

VC 00000 678
Tobolsan

47

Ergebnisse der
Inneren Medizin und
Kinderheilkunde

Advances in
Internal Medicine and
Pediatrics

Reference

Neue Folge

Herausgegeben von

P. Frick G.-A. von Harnack K. Kochsiek
G. A. Martini A. Prader

Mit 24 Abbildungen und 23 Tabellen



Springer-Verlag
Berlin Heidelberg New York 1981

R&S 117056

Vinyl Chloride-Associated Disease

W.K. LELBACH and H.J. MARSTELLER¹

Review ✓
Germany ✓
Homen ✓

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

¹ Department of Medicine, Director: Prof. Dr. H.J. Dengler, University of Bonn, FRG

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	Peritoneoscopy	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 toxic. It was later turned out that a careful evaluation of its toxicity might have been possible, considering its vapour phase and its reactive double-bond.

Today vinyl chloride is a major cause of cancer formation and data on its carcinogenicity are precisely a quarter of a century old. It is attributable to this new cancer with the shocking discovery that the monomer was found did not alert the workers engaged in the industry in 1949 (Tribukh

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

It should be stressed that it is not precise, an intermediate product, mainly in the mammalian metabolism, polymerization products (PVC) are released from the polymer. They contain unreacted VCM (PVC (thermal decomposition) toxicity of pyrolysis products mainly due to the release of VCM (Abar 1969; Dyer and Esch 1969) and only very small or none (O'Mara et al. 1971 cite

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 Abar* 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).

R&S 117059

89

... Portal
... chloride

... axis is a
... would help to
... carrying rather
... tially hazard-
... nt, this ac-
... tely for
... ill develop

... a thermo-
... begun
... chloride
... 960s to be

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 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:	<table><tr><td>mm Hg</td><td>10</td><td>100</td><td>692</td><td>2300</td><td>2660</td></tr><tr><td>°C</td><td>-87.5</td><td>-55.8</td><td>-15.8</td><td>+ 20</td><td>+ 25</td></tr></table>	mm Hg	10	100	692	2300	2660	°C	-87.5	-55.8	-15.8	+ 20	+ 25
mm Hg	10	100	692	2300	2660								
°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°C/4°C 0.99 at -25°C/4°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 *Saytsev* and *Glinsky* (who

succeeded
izing subst.

2.1.2 Production

Large-scale
oyi

R&S 117060

2)

C

$\text{CH}_2\text{Cl}-\text{C}$

VCM was
Thus, any le
tions in the
in the range
(IARC 197
when VCM
mayer 1967
in commer.
1966; Oster

In the c
conjectured
retrieved V
yses carried
sum of all i
genates) wa
reacted mon
in prepoly
the concentr
that even 10
methyl chlo
isobutane, n
ference in p

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

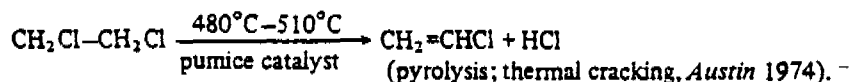
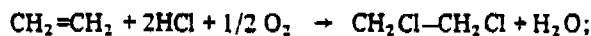
2.1.2 Production of VCM

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 (Lefaux 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.

yl chloride ($\text{CH}_2=\text{CHCl}$) is a gas with a faintly sweetish odour in air, which is slightly soluble in ether and is not very soluble in water. Its manufacture is usually employed as a gas, usually handled and stored at 101.3 kPa (1 Torr). Its properties are listed in Table 1. Its high specific gravity in water and the

boiling point -78.5°C

	2300	2660
8	+ 20	+ 25

at 760 mmHg

ref. 967:

R&S 117061
 stu ratically
 so prelim-
 oun eignault
 tain nyl

ous polymerization of
 i sunlight was first
 and Glinsky (who

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 a–c; *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 the fin. and m. Raw P (VKE 1 proxima The large en are then wet poly drying m merization, yieldi fine solid particles drying temperatur polymer. A cycl The solid polymer storage bins or sil dried powder con

R&S 117062

2.2.2 Methods of

Four different me PVC (*Frey* 1973).

Suspension Polymer which monomer (such as polyvin conjunction with b this method whi

Emulsion Polymer was added in the except that large are added. Emuls emulsifiers cannot

Bulk (Mass) Polymer the addition of oil The first reactor (second one is use solid state, to esse reaches a level of characterized by l good optical clari

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%–80%. The resins obtained by bulk polymerization are characterized by high purity and particle uniformity, resulting in an end-product of good optical clarity.

R&S 117063

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, calendaring, 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 (Aryapur 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 prenarcoctic symptoms (dizziness etc.)

Vi
per
in
clay
wal
tors
deg
and
were op
ed the fr
tion still
marily, th
those wo
(centrifug
ties of un
ventilatio
shipment
nomer, w
are driven

Table 2.

1 ppm
1 mg
(Parti
1 mg/litr
1 mg/m ³
1 ppm
1%

2.2.5 T

In the pa
nant mon
covers a
(Lefaux
lect as a
opened
became k

out in
1 percent-
fraction of
vinyl-

The co-
solvents

R&S 117065

compound-

products.
ducts is
pression
used in
the of
technica-
monomer
contained
gained
(foils)

screen-
and in
that re-
venings
of pollu-
area of
monitoring
g and
work en-
as etc.)

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 ('polycleaners'), 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

$1 \text{ ppm} = \frac{\text{Mol. wt.}}{1\,000 \times 24.45} \text{ mg/litre}$		
$1 \text{ mg per litre} = \frac{24.45 \times 1\,000}{\text{Mol. wt.}} \text{ ppm}$		
(Parry 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

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 Suciuc 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 odoriferous 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

Lower limit	
5 000–10 000	
5 000	
4 100	
3 500	
500	
400–500	
400	
400	

anaesthesia be
tic and lethal
oxygen; conce
however, that
cluded. In to
10% VCM to i
several hours t
commented up
mi. tic
3.5 R&S 1 (c
mn 10
Ost in
can 3
mai o
like lo
ami i
the n.

2.2.8 Effects

Some individu
listed in Table
without acute
symptoms such
adequate warni
exposure to hig
A 21-year-old
10 min after en
which had bee
cardiac enlarge
have been acut
which occurred
doubt that hear
found dead wirl

detonated
operating
concentrations
ing VCM

erties. Its
PVC
gas', which
roduction,
workers' re-
al evidence
mind, how-
chemicals
ual sensitiv-
of a certain

s practically
977a, b)
to-VCM
ppm for
sleepiness
ximately
he

971
R&S 117067
hai
the
lif
p
as
in l

inc
eye and
a concen-

midt and
centra-
oxygen

Table 3. Odour threshold

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

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 *Partz 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)	Baretta 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	5 min ^a (twice on each of 3 successive days)	2 of 6 subjects 'slightly heady'	Lester et al. (1963)
		1 of 6 subjects had reeling, swimming head, 'just like getting gas'	
16 000 ppm		5 of 6 subjects, various degrees of intoxication	
20 000 ppm		All 6 subjects had more intense symptoms of acute intoxication than at 16 000 ppm	
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 (Spirtas 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 (Ward 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 Rety et al. (1974).

2.2.9 Monitoring

During the field data on VCM was directed to an apparently 1954; Pleshchinskii and Gronsberg to a Russian polymerization concentration of 0.05–0.08 mg/litre (= 11 mg/litre (= 3.4

In the central air ranged from ppm, which was ventilation. The concentrations, some pursuit of improvement in the vicinity drying facilities concentrations of continued to be permitted concentrations.

In a plant the range of 0.0 ppm (2.93 mg/l) indication apparatus remarkable that the liver, although past have probable

Byrén et al. which occurred cated peak exposure between

Rumanian about 1 exposure. 300 Rumanian Greek resultec (Gitsios of the up to 11

R&S 117068

VCM

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; *Pleshchitsker et al.*, cited in *Filatova and Gronsberg* 1957) induced *Filatova* and *Gronsberg* 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

away from reactor walls during cleaning was placed, concentrations of up to 600 ppm were measured.

In the report of a World Health Organization (WHO) working group on vinyl chloride (IARC 1974) it was stated that in a reactor of 15 m³ (production of 4–5 tons of PVC per cycle) a crust of 4 kg PVC containing 3%–5% VCM can be formed on the inner surface. During the cleaning procedure 30%–50% of this VCM content is liberated. It was calculated that the probable concentration of VCM within the reactor after a 1-h cleaning operation was about 2700 ppm, but that it could be reduced to 90 ppm by 30 renewals of air per hour. In the past a polycleaner used to spend 4–5 h/day inside the reactor but later the introduction of (not fully sufficient) automated cleaning reduced manual cleaning procedures to shorter periods of 10–15 min following every 20th–30th reactor cycle. A Belgian company, where monitoring in the working area was started in 1967, claimed that measurements at various sites inside a 9000-litre autoclave during the manual cleaning operations had shown VCM concentrations varying between 50 and approximately 540 ppm, with a mean of 413 ppm (Hubler et al. 1977). According to data provided by Cook et al. (1971), VCM concentrations within the reactors prior to ventilation were in the order of 3000 ppm. The reactor cleaners usually did not enter the autoclaves until an aeration period of 15–20 min had reduced the VCM concentration to what was considered satisfactory limits. In the early days, this was tested either by 'sniffing at the manhole opening' (the lower limit of detection of VCM by its odour having then been accepted as 400 ppm) or by use of a flammable vapour indicator which required a minimum of 400 ppm for positive readings, equalling 4% of the lower explosive limit of VCM. Later more sensitive methods such as gas chromatography were said to have shown that VCM concentrations inside the reactors tended to be below 100 ppm during cleaning operations, but VCM released from the residue during scraping resulted in concentrations of 600–1000 ppm measured close to the hand.

The Dow Chemical Company started monitoring the work environment in 1950 by means of grab samples; continuous monitoring was installed in 1959. While time-weighted average (TWA) concentrations ranged from 10 to 385 ppm during this period (1950–1959), excursions up to 4000 ppm occurred, agreeing with employees' reports of experiencing dizziness while loading or unloading reactors (Orr et al. 1975). In a second unit with modernized equipment excursions up to 600–1300 ppm still occurred during the period of 1953–1959. In 1959, when toxicological data indicating adverse effects in animals exposed to 100–500 ppm VCM had become available (Torkelson et al. 1961), the Dow Chemical Company introduced a new 50 ppm guideline for the work environment. Excursions and peaks up to 500 ppm did continue. Measurements of TWA exposures for various specified job categories in two production units of this plant between 1950 and 1966 were presented by Orr et al. (1975). In 1968 BASF (West Germany) introduced continuous monitoring by infrared absorption spectrophotometry for VCM concentrations well below 500 ppm; in 1974 more sensitive equipment was installed and concentrations were kept below 25 ppm and later below 10 ppm, with occasional ceiling values of 70 ppm (Fleig and Thiess 1974).

In several surveys individual jobs were grouped into three exposure categories according to job classification to evaluate past exposure experiences (Spiras et al. 1975; Williams et al. 1976; Blendis et al. 1978). These exposure indices were: (a) light = less

Vinyl

than 5
ppm).
plants
sample
Estima
more c
average

Table 5
atmos
Chemie

1945–1
1955–1
1960–1
mid-197
197
197

a Acco

Equi
tions in
equipme
vidual ex
bination
(3) The l
ly specifi
ment she
peak con
for the d
Curre
compris
tion dete

lu
R&S 117070
on
asp
itr
al
b

E

Raw PVC
unreacted

600 ppm

vinyl chlor-
 ions of
 on the
 is liber-
 reactor
 need to
 and 4-5 h/
 ommated
 in follow-
 the work-
 le a 9000-
 ntrations
 /hublet et
 ations
 reactor
 20 min
 uts. In the
 ower limit
 by use of
 itive read-
 methods
 ns inside
 M releas-
 ppm

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	~200-400 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

R&S 117071

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 (Piver 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 Bruder 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-

consp
sponse
quantit
observ
progre
male P
find an
A r
two G
died re
lation
'health
overall
records

2.2.11

Industri
of expo
tion' or
industr
trati
erica
redic
t sh
ap
to
)
n
m

R&S 117072

red to t
The
not a se
should b
tently
available
new inf
list of M
various
so-called
tool for
ysis of th
In th
ppm in l

pes of raw
range
apes into the
riod, tempera-
polymer and,
976; Schütz
ry announced
10 ppm would
ologies (VKE
hich are now
ected mono-
d between
ation between

re which usu-
omer and,
tent of residual

cess.
ther-
lited
on-
in
lited
s up
77).
om)
ed
stadt

ust levels of
C resins was
ling units.
ely assumed
ays been con-

o have afflict-
though no
are observed.
us lesions such
enia and slight
I been em-
S, 1976a:
entical with
mage attribut-
onsidered suf-
hough the in-

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 35 000 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 (*Reinl 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 *Ziellhuis* (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

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

R&S 117074

Sw.

United Kingdom

USA

USSR

Federal Republic of Germany

Sources: Sn 73; IARC R 1977; Schui

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

which was based on carcinogenic properties of this chemical was re-evaluated (Schlichtkonzentration) in 1975. The TLV was originally set at 500 ppm in 1947.

Emergency standards summarized the conflict between industry and health in 1974.

Plants in the environment dissolved in water (Schweitzer 1975). In the ambient air near plants and 100–200 ppm were later used since these figures since (Schweitzer 1975) production facilities years of uncontrol-

either alone or mixed household and cosmetics, paint sprays, proposed as propellant and as a propellant since 1962 (Schweitzer 1975) of exposure for the health implications has been re-evaluated in closed rooms. persist for several

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 (Bridbord 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 Lierop and Stek 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 To of
3.1 Act R&S ity

Dunning the assess: concentr and Leake matteo et a anaesthesia, deep narc this range of exposure tive and haemorrhagic hepatocellular injury inducing substances (se

3.2 Chronic Toxicity

Torkelson et al. (1961) exposure to concentrati 4.5–6 months. All spec however, caused an incre histological changes in ti pigs and dogs. An incre in rats exposed to 20 00 (1963); no histological Gor'kij Institute were m exposure of experiment. mias, bradycardia, chang 0.05 mg/litre) for 5 mon creased secretion of cate posterior hypothalamus 3500–4000 ppm (9–10 of the cortex and the ant comitant changes in circ posure of rats and rabbit resorptive bone changes nervous system dysfunct available evidence for VC VCM should be suspected statutory maximal allowa cratic Republic) should b

Of particular importan Viola et al. 1971) with ex full year. It was only after

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 (*Patty et al. 1930; Peoples and Leake 1933; Schaumann 1934, 1938; Oster et al. 1947; Carr et al. 1949; Mastro-matteo 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 (*Vazin and Plokhova 1969b*) as well as increased secretion of catecholamines in rabbits and changes in the biopotential of the posterior hypothalamus (*Vazin 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 (*Vazin 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 (*Basalaev 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 *Viola's* experiments (1970a, b: *Viola 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

er (1975) pre-
registered for
stration. In
974, 229:855).
hypertension
plant in south-
(Reint and
ical Raynaud's
lysis who never
to make one
cans (*Bridbord*
ed from frequent
found to con-
bronchial cells

ngi nd
and t
was
ap om
ed n
mon VC
n s
me
07 and
11 les
pectively, after
strations in
08 ppm and
in British
own analyses
i concentra-
of VCM in
and *Stek 1976*:
uring the years
tial source of
source could
calculated
g a whole
CM in diseased
ing a period
of the
present for
rent of food-
75). Results
n of VCM

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 parauricular 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 parauricular 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 parauricular 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-

tential carcinogen was not dissolved in so. 6 days/week ratio only a tion not ne placed the o the no-toxic angiosarcoma Sprague-Daw proved to ha genic in rats be carcinoge 10, 5 and 1 p 1979). Anot the dose-rela exposure lev histological s the liver and the induction posure to 10 al. 1974b; 1A endothelial ti perplasia and even in the al was scanty in doses. In the fibrosis was l of ossifying a fact was sugg offspring of b mine posed ed fro it was matu to 20 foci c A week splee mal cutaneous an ppm group ar

R&S 117078

1 See also II

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 carcinoma, 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 acanthomas 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, 6 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 18 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)

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 Hathway* 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-

lin
ma
cre
197
tive
tion
ratio
so tha
follow
cordan

R&S 117080

3.4.1 Uptake

Pulmonary uptake in the animal's with the pool shown by com *Bolt et al.* (197 as albumin, are pound goes into After oral ingestion has to be considered is excreted via (1976c). This is a able process. Per body wt. administration investigation of gavage in dose found a significant plasmic reticulum but only minor rats on a diet of almost all the testinal tract, but in this way.

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

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

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 92% 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- ^{14}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 metabolization 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

micro
ly hig
via th
bon m
precia
in vit
system
1976a

R&S 117082

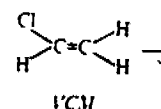


Fig. 1. Metabo

metabolized to
acetic acid are
roethylene oxi
protein sulphy
way (1977). Su
(*Norpoth et al.*
S-carboxymethi
acid) (*Henschl*
identified in th

microsomal mixed-function oxidase system, forming *chloroethylene 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

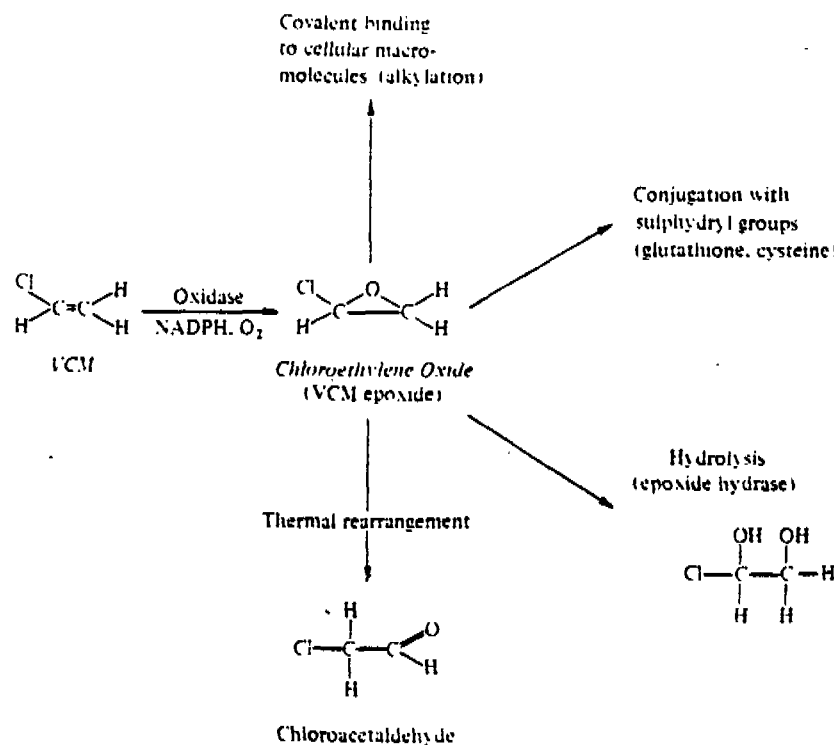


Fig. 1. Metabolic pathways. Adapted from Henschler (1977b)

metabolized to monochloroacetic acid. Both chloroacetaldehyde and monochloroacetic acid are also metabolites which are chemically reactive but less potent than chloroethylene oxide. All three intermediates can be detoxified by conjugation with non-protein sulphydryl 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 thiodiglycolic 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 hydrase.

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 hydrase. 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

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

This aspect of the work will be of importance to the endoplasmic reticulum, which is physiologically a mixed function organ. In the lobular, microvascular, microcirculatory system (Jaeschke 1978). Secondary endothelial

At present, the processes are not clear. The hepatotoxicity of some metabolites (3) Mechanisms of

other factors. R&S 117084. The qualitative and quantitative aspects of the data as to the degree of damage to the lining cells of the (tion) or when

4 Clinical

During the past few years, it might prove that the data presented in this paper marked the beginning of a new pattern of occupational hazard.

ter expo-
ssion was
nt reduc-
ained
omal mono-
cynolds et
bolism and

epoxide, is
enzyme

ylating
tal proteins
the metab-
hus exert its
nly fraction
detoxified
tathione or
es which
chanisms. In
there might
it be ex-
detoxifica-

to VCM
e binding
nce the po-
ations of
y covalent-
e increase
oints be-
a function
relates well
ngiosarcoma
con-

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.

