Particularly, the discovery of a cluster of four cases of this extremely rare malignancy among a comparatively small group of workers (Creech et al. 1974a) was an alarming experience which called for immediate action. It can easily be imagined that a connection between VCM and the more common malignancies, such as cancer of the lungs or the gastrointestinal tract, might still have gone unnoticed. On the other hand, the prolonged latency periods of both non-cirrhotic portal hypertension and angiosarcoma of the liver, roughly 10 and 20 years respectively, delayed the recognition of these two fatal consequences of chronic exposure to VCM. But one can hardly escape the conclusion that Viola's discovery of cancer in experimental animals, presented at a cancer meeting in Houston in 1970, was sufficient evidence to indicate that exposure to VCM was a very serious occupational hazard (Peters 1976).

It should be stressed that the noxious agent is solely the monomer, or to be more precise, an intermediate of the monomer's metabolic bioactivation, which takes place mainly in the mammalian liver and yields certain highly reactive epoxides. The polymerization products (PVC), i.e., the solid plastic and the plastic consumer goods fabricated from the polymer, are chemically inert articles which carry no health risk unless they contain unreacted residual monomer. Even the combustion of articles made from PVC (thermal decomposition in fires) does not yield free vinyl chloride monomer; the toxicity of pyrolysis products of polyvinyl chloride polymers and formulations is mainly due to the release of hydrochloric acid and carbon monoxide (Cornish and Aber 1969; Dyer and Esch 1976; Sorenson 1976; Moser 1976; Colardyn et al. 1976) and only very small or no quantities of phosgene derived from residual monomer (O'Mara et al. 1971 cited by Colardyn et al. 1976).

UCC
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2 Technological Details

2.1 Vinyl Chloride Monomer (VCM)

At standard (ambient) conditions of temperature and pressure, vinyl chloride ($\text{CH}_2=\text{CHCl}$; chloroethylene, chloroethene) is a non-irritating, colourless gas with a faintly sweet odour, inflammable at concentrations above 3.8% by volume in air, which is only slightly soluble in water, soluble in ethyl alcohol and easily soluble in ether and carbon tetrachloride. VCM is mainly used as an intermediate in the manufacture of plastics, as a refrigerant and in organic synthesis. It was formerly also employed as a propellant for aerosols. It is easily liquefied under pressure and is usually handled and shipped as a liquid. Gaseous VCM condenses at -13.8°C and 760 Torr ($=101.3\text{ kPa}$) to a colourless liquid of low viscosity (Lefaux 1966). Its physical properties are listed in Table 1, the most important of which are its low boiling point, its high specific gravity (gaseous VCM is 2.15 times heavier than air), its low solubility in water and the half-life in air, ranging from 3 to 20 h.

Table 1. Physical properties of VCM

Mol. wt.:	62.503
B. p.:	-13.8°C (-13.7 to -13.9)
F. p.:	-153.7°C
Flash point:	-78.5°C (Cleveland open cup)
Limits of flammability:	3.8%–29.3% by volume in air above -78.5°C ($=38\,000$ – $293\,000$ ppm)
Autoignition temperature:	472°C
Vapour pressure:	mm Hg 10 100 692 2300 2660 $^\circ\text{C}$ -87.5 -55.8 -15.8 $+20$ $+25$
Vapour density:	2.15 g/litre (calculated at 25°C and 760 mmHg (air = 1))
Sp. gr. of liquid VCM:	0.9121 at $-20^\circ\text{C}/4^\circ\text{C}$ 0.99 at $-25^\circ\text{C}/4^\circ\text{C}$

Sources: Fairhall 1957; Irish 1963; Zapp 1964; Lefaux 1966; Ostermayer 1967; Roubal 1972.

2.1.1 History

The French chemist, *Regnault* (1835) was apparently the first to study systematically the synthesis and analysis of vinyl chloride. *Liebig*, who had done some earlier preliminary experiments, encouraged *Regnault* to investigate this compound when *Regnault* spent several months in *Liebig*'s laboratories. All compounds containing the vinyl group ($\text{CH}_2=\text{CH}-$) polymerize readily (Fairhall 1957). Spontaneous polymerization of vinyl chloride to a white opaque solid mass under the influence of sunlight was first described by *Baumann* in 1872; he also quotes a paper by *Saytser* and *Glinsky* (who

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2.1.2 Production

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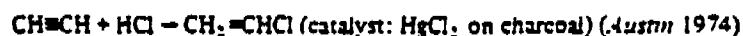
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succeeded in decomposing vinyl chloride to monochloroaldehyde with the aid of oxidizing substances such as hypochlorous acid.

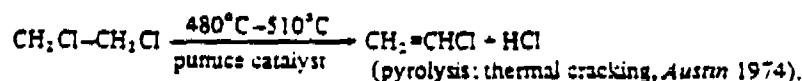
2.1.2 Production of VCM

Large-scale commercial synthesis of VCM with a high yield was made possible much later by employing two principle methods, the second having now largely replaced the first:

1) Conversion of acetylene to VCM by hydrochlorination:



2) Conversion of ethylene by vapour-phase or liquid-phase oxychlorination to 1,2-dichloroethane and subsequent pyrolysis (thermal cracking) to VCM (Albright 1967a):



VCM was usually manufactured in closed systems and stored in outdoor facilities. Thus, any leakage of the gas was readily diluted in the ambient air. VCM concentrations in the atmosphere at some distance from manufacturing plants were found to be in the range 1–2 ppm. In close proximity, the concentration ranged up to 50 ppm (IARC 1974). Spontaneous polymerization in light has also been repeatedly observed when VCM comes into contact with atmospheric air due to container leakage (Ostermayer 1967). A prerequisite for the polymerization process is a high degree of purity in commercially produced VCM. Impurities retard the polymerization process (Lefau 1966; Ostermayer 1967).

In the early discussion about the cause of vinyl chloride-associated disease it was conjectured that other compounds or impurities contained in prepolymerization or in retrieved VCM might have been the causative agent(s) (Thiess and Versen 1974). Analyses carried out by six West German manufacturers of PVC, however, showed that the sum of all impurities (such as saturated or unsaturated hydrocarbons and their halogenates) was 0.01% by volume for prepolymerization VCM and 0.1% for retrieved unreacted monomer. Only methyl chloride was found in concentrations of 50–300 ppm in prepolymerization VCM and 100–500 ppm in retrieved VCM (in one instance only, the concentration ranged between 1000 and 3000 ppm). But it should be kept in mind that even 1000 ppm methyl chloride in VCM would mean, at 500 ppm VCM in air, a methyl chloride concentration in air of only 0.5 ppm. All other impurities (propylene, isobutane, *n*-butane etc.) would then be in the ppb range. Besides, no significant difference in purity could be found between VCM from acetylene and from ethylene.

chloride ($\text{CH}_2=\text{CHCl}$) is a gas with a faintly sweet odour in air, which is soluble in ether and alcohol. The manufacture of VCM is usually employed as a high-pressure process (101.3 kPa). Properties are listed in Table 1. Its high specific gravity in water and the

boiling point -73.5°C

melting point -133.5°C

density 0.91 g/cm³ at 20°C

refractive index 1.2660

study systematically. Some earlier preliminary studies by Regnault (1822) and Glinsky (1900) had shown that the polymerization of VCM in sunlight was first observed by Glinsky (who

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044223

2.2 Production of Polyvinyl Chloride (PVC)

2.2.1 Technology of Polymerization

The following description is meant to serve merely as a rough sketch of the procedures and technological details involved in the production of polyvinyl chloride.

Vinyl chloride monomer is polymerized in large autoclaves (reactors) at temperatures between 40°C and 80°C and pressures of 6–16 (8–12) atmospheres. There are usually several reactors (up to 10–30) located in one building. The reactivity of the monomer is a function of its double-bond. The second functional site of the vinyl chloride molecule, the chlorine atom, does not react easily. The double-bond of VCM is not only the site from which the polymerization originates but is also the source of the toxicity and carcinogenicity of this compound when it is being metabolized in the body. The polymerization of VCM, which is a strongly exothermic reaction (Barnes 1976), is initiated with the aid of compounds soluble in VCM that form free radicals at relatively low temperatures. Initiators are such compounds as lauroyl peroxide, isopropyl percarbonate, azo-bis-isobutyronitrile, and others. The free radicals react with the double-bond of the monomer, transforming it in turn into a free radical and thus propagating the growth of a chain of molecules with a terminal free radical. Chain growth is interrupted by saturation of the terminal free radical which often involves a reaction between two growing chains (Malten and Zielhuis 1964; Lefaux 1966; Albright 1967; Dominighaus 1972; Slater 1972). The random character of such termination steps accounts for the production of chains of different length and hence different degrees of polymerization, with molecular weights of the finished PVC being statistically distributed around a mean value.

Commercial PVC polymers have average molecular weights that vary from about 50 000 to 150 000 daltons (Albright 1967b). Degree and velocity of polymerization, which are influenced by temperature and the concentration of initiators, determine the specific type of PVC produced (Frey 1973). During polymerization considerable amounts of the monomer are at first dissolved in the polymer, but most of this is later also transformed to PVC as polymerization progresses. The polymer which is not soluble in the liquid monomer precipitates out. The process of polymerization slows down towards the end of the reaction. It is terminated, depending on the method used, when approximately 80%–90% of VCM is polymerized. The timing of this termination of the process is essential for the physical properties of the resins produced. The heat generated during the exothermic process of polymerization must be removed to keep the temperature of the reaction under control. Mechanical agitation aids in transferring the heat across the colloidal system to the cooling jacket of the reactor. During the process of polymerization certain quantities of the polymer adhere to the walls of the reactor and form a slowly thickening continuous film or crust. This polymer crust on the inner surface of the reactor vessel, which contains cavities filled with unreacted monomer, impedes the conductance of heat; it has, therefore, to be cleaned away after termination of the batch process (Barnes 1976).

After completion of the polymerization process, the slurry is released from the reactor into a dump tank. Residual unreacted vinyl chloride monomer is partly solvated in the polymer (about 10%); the remainder is dispersed in the water phase or is present

in the vapour phase. VC monomer is then purified by the finished polymer and must diffuse. Raw PVC resin is (VKE 1975). Approximately 500

The slurry from large enough to be are then pumped wet polymer, a drying methods, merization, yield fine solid particle drying temperature polymer. A cycle The solid polymer storage bins or dried powder color

2.2.2 Methods of

Four different in PVC (Frey 1973)

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Emulsion Polymerization was added in the except that large are added. Emulsifiers cannot

Bulk (Mass) Polymerization the addition of oxygen. The first reactor second one is used solid state, to even reaches a level of characterized by good optical clarity

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in the vapour phase above the slurry. While a batch is in the dump tank, this unreacted VC monomer is retrieved by pumping it off into a VCM storage tank. Retrieved VCM is then purified by subsequent distillation for recycling purposes. Monomer solvated in the finished polymer cannot easily be extracted since it has a strong affinity for PVC and must diffuse through the particles: this diffusion depends on time and temperature. Raw PVC resin, therefore, still contains certain quantities of unreacted monomer (VKE 1975). Barnes (1976) reported that the polymer in the slurry still contains approximately 500 ppm of vinyl chloride.

The slurry from the dump tank is pumped into a storage tank (blend tank) which is large enough to hold several batches of the product. The contents of the blend tank are then pumped into a centrifuge which separates the wet solids from the water. The wet polymer, a granular mass, is dried either in rotating tubular dryers or by spray-drying methods, the latter being used mainly for products formed by emulsion polymerization, yielding a polymer which is similar to a very fine white flour. These very fine solid particles are fed directly into a spray-drying column without dewatering. The drying temperature should not exceed 60°C to prevent thermal decomposition of the polymer. A cyclon separator at the exit end of the dryers removes coarser particles. The solid polymer particles are then sized by multiple-layer screens, air-conveyed to storage bins or silos and finally packaged for shipment (Albright 1967d). The resultant dried powder contains about 50 ppm of monomer (Barnes 1976).

2.2.2 Methods of Polymerization

Four different methods of polymerization are used for the commercial production of PVC (Frey 1973), the first two now being the most widely used:

Suspension Polymerization. Polymerization is carried out in an aqueous system in which monomer droplets are maintained in suspension by means of protective colloids (such as polyvinyl alcohol, gelatin, substituted celluloses) under heat and pressure in conjunction with brisk agitation. Relatively large polymer particles can be obtained by this method which 'dry blend' well.

Emulsion Polymerization is the oldest technique, to which suspension polymerization was added in the 1950s. The process is similar to that in suspension polymerization, except that large amounts of emulsifying agents (such as soaps or other surfactants) are added. Emulsion polymerization yields resins of a very small particle size. The emulsifiers cannot be completely removed.

Bulk (Mass) Polymerization. In this process VCM is polymerized in two stages without the addition of other liquids. The two reactors are operated batch-wise and in series. The first reactor (a 'prepolymerizer') provides for the initial liquid phase, while the second one is used for agitating the slurry, which is transformed, through a sticky solid state, to essentially dry particles until the conversion from monomer to polymer reaches a level of about 75%–90%. The resins obtained by bulk polymerization are characterized by high purity and particle uniformity, resulting in an end-product of good optical clarity.

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Solution Polymerization. This type of precipitation polymerization is carried out in organic solvents such as *n*-butane or cyclohexane. It accounts for only a small percentage of the total amount of all PVC resins produced and it is used for the production of copolymers. Copolymers are mixtures of comonomers (such as vinyl acetate, vinyl stearate, vinylidene chloride, propylene, acrylonitrile etc.) and vinyl chloride. The comonomers tend to improve flexibility and limited solubility of the product in solvents and exert an influence on the temperatures required for compounding.

2.2.3 Compounding

As a next step, depending on the end use, the dried polymer, a whitish powdery or granular product, is then compounded (or dry blended) under pressure at fusion temperature with the aid of plasticizers (mainly phthalate or other organic esters) and light and heat stabilizers (heavy metal salts, organotin compounds, and other stabilizers). Lubricants or dyes can be added. Plasticizers are added for the production of flexible PVC; rigid PVC contains little or no plasticizer. These additives can also be a source of toxicity. The plasticizers may slowly diffuse out of the final product depending on its compatibility. Lead-containing stabilizers may also pollute the working atmosphere (Smolčić 1966; Tola 1975). Compounding is carried out by hot mixing at fusion temperatures below or within the softening range (120°C–160°C). Diversified compounding and processing technologies were developed about 1950.

The compounded polymers are used for the production of diverse end-products. The final conversion of the thermoplastic PVC resins into consumer end-products is accomplished by such procedures as extruding, calendering, injection or compression moulding, blow moulding, dipping (coating) and hot spraying. Temperatures used in these processes range from 100°C to 300°C. End-products include a vast number of articles used in almost every sphere of daily life. The temperatures during the fabrication operations (compounding and conversion of compound polymer into consumer articles) drive off part of the small concentrations of residual monomer still contained in the polymer. Barnes (1976) calculated that the final fabricated articles contained approximately 5 ppm VCM and those for foodstuff packaging (bottles, films, foils) even less.

2.2.4 Sources of Exposure to VCM in PVC Production

Both polymerization of VCM and subsequent processing (centrifuging, drying, screening, bagging) are usually carried out in closed buildings. Exceptions can be found in hot climates (Aryampur 1977). Polymerization is of necessity a batch process that requires a large number of single operations. Therefore, valves, gaskets, shaft-openings and control gear are subject to heavy wear and thus to leakage. Other sources of pollution of the working atmosphere are exchange of parts and repair jobs. The degree of pollution also depends to a large extent on the quality and effectivity of monitoring equipment and special exhaust systems. Opening of autoclave vats for cleaning and control purposes resulted in larger spill-over of the tank atmosphere into the work environment. Numerous reports of workers with pre-narcotic symptoms (dizziness etc.)

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permit the conclusion that episodes of acute overexposure to VCM were not rare events in the past.

There is no doubt, however, that those workers who manually cleaned the auto-clave vats by scraping away or chipping off the 'polymer skin' formed on the reactor walls ('poly cleaners'), and who in the past had to spend several hours inside the reactors, had been exposed to the highest concentrations of VCM. Although the vats were degassed prior to entry, unreacted monomer remained trapped in the polymer skin, and larger amounts of VCM were released when cavities formed in the polymer crust were opened by chipping. The later introduction of automatic cleaning systems reduced the frequency of entry into the reactors, but some manual cleaning of shorter duration still had to be done after every 20th-30th run. It is, therefore, plausible that, primarily, the most severe adverse effects of exposure to VCM were fully recognized in those workers who had been employed in this job category. But the subsequent steps (centrifuging, drying, screening) also involve the release of some of the lesser quantities of unreacted residual monomer from the particles to pollute the environment if ventilation, notably of the drying facilities, is inadequate. Finished polymer, ready for shipment or subsequent compounding, still contains small quantities of unreacted monomer, which either slowly diffuse out and pollute the bagging areas during storage or are driven out by the high temperatures necessary for compounding.

Table 2. Conversion table for concentration of VCM in ambient air

$1 \text{ ppm} = \frac{\text{Mol. wt.}}{1000 \times 24.45} \text{ mg/litre}$	
$1 \text{ mg per litre} = \frac{24.45 \times 1000}{\text{Mol. wt.}} \text{ ppm}$	
(Perry 1958)	
1 mg/litre =	391 ppm
1 mg/m ³ =	0.391 ppm
1 ppm = 2.56 mg/m ³ =	0.00256 mg/litre
1% = 10 000 ppm =	25.6 mg/litre

2.2.5 The Explosion Hazard

In the past only the explosion and fire hazard of VCM was thought to be the dominant monitoring problem in handling gaseous vinyl chloride (Irish 1963). This hazard covers a concentration range of 4%-22% by volume of air (40 000-220 000 ppm) (Lefaux 1966). It was observed that VCM, being 2.15 times heavier than air, may collect as a compact layer at the floor of a polymerization building after spill-over from opened tanks and may catch fire. At least two instances of disastrous VCM explosions became known: In 1964, a large plant for the polymerization of VCM in the United

UCC
044227

States was almost completely destroyed when VCM escaping from a leak detonated (Albright 1967a). Another explosion in one of the two Rumanian factories operating at that time was mentioned by Suciu et al. (1975). Monitoring of VCM concentrations polluting the work environment was then directed largely towards preventing VCM from reaching the flammability limit.

2.2.6 The Odour Threshold

Unfortunately, gaseous VCM has no irritating or unpleasant warning properties. Its mild odour is described as faintly pleasant, sweet or ethereal. Some of the PVC workers we interviewed reported that they had even enjoyed 'sniffing the gas', which soon resulted in a feeling of light-headedness. For the early days of PVC production, when appropriately sensitive monitoring equipment was not yet available, workers' reports about perception of the odour of VCM can be taken as circumstantial evidence for a rough estimate of the actual degree of exposure. It should be kept in mind, however, that in chemical production units the presence of other odouriferous chemicals and the possibility of olfactory fatigue, as well as different levels of individual sensitivity, may render it very difficult to determine the factual odour threshold of a certain gaseous substance unless it possesses irritating warning properties.

In 1929, Schmidt and Schaumann declared that the faintly sweet gas is practically odourless at concentrations of 5%–10% by volume. Veltman and Lange (1977a, b) assumed an odour threshold of 5 000–10 000 ppm. Volunteers exposed to VCM detected a slight odour at 4 100 ppm; a distinct odour was noted at 6 600 ppm for 30 min and this was accompanied by subjective symptoms of dizziness and sleepiness (Irish 1963). Gehring et al. (1979) recently mentioned a threshold of approximately 3500 ppm. Others have claimed that a concentration of 400–500 ppm is the lower limit for detection of VCM by its odour (Baretta et al. 1969; Cook et al. 1971; Markowitz et al. 1972; Lefèvre 1975, cited by Hubler 1975). Baretta et al. (1969) conducted experiments with concentrations of 50, 250 and 500 ppm in an exposure chamber, in which 13 volunteers participated. At 500 ppm only some of them claimed that they were able to detect the odour, but this was inconstant. Table 3 shows that differences between the various estimates are at least one order of magnitude. The close proximity between the perception of the odour of VCM and incipient CNS symptoms as reported by Irish (1963), however, makes it likely that the actual odour threshold can be assumed at or above 4000 ppm.

In contrast to VCM, the comonomer vinyl acetate, for instance, has distinct warning properties and can be detected by its odour at a level as low as 0.4 ppm; eye and throat irritation begin upward of 5 ppm and are noted by all test subjects at a concentration of 21.6 ppm (Deese and Joyner 1969).

2.2.7 VCM as an Anaesthetic Agent

VCM was once even considered for use as an anaesthetic agent. In 1929, Schmidt and Schaumann speculated about using VCM as a supplementary narcotic at concentrations of 3%–5% (v/v) (= 30 000–50 000 ppm) in combined nitrogen oxide oxygen

Table 3. Odour

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Table 3. Odour threshold

Lower limit of detection	Author
5 000-10 000 ppm	Veltman and Lange 1977a, b
5 000 ppm	Viola 1974
4 100 ppm	Irish 1963
3 500 ppm	Gehring et al. 1979
500 ppm	Baretta et al. 1969
400-500 ppm	Lejèvre 1975 (cited by Hublet 1975)
400 ppm	Cook et al. 1971
400 ppm	Markowitz et al. 1972

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anaesthesia because of its potent narcotic action and the wide margin between narcotic and lethal concentrations. In animals it produced anaesthesia at 7%-10% in air or oxygen; concentrations above 12% proved to be dangerous. The authors pointed out, however, that adverse late effects of this halogenated hydrocarbon could not be excluded. In toxicity studies with guinea pigs *Perry et al.* (1930) found concentrations of 10% VCM to be lethal within 30-60 min, 5% to cause marked narcosis, and 0.5% for several hours to be the maximum tolerable exposure without serious effects. They also commented upon the potential use of VCM for surgical anaesthesia but were undetermined about its practicability. In mice, the minimal anaesthetic range was found to be 3.5-5 mmol (85 000-122 000 ppm) for 10 min, the minimal lethal range 10-12 mmol (244 000-293 000 ppm) (*Peoples and Leake* 1933). It was not until 1947 that *Oster et al.*, in contrast to *Schaumann's* earlier assumption (1934) of a relatively low cardiotoxicity, warned against the use of VCM as a potential general anaesthetic in man because of serious cardiac irregularities and ECG changes observed in dogs. VCM, like other halogenated hydrocarbons, sensitizes the heart to the effect of catecholamines (*Irish* 1963). We could not ascertain whether VCM has actually been used in the past for anaesthesia in man.

2.2.8 Effects of Acute Overexposure in Man

Some individual responses of volunteers to increasing concentrations of VCM are listed in Table 4. *Lester et al.* concluded in 1963 that the maximum concentration without acute effects in man lies between 8 000 and 12 000 ppm for 5 min, and that symptoms such as dizziness, light-headedness and disorientation should be taken as adequate warning signs for imminent acute danger. Two fatalities after occupational exposure to high concentrations of VCM are reported in the literature (*Danziger* 1960). A 21-year-old autoclave cleaner at a Canadian polymerization plant was found dead 10 min after entry at the bottom of a probably insufficiently ventilated reactor tank which had been declared safe solely after an explosiometer test. Heart failure cells and cardiac enlargement found at autopsy, however, implied that the cause of death might have been acute functional disturbance in pre-existing heart disease. In the second case which occurred at the same plant, however, circumstantial evidence apparently left no doubt that heavy VCM exposure was the cause of death in a 39-year-old worker. He was found dead within 20 min, lying in a pit near the opened valve of a recycling pipeline

Table 4 Individual responses of volunteers to increasing concentrations of VCM

Concentration	Duration of exposure	Symptoms	Reference
500 ppm	7.5 h	(Inconstant odour detection) mild headache, dryness of eyes and throat in 2 of 7 subjects)	Burrella et al. (1969)
4 000 ppm	—	Generally accepted odour threshold	Irish (1963)
6 600 ppm	30 min	(Distinct odour) dizziness, sleepiness	Irish (1963)
8 000 ppm 12 000 ppm 16 000 ppm 20 000 ppm	5 min ^a (twice on each of 3 successive days)	2 of 6 subjects 'slightly heady' 1 of 6 subjects had reeling, swimming head, 'just like getting gas' 5 of 6 subjects, various degrees of intoxication All 6 subjects had more intense symptoms of acute intoxication than at 16 000 ppm	Lester et al. (1963)
25 000 ppm	3 min	2 experimenters: dizziness, disorientation, burning sensation in the soles of the feet	Patty et al. (1963)

^a Exposure to six different concentrations: 0 ppm: 4 000 ppm: 8 000 ppm: 12 000 ppm: 16 000 ppm: 20 000 ppm

through which non-polymerized residual VCM was pumped back into a reserve tank: another man coming to his rescue was himself overcome by the gas and only just escaped.

Two non-fatal cases of VCM gassing were reported in Great Britain in 1951 (Spittas et al. 1975). A maintenance worker experienced acute narcosis while repairing a VCM leak, and a worker cleaning a polymerization vat from outside with a water jet suddenly collapsed across the open manhole. Subsequently he complained about tightness of the chest, nausea, abdominal pain and headache. Occasional loss of consciousness was also reported by Lilis et al. (1975) in 14 of 354 workers at Niagara Falls and by Suciu et al. (1963) at a Rumanian plant. VCM-induced narcosis, at least on one occasion in the past, had occurred in 46 of 58 workers (79%) referred for medical surveillance from one British PVC-producing plant (Ivan et al. 1976), with a 100% incidence of narcosis in 28 symptomatic workers (Raynaud's syndrome and/or acroosteolysis). Successful resuscitation after VCM-induced narcosis of several hours' duration without evidence of permanent damage was mentioned by Rery et al. (1974).

2.2.9 Monitoring

During the field data on VCM was directed an apparently 1954. Pleshic Gronsberg to Russian poly: 0.05–0.08 mg concentration of Inspectorate or from the d mg/litre (= 1 mg/litre (= 3-

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2.2.9 Monitoring VCM Concentrations in Working Areas

During the first two decades of PVC production (1930-1950) no publication contained data on VCM concentrations in the working environment. The main interest then was directed towards prevention of the explosion hazard. In 1957, the observation of an apparently toxic angioneurosis in Russian PVC production workers (Smirnova 1954; Pleschchitsker et al., cited in Filatova and Gronsborg 1957) induced Filatova and Gronsborg to investigate environmental VCM concentrations in various parts of a Russian polymerization plant in Gor'kij. Although most readings were in the range of 0.05-0.08 mg/litre (= 20-313 ppm), e.g. below the maximum permitted VCM concentration of 1 mg/litre (approximately 400 ppm) as specified by the State Sanitary Inspectorate at that time, escapes of VCM in the reactor areas from defective fittings or from the discharge of operating autoclaves resulted in excursions up to 29.5-41.4 mg/litre (= 11 500-16 200 ppm) for periods of 5-10 min. One peak reading of 87.3 mg/litre (= 34 000 ppm) was recorded.

In the centrifuging and drying area of this plant the VCM content of the ambient air ranged from 4 ppm to 3 100 ppm with most readings between 20 ppm and 195 ppm, which was attributed to release of residual VCM from wet PVC resin and poor ventilation. The screening and bagging area was characterized by high dust concentrations, sometimes exceeding the official upper limits set for non-toxic dusts. In the pursuit of improving industrial hygiene, the installation of modern ventilation equipment in the vicinity of the autoclaves, substitution of hand-operated by semi-automatic drying facilities, and avoidance of leakages succeeded in reducing the ambient concentrations of VCM to below 0.05 mg/litre (= 20 ppm), but toxic angioneurosis still continued to be diagnosed. This led the authors to recommend that the maximum permitted concentration of VCM should be reconsidered.

In a plant producing VCM, Filatova et al. (1958) found lower concentrations in the range of 0.04-1.1 mg/litre (16-430 ppm), with maximum values of about 1200 ppm (2.93 mg/litre), the latter having been observed in close proximity to the rectification apparatuses and having resulted from spillage during sample collection. It is remarkable that up to now the Soviet Union has reported no cases of angiosarcoma of the liver, although production of PVC resins started early and VCM exposures in the past have probably been in the same range as those observed in Western countries.

Byrén et al. (1976) pointed out that during the 1950s episodes of unconsciousness which occurred among workers of the one Swedish plant operating at that time indicated peak exposures of at least 10 000-15 000 ppm. Suciu et al. (1975) noted that between 1962 and 1972 a reduction of the average VCM concentration in the two Rumanian PVC plants had been achieved from 2298 mg/m³ (= 900 ppm) in 1962 to about 120 mg/m³ (= 50 ppm) in 1965-1972. In 1969, Anghelescu et al. mentioned exposures to VCM concentrations of 112-545 mg/m³ (44-213 ppm) for a group of 300 Rumanian workers, eight of whom (2.7%) had Raynaud's phenomenon. At a Greek plant which started operation in 1967, certain stages in the production process resulted in high concentrations of VCM in the work environment for brief periods (Gitsios 1971). In air displaced from reactors during addition of water and on opening of the reactors to obtain PVC samples at the end of a reaction cycle, concentrations of up to 10 000 ppm were found. In open waste drums into which waste polymer scraped

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than 50 ppm: (b) medium = 50-200 ppm: (c) high = 200 ppm and above (up to 1500 ppm). In the past, however, estimates of exposure concentrations were based in most plants not on continuous monitoring during the entire work shift but at best on spot samples not necessarily representative of the different phases of a given operation. Estimates of past exposure levels such as those represented in Table 5 are, therefore, more or less conjectural. It can be assumed that considerable deviations from these average values have occurred all too often in the past.