R&S sm
1
ster-
F
R&S 117085
re
IS 1003 NOT

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>	<i>CNS:</i> prenarcoctic symptoms (dizziness, euphoria, somnolence), nervousness, insomnia, blunting of memory, general asthenia, headache <i>Vascular:</i> Raynaud's syndrome <i>Dermatol.:</i> pruritus, reversible sclerodermalike skin induration, chemical and allergic dermatitis <i>Digest. symptoms:</i> anorexia, nausea, fullness, hepatomegaly without hyperbilirubinaemia, splenomegaly <i>Endocrine:</i> 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

Table 7 (cont.)

Year	Reference
1972	<i>Mc</i>
1972	<i>Jül</i>
1973	<i>Ma</i>
1974(a)	<i>Cre</i>

4.1 The Triad

A first indication of plant production non ('toxic an' in detail in her personnel with hourly sampling drome was also (Kubota 1957 more regulation, and CNS symptoms (1954) also mentioned on there was evidence of red cells, no evidence of de acroosteolysis operators) after junction with was found in lesions to be reversible character vibration trauma the full range of occupational acroosteolysis. In 1963 Smith analysis of the

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	Jühe 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
1974(a)	Creech et al.	4 cases of angiosarcoma of the liver

4.1 The Triad: Raynaud's Phenomenon, Pseudoscleroderma 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 *Suciu* et al. (see also 1967 and 1975) published the first comprehensive analysis of their observation of a multiform symptomatology in subacute and chronic

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 plaquelike 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 a classifiable disease marked the beginning of the syndrome was followed in 1967 by a number of cases in the United States. In 1970, the various phases of the syndrome began with ill-effects on the fingers and tips on hard soles to cold accommodation are likewise associated with the appearance of painful osteolytic growth with striation.

Table 8. Publications

Year
1966
1967
1967
1967
1967
1969
1969
1971
1972
1972/1973

1
1
1
15
15
19
19
197
197
R&S 117088
1
0

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 discolouration. 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; Chatelain and Monillon
1967	France	5	Bourrichon (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	Kovač 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	Lilis et al.
1975	United Kingdom	1	Stewart et al.
1976	United Kingdom	4	Preston et al.; Walker; Mitchell Johnston (1978)
1978	Brazil	5	Gama and Meira
1979	Israel	2	Hahn et al.
		126	

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

g workers
employed in
rious cen-
in their
les of
eval of
edness
panied by
ral workers
ceable
ns, workers
odily
leakages,
months of
sistent
at the work
ability,
ne workers

6 years
of their oc-
ged period
ped, such
omfort,
ets (30%);
nd in 6%.

vasospastic
Pruritus

hat
rm. R&S
ed 117089
a fi
ye e
ter
ro
en t

quel
doc.....

la com-
ication.

viding ad-
ngiograph-
ronically

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 (*Lefèvre* 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. *Hublet 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

exclusively v
only 25 clear
defined as ch
enon; 18 of
with experie
drome were
jobs, both re
(1 case per 7
appeared not
was detected
use for react
entry into th

Table 9. Prev

Country	S
France	1
USA	3
Uni	
Ki	
Fed	
Ge	
Unit	
Kin	
Total	R&S 117090

Mi
related
Lange and V
ological check
pathological
were affected
cold, 15 work
morbidity wa
found classic
numbness and
8.7% and inve
Allen test ind
people with p
pseudoclubb
finding that th
duration of pu

exclusively with the finished PVC-derived consumer products. *Dinman et al.* found only 25 clear-cut cases of OAOL among the 5011 employees (mean age: 35.8 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	Sclerodermoid skin lesions	
France	130	5	12	15	5	<i>Benoit 1967</i>
USA	354	4	20	63	23	<i>Lillis 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>Maricq 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; Lillis 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 *Lillis 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 *Lillis'* finding that the prevalence of all these abnormalities increased significantly with the duration of past exposure to VCM.

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

defects in osteoporosis, skull defects, shortening, nonoccupational, genologic.

1) The one or more.

2) In the tufts, or a

3) The et

er,

sec

2.

1

117092



Fig. 2. Occupational acroosteolysis in a 31-year-old male.

4) In the and broader fragments, and increased

Sodium mineralization, simultaneous.

ved in younger
ed fell in the 30-39
aud's phenomenon
latency period was
oped insidiously
om OAOL was first

L al studies
of titution,
e: emoval
esi persist
art g with
te alanges

wc o had at
th en ob-
ed sub-
eye ite male

d typical bilateral
ent by an industrial
ions of vinyl chlo-
r after 6 years' em-
arging operator who
to routine plant
as chromatography
d limit values of
st year during an
ynaud's phenom-
nds and wrists. Ar-
n fingers without
s of deformed

dermal - Dinman
ptibility or idio-
opment of the syn-
crotrauma during
chiselling) was a
culated by Wilson

s. Involvement of
lieve that OAOL
Although the bone

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').

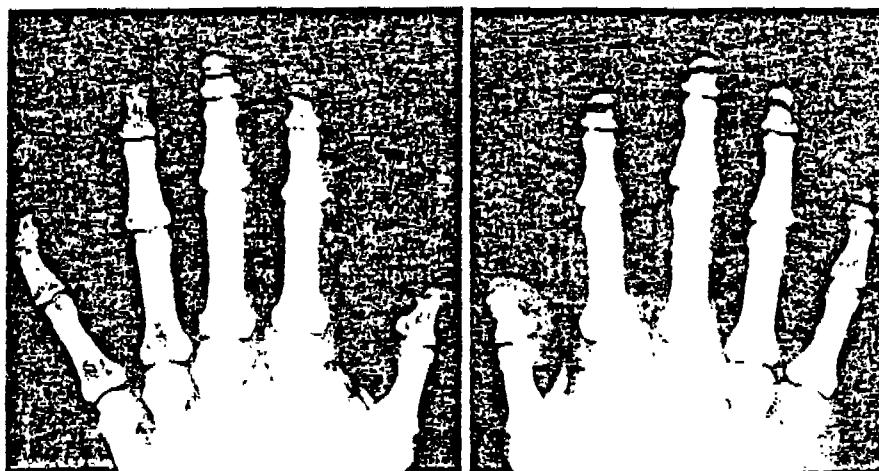


Fig. 2. Occupational acroosteolysis. Transverse or oblique bone defects ('bandlike acroosteolysis') or partial loss of terminal phalanges in all fingers of both hands. (33-year-old autoclave cleaner; duration of exposure 3 1/2 years)

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

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; Harris and Adams 1967; Dodson et al. 1971; Jühe 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 paraesthesias, 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; anhydrosis; 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

Vinyl C

izing scl
tional sy
readily t

4.1.4 H

4.1.4.1

Several in...
disease (Cordier
al. 1972; Lange
we found only o
1967; Marin et a
neural changes w
who suffered 'm

Dermal chan
mis with disorie
broad interlacing
faintly stained n
Schiff (PAS). An
histiocytes was s
The most notabl
of elastic fibres.
full thickness of
sue. Skin append
Walker (1976) f
not exceeding n
some fibrous thi

Vascular les
capillaries were
and pericapillar
thelial cells with
tion of lumina.
myocytes, was a
to narrowing or
Degenerative
(Benoit 1967; M
hyalinosis of the
Meissner, Pacini

4.1.4.2 Bone l.

The most strikin
worker with OA
ening and hyalu
most layer. Supi

R&S 117094

the sacro-iliac
1, clavicle, man-
neiform and
Harris and Adams
et al. 1976;

izing sclerosis of the skin with tapering off of fingertips was never seen in the occupa-
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

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; Velman 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 plaquelike 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 pericapillar oedema. Capillaries of the cutis showed cufflike hyperplasia of peri-
thelial cells with fibroblast transformation, hyalinosis of vessel walls and final obliteration
of lumina. Marked medial thickening of dermal arterioles, due to hypertrophy of
myocytes, was accompanied by parietal 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; Chatelain and Motillon 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 periosteum with chondroid metaplasia of the inner-
most layer. Supplying capillaries and arterioles showed occlusive changes identical with

of i
pro
arm
e fac
ated,
inger
binat
ech fo
ndror
diffuse immobil-

R&S
117095

s and
le-
nes
on
le-
is
y-

ysis (Raynaud's
dema with (rare)

ive scleroderma

ar l tapering off
tip anhydrosis;
e lesions

kin appendages

ptom

spontaneous
sion

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).

R&S 117096

for control
laroscopy
control
ence in
PVC w
of distu
induced

A sin
a PVC-p
chemical
normali
was con
number
employ
related
It also s
more se

There was
the bone

liopathic
uld be ob-
inflammatory
il. 1936:
7).
ducing
small meta-
rved in man.
ths and de-

v of the
bly con-
arterial
(Lange et
were ir-
or diffuse
l vessels.
and peculiar
arity of
Renoit
al.

symp-
sis (5/19)
enomenon
mination
e bone
to vary-
ll collat-

R&S 117097
of



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

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 Langauer-Lewowicka 1974).

Infrared thermography, another non-invasive method, used by *Reidy 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

and lung
T
and b
bolic
plasm
which
cular c
as a re
ators o
to further ac
Jayson et al.
suffering fro
than in norm
rside disease

In an ear
in four Polis
decrease in l
ever, *Langau*
after Sephae
6 together w
agglutinins d
were observ
sponses play
(1974a) and
dence of au
tion of rheu
termination
immunofluo
were later a
creases in im
taken up ag
ed to suggest
hypergamm
with far adv
three patien
with Raynaud
degrees of
nins were fo
range: $\bar{x} \pm s$
scleroderma
of which is d

In summ
autoimmunc
establish the
in VCM-indi

R&S
117098

nt (termination
n that among
is condition,
apillaroscopic
rs, 2 fitters)
for 2-5 years

et al. (1974)
perature rang-
ly warmer than
workers suf-
by infrared
et al. (1975)
ia in the distal
d case. Local-
angiographic
satory collat-
survey involv-
assessed the
water bath kept
controls and be-

tested certain
cessive systemic
ed conditions
h for other
tures, as pro-
ological stu-
hem out of a
VCM was 39
ynaud's phen-
d, excessive
ually IgG, the
C₄ were
e of reduced
s in vivo con-
evidence for
demonstrated
tients with
in were reveal-
iscular endo-
ons of small

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-Lewowicka 1974). Later, however, Langauer-Lewowicka 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 (Marsteller 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.

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 clin
many as
survey wa
developin
character c

In 1972
had been ro
time-weighte
environment;
wise multiple
tion and, to a lesser
level of past exposur
the individuals studi
TWA levels of 300 pp
in clinical laborator
ed BSP retention wa
ease (*Marsteller et al.*

In West German
dermatologists in Bc
At first sight, the sy
derma. This provoked
Progressive systemic
a first group of 13 pe
from a nearby PVC-
from either OAOL o
phageal varices due to
a group of 20 relativ
previous liver disease
Medical Department
patient and revealed
capsular fibrosis of
ly, marked portal hy
al. 1973). It was now
encompassed a large
Hence *Jühe et al.* (197

In retrospect, the
spleen alterations in
the long latency perio
disease which is accom
hepatic parenchymal c

Only 3 months lat
was surpassed by the
liver, an exceedingly r
work force of 274 emp
ican plant (*Creech et al.*
upper gastrointestinal

R&S 117100

R&S 117101

man
le-
in-
n
as-
tible
circulation (*Gama*)
of peripheral
largely a matter of
on, distributed
the liver, can
als, after a vari-
damage to peri-
ous chapter (see
ificance.

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 stepwise 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 (*Jühe* and *Lange* 1972; *Jühe et al.* 1973; *Stein 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 (*Jühe 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 *noncirrhotic 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 *Jühe 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.

ed in PVC pro-
ons in a Russian
Without going
galy was found
mostly engaged
(15 ♂, 6 ♀). Al-
ons of VCM
hey explicitly
the powdery
ther volatile
chlorinated
stemic toxicity.
kers should be
y suggested the

14 years later
s) of two Rum-
megaly. Liver
prevalence of
the Sverdlovsk
employees of the
ction of non-
ontrol subjects.

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 gastroesophageal 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; *Imanaga* 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; *Knolle* et al. 1974; *Morris* et al. 1974; *Huet* 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 (*Nothnagel* and *Rosbach* 1880) Fowler's solution is also listed as a traditional antimalarial drug of

chloride monomer can
experimental animals:

h rare disorders

portal fibrosis are not
eal haemorrhage due
e development of
ne', this symptom
a matter of debate.
on' the syndrome has
ns (Ramalingaswami
1967; Sama et al.
Bousselot 1940;
Brandt 1962; Siderys
in et al. 1974;
er (1969) estimated
th portal hyperten-
category of cirrhosis

ed that in noncirrhotic
i ugs, herbal
o 1 (Sama et
l ganic
c. Idio-
th known
e) tion of

R&S 117103

Snolle et al.
v et al.

73, 1974; Hruban et

Pimentel and Menezes

— potassium
an adjunct to iron
Os for the treatment
(1898) that anaemia
preparations is of
iod (Nothnagel and
malaria drug of

long standing. *Chainuvatti* and *Viranuvatti* (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 toxification 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; *Kistler 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 Nemoto* 1952)] could be demonstrated by fluorescence microscopy. Stimulation and proliferation of Ito cells, which are probably fibroblast precursors (*Popper and Udenfriend* 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 Menezes* 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

oesophageal

oscopic and
al diagnosis

otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic cirrhosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic fibrosis
 otic cirrhosis
 otic fibrosis

ngiosarcoma of
 Patients 6 and
 nt of angio-
 of portal fi-

pment of
 all series w e
 individuals suffer-
 to develop
 ably not a pre-

ges of VCM-
 y to moderate-
 hepatomegaly
 who had been
 reported hepa-

oyees
 n
 uc-
 hose

R&S
 117105

exposed for more than 5 years, whereas the difference in the prevalence of palpable splenomegaly was not significant.

In contrast to cirrhosis of the liver, clinical symptoms indicating serious impairment of hepatic function such as jaundice, vascular spiders, palmar erythema, telangiectases, gynaecomastia, peripheral oedema and ascites or hepatic encephalopathy are not seen. Even after massive bleeding from oesophageal varices portosystemic encephalopathy does not develop. Ascites and hepatic coma have been observed in these workers only in terminal stages of angiosarcoma of the liver.

It is puzzling that acroosteolysis and sclerodermoid skin induration have only rarely preceded advanced stages of VCM-induced liver disease. To our knowledge there is only one case of angiosarcoma of the liver on record which was associated with prior development of acroosteolysis (Roche et al. 1978).

4.2.2 Laboratory Findings

Owing to the fact that hepatocytes, although being the primary site of metabolism, are not the target of toxicity, standard biochemical liver function tests are only of limited value for the detection of liver disease in populations at risk (Williams et al. 1975b). This makes it very difficult to devise adequate screening programmes (Martin et al. 1974; Creech and Makk 1975; Wyatt et al. 1975; Berk et al. 1975, 1976). Apart from thrombocytopenia, we found 45-min BSP retention to be the most consistently pathological biochemical test; usually minimal hyperbilirubinaemia and minor elevation of the levels of serum alkaline phosphatase, SGOT and SGPT were considerably less frequent (Marsteller et al. 1975a). Another dye-removal test, indocyanine green clearance (ICG; 0.5 and 5.0 mg/kg), also proved to be more reliable than standard biochemical liver function tests in correctly identifying early hepatic injury in 1200 vinyl chloride workers of a chemical plant in Louisville, Kentucky, during a 4-year screening period (Tamburro et al. 1978b). The exposure rank was found to be closely correlated with progressively increasing frequency of abnormal ICG clearance, whereas the frequency of abnormal SGOT, and alkaline phosphatase only increased in late stages, often when there was overt clinical disease. In the survey conducted by Lillis et al. (1975), alkaline phosphatase levels were elevated in 16.6% of the 354 workers examined. In their series, alkaline phosphatase was also closely correlated with the clinical symptom of hepatomegaly and/or splenomegaly.

Except for thrombocytopenia (less than 150×10^9 platelets/litre) which Lange and Veltman (1977) found to be present in 76 of 100 workers, and a slight increase in the reticulocyte count (in 35 of 79 workers, Lange and Veltman 1977), haematological parameters usually do not contribute to the diagnosis. Thrombocytopenia was also the presenting feature in two of seven British workers with noncirrhotic portal hypertension (Smith et al. 1976a). Thrombocytopenia and abnormal platelet function tests will be dealt with separately in Sect. 4.4.1.

Assessment of urinary excretion of porphyrins and porphyrin precursors in symptomatic workers who had been engaged in the production of PVC ($n = 23$) or the manufacture of PVC articles ($n = 17$) revealed varying but mostly mild degrees of secondary coproporphyrinuria in the majority of them (Lange et al. 1976b). The significance of

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 peritoneoscopy (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 peritoneoscopy 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 peritoneoscopic probe), the texture of the liver is normal or only slightly firmer than usual. Indirect peritoneoscopic 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 sharply with the expected smooth surface of a normal liver. It is a focal or multifocal process, with stellate scarring (Marsteller et al. 1975a, b) extending into the connective tissue processes of the liver or more diffusely seen in the

4.2.4 Histology

Histological changes are generally mild, striking portal fibrosis and periportal reactions, in the absence of portal fibrosis. Subsequent evolution (1978).

Dependence of biopsy on liver biopsy is subject to marked variations is seen (Thomas 1976), but (Popper et al. 1978).

4.2.4.1 Histology

In its fully developed stage, portal fibrosis and bile ducts are associated with formation of central and peripheral nodules of connective tissue with enlarged perisinusoidal walls. (Müller et al. 1978).

relation to

der et al.
at exploratory
organ with
oneoscopy also
lock et al.
a with shallow
d'orange-like
arse nodularity
derangement
74), and also
coma.
liver is normal
portal hyper-
and the intes-
the abdomi-
rtension often

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. 1978).

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

R&S 117107

vp
conspicuous
1963-74.
ession of
oesophageal



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 fibrosed portal tract towards parenchyma (*left*). Proliferation of capillaries ($> <$) with polymorphism and hyperchromasia of endothelial cells. PAS, $\times 400$

R&S 117108

Fig.
with
ner)
and
Enlar
prec
Patn

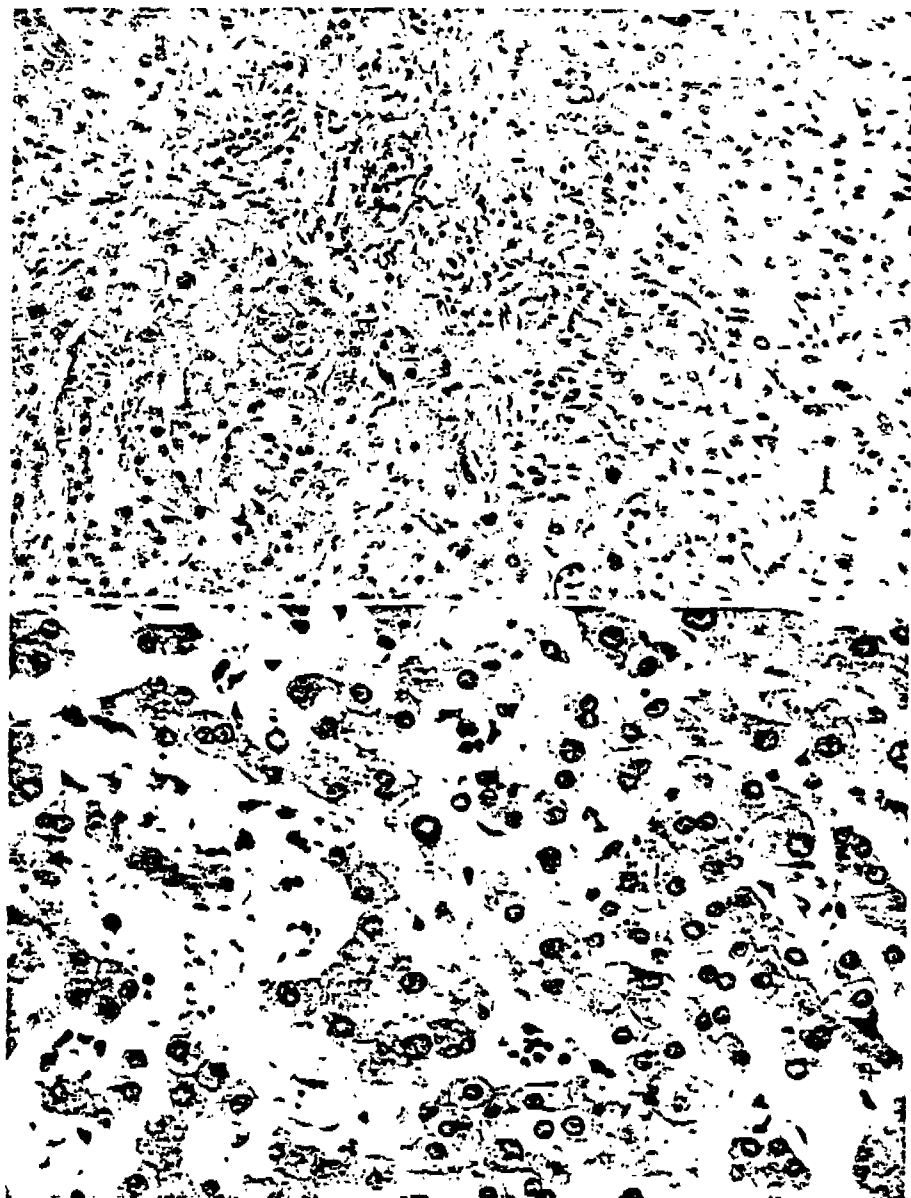


Fig. 5c. Focal portal fibrosis (*left upper corner*) and reticulated perisinusoidal fibrosis with activated proliferating and pleomorphic sinusoidal lining cells. Trichrome (Goldner) stain, blue filter, $\times 250$. d Conspicuous focal dilatation of sinusoids. Activation and moderate polymorphism of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

fibrosis
H & E
react to
and

R&S 117109

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) (*Sommerschild* 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 endoplasmic 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; *Müller* 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 characterized by a homogeneous red pulp, follicles with many endothelial cells, occasional fresh spicuous fibrosis.

In ten cases we observed (Heusermann and others), together with splenectomy. The process. Excess active tissue, notably and white pulp, present. There was scarring meshwork and reduction of diameter of sinusoids of the pulp cords, formation of bizarre collagen fibrils. Note the reticular congestion volume. R&S 117110. mation (found with thrombohanced p help to e stages of and Heus VCM-indi of the live in the spleen in vivo indicate a primary support correlating with patients is being prepared the spleen in noncomparable for comparison.

4.2.5 Pathophysiology

The pathophysiology is an unresolved problem due to splenoportography of intrahepatic venous radicles (Blum) and a normal, or or

pointed out
on and essen-
and easily over-
microscopy
s and in Disse's
ells (see also
oidal collagen
we could ob-
ages (enlarge-
e and resulting
ophysiology
n a number of
onal histories
lon et al.

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 fibrosis 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 periarterial 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

R&S 117111
reason to be-
ge.

nor degrees of
increase of
of hepato-
appear gradual-
opsy, in con-
redigk et al.
erplasia and
nucleated
g degrees of
y some as yet
8).

ens of the
thomas (1975)

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

flow at
veiled

4.2.6

In 197
tic fibro
could d
tests in

R&S 117112

oped (se
Live
determin
(BMHP)
after ho
and toll
aid of th
the reti
increase
PVC pol
sack et

4.3 An

4.3.1 F

Primary
(angiobl
haemang
cell sarco
sarcoma
vascular
one at co
hood (fo
the num



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)

level. In a group of five PVC (1978) could not demonstrate fibrosis in needle biopsy specimens and that the distribution of

by Popper and
and hepatic blood
properly be ac-
tive distension
idal fibrosis.
liver blood

R&S 117113

flow and the portal pressure. However, they point out that this relationship may be veiled by the amount of blood bypassing the liver via a collateral circulation.

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 peritoneoscopy 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 1973 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 (??) 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 -bromomercury-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 (Biersack 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

despite termination of exposure: 35 years. VCM-exposed workers had skin indurations, varices. Gradual progression of angiosarcoma of the liver in nontumorous

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 *Heath 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-

tion of /
inorganic
dioxide,
tem and
Thor
contrast
ing evide
reported
been the
had been
and Moti
A special
caused by
thorotra
from a lo
ASL (Re
Devel
man vine
tensively
1950–19
tion revea
of multipl

R&S 117114

hu
tension bu
woman w
ride) durin
had a high
manifesta

The pr
be elicited
period 18
history of
Among m
observed
other han
391 autops

iosarcoma
constituted
each of them-
the incidence
with a mean
(1975) it was
is 0.014 in

linic.
er, Minn..

cles,
Hosp., USA

Infirmary
U.K.

U.S.A.

R&S 117115

On during

icytoma

270 em-
nt near
uly recog-
rd (Creech

with the
al prepara-

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 Motta 1967; Wegener et al. 1971; Futh and Pitzke 1974; Selinger and Koff 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 (0.2-8.9 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 Büsscher (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, Fiechtner 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

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

No.

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

R&S

117116

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

(Tables 1
reference)

Table 13 (continued)

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	65	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	58	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)	00.00.23	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)

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

History Description Recurrence Thrombosis Acromioclavicular Raynaud's

R&S 117118

and H.J. Marsteller
 mal exposure to
 other three may
 be many
 igitation
 R&S 5-1973
 ear). An
 itional
 alists
 cal sec-
 2 diagno-
 se 14
 (low levels of?)

ization workers in
 the for Occupational
 situation continued
 ations with an im-
 is of August 1978,
 ization w rkers
 been observed
 On the basis of
 ish to thank Drs.
 ed to trace these
 information pub-
 ican cases of
 ivers published by
 e described in
 our clinic in Bonn
 nd, Marsteller 1977).
 51, 53-67 and
 Gewerbearzt,
 duced ASL in the
 978, to which we

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		Ø	Ø	Ø
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) 1 case: mediastinal lymph node 1 case: peritoneal spread 3 cases: local spread
3				Capsular, portal, perisinusoidal				
4				Sclerosis of wall of portal vein				
5				Capsular, portal, perisinusoidal				
6				?				
7				Capsular, portal, perisinusoidal				
8				Capsular, portal, perisinusoidal				
9				Portal, perisinusoidal				
10				Capsular, portal, perisinusoidal				
11				Capsular, portal, perisinusoidal				

Table 14 (continued)

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
12	+	Moderately enlarged	(+)	(Cirrhosis), fibrosis	?	Ø	+	Ø
13	+	(2750 g)	?	(Cirrhosis)	?	Ø	Ø	Left lung
14	+	Spleno- megaly	?	?	?	Ø	Ø	4th left rib
15	+	Slightly enlarged	?	?	?	Ø	Ø	Ø
16	+	Spleno- megaly (830 g)	+	Capsular, portal, septal	+	Ø	Ø	1st thoracic vertebra
	(2650 g)				(72 000, 65 000)			
17	+	Spleno- megaly	+	+	?	Ø	Ø	Brain
18	?	Perisplenitis	?	?	+	Ø	+	3rd lumbar vertebra
					(134 000, 68 000)			
19	(+)	Spleno- megaly (400 g)	(+)	Progressive perisinusoidal, portal and septal cirrhosis	+	Ø	Ø	Ø
	(1450 g)				(80 000, 47 000, 30 000)			
20	?	?	?	?	?	?	?	?
21	+	Spleno- megaly	+	+	?	Ø	Ø	Ø
	(1900 g)							
22	+	Spleno- megaly	?	Capsular, portal, perisinusoidal	+	Ø	Ø	Ø
23	+	Spleno- megaly (455 g)	Ø	Focal peri- sinusoidal	?	Ø	Ø	Ø
	(2700 g)							
24	+	"	"	"	"	Ø	"	"

R&S 117120

20	?	?	?	?	?	?	?	?
21	+	Spleno- megaly (1900 g)	+	+	?	Ø	Ø	Ø
22	+	Spleno- megaly	?	Capsular, portal, perisinusoidal	+	Ø	Ø	Ø
23	+	Spleno- megaly (455 g)	Ø	Focal peri- sinusoidal	?	Ø	Ø	Ø
24	+	?	?	Ø	?	Ø	?	Local spread to caval vein
25	+	Spleno- megaly (1610 g)	+	Portal, perisinusoidal fibrosis	+	Ø	Ø	Ø
26	+	?	Ø	?	?	Ø	Ø	Duodenal wall
27	+	Spleno- megaly (2230 g)	?	Reticulated capsular fibrosis, micronodular cirrhosis	?	Ø	Ø	Ø
28	+	Spleno- megaly (650 g)	+	Portal, peri- sinusoidal, capsular fibrosis	+	Ø	Ø	4th and 7th thoracic vertebra, 5th left rib, left adrenal
29	+	'Modifications fibro- congestive'	Ø	Slight portal fibrosis	Ø	+	?	Ø
30	+	Ø	Ø	Minimal fibrosis	Ø	Ø	Ø	Small intestine
31	+	Splenomegaly (270 g)	?	?	?	Ø	Ø	Para-aortal lymph nodes
32	+	?	?	Ø	+	Ø	Ø	Ø
33	+	?	?	Capsular, portal fibrosis	Ø	Ø	Ø	Ø

R&S 117121

Table 14 (continued)

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

45	+	Spleno- megaly	+	Markedly thickened capsule; marked fibrosis	+	Ø	Ø	Ø	
46	+	Spleno- megaly	?	Portal fibrosis	?	Ø	Ø	Spread to duodenum	
47	+	Spleno- megaly	?	Portal fibrosis	+	Ø	Ø	Spread to diaphragm and abdominal wall	
48	+	?	?	Slight focal hepatitis (minimal hepatitis)	?	Ø	Ø	Lungs, large and small bowel, pleura, pericardium myocardium, kidneys, left adrenal	
49	?	Normal	?	Capsular and portal fibrosis	?	Ø	Ø	Diaphragm, regional, retro- peritoneal and mediastinal lymph nodes, lungs, adrenal glands, cerebellum	
50	} Details not published								
51									
52	+	?	?	Peculiar portal fibrosis, moderate cirrhosis	?	Ø	Ø	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	+	?	+	?	+	Ø	Ø	Ø	

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		
4		
5		
6		
7		
8		
9		
10		
11		
12	Schmidt and Batora (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 Reinl and Weber (1974)
15	Gedigk et al. (1975)	See also Reinl 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 <i>lungs</i>
18	Reinl 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	Reinl et al. (1976)	
21	Reinl et al. (1977)	
22	Reinl 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 (c)

No. Ref

27 Ro

28 Ro

29 Ro

30

31 Ber

32

33

34 Le

35 Sm

36 Me

37 -

38 -

39 -

40 -

41 By

42 By

43 -

44 Bl

(cas

45 Blo

(cas

46 Bio

(cas

R&S 117124

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 sclerodermalike skin induration (hands), swelling of face, upper extremities and feet. 1971 bilateral <i>acroosteolysis</i> . Tumour penetration of the abdominal wall (fistula). Severe interstitial fibrosis of <i>testes</i> ; fibrosis of interstitial wall; slight mesangial fibrosis of <i>glomeruli</i> . Variable but generally slight fibrohyalinosis 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)

tothe-
cells

R&S 117125

typical
biliary

pancrea-
tes

hepatic
sch et
nd et

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>Zorica 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, rib, mamma, spermatic cord; glioma, melanoma, leukaemia, 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, *Hublet et al.* 1977; *Rübsamen* 1976). *Hublet 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-

R&S 117126

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 mix- ture onto fabric bases
D	I (1)	06.15.34	04.16.71	36	3	Fabrication of PVC sacks and wrappings (extrusion at tempera- tures of 120°C)
E	S (2)	11.27.11	08.16.71	61	23	Assistant factory chem- ist (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: 18 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

Table 17. Clinical and morphological data on eight cases of angiosarcoma of the liver among VCM-exposed personnel 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	+	Ø	Ø	Diaphragm, gastric mucosa, abdominal lymph nodes
B	+	Spleno- megaly (425 g)	+	Focal capsular fibrosis, portal and centrolobular fibrosis	Ø	Ø	Ø	Diaphragm, pleura, abdominal lymph nodes
C								
D	(+)	Not enlarged	Ø	?	?	Ø	Ø	Lungs, pericardium
E	+	?	?	?	+	Ø	Ø	?
F					(104 000)			
G	+	Splenomegaly	?	?	?	Ø	Ø	Dura, cranium
H								

W. K. Leibach and H. J. Marschall

R&S 117128

genetic cases of PVC VCM in the of ad- ences furth- Ther- and the VCM ne/ce- tion note

E

D

C

B

A

No.

Tabl
164

Vin

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>Reinl and Weber</i> (1974)	1967 idiopathic portal hypertension; portocaval shunt
B	<i>Zimmermann and Eck</i> (1975) <i>Reinl</i> (1975)	1973 right heminephrectomy for unilateral hydro-nephrosis 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 *Rochie et al.* (1978) also reported fibrosis/hyalinosis in vessels of skin, heart, lungs and intestinal wall.

CUMULATIVE
N^o OF CASES
REPORTED TO NIOSH

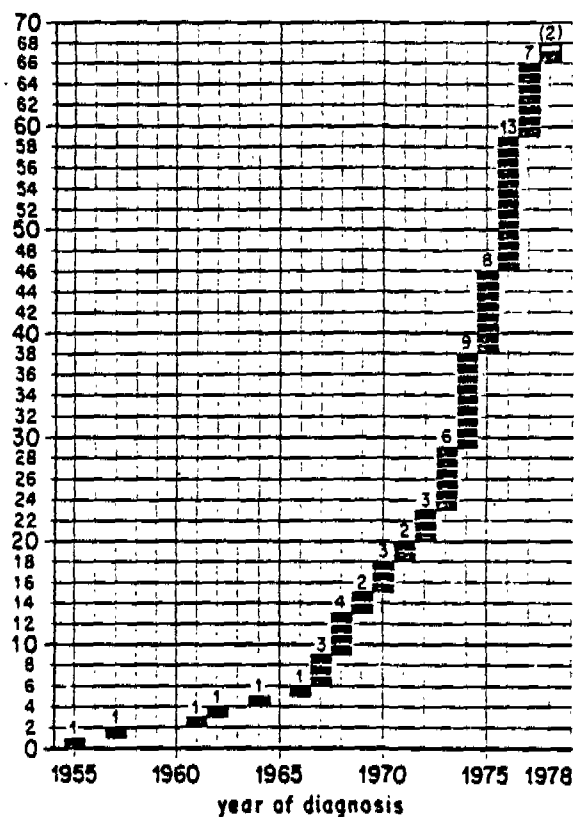


Fig. 7. Cumulative number of cases of ASL among PVC production workers reported to NIOSH up to August 1978, arranged according to year of diagnosis (data from *Spirtas and Kaminski* 1977, 1978)

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

R8S 117130

V

of
hr
ar
fo
ph
se
pr
gr
are

19
be
are
me
sta
tio
rep
der

any
In
nat
nor
was

Fig.
the
Uni

testes
fibrosis/

R&S 117131

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 gammaglutamyl 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



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

reported
comally de-
ominal
first
cedent
number

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 hyperbilirubinaemia, 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).

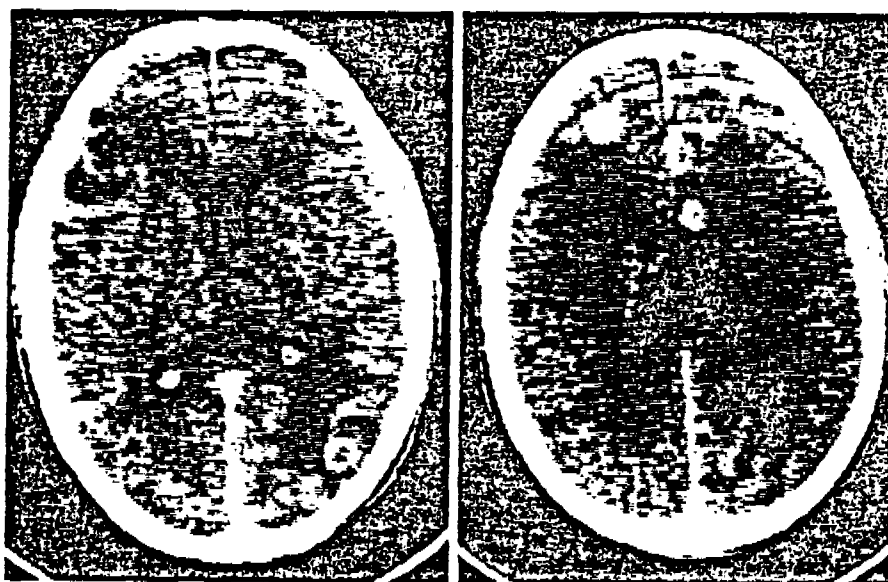


Fig. 9. Computer tomography showing multiple brain metastases of angiosarcoma of the liver. See text. Courtesy of Professor Thum, Department of Radiology, University of Bonn

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

R&S 117132

Fig.
Gul

quired
August
gastric
He com-
spleno-
om mod-
ochem-
umour
actically
ated the
ement
metastases
oma of

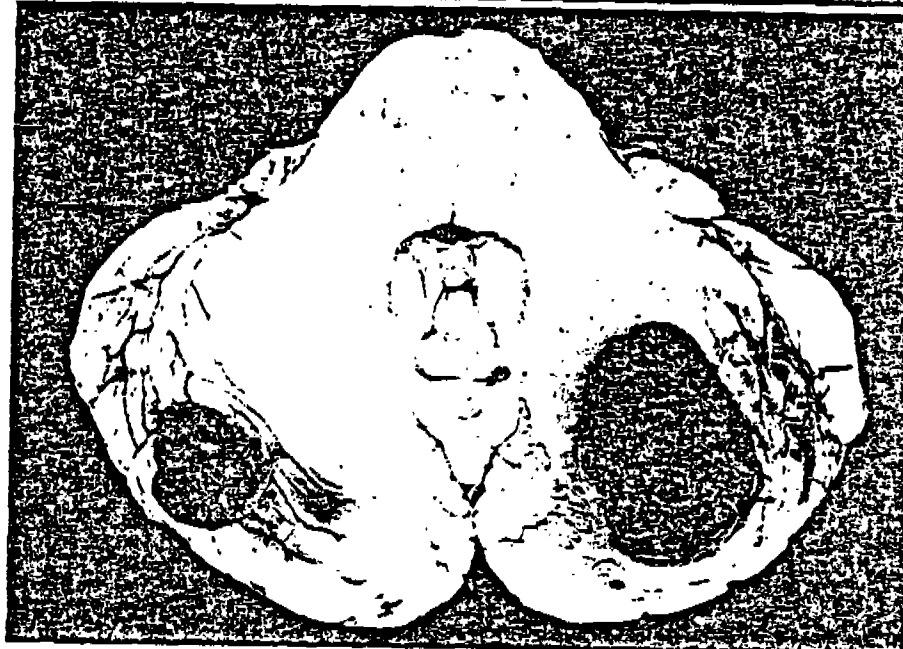
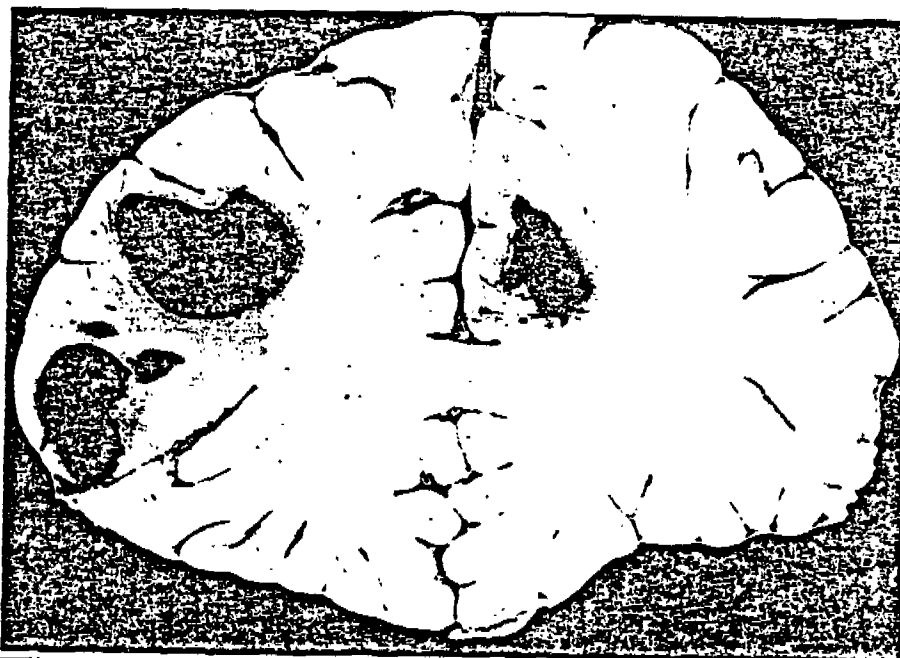