Table 5. Average concentrations of VCM in the working atmosphere of PVC-producing plants^a. (Estimated by Chemical Industries Association Ltd.)

1945-1955	~ 1000 ppm
1955-1960	~ 400-500 ppm
1960-1970	~ 300-400 ppm
mid-1973	~ 150 ppm
1974	~ 50 ppm and less
1975	~ 5 ppm

^a According to Fleig and Thiess 1974; Barnes 1976

Equipment for optimal continuous multipoint monitoring of exposure concentrations in the working areas should meet certain basic requirements: (1) For stationary equipment strategically placed sample probes should yield data representative of individual exposure levels in the breathing zone of workers, preferably to be used in combination with personal samplers. (2) Analysing methods should have a high selectivity. (3) The limit of detection should be at least one order of magnitude below the currently specified standard regulating the permissible upper level of exposure. (4) Measurement should be instantaneous (within seconds) to guarantee rapid detection of critical peak concentrations. (5) Recording and data processing techniques should be provided for the daily estimation of TWA exposure during the whole work shift.

Currently available methods for the determination of ambient VCM concentration comprise such analytical tools as long-path infrared spectrophotometry, flame ionization detection, gas chromatography, mass spectrometry, combustion-conductivity (ionoflux), and personal samplers in combination with gas chromatography, none of which can at present be considered as absolutely satisfactory for all individual plant conditions because they all differ with regard to selectivity, limit of detection and time lag of response.

A catalogue of the methodologies that have proved to be of value in the control of industrial hygiene and personnel protection regarding exposure to VCM was compiled in 1975 by Rowe.

2.2.10 Exposure to VCM in PVC-Processing (-Fabricating) Plants

Raw PVC powder ready for compounding and fabricating purposes contains residual unreacted vinyl chloride monomer in varying amounts. In the past, monomer content

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was reported to have been as high as 6000–7000 ppm (w/w) in some types of raw PVC, but a level of 500–1000 ppm probably was a more representative range (Schweitzer 1975; VKE 1974; Karstadt 1976). The monomer slowly escapes into the environment exponentially with time. Depending on length of storage period, temperature, size and porosity of particles and other physical properties of the polymer and, more recently, on the effectivity of special degassing techniques (Paver 1976; Schütz and Wolf 1977). In 1975, the Association of the German Plastics Industry announced that in future only PVC powder with a maximum monomer content of 10 ppm would be put on the market due to the development of special degassing technologies (VKE 1975). Analyses of the types of raw PVC, chiefly suspension polymer, which are now used in German plants showed that in most products the content of unreacted monomer was now less than 20 ppm but in some foreign products it still ranged between 150 and 250 ppm; it also turned out that there may be considerable variation between different batches of the same product (Schütz and Wolf 1977).

Cold and particularly hot mixing or compounding of PVC, a procedure which usually precedes fabricating processes, favours the escape of unreacted monomer and, therefore, requires special ventilation equipment. Depending on the content of residual monomer, considerable amounts of VCM could be set free during the mixing process, as was shown by Bräuer and Straby (1975). Apart from hot compounding, other thermoplastic operations, such as extruding, calendaring and welding of tiles, also resulted in release of unreacted monomer into the work environment. Although recently conducted measurements of the concentration of VCM in working areas of six German PVC fabricating plants have shown that in 90% of the readings mean levels integrated over 1-h periods now range below 0.1 ppm, numerous short bursts with excursions up to 60 ppm during a workshift were recorded in one instance (Schütz and Wolf 1977). Similarly low concentrations of VCM in breathing zone samples (maximum: 12 ppm) with 60% of the values ranging below 1 ppm had been found in 1974 in nine United States fabricating plants, but source samples had ranged up to 340–540 ppm (Karstadt 1976).

These present results, however, do not permit any conclusions as to past levels of atmospheric VCM during the years when residual monomer content of PVC resins was high and ventilation insufficient, particularly in compounding and extruding units. Whatever the extent of the risk might have been in the past, it can be safely assumed that the ambient monomer concentrations in fabricating plants have always been considerably lower than in PVC-producing plants.

When it was suspected that certain VCM-related symptoms might also have afflicted PVC process workers, this problem was investigated by our group. Although no cases of acroosteolysis, pseudoscleroderma or angiosarcoma of the liver were observed, evidence was presented which demonstrated that minor and inconspicuous lesions such as mild hepatic fibrosis, bromsulphalein (BSP) retention, thrombocytopenia and slight enlargement of the spleen could be found in 28 process workers who had been employed for years in compounding and fabricating units (Lange et al. 1975, 1976a; Wegman 1975; Marsteller et al. 1976). In principle, these lesions were identical with those seen after heavy exposure as we will describe, but the degree of damage attributable to occupational VCM exposure observed in these workers was not considered sufficient to entitle them to disability compensation under German law. Although the in-

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conspicuous character of these lesions agrees well with the assumption of a dose-response relationship of VCM-related disorders and the alterations may seem to be, quantitatively, of little importance, they should not be minimized. Nevertheless, an observation period up to the present of almost 7 years did not reveal any spontaneous progression. In a proportional mortality study for 1970-1972 among roughly 55 000 male PVC fabrication workers in England and Wales, *Baxter and Fox* (1976) did not find an excess of angiosarcoma or other liver diseases.

A recently completed cohort study of 4007 people who had been employed by two German PVC-fabricating plants between 1934 and 1974 and of whom 360 had died revealed that overall mortality, although marginally below that of the male population of the Federal Republic of Germany, was slightly elevated with respect to the 'healthy worker effect'. No angiosarcomas of the liver were observed and no excess in overall cancer mortality was noted, but an excess mortality from brain tumours was recorded in one of the two plants (*Reul et al.* 1978).

2.2.11 National Standards for the Control of Exposure

Industrial hygienists have used several designations for acceptable or permissible limits of exposure to chemicals at the work place, such as 'maximum allowable concentration' or 'maximum acceptable concentration' (MAC), 'threshold limit value' (TLV), 'industrial hygiene standard' in the United States and as 'Maximale Arbeitsplatzkonzentration' (MAK) in West Germany. These empirical standards were defined by the American Standards Association as setting a limiting concentration "for exposures not exceeding 8 hours daily during a 40-hour work week with the understanding that variations should fluctuate below this value" (*Irish* 1963). An extensive discussion of the basic approach to the principles used in setting environmental quality standards for occupational respiratory exposure to toxic agents can be found in the paper of *Zielhuis* (1974). In this paper, the conceptual differences between threshold limit values as used in the United States and maximum allowable concentrations as used in the USSR are summarized and the differences in approach and emphasis, which may explain past discrepancies between permissible limits, are elucidated. For details the reader is referred to this paper.

The standard is *not* an index of relative toxicity, far less of hazard, and certainly not a sort of 'average'. A standard set as the ceiling level implies that any fluctuations should be around a median of perhaps half the standard and that it should be competently used in full awareness of its physiological basis and the limitations of currently available knowledge (*Irish* 1963). The standard will be subject to revision as soon as new information is available. An essential element of the annually published German list of MAK values (MAK-Werte) is its preamble, which exhaustively defines the various modalities for the interpretation of such standards (*Henschler* 1972/73). The so-called TWA, an integration over time of fluctuating concentrations, will be a useful tool for estimating the probability of injury only if it represents a comprehensive analysis of the normal fluctuation below the standard.

In the Federal Republic of Germany the standard for VCM (MAK) was set at 500 ppm in 1966. The German Standards Advisory Committee reduced this to 100 ppm

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in 1970 in conformity with the proposal of *Torkelson et al.* (1961), which was based on the results of their animal experiments. In June 1974, when the carcinogenic properties of VCM had been well established, the MAK regulation for this chemical was repealed and instead a preliminary technical guideline (Technische Richtkonzentration) of 50 ppm was instituted (VKE 1975). The Chemical Industries' Liability Insurance Association (Berufsgenossenschaft der Chemischen Industrie) also issued instructions for the prevention of health hazards arising from handling of VCM in July 1974. As of July 1975, a technical guideline (TRK = Technische Richtkonzentration) of 5 ppm, defined as annual mean, for PVC-producing and -fabricating plants was instituted, permitting excursions up to 15 ppm during periods of not more than 1 h. In order to adapt operating plants, a provisional regulation was issued with reduction of the annual mean concentration to 20 ppm as of July 1975, and to 10 ppm as of July 1976 and peak concentrations over 1-h periods not exceeding 60 or 30 ppm, respectively (*Veltman and Lange* 1977a). The technical guideline (TRK value) was revised in 1977 (2 ppm annual mean/5 ppm per 1 h).

In the United States the threshold limit value for VCM was originally set at 500 ppm in 1947. It was reduced to 50 ppm in April 1974 as a temporary emergency standard and finally reduced to 1 ppm/8 h in 1976. *Haley* (1975) summarized the conflicting views on vinyl chloride regulations proposed by Government and industry in 1974. Table 6 shows threshold limit values in a number of PVC-producing countries.

2.2.12 Exposure to VCM Outside the Working Area

The Environmental Protection Agency estimated that PVC-producing plants in the United States discharged about 90 million kg VCM annually into the environment (4%–8% losses), most of it as air emissions and lesser quantities dissolved in water effluent streams and entrapped in sludge and solid wastes (*Schweitzer* 1975). In a pioneer study, concentrations of 1–2 ppm VCM were found in the ambient air near such a plant (IARC 1974), 2–3 ppm in the primary water effluent and 100–200 ppm in the sludge at the plant site, but sampling and analysis methods used were later found to have been inadequate so no conclusions were drawn from these figures since they could have been in error by as much as one order of magnitude (*Schweitzer* 1975). For people who live within 5 miles of monomer and polymer production facilities in the United States an average exposure of 17 ppb during the years of uncontrolled emissions was calculated (*Nicholson* 1977).

In the past VCM has been widely used as an aerosol propellant, either alone or mixed with fluorocarbons, hydrocarbons and inert organic gases, in household and cosmetic products (hair sprays, deodorants, pesticides, room disinfectants, paint sprays, furniture polish and window cleaners). In Germany, VCM was proposed as propellant for aerosols in 1958 (*Ostermayer* 1967), in Japan it has been used as a propellant since 1958, in the United States this use was probably introduced after 1962 (*Schweitzer* 1975). As an aerosol propellant, VCM has been a possible source of exposure for the public at large, particularly for women, the extent and the potential health implications of which are unknown. Use of aerosol products in confined spaces has been reported to result in air concentrations of VCM of up to 400 ppm in closed rooms, even after only short bursts (30 s) (*Gay et al.* 1975), which could persist for several

Vinyl Chloride

Table 6. T

Country

Belgium
Canada
Finland
France
German Democratic Republic
Iran
Italy
Japan
Netherlands
Rumania
Sweden
Switzerland
United Kingdom
USA
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Federal Republic of Germany

Sources: Sn
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which was based on carcinogenic properties of this chemical was re-evaluated (Luftkonzentrationen) by the Liability Insurance Association. It issued instructions in July 1974. As a result, a concentration of 5 ppm was instituted, permitted for 1 h. In order to reduce the amount of the substance as of July 1976 to 1 ppm, respectively, the limit was revised in 1977.

originally set at 500 ppm. In a temporary emergency standard, summarized the conflict between industry in 1974 and living countries.

ing plants in the environment involved in water pollution (1975). In a study, the ambient air near the plants and 100-200 ppm were used. These figures since then have been used (Schweitzer 1976) for the production facilities in the years of uncontrolled

or, either alone or mixed with household and cosmetic products, paint sprays, and aerosols, proposed as propellant and as a propellant since 1962 (Schweitzer 1976). The level of exposure for the general health implications in closed rooms has been revised. It can persist for several

Table 6. Threshold limit values (TLV) in various countries

Country	Year	TLV (ppm)	Comment
Belgium	1975	25/50	TWA (8 h/15 min)
Canada	1975	10/25	TWA (8 h/15 min)
Finland	1975	5/10	TWA (8 h/15 min)
France	1975	25	TWA (8 h)
German Democratic Republic (DDR)	— 1976	200 25/12	MAC (Schottek 1969) (Konezke et al. 1978)
Iran	1976	25/50	TWA (8 h/1 h)
Italy	1975 (future)	50 (25/50)	TWA (8 h) (TWA 8 h/15 min)
Japan	1970 1974 1975	500 200 25/10	MAC MAC (25 mg/m ³)
Netherlands	1975	10	TWA (8 h)
Rumania	—	100 mg/m ³ (40 ppm)	MAC (Prodan et al. 1975)
Sweden	1975 1976	5/20 1/5	TWA (8 h/15 min) TWA (8 h/15 min)
Switzerland	1975 (future)	100 10	MAC TWA (8 h)
United Kingdom	1975 October 1975	25/50 10/30	TWA (8 h/15 min) TWA (personal/ceiling)
USA	1947 April 1974 October 1974 1976	500 50 25 1/5	MAC (Amer. Conf. Governm. Industr. Hygienists) TWA (8 h), temporary emergency standard (OSHA) TWA (8 h), temporarily permitted exposure TWA (8 h/15 min)
USSR	— —	1 mg/litre (391 ppm) 30 mg/m ³ (25 ppm)	MAC, provisional ceiling concentration: State Sanitary Inspectorate, 1957 (Filatova and Gronsberg 1957) MAC (Schottek 1969; Kettner 1975) (Sanitary normy)
Federal Republic of Germany	1966 1970 June 1974 1975 1977	500 100 50 5/15 2/5	MAK MAK TRK (preliminary technical guideline), Amendment of MAK regulation. TRK (annual mean/1 h) TRK (annual mean/1 h)

Sources: Smyth 1956; Filatova and Gronsberg 1957; Schottek 1969; Henschler 1972/73; IARC Report 1974; Haley 1975; Sakabe 1975; Prodan et al. 1975; Aryanpur 1977; Schütz and Wolf 1977; MAK-Werte-Liste 1977; Kettner 1975

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hours after repeated spraying in smaller-sized rooms (IARC 1974). Haley (1975) presented a list of pesticide products containing VCM as a propellant and registered for indoor use, which were banned in 1974 by the Food and Drug Administration. In Japan, the monomer was also banned as a propellant in 1974 (JAMA 1974, 229:855). There is a case on record of a worker who died from noncirrhotic portal hypertension and angiosarcoma of the liver after 14 years' employment at a chemical plant in southern Germany where he had been engaged in loading such pesticide cans (Reint and Weber 1974). The report of a female office worker suffering from typical Raynaud's phenomenon, pseudoscleroderma, acroosteolysis and mandibular osteolysis who never had occupational contact with VCM (Meyerson and Meier 1972) is apt to make one wonder what influence the frequent indoor use of VCM-propelled spray cans (Bridford et al. 1975) may have had in this unique case. Sputum samples collected from frequent users of pressurized spray cans who had no respiratory symptoms were found to contain a significant excess of moderate and marked atypical metaplastic bronchial cells compared with two groups of controls (Good et al. 1975).

PVC bottles, films and foils have been used for many years for packaging food and beverages (cooking oil, margarine, meat, mineral water, fruit squashes and other soft drinks, hard liquor etc.). The content of residual VCM in PVC bottles was found to have ranged formerly between 5 and 400 ppm (w/w), and in PVC foils up to 800 ppm (van Esch and van Logten 1975). The problem of migration of unreacted VCM from the PVC containers into the foodstuffs became recognized in 1973. Reports of unpleasant tastes in American brands of vodka and whisky which had been stored in PVC bottles led to the discovery that VCM had leaked into the liquors; in some samples levels up to 10–20 ppm (w/w) were found (van Esch and van Logten 1975; Davies and Perry 1975). Data available in 1974 to a group of WHO experts revealed that samples of gin and whisky had contained 0.57 and 0.62 ppm (w/w) of VCM respectively, after storage in miniature PVC bottles for periods up to 3 years; VCM concentrations in orange squash and cooking oil were found to be in the range of 0.01–0.08 ppm and 0.01–0.04 ppm, respectively (IARC 1974). Levels of 0–0.4 ppm found in British PVC-bottled liquids were mentioned by Davies and Perry (1975); in their own analyses of samples of PVC-bottled spirits supplied by British Airways they found concentrations of 0–0.25 ppm (w/w). Methods were developed for the detection of VCM in liquids with a maximum sensitivity down to the 1 ppb level (van Liemp and Siek 1976; Dressman and McFarren 1977). It was tentatively estimated that even during the years when PVC-packaged food and beverages had not been heeded as a potential source of contamination, the likely average daily human intake of VCM from this source could have been in the order of 0.1 mg/person (IARC 1974). Schlatter (1976) calculated that today it would be less than 0.01 mg/person (equalling 250 mg during a whole life time); in comparison, he calculated that the inhalational intake of VCM in diseased workers who had been exposed to concentrations of 500–1000 ppm during a period of 10–20 years would have amounted to at least 25 kg. The Association of the German Plastics Industry expects that the use of technology available at present for the production of PVC food-packaging materials decreases the VCM content of foodstuffs to below 50 µg/kg (50 ppb) even after prolonged storage (VKE 1975). Results of carcinogenicity assays in experimental animals after oral administration of VCM are discussed in Sect. 3.3.

3 Toxicology of

3.1 Acute Toxicity

During the first three the assessment of the concentrations varyin and Leake 1933; Schimatteo et al. 1960; L anaesthesia, deep nar: this range of exposure tive and haemorrhagic hepatocellular injury inducing substances (s

3.2 Chronic Toxicity

Torkelson et al. (1961) exposure to concentra: 4.5–6 months. All spe: however, caused an inc histological changes in pigs and dogs. An incre in rats exposed to 200 (1963); no histological Gor'kij Institute were n exposure of experiment: mias, bradycardia, chan 0.05 mg/litre) for 5 mo creased secretion of cat: posterior hypothalamus 3500–4000 ppm (9–10 of the cortex and the an comitant changes in circ: posure of rats and rabbit resorptive bone changes nervous system dysfunc: available evidence for V: VCM should be suspecte statutory maximal allow cratic Republic) should i

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(1975) pre-registered for litigation. In 1974, 229:855). Hypertension plant in south- (Reyl and al Raynaud's lysis who never to make one cans (Bridbord from frequent found to con-bronchial cells

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3 Toxicology of VCM

3.1 Acute Toxicity

During the first three decades of PVC production, animal experiments were limited to the assessment of the acute inhalational toxicity of VCM in short-term exposures to concentrations varying between 50 000 and 400 000 ppm (Parr et al. 1950; Peoples and Leake 1953; Seitzmann 1934, 1938; Oster et al. 1947; Carr et al. 1949; Mastromarino et al. 1960; Lester et al. 1963). In mice, rats, guinea-pigs, rabbits and dogs anaesthesia, deep narcosis, cardiac arrhythmias and lethal effects were observed within this range of exposure but no relevant organ pathology was noted except for congestive and haemorrhagic changes in lungs, liver and kidneys on fatal outcome. Acute hepatocellular injury was later found only in animals pretreated with potent enzyme-inducing substances (see Sect. 3.4.2.2).

3.2 Chronic Toxicity

Torkelson et al. (1961) were the first to describe results of experiments with prolonged exposure to concentrations ranging from 50 to 500 ppm, 7 h/day, 5 days/week, for 4.5–6 months. All species tolerated exposure to 50 ppm for 6 months; 100 ppm, however, caused an increase in liver weight and 200–500 ppm caused, in addition, histological changes in the liver and kidneys of rats and rabbits, but not in guinea-pigs and dogs. An increase in liver weight and decrease in spleen weight was also seen in rats exposed to 20 000 ppm, 8 h/day, 5 days/week, for 3 months by Lester et al. (1963); no histological lesions were found after 3 months. Soviet investigators at the Gor'kij Institute were mainly interested in neuroendocrine changes after prolonged exposure of experimental animals to various concentrations of VCM. Cardiac arrhythmias, bradycardia, changes in phonocardiogram in rats exposed to 12–20 ppm (0.03–0.05 mg/litre) for 5 months were reported (Vazm and Plokhova 1969b) as well as increased secretion of catecholamines in rabbits and changes in the biopotential of the posterior hypothalamus (Vazm and Plokhova 1969a). After a 5.5-month exposure to 3500–4000 ppm (9–10 mg/litre) changes in the bioelectric activity (EEG recordings) of the cortex and the anterior and posterior hypothalamic nuclei in rabbits with concomitant changes in circulatory functions were seen (Vazm and Plokhova 1968). Exposure of rats and rabbits to 0.03–0.04 mg/litre (12–16 ppm) for 6 months produced resorptive bone changes and osteoporosis in addition to cardiovascular and central nervous system dysfunction (Basalaer et al. 1972). In 1969 Schorrek summarized available evidence for VCM toxicity and warned urgently that chronic exposure to VCM should be suspected of causing toxic liver damage. He moved that the currently statutory maximal allowable concentration of 200 ppm (MAC value, German Democratic Republic) should be lowered.

Of particular importance as pioneer work were Vinla's experiments (1970a, b; Vinla et al. 1971) with exposure of rats to 30 000 ppm, 4 h/day, 5 days/week, for a full year. It was only after this length of exposure that histopathological examination

revealed lesions similar to human acroosteolysis and also similar to the type of non-tumorous liver diseases which we observed in PVC workers 3 years later (Marsteller et al. 1973). *Viola* described lesions of the skin, the small arterial vessels, the connective tissue and elastic reticulum of the paws, and periosteal proliferation with chondroid metaplasia of metatarsal bones. Fibrosis of small peripheral nerves and degenerative changes of the grey and white matter of the brain were prominent, whereas the kidneys were not markedly affected. The liver showed pronounced degenerative lesions with parenchymal necrosis, cytoplasmic and nuclear polymorphism, abnormal proliferation of hypertrophic Kupffer cells and intense fibrosclerotic reactions.

3.3 Oncogenic Properties

The earliest documentation of the carcinogenic action of VCM was *Viola*'s preliminary report presented at the 10th International Cancer Congress in Houston, Texas in May 1970a. Of 26 Wistar rats exposed to 30 000 ppm for 12 months 17 developed epidermoid carcinoma, mostly in the paraauricular region; 6 also developed adenocarcinoma of the lungs and 5 osteochondroma of metacarpal and metatarsal regions of all 4 limbs (*Viola* et al. 1971; *Viola* 1974). *Maltoni* and *Lefemine* (1975) later interpreted these paraauricular tumours as arising from the sebaceous glands of the exterior acoustic duct, also known as Zymbal's glands, the cell matrix of which seems to be the target tissue of a number of carcinogens. They were of the opinion that the pulmonary malignancies were metastases from the Zymbal gland tumours. Autoradiograms of sections of whole rats dosed orally with [^{14}C]labelled VCM revealed a discrete localization of ^{14}C in the paraauricular region (Zymbal gland?) and in the region of salivary glands and Harder's glands (*Green* and *Hathway* 1975). In this context *Neumann* et al. (1979), who analysed the peroxidase activity in Zymbal glands of Wistar rats, proposed the concept that peroxidase-mediated bioactivation of carcinogens (in their study: stilbene derivatives) might offer an explanation for these tissue-specific effects.

At the end of 1970 *Maltoni* and his group, with the support of Italian, British, Belgian and French chemical companies, started to plan and subsequently execute a large-scale carcinogenicity bioassay designed to study the effects of chronic exposure to VCM in relation to various experimental factors such as route of administration, dose level, length of treatment, and species, strain, sex and age of animals (*Maltoni* 1973, 1977; *Maltoni* and *Lefemine* 1974a, b, 1975; *Maltoni* et al. 1974a, 1975). Concentrations used in the inhalation experiments were 30 000, 10 000, 6000, 2500, 500, 250 and 50 ppm, with length of exposure ranging up to 52 weeks and observation periods up to 143 weeks. Apart from the induction of Zymbal gland carcinoma other malignancies developed, notably angiosarcoma of the liver but also extrahepatic angiosarcomas, nephroblastomas, pulmonary tumours and mammary carcinoma, as well as a number of single tumours of other target tissues. Different types of tumours were found to coexist in the same animal. On oral administration of VCM dissolved in olive oil (5 days/week) angiosarcoma of the liver was found after 50 weeks in two animals of the two groups of 80 Sprague-Dawley rats each of which had been treated with the highest doses of 50 and 16.65 mg/kg body wt. (*Maltoni* et al. 1975). *Maltoni* (1977) succeeded in demonstrating that the route of administration of this clearly multipo-

Vinyl Chloride

tential carcinogen was not solved in 50 6 days/week: ratio only a tion not ne. placed the t the no-toxic angiosarcom Sprague-Dawley proved to be carcinogenic in rats 10, 5 and 1 (1979). And the dose-related exposure level histological the liver and the inductive posture to 10 (al. 1974b; 1, endothelial perplasia an even in the : was scanty : doses. In the fibrosis was of ossifying fact was suggested of (mine 1975). posed to VC ed from *Gri* it was seen to maturity of to 2000 ppm foci of hepat

Holmberg week, for 52 spleen changes in exposed animals cutaneous angiosarcoma in the ppm group a

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tential carcinogen may significantly vary the type of neoplastic response. In a subacute study of oral VCM toxicity, lasting only 13 weeks, in which rats were given VCM dissolved in soya bean oil by gavage in daily doses of 30, 100 and 300 mg/kg body wt., 6 days/week, *Feron et al.* (1975) found a significant increase in liver-to-body weight ratio only at the highest dose level. This was interpreted as a merely nonspecific reaction not necessarily indicative of a toxic response. Based on these results, *Feron et al.* placed the oral no-toxic-effect level at 30 mg VCM/kg body wt./day and suggested that the no-toxic-effect level may actually be even higher. Zymbal gland carcinomas, hepatic angiosarcomas and nephroblastomas had never occurred spontaneously in the breed of Sprague-Dawley rats used at the Bologna Institute. The neoplastic response to VCM proved to have a direct dose-time relationship. Even levels of 50 ppm were carcinogenic in rats and mice. Later *Maltoni* (1977) found exposure to 25 ppm VCM also to be carcinogenic in rats, whereas no carcinogenic effect was observed at lower levels of 10, 5 and 1 ppm in a study which, however, is still incomplete (quoted from *Griciute* 1979). Another American study designed to complement *Maltoni's* results confirmed the dose-related induction of liver angiosarcoma and mammary carcinoma in mice at exposure levels of 2500, 200 and 50 ppm (*Keplinger et al.* 1975). On reexamining histological slides of his past experiments, *Viola* later also detected angiosarcomas of the liver and other malignancies of skin, lung and intestine in his rats; he also reported the induction of skin scanthomas and pulmonary adenocarcinomas in rabbits after exposure to 10 000 ppm VCM, 4 h/day, 5 days/week, for at least 15 months (*Maltoni et al.* 1974b; IARC 1974). *Maltoni and Lefemine* (1975) considered the effect of VCM on endothelial tissue to be a systemic one since they found dilatation of blood spaces, hyperplasia and atypia of endothelial cells also in organs and tissues other than the liver, even in the absence of angiosarcomas or benign angiomas. Evidence of hepatic fibrosis was scanty and inconstant in their animals and was more likely to occur at the lower doses. In the spleen of treated rats and mice fibroangioblastic proliferation undergoing fibrosis was frequently observed. No acroosteolytic lesions were found, but a few cases of ossifying angiosarcoma were observed. A potential transplacental carcinogenic effect was suggested in 1975 by the development of subcutaneous angiosarcomas in the offspring of breeding animals exposed for 7 days during pregnancy (*Maltoni and Lefemine* 1975). Later, *Maltoni* (1976) detected angiosarcoma in the offspring of rats exposed to VCM during the period between the 12th and 18th day of pregnancy (quoted from *Griciute* 1979). Hepatocellular carcinoma was not found in adult animals but it was seen to develop readily in newborn animals, possibly in connection with the immaturity of their bioactivation pathways (*Maltoni* 1977). Exposure of newborn rats to 2000 ppm VCM, 8 h/day, 5 days/week, for at least 4 weeks elicited preneoplastic foci of hepatocellular ATPase deficiency, notably in female animals (*Laib et al.* 1979).

Holmberg et al. (1976) exposed mice to 50 and 500 ppm VCM, 5 h/day, 5 days/week, for 52 and 26 weeks respectively. They did not observe hepatic fibrosis or spleen changes, but multiple benign alveologenic adenomas developed in 13 of 24 animals exposed to 50 ppm and in all 24 animals exposed to 500 ppm¹. In addition, subcutaneous and/or subperitoneal haemangiosarcoma developed in 14 animals of the 50-ppm group and in 8 of the 500-ppm group. Only one haemangiosarcoma of the liver

¹ See also *Winell et al.* (1976)

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was found in an animal exposed to 500 ppm. A few mammary adenocarcinomas, one rhabdomyosarcoma and one renal haemangiosarcoma were also seen. From their experiments *Holmberg et al.* concluded that a lower exposure over a longer period may intensify the cancerogenic response and that an inverted relationship between dose level and latency time seems to exist in the case of VCM, as had already been observed with other carcinogens. Recently the results of still another animal experiment with exposure of Wistar rats to 5000 ppm, 7 h/day, 5 days/week, for 52 months was published by *Feron et al.* (1979a, b; *Feron and Kroes* 1979) in an eventually fruitless attempt to elaborate suitable parameters for early detection of VCM-disease in man. Early effects were a shortening of blood clotting time and the occurrence of swollen and malformed hepatocytic mitochondria. At a later stage progressive tubulonephrotic changes in the kidneys, foci of cellular alterations in the liver with reduced glucose-6-phosphatase activity in hepatocytes, strong sinusoidal activity of alkaline phosphatase and increase of smooth endoplasmic reticulum in parenchymal liver cells were observed. In the final stage areas of necrosis in the liver parenchyma, focal dilatation of sinusoids and proliferation of normal and atypical sinusoidal cells, multicentric hepatic angiosarcoma and Zymbal gland carcinoma occurred. *Feron et al.* (1979b) also observed hepatocellular carcinoma in three animals. Surprisingly, the induction of very malignant metastasizing carcinomas of the nasal cavity originating from the olfactory epithelium and Bowman's gland was noted, which had not been reported before in connection with VCM. Marked hepatic fibrosis was only seen within fully developed angiosarcoma or as a reaction to extensive necrosis of the hepatic parenchyma. The investigators were of the opinion that hepatic parenchymal changes preceded those of the hepatic stroma, but they stressed the fact that the true relationship between VCM-induced alterations of hepatocytes and sinusoidal cells has yet to be elucidated.

3.4 Toxicodynamics

Prior to 1974 very little information was available about the fate and the toxicodynamics of VCM in the mammalian organism, but the discovery of VCM-induced angiosarcoma of the liver in humans and experimental animals provoked a large number of studies which resulted in a flood of publications on the metabolism of VCM.

In 1934 *Schaumann* reported that in mammals unchanged VCM was excreted via the lungs after inhalational administration; the pulmonary route is the main excretory route of nonmetabolized VCM (*Green and Hartway* 1975). Blocking of nonprotein sulphhydryl groups in the blood of vinyl chloride operatives, less pronounced after discontinuous contact, was observed as early as 1964 by *Gabor et al.* and indicated depletion of the glutathione pool, which has since also been found in exposed rats (*Hefner et al.* 1975a). Hepatic glutathione plays a fundamental role in protecting tissues against attack by alkylating agents. The appearance of monochloroacetic acid in the urine of workers exposed to VCM was reported in 1966 by *Grigorescu and Toba*, indicating that a polar excretable metabolite of VCM had been formed (*Vainio* 1978).

Toxicodynamic studies have revealed that VCM *per se* is not the ultimate toxin or carcinogenic. It is the process of biotransformation (metabolic activation) of VCM, primarily by hepatic microsomal enzymes (mixed function oxidases) that yields short-

lived but highly mutagenic and excretable products (*Feron et al.* 1975). The relative velocities of its reactivation of VCM so that above following a concordance with

3.4.1 Uptake

Pulmonary uptake in the animal with the pool shown by *Bolt et al.* (1976) as albumin, and compound goes into. After oral ingestion has to be considered is excreted via (1976c). This is a complex process. In body wt. administration, investigation of gavage in dose found a significant plasmic reticulum but only minor rats on a diet of almost all the intestinal tract, in this way.

Percutaneous uptake following 800 ppm of ^{14}C was negligible.

Studies of that the liver (polar metabolites spleen, lungs and kidneys, spleen, of irreversibly and irreversibly bound

carcinomas, one from their exposure period may have been observed. Experiment with animals was publicly fruitless at least in man. Ear of swollen and glomerulonephrotic induced glucose-6-phosphate phosphatase cells were observed. Dilatation of sinusoidal hepatic arteries also observed. A lot of very malignant olfactory epithelium before in con- developed an- thyma. The included those of in between VCM- oxidated.

the toxicody- induced angio- large number of VCM. is excreted via main excretory of nonprotein induced after dis- indicated deple- ed rats (Hefner ing tissues against in the urine of he, indicating 1978). Itimate toxin or (wn) of VCM, that yields short-

lived but highly reactive alkylating intermediates which are responsible for the toxic, mutagenic and oncogenic effects. VCM is metabolized rapidly to polar nonvolatile excretable products (Hefner et al. 1975a; van Duuren 1975; Radwan and Henschler 1975). The toxicity of VCM seems to be largely determined by the ratio of the relative velocities of both biotransformation of the compound and protective detoxification of its reactive intermediates (Henschler 1977a). The capacity for metabolic elimination of VCM in rats is saturable at an atmospheric concentration of 200–250 ppm, so that above this concentration VCM is metabolized at a constant maximal velocity following a zero-order kinetic, whereas below 200–250 ppm it is metabolized in accordance with first-order rate kinetics (Hefner et al. 1975a; Bolt et al. 1977).

3.4.1 Uptake and Distribution

Pulmonary uptake of VCM from the atmosphere depends on the rate of its metabolism in the animal's organism. The atmospheric concentration of the compound equilibrates with the pool of unmetabolized VCM distributed in the animal's tissues, as has been shown by complete inhibition of microsomal oxidative metabolism (Bolt et al. 1977a). Bolt et al. (1977a) also concluded that lipids or lipoproteins, rather than proteins such as albumin, are the vehicles that transport VCM in the blood and from which the compound goes into the adipose tissue or is taken up by the liver for metabolic conversion. After oral ingestion and absorption from the gastrointestinal tract, a 'first pass effect' has to be considered, but an increasingly substantial percentage of unmetabolized VCM is excreted via the lungs in direct relation to the dose administered (Watanabe et al. 1976c). This confirms the finding that VCM metabolism is a dose-dependent and saturable process. Pulmonary elimination of over 90% within 4 h of a dose of 300 mg/kg body wt. administered orally to rats was also reported by Feron et al. (1975) in an investigation of the subacute toxicity of VCM incorporated in soya bean oil and fed by gavage in doses of 30, 100 and 300 mg/kg daily, 6 days/week, for 13 weeks. They found a significant increase in liver-to-body weight ratio and hypertrophy of the endoplasmic reticulum of hepatocytes as indications of a toxic effect at the highest dose but only minimal histological changes in the liver. In a second experiment, they fed rats on a diet containing PVC powder with a high monomer content and observed that almost all the VCM was released from the PVC powder during passage through the intestinal tract, but only about 10 mg VCM/kg body wt. per day could be administered in this way.

Percutaneous absorption was studied by Hefner et al. (1975b) in male Rhesus monkeys following whole-body exposure (head excluded) to concentrations of 7000 and 800 ppm of ^{14}C -labelled VCM for 2–2.5 h. The quantity absorbed via the intact skin was negligible (0.02%–0.03%) and most of it was expired.

Studies of the distribution of [$1,2\text{-}^{14}\text{C}$]labelled VCM in the body clearly revealed that the liver (predominant site of metabolism) and the kidneys (site of excretion of polar metabolites) contain the highest concentrations of ^{14}C activity, followed by spleen, lungs and small intestine (Watanabe et al. 1976c; Bolt et al. 1976a, b). Liver, kidneys, spleen, lung and small intestine (in this order) also contain the largest amounts of irreversibly protein-bound metabolites (Bolt et al. 1976a). Only minor amounts of irreversibly bound metabolites of VCM were found in muscle, adipose tissue and brain.

Total radioactivity 48 h after a single exposure decreased considerably in these organs, in accordance with the relatively rapid metabolism of VCM and excretion of its polar metabolites. In contrast, the amount of irreversibly protein-bound radioactivity remained constant during this time. *Buchter et al.* (1977) also showed that unmetabolized VCM possesses a great affinity for adipose tissue, in contrast to its metabolites, which are concentrated primarily in liver and kidneys.

3.4.2 Metabolism

3.4.2.1 Relation between Chemical Structure, Reactivity and Mutagenic or Carcinogenic Effect

Before discussing the metabolic pathways of VCM (monochloroethylene) and its presumptive toxic intermediates two features of the chemical structure of this compound should be mentioned. Vinyl chloride is a *monohalogenated* ethylene and its chlorine substitution is *asymmetric*. Chlorination of alkenes (olefinic compounds), in general, tends to stabilize the double bond by exerting an electron withdrawal effect on the carbon atom involved. Thus, the chemical reactivity of alkenes decreases with increasing degree of chlorine substitution, as was shown in 1968 by *Williamson and Cvetanović* for reaction rates with ozone. Vinyl chloride, as a monohalogenated alkene, is the least stable compound with the highest reaction rate in the series of chlorinated ethylenes and ranks next to unsubstituted ethylene.

Secondly, the first step in the oxidative metabolism of all chlorinated alkenes is a transformation to epoxides (oxiranes) which are short-lived, highly reactive electrophilic intermediates (*Bonse et al.* 1975; *Henschler* 1977b). Such chlorinated epoxides may react, by alkylation, with essential cellular constituents, a mechanism which *Rannug et al.* (1974), *Bartsch et al.* (1975a, b) and *Malaveille et al.* (1975) claimed to be responsible for the carcinogenic and mutagenic effects of VCM and vinylidene chloride. Epoxides resulting from biotransformation of *asymmetrically* substituted ethylenes, such as VCM, vinylidene chloride and trichloroethylene, seem to be particularly unstable with increased electrophilicity and thus enhanced alkylating effect. Their mutagenicity and, inversely, the nonmutagenicity of oxiranes of symmetrically chlorine-substituted ethylenes was indicated by the studies of *Greim et al.* (1975, 1977).

3.4.2.2 Metabolic Pathways

From 1974 onwards the fate of VCM has been studied extensively in vitro with rat liver microsomes in the presence of a NADPH-generating system (*Kappus et al.* 1975, 1976; *Bartsch et al.* 1975b, 1976; *Malaveille et al.* 1975; *Bolt et al.* 1976a; *Pessayre et al.* 1979), with the aid of isolated perfused liver preparations (*Radwan and Henschler* 1975; *Bonse et al.* 1975; *Radwan* 1977; *Henschler* 1977a) and in vivo (*Hefner et al.* 1975a; *Watanabe et al.* 1976d, 1978a, b; *Bolt et al.* 1977a, b) in both control animals and animals pretreated with various types of enzyme-inducing and enzyme-inhibiting substances.

Present biochemical knowledge strongly suggests that the first step of the predominant metabolic pathway is the oxidation of the double-bond of VCM by the hepatic

microsomal system. This reaction is highly reactive via the formation of a carbon monoxide. It plays a considerable role in vitro and in vivo systems and in vivo (1976a). The

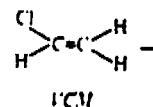


Fig. 1. Metabolism

metabolized to acetic acid are roethylene oxide protein sulphhydryl (1977). Since *Norpoth et al.* (1977) identified in the

microsomal mixed-function oxidase system, forming *chloromethylene oxide*, a chemically highly reactive epoxide (Fig. 1). A negligible amount of VCM can be metabolized via the formation of peroxides, very unstable compounds decomposing rapidly to carbon monoxide, HCl and formaldehyde which, however, do not seem to play any appreciable role in the toxicity of VCM (Henschler 1977b). It has also been shown that in vitro an artificial superoxide (O_2^-) generating system can replace rat liver microsomal systems and transform VCM to the active intermediate (Kappus et al. 1975; Bolt et al. 1976a). The epoxide rearranges spontaneously to chloroacetaldehyde, which is rapidly

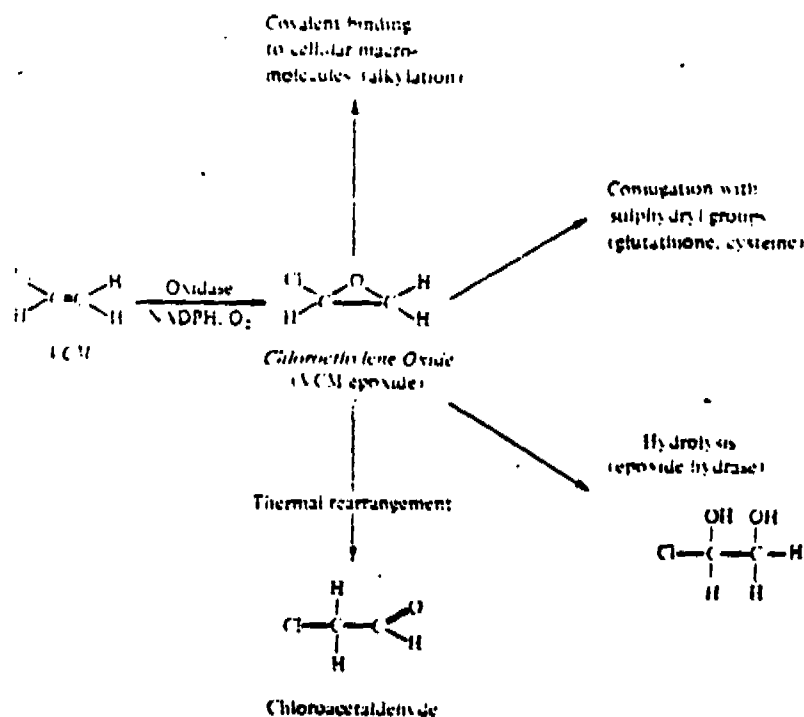


Fig. 1. Metabolic pathways. Adapted from Henschler (1977b)

metabolized to monochloroacetic acid. Both chloroacetaldehyde and monochloroacetic acid are also metabolites which are chemically reactive but less potent than chloromethylene oxide. All three intermediates can be detoxified by conjugation with non-protein sulphhydryl compounds (glutathione, cysteine) as described by Green and Hathway (1977). Sulphur-containing excretable metabolites such as S-hydroxyethylcysteine (Norpoth et al. 1976), N-acetyl-S-(2-chloro)-ethyl-cysteine (Green and Hathway 1975), S-carboxymethylcysteine (Watanabe et al. 1976a), and thioldiglycolic acid (thiodiacetic acid) (Henschler 1977a; Müller et al. 1976, 1978; Müller and Norpoth 1975) have been identified in the urine of exposed workers and animals. A progressive depression of the

level of hepatic nonprotein sulphhydryl content has been observed in rats after exposure to VCM in concentrations from 150 to 2000 ppm for 2-7 h. No depression was seen after 10 ppm and a concentration of 50 ppm caused only an inconsistent reduction (Watanabe et al. 1976b). Protein-bound hepatic sulphhydryl content remained unaffected. Hepatic microsomal cytochrome P_{450} , the coenzyme of microsomal monooxygenases, also decreases linearly with time in animals exposed to VCM (Reynolds et al. 1975b). This destruction of cytochrome P_{450} may prevent further metabolism and toxicity of VCM (Pessayre et al. 1979).

Another mode of deactivation of the primary reactive intermediate, the epoxide, is its transformation to the inactive dihydrodiol by the inducible microsomal enzyme epoxide hydrolase.

The reactive metabolite of VCM, chloroethylene oxide, is a powerful alkylating agent which covalently binds to various cellular macromolecules, notably vital proteins and nucleic acids. By binding to cellular DNA and RNA or critical proteins the metabolite may alter vital functions and the genetic information of the cell and thus exert its hepatotoxic, mutagenic and carcinogenic effect. Eventually, however, the only fraction of the formed epoxide that binds to macromolecules is the one that is not detoxified by protective scavenging mechanisms such as conjugation with cytosolic glutathione or inactivation by epoxide hydrolase. Simultaneous presence of other xenobiotics which have to be detoxified will impair the effectiveness of the detoxification mechanisms. In assessing the risk of exposure to VCM, Henschler (1977a) concluded that there might be a greater risk in intermittent peak exposures over brief periods than might be expected from simple integration over time and that the chances for effective detoxification are greater in long-term exposure to relatively low levels.

It was shown by Watanabe et al. (1978a) that repeated exposures of rats to VCM do not appear to induce its biotransformation, but significantly augment the binding of the reactive metabolite with hepatic macromolecules and may thus enhance the potential toxicity of VCM. On single exposures of rats to increasing concentrations of labelled VCM ranging from 1 ppm to 5000 ppm, the amount of radioactivity covalently bound to hepatic macromolecules did not increase proportionately to the increase in concentration but followed a sigmoid curve with low and high inflection points below 50 ppm and above 250 ppm, respectively, when binding was plotted as a function of the log of the exposure concentration (Watanabe et al. 1978b). This correlates well with Maltoni's report (1975) of a linear percentage induction of hepatic angiosarcoma in rats between 50 ppm and 500 ppm when expressed as the log of the exposure concentration.

Metabolites of VCM can alkylate nucleic acids, a commonly accepted mechanism for carcinogenesis. Covalent binding to the adenosine (Barbin et al. 1975; Laib and Bolt 1977), cytidine (Laib and Bolt 1978), and guanine moiety of nucleic acids (Ostermann-Golkar et al. 1977) has been described. But the degree of covalent binding of electrophilic metabolites of labelled VCM to hepatic nucleic acids seems to be very small (Watanabe et al. 1978b; Laib and Bolt 1977). Laib and Bolt (1977) presented evidence showing that the alkylating potency of VCM metabolites cannot be determined solely by measuring the incorporation of label into nucleic acids after exposure to radioactive VCM. Watanabe et al. (1978b) concluded that covalent binding to nucleic acids is not the preferential reaction, but they pointed out that this does not

Vinyl Chloride

exclude the possibility of cellular damage caused as a result of above all, i

This aspect of the work will be endoplasmic reticulum, physiologically mixed function, lobular, microfound (Jae. 1978). Secondary endothelial

At present, processes are at the hepatocellular level some metabolic (3) Mechanisms in tissues other than cell repair (1978b).

An equine nonneoplastic Raynaud's syndrome was described. Besides liver lesions, bioactivation of portal fibrosis, ment of the a direct or indirect nervous system lining cells (action) or when

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exclude the possibility of other, more subtle interactions which may impair the control of cellular replication. Alkylation of nucleic acids, however, cannot at present be excluded as the mechanism for VCM-induced carcinogenesis after repeated exposure and, above all, in the target cells rather than the hepatocytes.

This aspect carries on to an unresolved problem on which future experimental work will have to focus. Although the site of formation of the active metabolite is the endoplasmic reticulum of the hepatocyte, the liver cell itself is not particularly susceptible to VCM-induced toxicity. Acute hepatocellular injury has not been observed morphologically after exposure to VCM unless pretreatment with potent inducers of the mixed function oxidase system had preceded the exposure; in pretreated rats centrilobular, midzonal and panlobular hepatocellular vacuolization and even necrosis was found (Jaeger et al. 1974, 1975, 1977; Reynolds et al. 1975a, 1976; Conolly et al. 1978). Secondly, the site of carcinogenicity in the liver is not the hepatocyte but the endothelial cell of the hepatic sinuses.

At present it can only be speculated which of the following four most likely processes are effective, either singly or in conjunction: (1) The active metabolite leaves the hepatocyte and is conveyed to the endothelial cell. (2) The endothelium itself has some metabolic capacity (Bolt 1978), as may tissues of organs other than the liver. (3) Mechanisms for the detoxification of the active metabolite(s) are insufficient in tissues other than the hepatocytes. (4) Repair mechanisms for the correction of aberrant cell replication are less effective than they are in the hepatocyte (Watanabe et al. 1978b).

An equally puzzling problem is the role of VCM in the pathogenesis of the distal nonneoplastic vascular lesions which are responsible for the development of the triad, Raynaud's phenomenon, sclerodermoid skin indurations and acroosteolysis. This syndrome was the earliest indication of adverse effects of chronic exposure to VCM in man. Besides, its latency period was considerably shorter than either the nonmalignant liver lesions or angiosarcoma of the liver. Whereas it is now established that hepatic bioactivation of VCM plays the central part in the pathogenesis of both noncirrhotic portal fibrosis and angiosarcoma of the liver, it is not at all clear whether the development of the acral lesions is due to VCM itself or to active metabolites which may exert a direct or indirect toxic action on (a) medullary vasomotor centres, (b) the sympathetic nervous system, (c) smooth muscle cells of the media of arterioles, (d) endothelial lining cells of small arteries (with fibroblast transformation and endothelial proliferation) or whether (e) the action is mediated by the formation of immune complexes.

4 Clinical Spectrum

During the mid-1950s it began to emerge that chronic occupational exposure to VCM might prove to be not quite as harmless as had been claimed. The historical synopsis presented in Table 7 summarizes those clinical studies from the world literature that marked the gradual recognition of the full spectrum of damage due to this new occupational hazard.

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044247

Table 7. Gradual emergence of evidence for VCM-associated pathology

Year	Reference	Findings
1949	<i>Tribukh et al.</i>	Hepatomegaly, more or less marked 'anicteric hepatitis', 'chronic gastritis', hypotension, anaemia, skin lesions
1954	<i>Smirnova</i>	Toxic angioneurosis
1957	<i>Filatova and Gronsberg</i>	Toxic angioneurosis
1957	<i>Kubota</i>	Symptoms similar to Raynaud's phenomenon
1960	<i>Danziger</i>	Two cases of accidental fatal poisoning by VCM, 1 nonfatal acute overexposure
1961	<i>Smirnova</i>	Reversible osteolytic lesions of distal phalanges. Pseudoclubbing, thickening of skin on volar side of forearms, slight haemolysis and reticulocytosis
1963	<i>Suciu et al.</i>	CNS: prenarcoptic symptoms (dizziness, euphoria, somnolence), nervousness, insomnia, blunting of memory, general asthenia, headache Vascular: Raynaud's syndrome Dermatol.: pruritus, reversible sclerodermalike skin induration, chemical and allergic dermatitis Digest. symptoms: anorexia, nausea, fullness, hepatomegaly without hyperbilirubinaemia, splenomegaly Endocrine: hypothyroidism
1966	<i>Cordier et al.</i>	Raynaud's syndrome, sclerodermalike skin changes, acroosteolysis, pseudoclubbing, joint pain, tiredness, sleep reversal; 2 episodes of acute overexposure (loss of consciousness)
1967	<i>Harris and Adams</i>	Acroosteolysis, skin lesions, Raynaud's phenomenon, pseudoclubbing, involvement of sacroiliac joints and patella, hepatomegaly with persistently raised serum bilirubin. Skin biopsy
1967	<i>Benoit</i>	Arteriography. Skin and bone biopsy
1967	<i>Wilson et al.</i>	'Occupational acroosteolysis' with Raynaud's symptoms, sclerodermalike skin changes, pseudoclubbing
1968	<i>Antonyuzhenko</i>	Mentions thrombocytopenia
1971	<i>Dinman et al.</i>	Prevalence of acroosteolysis and Raynaud's phenomenon
1971	<i>Dodson et al.</i>	Vascular lesions preceding the bone lesions
1972	<i>Kramer and Mutschler</i>	Increased BSP retention and raised icterus index related to degree of exposure

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Table 7 (continued)

Year	Reference	Findings
1972	Markowitz et al.	Progressive thickening of hands and forearms, arthralgia. Blanching upon exposure to cold with cyanosis of hands accompanied by severe pain. Skin biopsy
1972	Jähn and Lange	1st German report of 7 workers with scleroderma-like skin lesions, Raynaud's syndrome, and acroosteolysis. Tests showed abnormal liver in 2. Occlusion of digital arteries in 1 worker
1973	Marsteller et al.	Noncirrhotic portal fibrosis with portal hypertension and splenomegaly
1974a)	Creech et al.	4 cases of angiosarcoma of the liver

4.1 The Triad: Raynaud's Phenomenon, Pseudosclerodenna and Acroosteolysis

A first indication of adverse effects due to chronic VCM exposure arose in workers at a plant producing VCM who presented with symptoms similar to Raynaud's phenomenon ('toxic angioneurosis'). This was reported by *Smirnova* in 1954 and later described in detail in her thesis (1959). The syndrome was found predominantly in laboratory personnel who had intermittently been exposed to high concentrations of VCM during hourly sampling for chemical analysis (purity of the product). In 1954 Raynaud's syndrome was also observed among several workers at a Japanese PVC producing plant (*Kubota* 1957). Apart from a painful vasospastic disorder of the hands, impaired thermoregulation, acrocyanosis, positive cold test, capillaroscopic alterations, paraesthesias, and CNS symptoms such as headache, blunting of memory and sleep reversal, *Smirnova* (1954) also mentioned swelling of fingers and development of circumscribed skin indurations on the volar side of the forearms in those most severely affected. In addition, there was evidence of mild haemolysis (borderline anaemia, decreased osmotic fragility of red cells, urobilinuria, and reticulocytosis). In 1961 *Smirnova* described radiographic evidence of destructive bone lesions of terminal phalanges in the hands identical with acroosteolysis in three workers at a PVC-producing plant (one fitter, two centrifuge operators) after exposure for 3-9 years. Since these bone lesions developed in conjunction with 'toxic angioneurosis' and since complete recalcification of the defects was found in two workers 3 years after removal from exposure, *Smirnova* believed the lesions to be characteristic of chronic VCM intoxication. She pointed out that their reversible character might serve to distinguish the lesions from similar defects seen in vibration trauma. In retrospect, *Smirnova's* observations are the earliest descriptions of the full range of symptoms which much later became known as 'the syndrome of occupational acroosteolysis'.

In 1963 *Sucht* et al. (see also 1967 and 1975) published the first comprehensive analysis of their observation of a multiform symptomatology in subacute and chronic

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044249

VCM intoxication. During a 4-year period, they examined 168 mostly young workers from two Rumanian PVC-producing plants who had not previously been employed in other industries. In their classic paper, the authors described in detail the various central nervous, digestive, angioneurotic and cutaneous symptoms (listed here in their order of manifestation). Acroosteolysis, however, was not mentioned. Episodes of acute overexposure (usually occurring at the end of a batch run, during retrieval of unreacted monomer, or at repair jobs) rapidly resulted in a state of light-headedness and transient euphoria similar to a mild degree of inebriety and were accompanied by a feeling of heaviness in the legs and disturbed locomotor coordination. Several workers claimed to have been able to identify escaping monomer by its faint but agreeable odour. Apparently during periods of particularly high ambient concentrations, workers repeatedly noticed formication in the lower limbs and a general feeling of bodily warmth. Six subjects had experienced loss of consciousness when repairing leakages, but recovered rapidly after being carried out into the open air. After a few months of work, unusual fatigue and sleepiness set in, there were complaints about persistent somnolence, even outside the work premises, and a tendency to fall asleep at the work place, particularly during night-shifts. In addition, headache, dizziness, irritability, blunting of memory, paraesthesias, and general weakness were reported; some workers noticed insomnia or sleep reversal.

A reappraisal of these nonspecific complaints (see also *Vale et al.* 1976) 6 years later, after improvement in industrial hygiene, revealed that the frequency of their occurrence had considerably decreased (*Suciu et al.* 1975). Following a prolonged period of repeated overexposure, vague nonspecific digestive symptoms also developed, such as anorexia with ensuing weight loss, nausea, fullness, upper abdominal discomfort, bloating and epigastric pains. Enlargement of the liver was found in 51 workers (30%); in 6% there was also splenomegaly. Classic Raynaud's phenomenon was found in 6%, but a tenfold higher percentage of the total work force showed evidence of vasospastic alterations on plethysmography (*Raucher et al.*, cited by *Suciu et al.* 1975). Pruritus of the hands, forearms and face was an early complaint followed later by what was thought to be (allergic?) 'contact dermatitis'; finally, nodular and scleroderma- or scleroedema-like cutaneous lesions developed in some workers, involving the dorsal surface of the hands, the volar side of wrists and forearms and the face, with firm thickening of subcutaneous tissue or formation of whitish papular or slightly elevated plaque-like indurations. The cutaneous manifestations largely disappeared after removal from the work place. In addition, mention was made of features of hypothyroidism in a few workers. Also, transient loss of libido in 24% was recorded, with return to normal after a break from work or during holidays.

With the exception of acroosteolysis and the two most alarming late sequelae — noncirrhotic portal hypertension and hepatic angiosarcoma — *Suciu's* early documentation of the prevalence of disease in PVC production workers encompassed a comparatively complete description of the various aspects of chronic VCM intoxication. Later publications supplemented the spectrum of knowledge mainly by providing additional information on epidemiological, roentgenological, thermographic, angiographic, and histomorphological aspects of the lesions encountered in subjects chronically exposed to VCM.

The discovery of two Belgian cases of classifiable disease marked the beginning of the syndrome worldwide. In 1970, a number of United States cases of OAO were reported. The various phases of the disease by the end of 1979, the vascular phenomena began with numbness in the fingers and tips on hard exposure to cold air. These are likewise a consequence of painful osteolytic process with striation

Table 8. Publications

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The discovery of unusual osteolytic defects in the distal phalanges of the hands of two Belgian autoclave cleaners who had suffered from Raynaud's phenomenon and unclassifiable degenerative lesions of the dermal connective tissue (Cordier et al. 1966) marked the recognition of this new occupational disease in the Western World. The syndrome was termed 'occupational acroosteolysis' (OAOL), and during the following year a number of additional cases were reported from France, Great Britain and the United States. Later Lefèvre (1972) who together with Cordier described the first two cases of OAOL, reported that a subsequent investigation revealed another ten cases in the various plants affiliated to the same corporation in Spain, Italy and Brazil. By the end of 1979, a total number of 126 cases had been published in detail (Table 8). The vascular phenomena preceding or accompanying OAOL comprise a broader range of symptoms than those characteristic of Raynaud's syndrome. The conditions seems to begin with ill-defined pains in fingers, wrists and also large joints (shoulders, knees); the fingers are numb and tingling, tender on palpation, handgrip and tapping finger tips on hard surfaces is painful; there is increasing sensitivity of the hands and fingers to cold accompanied by a tendency to cyanotic discoloration. In some cases, the toes are likewise affected. Later, classic Raynaud's phenomenon develops (sudden appearance of painful, sharply demarcated blanching) and, concomitant with the onset of osteolytic processes, there is a shortening and broadening of the terminal phalange with striation of nails (pseudoclubbing).