Fig. 10. Multiple brain metastases of angiosarcoma of the liver. Courtesy of Professor Gullotta, Institute of Neuropathology, University of Bonn



oma of
iversity

asp
mo
le t
AS

R&S 117133

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 fibrotic 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 perilobular 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

R&S 117134

Fig
liver
nuc
per
Ins

of G
lym
The
or c
lifer
oidal
plast

incr
retic
cytes
degen
retic

T
creas

19; see also
connection with
non visible on
hepatic me-
liver. It should
is any suspi-

R&S 117135

ed fi
unce
ic tu
ules,
nd sp
lary

ur basic devel-
fferent por-
ive evolution:
of transition

oma cells with
erize the
ing differen-
tal tracts, ac-
arcoma atro-
spaces, into
reactive tissue
filled spaces
fibrotic walls.
ma are found,
e of tumour.
ferentiation of
ial lining cell
ally, vinyl
other aetiolo-

egrees of ex-
us to that seen
ortal tracts
n of lympho-
sue septa ex-
tiguous intra-
methods for
thickening of

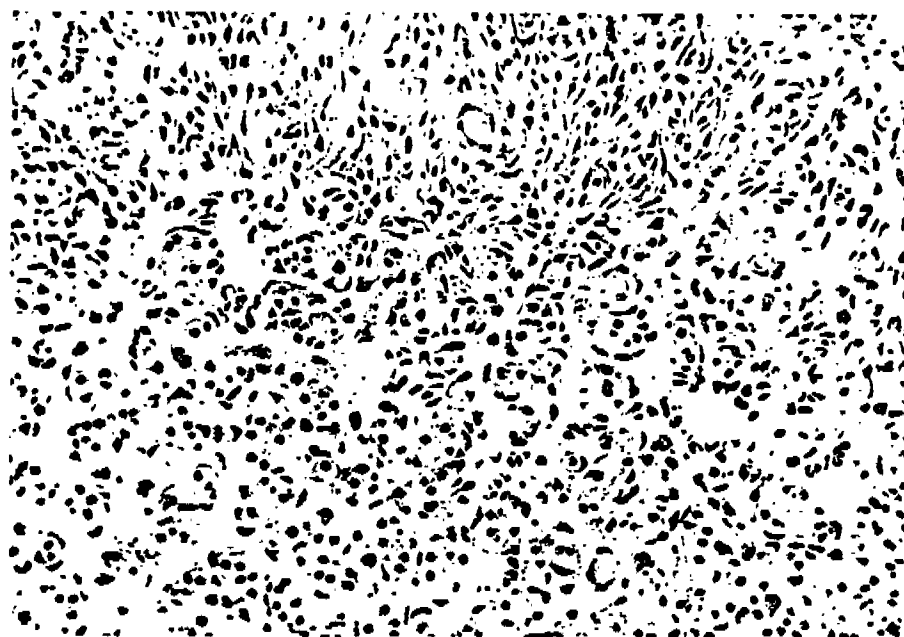


Fig. 11. Angiosarcoma of the liver (upper part of photomicrograph) invading adjacent liver parenchyma (case 14 = D1; see Table 13). Note hyperplastic and hyperchromatic nuclei of proliferating neoplastic lining cells enveloping hepatic cords. Reproduced by permission, Ann NY Acad Sci 246:278-285 (1975).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

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

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 cirrhosislike 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).

Re
(excl
ASL
This
the U
confi
had d
the re
polym
was of
vironm
ceeder
lesser
magnit
ting, a
million
vinyl c
model

R&S 117136

the nu
al. 197
Waxw
of Bnt
1976; /
posed
et al. 1
voiced
Berry
emplo
and car
but no
1976).
In
(1974)
epidem
(1978).
factor

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, ThO_2 or VCM. Five (all female) of the remaining 19 patients lived at a distance of 500–4500 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 1618 employees of a West German chemical plant (*Frentzel-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; *Dalderup* 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 (*Reinl and Weber* 1976) was completed in 1977 by *Reinl 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

R&S 117137

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 Antonyuzhenko 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

R&S 117138

of
in
al.
cyt-
or
xyp
Ta-
wo
Gro
A
B
C
D
a

pea
pre
litre
limi
Fisc
The

bone lesions presented with mild to marked thrombocytopenia ($30-119 \times 10^9/\text{litre}$). 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; Seiert-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 *Seiert-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 ^{197}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 ($\times 10^9/\text{litre}$)		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 ($100-120 \times 10^9/\text{litre}$) 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 (Born 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 (Suchi et al. 1963, 1975; Schottek 1969; Lillis et al. 1975 and others). This prenarcoptic 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-

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 18.8%, 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 (Parmeggiani 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 VPC 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 Golovatyuk and later by Shlyakhetskii. 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.

74; Darke
in the drying,
in Karstadt's
ents of the
reported as
the possibil-
dust. The
ngs blocking
mination of
ment of the
thout hilar

resented with
pulmonary
a processing
ranulomatous
could be
ion of PVC
morphologic-

ent in a PVC

S u-
al.,
R&S 117143
to-
ol-

1974), who
and rats ex-
gging area.
rophage re-
of foreign
omatous
the manu-
ortion of
broncho-
ey quoted
d later by
animals to
ally to a sort

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

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 Painsville, one of the three Ohio communities, had ever worked at either of the two PVC polymerization plants in Painsville 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

between pred
tissue such as
short exposu
will carry the

References

- Albright LF (1971)
- Albright LF (1972)
- Albright LF (1973)
- Albright LF (1974)
- Albright LF (1975)
- Albright LF (1976)
- Albright LF (1977)
- Albright LF (1978)
- Albright LF (1979)
- Albright LF (1980)
- Albright LF (1981)
- Albright LF (1982)
- Albright LF (1983)
- Albright LF (1984)
- Albright LF (1985)
- Albright LF (1986)
- Albright LF (1987)
- Albright LF (1988)
- Albright LF (1989)
- Albright LF (1990)
- Albright LF (1991)
- Albright LF (1992)
- Albright LF (1993)
- Albright LF (1994)
- Albright LF (1995)
- Albright LF (1996)
- Albright LF (1997)
- Albright LF (1998)
- Albright LF (1999)
- Albright LF (2000)
- Albright LF (2001)
- Albright LF (2002)
- Albright LF (2003)
- Albright LF (2004)
- Albright LF (2005)
- Albright LF (2006)
- Albright LF (2007)
- Albright LF (2008)
- Albright LF (2009)
- Albright LF (2010)
- Albright LF (2011)
- Albright LF (2012)
- Albright LF (2013)
- Albright LF (2014)
- Albright LF (2015)
- Albright LF (2016)
- Albright LF (2017)
- Albright LF (2018)
- Albright LF (2019)
- Albright LF (2020)
- Albright LF (2021)
- Albright LF (2022)
- Albright LF (2023)
- Albright LF (2024)
- Albright LF (2025)
- Albright LF (2026)
- Albright LF (2027)
- Albright LF (2028)
- Albright LF (2029)
- Albright LF (2030)
- Albright LF (2031)
- Albright LF (2032)
- Albright LF (2033)
- Albright LF (2034)
- Albright LF (2035)
- Albright LF (2036)
- Albright LF (2037)
- Albright LF (2038)
- Albright LF (2039)
- Albright LF (2040)
- Albright LF (2041)
- Albright LF (2042)
- Albright LF (2043)
- Albright LF (2044)
- Albright LF (2045)
- Albright LF (2046)
- Albright LF (2047)
- Albright LF (2048)
- Albright LF (2049)
- Albright LF (2050)
- Albright LF (2051)
- Albright LF (2052)
- Albright LF (2053)
- Albright LF (2054)
- Albright LF (2055)
- Albright LF (2056)
- Albright LF (2057)
- Albright LF (2058)
- Albright LF (2059)
- Albright LF (2060)
- Albright LF (2061)
- Albright LF (2062)
- Albright LF (2063)
- Albright LF (2064)
- Albright LF (2065)
- Albright LF (2066)
- Albright LF (2067)
- Albright LF (2068)
- Albright LF (2069)
- Albright LF (2070)
- Albright LF (2071)
- Albright LF (2072)
- Albright LF (2073)
- Albright LF (2074)
- Albright LF (2075)
- Albright LF (2076)
- Albright LF (2077)
- Albright LF (2078)
- Albright LF (2079)
- Albright LF (2080)
- Albright LF (2081)
- Albright LF (2082)
- Albright LF (2083)
- Albright LF (2084)
- Albright LF (2085)
- Albright LF (2086)
- Albright LF (2087)
- Albright LF (2088)
- Albright LF (2089)
- Albright LF (2090)
- Albright LF (2091)
- Albright LF (2092)
- Albright LF (2093)
- Albright LF (2094)
- Albright LF (2095)
- Albright LF (2096)
- Albright LF (2097)
- Albright LF (2098)
- Albright LF (2099)
- Albright LF (2100)
- Albright LF (2101)
- Albright LF (2102)
- Albright LF (2103)
- Albright LF (2104)
- Albright LF (2105)
- Albright LF (2106)
- Albright LF (2107)
- Albright LF (2108)
- Albright LF (2109)
- Albright LF (2110)
- Albright LF (2111)
- Albright LF (2112)
- Albright LF (2113)
- Albright LF (2114)
- Albright LF (2115)
- Albright LF (2116)
- Albright LF (2117)
- Albright LF (2118)
- Albright LF (2119)
- Albright LF (2120)
- Albright LF (2121)
- Albright LF (2122)
- Albright LF (2123)
- Albright LF (2124)
- Albright LF (2125)
- Albright LF (2126)
- Albright LF (2127)
- Albright LF (2128)
- Albright LF (2129)
- Albright LF (2130)
- Albright LF (2131)
- Albright LF (2132)
- Albright LF (2133)
- Albright LF (2134)
- Albright LF (2135)
- Albright LF (2136)
- Albright LF (2137)
- Albright LF (2138)
- Albright LF (2139)
- Albright LF (2140)
- Albright LF (2141)
- Albright LF (2142)
- Albright LF (2143)
- Albright LF (2144)
- Albright LF (2145)
- Albright LF (2146)
- Albright LF (2147)
- Albright LF (2148)
- Albright LF (2149)
- Albright LF (2150)
- Albright LF (2151)
- Albright LF (2152)
- Albright LF (2153)
- Albright LF (2154)
- Albright LF (2155)
- Albright LF (2156)
- Albright LF (2157)
- Albright LF (2158)
- Albright LF (2159)
- Albright LF (2160)
- Albright LF (2161)
- Albright LF (2162)
- Albright LF (2163)
- Albright LF (2164)
- Albright LF (2165)
- Albright LF (2166)
- Albright LF (2167)
- Albright LF (2168)
- Albright LF (2169)
- Albright LF (2170)
- Albright LF (2171)
- Albright LF (2172)
- Albright LF (2173)
- Albright LF (2174)
- Albright LF (2175)
- Albright LF (2176)
- Albright LF (2177)
- Albright LF (2178)
- Albright LF (2179)
- Albright LF (2180)
- Albright LF (2181)
- Albright LF (2182)
- Albright LF (2183)
- Albright LF (2184)
- Albright LF (2185)
- Albright LF (2186)
- Albright LF (2187)
- Albright LF (2188)
- Albright LF (2189)
- Albright LF (2190)
- Albright LF (2191)
- Albright LF (2192)
- Albright LF (2193)
- Albright LF (2194)
- Albright LF (2195)
- Albright LF (2196)
- Albright LF (2197)
- Albright LF (2198)
- Albright LF (2199)
- Albright LF (2200)
- Albright LF (2201)
- Albright LF (2202)
- Albright LF (2203)
- Albright LF (2204)
- Albright LF (2205)
- Albright LF (2206)
- Albright LF (2207)
- Albright LF (2208)
- Albright LF (2209)
- Albright LF (2210)
- Albright LF (2211)
- Albright LF (2212)
- Albright LF (2213)
- Albright LF (2214)
- Albright LF (2215)
- Albright LF (2216)
- Albright LF (2217)
- Albright LF (2218)
- Albright LF (2219)
- Albright LF (2220)
- Albright LF (2221)
- Albright LF (2222)
- Albright LF (2223)
- Albright LF (2224)
- Albright LF (2225)
- Albright LF (2226)
- Albright LF (2227)
- Albright LF (2228)
- Albright LF (2229)
- Albright LF (2230)
- Albright LF (2231)
- Albright LF (2232)
- Albright LF (2233)
- Albright LF (2234)
- Albright LF (2235)
- Albright LF (2236)
- Albright LF (2237)
- Albright LF (2238)
- Albright LF (2239)
- Albright LF (2240)
- Albright LF (2241)
- Albright LF (2242)
- Albright LF (2243)
- Albright LF (2244)
- Albright LF (2245)
- Albright LF (2246)
- Albright LF (2247)
- Albright LF (2248)
- Albright LF (2249)
- Albright LF (2250)
- Albright LF (2251)
- Albright LF (2252)
- Albright LF (2253)
- Albright LF (2254)
- Albright LF (2255)
- Albright LF (2256)
- Albright LF (2257)
- Albright LF (2258)
- Albright LF (2259)
- Albright LF (2260)
- Albright LF (2261)
- Albright LF (2262)
- Albright LF (2263)
- Albright LF (2264)
- Albright LF (2265)
- Albright LF (2266)
- Albright LF (2267)
- Albright LF (2268)
- Albright LF (2269)
- Albright LF (2270)
- Albright LF (2271)
- Albright LF (2272)
- Albright LF (2273)
- Albright LF (2274)
- Albright LF (2275)
- Albright LF (2276)
- Albright LF (2277)
- Albright LF (2278)
- Albright LF (2279)
- Albright LF (2280)
- Albright LF (2281)
- Albright LF (2282)
- Albright LF (2283)
- Albright LF (2284)
- Albright LF (2285)
- Albright LF (2286)
- Albright LF (2287)
- Albright LF (2288)
- Albright LF (2289)
- Albright LF (2290)
- Albright LF (2291)
- Albright LF (2292)
- Albright LF (2293)
- Albright LF (2294)
- Albright LF (2295)
- Albright LF (2296)
- Albright LF (2297)
- Albright LF (2298)
- Albright LF (2299)
- Albright LF (2300)
- Albright LF (2301)
- Albright LF (2302)
- Albright LF (2303)
- Albright LF (2304)
- Albright LF (2305)
- Albright LF (2306)
- Albright LF (2307)
- Albright LF (2308)
- Albright LF (2309)
- Albright LF (2310)
- Albright LF (2311)
- Albright LF (2312)
- Albright LF (2313)
- Albright LF (2314)
- Albright LF (2315)
- Albright LF (2316)
- Albright LF (2317)
- Albright LF (2318)
- Albright LF (2319)
- Albright LF (2320)
- Albright LF (2321)
- Albright LF (2322)
- Albright LF (2323)
- Albright LF (2324)
- Albright LF (2325)
- Albright LF (2326)
- Albright LF (2327)
- Albright LF (2328)
- Albright LF (2329)
- Albright LF (2330)
- Albright LF (2331)
- Albright LF (2332)
- Albright LF (2333)
- Albright LF (2334)
- Albright LF (2335)
- Albright LF (2336)
- Albright LF (2337)
- Albright LF (2338)
- Albright LF (2339)
- Albright LF (2340)
- Albright LF (2341)
- Albright LF (2342)
- Albright LF (2343)
- Albright LF (2344)
- Albright LF (2345)
- Albright LF (2346)
- Albright LF (2347)
- Albright LF (2348)
- Albright LF (2349)
- Albright LF (2350)
- Albright LF (2351)
- Albright LF (2352)
- Albright LF (2353)
- Albright LF (2354)
- Albright LF (2355)
- Albright LF (2356)
- Albright LF (2357)
- Albright LF (2358)
- Albright LF (2359)
- Albright LF (2360)
- Albright LF (2361)
- Albright LF (2362)
- Albright LF (2363)
- Albright LF (2364)
- Albright LF (2365)
- Albright LF (2366)
- Albright LF (2367)
- Albright LF (2368)
- Albright LF (2369)
- Albright LF (2370)
- Albright LF (2371)
- Albright LF (2372)
- Albright LF (2373)
- Albright LF (2374)
- Albright LF (2375)
- Albright LF (2376)
- Albright LF (2377)
- Albright LF (2378)
- Albright LF (2379)
- Albright LF (2380)
- Albright LF (2381)
- Albright LF (2382)
- Albright LF (2383)
- Albright LF (2384)
- Albright LF (2385)
- Albright LF (2386)
- Albright LF (2387)
- Albright LF (2388)
- Albright LF (2389)
- Albright LF (2390)
- Albright LF (2391)
- Albright LF (2392)
- Albright LF (2393)
- Albright LF (2394)
- Albright LF (2395)
- Albright LF (2396)
- Albright LF (2397)
- Albright LF (2398)
- Albright LF (2399)
- Albright LF (2400)
- Albright LF (2401)
- Albright LF (2402)
- Albright LF (2403)
- Albright LF (2404)
- Albright LF (2405)
- Albright LF (2406)
- Albright LF (2407)
- Albright LF (2408)
- Albright LF (2409)
- Albright LF (2410)
- Albright LF (2411)
- Albright LF (2412)
- Albright LF (2413)
- Albright LF (2414)
- Albright LF (2415)
- Albright LF (2416)
- Albright LF (2417)
- Albright LF (2418)
- Albright LF (2419)
- Albright LF (2420)
- Albright LF (2421)
- Albright LF (2422)
- Albright LF (2423)
- Albright LF (2424)
- Albright LF (2425)
- Albright LF (2426)
- Albright LF (2427)
- Albright LF (2428)
- Albright LF (2429)
- Albright LF (2430)
- Albright LF (2431)
- Albright LF (2432)
- Albright LF (2433)
- Albright LF (2434)
- Albright LF (2435)
- Albright LF (2436)
- Albright LF (2437)
- Albright LF (2438)
- Albright LF (2439)
- Albright LF (2440)
- Albright LF (2441)
- Albright LF (2442)
- Albright LF (2443)
- Albright LF (2444)
- Albright LF (2445)
- Albright LF (2446)
- Albright LF (2447)
- Albright LF (2448)
- Albright LF (2449)
- Albright LF (2450)
- Albright LF (2451)
- Albright LF (2452)
- Albright LF (2453)
- Albright LF (2454)
- Albright LF (2455)
- Albright LF (2456)
- Albright LF (2457)
- Albright LF (2458)
- Albright LF (2459)
- Albright LF (2460)
- Albright LF (2461)
- Albright LF (2462)
- Albright LF (2463)
- Albright LF (2464)
- Albright LF (2465)
- Albright LF (2466)
- Albright LF (2467)
- Albright LF (2468)
- Albright LF (2469)
- Albright LF (2470)
- Albright LF (2471)
- Albright LF (2472)
- Albright LF (2473)
- Albright LF (2474)
- Albright LF (2475)
- Albright LF (2476)
- Albright LF (2477)
- Albright LF (2478)
- Albright LF (2479)
- Albright LF (2480)
- Albright LF (2481)
- Albright LF (2482)
- Albright LF (2483)
- Albright LF (2484)
- Albright LF (2485)
- Albright LF (2486)
- Albright LF (2487)
- Albright LF (2488)
- Albright LF (2489)
- Albright LF (2490)
- Albright LF (2491)
- Albright LF (2492)
- Albright LF (2493)
- Albright LF (2494)
- Albright LF (2495)
- Albright LF (2496)
- Albright LF (2497)
- Albright LF (2498)
- Albright LF (2499)
- Albright LF (2500)
- Albright LF (2501)
- Albright LF (2502)
- Albright LF (2503)
- Albright LF (2504)
- Albright LF (2505)
- Albright LF (2506)
- Albright LF (2507)
- Albright LF (2508)
- Albright LF (2509)
- Albright LF (2510)
- Albright LF (2511)
- Albright LF (2512)
- Albright LF (2513)
- Albright LF (2514)
- Albright LF (2515)
- Albright LF (2516)
- Albright LF (2517)
- Albright LF (2518)
- Albright LF (2519)
- Albright LF (2520)
- Albright LF (2521)
- Albright LF (2522)
- Albright LF (2523)
- Albright LF (2524)
- Albright LF (2525)
- Albright LF (2526)
- Albright LF (2527)
- Albright LF (2528)
- Albright LF (2529)
- Albright LF (2530)
- Albright LF (2531)
- Albright LF (2532)
- Albright LF (2533)
- Albright LF (2534)
- Albright LF (2535)
- Albright LF (2536)
- Albright LF (2537)
- Albright LF (2538)
- Albright LF (2539)
- Albright LF (2540)
- Albright LF (2541)
- Albright LF (2542)
- Albright LF (2543)
- Albright LF (2544)
- Albright LF (2545)
- Albright LF (2546)
- Albright LF (2547)
- Albright LF (2548)
- Albright LF (2549)
- Albright LF (2550)
- Albright LF (2551)
- Albright LF (2552)
- Albright LF (2553)
- Albright LF (2554)
- Albright LF (2555)
- Albright LF (2556)
- Albright LF (2557)
- Albright LF (2558)
- Albright LF (2559)
- Albright LF (2560)
- Albright LF (2561)
- Albright LF (2562)
- Albright LF (2563)
- Albright LF (2564)
- Albright LF (2565)
- Albright LF (2566)
- Albright LF (2567)
- Albright LF (2568)
- Albright LF (2569)
- Albright LF (2570)
- Albright LF (2571)
- Albright LF (2572)
- Albright LF (2573)
- Albright LF (2574)
- Albright LF (2575)
- Albright LF (2576)
- Albright LF (2577)
- Albright LF (2578)
- Albright LF (2579)
- Albright LF (2580)
- Albright LF (2581)
- Albright LF (2582)
- Albright LF (2583)
- Albright LF (2584)
- Albright LF (2585)
- Albright LF (2586)
- Albright LF (2587)
- Albright LF (2588)
- Albright LF (2589)
- Albright LF (2590)
- Albright LF (2591)
- Albright LF (2592)
- Albright LF (2593)
- Albright LF (2594)
- Albright LF (2595)
- Albright LF (2596)
- Albright LF (2597)
- Albright LF (2598)
- Albright LF (2599)
- Albright LF (2600)
- Albright LF (2601)
- Albright LF (2602)
- Albright LF (2603)
- Albright LF (2604)
- Albright LF (2605)
- Albright LF (2606)
- Albright LF (2607)
- Albright LF (2608)
- Albright LF (2609)
- Albright LF (2610)
- Albright LF (2611)
- Albright LF (2612)
- Albright LF (2613)
- Albright LF (2614)
- Albright LF (2615)
- Albright LF (2616)
- Albright LF (2617)
- Albright LF (2618)
- Albright LF (2619)
- Albright LF (2620)
- Albright LF (2621)
- Albright LF (2622)
- Albright LF (2623)
- Albright LF (2624)
- Albright LF (2625)
- Albright LF (2626)
- Albright LF (2627)
- Albright LF (2628)
- Albright LF (2629)
- Albright LF (2630)
- Albright LF (2631)
- Albright LF (2632)
- Albright LF (2633)
- Albright LF (2634)
- Albright LF (2635)
- Albright LF (2636)
- Albright LF (2637)
- Albright LF (2638)
- Albright LF (2639)
- Albright LF (2640)
- Albright LF (2641)
- Albright LF (2642)
- Albright LF (2643)
- Albright LF (2644)
- Albright LF (2645)
- Albright LF (2646)
- Albright LF (2647)
- Albright LF (2648)
- Albright LF (2649)
- Albright LF (2650)
- Albright LF (2651)
- Albright LF (2652)
- Albright LF (2653)
- Albright LF (2654)
- Albright LF (2655)
- Albright LF (2656)
- Albright LF (2657)
- Albright LF (2658)
- Albright LF (2659)
- Albright LF (2660)
- Albright LF (2661)
- Albright LF (2662)
- Albright LF (2663)
- Albright LF (2664)
- Albright LF (2665)
- Albright LF (2666)
- Albright LF (2667)
- Albright LF (2668)
- Albright LF (2669)
- Albright LF (2670)
- Albright LF (2671)
- Albright LF (2672)
- Albright LF (2673)
- Albright LF (2674)
- Albright LF (2675)
- Albright LF (2676)
- Albright LF (2677)
- Albright LF (2678)
- Albright LF (2679)
- Albright LF (2680)
- Albright LF (2681)
- Albright LF (2682)
- Albright LF (2683)
- Albright LF (2684)
- Albright LF (2685)
- Albright LF (2686)
- Albright LF (2687)
- Albright LF (2688)
- Albright LF (2689)
- Albright LF (2690)
- Albright LF (2691)
- Albright LF (2692)
- Albright LF (2693)
- Albright LF (2694)
- Albright LF (2695)
- Albright LF (2696)
- Albright LF (2697)
- Albright LF (2698)
- Albright LF (2699)
- Albright LF (2700)
- Albright LF (2701)
- Albright LF (2702)
- Albright LF (2703)
- Albright LF (2704)
- Albright LF (2705)
- Albright LF (2706)
- Albright LF (2707)
- Albright LF (2708)
- Albright LF (2709)
- Albright LF (2710)
- Albright LF (2711)
- Albright LF (2712)
- Albright LF (2713)
- Albright LF (2714)
- Albright LF (2715)
- Albright LF (2716)
- Albright LF (2717)
- Albright LF (2718)
- Albright LF (2719)
- Albright LF (2720)
- Albright LF (2721)
- Albright LF (2722)
- Albright LF (2723)
- Albright LF (2724)
- Albright LF (2725)
- Albright LF (2726)
- Albright LF (2727)
- Albright LF (2728)
- Albright LF (2729)
- Albright LF (2730)
- Albright LF (2731)
- Albright LF (2732)
- Albright LF (2733)
- Albright LF (2734)
- Albright LF (2735)
- Albright LF (2736)
- Albright LF (2737)
- Albright LF (2738)
- Albright LF (2739)
- Albright LF (2740)
- Albright LF (2741)
- Albright LF (2742)
- Albright LF (2743)
- Albright LF (2744)
- Albright LF (2745)
- Albright LF (2746)
- Albright LF (2747)
- Albright LF (2748)
- Albright LF (2749)
- Albright LF (2750)
- Albright LF (2751)
- Albright LF (2752)
- Albright LF (2753)
- Albright LF (2754)
- Albright LF (2755)
- Albright LF (2756)
- Albright LF (2757)
- Albright LF (2758)
- Albright LF (2759)
- Albright LF (2760)
- Albright LF (2761)
- Albright LF (2762)
- Albright LF (2763)
- Albright LF (2764)
- Albright LF (2765)
- Albright LF (2766)
- Albright LF (2767)
- Albright LF (2768)
- Albright LF (2769)
- Albright LF (2770)
- Albright LF (2771)
- Albright LF (2772)
- Albright LF (2773)
- Albright LF (2774)
- Albright LF (2775)