Table 8. Publications on 'Occupational Acroosteolysis' since 1966

Year	Country	Number of cases	Authors
1966	Belgium	2	Cordier et al.
1967	France	5	Benoit, Chatelet and Morillon
1967	France	5	Bourmicheon (cited by Marin et al. 1967)
1967	United Kingdom	2	Harris and Adams
1967	USA	31	Wilson et al.
1969	Rumania	2	Anghelescu et al.
1969	Yugoslavia	8	Korec et al.
1971	USA	41	Dinman et al.
1972	USA	2	Markowitz et al.
1972/1973	Fed. Republic of Germany	6	Jühe and Veltman; Stein et al. (a, b)
1973	Japan	1	Takeuchi and Mabuchi ^a
1974	France	4	Moulin et al.
1974	USA	1	Trapp et al.
1975	USA	4	Lillis et al.
1975	United Kingdom	1	Stewart et al.
1976	United Kingdom	4	Preston et al.; Welker; Mitchell Johnston (1978)
1978	Brazil	5	Game and Meira
1979	Israel	2	Hahn et al.
		126	

^a One of 2 clear cases, in addition, 48 suspected cases (see Sakabe 1975)

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4.1.1 Familial and Idiopathic Acroosteolysis

Acroosteolysis is a very rare disease. The aetiology and pathogenesis of this condition is still obscure. Osteolytic bone changes in late stages of so-called Raynaud's disease (accompanied by necrosis and gangrene), characteristically presenting as loss of part or of an entire distal phalanx of one or more fingers and also of toes, have been mentioned in the literature since 1921 (Assmann 1921; Monahan 1926; Borak 1927; Kornblum 1929). Kornblum attributed the lytic bone defects to vascular abnormalities and noted that he had found identical lesions in early stages of scleroderma and in leprosy. The term acroosteolysis was first introduced by Laroche and Hochfeld (1948), who held a neuroendocrine syndrome responsible for the lesions. Independently Harnasch (1949) reported another case of symmetrical idiopathic acroosteolysis, particularly involving the terminal phalanges of the fingers with preservation of tufts, progressive clubbing and shortening, and ill-defined symptoms of disturbed peripheral circulation. By 1952 Giacci mentioned that 68 cases of the familial type of acroosteolysis and 33 cases of the nonfamilial, idiopathic form had been reported in the medical literature. He added another five cases, but his case reports pertain almost exclusively to mutilating processes involving only the feet, with recurrent ulceration and discharge of bone fragments (see also Harms 1954). In 1957 Lièvre and Gama listed 16 observations of idiopathic acroosteolysis and commented extensively upon these lesions; the whole range of differential diagnosis (various congenital, neurogenic and endocrine osteolytic diseases, leprosy, arthritis mutilans, progressive systemic sclerosis, ainhum etc.) was considered in their study and could be rejected with reasonable certainty. In a later review, Cheney (1965), who added another four cases of the familial type, stated that this variety and the nonfamilial idiopathic type may actually belong to the same disease entity and may be part of a degenerative bone process more generalized than the term implies. It was the puzzling character and the rarity of this peculiar bone lesion that captured the attention of site medical personnel and industrial hygienists when in November 1963 the condition was detected in two Belgian autoclave cleaners (Lejve 1972).

4.1.2 Epidemiology of Occupational Acroosteolysis

Attempts at assessing the prevalence of OAOL among personnel involved in VCM manufacture and polymerization revealed that in general this occupational type of osteolytic bone lesion was found in only 1%–3% of the work population at risk. Hubler et al. (1977) considered the fact that only 3% of all workers who had been engaged in manual cleaning of autoclaves at a Belgian plant suffered from OAOL and Raynaud's phenomenon to be indicative of the importance of individual factors. Wilson et al. (1967) observed 31 cases among 3000 employees of one large company. In 1971 Dinman et al. conducted a survey in 32 plants belonging to 19 corporations throughout the United States and Canada. The details of this elaborate epidemiological study, comprising a total of 5011 employees, illustrates the difficulties and limitations encountered in a retrospective study of this dimension. All of these 5011 workers had been engaged in various stages of VCM and PVC manufacturing, but 1257 of them were workers who only handled finished PVC polymer. Five of the 32 plants worked

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exclusively with the finished PVC-derived consumer products. *Dunman et al.* found only 25 clear-cut cases of OAOL among the 5011 employees (mean age: 35.5 years), defined as characteristic X-ray film abnormalities combined with Raynaud's phenomenon: 18 of them had been reactor cleaners at some time; another 16 individuals (10 with experience in reactor cleaning) with early stages or minimal degrees of the syndrome were suspected of suffering from OAOL. It emerged that the two lowest-paid jobs, both reactor cleaning and bagging/packing, had a strong association with OAOL (1 case per 72, or 86 workers at risk, respectively). Manipulation of the finished polymer appeared not to be associated with a risk of contracting OAOL. Only 1 case of OAOL was detected in those plants where high-pressure water lances or solvents had been in use for reactor cleaning. Furthermore, it seemed that the extent of degassing prior to entry into the autoclaves correlated with the manifestation of the disease.

Table 9. Prevalence of acral disease in VCM-exposed populations

Country	Size of group at risk	Number of cases				References
		OAOL	Classical Raynaud's phenomenon	Severe sensitivity to cold	Sclero-dermoid skin lesions	
France	130	5	12	15	5	<i>Benoit 1967</i>
USA	354	4	20	63	23	<i>Lilis et al. 1975</i>
United Kingdom	37	1	5	8	4	<i>Walker 1976</i>
Fed. Rep. Germany	100	9	9	33	10	<i>Lange and Veltman 1977</i>
United Kingdom	104	1	25	—	1	<i>Manco et al. 1978</i>
Total	725	20 (~3%)	71 (~10%)	119 (~16%)	43 (~6%)	

More commonly seen than OAOL were Raynaud's phenomenon (see Table 9) and related symptoms of abnormal peripheral circulation (*Benoit 1967; Lilis et al. 1975; Lange and Veltman 1977*). *Benoit* pointed out that a complete medical and roentgenological check-up of all 528 employees at a French PVC-producing plant revealed pathological manifestations only among the group of 130 reactor cleaners of whom 32 were affected (OAOL, 5; Raynaud's phenomenon without OAOL, 12; sensitivity to cold, 15 workers). He stressed the fact that in this group of workers at risk the overall morbidity was almost 25%. Similar results were obtained by *Lilis et al. (1975)*, who found classic Raynaud's phenomenon in 5.6% of 354 heavily exposed PVC workers, numbness and tingling in 24%, excessive sensitivity to cold in 18%, pseudoclubbing in 8.7% and involvement of the toes in 7%. Besides, in 26.6% of the total an abnormal Allen test indicated impaired peripheral arterial circulation. It was noted that in some people with past exposure Raynaud's phenomenon had gradually faded, whereas pseudoclubbing persisted or even progressed. Most important, however, was *Lilis'* finding that the prevalence of all these abnormalities increased significantly with the duration of past exposure to VCM.

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Occupational acroosteolysis is a condition predominantly observed in younger workers. The age range was 20–45 years and half of all cases reported fell in the 30–39 years age-group. Duration of VCM exposure prior to onset of Raynaud's phenomenon ranged from 1 to 23 months (Dodson et al. 1971). For OAOL the latency period was at least 12 months (Wilson et al. 1967); in most cases, OAOL developed insidiously within 2 to 4–6 years. There is at least one patient on record in whom OAOL was first discovered two years after termination of exposure (Benoit 1967). Longitudinal studies of the bone lesions demonstrated partial or complete but mostly defective restitution, resulting in shortened and deformed distal phalanges, within 2–3 years after removal from VCM exposure, but Raynaud's phenomenon and cutaneous lesions may persist (Williams and McLachlan 1976). Stein et al. (1973a, b) reported partial healing with restitution of tufts but progressive lysis of the proximal portion of terminal phalanges 3 years after termination of exposure.

Although OAOL developed predominantly in PVC production workers who had at least for some time been engaged in reactor cleaning, the syndrome has also been observed in association with other job assignments which were believed to carry a substantially lower risk of exposure. Trapp et al. (1974) reported a 31-year-old white male suffering from Raynaud's phenomenon, clubbing of the fingers and typical bilateral acroosteolysis, in whom specific inquiry revealed that his employment by an industrial chemical company had included daily handling of small concentrations of vinyl chloride (no details given). Typical OAOL was also observed in a worker after 6 years' employment as spray dryer/bagger, pre-mix operator, recovery and charging operator who had never cleaned autoclave vats (Stewart et al. 1975). According to routine plant monitoring of VCM levels in the past and as measured in 1973 by gas chromatography of grab samples, his average exposure had been within the threshold limit values of the day (200 ppm). Radiographs taken in 1966 at the end of his first year during an earlier survey of OAOL were normal; in 1972 he presented with Raynaud's phenomenon, pseudoclubbing, typical OAOL and dermal thickening of hands and wrists. Arteriography demonstrated narrowing of most digital arteries, even in fingers without bone defects, and abnormal collections of small vessels in the pulps of deformed finger tips, but no vascular occlusion.

Apart from the chemical insult by inhalational (rather than transdermal – Dinman et al. 1971; Stewart et al. 1975) exposure to VCM, individual susceptibility or idiosyncrasy appears to have played some (undefined) role in the development of the syndrome. It does not seem likely, however, that repeated physical microtrauma during cleaning operations (removal of polymer crusts by hand scraping or chiselling) was a decisive factor in the pathogenesis of the condition as had been speculated by Wilson et al. (1967).

4.1.3 Clinical and Roentgenological Features

4.1.3.1 Occupational Acroosteolysis

In the majority of cases osteolytic lesions are confined to the hands. Involvement of the feet was observed only rarely in OAOL. Wilson et al. (1967) believe that OAOL differs from familial or idiopathic acroosteolysis in several respects. Although the bone

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defects in the distal phalanges are similar in both conditions, other features, such as osteoporotic compression fractures of the spine, basilar impression fracture of the skull, destruction of mid-phalanges or osteosclerotic changes of wrists and hand bones, shortening of metacarpals and cortical thickening of the shafts of long bones seen in the nonoccupational type have never been found in OAOL. *Wilson et al.* worked out roentgenological criteria for the diagnosis of OAOL:

- 1) The earliest changes in OAOL are marginal defects and loss of cortex in tufts of one or more of the terminal phalanges of the hands.
- 2) In the next stage this is followed by small 'half-moon' cuts in the cortex of the tufts, or a so-called slice-effect along one or more tufts.
- 3) The advanced stage of destruction is characterized by either a complete loss of tufts together with a portion of the shaft or there may be transverse or oblique bone defects (see Fig. 2) cutting off the shafts from the remaining distal rim of the tufts ('bandlike acroosteolysis').

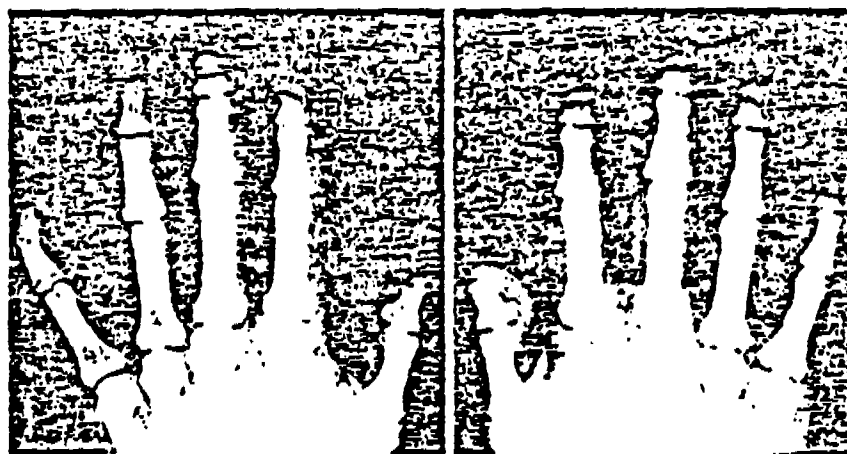


Fig. 2. Occupational acroosteolysis. Transverse or oblique bone defects ('bandlike acroosteolysis') or partial loss of terminal phalanges in all fingers of both hands. (33-year-old autoclave cleaner; duration of exposure 3 1/2 years)

- 4) In the healing stage there may be either complete bony union with shortening and broadening of the residual parts of the end phalanx or a fibrous union of bone fragments. Fingertips remain short and plump with persistent clubbing of soft tissues and increased lateral and longitudinal curvature of fingertips.

Sodium fluoride ^{18}F scintiscan data of affected bones suggested that active demineralization (resorptive) and remineralization (reparative) processes may occur simultaneously even in the same hand (*Dodson et al. 1971*). In some cases, bones of

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other body regions were also involved. Erosive and sclerotic changes in the sacro-iliac joints and circumscribed resorptive defects (cortical erosions) in patella, clavicle, mandible, humerus, styloid process of ulna, femoral condyles, os calcis, cuneiform and metatarsal bones have repeatedly been observed (Cordier et al. 1966; Hurris and Adams 1967; Dodson et al. 1971; Juhe et al. 1974; Lange et al. 1974a; Preston et al. 1976; Jayson et al. 1976a; Lange and Veltman 1977).

4.1.3.2 Pseudoscleroderma

Concomitant with the manifestation of parasthesias, pain, tenderness of the fingers and Raynaud's phenomenon, cutaneous lesions similar to stigmata seen in progressive scleroderma develop with thickening of the skin of fingers, hands and forearms, sometimes accompanied by swelling or puffiness and coarsening of the skin of the face (mostly on the forehead and cheeks). Raised, ivory-coloured, firm nodules or elevated, sharply delineated plaquelike skin indurations are seen on the dorsal surface of fingers and hands and on the volar side of the wrists and lower forearms. It was this combination of Raynaud's phenomenon and cutaneous lesions which first prompted a search for other symptoms of progressive systemic sclerosis in affected workers. The syndrome of OAOL, however, can be clearly distinguished (Table 10). Notably, the diffuse immobil-

Table 10. Differential diagnosis: syndrome of occupational acroosteolysis (Raynaud's phenomenon, sclerodermoid skin changes, AOL) / progressive scleroderma with (rare) osteolytic lesions

	Occupational AOL	Progressive scleroderma
Sex ratio	Exclusively σ	$\sigma:\eta = 1:2$
Hands	Clubbing and shortening of finger tips; hyperhidrosis; no ulceration	Atrophy and tapering off of fingertips; anhidrosis; ulcerative lesions
Perioral puckering of skin	Not observed	Common
Skin appendages	Preserved	Loss of skin appendages
Telangiectases	Not observed	Common
Shortening of frenulum	Not observed	Early symptom
Subcutaneous deposits of calcium salts	Not observed	Common
Dysphagia (oesophageal involvement)	Not observed	Common
Renal, cardiac and intestinal involvement	Not observed	(Common)
Occupational history	Obligatory	—
Prognosis	Favourable (skin and bone lesions tend to heal after removal from exposure)	Usually spontaneous progression

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4.1.4 Histology

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tional syndrome. After cessation of exposure the skin lesions seem to regress more
readily than the osteolytic changes.

4.1.4 Histology

4.1.4.1 Cutaneous Lesions

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Several investigators described the histomorphology of skin lesions in vinyl chloride
disease (Cordier et al. 1966; Harris and Adams 1967; Marin et al. 1967; Markowitz et
al. 1972; Lange et al. 1974a; Feltman et al. 1975; Walker 1976; Hahn et al. 1979), but
we found only one description of bone histology in OAOL in the literature (Benoit
1967; Marin et al. 1967). Skin biopsies showed various degrees of dermal, vascular and
neural changes which were essentially identical in patients showing OAOL and in those
who suffered 'merely' from Raynaud's phenomenon.

Dermal changes consisted of hyperkeratosis and pronounced thickening of the der-
mis with disorientation, swelling and nonfibrillary eosinophilic homogenization of
broad interlacing collagen bundles. There was some degree of interstitial oedema which
faintly stained metachromatically with toluidine blue, alcian blue and periodic acid-
Schiff (PAS). An inflammatory reaction with infiltration of lymphocytes and a few
histiocytes was scanty and, if present at all, of predominantly perivascular distribution.
The most notable feature was marked disorganization, fragmentation and rarefaction
of elastic fibres. In areas corresponding to nodular or plaque-like skin indurations, the
full thickness of the dermis consisted of an acellular, partly hyalinized collagenous tis-
sue. Skin appendages were preserved. In 15 apparently less severely affected workers,
Walker (1976) found only some destruction of elastic tissue of the dermis, probably
not exceeding normal age changes: in one worker with severe Raynaud's phenomenon
some fibrous thickening of the media of dermal arterial was seen.

Vascular lesions affected capillaries and small dermal arteries. Numerous dilated
capillaries were seen in the subepidermal papillae with swelling of endothelial cells
and pericapillary oedema. Capillaries of the cutis showed cuff-like hyperplasia of peri-
thelial cells with fibroblast transformation, hyalinosis of vessel walls and final oblitera-
tion of lumina. Marked medial thickening of dermal arterioles, due to hypertrophy of
myocytes, was accompanied by perivascular fibrosis and hyalinosis, which ultimately led
to narrowing or even complete occlusion of the lumen.

Degenerative lesions of small *dermal nerves* were mentioned by French investigators
(Benoit 1967; Marin et al. 1967; Chatelet and Morillon 1967). They found sclerosing
hyalinosis of the perineurium with atrophy of neurofibrils. Tactile corpuscles (Wagner-
Meissner, Pacini) were unaffected.

4.1.4.2 Bone Lesions

The most striking feature in a biopsy specimen of the bone, obtained from a French
worker with OAOL (case 4 of both Benoit 1967; Marin et al. 1967) was marked thick-
ening and hyalinization of the perosteum with chondroid metaplasia of the inner-
most layer. Supplying capillaries and arterioles showed occlusive changes identical with

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those observed in the dermis. The bone matrix per se was barely affected. There was minimal thinning of cortex, normal spongy bone and only mild fibrosis of the bone marrow.

Experience with histomorphology of bone lesions in the familial and idiopathic type of acroosteolysis is limited. In the few cases where biopsy material could be obtained, there was replacement of bone by nonspecific fibrous tissue, but inflammatory and degenerative changes or osteoid formation were not found (Dipas et al. 1936; Elson and Burnstein 1954; Greenberg and Street 1957; Schwarzweiler 1957).

In this context, it should be kept in mind that Viola succeeded in reproducing dermal, vascular, neural and skeletal lesions in the skin of the paws and in small metatarsal bones of experimental animals which were very similar to those observed in man. Viola exposed rats to 30 000 ppm VCM, 4 h/day, 5 days/week, for 12 months and described the histology of these lesions in detail (1970b).

4.1.5 Arteriography, Capillaroscopy, Infrared Thermography

Arteriographic evaluation of the vascular tree of the hands revealed patency of the large arteries in all cases examined. The vascular lesions were almost invariably confined to the small digital arteries, although the superficial and deep palmar arterial arch may occasionally show some narrowing and a paucity of side-branches (Lange et al. 1974a; Moulin et al. 1974). The most prominent arteriographic features were irregularities and segmental stenosis of digital arteries, ranging from localized or diffuse narrowing to subtotal or even total occlusion with development of collateral vessels. Besides, a conspicuous retardation of flow of contrast medium was noted, and peculiar tortuosities of patent digital arteries were found. Circumscribed hypervascularity of the terminal tufts and in the region of the wrists was noted in some cases (Benoit 1967; Lange et al. 1974a; Veltman et al. 1975; Preston et al. 1976; Stewart et al. 1975; Gama and Meira 1978). Angiographic findings in a larger group of 19 symptomatic PVC workers with either Raynaud's phenomenon and/or acroosteolysis (5/19) were recently described in detail by Koischwitz et al. (1980). Raynaud's phenomenon had been observed to persist in these patients for prolonged periods after termination of exposure and even after roentgenological evidence of healing of resorptive bone defects in those who had formerly suffered from acroosteolysis. In addition to varying degrees of stenosis or occlusion of digital arteries with reopening of small collateral vessels, acral hypervascularity and considerable retardation of perfusion in spite of premedication with tolazoline (Priscoline, United States), the most conspicuous features observed in the majority of these patients (14/19) were circumscribed elongations and tortuosities of digital arteries resembling cirroid aneurysms. An example is shown in Fig. 3 of generalized tortuosity and elongation of digital arteries in a 54-year-old patient who started to complain of severe sensitivity to cold 3 years after cessation of VCM exposure (about 1 year prior to death from both angiosarcoma of the liver and hepatocellular carcinoma). The pathogenesis of these peculiar vascular alterations is not clear, but the possibility presents itself that they may be due to destruction of elastic fibres in the vessel walls in analogy to similar alterations of digital arteries seen in rheumatoid arthritis (Laws et al. 1963, 1967).

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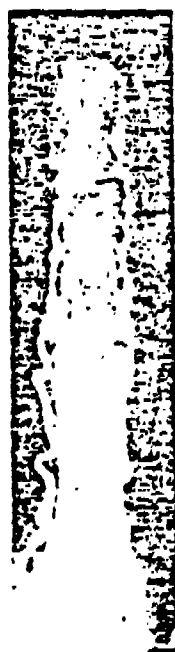


Fig. 3. Conspicuous tortuosities and elongation of digital arteries

Studies of microvascular changes by wide-field *capillary microscopy* (direct observations complemented by photography) of selected skin sites — such as nail folds, fingerpads, dorsum of phalanges and of proximal interphalangeal joints — demonstrated a variety of capillary abnormalities, i.e. dilated or giant capillary loops, pale avascular areas, capillary and subungual haemorrhages. The abnormalities were similar to those seen in scleroderma but were usually less conspicuous, less numerous and of different distribution. In a survey of a group of 152 American PVC workers, these capillaroscopic findings proved to be significantly more prevalent than in 50 nonexposed control subjects (Maricq et al. 1976). There was also a statistically significant difference in the prevalence of these abnormalities between symptomatic and asymptomatic PVC workers. The alterations were not only found in workers with clinical symptoms of disturbed acral circulation but also in 6 nonsymptomatic males with either VCM-induced angiosarcoma of the liver (2) or splenomegalic portal hepatic fibrosis (4).

A similar survey was later undertaken in an unselected sample of 129 employees of a PVC-producing chemical plant in England with 26 employees of a non-PVC-producing chemical plant serving as controls (Maricq et al. 1978). The prevalence of capillary abnormalities found in these British workers, which were of the same type and degree, was comparable to that in the American sample, although the latter included a larger number of more severely affected symptomatic patients with greater mean length of employment (15 years vs 3.5 years). In the authors' opinion, this suggested that VCM-related disease may develop independently of differences in manufacturing procedures. It also suggested that this easily detectable type of microvascular lesion may precede more serious VCM-induced disorders. In a small subgroup of 15 clinically affected

UCC

044259

British workers who were examined 6–24 months after leaving the plant (termination of exposure), the prevalence of capillary abnormalities was not less than that among those who continued work. For an evaluation of the reversibility of this condition, however, the group was considered to be too small. The same type of capillaroscopic changes was also observed in three of 4 Polish workers (2 reactor cleaners, 2 fitters) who were found to suffer from Raynaud's phenomenon after exposure for 2–5 years (Byczkowska and Laigauer-Lewowicka 1974).

Infrared thermography, another non-invasive method, used by Røij et al. (1974) for the study of acral circulation, revealed abnormalities of surface temperature ranging from marked hypothermia of terminal phalanges (which are normally warmer than the rest of the fingers) to "complete terminal amputation" in four PVC workers suffering from OAOL. In one of them vascular disturbances as evidenced by infrared thermography persisted in spite of complete healing of OAOL. Stewart et al. (1975) demonstrated uneven blood flow in the fingers and patchy hyperthermia in the distal part of the OAOL-affected left index and middle finger of their atypical case. Localized acral hyperthermia seen on IR thermography corresponded to the angiographic finding of circumscribed abnormal collections of small vessels (compensatory collaterals?) in the pulps of the affected fingers. Using IR thermography in a survey involving 143 PVC production workers and 56 controls, Williams et al. (1977) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted.

4.1.6 Immunological Studies

Early experience with the syndrome of occupational acroosteolysis suggested certain similarities between this disorder and corresponding lesions seen in progressive systemic sclerosis (diffuse scleroderma). Differential diagnosis of these two unrelated conditions is now well established (Table 10). Such similarities stimulated the search for other manifestations of a systemic collagen disease, notably immunological features, as proposed by Marin et al. in 1967. Ward et al. (1976a, b) carried out immunological studies in 58 workers from a British polymerization plant who were referred to them out of a total past and present work force of 320. Mean duration of exposure to VCM was 39 months (6–75 months). Of these 58 workers, 28 were symptomatic (Raynaud's phenomenon, 9; scleroderma of hands or feet, 6; OAOL, 2; sensitivity to cold, excessive fatigue, limb pain, paraesthesias). Slight hyperimmunoglobulinaemia, usually IgG, the presence of mixed cryoglobulins, and in vivo conversion of both C₃ and C₄ were found in 19 patients in the symptomatic group, with additional evidence of reduced T-cell population and increased B-cell proliferation. Mixed cryoglobulins, in vivo conversion of complement and depressed values for C₃ or C₄ were taken as evidence for the presence of circulating immune complexes. Autoantibody screening demonstrated low-titre antinuclear antibodies (IgG 1/20–1/50) in eight of the nine patients with Raynaud's phenomenon. Aggregates of IgG, C₄, C₃, and fibrinogen/fibrin were revealed by direct immunofluorescence in the lumen of vessels, adherent to vascular endothelium. Aggregates were similarly seen in the media and subintimal regions of small

Vinyl Chloride

and medium lung (1 case).

The autopsies showed bone marrow, bolic interstitial plasma protein which surrounded occluded as a result of the factors of this condition to further. Jayson et al. (1974) reported that patients suffering from this condition had more than in normal disease.

In an earlier study in four Polish workers, there was a decrease in serum IgG, however, Lang et al. (1974) after Sephadex 6 together with agglutinins were observed. Responses plus (1974a) an increase of the titer of the termination of immunofluorescence were later increases in it taken up and used to suggest hypergammaglobulinemia with far advanced three patients with Raynaud's degrees of involvement. The range: $\bar{x} \pm s$ scleroderma of which is

In summary, autoimmune establishment in VCM-induced

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044280

and medium-sized arterioles in biopsy specimens of the skin (10 cases), muscle and lung (1 case each).

The authors proposed as explanation for the induction and pathogenesis of skin and bone changes in VCM-induced disease a theoretical model based on reactive metabolic intermediates of VCM formed during biotransformation binding covalently to plasma proteins. These may act as antigens (as a result of a structurally abnormal protein) which stimulate B-cell proliferation and antibody response. Platelet aggregation, vascular occlusion and ischaemia were thought to be secondary to complement activation as a result of formation of immune complexes which were implicated as possible mediators of tissue injury. Ischaemia, in turn, by leading to collagen synthesis, was believed to further activate the complement pathway and thus to recycle the mechanism. Jayson et al. (1976b), who carried out collagen studies in a skin biopsy of one patient suffering from OAOL found the rate of collagen synthesis to be considerably higher than in normal controls. The pathogenesis of excess collagen formation in vinyl chloride disease has not been fully elucidated.

In an earlier study no cryoglobulinaemia or presence of cold agglutinins was found in four Polish workers with severe Raynaud's phenomenon: in two of them a slight decrease in IgG was noted (Byczkowska and Langauer-Levowicka 1974). Later, however, Langauer-Levowicka et al. (1976) observed latent cryoglobulinaemia, detectable after Sephadex G-200 filtration, in 18 of 22 workers with Raynaud's phenomenon (in 6 together with acroosteolysis and scleroderma-like changes). Again, there were no cold agglutinins detectable, but in five patients marginal to slight elevations of IgG levels were observed. The authors suggested that a pathological alteration of immune responses plays a key role in the pathogenesis of vinyl chloride disease. Lange et al. (1974a) and Veltman et al. (1975) concluded from their results that convincing evidence of autoimmune disease was lacking. Immunological studies including determination of rheumatoid factor (latex agglutination test), quantitative immunoglobulin determination (Manzini radial diffusion technique) and autoantibody screening (indirect immunofluorescence) were initially introduced in our first series of 50 patients but were later abandoned because of mostly negative results, except for occasional increases in immunoglobulin levels (Marszeller et al. 1975a). These studies were later taken up again with an additional 43 patients engaged in PVC production but still failed to suggest more than an erratic connection (unpublished data). We did not observe hypergammaglobulinaemia (see comment in Ward et al. 1976a) except in a few patients with far advanced portal fibrosis and portal hypertension and in the terminal phase of three patients who died from angiosarcoma of the liver. In a group of 18 PVC workers with Raynaud's phenomenon in whom arteriography of the hands disclosed various degrees of occlusion of digital arteries, autoantibodies, cryoglobulins and cold agglutinins were found in none; a moderately increased IgG level (1.93–3.68 g/litre; normal range: $\bar{x} \pm s = 0.8-1.8$ g/litre) was seen in five patients who suffered from OAOL and sclerodermoid skin changes (unpublished data). Elastin antibody titres (the specificity of which is doubtful) were negative.

In summary, currently available evidence does not seem sufficient to suggest an autoimmune disease as a pathogenetic mechanism. Further studies will be needed to establish the true significance of the possibly transient immunological abnormalities in VCM-induced disorders.

UCC
044261

4.1.7 Pathogenetic Considerations

Raynaud's phenomenon as a premonitory clinical symptom, histomorphology in man and experimental animals and angiological experience suggest that the common denominator in the pathophysiology of both skin and bone lesions in chronic VCM intoxication is probably to be sought in the local impairment of blood circulation in peripheral regions, as *Benoit* pointed out as long ago as 1967. By reason of their vasculature, the distal phalanges are the skeletal segments which may be most susceptible to impairment of blood supply, particularly to disturbances of microcirculation (*Gama and Meira* 1978). Yet the answer to the next question, the pathogenesis of peripheral vascular injury in vinyl chloride disease, is unknown. It still remains largely a matter of conjecture how a volatile toxic compound that is taken up via inhalation, distributed throughout the systemic circulation and metabolized (bioactivated) in the liver, can bring about, apparently only in a small number of predisposed individuals, after a variable period of latency severe vascular injury and (probably secondary) damage to peripheral tissue. Some conceivable mechanisms are briefly listed in a previous chapter (see Sect. 3.4.2.2), but no conclusion can be drawn as to their relative significance.

4.2 Non-malignant Liver Disease in Vinyl Chloride/Polyvinyl Chloride Production Workers

Long before Raynaud's phenomenon or osteolytic lesions were observed in PVC production workers, *Tribukh* et al. (1949) studied environmental conditions in a Russian plant where polyvinyl chloride resins were produced and compounded. Without going into detail, the authors pointed out that moderate nontender hepatomegaly was found in a larger proportion of a group of 73 workers (48 males, 25 females) mostly engaged in PVC compounding; 'anicteric hepatitis' was diagnosed in 21 of them (15 ♂, 6 ♀). Although the authors knew about the narcotic action of high concentrations of VCM (75–250 mg/litre = 30 000–98 000 ppm) from the literature, which they explicitly mention, and also knew about the release of unreacted monomer from the powdery PVC resins during thermoplastic compounding, they apparently held other volatile compounds derived from halogenated aromatic hydrocarbons (such as chlorinated naphthalenes and diphenyls) used as plasticizers responsible for the systemic toxicity. They urged, however, that strict monitoring of the health of these workers should be introduced to prevent the development of severe liver damage, and they suggested the installation of ventilation facilities of sufficient capacity.

Nonicteric hepatomegaly was again recorded by *Suciu* et al. (1963) 14 years later in almost one-third of the total work population (51 of 168 employees) of two Rumanian PVC-producing plants, including 10 cases with additional splenomegaly. Liver biopsy in two of these workers revealed chronic hepatitis. Studying the prevalence of temporary disablement due to liver disease among 350 employees of the Sverdlovsk plastics industry, *Pushin* (1965) found the highest morbidity among employees of the PVC production unit, compared with other units engaged in the production of non-PVC plastic materials; 170 workers of ancillary industries served as control subjects.

The clinical symptomatology as 15% of the survey was described developing chronic character of nonmalignant.

In 1972 *Kram* had been routinely time-weighted average environmental data wise multiple linear regression and, to a lesser level of past exposure the individuals studied TWA levels of 300 ppm in clinical laboratory BSP retention was ease (*Marsteller et al.*

In West Germany dermatologists in Bonn At first sight, the syndrome. This provoked Progressive systemic a first group of 13 patients from a nearby PVC-plant from either OAOL or phageal varices due to a group of 20 relatively previous liver disease. Medical Department patient and revealed capsular fibrosis of the liver, marked portal hypertension. (al. 1973). It was now encompassed a large group. Hence *Jilke* et al. (1973)

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The clinical symptomatology of - typically nonicteric - liver disease observed in as many as 15% of the current work force of the PVC production unit during a 3-year survey was described as having been consistent with the diagnosis of an insidiously developing chronic hepatitis. No histological data were available, however, and the true character of nonmalignant liver disease found in these workers remained obscure.

In 1972 *Kramer and Mutchler* examined a group of 98 healthy male workers who had been routinely exposed to VCM for periods up to 25 years and for whom career time-weighted average exposure estimates were available. In an attempt to correlate environmental data and results of a medical surveillance programme by means of step-wise multiple linear regression analysis, it emerged that bromsulphthalein (BSP) retention and, to a lesser degree, the icterus index were significantly correlated with the level of past exposure to VCM. Although no overt clinical disease was found in any of the individuals studied, *Kramer and Mutchler* concluded that exposure to VCM at TWA levels of 300 ppm or more for a working lifetime could result in certain changes in clinical laboratory parameters. As it later turned out, slightly to moderately increased BSP retention was the most consistently pathological test for VCM-induced liver disease (*Marsteller et al. 1975a*).

In West Germany the first cases of occupational OAOL were observed in 1972 by dermatologists in Bonn (*Jülic and Lange 1972; Jülic et al. 1973; Strem et al. 1973a, b*). At first sight, the symptomatology appeared to resemble atypical progressive scleroderma. This provoked a thorough search for manifestations of visceral involvement. Progressive systemic sclerosis, however, could be excluded. On medical examination of a first group of 13 polycleaners who were referred to the Department of Dermatology from a nearby PVC-producing plant it emerged that 3 of them, who did not suffer from either OAOL or scleroderma, had a history of unheralded bleeding from oesophageal varices due to portal hypertension (*Jülic et al. 1973*). Further investigation of a group of 20 relatively young PVC production workers (mean age: 40 years), in whom previous liver disease could be excluded, was carried out in collaboration with the Medical Department. Peritoneoscopy and guided liver biopsy were performed in each patient and revealed varying degrees of *noncarcinotic portal, perisinusoidal and subcapsular fibrosis of the liver*, with splenomegaly, thrombocytopenia and, less frequently, marked portal hypertension, but strikingly little hepatic dysfunction (*Marsteller et al. 1973*). It was now realized that the disease spectrum in VCM-exposed individuals encompassed a larger scope of injuries and, in fact, suggested a systemic toxic effect. Hence *Jülic et al. (1973)* proposed the term 'vinyl chloride disease'.

In retrospect, this comparatively late recognition of the true nature of liver and spleen alterations in chronic VCM intoxication can be attributed, at least in part, to the long latency period as well as the insidious onset and course of this type of liver disease which is accompanied, even far into the advanced stages, by only minimal hepatic parenchymal dysfunction.

Only 3 months later, however, in February 1974 the significance of this discovery was surpassed by the alarming announcement that four cases of *angiosarcoma of the liver*, an exceedingly rare malignant tumour, had been found among a comparatively small work force of 274 employees of the PVC polymerization section of a large North American plant (*Creech et al. 1974a*). Two of these four patients had first presented with upper gastrointestinal bleeding due to portal hypertension between 1964 and 1970.

There is no longer any doubt that chronic exposure to vinyl chloride monomer can produce two different types of liver disease in man as well as in experimental animals:

- 1) Noncirrhotic portal hypertension
- 2) Angiosarcoma of the liver.

The two conditions have one feature in common: they are both rare disorders which are not easily recognized during life.

Noncirrhotic portal hypertension and (often inconspicuous) portal fibrosis are not pathognomonic. Primary splenic enlargement and gastrooesophageal haemorrhage due to marked portal hypertension in the absence of, or preceding, the development of cirrhosis was first described by *Banti* in 1894. As 'Banti's syndrome', this symptom complex and its aetiology and pathogenesis have continued to be a matter of debate. Under the designation 'idiopathic', or 'primary, portal hypertension' the syndrome has been observed notably in India and other South-East Asian regions (*Ramalingaswami* et al. 1962; *Inanaga* et al. 1962; *Basu* et al. 1967a, b; *Boyer* et al. 1967; *Sama* et al. 1971). It has been seen only sporadically in the Western World (*Rousselot* 1940; *Ravenna* 1940; *Tisdale* et al. 1959; *Polish* et al. 1962; *Miller* and *Brandt* 1962; *Siderys* and *Vellios* 1964; *Mikkelsen* et al. 1965; *Iber* 1970; *Escartin*, *Marin* et al. 1974; *Mendenhall* et al. 1974; *Grannis* 1975; *Villeneuve* et al. 1976). *Iber* (1969) estimated that "centers throughout the world reviewing their experience with portal hypertension encounter 3 to 5% of patients who do not clearly fit into the category of cirrhosis or blockage of the portal vein."

In the absence of an identifiable aetiology it has been speculated that in noncirrhotic portal fibrosis observed in India, unknown toxins contained in indigenous drugs, herbal medicines or adulterated food might have been responsible for the condition (*Sama* et al. 1971). *Villeneuve* et al. (1976) suggested that, apart from VCM and inorganic arsenicals, other still unidentified toxins could be the cause of this syndrome. Idiopathic portal hypertension has also been observed to occur in association with known hepatotoxic agents, their common link with VCM being, so far with the exception of vitamin A, the induction of angiosarcoma of the liver. These agents are:

- a) *Inorganic arsenicals* (*Zeegen* et al. 1970; *Neale* and *Azzopardi* 1971; *Kuolke* et al. 1974; *Morris* et al. 1974; *Huer* et al. 1975; *Villeneuve* et al. 1976; *Cowlshaw* et al. 1979);
- b) *Hypervitaminosis A* (*Muenter* et al. 1971; *Russell* et al. 1973, 1974; *Hruban* et al. 1974; *Kistler* et al. 1977); and
- c) Recently, *copper sulphate* in Portuguese vineyard workers (*Pimentel* and *Menezes* 1977).

Arsenical preparations (usually prescribed as *Fowler's solution* — potassium arsenite) have in the past been used as a tonic in neurasthenia, as an adjunct to iron therapy for anaemia, as antiepileptic drugs and well into the 1950s for the treatment of psoriasis. In this context, *Banti's* remark in his original paper (1898) that anaemia accompanying primary splenomegaly responded best to arsenical preparations is of note. In a renowned German pharmacology textbook of this period (*Notlingel* and *Rosbach* 1880) *Fowler's solution* is also listed as a traditional antimalarial drug of

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long standing. *Chaitinvar* and *Viranuvarti* (1979) recently implicated an indigenous Thai medicine containing arsenic as a possible aetiological factor in a case of idiopathic portal hypertension. *Datta et al.* (1979) found significantly elevated levels of arsenic in liver tissue specimens of four of nine Indian patients with idiopathic portal hypertension resulting from chronic arsenic intoxication (contaminated drinking water, use of Ayurvedic medicines). Typically, liver disease in these cases occurs in conjunction with other evidence of chronic arsenic intoxication, such as skin pigmentation, palmar and plantar hyperkeratosis, skin cancer and sometimes carcinoma of other sites. However, neither histological nor radiological or haemodynamic criteria permit a clear distinction between 'idiopathic' portal hypertension and noncirrhotic portal hypertension caused by chronic arsenic intoxication or chronic exposure to VCM, as was demonstrated by *Villeneuve et al.* (1976) in a study of five patients.

After prolonged treatment with excessively high doses of vitamin A (psoriasis, ichthyosis and other dermatological conditions, adjuvant cancer therapy and in health faddism) chronic intoxication has been seen to cause hepatic fibrosis and cirrhosis (*Muenter et al.* 1971; *Fleischmann et al.* 1977; *Kisler et al.* 1977; *Russell et al.* 1973, 1974). Storage of vitamin A in hepatocytes and one type of fat storing, nonphagocytic perisinusoidal cells (Ito cells (*Ito and Vemoto* 1952)) could be demonstrated by fluorescence microscopy. Stimulation and proliferation of Ito cells, which are probably fibroblast precursors (*Popper and Lidenfriend* 1970; *Schnack et al.* 1967), provokes an increase in basement-membrane-like material and collagen within the perisinusoidal space and leads to perisinusoidal fibrosis with partial obliteration of Disse's spaces and the sinusoidal lumen (*Hruban et al.* 1974).

The recognition of idiopathic portal hypertension, hepatic fibrosis, cirrhosis and angiosarcoma of the liver coexistent with excessively abundant hepatic deposition of copper (besides evidence of 'vineyard sprayer's lung') in a group of 30 vineyard workers in Portugal is, to our knowledge, the first report in which chronic copper intoxication is implicated as the aetiological agent. For periods varying from 3 to 45 years, these workers had been engaged in spraying vineyards with a mixture containing copper sulphate on 15–100 days per year. The authors noted a close morphological resemblance of the lesions to those resulting from exposure to inorganic arsenicals and to vinyl chloride (*Pimentel and Meneses* 1977). Although extrinsic chronic copper intoxication is virtually unknown in man, potential hepatotoxicity of long-continued uptake of copper was discussed by *Blomfield et al.* in 1971 in connection with recurrent haemodialysis.

Although nonmalignant liver disease seems to be a more common lesion in PVC production workers than angiosarcoma, it has received less attention than the spectacular discovery of the rare hepatic neoplasm. In continuation of our first two surveys (*Marsteller et al.* 1973, 1975a, b), we have now (end of 1980) observed 17 patients (all members of a total work force of approximately 180 polymerization workers) in whom clinical and morphological examination, including peritoneoscopy and guided liver biopsy, revealed advanced portal hypertension (Table 11). A larger proportion of them first presented with symptoms of unheralded gastrointestinal bleeding. On follow-up, we strongly suspected that angiosarcoma was developing in four of them but were unable to prove it during life. Only post-mortem examination finally confirmed the diagnosis. In a smaller series of seven patients with noncirrhotic portal fibrosis and

UCC
044265

Table 11. 17 PVC workers with advanced portal hypertension (marked oesophageal varices, episodes of upper GI bleeding, splenomegaly)

No.	Age at diagnosis (years)	Duration of exposure (years-months)	Peritoneoscopic and histological diagnosis
1	30	5	Noncirrhotic fibrosis
2	31	5/9	Noncirrhotic fibrosis
3	32	3/6	Noncirrhotic fibrosis
4	35	4	Noncirrhotic fibrosis
5 ^a	35	9	Noncirrhotic fibrosis
6	39	10/6	Noncirrhotic fibrosis
7	39	13/6	Noncirrhotic fibrosis
8	41	7	Noncirrhotic fibrosis
9 ^a	41	18	Postnecrotic cirrhosis
10 ^a	47	18	Noncirrhotic fibrosis
11	50	6/6	Noncirrhotic fibrosis
12	51	17	Noncirrhotic fibrosis
13	52	15/3	Noncirrhotic fibrosis
14	52	11	Noncirrhotic fibrosis
15	54	6/6	Noncirrhotic fibrosis
16 ^a	58	21	Postnecrotic cirrhosis
17 ^a	61	13	Noncirrhotic fibrosis

^a On follow-up patients 5, 9, 10, 16 and 17 subsequently developed angiosarcoma of the liver and died 3-6 years after diagnosis of portal hypertension. Patients 6 and 14 are at present (1981) under observation for suspected development of angiosarcoma of the liver, 6 and 11 years after peritoneoscopic diagnosis of portal fibrosis

associated portal hypertension, *Smith et al.* (1976a) observed later development of angiosarcoma in one of them. If a rough estimate based on these two small series were acceptable, it would appear that approximately one of five to seven individuals suffering from advanced VCM-induced portal hypertension might be expected to develop angiosarcoma later, although PVC-induced hepatic fibrosis per se is probably not a premalignant lesion.

4.2.1 Clinical Manifestations of Non-malignant Liver Disease

Physical examination is usually disappointing. In the more advanced stages of VCM-induced nonmalignant liver disease, palpable splenomegaly and a slightly to moderately enlarged liver may be the only physical signs. On palpation, we found hepatomegaly in 31 and splenomegaly in 16 of 50 selected PVC production workers who had been heavily exposed in the past (*Marsteller et al.* 1975a). *Lilis et al.* (1975) reported hepatomegaly in 15% and splenomegaly in 3.4% of 354 consecutively examined employees (267 currently employed, 87 former workers) of one PVC polymerization plant in New York State, USA, a number which included virtually the entire current production work force. A significantly higher prevalence of hepatomegaly was found in those

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these findings as an indication of toxic liver damage is not clear and the relation to previous exposure to VCM remains to be determined.

4.2.3 Gross Inspection of the Liver and Spleen

The gross appearance of the liver, as assessed by pentoneoscopy (Marsteller et al. 1975a, b; Marsteller and Leibach 1977; Leibach and Marsteller 1977) or at exploratory laparotomy, is that of a normal-sized or slightly to moderately enlarged organ with often blunted and irregular anterior edge. Inspection of the liver at pentoneoscopy also permits exclusion of partial nodular transformation as described by Sherlock et al. (1966). In most cases, the surface of the liver is smooth or slightly uneven with shallow indentations, but it may be finely granular, trabeculated or have a peau d'orange-like appearance. At most, there are micronodular changes but the diffuse coarse nodularity of cirrhosis is only rarely seen. Progression to frank cirrhosis with severe derangement of hepatic lobular architecture was observed by Smith and Williams (1974), and also in two of our recent cases in combination with development of angiosarcoma.

On palpation (direct or by pentoneoscopic probe), the texture of the liver is normal or only slightly firmer than usual. Indirect pentoneoscopic evidence of portal hypertension is presented by increased vascularity of the falciform ligament and the intestinal serosa or numerous dilated tortuous vessels in adhesions draining to the abdominal wall. Even in advanced stages, symptoms of pronounced portal hypertension often

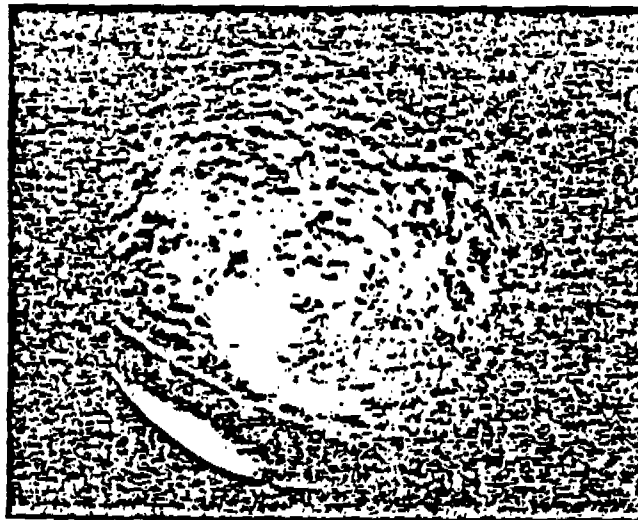


Fig. 4. Peritoneoscopic view of left hepatic lobe in noncirrhotic portal hypertension (January 1979). Blunted anterior edge, smooth to finely granular surface, conspicuous patchy capsular fibrosis. (42-year-old autoclave cleaner. VCM exposure 1963-74. 1973 thrombocytopenia as first sign. From 1974 to 1979, marked progression of portal hypertension with splenomegaly and one episode of bleeding from oesophageal varices.) See also Fig. 5 (patient 6 in Table 11)

contrast suspected is a focal opacities. stellate scarring (Marsteller et al. 1975a, b) extending necrotic tissue processes or more distal are seen in

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contrast sharply not only with minimal alterations of the surface but also with unexpectedly scanty histological evidence of hepatic fibrosis. The most conspicuous feature is a focal or diffuse capsular fibrosis of varying pattern (Fig. 4), presenting as whitish opacities. The degree of capsular involvement ranges from diffuse tiny commalike or stellate scars to coarsely reticular and irregularly patchy milk-white capsular thickening (Marsteller et al. 1975a). Histology showed that this focal increase of connective tissue in Glisson's capsule may extend into the parenchyma and connect with septa extending from enlarging fibrosed portal tracts (Popper and Thomas 1975). The connective tissue capsule of the enlarged spleen also seems to be sensitive to VCM-induced processes that have taken place in the underlying tissue so that focal white thickening or more diffuse opacities together with circumscribed subcapsular haemorrhagic cysts are seen in cases with marked splenomegaly.

4.2.4 Histology

Histological examination of biopsy specimens shows that normal lobular architecture is generally maintained, but varying patterns of portal and, in some cases, septal fibrosis, striking intralobular perisinusoidal fibrosis, and focal capsular and subcapsular fibrosis are found in combination with peculiar alterations of sinusoidal lining cells (Fig. 5a-d). Hepatocellular changes usually play a negligible role and inflammatory reactions, if present at all, are insignificant. The lesions are distributed quite irregularly throughout the liver and may vary from minor inconspicuous degrees to quite striking fibrosis. Surgical wedge biopsy of sufficient depth appears to be more suitable for histological evaluation than needle biopsy specimens (Smith et al. 1976a; Blendis et al. 1978).

Depending on length and degree of exposure, interval between last exposure and date of biopsy, as well as individual factors, histopathology of VCM-induced nonmalignant liver disease is represented by the following features whose manifestation is subject to marked interindividual and topical variation: the same variability of tissue alterations is seen in the nontumorous areas of the liver in angiosarcoma (Popper and Thomas 1975; Thomas et al. 1975; Berk et al. 1976; Gedigk et al. 1975; Weinbren 1976), but in these cases the nontumorous lesions may be even more conspicuous (Popper et al. 1973).

4.2.4.1 Hepatic Fibrosis

In its fully developed form, minimal to marked enlargement of portal tracts by excess of dense, paucicellular connective tissue, which in advanced cases contains proliferated bile ducts and some periductular inflammation, may in rare instances be combined with formation of periportal septa linking portal tracts or, even more rarely, connect central and portal canals. Other portal areas appear almost normal. Focal accumulation of connective tissue in the thickened Glisson's capsule may be connected by septa with enlarged infracapsular portal tracts. A more striking feature is an intralobular perisinusoidal 'netlike' fibrosis with more or less prominent collagenization of sinusoidal walls, in some areas even progressing to frank capillarization (Gedigk et al. 1975; Müller et al. 1975). The focal intrasinusoidal fibrosis may be subtle and in some cases

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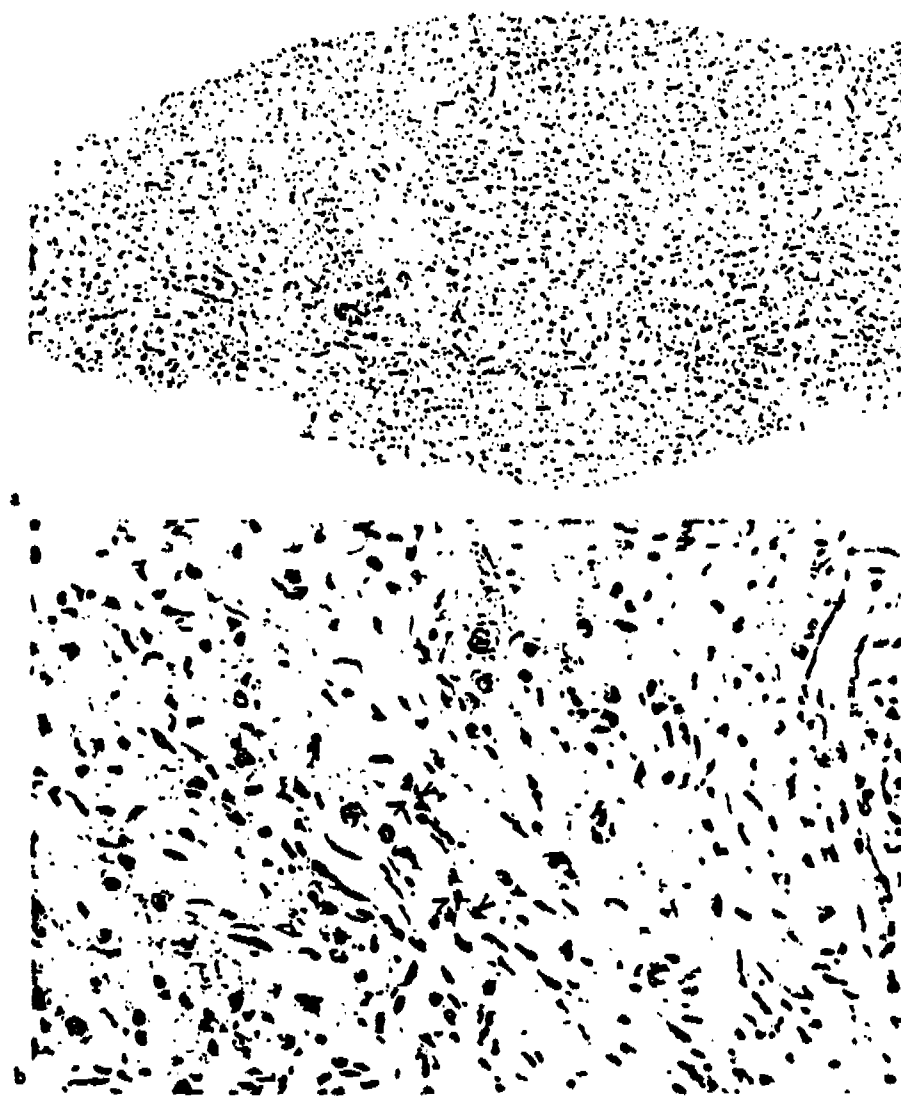
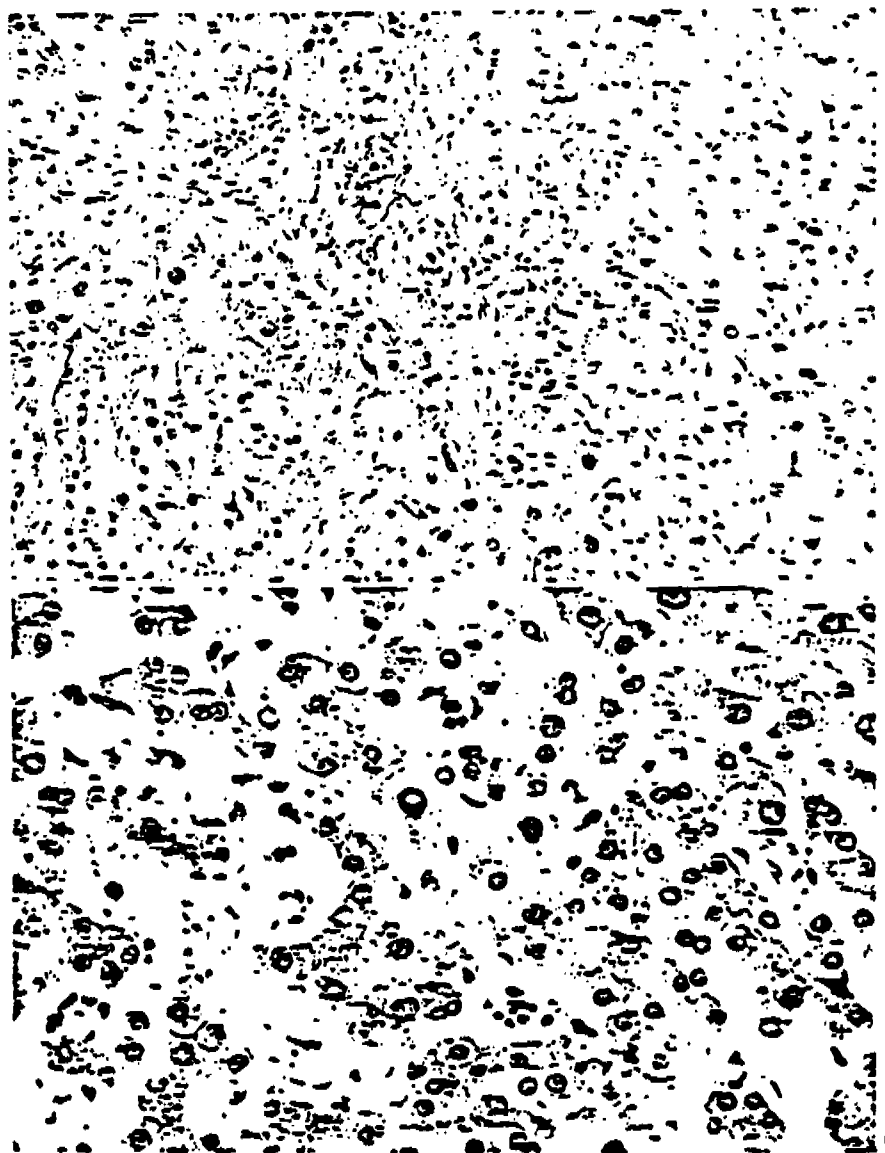


Fig. 5a. Needle biopsy specimen of the liver shown in Fig. 4. Enlargement and fibrosis of portal tracts. Moderately large droplet steatosis. Focal dilatation of sinusoids. H & E, $\times 80$. b Close-up of Fig. 5a. Indistinct border of enlarged and fibrotic portal tract towards parenchyma (left). Proliferation of capillaries ($> <$) with polymorphism and hyperchromasia of endothelial cells. PAS, $\times 400$

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Fig. 5c. Focal portal fibrosis (left upper corner) and reticulated perisinusoidal fibrosis with activated proliferating and pleomorphic sinusoidal lining cells. Trichrome (Goldner) stain, blue filter, $\times 250$. d Conspicuous focal dilatation of sinusoids. Activation and moderate polymorphism of proliferated hyperchromatic sinusoidal lining cells. Enlarged hepatocytes with hyperchromatic nuclei, some of them binuclear. (Potential precursor stage of angiosarcoma?) Courtesy of Professor Müller-Wallrat, Institute of Pathology, Amberg. H & E, $\times 400$

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may be recognized only in connective tissue stains. *Triche et al.* (1975) pointed out that in one worker with severe acroosteolysis but normal hepatic function and essentially normal liver histology on light microscopy (except for a minimal and easily overlooked increase of perisinusoidal collagen in occasional lobules), electron microscopy revealed a striking centrilobular increase in collagen between hepatocytes and in Disse's spaces together with proliferation and hyperplasia of sinusoidal lining cells (see also *Kurokawa et al.* 1977). The same ultrastructural deposition of perisinusoidal collagen was observed by *Schattenberg et al.* (1977) in 15 PVC workers in whom we could obtain liver tissue for electron microscopy at peritoneoscopy. Similar changes (enlargement of Kupffer cells, abundant deposits of collagen in the Disse's space and resulting reduction of sinusoidal diameter suggesting a possible factor in the pathophysiology of 'sinusoidal' portal hypertension) were seen on electron microscopy in a number of cases of idiopathic portal hypertension of unknown aetiology (occupational histories not mentioned) (*Sommerschield and Kluge* 1971; *Kluge et al.* 1970; *Tandon et al.* 1970).