this study
suggestion
a possible

ongenital
studies in
ther study
e of the par-
had ever
ed within

at the full
re to vinyl
lem may
re inevitably

tance of
v safe com-
ng latency
rties would
n any can-
l, days
al com-

be widely
nt length
tial car-
roundings
upational
roblem.
d to, there
of the
ed that in
appear dur-

future re-
o establish
studies in
interaction

between predominantly hepatocytic metabolism and oncogenic effect on mesenchymal tissue such as vascular endothelium, and also the question of whether intermittent short exposures at high concentrations or continuous exposure at a low concentration will carry the greater risk.

References

- Albright LF (1967a) Vinyl Chloride processes. *Chem Eng* 74:123-130
- Albright LF (1967b) Manufacture of vinyl chloride. *Chem Eng* 74:219-224
- Albright LF (1967c) Polymerization of vinyl chloride. *Chem Eng* 74:151-158
- Albright LF (1967d) Vinyl chloride polymerization by suspension processes yields polyvinyl chloride resins. *Chem Eng* 74:145-152
- Albright LF (1967e) Vinyl chloride polymerization by emulsion, bulk and solution processes. *Chem Eng* 74:85-92
- Alrenga DP (1975) Primary angiosarcoma of the liver. Review article. *Int Surg* 60:198-203
- Amann R (1975) Beitrag zur Vinylchlorid-Krankheit. — Ein Fall von Angiosarkom der Leber. Dissertation, Universität Freiburg
- Anderson HA, Snyder S, Lewinson T, Woo C, Lillis R, Selikoff IJ (1978) Levels of CEA among vinyl chloride and polyvinyl chloride exposed workers. *Cancer* 42:1560-1567
- Andrews AW, Zawistowski ES, Valentine CR (1976) A comparison of the mutagenic properties of vinyl chloride and methyl chloride. *Mutat Res* 40:273-276
- Angheliescu F, Otoju M, Dobrinescu E, Hagi-Paraschiv-Dossios L, Dobrinescu G, Ganea V (1969) Clinico-pathogenetic considerations on Raynaud's phenomenon among employees of the polyvinyl chloride industry. (Rumanian text) *Med Interna* 21:473-482
- Annual Report of the Chief Inspector of Factories for the Year 1951 (1953) HMSO London, Cmd 8772
- Antonyuzhenko VA (1968) On the occupational vinyl chloride intoxication. (Russian text). *Gig Tr Prof Zabol* 12: 50-52
- Antweiler H (1976) Studies on the metabolism of vinyl chloride. *Environ Health Perspect* 17:217-219
- Arnaud A, Pommier de Santi P, Garbe L, Payan H, Charpin J (1978) Polyvinyl chloride pneumoconiosis. *Thorax* 33:19-25
- Aryanpur J (1977) Vinyl chloride: its impact on occupational medicine practice in Iran. *J Occup Med* 19:689-692
- Assmann H (1921) Die Röntgendiagnostik der inneren Erkrankungen. Vogel, Leipzig
- Austin GT (1974) Industrially significant organic chemicals, part 3. *Chem Eng* 81:87-89
- Bachner U, Etzel F, Lange CE, Marsteller HJ, Veltman G (1974a) Hämostasebefunde und Ösophagusvarizen bei Vinylchlorid-Krankheit. *Dtsch Med Wochenschr* 99:2409-2410
- Bachner U, Etzel F, Lange CE, Jühe S, Veltman G (1974b) Gerinnungsphysiologische Befunde bei Vinylchloridkrankheit. In: Lehnert G, Szadkowski D, Weber HJ (eds) Jahresbericht der 14. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin. Gentner, Stuttgart, pp 275-280
- Bachner U, Müller R, Egli H (1975a) Clinical relevance of platelet function tests in 1000 patients with hemorrhagic diathesis. *Thromb Res* 6:139-149
- Bachner U, Etzel F, Lange CE, Marsteller HJ, Veltman G (1975b) Hämostasebefunde und Ösophagusvarizen bei Vinylchlorid-Krankheit. In: Marx R, Thies HA (eds) Blutungen des Gastrointestinaltraktes. Schattauer, Stuttgart New York, pp 67-73

- Bachner U, Etzel F, Müller N, Lange CE, Egli H (1976) Präneoplastische und kollagenisierende Veränderungen der Leber und Hämostasebefunde bei PVC-Arbeitern. In: Gastpar H (ed) Onkohämostaseologie. Schattauer, Stuttgart New York, pp 319-326
- Banti G (1898) Splenomegalie mit Leberzirrhose. Beitr Pathol Anat Allg Pathol 24: 21-33
- Barbin A, Bresil H, Croisy A, Jacquignon P, Malaveille C, Montesano R, Bartsch H (1975) Liver-microsome mediated formation of alkylating agents from vinyl bromide and vinyl chloride. Biochem Biophys Res Commun 67:596-603
- Baretta ED, Stewart RD, Mutchler JE (1969) Monitoring exposures to vinyl chloride vapor: breath analysis and continuous air sampling. Am Ind Hyg Assoc J 30:537-544
- Barnes AW (1976) Vinyl chloride and the production of PVC. Proc R Soc Med 69: 277-281
- Bartsch H, Malaveille C, Montesano R, Tomatis L (1975a) Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in *Salmonella typhimurium*. Nature 255:641-643
- Bartsch H, Malaveille C, Montesano R (1975b) Human, rat, and mouse liver mediated mutagenicity of vinyl chloride in *S. typhimurium* strains. Int J Cancer 15/3:429-437
- Bartsch H, Malaveille C, Barbin A, Bresil H, Tomatis L, Montesano R (1976) Mutagenicity and metabolism of vinyl chloride and related compounds. Environ Health Perspect 17:192-198
- Basalae AV, Vazin AN, Kosetkov AG (1972) On the pathogenesis of changes developing due to long-term exposure to the effects of vinyl chloride. Gig Tr Prof Zabol 16:24-27 (Russian text)
- Basu AK, Boyer J, Bhattacharya R, Basu Mallik KC, Sen Gupta KP (1967a) Non-cirrhotic portal fibrosis with portal hypertension: a new syndrome. I. Clinical and function studies and results of operations. Indian J Med Res 55:336-350
- Basu Mallik KC, Sen Gupta KP, Basu AK, Biswas SK, Pal NC, Boyer J (1967b) Non-cirrhotic portal fibrosis with portal hypertension: a new syndrome. II. Histopathological studies. Indian J Med Res 55:351-359
- Baumann E (1872) Über einige Vinylverbindungen. Liebigs Ann Pharm 163:308-322
- Baxter PJ (1976) Epidemiological studies of PVC manufactures and fabricators, and primary angiosarcoma of the liver. Proc R Soc Med 69:297-299
- Baxter PJ, Fox AJ (1975) Angiosarcoma of the liver as the certified cause of death 1963-1973. Lancet II:27-28
- Baxter PJ, Fox AJ (1976) Angiosarcoma of the liver in P.V.C. fabricators. Lancet I:245
- Baxter, PJ, Anthony PP, McSween RNM, Scheuer PJ (1977) Angiosarcoma of the liver in Great Britain, 1963-1973. Br Med J II:919-921
- Becker V, Büsscher K (1961) Über das Hämangioendotheliom der Leber. Acta Hepato-Splenol 8:356-379
- Benoit J-P (1967) L'acro-osteolyse d'origine professionnelle. Thèse, University of Lyon
- Berk PD, Martin JF, Waggoner JG (1975) Persistence of vinyl chloride induced liver injury after cessation of exposure. Ann NY Acad Sci 246:70-77
- Berk PD, Martin JF, Young RS, Creech J, Selikoff IJ, Falk H, Watanabe P, Popper H, Thomas L (1976) Vinyl chloride-associated liver disease. Ann Intern Med 84: 717-731
- Berrod JL, Lazard P, Pierre C, Puech A, Ravier E, Rety J, Smaghe G (1978) A Propos de 10 observations d'angiosarcomes hépatiques survenus chez des ouvriers exposés au chlorure de vinyle. Paper presented at the 19th International Congress of Occupational Medicine, Dubrovnik, 25-30 September, 1978
- Berry G, Rossiter CE (1976) Vinyl chloride and mortality? Lancet II:416-417
- Berufsgenossenschaftliche Grundsätze für arbeitsmedizinische Vorsorgeuntersuchungen. Gefährdung durch Vinylchlorid. Fassung Juli 1974. Arbeitsmed Sozialmed Praeventivmed 9:226-229
- Bie: C te Biers gra (St Biersa schä Vinylchlor 88
- Blendis LM, S sion in vin 75:206-2
- Block JB (197 229:53-54
- Blomfield J, c current he: Bolt HM (197 HM, Banna England, p Bolt HM, Kap I:1425 Bolt HM, Kap of 14C vinyl Bolt HM, Kap in the rat Bolt HM, Lash in the rat Bolt HM, Kap lite. In: G chlorid-Kra Bonneton G de rupture rure de vinyl Bonneton G Marty F, P leurs du chl Bonse G, Urba oxirane ion perfused rat Borak J (1927 Neurol Psyc Border EA, W oxide and Interact 17 Boyer JL, Sen (1967) Idi cirrhosis and Brady J, Liber Polan A, Vi Natl Cancer

und kollageni-
seitern. In:
pp 319-326
Pathol 24:

irtsch H
vinyl bro-

vinyl chloride
J 30:537-

Me

d m
nu

er n

15/1

16) A

He

ages

rof 4

1) Non-

Unical and

50

17b) Non-

Histopathol

308-322

ators, and

death

Lancet

a of the liver

Acta Hepato

ity of Lyon
uced liver

Popper H,
d 84:

18) A Propos

ss of

417

ersuchungen.

ned

- Biersack HJ, Lange CE, Veltman G, Winkler C (1975a) Bedeutung der Leber- und Milzszintigraphie für die Diagnose der Vinylchlorid-Krankheit. Bericht über die 15. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin. 24.-26.4.1975, pp 305-310. (Brenner W, Rohmert W, Rutenfranz J, eds), Gentner, Stuttgart
- Biersack HJ, Lange CE, Ebinger H, Marsteller HJ, Leibach WK, Veltman G, Winkler C (1975b) Sequenzszintigraphische Untersuchungen von Leber und Milz bei Patienten mit Vinylchlorid-Krankheit. Dtsch Med Wochenschr 100:615-617
- Biersack HJ, San Luis T Jr, Lange CE, Thelen M, Veltman G, Winkler C (1977a) Scintigraphy of liver and spleen in vinyl chloride workers. Acta Hepato Gastroenterol (Stuttg) 24:357-361
- Biersack HJ, Ebinger H, Winkler C (1977b) Leber-Milz-Szintigramm bei Vinylchloridschäden. In: Gutacker HW, Leibach WK (eds) Leberschäden durch Vinylchlorid - Vinylchlorid-Krankheit. Witzstrock, Baden-Baden Brüssel Köln New York, pp 84-88
- Blendis LM, Smith PM, Lawrie BW, Stephens MR, Evans WD (1978) Portal hypertension in vinyl chloride monomer workers. A hemodynamic study. Gastroenterology 75:206-211
- Block JB (1974) Angiosarcoma of the liver following vinyl-chloride exposure. JAMA 229:53-54
- Blomfield J, Dixon SR, McCredie DA (1971) Potential hepatotoxicity of copper in recurrent hemodialysis. Arch Intern Med 128:555-560
- Bolt HM (1978) Metabolic activation of halogenated ethylene. In: Remmer H, Bolt HM, Bannasch P, Popper H (eds) Primary liver tumors. MTP Press, Lancaster/England, pp 285-294
- Bolt HM, Kappus H, Buchter A, Bolt W (1975) Metabolism of vinyl chloride. Lancet 1:1425
- Bolt HM, Kappus H, Kaufmann R, Appel KE, Buchter A, Bolt W (1976a) Metabolism of ^{14}C vinyl chloride in vitro and in vivo. INSERM Symp Ser 52:151-164
- Bolt HM, Kappus H, Buchter A, Bolt W (1976b) Disposition of $[1,2-^{14}\text{C}]$ vinyl chloride in the rat. Arch Toxicol 35:153-162
- Bolt HM, Laib RJ, Kappus H, Buchter A (1977a) Pharmacokinetics of vinyl chloride in the rat. Toxicology 7:179-188
- Bolt HM, Kappus H, Buchter A, Bolt W (1977b) Reaktivität der Vinylchloridmetabolite. In: Gutacker HW, Leibach WK (eds) Leberschäden durch Vinylchlorid - Vinylchlorid-Krankheit. Witzstrock, Baden-Baden Brüssel Köln New York, pp 32-35
- Bonneton G, Champetier J, Sotto J, Guidicelli G, Letoublon C, Panh M (1975) Un cas de rupture spontanée d'angiosarcome hépatique chez un travailleur exposé au chlorure de vinyle. Chirurgie 101:936-942
- Bonneton G, Champetier J, Fournet J, Guidicelli H, Legrand J, Dupré A, Hostein M, Marty F, Panh M (1977) Angiosarcome hépatique et fibrose portale chez les travailleurs du chlorure de vinyle. Nouv Presse Méd 6:735-742
- Bonse G, Urban T, Reichert D, Henschler D (1975) Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem Pharmacol 24:1829-1834
- Borak J (1927) Zur Pathogenese und Therapie der Raynaud'schen Krankheit. Z Ges Neurol Psychiatr 3:1-16
- Border EA, Webster I (1977) The effect of vinyl chloride monomer, chloroethylene oxide and chloroacetaldehyde on DNA synthesis in regenerating rat liver. Chem Biol Interact 17:239-247
- Boyer JL, Sen Gupta KP, Biswas SK, Pal NC, Basu Mallik KC, Iber FL, Basu AK (1967) Idiopathic portal hypertension. Comparison with the portal hypertension of cirrhosis and extrahepatic portal vein obstruction. Ann Intern Med 66:41-68
- Brady J, Liberatore F, Harper P, Greenwald P, Burnett W, Davies JNP, Bishop M, Polan A, Vianna N (1977) Angiosarcoma of the liver: an epidemiologic survey. J Natl Cancer Inst 59:1383-1385