4.2.4.2 Sinusoidal Lining Cells

Marked focal proliferation and hyperplasia of sinusoidal lining cells with nuclear polymorphism and hyperchromasia are the most impressive features of the mesenchymal lesion. The hyperchromatic nuclei of these cells may show a bizarre shape or resemble short pegs, and are often arranged in a chainlike fashion (*Gedigk et al.* 1975). These perisinusoidal and sinusoidal cells include three types: (1) normal endothelial cells, (2) lipocytes (Ito cells), considered to be precursors of fibroblasts and (3) plump cells with spindle-shaped nuclei and PAS-positive cytoplasm. Formation of excess reticulin suggests fibroblastic activity of some of these cells. Focal dilatation of sinusoids, not explained by passive congestion, is another peculiar feature usually associated with particularly pronounced alterations of these mesenchymal cells. There is reason to believe that this combination of changes may represent a premalignant stage.

4.2.4.3 Hepatocytes

Unimpressive, nonspecific, degenerative and adaptive lesions (such as minor degrees of fatty degeneration, cloudy swelling, ballooning or vacuolar degeneration, increase of lipofuscin pigment and proliferation of smooth endoplasmatic reticulum of hepatocytes in focal areas without inflammatory reactions), can be seen to disappear gradually with increasing intervals between the last exposure and the date of biopsy, in contrast to the apparently irreversible damage to mesenchymal structures (*Gedigk et al.* 1975, 1977; *Muller et al.* 1975). In poorly demarcated areas there is hyperplasia and hypertrophy of hepatocytes with polyploidy and increased number of binucleated cells. Two types of focal hepatocytic proliferation associated with varying degrees of sinusoidal cell alterations were recently described and are thought to play some as yet undefined role in the precursor stage of angiosarcoma (*Popper et al.* 1978).

4.2.4.4 Histology of the Spleen

Unless splenectomy is carried out in vinyl chloride disease, tissue specimens of the spleen are less easily obtainable than liver biopsy material. *Popper and Thomas* (1975)

and *Thomas et al.* to be characteristic of the disease, namely, to be characterized by congested red pulp follicles with many endothelial cells, occasional fresh spicuous fibrosis.

In ten cases of *Heusermann* and *terl*, together with splenectomy. The process. Excess of tissue, not at and white pulp. There was scarred meshwork and reduction of diameter of the pulp cords, formation of bizarre collagen fibrils. In the reticular connective tissue volume with paraformation of capillaries found within the thrombocytes by enhanced pooling of help to explain the stages of vinyl chloride and *Heusermann*. VCM-induced splenomegaly of the liver or extrahepatic in the spleen in vinyl chloride disease indicate a primary process correlating with the patients is being present in the spleen in nonalcoholic liver disease, suitable for comparison.

4.2.5 Pathophysiology

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and Thomas et al. (1975) found the cut surface of surgically removed enlarged spleens to be characterized by conspicuously hyperplastic Malpighian follicles in a beefy homogeneous red pulp. Histologically, they noted large germinal centres of the Malpighian follicles with merging of perifollicular zones, dilatation of red pulp sinuses lined by endothelial cells of variable, often cuboidal shape, thickening of the pulp cords with occasional fresh haemorrhages, and in one case Gandy-Gamna bodies, but only inconspicuous fibrosis of the red pulp.

In ten cases we obtained needle biopsy specimens of spleen tissue at peritoneoscopy. Heusermann and Stutte (1977b) and Stutte and Heusermann (1978) studied this material, together with spleen tissue specimens available from three spleens obtained at splenectomy. They found evidence for an involvement of the spleen in the fibrotic process. Excess amounts of newly formed extracellular elements of reticular connective tissue, notably collagen, produced by stimulation of fibroblastic cells of the red and white pulp, particularly in perifollicular and subcapsular areas, were observed. There was scarring of perarterial lymphatic sheaths, obliteration of the pulp cord meshwork and reduction of pulp cord volume, in addition to an increase in number and diameter of sinuses. The reticular connective tissue of the walls of the sinuses and of the pulp cords showed marked alterations with thickening of reticular fibres and formation of bizarre platelike amorphous structures containing irregularly distributed collagen fibrils. Narrowing of the labyrinthine cordal tissue with marked increase of the reticular connective tissue caused a reduction of microcirculatory sequestration volume with parallel decrease of the number of pulp cord macrophages and approximation of capillaries and sinuses. Frequently, focal accumulation of platelets was found within the narrowed pulp cordbed in addition to increased phagocytosis of thrombocytes by residual macrophages. This lends support to the hypothesis of enhanced pooling of platelets in the spleen (Heusermann and Stutte 1977a), and may help to explain the pathogenesis of thrombocytopenia often seen even in the early stages of vinyl chloride disease. By structural analysis of histometrical results, Stutte and Heusermann (1978) outlined certain diagnostic criteria for the differentiation of VCM-induced splenic alterations from those seen in portal hypertension due to cirrhosis of the liver or extrahepatic portal vein occlusion. They concluded that fibrotic changes in the spleen in vinyl chloride disease are not the result of portal hypertension but indicate a primary action of VCM or its metabolites on the spleen. A comprehensive report correlating clinical and morphological data gathered from this group of 13 patients is being prepared for publication at present. Results of histometrical studies of the spleen in noncirrhotic portal hypertension of unknown aetiology are now available for comparison (Seki 1965; Yamamoto 1978, 1979).

4.2.5 Pathophysiology of Portal Hypertension

The pathophysiology of portal hypertension in VCM-induced liver disease is as yet an unresolved problem. Patency of the portal vein was demonstrated in all cases subjected to splenoportography. Portography usually showed no or only minimal derangement of intrahepatic vascular pattern such as tapering or 'cut-off' of small peripheral portal venous radicles (Blendis et al. 1978; Villeneuve et al. 1976). High intrasplenic pressure and a normal, or only slightly raised, wedged hepatic vein pressure indicate that the

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portal flow is obstructed at the sinusoidal or presinusoidal level. In a group of five PVC workers selected for haemodynamic studies, *Blendis et al.* (1978) could not demonstrate a direct relationship between the degree of hepatic fibrosis in needle biopsy specimens and portal hypertension. But it should be kept in mind that the distribution of fibrosis in these workers is quite irregular. It has also been suggested by *Popper and Thomas* (1975) and *Thomas et al.* (1975) that the increased splenic and hepatic blood flow as a result of decreased splenic resistance in splenomegaly cannot properly be accommodated in the hepatic portal vein bed owing to impairment of adaptive distension of portal veins and sinusoids by the subcapsular, portal and perisinusoidal fibrosis. *Blendis et al.* (1978) found no correlation between spleen or estimated liver blood

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Fig. 6a, b. Progression of noncirrhotic portal hypertension despite termination of exposure. Oesophageal varices. (Autoclave cleaner, age at diagnosis: 35 years. VCM-exposure, 1962-1972. 1972 Raynaud's phenomenon, sklerodermoid skin indurations, thrombocytopenia, splenomegaly, and grade I oesophageal varices. Gradual progression of portal hypertension. Sudden death from ruptured anaplastic angiosarcoma of the liver in June 1978. Histologically only mild perisinusoidal fibrosis in nontumorous areas)

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4.2.6 Follow-up of Non-malignant VCM-induced Liver Disease

In 1974 Martin et al. (see also Berk et al. 1975) pointed out that VCM-associated hepatic fibrosis, once established, may progress even after cessation of exposure. They could demonstrate this progression despite normalization of all routine liver function tests in a 27-year-old worker on a follow-up examination including pentoscopia and biopsy 2 1/2 years after cessation of exposure. Progression of fibrosis and appearance of bridging between portal and central veins were indicative of persisting activity of the fibroblastic process, whereas the previously observed activation of both hepatocytes (marked variation of cell size and numerous binucleated cells) and sinusoidal lining cells had disappeared. Since 1975 we have observed a number of workers who on follow-up showed evidence of progressing portal hypertension with development of massive oesophageal varices and subsequent bleeding episodes despite removal from exposure (Fig. 6). In five (77) of these patients with progressing portal hypertension angiosarcoma of the liver finally developed. In this context, it is of interest to note that more or less conspicuous hepatic fibrosis (or rare progression to cirrhosis) was the parental terrain in which the majority of cases of VCM-induced angiosarcoma of the liver developed (see Tables 13-18).

Liver and spleen scans with 99m technetium-labelled sulphur colloid, quantitated determination of spleen size with the aid of ^{197}Hg -bromomercure-hydroxypropane (BMHP) labelled artificially damaged red cells, and sequential perfusion scintigrams after bolus injection of ^{99m}Tc -pertechnetate have been found useful in the diagnosis and follow-up of nonmalignant liver disease in PVC-polymerization workers. With the aid of these noninvasive methods, inhomogeneous uptake of labelled sulphur colloid in the reticuloendothelial system of the liver and enhanced uptake in the spleen, gradual increase in spleen size and reduction of portal venous perfusion have been observed in PVC polymerization workers developing portal fibrosis and portal hypertension (Bierack et al. 1975a, b, 1977a, b).

4.3 Angiosarcoma of the Liver

4.3.1 Epidemiology

Primary angiosarcoma of the liver (ASL) is described under a variety of synonyms (angioblastic sarcoma, angioblastic reticulosarcoma, endothelioma, endothelioblastoma, haemangioblastoma, haemangioendothelioma, haemangioendothelial sarcoma, Kupffer cell sarcoma, malignant haemangioma, metastasizing haemangioma, reticuloendothelial sarcoma, primary sarcoma of the liver). It is an exceedingly rare malignancy, arising from vascular lining cells. It occurs spontaneously with two peaks in the age distribution: one at early infancy (infantile haemangioendothelioma) and the other in late adulthood (fourth to sixth decade). The numerous synonyms render it difficult to estimate the number of reported cases and to determine its true incidence. In a recent review

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of the literature. *Alrenga* (1975) listed 165 published cases of primary angiosarcoma of the liver in adults. In the six autopsy series collected by *Alrenga*, ASL constituted only 1.8% (0.9%–2.7%) of all primary malignant tumours of the liver, which of themselves are rare findings in the Western World. Autopsy statistics show that the incidence of ASL ranged from 2 to 20/100 000 autopsies during different periods with a mean incidence of 12/100 000 autopsies (Table 12). According to *Heuth* et al. (1975) it was estimated that in the United States the expected annual incidence of ASL is 0.014 in 100 000 inhabitants or 25–30 cases per year for the entire United States.

Table 12. Incidence of angiosarcoma of the liver (ASL) in autopsy series

Authors	Year	Observation period	No. of autopsies	No. of cases of ASL	Region
<i>Simpson et al.</i>	1955	1914–1953	24 196	1	Mayo Clinic, Rochester, Minn., USA
<i>Edmondson</i>	1958	1918–1954	52 000	1	Los Angeles, County Hosp., USA
<i>MacSween et al.</i>	1973	1900–1969	— ^a	3	Western Infirmary Glasgow, U.K.
<i>Alrenga</i>	1975	1951–1973	39 700	6	Cook County Hosp. Chicago, USA
<i>Rein and Huth</i>	1975	1954–1974	30 079	4 (6) ^c	Düsseldorf, Fed. Rep. Germany
<i>Byrén and Holmberg</i>	1975	1958–1969	— ^b	12 (adult cases)	Sweden
<i>Dalderup et al.</i>	1976	1960–1975	At least 40 000	8	Netherlands (population: 10–14 million)

^a Among 120 cases of primary malignant liver tumours studied post mortem during this 70-year period.

^b Among 8 million inhabitants.

^c 4 Angiosarcomas, 1 haemangioendothelioma, 1 malignant haemangiopericytoma

Accordingly, the identification of 4 cases of ASL among approximately 270 employees of the vinyl chloride polymerization section at a B.F. Goodrich plant near Louisville, Kentucky, between September 1967 and December 1973 was duly recognized as an alarming situation indicative of a serious new occupational hazard (*Creech et al. 1974a; Creech and Johnson 1974*).

Until 1974, only two carcinogenic agents were known to be associated with the development of ASL in man, i.e. the administration of a radioactive colloidal prepara-

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tion of *thorium dioxide* (thorotrast) for diagnostic purposes, and chronic exposure to *inorganic arsenicals*. Both substances are stored mainly in the liver: injected thorium dioxide particles are rapidly taken up by phagocytic cells of the reticuloendothelial system and are permanently retained; arsenicals are only slowly released from the liver.

Thorotrast came into use in 1928 and was internationally employed as an injectable contrast medium until the mid-1950s, when its use was abandoned because of mounting evidence of the carcinogenic action of thorium dioxide deposits. MacMahon et al. reported the first case of thorium dioxide-induced ASL in 1947. Since then ASL has been the type of liver tumour which occurred most frequently among patients who had been given thorotrast injections in the past (da Silva Horta 1967; da Silva Horta and Morra 1967; Wegener et al. 1971; Futh and Pirzke 1974; Selinger and Kuff 1975). A special type of progressive portal and subcapsular hepatic fibrosis was another lesion caused by thorium dioxide retained in the liver. da Silva Horta (1967) considered this 'thorotrast fibrosis' to be clearly distinguishable from true cirrhosis. Gamma radiation from a lost radium needle has also been implicated as a causative agent in one case of ASL (Ross 1932).

Development of ASL as a late complication of *chronic arsenic intoxication* in German vineyard workers was first described by Liebegott (1949, 1952) and has been extensively documented by Roth (1956, 1957a, b, 1959). During the 10-year period, 1950-1959, autopsies of 82 Moselle vintners suffering from chronic arsenic intoxication revealed ASL in 8 cases among a total of 61 individuals (74%), with cancer often of multiple sites (Roth 1959). In 1925, arsenic insecticide sprays and dusts had been approved for use in German vineyards but they were banned by law in 1942. Exposure occurred not only via inhalation during spray periods (approximately 30 days/year) but notably by daily consumption of quantities of cheap grape wine ('Haustrunk'), produced from a second pressing of the grape skin residue by addition of water. This Haustrunk, an allowance in kind to the vineyard workers, had a low alcohol content (3%-5% v/v) but contained high levels of residual arsenic (0.2-6.9 mg As₂O₃/litre). Roth (1956) calculated the mean total ingestion of As₂O₃ to have been 53.7 g (range: 18.6-88.8 g) for a 12-year period. ASL was also seen after long-term treatment with Fowler's solution for psoriasis (Regelson et al. 1968; Lander et al. 1975).

Chowdury et al. (1977) reported an anecdotal case of apparently benign diffuse haemangioendotheliomatosis of the liver with considerable fibrosis and portal hypertension but normal liver function. This condition was found in a middle-aged black woman who had been exposed to various chemical fumes (including carbon tetrachloride) during 20 years in a dry-cleaning establishment, though it must be noted that she had a high alcohol consumption. The possibility that these symptoms could have been manifestations in later life of congenital disease cannot be ruled out.

The proportion of patients with ASL in whom a pertinent history of exposure could be elicited has varied considerably. In an earlier survey of the literature covering the period 1875-1960, von Becker and Büscher (1961) listed 12 of 54 adult cases with a history of exposure to either thorium dioxide (7) or arsenicals (5 of Roth's cases). Among more than 15 000 autopsies performed in Bonn during 1950-1959, all 8 cases observed were found exclusively in vintners exposed to arsenicals (Roth 1959). On the other hand, Fiechter and Ryes (1976) recently observed a cluster of 4 cases among 391 autopsies during a 29-month period at a hospital in rural central Wisconsin serving

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Table 13. Personal data of 68 polyvinyl chloride production workers with angiosarcoma of the liver reported to NIOSH up to August 1978 (Spiras and Kaminski 1978)

No.	Country ^a	Birth date (m/d/y) ^b	Date of death (m/d/y)	Age at death	Total years exp.	Job classification ^c
1	B (1)	01.12.13	06.29.76	63	17	1, 2
2	CND (1)	12.15.13	09.02.55	41	11	1, 2
3	CND (2)	03.06.14	12.21.57	43	14	2, 3, 12, 13
4	CND (3)	08.26.19	03.22.62	42	20	2, 5
5	CND (4)	04.05.19	01.21.68	48	22	1, 2, 5, 14
6	CND (5)	05.07.11	07.05.68	56	5	1, 14
7	CND (6)	12.15.19	04.10.71	51	23	1, 12, 13, 15
8	CND (7)	11.09.19	12.24.72	52	25	1, 9, 17
9	CND (8)	05.13.20	06.12.73	53	5	1, 12, 17
10	CND (9)	07.19.21	09.04.74	53	26	3, 12, 16
11	CND (10)	05.16.15	04.00.77	61	14	2, 16
12	CSR (1)	00.00.28	12.00.73	45	16	1
13	CSR (2)	00.00.26	00.00.66 (64?)	40 (37?)	15 (14?)	1
14	D (1)	06.04.30	01.25.69	38	12	2
15	D (2)	07.26.31	12.14.71	39	11	2
16	D (4)	09.04.30	11.25.74	44	17	2
17	D (5)	01.01.32	01.09.75	43	12	2, 4, 5
18	D (7)	09.29.26	11.13.75	49	12	11, (1)
19	D (8)	10.19.17	12.25.75	58	21	2
20	D (9)	12.13.34	03.24.78	42	15	10
21	D (10)	07.23.29	06.28.77	47	22	10
22	D (11)	12.29.36	03.07.77	41	16	10
23	D (12)	06.14.38	10.07.77	39	6	1
24	F (1)	04.15.24	02.19.67	43	19	1, 2
25	F (2)	06.03.11	01.24.75	63	12	2
26	F (3)	01.06.20	06.26.75	55	29	2
27	F (4)	01.27.27	01.03.76	49	26	2, 6
28	F (5)	01.29.38	05.13.76	38	11	1, 2
29	F (6)	04.14.34	09.12.76	42	13	6, 7
30	F (7)	00.00.27	07.02.76	49	22	2
31	F (8)	04.01.34	01.30.77	42	19	2
32	F (9)	10.08.14	12.25.77	62	28	2
33	F (10)	05.24.19	01.20.78	58	21	2
34	GB (1)	04.20.01	12.03.72	71	22	8
35	GB (3)	06.02.37	12.24.74	37	4 (3 1/2?)	1
36	I (2)	11.13.29	12.27.72	43	6	2
37	I (3)	03.14.20	07.10.75	55	21	
38	J (1)	08.01.22	10.24.75	52	22	
39	J (2)	08.02.29	08.10.76	37	13	
40	N (1)	12.23.15	01.04.72	56	21	

Table

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Table 13 (continued)

Occupation^c

No	Country ^a	Birth date (m/d/y) ^b	Date of death (m/d/y)	Age at death	Total years exp	Job, classification ^c
41	S (1)	06.23.27	10.20.70	43	18	2
42	S (3)	06.10.10	03.19.76	66	21	2
43	S (4)	11.16.14	05.12.77	62	31	
44	USA (1)	10.17.23	03.03.73	49	21	9
45	USA (2)	08.19.33	09.27.71	37	13	9
46	USA (3)	05.25.15	12.19.73	58	28	10
47	USA (4)	01.15.24	01.07.68	43	15	10
48	USA (5)	01.25.12	04.09.64	52	20	10
49	USA (6)	11.23.28	07.24.75	46	12	10
50	USA (7)	05.03.22	03.23.68	45	17	
51	USA (8)	05.06.20	08.28.61	41	15	
52	USA (9)	11.08.31	03.00.75	43	24	9 (1)
53	USA (10)	08.16.13	05.10.68	55	17	
54	USA (11)	05.27.09	03.16.70	61	23	
55	USA (12)	11.17.18	05.02.69	50	19	
56	USA (13)	12.01.21	07.04.74	52	28	
57	USA (16)	11.04.27	03.27.69	41	4	
58	USA (17)	05.06.31	1978 alive	43	19	
59	USA (18)	04.22.28	11.02.75	46	11	
60	USA (19)	00.00.15	04.06.76	60	22	
61	USA (20)	08.31.17	01.30.77	59	21	
62	USA (21)	09.02.09	01.02.77	67	21	
63	USA (22)	10.02.23	12.04.76	52	28	
64	USA (23)	00.00.22	04.06.73	50	14	
65	USA (24)	05.07.17	05.27.77	60	26	
66	USA (25)	08.07.10	03.10.77	67	20	
67	USA (26)	? (1978)	? (1978)	? (1978)	? (1978)	
68	YU (1)	04.05.14	08.04.73	59	20	1, 2, 5

- ^a B. Belgium
 CND, Canada
 CSR, Czechoslovakia
 D, West Germany
 F, France
 GB, Great Britain
 I, Italy
 J, Japan
 N, Norway
 S, Sweden
 USA, United States of America
 YU, Yugoslavia.

^b 00, data not available.

- ^c 1, autoclave cleaner
 2, autoclave operator,
 3, pipe fitter
 4, polymerizer
 5, foreman
 6, 'filtreur'
 7, 'préparateur de solution'
 8, process worker
 9, chemical operator
 10, polymerization worker
 11, technical assistant
 12, maintenance worker
 13, millwright
 14, water cooling unit
 15, reager
 16, furnace operator
 17, machine shop worker

(Tables 13-15 are compiled with the aid of information contained in the literature; references see Table 15)

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a population of 130 000. One of the four had a history of occupational exposure to polyvinyl acetate, which has hitherto not been related to ASL. The other three may have had nondocumented exposure to arsenical pesticides, which were used for many years in this region, but such conjectural deliberations must await further investigation for confirmation.

Death certificates for the periods 1963–1973 in England and Wales and 1965–1973 in Scotland recorded 41 cases of ASL (1–9 cases per year; mean: 4 cases per year). An unexplained peak was observed in 1968/1969 (Baxter and Fox 1975). Six additional cases not mentioned on the death certificates were detected by a panel of specialists (Baxter et al. 1977). In reassessing 36 of these 47 patients for whom histological sections were available, the panel of histopathologists unanimously agreed on the diagnosis in only 14 cases (7 doubtful, 3 unclassifiable, 12 non-ASL). For 12 of these 14 cases occupational and residential histories were obtained which revealed one undoubtedly VCM-induced case, two cases with possible exposure to (low levels of?) VCM and one case attributable to thorium dioxide.

After the first three cases of ASL among vinyl chloride polymerization workers in the United States had come to the attention of the National Institute for Occupational Safety and Health (NIOSH) in January 1974 (Lloyd 1974), this institution continued to collect information on additional cases reported to them from nations with an important PVC industry (Lloyd 1975; Spirtas and Kaminski 1977). As of August 1978, data had been presented on a total of 68 cases of ASL among polymerization workers (Spirtas and Kaminski 1978, pers. comm.); another eight cases had been observed among nonpolymerization workers exposed to VCM in various jobs. On the basis of this data collection communicated to us in 1978 – for which we wish to thank Drs. R. Kaminski and R. Spirtas, NIOSH, Cincinnati, USA – we attempted to trace these cases and their individual symptomatology as well as other relevant information published in the literature up to 1979 (see Tables 13–18). The ten Canadian cases of VCM-induced ASL (cases 2–11) are dealt with summarily in the papers published by Delorme (1978a) and Delorme and Makk (1975); seven of them were described in more detail by Makk et al. (1976). Cases 19 and 23 were observed at our clinic in Bonn but details have only been published for case 19 (E.U. in Leibach and Marsteller 1977). In reviewing the literature we could not trace cases 37–40, 43, 50, 51, 53–67 and C, F and H. According to the latest annual report of the Staatlicher Gewerbearzt, Düsseldorf (Reinl et al. 1978), the number of deaths from VCM-induced ASL in the Federal Republic of Germany had increased to 16 by the end of 1978, to which we now add a 17th case (Figs. 8 and 9).

In retrospect, it was discovered that the first case of VCM-induced ASL had already occurred in 1955 in a Canadian polymerization worker. For the 67 VCM polymerization workers for whom details were available, total years of exposure ranged from 4 to 31 years (mean and median 18 and 19 years, respectively). In comparison, mean duration of exposure in our group of 17 individuals with advanced nonmalignant liver disease (see Table 11) was 10 3/4 years (range: 3 1/2–21 years). The latency period (years from first exposure to diagnosis of ASL) ranged from 9 to 38 years (mean and median: 21 years). The average age at diagnosis of ASL was 50 years (range: 37–71 years).

Table 14. Clinical and morphological data on 68 polyvinyl chloride (PVC) production workers with angiosarcoma of the liver reported to NIOSH by August 1978

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Table 14. Clinical and morphological data on 68 polyvinyl chloride (PVC) production workers with angiosarcoma of the liver reported to NIOSH by August 1978

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
1	+	Atrophic, slightly indurated	(+)	Noncirrhotic perisinusoidal & capsular	?	0	0	0
2	7 cases: (+) - + (1860- 5200 g)	No details available		Capsular		No details available		1 case: multiple metastases (lung, pleura, pericardium, ileum, colon, kidneys, left adrenal)
3			Capsular, portal, perisinusoidal					
4			Sclerosis of wall of portal vein					
5			Capsular, portal, perisinusoidal					
6			?					
7			Capsular, portal, perisinusoidal	1 case: mediastinal lymph node				
8			Capsular, portal, perisinusoidal	1 case: peritoneal spread				
9			Portal, perisinusoidal	3 cases: local spread				
10			Capsular, portal, perisinusoidal					
11			Capsular, portal, perisinusoidal					

UCC
044281

Table 14 (continued)

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
12	+	Moderately enlarged	(+)	(Cirrhosis), fibrosis	?	β	+	β
13	+	(2750 g) ?	+	(Cirrhosis)	?	β	β	Left lung
14	+	Spleno- megaly	?	?	?	β	β	4th left rib
15	+	Slightly enlarged	?	?	?	β	β	β
16	+	Spleno- megaly (830 g)	+	Capsular, portal, septal	+	β	β	1st thoracic vertebra
17	+	Spleno- megaly	+	+	?	β	β	Brain
18	?	Perisplenitis	?	?	+	β	+	3rd lumbar vertebra
19	(+)	Spleno- megaly (400 g)	(+)	Progressive perisinusoidal, portal and septal cirrhosis	+	β	β	β
20	?	?	?	?	?	?	?	?
21	+	Spleno- megaly (1900 g)	+	+	?	β	β	β
22	+	Spleno- megaly	?	Capsular, portal, perisinusoidal	+	β	β	β
23	+	Spleno- megaly (455 g)	β	Focal peri- sinusoidal	?	β	β	β
24	+	+	+	+	+	β	β	β

UCC
044282

20	?	?	?	?	?	?	?	?	
21	+	Spleno- megaly (1900 g)	+	+	+	β	β	β	
22	+	Spleno- megaly	?	Capsular, portal, perisinusoidal	+	β	β	β	
23	+	Spleno- megaly (455 g)	β	Focal peri- sinusoidal	?	β	β	β	
24	+	?	?	β	?	β	?		Local spread to caval vein
25	+	Spleno- megaly (1610 g)	+	Portal, perisinusoidal fibrosis	+	β	β	β	
26	+	?	β	?	?	β	β		Duodenal wall
27	+	Spleno- megaly (2230 g)	?	Reticulated capsular fibrosis, micronodular cirrhosis	?	β	β	β	
28	+	Spleno- megaly (650 g)	+	Portal, peri- sinusoidal, capsular fibrosis	+	β	β		4th and 7th thoracic vertebra, 5th left rib, left adrenal
29	+	'Modifications fibro- congestive'	β	Slight portal fibrosis	β	+	?	β	
30	+	β	β	Minimal fibrosis	β	β	β		Small intestine
31	+	Spleno- megaly (3000 g)	?	?	?	β	β		Para-aortal lymph nodes
32	+	?	?	β	+	β	β	β	
33	+	?	?	Capsular, portal fibrosis	β	β	β	β	

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Viral Chlora-Associated Disease

UCC
044283

Table 14 (continued)

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- ostenolysis	Raynaud's phenomenon	Metastases
34	+	Slight splenomegaly	β	β	+	β	β	β
	(2625 g)				(80 000)			
35	+	Congested, firm (200 g)	+	Noncirrhotic fibrosis	?	β	β	β
36	+	?	+	?	?	β	β	Local spread to abdominal wall and colon; lymph nodes
37								
38								
39								
40								
41	+	Splenomegaly	?	?	?	?	?	?
42	?	?	?	?	?	?	?	?
43								
44	+	Splenomegaly	+	Subcapsular and portal fibrosis	+	β	β	β
45	+	Spleno- megaly	+	Markedly thickened capsule; marked fibrosis	+	β	β	β
46	+	Spleno- megaly	?	Portal fibrosis	?	β	β	Spread to duodenum
	(1860 g)							
47	+	Spleno- megaly	?	Portal fibrosis	+	β	β	Spread to diaphragm and abdominal wall
					(35 000)			
48	+	?	?	Slight focal	?	β	β	Lines, large and small

45	+	Spleno- megaly	+	Marked thickened capsule; marked fibrosis	+	β	β	β	
46	+	Spleno- megaly (1060 g)	?	Portal fibrosis	?	β	β		Spread to duodenum
47	+	Spleno- megaly	?	Portal fibrosis	+	β	β		Spread to diaphragm and abdominal wall
48	+	?	?	Slight focal hepatitis (“minimal hepatitis”)	?	β	β		Lungs, large and small bowel, pleura, pericardium, myocardium, kidneys, left adrenal
49	?	Normal	?	Capsular and portal fibrosis	?	β	β		Diaphragm, regional, retro- peritoneal and mediastinal lymph nodes, lungs, adrenal glands, cerebellum
50	Details not published								
51									
52	+	?	?	Peculiar portal fibrosis, moderate cirrhosis	?	β	β		Diaphragm, gallbladder, regional lymph nodes, lungs, scalp, skull
53	Details not published								
54									
55									
56									
57									
58									
59									
60									
61									
62									
63									
64									
65									
66									
67									
68	+	?	+	?	+	β	β	β	

UCC
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Table 15. Publications on the 68 cases of angiosarcoma of the liver listed in Tables 13 and 14

No	References	Additional relevant information
1	Hublet et al. (1977)	Hypertrophic, hyperchromatic and atypical endothelial cells in the <i>glomeruli</i> ; foci of haematopoietic cells in liver and spleen
2	Delorme and Makk (1975) Makk et al. (1976) Delorme (1978a, b) Delorme and Thériault (1978)	Case no. 7: ASL associated with hepatocellular carcinoma (Delorme 1978b) (All cases from one plant in Shawinigan, district Trois Rivières, Quebec)
3		
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10		
11		
12	Schmidt and Bátor (1976)	At the same plant: 4 cases of VCM-induced cirrhosis of the liver plus 1 case of cirrhosis and generalized reticulosarcoma and 4 cases of carcinoma of the GI tract or lungs
13		
14	Lange et al. (1974b)	See also Reini and Weber (1974)
15	Gedigh et al. (1975)	See also Reini and Weber (1974)
16	Gokel et al. (1976)	Foci of haematopoiesis within the tumour areas
17	Amann (1975) Rübsamen (1976)	1974 portocaval anastomosis; cholecystectomy. Hypertrophic, hyperchromatic and markedly atypical endothelial cells in the <i>glomeruli</i> and in the capillaries of the lungs
18	Reini et al. (1976)	
19	(Observed in Bonn)	Moderate hepatic siderosis; chronic fibrosing <i>pancreatitis</i> ; tubular and interstitial fibrosis of the <i>testes</i>
20	Reini et al. (1976)	
21	Reini et al. (1977)	
22	Reini et al. (1977)	
23	(Observed in Bonn)	Focal interstitial fibrosis of the <i>pancreas</i>
24	Ravier et al. (1975)	See also Berrod et al. (1978)
25	Roche et al. (1978)	1942 gastrectomy, 1974 splenectomy, right hepatic lobectomy (640 g). See also Roche (1977); Puech et al. (1977); Bonneton et al. (1975, 1977); Berrod et al. (1978)
26	Rety et al. (1976)	No autopsy (see also Berrod et al. 1978)

Table 15 (cont.)

No.	Ref.
27	Ro.
28	Ro.
29	Ro.
30	Ber
31	
32	
33	
34	Le
35	Sm.
36	Ma.
37	-
38	-
39	-
40	-
41	Byr.
42	Byr.
43	-
44	Bl. (cas)
45	Bl. (cas)
46	Bic. (cas)

UCC
044286

Table 15 (continued)

No.	References	Additional relevant information
27	<i>Roche et al. (1978)</i>	Chronic alcoholic. See also <i>Roche (1977)</i> ; <i>Puech et al. (1977)</i> ; <i>Berrod et al. (1978)</i>
28	<i>Roche et al. (1978)</i>	First symptom: vertebral and costal metastases. Right hepatic lobectomy. See also <i>Roche (1977)</i> ; <i>Puech et al. (1977)</i> ; <i>Pilichowski et al. (1979)</i> ; <i>Coudere et al. (1976)</i> ; <i>Berrod et al. (1978)</i>
29	<i>Roche et al. (1978)</i>	1960 scleroderma-like skin induration (hands), swelling of face, upper extremities and feet. 1971 bilateral acroosteolysis. Tumour penetration of the abdominal wall (fistula). Severe interstitial fibrosis of testes: fibrosis of interstitial wall, slight mesangial fibrosis of glomeruli. Variable but generally slight fibronyalinosis of arterial and venous vessel walls (skin, heart, lungs, intestine, testes)
30	<i>Berrod et al. (1978)</i>	
31		
32		
33		
34	<i>Lee and Harry (1974)</i>	
35	<i>Smith et al. (1976b)</i>	Latency period (1st exposure — death) only 8 years (see also <i>Fox and Collier 1977</i>)
36	<i>Maltoni (1974)</i>	
37	—	
38	—	
39	—	
40	—	
41	<i>Byrén and Holmberg (1975)</i>	
42	<i>Byrén et al. (1976)</i>	
43	—	
44	<i>Block (1974)</i> (case 3)	1965 portocaval shunt. 1970 cholecystectomy. See also <i>Falk et al. (1974a)</i> (case 4); <i>Whelan et al. (1976)</i> (case 1)
45	<i>Block (1974)</i> (case 2)	No autopsy. See also <i>Creech and Johnson (1974)</i> ; <i>Falk et al. (1974a)</i> (case 3); <i>Whelan et al. (1976)</i> (case 2); <i>Makk et al. (1976)</i> (case 6)
46	<i>Block (1974)</i> (case 4)	See also <i>Falk et al. (1974a)</i> (case 5); <i>Makk et al. (1976)</i> (case 10)

UCC
044287

Table 15 (continued)

No.	References	Additional relevant information
47	<i>Block</i> (1974) (case 1)	See also <i>Falk et al.</i> (1974a) (case 2); <i>Makk et al.</i> (1976) (case 4)
48	<i>Block</i> (1974) (case 5)	See also <i>Falk et al.</i> (1974a) (case 1); <i>Makk et al.</i> (1976) (case 2)
49	<i>Block</i> (1974) (case 6)	See also <i>Falk et al.</i> (1974a) (case 6); <i>Whelan et al.</i> (1976) (case 4); <i>Makk et al.</i> (1976) (case 14)
50	—	
51	—	
52	<i>Whelan et al.</i> (1976) (case 3)	Chronic alcoholic. See also <i>Makk et al.</i> (1976) (case 13); <i>Berk et al.</i> (1976) (case 2)
53-67	—	
68	<i>Zonica et al.</i> (1975)	Among a work force of 180 (120 PVC polymerization; 60 production of VCM) employed at this plant, 15 died of malignant disease (2 ASL, 5 bronchogenic carcinomas, 1 case each of carcinoma of the larynx, nb, mamma, spermatic cord; glioma, melanosarcoma, leukemia, Hodgkin's disease)

First exposure to VCM for these 67 cases of ASL dated back to the period 1939-1966 (median: 1951). Twenty-one years later, i.e. from 1972 onwards, a gradual increase in the number of new cases diagnosed and reported to NIOSH can be observed (Fig. 7). The onset of this gradual increase coincides with the calculated mean latency period of 21 years (*Spiras and Kaminski* 1977). *Spiras and Kaminski* also suggested that in future cases the age at diagnosis and the length of the latency period may increase as a result of the later reduction in levels of exposure.

From the synopsis in Table 13-18 it can be seen that in about two-thirds of the cases of ASL for which morphological details are available varying degrees of associated hepatic fibrosis in nontumorous areas of the liver were mentioned. Less often, evidence of portal hypertension and splenomegaly were noted. Metastasis of angiosarcoma to distant sites was observed in approximately half the published cases. It is of note that acroosteolysis and cutaneous stigmata of scleroderma have been observed in only 1 of these 76 patients, a French PVC worker who had apparently not been engaged in reactor cleaning (case 29; *Roche et al.* 1978). Another noteworthy piece of information is that strikingly atypical endothelial cells with hypertrophic and hyperchromatic nuclei have also been found in organs other than the liver (kidneys, lungs) in autopsy material from two patients (cases 1 and 17, *Hubler et al.* 1977; *Rübsamen* 1976). *Hubler et al.* (1977) also found such cells in the myocardium and in the adipose tissue enveloping the adrenals. All this may lend support to the idea that the effect of VCM metabolites is not restricted to the vascular endothelium of the liver and spleen. Angio-

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044288

Table 16. Personal data on eight cases of angiosarcoma of the liver among VCM-exposed personnel not employed in PVC production (as reported to NIOSH by August 1978)^a

No.	Country	Birth date (m/d/y) ^b	Date of death (m/d/y)	Age at death	Total years exp.	Job classification
A	D (3)	07.16.30	10.10.73	43	14	Loading pesticide cans with VCM propellant
B	D (6)	05.09.36	12.16.74	38	3.5	Assistant factory chemist
C	GB (2)	09.08.14	12.00.70	55	11	Pouring PVC oil mixture onto fabric bases
D	I (1)	06.15.34	04.16.71	36	3	Fabrication of PVC sacks and wrappings (extrusion at temperatures of 120°C)
E	S (2)	11.27.11	08.16.71	61	23	Assistant factory chemist (production of VCM)
F	USA (15)	00.00.25	02.15.73	47	?	Accountant at plant producing PVC fabric
G	YU (2)	11.15.31	07.12.73	42	18	Production of VCM
H	YU (3)	12.21.31	01.11.76	45	22	Production of VCM

^a Update of NIOSH register, August 1978, prepared by Kaminski as in Table 13.

^b 00, data not available

sarcoma arising from the kidneys or other types of malignant renal neoplasms, however, have not been described in VCM-exposed individuals, although malignant nephroblastoma has been induced in experimental animals.

The extremely rare coincidence of angiosarcoma and hepatocellular carcinoma was found in three instances (case 7, *Delorme* 1978b; case E, *Byrén* and *Holmberg* 1975, and a case not included in the 1978 NIOSH update *Tamburro et al.* 1978a). In the case reported by *Tamburro et al.* chronic alcoholism may have played a cofactor role in the development of liver cancer. We can now add a fourth case observed in 1978 at the Department of Medicine in Bonn (see Sect. 4.1.5 and Fig. 3). This patient (patient 9 in Table 11), a PVC-polymerization worker (total period of exposure: 13 years) was first admitted to our department in February 1975 and was found to suffer from atypical cirrhosis of the liver with portal hypertension, splenomegaly and Raynaud's phenomenon. During follow-up ASL was clinically suspected but could not be confirmed during life, despite exploratory laparotomy and generous surgical biopsies. The patient

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Table 17. Clinical and morphological data on eight cases of angiosarcoma of the liver among VCM-exposed persons not employed in PVC polymerization

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
A	+	Spleno- megaly	+	Portal fibrosis	+	β	β	Diaphragm, gastric mucosa, abdominal lymph nodes
B	+	Spleno- megaly (425 g)	+	Focal capsular fibrosis, portal and centrilobular fibrosis	β	β	β	Diaphragm, pleura, abdominal lymph nodes
C								
D	(+)	Not enlarged	β	?	?	β	β	Lungs, pericardium
E	+	?	?	?	+	β	β	?
					(104 000)			
F								
G	+	Splenomegaly	?	?	?	β	β	Dura, cranium
H								

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Table 18. Publications on the eight cases of angiosarcoma of the liver listed in Tables 16 and 17

No	References	Additional relevant information
A	<i>Reini and Weber</i> (1974)	1967 idiopathic portal hypertension, portocaval shunt
B	<i>Zimmermann and Eck</i> (1975) <i>Reini</i> (1975)	1973 right heminephrectomy for unilateral hydronephrosis associated with bilateral double kidney. Foci of haematopoietic cells in spleen and kidney. Fibrosis of the pancreas. Slight fibrosis of testes and of the small intestinal serosa
C		
D	<i>Maltoni</i> (1974)	Autopsy: angiomatous epulis. Angiosarcoma involving liver, lungs and pericardium. The pericardium might have been the primary site!
E	<i>Byrén and Holmberg</i> (1975)	Probable coexistence of a hepatocellular cancer of both low and high grade differentiation
F		
G	<i>Zorica et al.</i> (1975)	
H		

died on 7 August 1978, after a massive haemorrhage from oesophageal varices. Autopsy revealed both multicentric metastasizing angiosarcoma and hepatocellular carcinoma of the liver as well as slight fibrosis of the pancreas (to be published in detail).

It is still unexplained why hepatocytes are generally exempted from the carcinogenic effect of VCM metabolites but, as predicted by *Popper* in 1975, three anecdotal cases of hepatocellular carcinoma, one German (*Gokel et al.* 1976) and two British PVC workers (*Fox and Collier* 1977), have now also been observed after exposure to VCM. It may be mentioned that a review of the distribution of primary liver cancer in the Province of Quebec covering the period 1969-1972 showed a preponderance of adult male cases in urban areas clustered in the district of Trois-Rivières in congruence with the distribution of the plastics industry, a coincidence which calls for further investigation of a possible exposure to industrial carcinogens (*Jacob and Thériault* 1975).

Not included in the NIOSH register are several anecdotal cases of ASL, capillary and cavernous angiosarcoma of the liver and haemangiosarcomatosis of sites other than the liver, for which a relation to occupational or even possibly residential exposure to VCM has been discussed (*Noria et al.* 1977; *Brady et al.* 1977; *Dor et al.* 1975; *Wallnöfer and Zinnagl* 1977).

Although of undetermined relevance, it should finally be mentioned that, in addition to hepatic fibrosis, varying degrees of interstitial fibrosis of the pancreas were noted at autopsy in four German workers (cases 19, 23, B and the above-mentioned

patient with both angiosarcoma and hepatocellular carcinoma). Fibrosis of the testes was observed in three cases (19, 29, B), and Roche et al. (1978) also reported fibrosis/hyalinosis in vessels of skin, heart, lungs and intestinal wall.

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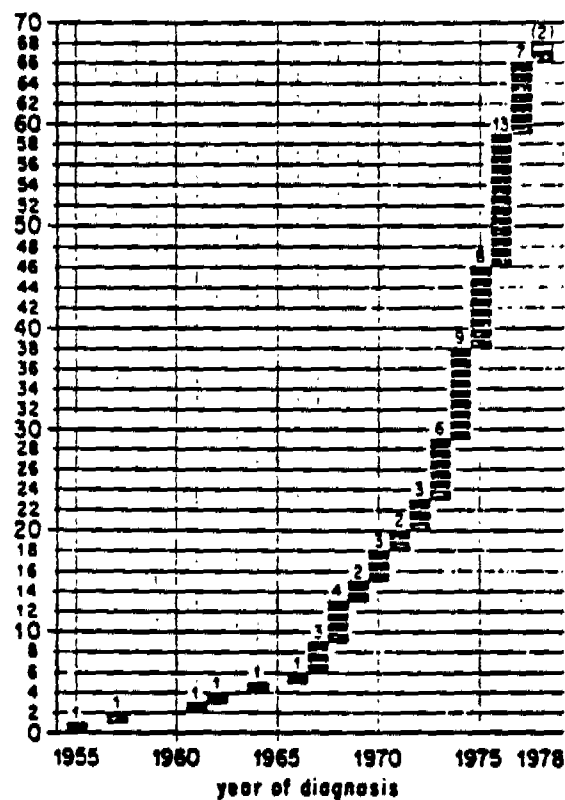


Fig. 7. Cumulative number of cases of ASL among PVC production workers reported to NIOSH up to August 1978, arranged according to year of diagnosis (data from Spirias and Kaminski 1977, 1978)

4.3.2 Clinical Manifestations

The clinical symptomatology of usually multicentric ASL is unspecific. Gradually declining general health and loss of weight combined with ill-defined upper abdominal discomfort and slight epigastric or right upper quadrant pain are usually the first symptoms. Recurrent bleedings from oesophageal varices may have been antecedent events in patients with portal hypertension who otherwise felt fairly well. In a number

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of cases, the tumour first came to attention with massive, often fatal, intraperitoneal haemorrhage. Important tender hepatomegaly (hepatosplenomegaly), slight jaundice and occasionally development of moderate ascites and oedema were observed. Except for mild to moderate hyperbilirubinaemia, some elevation of serum levels of alkaline phosphatase and gamma-glutamyl transpeptidase and only slightly abnormal levels of serum transaminases, the spectrum of biochemical tests is hardly revealing. Alpha-feto-protein determination has not been helpful in the diagnosis. Ultrasonography, scintigraphy, hepatic angiography and, notably, computer tomography of the upper abdomen are the diagnostic procedures of choice if ASL is suspected.

A technetium-^{99m} liver scan visualizes intrahepatic tumour defects (Biersack et al. 1977b) together with abnormal splenic fixation, but peripheral defects of uptake may be difficult to interpret (Whelan et al. 1976). Characteristic features of angiography are a normal-sized hepatic artery with possible displacement caused by tumour enlargement, a certain degree of central hypervascularity of the tumour, a peripheral tumour stain, and puddling of contrast medium persisting into the late venous phase. In addition, varying degrees of peliosis hepatis may be observed in some cases. However, even repeated hepatic angiography may fail to confirm the suspected diagnosis, as was evident in one case reported by Roche et al. (1978).

The example of a 54-year-old polymerization worker who died of metastasizing angiosarcoma of the liver in February 1980 may serve to illustrate the clinical course. In 1972/73, after an exposure of 18 years' duration, we found him to suffer from Raynaud's phenomenon and noncirrhotic portal fibrosis and portal hypertension with splenomegaly and moderate thrombocytopenia. Despite termination of exposure, there was progressive splenomegaly and development of massive oesophageal and gastric

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Fig. 8. Computer tomography showing a large, irregular, hypodense angiosarcoma of the liver involving both lobes. Courtesy of Professor Thum, Department of Radiology, University of Bonn

varices during the following years with repeated episodes of bleeding which required (successful) sclerosing therapy (major surgery was declined by the patient). In August 1979 he presented again with recurrent epistaxis and slight but permanent epigastric and upper right quadrant pain, but declared that he felt otherwise fairly well. He complained about a sharp localized epigastric pain on sneezing. There was marked splenomegaly, and an ill-defined hard mass was palpable in the epigastrium. Apart from moderate elevation of alkaline phosphatase and borderline hyperbilirubinemia, biochemistry was normal. Computer tomography showed a large irregular hypodense tumour mass in the liver, involving both right and left lobes (Fig. 8), which became practically isodense after intravenous injection of contrast medium. A liver scan corroborated the tumour defect. Shortly after this there was mounting evidence of brain involvement and rapid deterioration. Computer tomography now revealed multiple brain metastases (Fig. 9). Autopsy confirmed the tentative diagnosis of metastasizing angiosarcoma of the liver (Fig. 10).

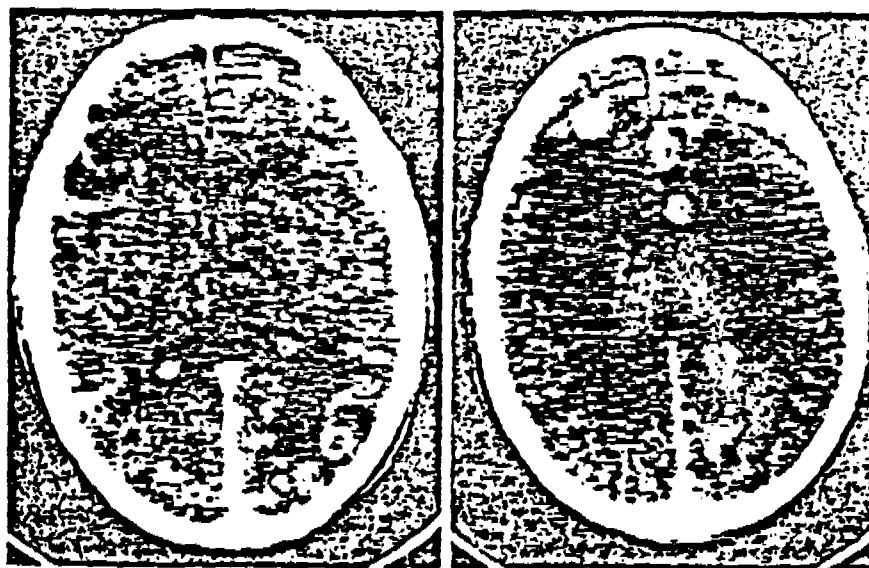


Fig. 9. Computer tomography showing multiple brain metastases of angiosarcoma of the liver. See text. Courtesy of Professor Thum, Department of Radiology, University of Bonn

4.3.3 Peritoneoscopy

Little information is available in the literature concerning the peritoneoscopic aspect of VCM-induced ASL (Roche et al. 1978). It may be impossible to make a diagnosis of the initial phase of ASL in VCM-exposed workers by peritoneoscopy and needle biopsy of the liver, as documented in one of our patients who died of multicentric ASL

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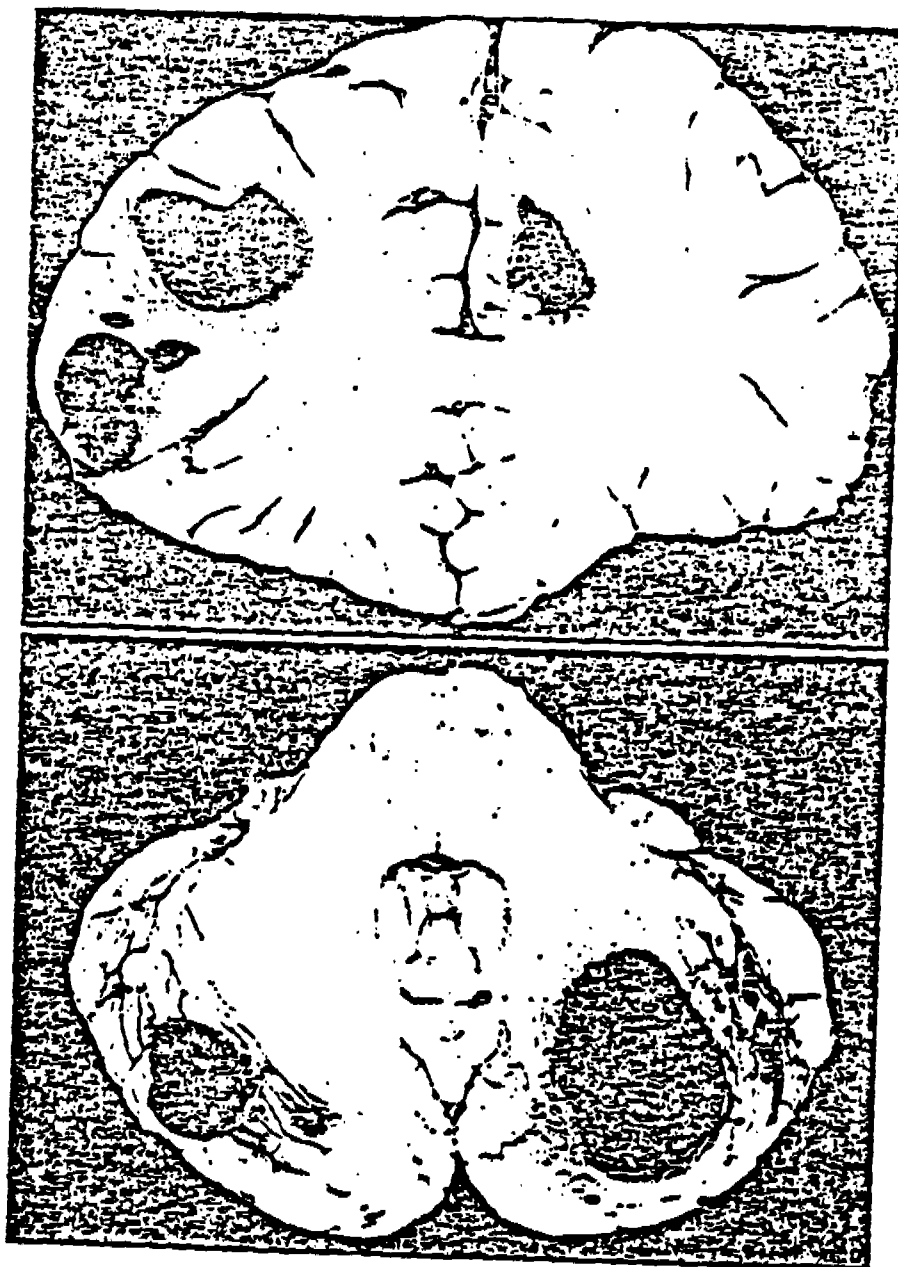


Fig. 10. Multiple brain metastases of angiosarcoma of the liver. Courtesy of Professor Gullotta, Institute of Neuropathology, University of Bonn

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11 months after peritoneoscopic diagnosis of severe hepatic fibrosis (case 19; see also Leibach and Marsteller 1977). In addition to the findings described in connection with hepatic fibrosis, there may be hypervascularized or cystic tumour formation visible on the surface of a nodular, quasi-cirrhotic liver, or a gross aspect resembling hepatic metastases if the vascular malignancy involves the superficial regions of the liver. It should be stressed here that needle biopsy is absolutely contraindicated if there is any suspicion of ASL.

4.3.4 Gross and Histological Morphology

The liver is usually markedly enlarged. Liver weight in cases of ASL ranged from 1600 to 7300 g (Thomas and Popper 1975; Roche et al. 1978). The gross appearance of angiosarcoma of the liver is mostly that of large bulky, irregularly shaped cystic tumour masses; a multinodular form with numerous, sometimes umbilicated nodules, is less often encountered. Extensive haemorrhagic and necrotic areas or solid and spongy portions of tumour tissue replace much of the liver parenchyma. Rupture of large cavernous cysts may cause fatal intraperitoneal haemorrhage.

Thomas et al. (1975) and Thomas and Popper (1975) distinguished four basic developmental patterns of histomorphology of ASL, which can be found in different portions even of the same tumour and appear to represent stages of progressive evolution: sinusoidal, papillary, cavernous and anaplastic patterns. Indistinct areas of transition and merging of patterns can be observed.

Dilated sinusoidal spaces lined by hypertrophic and hyperplastic sarcoma cells with pleomorphic, elongated, hyperchromatic and often bizarre nuclei characterize the sinusoidal pattern, which is the most frequent type. Tumour cells of varying differentiation envelop liver cell plates and may invade enlarged and fibrosed portal tracts, accompanied by proliferation of bile ductules (Fig. 11). In papillary angiosarcoma atrophy of liver cells results in larger and more irregular blood-filled vascular spaces, into which loose papillary strands of surviving hepatic cords on an axis of connective tissue project, lined by sarcomatous cells (Weinbren 1976). Even larger blood-filled spaces are seen in the cavernous type, where they may be surrounded by thick fibrous walls. In a smaller percentage of cases, solid areas or nodules of anaplastic sarcoma are found, resembling solid spindle-cell sarcoma, or even suggesting an epithelial type of tumour. Gedigk et al. (1975) also observed a reticulosarcomalike pattern. The differentiation of the tumour cells varies widely: it ranges from the inconspicuous endothelial lining cell type to irregularly shaped, grossly distorted giant-cell forms. Morphologically, vinyl chloride-related ASL cannot be distinguished from ASL associated with other aetiological factors or from the cryptogenic type (Popper et al. 1978).