- Bridbord K, Brubaker PE, Gay B, French JG (1975) Exposure to halogenated hydrocarbons in the indoor environment. *Environ Health Perspect* 11:215-220
- Bronfenmajer S, Schaifner F, Popper H (1966) Fat-storing cells (lipocytes) in human liver. *Arch Pathol* 82:447-453
- Broussard G (1969) Patologia da resina polivinilica. *Med Bull (Naples)* 52:102-108
- Bruder U, Straby A (1975) Exposure to vinyl chloride in PVC processing industries. - Report TK 176 on a survey in collaboration with the Swedish Plastics Industry and the Agency for the Protection of Workers, Stockholm, February 1975 (Swedish text)
- Buchter A, Bolt HM, Kappus H, Bolt W (1977) Die Gewebsverteilung von 1,2-¹⁴C-Vinylchlorid bei der Ratte. *Int Arch Occup Environ Health* 39:27-32
- Buffler PA, Wood S, Suarez L, Kilian DJ (1979) Mortality experience of workers in a vinyl chloride monomer production plant. *J Occup Med* 21:195-203
- Byczkowska Z, Langauer-Lewowicka H (1974) Raynaud's syndrome in workers employed in production of polyvinyl chloride. (Polish text). *Pol Tyg Lek* 29:1461-1464
- Byrén D, Holmberg B (1975) Two possible cases of angiosarcoma of the liver in a group of Swedish vinyl chloride-polyvinyl chloride workers. *Ann NY Acad Sci* 246:249-250
- Byrén D, Engholm G, Englund A, Westerholm P (1976) Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. *Environ Health Perspect* 17:167-170
- Carr J, Burginon RM, Vitcha JF, Krantz JC (1949) Anesthesia. XXIV. Chemical constitution of hydrocarbons and cardiac automaticity. *J Pharmacol Exp Ther* 97:1
- Chainuvatti T, Viranuvatti V (1979) Idiopathic portal hypertension and chronic arsenic poisoning. Report of a case. *Am J Dig Dis* 24:70-73
- Chatelain A, Motillon P (1967) Un syndrome d'acro-ostéolyse d'origine professionnelle et de constatation nouvelle en France. *J Radiol Electrol Med Nucl* 48:277-280
- Cheney WD (1965) Acro-osteolysis. *Am J Roentgenol* 94:595-607
- Chowdhury AR, Black M, Lorber SH, Chey WY (1977) Haemangioendotheliomatosis of the liver. A 12-year follow-up. *Gastroenterology* 72:157-160
- Colardyn F, van der Straeten M, Lamont H, van Peteghem T (1976) Acute inhalation-intoxication by combustion of polyvinylchloride. *Int Arch Occup Environ Health* 38:121-127
- Conolly RB, Jaeger RJ, Szabo S (1978) Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride and vinyl bromide after aroclor 1254 pretreatment. *Exp Mol Pathol* 28:25-33
- Cook WA, Giever PM, Dinman BD, Magnuson HJ (1971) Occupational acroosteolysis. II. An industrial hygiene study. *Arch Environ Health* 22:74-82
- Corbett TH (1975) Inhalation anesthetics - more vinyl chloride? *Environ Res* 9:211-214
- Cordier JM, Fievez C, Lefèvre MJ, Sevrin A (1966) Acroostéolyse et lésions cutanées chez deux ouvriers affectés au nettoyage d'autoclaves. *Cah Med Tra* 4:14, 3-39
- Cornish HH, Abar EL (1969) Toxicity of pyrolysis products of vinyl plastics. *Arch Environ Health* 19:15-21
- Couderc P, Panh MH, Pasquier B, Pasquier D, N'Golet A, Faure H (1976) Angiosarcome osseuse révélateur d'une tumeur hépatique chez un travailleur exposé au chlorure de vinyle. *Sem Hôp Paris* 52:1721-1722
- Cowlshaw JL, Pollard EJ, Cowen AE, Powell LW (1979) Liver disease associated with chronic arsenic ingestion. *Aust NZ J Med* 9:310-313
- Creech JL, Johnson MN (1974) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-151
- Creech JL, Makk L (1975) Liver disease among polyvinyl chloride production workers. *Ann NY Acad Sci* 266:88-94
- Creech JL, Johnson MN, Block A (1974a) Epidemiologic notes and reports. Angiosarcoma of the liver among polyvinyl chloride workers. *Morbid Mortal Weekly Rep* 23:49-50
- Creech JL, Makk L (1975) Liver disease among polyvinyl chloride production workers. *Ann NY Acad Sci* 266:88-94
- Dalderup LM (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Lancet* i:24
- Dannaher C, Y. (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *May* 16-29
- Danziger H (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Med Assoc J* 197:1000-1001
- Darke CS (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *tion of PVC*
- Datta DV, Mitra (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *toxication and cirrhotic po*
- Davies IW, Perr (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Environ Poll*
- Deese DE, Joy (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Ind Hyg Assoc*
- Delorme F (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Delorme F (1975)*
- Delorme F (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *ouvriers de la*
- Delorm tact
- Uni
- Delorm Que
- Deign: poly
- Dinmar tion:
- Dodson tiona
- Doll R (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Dominique*
- Anwend: (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Dor JF, Arlaud*
- (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Dressman RC, M*
- mination of v (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Sci* 15:69-71
- Du JT, Tamburri (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *chloride expo*
- Ducatman A, H (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *chromosome*
- Duck BW (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Duck BW (1975)*
- Duck BW (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *307-309*
- Duck BW, Carter (1975) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *Duck BW, Carter*
- chlondre produ

R&S 117148

ated hydro-
220
in human
2:102-108
industries. --
Industry and
(Swedish text)
1,2-¹⁴C-
workers in a
workers em-
29:1461-
liver in a
Acad Sci 246:
necr morbid-
Health Per-
Chemical con-
Ther 97:1
chronic arsenic
professionnelle
277-280
hepatomatosis
inhalation-
ron Health
vinyl fluo-
Exp Mol
osteolysis.
Res 9:211
ms cutanées
14, 3-39
ics. Arch
R&S
117149
th
y-
rs.
p

- Creech JL, Makk L, Whelan JC Jr, Tamburro CH (1974b) Hepatotoxicity among polyvinyl chloride (PVC) production workers during first year of surveillance program. *Gastroenterology* 67:786
- Dalderup LM (1975) Vinyl chloride and haemangiosarcoma of the liver. *J Occup Med* 17:285-286
- Dalderup LM, Freni SC, Bras G, Bronckhorst FB (1976) Angiosarcoma of the liver. *Lancet* I:246
- Dannaher C, Yam LT, Tamburro C (1979) Vinyl chloride associated hepatic angiosarcoma chemotherapy. American Association for Cancer Research, Inc., Meeting May 16-29, 1979. New Orleans, Louisiana
- Danziger H (1960) Accidental poisoning by vinyl chloride. Report of two cases. *Can Med Assoc J* 82:828-830
- Darke CS (1976) Discussion remark to: A.W. Barnes: Vinyl chloride and the production of PVC. *Proc R Soc Med* 69:280-281
- Datta DV, Mitra SK, Chhuttani PN, Chakravarti RN (1979) Chronic oral arsenic intoxication as a possible aetiological factor in idiopathic portal hypertension (non-cirrhotic portal fibrosis) in India. *Gut* 20:378-384
- Davies IW, Perry R (1975) Vinyl chloride monomer's effect on liquids in PVC bottles. *Environ Pollut Manage* 5:22-23
- Deese DE, Joyner RE (1969) Vinyl acetate: a study of chronic human exposure. *Am Ind Hyg Assoc J* 30:449-457
- Delorme F (1978a) 10 cas canadiens d'angiosarcomes du foie chez des ouvriers du chlorure de vinyle. *Ann Anat Pathol (Paris)* 23:97-104
- Delorme F (1978b) Association d'un angiosarcome du foie et d'un hépatome, chez un ouvrier du chlorure de vinyle. *Ann Anat Pathol (Paris)* 23:105-114
- Delorme F, Makk L (1975) Angiosarcoma du foie chez des ouvriers ayant été en contact prolongé avec le chlorure de vinyle: description morphologique des lésions. *Union Med Can* 104:1836-1844
- Delorme F, Thériault G (1978) Ten cases of angiosarcoma of the liver in Shawinigan, Quebec. *J Occup Med* 20:338-340
- Devigneville D, Flucher AM (1953) Etude toxicologique expérimentale des résines polyvinyliques. Service Médicale des Manufactures de Saint-Marcel. Vemon
- Dinman BD, Cook WA, Whitehouse WM, Magnuson HJ, Ditchcock T (1971) Occupational acroosteolysis. I. An epidemiological study. *Arch Environ Health* 22:61-73
- Dodson VN, Dinman BD, Whitehouse WM, Nasr ANM, Magnuson HJ (1971) Occupational acroosteolysis. III. A clinical study. *Arch Environ Health* 22:83-91
- Doll R (1975) Discussion paper. *Ann NY Acad Sci* 246:320-321
- Domininghaus H (1972) Kunststoffe. I. Aufbau und Eigenschaften - Kunststoffsorten - Anwendungen, 2nd ed. VDI-Verlag, Düsseldorf
- Dor JF, Arlaud J, Coste C, Faure F, Kasbarian M, Lebreuil G, Padovani J, Mongin M (1975) Angiome capillaire et caverneux diffus du foie, chez un travailleur du chlorure de polyvinyle. *Marseille Med* 112:709-720
- Dressman RC, McFarren EF (1977) A sample-bottle purging method for the determination of vinyl chloride in water at submicrogram per liter levels. *J Chromatogr Sci* 15:69-72
- Du JT, Tamburro CH (1976) Decreased glucose-6-phosphatase activity in liver in vinyl chloride exposed rats. *Fed Proc* 35:1422
- Ducatman A, Hirschhorn K, Selikoff IJ (1975) Vinyl chloride exposure and human chromosome aberrations. *Mutat Res* 31/3:163-168
- Duck BW (1975) Vinyl chloride carcinogenesis. *Br J Cancer* 32:260-261
- Duck BW (1976) Medical surveillance of vinyl chloride workers. *Proc R Soc Med* 69:307-309
- Duck BW, Carter JT (1976) Letter to the editor. *Lancet* II:195
- Duck BW, Carter JT, Combes EJ (1975) Mortality study of workers in a polyvinyl-chloride production plant. *Lancet* II:1197-1199

- Dugois P, Amblard P, de Bignicourt B, Legrand J (1972) Acropathie polyvinylque professionnelle. *Bull Soc Fr Dermatol Syphiligr* 79: 197-198
- Dupas J, Badelon P, Daydé G (1936) Ostéolyse essentielle progressive de la main gauche d'origine indéterminée. *Mem Acad Chir* 62: 148-158
- van Duuren L (1975) On the possible mechanism of carcinogenic action of vinyl chloride. *Ann NY Acad Sci* 246: 258-267
- Dyer RF, Esch HV (1976) Polyvinyl chloride toxicity in fires. Hydrogen chloride toxicity in fire fighters. *JAMA* 236: 393-397
- Edmonds LD, Falk H, Nissin JE (1975) Congenital malformations and vinyl chloride. *Lancet* II: 1098
- Edmondson HA (1958) Tumours of the liver and intrahepatic bile ducts. In: Edmondson HA (ed) *Atlas of tumor pathology*, sect VII, fasc 25. Published by Armed Forces Institute of Pathology, Washington, pp 1-216
- Elmore JD, Wong JL, Laumbach AD, Streips UN (1976) Vinyl chloride mutagenicity via the metabolites chloro-oxirane and chloroacetaldehyde monomer hydrate. *Biochem Biophys Acta* 442: 405-419
- Elson L, Burnstein N (1954) Idiopathic atrophy of bones of feet with typical "neurotrophic" changes. *Am J Med* 16: 909-914
- Escartin Marin P, Alvarez Bustos G, Garcia Plaza A, Fernandez Corugedo A, Arenas Mirave I, Chantar Barrios C (1974) Hipertensión porta idiopática. *Rev Clin Esp* 133: 255-262
- van Esch GJ, van Logten MH (1975) Vinyl chloride: a report of a European assessment. *Toxicology* 4: 1-4
- Fairhall LT (1957) *Industrial toxicology*. 2nd ed. Williams & Wilkins, Baltimore
- Falk H, Waxweiler RJ (1976) Epidemiological studies of vinyl chloride health effects in the United States. *Proc R Soc Med* 69: 303-306
- Falk H, Creech JL Jr, Heath CW Jr, Johnson MN, Key MM (1974a) Hepatic disease among workers at a vinyl chloride polymerization plant. *JAMA* 230: 59-63
- Falk H, Heath CW Jr, Carter CD, Wagoner JK, Waxweiler RJ, Stringer WT (1974b) Mortality among vinyl chloride workers. *Lancet* II: 784
- Feron VJ, Kroes R (1979) One-year time sequence inhalation toxicity study of vinyl chloride in rats. II. Morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart, and spleen. *Toxicology* 13: 131-141
- Feron VJ, Speek AJ, Willems ML, van Battum D, de Groot AP (1975) Observations on the oral administration and toxicity of vinyl chloride in rats. *Food Cosmet Toxicol* 13: 633-638
- Feron VJ, Kruijsse A, Til HP (1979a) One-year time sequence inhalation toxicity study of vinyl chloride in rats. I. Growth, mortality, haematology, clinical chemistry and organ weights. *Toxicology* 13: 25-28
- Feron VJ, Spit BJ, Immel HR, Kroes R (1979b) One-year time sequence inhalation toxicity study of vinyl chloride in rats. III. Morphological changes in the liver. *Toxicology* 13: 143-154
- Fiechtner JJ, Reyes CN Jr (1976) Angiosarcoma of the liver in a rural population. Four cases diagnosed in a 29-month period. *JAMA* 236: 1704-1706
- Filatova VS, Babochkina MS (1964) Hygienic assessment of some types of equipment employed for drying and screening of polyvinyl chloride resins. *Gig Tr Prof Zabol* 8: 9-13 (Russian text)
- Filatova VS, Gronsborg ES (1957) Hygienic working conditions in the production of polyvinyl chloride resins and measures for improvement. *Gig Sanit* 1: 38-42 (Russian text)
- Filatova VS, Balakhonova LI, Gronsborg ES (1958) Hygienic characteristics of vinyl chloride production. *Gig Tr Prof Zabol* 2: 6-9 (Russian text)
- Filatova VS, Blagodatina VM, Goffman FE (1964) The efficacy of health measures in the production of polyvinyl chloride resins. *Gig Tr Prof Zabol* 8: 3-6 (Russian text)
- Fischer J, Wolf R (1963) Die quantitative Abschätzung der Milzgröße mit Hilfe der Scintigraphie. *Dtsch Med Wochenschr* 88: 1430-1437

Vinyl

Fischer

(19

Fleig

Art

Fleisch

Hoc

sion

Woo

Fomen

of t

poly

Fox AJ

Fox AJ

selec

Fox AJ

mon

34:1

Frenze

Arbe

Sozia

Frey HJ

hand

A-3

Frongia

zione

Funes-C

Golk

Lanc

Futh U

tion

Gabor

Apr

si p

Gama

86

Garro A

effec

Gay BW

ride

Gedick

vinyl

278

Gedick

bei

Lebe

York

Gehring

for

App

Gehring

to vi

15

Gerrits

R&S 117150

polyvinylque
de la main
on of vinyl chlo-
gen chloride tox-
l vinyl chloride.
ets. In: Edmond-
by Armed
le mutagenicity
er hydrate.
a typical "neuro-
edo A. Arenas
Rev Clin Esp
ropean assess-
Baltimore
le health effects
epatic disease
0:59-63
- WT (1974b)
study of vinyl
cruminous
Observations on
Cosmet Toxicol
tion toxicity
clinical chem-
nce inhalation
in the liver
il population.
06
pes of equipment
g Tr Prof Zabol
re production of
1:38-42 (Russian
er inyl
all R&S es in
n text)
der

- Fischer J, Mundschenk H, Wolf R (1965) Milzszintigraphie mit 1-Bromomercuri (197Hg)-2-hydroxypropan (BMHP). ROEFO 103:349-366
- Fleig I, Thiess AM (1974) Chromosomen-Untersuchungen bei Vinylchlorid-Exposition. Arbeitsmed Sozialmed Praeventivmed 9:280-283
- Fleischmann R, Schlote W, Schomerus H, Wolburg H, Castrillon-Oberndorfer WL, Hoensch H (1977) Kleinknotige Leberzirrhose mit ausgeprägter portaler Hypertension als Folge einer Vitamin-A-Intoxikation bei Psoriasis-Behandlung. Dtsch Med Wochenschr 102:1637-1640
- Fomenko VN, Katosova LD, Pavlenko GI (1976) Cytogenetic analysis of lymphocytes of the peripheral blood from workers employed in the process of vinyl chloride polymerization. Gig Tr Prof Zabol 20:48-50 (Russian text)
- Fox AJ (1976) Vinyl chloride and mortality? Lancet II:417
- Fox AJ, Collier PF (1976) Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. Br J Prev Soc Med 30:225-230
- Fox AJ, Collier PF (1977) Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34:1-10
- Frentzel-Beyme R, Schmitz T, Thiess AM (1978) Mortalitätsstudie bei VC-/PVC- Arbeitern der BASF Aktiengesellschaft, Ludwigshafen am Rhein. Arbeitsmed Sozialmed Praeventivmed 13:218-228
- Frey HE (1973) Vinyl chloride and polyvinyl chloride resins. In: Chemical economics handbook. Stanford Research Institute (SRI), Menlo Park, California, pp 580.1881 A-580.1885 B
- Frongia N, Spinazzola A, Bucarelli A (1974) Lesioni polmonari sperimentali da inalazione prolungata di polveri di PVC in ambiente di lavoro. Med Lav 65:321-342
- Funes-Cravioto F, Lambert B, Lindsten J, Ehrenberg L, Natarajan AT, Osterman-Golkar S (1975) Chromosome aberrations in workers exposed to vinyl chloride. Lancet I:459
- Futh U, Pietzke HU (1974) Hämangioendotheliom der Leber nach Thorotrast-Applikation vor 30 Jahren. ROEFO 121:398-399
- Gabor S, Radu M, Preda N, Abrudean S, Ivanof L, Anca Z, Valaczkay C (1964) Aprecieri asupra unor modificari biochimice la muncitorii din industria sintezei si polimerizati chlorurii de vinil. Igiena (Bucharest) 13:409-418
- Gama C, Meira JBB (1978) Occupational acro-osteolysis. J Bone Joint Surg (Am) 60:86-90
- Garro AJ, Guttenplan JB, Milvy P (1976) Vinyl chloride dependent mutagenesis: effects of liver extracts and free radicals. Mutat Res 38:81-88
- Gay BW, Lonneman WA, Bridbord K, Moran JB (1975) Measurements of vinyl chloride from aerosol sprays. Ann NY Acad Sci 246:286-295
- Gedigk P, Müller R, Bechtelsheimer H (1975) Morphology of liver damage among polyvinyl chloride production workers. A report of 51 cases. Ann NY Acad Sci 246:278-285
- Gedigk P, Müller R, Schattenberg PJ, Totović V (1977) Morphologie der Leberschäden bei chronischer Vinylchlorid-Intoxikation. In: Gutacker HW, Leibach WK (eds) Leberschäden durch Vinylchlorid. Witzstrock, Baden-Baden, Brüssel Köln New York. pp 43-52
- Gehring PJ, Watanabe PG, Park CN (1978) Resolution of dose response toxicity data for chemicals requiring metabolic activation: example - vinyl chloride. Toxicol Appl Pharmacol 44:581-591
- Gehring PJ, Watanabe PG, Park CN (1979) Risk of angiosarcoma in workers exposed to vinyl chloride as predicted from studies in rats. Toxicol Appl Pharmacol 49:15-21
- Gerrits WBJ, van Aken WG, van der Meer J, Vreeken J (1974) Splenomegaly associated with chronic consumption coagulopathy. Acta Med Scand 195:425-430
- Giaccai L (1952) Familial and sporadic neurogenic acroosteolysis. Acta Radiol 38:17-29