In tumour-free portions of livers with angiosarcoma widely varying degrees of excess formation of fibrous connective tissue are usually observed, analogous to that seen in nontumorous livers of heavily exposed persons. Fibrosis of enlarged portal tracts with modest proliferation of bile ductules, mostly only scanty infiltration of lymphocytes and occasional formation of perlobular septa or thin connective-tissue septa extending into the lobular parenchyma can be found. A more or less conspicuous intra-lobular, perisinusoidal fibrosis is often detected only by special staining methods for collagen or reticulin fibres. As a rule, irregular focal or nodular fibrotic thickening of

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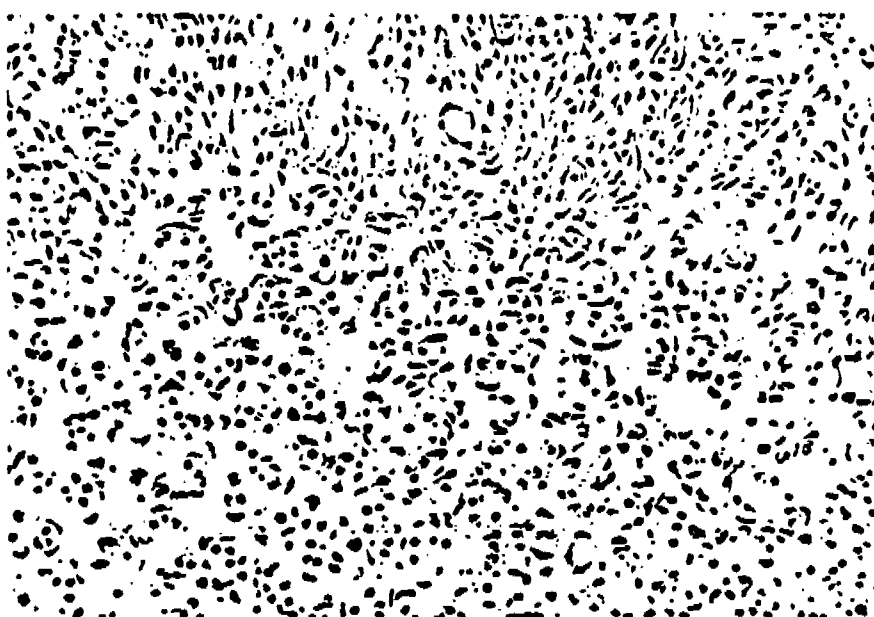


Fig. 11. Angiosarcoma of the liver (upper part of photomicrograph) invading adjacent liver parenchyma (case 14 = D1; see Table 13). Note hyperplastic and hyperchromatic nuclei of proliferating neoplastic lining cells enveloping hepatic cords. Reproduced by permission, Ann NY Acad Sci 246: 278-285 (1975). Courtesy of Professor Gedick, Institute of Pathology, University of Bonn. H & E, x 250

of Glisson's capsule is present: these fibrotic capsular areas may extend into the underlying parenchyma and may connect with adjacent enlarged subcapsular portal tracts. The cellular and nuclear size of hepatocytes may vary widely; groups of binucleated or even multinuclear parenchymal cells with abundant cytoplasm are seen. Focal proliferation of sinusoidal lining cells may be encountered, especially within foci of sinusoidal dilatation.

In connection with conspicuous sinusoidal dilatation, two types of focal hyperplastic precursor lesions were described by Popper et al. (1978):

1) Poorly circumscribed foci of hyperplastic, often binucleated hepatocytes with increased number of various sinusoidal lining cells and only insignificant increase of reticulum framework.

2) Almost nodular areas of conspicuously hyperplastic and hypertrophic hepatocytes with more pronounced variation of markedly increased sinusoidal cells without degeneration or necrosis of liver parenchyma, but accompanied by excess formation of reticulum framework and compression of surrounding parenchyma.

The transition of sinusoidal lining cells to angiosarcoma cells is characterized by increasing atypia and anaplasia of these proliferating endothelial cells accompanied either

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by formation of excess connective tissue or by accentuation of sinusoidal dilatation leading to primary peliosis. Involvement of portal areas in the evolution of angiosarcoma results in considerable fibroplasia and formation of hyalinized collagen together with proliferation of bile ductules. In occasional cases connective tissue bridging between portal tracts or between portal tracts and central veins with subdivision of lobules followed by rearrangement of hepatocytic plates may lead to a cirrhotic picture.

4.3.5 Therapy

The multicentric development of ASL (Thomas and Popper 1975) as well as the diffuse spread of the tumour usually encountered by the time of diagnosis precludes effective surgical or radiation therapy in the majority of cases. A survival period of two years after surgery (Berrod et al. 1978) or chemotherapy (Dannaher et al. 1979) is a rare exception. Results of systemic chemotherapy studied in a small group of five patients showed that, at best, quality and duration of survival may improve to a very limited extent (Dannaher et al. 1979). At present, no generally accepted guidelines for chemotherapy are available.

4.3.6 Risk Assessment

When in the United States 13 white male cases of ASL had been detected from 1961 to May 1974, among an estimated total population of VCM polymerization workers of roughly 20 000, a risk ratio (ratio of observed to expected cases) for this population of at least 400:1 was calculated (Heath et al. 1975). This calculation was based on data from the National Cancer Institute's Third National Cancer Survey (1969-1971), which expected for the total United States population an annual incidence of this tumour in the order of 0.014/100 000. This would have meant only about 0.03 cases per 20 000 polymerization workers within a 10-year period. Dose-response and attendant biotransformation data on experimental animals have since been used to elaborate several different models of extrapolation to man. These were calculated with reference to relative body surface areas, for estimating the risk of ASL in human populations exposed to VCM and for establishing guidelines to assist the research for 'realistic safe doses' that do not affect the average lifespan of a person exposed (Schneiderman et al. 1975; Gehring et al. 1979, 1978; Woods 1979). Gehring et al. (1979) consider a probit percent model to be a reliable tool for risk prediction, which works without the assumption of a threshold. They predicted a cancer risk of 1.5 cases of ASL in 100 000 000 workers on exposure to the current National Standard in the United States of 1 ppm VCM 8 h/day, 5 days/week, for a 35-year working life, an incidence which does not significantly deviate from the spontaneous incidence rate. A linear model modified by adjustments for differences in the rate of inhalation, distribution, metabolism, cell proliferation and tumour latency times between rats and humans was described by Woods (1979). This model arrives at an incidence of 3.9 cases per 100 000 000 workers after a lifetime exposure to 1 ppm. Much controversy, however, about the validity of risk extrapolation from animal experiments to man and from high- to low-level exposure and the problem of threshold doses has been voiced (Maugh 1978; Hooper et al. 1979; Schneiderman 1979; Weigert 1979; Reitz et al. 1979).

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Results of a recent survey by Brady et al. (1977) indicated that for New York State (excluding New York City), a highly industrialized area, the annual incidence rate of ASL during the 6-year period from 1970 through 1975 was 0.25 per million residents. This considerably exceeded the national average rate of 0.14 per million per year in the United States. In a concomitant case-control study, 26 patients with histologically confirmed ASL were found in the study area from 1958 to 1975, and 7 of these had had documented long-term exposure to either As, ThO₂ or VCM. Five (all female) of the remaining 19 patients lived at a distance of 500–1500 feet from VC fabrication or polymerization facilities for long periods. No pertinent exposure or residential history was obtained from the other 14 patients. Discharge of unreacted monomer into the environment as result of losses in the PVC production process was estimated to have exceeded 200 million pounds annually, most of which escaped into the atmosphere with lesser amounts dissolved in water effluent (Schweitzer 1975). Concerning the order of magnitude of ambient exposure beyond the work place, i.e. outside the industrial setting, an average annual exposure concentration of 17 ppb was estimated for the 4.6 million persons throughout the United States who resided within a 5-mile radius of vinyl chloride emission sources (Kuzmack and McGaughy 1975). If the risk assessment model elaborated by Woods (1979) is applied to this population of 4.6 million people, the estimated incidence of angiosarcoma per year would not be above expected background levels.

4.3.7 Mortality and Cancer Morbidity Studies

For a tumour disease as rare as angiosarcoma of the liver even quite small increases in hazard over background levels should be detectable (Doll 1975). The situation with the common types of cancer is far more difficult. Since 1974 a number of mortality studies of VCM-exposed populations have suggested that in humans long-term exposure to VCM may also be associated with cancer of sites other than the liver, notably the lungs, and the lymphatic and central nervous system (Monson et al. 1974; Ott et al. 1975; Tabershaw and Gaffey 1974; Nicholson et al. 1975; Wagoner et al. 1976; Waxweiler et al. 1976; Nicholson 1977; Buffler et al. 1979). Epidemiological studies of British workers failed to confirm this suggestion (Duck et al. 1975; Duck and Carter 1976; Fox and Collier 1976, 1977), as did a prospective study of a VCM/PVC-exposed cohort of 1613 employees of a West German chemical plant (Frenzel-Beyme et al. 1978). Criticism of design and interpretation of some of the studies has been voiced (Falk et al. 1974b; Purchase and Williamson 1974; Reger 1977; Daldorup 1975; Berry and Rossiter 1976). A follow-up of all VCM-exposed persons (750 traced) ever employed at the one Swedish factory, which started operation in 1945, for mortality and cancer morbidity patterns revealed a fourfold excess of pancreas/liver tumours but no deviation in the number of brain tumours from the expected level (Byrén et al. 1976).

In addition to the three extensive mortality studies of Tabershaw and Gaffey (1974), Waxweiler et al. (1976), and Fox and Collier (1977), a fourth comprehensive epidemiological study (Reini and Weber 1976) was completed in 1977 by Reini et al. (1978), which included three study populations from 11 VCM- and PVC-producing factories in the Federal Republic of Germany, covering the period from before 1959

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through 1974: (a) 7021 workers engaged in the production of VCM and PVC; (b) 4910 chemical workers from the same plants not exposed to VCM; and (c) 4007 workers engaged in PVC manufacture. Not included were non-German workers of Mediterranean origin. This German study permits comparison not only with the mortality ratio of the total male population but also with a comparable occupational group exposed to VCM. With regard to the 'healthy worker effect' (McMichael et al. 1975), overall mortality was elevated for the VCM-exposed population (group a), but not for the other chemical workers (group b). Apart from the markedly elevated standardized mortality ratio (SMR) for malignant liver tumours (1523), which proved to have been closely related to the duration of exposure, a significantly elevated SMR was found for tumours of the lymphatic and haematopoietic system (214). The group of chemical workers not exposed to VCM (b) also showed a significant elevation of the SMR for liver tumours (401), a result that deserves further investigation. No significantly increased risk was found concerning tumours of the central nervous system or the respiratory tract.

It has already been mentioned (Sect. 2.2.10) that an excess mortality from brain tumours (SMR 535) was recorded among PVC workers engaged in manufacture at one of two plants: in the second plant an elevated SMR (434) for liver tumours was found. At present, there is no explanation for the increased SMR for accidents found in the VCM-exposed population, particularly during the period 1970 through 1974, about 40% of deaths having occurred in ex-PVC workers. A recalculation of the available data would have been necessary for the evaluation of a conceivable influence of VCM on vigilance.

As an addendum it may be noted that determination of plasma carcinoembryonic antigen titre (CEA) in 200 Canadian PVC production workers (mean duration of employment: 10 years) showed a more than threefold higher frequency of levels above 10 ng/ml than in a normal healthy population (1.7% vs. 0.5%) (Page et al. 1976). Levels of CEA were also determined in 1363 workers of five different VCM polymerization (3) and PVC processing (extrusion) plants (2) in the United States (Anderson et al. 1978). After removal of possible confusing factors (smoking, alcohol intake, past medical history), it emerged that the distribution of CEA titres among the polymerization workers was significantly different from that in the extrusion plant group and in a nonexposed reference group. Significant differences were also found for two of six job categories examined (polymerization and maintenance) compared with extrusion workers and the reference group. However, the usefulness of the CEA titre as a predictive indicator of possible increased risk seems doubtful.

4.4 Miscellaneous Aspects

4.4.1 Thrombocytopenia and Platelet Function Tests

Thrombocytopenia in chronic VCM intoxication was first mentioned – rather parenthetically and without further comment – in a paper published by Antonovychenko in 1968. Later Jühe et al. (1973) noticed that each of the first 13 autoclave cleaners referred to them during 1972 from a West German plant because of suspected skin and

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bone lesions presented with mild to marked thrombocytopenia ($30-119 \times 10^9$ /litre). Bone marrow aspirates in 6 patients permitted exclusion of disturbed platelet formation or osteomyelofibrosis/sclerosis, but in 12 of them splenomegaly was found. Except for slight reticulocytosis in 8 and leucopenia in 5 of the workers, other haematological tests were negative. The reduction of the number of leucocytes and platelets as well as reticulocytosis appeared to be attributable to splenomegaly, but further studies on the nature of thrombocytopenia were thought necessary, and it was suggested by the authors that a decrease in the number of platelets might serve as an early and easily detectable symptom. The high prevalence of thrombocytopenia (as determined by phase-contrast microscopy) found later on detailed analysis of platelet function and other parameters of blood coagulation in the total cohort of PVC production (and also fabrication) workers from this plant strengthened this suggestion (Bachner et al. 1974a, b, 1975a, b, 1976; Sehn-Bachner and Etzel 1977). Wegman (1975) also commented upon abnormal platelet counts in 13 of 37 PVC fabricating workers who had only handled PVC powder which, however, might have contained substantial amounts of residual monomer. In contrast, Lillis et al. (1975) detected thrombocytopenia in only 1 of 354 polymerization workers, but an electronic cell counter was used for platelet counts (personal communication).

According to Sehn-Bachner and Etzel (1977), the mean platelet count in a cohort of 132 PVC polymerization (and processing) workers was significantly lower than that in a nonexposed control group of 150 healthy men. As could be expected, Bachner et al. (1975b) also demonstrated a positive correlation between the degree of thrombocytopenia and the prevalence of an enlargement of the spleen (palpable splenomegaly or spleen size determined by selective scintigraphy with ^{199}Hg -bromo-mercury-hydroxypropane-labelled red cells) in 70 PVC polymerization workers (see Table 19). It ap-

Table 19. Prevalence of enlargement of the spleen^a among 70 PVC-polymerization workers in relation to increasing degrees of thrombocytopenia (Bachner et al. 1975a)

Group	No. of workers examined	Platelets ($\times 10^9$ /litre)		Enlargement of the spleen
		Range	Mean	
A	14	> 130	168	3 (21%)
B	24	100-130	117	11 (46%)
C	25	70-99	87	19 (76%)
D	7	< 70	44	6 (86%)

^a As determined by palpation or by selective spleen scintigraphy.

pears, however, that the development of thrombocytopenia is not dependent on the presence of splenomegaly since we observed mild thrombocytopenia ($100-120 \times 10^9$ /litre) in a small number of workers in whom spleen size was definitely within normal limits on selective spleen scintigraphy (Milzflächenindex $< 4.5 \times 10^3$ according to Fischer and Wolf 1963).

Thrombocytopenia was accompanied by abnormalities in platelet function tests. There was an increase in the number of large ($> 10 \mu\text{m}$) 'juvenile' platelets (increased

platelet spreading), enhanced response (platelet aggregation) to addition of ADP and collagen (Bom test) and increased availability of phospholipid-containing platelet factor 3 (Bachner et al. 1975a). This pattern was thought to be compatible with the notion of an increased turnover rate due to derangement of microcirculation (CDIC) in liver and spleen and defective reticuloendothelial system (RES) clearance of activated clotting factors (Bachner et al. 1974b). Ward (1976) and Ward et al. (1976) suggested that thrombocytopenia could be construed as confirmatory evidence of an immune complex disorder. Heusermann and Stutte (1977a) noted unusual focal aggregation of platelets in klatsch preparations of spleen tissue and increased platelet pooling (platelets trapped within the subsinusoidal meshwork of pulp cords) in the red pulp of the spleen on electron microscopy as well as phagocytosis of thrombocytes by sinusoidal macrophages. Schaffner et al. (1976) found platelet thrombi in and around hepatic sinusoids in mice after exposure to VCM. A direct toxic action of VCM (or metabolites) on the bone marrow has not been demonstrated so far.

Although the pathogenesis of thrombocytopenia in VCM-induced disease is not fully understood, it seems at present most likely that it is caused by increased turnover and consumption of platelets within the abnormal vascular spaces of the liver and spleen. A similar type of consumption coagulopathy was described as complication of spontaneous haemangiosarcoma of the liver by Truell et al. (1973). A haemostatic defect more complex than mere pooling and destruction of platelets in the enlarged spleen has also been commented upon in the paper by Gerrits et al. (1974) in connection with splenomegaly of various noncirrhotic origin.

4.4.2 Central and Peripheral Nervous System

Miscellaneous nonspecific and somewhat indefinite symptoms have been described in connection with chronic inhalational exposure to VCM in PVC-production workers, such as dizziness, disorientation, blurring of vision and memory, headache, irritability, excessive fatigue and somnolence, sleep reversal or insomnia and other pseudoneurasthenic symptoms (Sucht et al. 1963, 1975; Schottek 1969; Lillis et al. 1975 and others). This prenarctic syndrome was interpreted as a manifestation of a potentially reversible acute toxic encephalopathy. Its danger to the individual was thought to lie mainly in resultant inadequate reactions to critical situations (Schottek 1969). However, Vale et al. (1976) reported that several individuals in a group of 95 comparatively young ex-workers, the majority of whom had no other symptoms, complained of fatigue, headache, listlessness and depression, with onset of symptoms having been delayed as long as 2 years after cessation of employment.

With reference to such 'pseudoneurasthenic complaints', which may be interpreted as the mildest degree of a toxic encephalopathy, Penin et al. (1975) examined a group of 21 autoclave cleaners at varying intervals after cessation of exposure, all of whom presented with other (cutaneous, angioneurotic, hepatic) manifestations of vinyl chloride disease. Clinical symptoms of a more or less distinct encephalopathy (including cerebellar ataxia in 4) were found in all but one of them. EEG recordings were normal in only five of these patients; in the others, paroxysmal, dysrhythmic or a so-called subvigil electroencephalogram was observed. Evidence of distal polyneuropathy, found in 19 patients, was attributed in the first place to an abnormal peripheral circu-

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lation with resultant hypoxic damage. The pathogenesis of a possibly VCM-induced encephalopathy is not clear. It would be conceivable that clinical and bioelectric alterations found in some patients, in whom portosystemic encephalopathy could be excluded, may have been due to toxic or hypoxic brain damage. However, no other convincing evidence has so far emerged to indicate that chronic irreversible cerebrotoxic damage may have resulted from prolonged exposure to VCM, notwithstanding the possibility of an induction of brain tumours.

4.4.3 Pulmonary Changes

The suspected development of nonmalignant pulmonary changes due to VCM and/or PVC dust exposure is still a matter of controversy. Soon after VCM was recognized as a potent carcinogen, three groups of employees ($n = 290, 250, 445$, respectively) from three large North American PVC-producing plants (A, B, C), characterized by different duration and levels of past environmental exposure to VCM as well as to PVC dust, were studied with respect to chest x-ray film abnormalities and pulmonary function defects as assessed by spirometry and determination of maximum expiratory flow volume (Miller 1975; Miller et al. 1975; Lillis et al. 1975, 1976, 1977). All cases with previous exposure to asbestos, silica or coal dust had been excluded in these studies. Unexpected linear, reticular and, less often, rounded opacities on chest x-ray films were found in about one-fifth of the two groups of employees from plants A (highest exposure) and B (22.7% and 18.3%, respectively), but in only 4.3% of those from plant C, with the lowest exposure level. The prevalence of these radiological abnormalities, for which no pathogenetic explanation was available, was found to be significantly increased with longer duration of VCM-PVC exposure (more than 10 years), but the prevalence of a positive history of smoking, although identical in both groups A and B, was also found to be significantly higher in workers with abnormal chest x-ray plates. The overall prevalence of a positive history of chronic bronchitis (British Medical Research Council criteria) was 20.4% in group A (highest exposure) and 16.0% in group B, although group B was significantly older. The somewhat higher prevalence of chronic bronchitis in workers with abnormal chest x-ray plates did not attain statistical significance.

On the other hand, age did not appear to be an important factor. Pulmonary function tests showed a strikingly high prevalence of obstructive changes, but since both smoking and age were related to changes in pulmonary function, it appeared difficult to isolate potential specific effects of occupational exposure to VCM and PVC dust. A restrictive pattern was found in 9.3% of group A and in only 2.3% of group B, although group A was significantly younger. In conclusion, this extensive study, including a total of 985 workers exposed in the past to VCM as well as PVC dust, may point to a potential multiple factor effect of smoking and VCM-PVC exposure. In this connection, it is of interest to note that according to a cohort study of mortality among VCM polymerization workers the SMRs for respiratory cancer as well as for 'other respiratory disease' were found to have been in excess of expected figures (156 and 176, respectively) (Waxweiler et al. 1976).

Bronchopulmonary changes thought to be due to long-continued, intense exposure to PVC dust were observed by several authors (Parneggiani and Sassi 1955; Broussard

1969; Szende et al. 1970; Vertkin and Mamontov 1970; Frongia et al. 1974; Darke 1976; Arnaud et al. 1978). Considerable exposure to PVC dust is the rule in the drying, bagging and storage areas of PVC-producing plants. Photographs contained in Karstadt's paper (1976) give a general idea of the potential dust exposure. Measurements of the concentration of PVC dust at various sites of the bagging operations were reported as long ago as 1955 by Parmeggiani and Sassi. In 1969 Broussard mentioned the possibility of development of chronic bronchitis caused by the inhalation of PVC dust. The insoluble and inactive dust particles were thought to accumulate in the lungs blocking alveolar spaces and being taken up by alveolar cells. This could lead to elimination of these cells via lymph vessels to regional lymph nodes, with either enlargement of the hilar region or a micronodular aspect of interstitial pulmonary fibrosis without hilar lymph node enlargement but progressive respiratory insufficiency.

Szende et al. (1970) reported the case of a 31-year-old worker who presented with severe dyspnoea; a chest x-ray examination revealed diffuse micronodular pulmonary lesions. He had been engaged for only 1 year in shovelling PVC powder at a processing factory. Lung biopsy revealed moderate diffuse fibrosis and small focal granulomatous lesions containing ovoid or polygonal birefringent foreign material which could be eluted by treatment with a known solvent of PVC. Microscopic examination of PVC dust particles collected at the patient's place of work showed them to be morphologically identical with the particles found in the patient's lungs.

Another anecdotal case of pneumoconiosis after 23 years of employment in a PVC bagging area, with radiological evidence of diffuse micronodular infiltrates and granulomatous lesions found in a lung biopsy identical with those recorded by Szende et al., was published by Arnaud et al. in 1978. Histology of open lung biopsies in 1 of 14 VCM-exposed British workers, who complained of breathlessness, revealed focal alveolar wall thickening with macrophages in alveolar spaces and increased reticulin and collagen on electron microscopy (Darke 1976). Although chest x-ray appearances were normal and routine respiratory function tests showed only slightly impaired CO₂ diffusion in six individuals, perfusion and ventilation scans revealed strikingly abnormal pictures, including marked perfusion defects of upper lobes. Darke pointed out that some of the men worst affected had been engaged in the polymerization of 'plastisol', a very fine PVC powder with particle size around 0.5 µm.

Selikoff (1976) called attention to results obtained by Frongia et al. (1974), who observed significant histopathological changes in the lungs of guinea-pigs and rats exposed for 2-7 months to inhalation of the airborne PVC dust in a PVC bagging area. Lesions began to appear at 2 months of exposure (alveolar histiocyte-macrophage reactions); they proved to be fairly marked after 4 months, with appearance of foreign body giant cells, and proceeded to development of large interstitial granulomatous foci. Vertkin and Mamontov (1970) who examined 96 workers engaged in the manufacture of articles made from PVC powder, also found a considerable proportion of them were suffering from functional and morphological alterations of the broncho-pulmonary system, which they ascribed to their exposure to PVC dust. They quoted results of earlier animal experiments conducted in 1963 by Golovaryuk and later by Shlyakhterskii. These last authors had apparently shown that exposure of animals to PVC dust may lead to the development of chronic pneumonia and eventually to a sort of mild fibrosis of the lungs.

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Certain types of PVC dust (one of two samples tested) were found to exhibit a strong haemolytic potential due to the presence of an undetermined but readily soluble surface-associated agent which was not VCM (Richards et al. 1975). These authors also studied the effect of the haemolytic sample of PVC dust on lung fibroblast cultures, but they did not obtain any significant results.

Contrary to earlier indications (Lange et al. 1974a) and despite continued efforts we failed to detect any significant restrictive changes of pulmonary function in the overwhelming majority of patients we had occasion to examine.

It may be of interest to note that Maltoni et al. (1974b) reported a high prevalence of pathological changes of respiratory epithelium (squamous metaplasia, squamous dysplasia, typical and atypical adenomatous proliferation) in sputum samples from employees of Italian VCM-PVC factories.

Nevertheless, contrary to the now well-established role of VCM in the production of nonmalignant lesions of bone, skin, small vessels, liver and spleen, it is still open to debate precisely what importance can be ascribed to pulmonary changes within the spectrum of VCM-induced disease.

4.4.4 Genetic Effects of VCM

The discovery of the carcinogenic properties of VCM also stimulated interest in its mutagenic potential. A number of studies have been carried out that demonstrated a mutagenic response to VCM or its metabolites in microbial test systems. Point mutations due to base-pair substitution have been produced in various strains of *Salmonella typhimurium* by VCM in the presence of animal and human liver microsomes as a system of metabolic activation (Rannug et al. 1974, 1976; Bartsch et al. 1975a, 1976; McCann et al. 1975; Malaveille et al. 1975; Garro et al. 1976). Mutagenicity of VCM metabolites was also demonstrated in yeast strains (Loprieno et al. 1976, 1977; Shahin 1976) and in mammalian cells (Huberman et al. 1975). In comparison to nonexposed controls, a significantly higher incidence of chromosomal aberrations (fragmentation, rearrangement) in lymphocytes of workers occupationally exposed to VCM was reported by Ducatman et al. (1975), Funes-Cravioto et al. (1975), Purchase et al. (1975, 1976), and Fomenko et al. (1976). Fleig and Thiess (1974) had failed to demonstrate an increased rate of chromosomal aberrations in six chemical engineers and four PVC fabrication workers. As to the influence on germ cells, Purchase et al. reported that no dominant lethal effects were seen in fetuses of female mice mated with males which had been exposed to 3000, 10 000 and 30 000 ppm VCM for 5 consecutive days. This, however, does not absolutely exclude genetic effects on human gonads. The outcome of pregnancy among wives of VCM-polymerization workers as against wives of rubber and PVC-fabrication workers (Infante et al. 1976a, b) and rates of congenital malformation per 1000 resident live births in three Ohio communities with PVC production plants have also been studied (Infante 1976).

As part of a larger survey of workers' health, interview questionnaires (Infante 1976a, b) showed that after paternal age adjustment a significantly higher incidence of fetal mortality subsequent to paternal exposure was recorded among the wives of VCM-exposed workers. This trend was found to be maintained after elimination of

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pregnancies in women who had more than two abortions. The findings of this study raised the question of possible genetic risks of VCM to man and led to the suggestion that germ-cell damage in the father through direct VCM exposure might be a possible explanation.

No clear-cut linkage of PVC production and increased occurrence of congenital malformations (primarily CNS malformations) emerged from preliminary studies in three Ohio communities with PVC production plants. But the need for further study of possible contributory factors was indicated (*Infante* 1976). In fact, none of the parents of affected children in Painesville, one of the three Ohio communities, had ever worked at either of the two PVC polymerization plants in Painesville or lived within two miles of these plants (*Edmonds et al.* 1975).

5 Conclusion and Outlook

The combined efforts of multiple disciplines have been necessary to arrive at the full recognition of the range of pathology associated with occupational exposure to vinyl chloride. It can only be hoped that the lesson from the vinyl chloride problem may help to bring about an increased awareness of the risks and hazards which are inevitably the consequence of an ever-expanding technology.

The importance of this lesson lies in its exemplary nature. A single substance of rather simple chemical structure, which was long held to be a comparatively safe compound, even by experts, turned out after all to be a carcinogen with a very long latency period for those who were heavily exposed to it. But its carcinogenic properties would most probably still have gone unnoticed if the resulting malignancy had been any cancer other than of an exceptionally rare type. Animal experiments in the early days later proved to have been broken off before the oncogenicity of this chemical compound could have been detected.

The lesson to be learned is that in future any new chemical which is to be widely introduced into the environment should be scrutinized closely, for a sufficient length of time, and with the aid of all available methods for the detection of potential carcinogenic effects. In addition, we should keep in mind that in industrial surroundings we almost never deal with a single compound, but with a very complex occupational environment whose carcinogenic potential is still a completely unresolved problem.

If currently adopted guidelines for industrial hygiene are strictly adhered to, there is reason to hope that initiation of new cases of VCM-induced angiosarcoma of the liver can be effectively prevented. Unfortunately, however, it can be expected that in view of the long latency period for tumour promotion additional cases will appear during the next decade.

Considering the ever-increasing complexity of environmental influences, future research will be faced with almost insurmountable obstacles in its endeavour to establish 'safe' levels for potentially hazardous chemicals. Promising areas for further studies in the field of vinyl chloride and allied compounds may be the problem of the interaction

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