- Gitsios CT (1971) Acro-osteolysis in PVC workers. *Med Bull Stand Oil Co* 31:49-56
- Gokel JM, Liebezeit E, Eder M (1976) Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl chloride exposure. *Virchows Arch (Pathol Anat)* 372:195-203
- Good WO, Ellison C, Archer VE (1975) Sputum cytology among frequent users of pressurized spray cans. *Cancer Res* 35:216-221
- Gordon DE, Thomas LB, Kent G, Calandra J, Bahu R, Popper H (1974) Hepatic angiosarcoma in man and rodents following prolonged exposure to vinyl chloride. *Gastroenterology* 67:794
- Grannis FW (1975) Guido Banti's hypothesis and its impact on the understanding and treatment of portal hypertension. *Mayo Clin Proc* 50:41-47
- Green T, Hathway DE (1975) The biological fate in rats of vinyl chloride in relation to its oncogenicity. *Chem Biol Interact* 11:545-562
- Green T, Hathway DE (1977) The chemistry and biogenesis of the S-containing metabolites of vinyl chloride in rats. *Chem Biol Invest* 17:137-150
- Green T, Hathway DE (1978) Interactions of vinyl chloride with rat liver DNA in vivo. *Chem Biol Interact* 22:211-224
- Greenberg BE, Street DM (1957) Idiopathic non-familial acro-osteolysis. *Radiology* 69:259-262
- Greim H, Bonse G, Radwan Z, Reichert D, Henschler D (1975) Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. *Biochem Pharmacol* 24:2013-2017
- Greim H, Bonse G, Henschler D (1977) Mutagenität von Vinylchlorid und anderen chlorierten Äthylenen. In: Gutacker HW, Leibach WK (eds) *Leberschäden durch Vinylchlorid*. Witzstrock, Baden-Baden Brüssel Köln New York, pp 36-40
- Griciute L (1979) The carcinogenicity of vinyl chloride. *IARC Sci Publ* 22:3-11
- Grigorescu I, Toba G (1966) Clorura di vinyl. Aspecte de toxicologie industriale. *Rev Chim (Bucharest)* 17:499
- Hahn E, Aderka D, Suprun H, Shtamler B (1979) Occupational acroosteolysis in vinyl chloride workers in Israel. *Isr J Med Sci* 15:218-222
- Haley TJ (1975) Vinyl chloride: how many unknown problems? *J Toxicol Environ Health* 1:47-73
- Harms I (1954) Über die familiäre Akroosteolyse. *ROEFO* 80:727-732
- Harnasch H (1949/50) die Akroosteolysis, ein neues Krankheitsbild. *ROEFO* 72:352-359
- Harris DK, Adams WGF (1967) Acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride. *Br Med J* III:712-714
- Heath CW, Falk H, Creech JL (1975) Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann NY Acad Sci* 246:231-236
- Hefner RE Jr, Watanabe PG, Gehring PJ (1975a) Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. *Ann NY Acad Sci* 246:135-148
- Hefner RE Jr, Watanabe PG, Gehring PJ (1975b) Percutaneous absorption of vinyl chloride. *Toxicol Appl Pharmacol* 34:529-532
- Henschler D (ed) (1972/73) *Gesundheitsschädliche Arbeitsstoffe*, Verlag Chemie, Weinheim
- Henschler D (1977a) Metabolismus von Vinylchlorid. In: Gutacker HW, Leibach WK (eds) *Leberschäden durch Vinylchlorid*. Witzstrock, Baden-Baden Brüssel Köln New York, pp 27-31
- Henschler D (1977b) Metabolism and mutagenicity of halogenated olefins - a comparison of structure and activity. *Environ Health Perspect* 21:61-64
- Henschler D (1977c) Mechanismen der Aktivierung chlorierter aliphatischer Verbindungen - experimentelle Zugänge und klinische Bedeutung. *Arzneim Forsch* 27:1827-1832
- Heusermann U, chlorid-Krank
- Heusermann U, strukturelle U
- Arch (Pathol
- Holmberg B, Kromm
- mice. *Acta Ve*
- Hooper NK, Har
- 603
- Hruban Z, Russe
- in livers of tw
- Huberman E, Ba
- cells by two vi
- hyde. *Int J Ca*
- Hublet P (1975)
- Belg Méd Soc
- Hublet P, Lefevr
- sarcome du fo
- vinyle monom
- Huet PM, Guilla
- sinusoidal port
- Gastroenterol
- Hussain S, Oster
- vinyl chloride
- IARC (1974) Inte
- vinyl chloride
- Iber FL (1969) O
- tension. *Ann I*
- Iber FL (1970) P
- NY Acad Sci
- Imanaga H, Yama
- tension accord
- Infante PF (1976
- ride production
- Infante PF, Wago
- of vinyl-chlor
- Infante PF, Wago
- of vinyl-chlor
- Irish E, W
- Toxicol
- pp 117
- Ito T, W
- len, W
- Oka, a
- Ivaneti, s
- hepa, s
- 74:1, 18
- Jacob F, e
- prov, u
- Jaeger R, (1975)
- action with 1,1
- Jaeger RJ, Reyno
- injury by vinyl
- 726
- Jaeger RJ, Conoli
- ated hydrocarb

Oil Co 31:49-56
 (cellular carcinoma
 (Pathol Anat) 372:

frequent users of

(1974) Hepatic angio-
 vinyl chloride. Gastro-

the understanding and

chloride in relation to

the S-containing metabo-

in rat liver DNA in

analysis. Radiology

mutagenicity in vitro
 action of metabolic

lorid und anderen
 überschäden durch

10

3-11

riale. Rev

sis in vinyl

Environ

1972:

the poly-

angiosarcoma of the
 NY Acad Sci 246:

of the fate of
 135-148

absorption of vinyl

Verlag Chemie.

er HW, Leibach WK
 len Brüssel Köln

d olefins - a com-
 1-64

phatischer Verbin-
 zneim Forsch 27:

Heusermann U, Stutte HJ (1977a) Zur Ätiologie der Thrombozytopenie bei der Vinyl-
 chlorid-Krankheit. Blut 35:317-322

Heusermann U, Stutte HJ (1977b) Enzymhistochemische, histometrische und ultra-
 strukturelle Untersuchungen von Milzen bei der Vinylchlorid-Krankheit. Virchows
 Arch (Pathol Anat) 375:303-317

Holmberg B, Kronevi T, Winell M (1976) The pathology of vinyl chloride exposed
 mice. Acta Vet scand 17:238-342

Hooper NK, Harris RH, Ames BN (1979) Chemical carcinogenesis. Science 203:602-
 603

Hruban Z, Russell RM, Boyer JL, Glagov S, Bagheri SA (1974) Ultrastructural changes
 in livers of two patients with hypervitaminosis A. Am J Pathol 76:451-462

Huberman E, Bartsch H, Sachs L (1975) Mutation induction in chinese hamster V79
 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloroacetalde-
 hyde. Int J Cancer 16:639-644

Hublet P (1975) Exposé des nuisances industrielles dues au chlorure de vinyle. Arch
 Belg Méd Soc 33:73-89

Hublet P, Lefèvre MJ, Decuyper L, Hanin C, Hamels J, Fievez M (1977) Un cas d'angio-
 sarcome du foie chez un travailleur ayant été longuement exposé au chlorure de
 vinyle monomère. Arch Belg Méd Soc 35:601-622

Huet PM, Guillaume E, Cote J, Legare A, Lavoie P, Viallet A (1975) Noncirrhotic pre-
 sinusoidal portal hypertension associated with chronic arsenical intoxication.
 Gastroenterology 68:1270-1277

Hussain S, Osterman-Golkar S (1976) Comment on the mutagenic effectiveness of
 vinyl chloride metabolites. Chem Biol Interact 12:265-267

IARC (1974) Internal Technical Report no. 74/005. Report of a working group on
 vinyl chloride. Lyon 24-25 June 1974, pp 1-55

Iber FL (1969) Obliterative portal venopathy of the liver and idiopathic portal hyper-
 tension. Ann Intern Med 71:660-661

Iber FL (1970) Portal hypertension in the presence of normal liver morphology. Ann
 NY Acad Sci 170:115-126

Imanaga H, Yamamoto S, Kuroyanagi Y (1962) Surgical treatment of portal hyper-
 tension according to state of intrahepatic circulation. Ann Surg 155:42-50

Infante PF (1976) Oncogenic and mutagenic risks in communities with polyvinyl chlo-
 ride production facilities. Ann NY Acad Sci 271:49-57

Infante PF, Wagoner JK, McMichael AJ, Waxweiler RJ, Falk H (1976a) Genetic risks
 of vinyl-chloride. Lancet i:734-735

Infante PF, Wagoner JK, McMichael AJ, Waxweiler RJ, Falk H (1976b) Genetic risks
 of vinyl-chloride. Letter to the editor. Lancet i:1289-1290

Irish DD (1963) Halogenated hydrocarbons: I. Aliphatic. In: Fasset DW, Irish DD (eds)
 Toxicology. Wiley, New York London (Industrial hygiene and toxicology, vol II,
 pp 241 ff)

Ito T, Nemoto M (1952) Die Kupfferschen Sternzellen und die "Fettspeicherungszei-
 len" (fat-storing cells) in der Blutkapillarenwand in der menschlichen Leber.
 Okajima Folia Anat Jpn 24:243-258

Ivanetich KM, Aronson I, Katz ID (1977) The interaction of vinyl chloride with rat
 hepatic microsomal cytochrome p-450 in vitro. Biochem Biophys Res Commun
 74:1411-1418

Jacob PJ, Thériault GP (1975) Distribution of primary cancers of the liver in the
 province of Quebec. Can Med Assoc J 112:305-307

Jaeger RJ (1975) Vinyl chloride monomer: comments on its hepatotoxicity and inter-
 action with 1,1-dichloroethylene. Ann NY Acad Sci 246:150-151

Jaeger RJ, Reynolds ES, Conolly RB, Moslen MT, Murphy SD (1974) Acute hepatic
 injury by vinyl chloride in rats pretreated with phenobarbital. Nature 252:724-
 726

Jaeger RJ, Conolly BB, Murphy SD (1975) Short-term inhalation toxicity of halogen-
 ated hydrocarbons. Arch Environ Health 30:26-31

- Jaeger RJ, Murphy SD, Reynolds ES, Szabo S, Moslen MT (1977) Chemical modification of acute hepatotoxicity of vinyl chloride monomer in rats. *Toxicol Appl Pharmacol* 41:597-607
- Jayson MIV, Lloyd-Jones K, Berry DC, Bromige M (1976a) Resorption of the mandible in vinyl chloride acroosteolysis. *Arthritis Rheum* 19:971
- Jayson MIV, Bailey AJ, Black C, Jones KL (1976b) Collagen studies in acroosteolysis. *Proc R Soc Med* 69:295-297
- Johnson MN, Creech JL Jr (1974) Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-151
- Jühe S, Lange CE (1972) Sklerodermieartige Hautveränderungen, Raynaud-Syndrom und Akroosteolysen bei Arbeitern der PVC-herstellenden Industrie. *Dtsch Med Wochenschr* 97:1922-1923
- Jühe S, Veltman G (1972) Zur Klinik der sogenannten Vinylchloridkrankheit. (Sklerodermie-ähnliche Veränderungen bei Arbeitern der PVC-herstellenden Industrie.) 1. Internationales Symposium der Werksärzte der chemischen Industrie, Ludwigshafen, 27.-29.4.1972, pp 267-276
- Jühe S, Lange CE, Stein G, Veltman G (1973) Über die sogenannte Vinylchlorid-Krankheit. *Dtsch Med Wochenschr* 98:2034-2037
- Jühe S, Lange CE, Stein G, Veltman G (1974) Über die sogenannte Vinylchlorid-Krankheit. *Berufsdermatosen* 22:4-22
- Kappus H, Bolt HM, Buchter A, Bolt W (1975) Rat liver microsomes catalyze covalent binding of ^{14}C -vinylchloride to macromolecules. *Nature* 257:134-135
- Kappus H, Bolt HM, Buchter A, Bolt W (1976) Liver microsomal uptake of ^{14}C vinyl chloride and transformation to protein alkylating metabolites in vitro. *Toxicol Appl Pharmacol* 37:461-471
- Karstadt M (1976) PVC: Health implications and production trends. *Environ Health Perspect* 17:107-115
- Keplinger ML, Goode JW, Gordon DE, Calandra JC (1975) Interim results of exposure of rats, hamsters, and mice to vinyl chloride. *Ann NY Acad Sci* 246:219-220
- Kettner H (1975) Umweltschutz in der Sowjetunion. III. Maximale Arbeitsplatz-Konzentrationen (MAK-Werte) von Schadstoffen und ihre Normierung. In: *Berichte des Osteuropa-Instituts*, Heft 108. Freie Universität, Berlin
- Kistler HJ, Plüer S, Dickenmann W, Pirozynski W (1977) Portale Hypertonie ohne Leberzirrhose bei chronischer Vitamin-A-Intoxikation. *Schweiz Med Wochenschr* 107:825-832
- Kluge T, Sommerschild H, Flatmark A (1970) Sinusoidal portal hypertension. *Surgery* 68:294-300
- Knolle J, Förster E, Roessner A, Themann H, Höhn P, Meyer zum Büschenfelde KH (1974) Die nichtzirrhotische portale Fibrose (hepatoportale Sklerose) nach chronischer Arsenvergiftung. *Dtsch Med Wochenschr* 99:903-908
- Koischwitz D, Marsteller HJ, Lackner K, Brecht G, Brecht T (1980) Veränderungen der Hand- und Fingerarterien bei der Vinylchloridkrankheit. *ROEFO* 132:62-68
- Konetzke G, Bittersohl G, Grund W, Schramm T, Teichmann B, Zschunke E (1978) Über die Bedeutung des Vinylchlorids als Schadstoff aus der Sicht der Arbeitsmedizin, experimentellen Onkologie und Industrietoxikologie. *Z ges Hyg* 24:501-507
- Kornblum K (1929) Bone changes in Raynaud's disease. *Am J Roentgenol* 21:448-452
- Kovač A, Kurajića L, Jurić-Ružić D, Parać B (1969) Acropathia extremitatum in polymerizatione vinyl-chloridi - nova profesionalna bolest. *Liječ Vjesn* 91:5-17
- Kramer CG, Mutchler JE (1972) The correlation of clinical and environmental measurements for workers exposed to vinyl chloride. *Am Ind Hyg Assoc J* 33:19-30
- Kubota J (1957) Occupational diseases in synthetic resin and fibre industries. (Japanese text). *J Sci Labour* 33:1-22
- Kurokawa S, Inagaki T, Okuyama S (1977) Electron microscopic observation of the liver in portal hypertension following chronic exposure to vinyl chloride monomer. *Gastroenterol Jpn* 12:64-69

Vinyl Chloride

Kuzmack A
posure to
Laib RJ, Be
and in vi
Laib RJ, Be
vinyl chl
Laib RJ, St
parative
Congress
Laib RJ, St
parative
463
Laib RJ, St
comparis
zyme det
Lander JJ, S
the liver
Langauer-L
ae
Hi
Lang
G
B
Lang
h
Lang
L
9
Lang
P
Lang
Veltman
heit bei A
sche und
tisch E, V
16. Jahre
Lange CE, B
workers
Paris Lor
Laroche G
neuro-en
Lassiter DV
176-178
Laws JW, Li
tis and or
Laws JW, El
digital art
Lee FI, Har
I:1316-
Lee FI, Har
chloride
Lefaux R (J
Lefèvre MJ
Internat
27.-29.4

R&S 117154

Chemical modifica-
toxicol Appl

n of the mandible

teolysis.

of poly-

ndrom

Med

(Sklero-

trie.)

idwigs-

id-

Vinylchlorid-

as catalyse covalent
1-135

ptake of ^{14}C vinyl
vitro. Toxicol

Environ Health

Results of exposure
16: 219-220

Arbeitsplatz-Kon-
In: Berichte des

bertonie ohne
ed Wochenschr

ension. Surgery

Broschenfelde KH
(ose) nach chroni-

Veränderungen
EFO 132:62-68
chunke E (1978)
it der Arbeitsme-
s Hyg 24:501-507
ntgenol 21:448-

premitatum in poly-
sn 91:5-17

Environmental mea-
ssoc J 33:19-30
industries.

Observation of the
chloride monomer.

- Kuzmack AM, McGaughy RE (1975) Quantitative risk assessment for community exposure to vinyl chloride. U.S. EPA/ORD Report, December 1975
- Laib RJ, Bolt HM (1977) Alkylation of RNA by vinyl chloride metabolites in vitro and in vivo: formation of 1-N⁶-etheno-adenosine. *Toxicology* 8:185-195
- Laib RJ, Bolt HM (1978) Formation of 3-N⁴-etheno-cytidine moieties in RNA by vinyl chloride metabolites in vitro and in vivo. *Arch Toxicol* 39:235
- Laib RJ, Stöckle G, Bolt HM (1978) Induction of premalignant hepatic lesions: comparative effects of vinyl chloride and trichloroethylene. Paper presented at the 20th Congress of European Society of Toxicology, Berlin (West), June 25-28, 1978
- Laib RJ, Stöckle G, Bolt HM (1979) Induction of premalignant hepatic lesions: comparative effects of vinyl chloride and trichloroethylene. *Arch Toxicol (Suppl)* 2: 463
- Laib RJ, Stöckle G, Bolt HM, Kunz W (1979) Vinyl chloride and trichloroethylene: comparison of alkylating effects of metabolites and induction of preneoplastic enzyme deficiencies in rat liver. *Cancer Res Clin Oncol* 94:139-147
- Lander JJ, Stanley RJ, Summer HW, Boswell DC, Aach RD (1975) Angiosarcoma of the liver associated with Fowler's solution. *Gastroenterology* 68:1582-1586
- Langauer-Lewowicka H, Dudziak Z, Byczkowsky Z, Marks J (1976) Cryoglobulin-aemia in Raynaud's phenomenon due to vinyl chloride. *Int Arch Occup Environ Health* 36:197-207
- Lange CE, Veltman G (1977) Dermatologische Aspekte der Vinylchloridschäden. In: Gutacker HW, Leibach WK (eds) *Leberschäden durch Vinylchlorid*. Witzstrock, Baden-Baden Brüssel Köln New York, pp 55-68
- Lange CE, Jühe S, Stein G, Veltman G (1974a) Die sogenannte Vinylchlorid-Krankheit - eine berufsbedingte Systemkierose? *Int Arch Arbeitsmed* 32:1-32
- Lange CE, Jühe S, Veltman G (1974b) Über das Auftreten von Angiosarkomen der Leber bei zwei Arbeitern der PVC-herstellenden Industrie. *Dtsch Med Wochenschr* 99:1598-1599
- Lange CE, Jühe S, Stein G, Veltman G (1975) Further results in polyvinyl chloride production workers. *Ann NY Acad Sci* 246:18-21
- Lange CE, Bloch H, Biersack HJ, Sehr U, Etzel F, Marsteller HJ, Leibach WK, Veltman G (1976a) Chronisch-toxische Schäden im Sinne der Vinylchlorid-Krankheit bei Arbeitern in PVC-weiterverarbeitenden Betrieben. Klinische, laborchemische und szintigraphische Untersuchungsbefunde. In: Bolt W, Buchter A, Reben-tisch E, Worth D (eds) *Jahresbericht der Deutschen Gesellschaft für Arbeitsmedizin*, 16. Jahrestagung, Köln 5.-8.5.1976. Gentner, Stuttgart, pp 195-200
- Lange CE, Bloch H, Veltman G, Doss M (1976b) Urinary porphyrins among PVC-workers. In: Doss M (ed) *Porphyrins in human diseases*. Karger, Basel München Paris London New York Sidney, pp 352-355
- Laroche G, Hochfeld M (1948) Un cas d'acro-ostéolyse associé à un syndrome ostéo-neuro-endocrinien complexe. *Sem Hôp Paris* 24:984-991
- Lassiter DV (1976) Vinyl chloride - best available technology. *Ann NY Acad Sci* 271: 176-178
- Laws JW, Lillie JG, Scott JT (1963) Arteriographic appearances in rheumatoid arthritis and other disorders. *Br J Radiol* 36:477-493
- Laws JW, El Sallab RA, Scott JT (1967) An arteriographic and histological study of digital arteries. *Br J Radiol* 40:740-747
- Lee FI, Harry DS (1974) Angiosarcoma of the liver in a vinyl chloride worker. *Lancet* i:1316-1318
- Lee FI, Harry DS, Adams WGF, Litchfield M (1977) Screening for liver disease in vinyl chloride workers. *Br J Ind Med* 34:142-147
- Lefaux R (1966) Chemie und Toxikologie der Kunststoffe. Krausskopf, Mainz
- Lefèvre MJ (1972) Akroosteolyse in Zusammenhang mit der PVC-Herstellung. In: *Internationales Symposium der Werksärzte der Chemischen Industrie*. Ludwigshafen 27.-29.4.1972, pp 69-79

- Leibach WK, Marsteller HJ (1977) Das laparoskopische Bild der Vinylchlorid-Krankheit. In: Lindner H (ed) Fortschritte der gastroenterologischen Endoskopie, vol 8. Witzstrock, Baden-Baden Brüssel, pp 37-40
- Lester D, Greenberg LA, Adams WR (1963) Effects of single and repeated exposure of humans and rats to vinyl chloride. *Am Ind Hyg Assoc J* 24:265-275
- Liebegott G (1949) Pathologische Anatomie der chronischen Arsenvergiftung. *Dtsch Med Wochenschr* 74:855-856
- Liebegott G (1952) Über die Beziehungen zwischen chronischer Arsenvergiftung und malignen Neubildungen. *Zentralbl Arbeitsmed Arbeitsschutz Prophyl* 2:15-16
- van Lierop JBH, Stek W (1976) Analysis of vinyl chloride in food simulants at low parts per billion levels by mass fragmentography. *J Chromatogr* 128:183-187
- Lièvre JA, Gama G (1957) L'acroosteolyse. *Bull Mem Soc Med Hôp* 73:109-120
- Lillis R, Anderson H, Nicholson WJ, Daum S, Fishbein AS, Selikoff IJ (1975) Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 246:22-41
- Lillis R, Anderson H, Miller A, Selikoff IJ (1976) Pulmonary changes among vinyl chloride polymerization workers. *Chest* 69:299-303
- Lillis R, Anderson H, Miller A, Selikoff IJ (1977) Modifications pulmonaires et exposition au chlorure et polychlorure de vinyle. *Med Hyg* 35:1542-1545
- Lloyd JW (1974) Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J Occup Med* 16:809
- Lloyd JW (1975) Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J Occup Med* 17:333-334
- Loprieno N, Barale R, Baroncelli S, Bauer C, Bronzetti G, Cammellini A, Cercignani G, Corsi C, Gervasi G, Leporini C, Nieri R, Rossi AM, Stretti G, Turchi G (1976) Evaluation of the genetic effects induced by vinyl chloride monomer (VCM) under mammalian metabolic activation: studies in vitro and in vivo. *Mutat Res* 40:85-96
- Loprieno N, Barale R, Baroncelli S, Bartsch H, Bronzetti G, Cammellini A, Corsi C, Freza D, Nieri R, Leporini C, Rosellini D, Rossi AM (1977) Induction of gene mutations and gene conversions by vinyl chloride metabolites in yeast. *Cancer Res* 36:253-257
- MacSween RNM, Vettters JM, Ross SL, Ferguson J, Johnstone JM, Sandison AT (1973) Haemangio-endothelial sarcoma of the liver. *J Pathol* 109:39-44
- MAK-Werte (1975) Umweltschutz in der Sowjetunion. III. Maximale Arbeitsplatz-Konzentrationen (MAK-Werte) von Schadstoffen und ihre Normierung. In: Berichte des Osteuropa-Instituts, Heft 108, Freie Universität, Berlin, p 67
- Makk L, Creech JL, Whelan JG Jr, Johnson MN (1974) Liver damage and angiosarcoma in vinyl chloride workers. *JAMA* 230:64-68
- Makk L, Delorme F, Creech JL (1975) Angiosarcomes du foie chez des ouvriers ayant été en contact prolongé avec le chlorure de vinyle: épidémiologie et programme de recherches chez les ouvriers. *Union Med Can* 104:1833-1835
- Makk L, Delorme F, Creech JL Jr, Ogden II LL, Fadell EH, Songster CL, Clanton J, Johnson MN, Christofferson WM (1976) Clinical and morphologic features of hepatic angiosarcoma in vinyl chloride workers. *Cancer* 37:149-163
- Malaveille C, Bartsch H, Barbin A, Camus AM, Montesano R, Croisy A, Jacquignon P (1975) Mutagenicity of vinyl chloride, chloroethyleneoxide, chloroacetaldehyde and chloroethanol. *Biochem Biophys Res Commun* 63:363-370
- Malten KE, Zielhuis RL (1964) Industrial toxicology and dermatology in the production and processing of plastics. Elsevier, Amsterdam London New York
- Maltoni C (1973) Occupational carcinogenesis. *Excerpta Medica Int Congr Ser* 322:19-26
- Maltoni C (1974) Angiosarcoma epatico in operai esposti a cloruro di vinile. Resoconto dei primi due casi riscontrati in Italia. *Med Lav* 65:445-450
- Maltoni C (1975) The value of predictive experimental environmental carcinogenesis. *Ambio* 4:18-23

lorid-Krank-
kopie, vol 8.

ed exposure of

ung. Dtsch

rgiftung und

2:15-16

nts at low

183-187

109-120

975) Preval-

Ann NY Acad

ong vinyl

ures et exposi-

chloride

chloride

Cercignani G.

G (1976) Eval-

M)

Res 6

A.

n of

ane

is a 3)

bei

ng. ite

ed a

ouvriers ayant

programme de

Clanton J.

tures of

Jacquignon P

etaldehyde

n the produc-

ork

gr Ser 322:

nile. Reso-

rcinogenesis.

Maltoni C (1976) Occupational chemical carcinogenesis: new facts, priorities, and perspectives. IARC Sci Publ 52:127-134

Maltoni C (1977) Recent findings on the carcinogenicity of chlorinated olefins.

Environ Health Perspect 21:1-5

Maltoni C, Lefemine G (1974a) Carcinogenicity bioassays of vinyl chloride. I. Research plan and early results. Environ Res 7:387-405

Maltoni C, Lefemine G (1974b) La potenzialità dei saggi sperimentali nella predizione dei rischi oncogeni ambientali. Un esempio: Il cloruro di vinile. Accademia Nazionale dei Lincei. Estratto dai Rendiconti della Classe di Scienze fisiche, matematiche e naturali, Ser VIII, vol LVI, fas 3

Maltoni C, Lefemine G (1975) Carcinogenicity bioassays of vinyl chloride: current results. Ann NY Acad Sci 246:195-218

Maltoni C, Crespi M, Burch PJ (eds) (1973) II. International Symposium on Cancer Detection and Prevention. Excerpta Medica Int Congr Ser 275:1-137

Maltoni C, Lefemine G, Chieco P, Carretti D (1974a) La cancerogenesi ambientale e professionale: Nuove prospettive alla luce della cancerogenesi da cloruro di vinile. Osp Vita 1:66

Maltoni C, Lefemine G, Chieco P, Carretti D (1974b) Vinyl chloride carcinogenesis: current results and perspectives. Med Lav 65:421-444

Maltoni G, Ciliberti A, Gianni L, Chieco P (1975) Insorgenza di angiosarcomi in ratti, in seguito a somministrazione per via orale di cloruro di vinile. Osp Vita 2:65-66

Maricq HR, Johnson MN, Whetstone CL, LeRoy EC (1976) Capillary abnormalities in polyvinyl chloride production workers. JAMA 236:1368-1371

Maricq HR, Darke CS, Archibald R McL, LeRoy EC (1978) In vivo observations of skin capillaries in workers exposed to vinyl chloride. An English-American comparison. Br J Ind Med 35:1-7

Marin A, Strauss J, Michels R, Benoit JP, Baltie R, Pierre C (1967) Acro-ostéolyse d'origine professionnelle. Rev Rhum Mal Ostéoartic 34:340-351

Markowitz SS, McDonald CH, Fethiere W, Kerzner MS (1972) Occupational acro-osteolysis. Arch Dermatol 106:219-223

Marleau D, Villeneuve JP, Huet PM, Côté J, Lafortune M, Légaré A, Lavoie P, Viallet A (1974) Noncirrhotic idiopathic portal hypertension (OPH): Radiological and hemodynamic evaluation of 4 cases by combined hepatic and umbilicoportal catheterization. Gastroenterology 67:813

Marsteller HJ, Leibach WK (1977) Das intermedizinsche Bild bei Vinylchlorid-schäden. In: Gutacker HW, Leibach WK (eds) Leberschäden durch Vinylchlorid - Vinylchlorid-Krankheit. Witzstrock, Baden-Baden Brüssel Köln New York, pp 69-83

Marsteller HJ, Leibach WK, Müller R, Jühe S, Lange CE, Rohner HG, Veitman G (1973) Chronisch-toxische Leberschäden bei Arbeitern in der PVC-Produktion. Dtsch Med Wochenschr 98:2311-2314

Marsteller HJ, Leibach WK, Müller R, Gedigk P (1975a) Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 246:95-134

Marsteller HJ, Leibach WK, Müller R, Gedigk P, Lange CE (1975) Klinische und laparoskopische Aspekte der Leberschäden bei Chemiearbeitern in der Vinylchlorid-Polymerisation. Leber Magen Darm 5:196-202

Marsteller HJ, Leibach WK, Lange CE, Veitman G (1976) Chronisch-toxische Schäden im Sinne der Vinylchlorid-Krankheit bei Arbeitern in PVC-weiterverarbeitenden Betrieben. In: Bolt W, Buchter A, Rebentisch, E, Worth D (eds) Verhandlungen der Deutschen Gesellschaft für Arbeitsmedizin, 16. Jahrestagung. Gentner, Stuttgart, pp 201-207

Martin JF, Waggoner JG, Berk PD (1974) Persistence of vinyl chloride (VC) induced liver injury after cessation of exposure. Gastroenterology 67:814

- Mastromatteo E, Fisher AM, Christie H, Danziger H (1960) Acute inhalation toxicity of vinyl chloride to laboratory animals. *Am Ind Hyg Assoc J* 5:394-398
- Maugh TH II (1978) Chemical carcinogens: how dangerous are low doses? *Science* 202:37-41
- McCann J, Simmon V, Streitwieser D, Ames BN (1975) Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene dichloride), chloroethanol (ethylene chlorohydrin), vinyl chloride, and cyclophosphamide. *Proc Natl Acad Sci* 72:3190-3193
- McMichael AJ, Haynes SG, Tyroler HA (1975) Observation on the evaluation of occupational mortality data. *J Occup Med* 17:128-131
- Mendenhall CL, Sherman J, Chedid A (1974) Intermittent idiopathic portal hypertension. *Gastroenterology* 67:142-148
- Meyerson LB, Meier GC (1972) Cutaneous lesions in acroosteolysis. *Arch Dermatol* 106:224-227
- Mikkelsen WP, Edmondson HA, Peters RL, Redeker AG, Reynolds TB (1965) Extra- and intrahepatic portal hypertension without cirrhosis (hepatoportal sclerosis). *Ann Surg* 162:602-620
- Miller A (1975) Pulmonary function defects in nonsmoking vinyl chloride workers. *Environ Health Perspect* 11:247-256
- Miller A, Teirstein AS, Chuang M, Selikoff IJ, Warshaw R (1975) Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. *Ann NY Acad Sci* 246:42-52
- Miller MC, Brandt JL (1962) Portal hypertension in the absence of both liver disease and vascular obstruction. *Am J Dig Dis* 7:442-448
- Mitchell Johnston EN (1978) Vinyl chloride disease. *Br J Dermatol (Suppl 16)* 99:45-48
- Monahan JJ (1926) Raynaud's disease; limitations of classical picture as a guide to diagnosis; report of a case showing extensive bone involvement. *Am J Med Sci* 171:346-358
- Monson RR, Peters JM, Johnson MN (1974) Proportional mortality among vinylchloride workers. *Lancet* II:397-398
- Morris JS, Schmid M, Newman S, Scheuer PJ, Sherlock S (1974) Arsenic and non-cirrhotic portal hypertension. *Gastroenterology* 66:86-94
- Moser KM (1976) Meat wrapper's asthma. *JAMA* 236:2846-2847
- Moulin O, Rety J, Palliard P, Vouillon G, Guttin G (1974) Aspects sclerodermiques de l'acro-osteolyse professionnelle. *Ann Dermatol Syphiligr* 101:33-44
- Müller G, Norpoth K (1975) Bestimmung zweier Urinmetabolite des Vinylchlorids. *Naturwissenschaften* 62:541
- Müller G, Norpoth K, Eckard R (1976) Identification of two urine metabolites of vinyl chloride by GC-MS-investigations. *Int Arch Occup Environ Health* 38:69-75
- Müller G, Norpoth K, Kusters E, Herweg K, Versin E (1978) Determination of thiodiglycolic acid in urine specimens of vinyl chloride exposed workers. *Int Arch Occup Environ Health* 41:199-205
- Müller R, Gedigk P, Bechtelsheimer H (1974) Neuere morphologische Befunde in der menschlichen Leber nach Vinylchlorid-Exposition. In: Lehnert G, Szadkowski D, Weber HJ (eds) 14. Jahresbericht der Deutschen Gesellschaft für Arbeitsmedizin. 17.-19.10.1974, Hamburg. Gentner, Stuttgart, pp 267-269
- Müller R, Bechtelsheimer H, Gedigk P, Marsteller HJ, Leibach WK (1975) Das morphologische Bild der Leberschädigung nach chronischer Vinylchlorid-Exposition. *Leber Magen Darm* 5:204-208
- Müller W, Balda BB (1975) Polyvinylchlorid-Krankheit unter dem Bild einer Akrosklerodermie. *Hautarzt* 26:387
- Münter MD, Perry HO, Ludwig J (1971) Chronic vitamin A intoxication in adults. *Am J Med* 50:129-136
- Myers SA, Quinn IJJ, Zook WC (1975) Determination of vinyl chloride monomer at the sub ppm level using a personal monitor. *Am Ind Hyg Assoc J* 36:332-337

Neale G
hype
Neuman
and
berg
Nichols
chlor
Nichols
coho
230
Noria D
expo
Patho
Norpoth
über
lation
Arbei
Nothnag
Hirs
Oster R
Anes
Osterma
Wach
chlor
Osterma
techn
Ott MG
trial
Pagé M
work
Panh M
by
Parmeg
lavor
Patty
edn
Patty F
new
196
Penin P
tree
Bren
Deut
Stut
Peoples
Exp
Pessay
and
Phar
Peters J
pet
ho
sta
nt
ast

lation toxicity
398
es? Science

of chloroacet-
lene dichloride).
osphamide. Proc

uation of occu-

portal hyperten-

ch Dermatol

(1965) Extra-
sclerosis). Ann

ride workers.

ges in pulmo-
chloride. Ann NY

in liver disease

Appl 16) 99:45-48
a guide to
Med Sci

ing vinylchloro-
and non-

odermique de
ylchlorides

olites of vinyl
69-75

tion of thiodi-
Arch Occup

funde in der
adkowski D.
tsmedizin.

Das morpho-
position. Leber

mer

in

nono
32-

- Neale G, Azzopardi JG (1971) Chronic arsenical poisoning and non-cirrhotic portal hypertension — a case for diagnosis. *Br Med J* II:725-730
- Neumann HG, Osborne JC, Metzler M (1979) Peroxidase activity in rat Zymbal's gland and its possible role for the metabolic activation of carcinogens. *Naunyn Schmiedeberg Arch Pharmacol (Suppl)* 307:R15
- Nicholson WJ (1977) Cancer following occupational exposure to asbestos and vinyl chloride. *Cancer* 39:1792-1801
- Nicholson WJ, Hammond EC, Seidman H, Selikoff IJ (1975) Mortality experience of a cohort of vinyl chloride — polyvinyl chloride workers. *Ann NY Acad Sci* 246:225-230
- Nona DF, Ritchie S, Silver MD (1977) Angiosarcoma of the liver after vinyl chloride exposure: report of a case and review of the literature. *International Academy of Pathology, 66th Annual Meeting, Toronto, Abstracts of Papers* 36:361
- Norpoth K, Müller G, Witting U, Gottschalk D, Gottschalk J (1976) Untersuchungen über den Stoffwechsel des Vinylchlorids und über Wirkungen der Vinylchlorid-inhalation auf Regulationsmechanismen des Leberstoffwechsels. *Verh Dtsch Ges Arbeitsmed* 16:187
- Nothnagel H, Rossbach MJ (1880) *Handbuch der Arzneimittellehre*. 4. Auflage. Hirschwald, Berlin
- Oster RR, Carr CJ, Krantz JC (1947) Anesthesia XXVII. Narcosis with vinyl chloride. *Anesthesiology* 8:359-361
- Osterman-Golkar S, Hultmark D, Segerbäck D, Calleman CJ, Göthe R, Ehrenberg L, Wachtmeister CA (1977) Alkylation of DNA and proteins in mice exposed to vinyl chloride. *Biochem Biophys Res Commun* 76:259-266
- Ostermayer H (1967) Vinylchlorid. In: Foerst W (ed) *Ullmanns Encyklopädie der technischen Chemie*, vol 16. Urban & Schwarzenberg, München, pp 87-94
- Ott MG, Langner RR, Holder BB (1975) Vinyl chloride exposure in a controlled industrial environment. *Arch Environ Health* 30:333-339
- Pagé M, Thériault L, Delorme F (1976) Elevated CEA levels in polyvinyl chloride workers. *Biomédecine* 1976:279
- Panh Meng H, Faure H, Pasquier D, Couderc P (1977) Liver angiosarcoma occasioned by exposition to vinyl chloride. *Acta Pharmacol Toxicol (Kbh) (Suppl)* 41:331
- Parmeggiani L, Sassi C (1955) Rischio e patologia professionale nella produzione e nella lavorazione di alcune materie plastiche. *Med Lav* 46:14-24
- Patty FA (ed) (1958) *Industrial hygiene and toxicology*, vol 1: General principles, 2nd edn. Interscience Publishers, New York
- Patty FA, Yant WP, Waite CP (1930) Acute response of guinea pigs to vapors of some new commercial organic compounds. V. Vinyl chloride. *Public Health Rep* 45:1963-1971
- Penin H, Sargar G, Lange CE, Veltman G (1975) Neurologisch-psychiatrische und elektroenzephalographische Befunde bei Patienten mit Vinylchlorid-Krankheit. In: Brenner W, Rohmert W, Rutenfranz J (eds) *Bericht über die 15. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin*, München 24.-26.4.1975. Gentner, Stuttgart, pp 299-304
- Peoples AS, Leake CD (1933) The anesthetic action of vinyl chloride. *J Pharmacol Exp Ther* 48:284
- Pessayre D, Wandscheer JC, Descatoire V, Artigou JY, Benhamou JP (1979) Formation and inactivation of a chemically reactive metabolite of vinyl chloride. *Toxicol Appl Pharmacol* 49:505-515
- Peters JM (1976) Public-Health rounds at the Harvard School of Public Health Perspectives. *N Engl J Med* 294:653-657
- Pillichowski P, Faure C, Aubert M, Pahn M, Latreille R, Barrie J (1979) Angiosarcome costal lié à une intoxication au chlorure de polyvinyl. *Nouv Presse Méd* 8:2485
- Pimentel Cortez J, Menezes Peixoto A (1977) Liver disease in vineyard sprayers. *Gastroenterology* 72:275-283

R&S 117159

- Piver WT (1976) Diffusion of residual monomer in polymer resins. *Environ Health Perspect* 17:227-236
- Polish E, Christie J, Cohen A, Sullivan B (1962) Idiopathic presinusoidal portal hypertension (Banti's syndrome). *Ann Intern Med* 56:624-627
- Polyvinyl chloride banned in Japan (1974) *JAMA* 229:855
- Popper H (1975) The heuristic importance of environmental pathology. Lessons from the vinyl chloride problem. *Arch Pathol* 99:69-71
- Popper H, Thomas LB (1975) Alterations of liver and spleen among workers exposed to vinyl chloride. *Ann NY Acad Sci* 246:172-193
- Popper H, Udenfriend S (1970) Hepatic fibrosis. Correlation of biochemical and morphologic investigations. *Am J Med* 49:707-721
- Popper H, Thomas LB, Falk H, Berk PD, Selikoff I (1974) Banti syndrome followed by hepatic angiosarcoma in vinyl chloride exposure. Paper presented at the Sixth Meeting of the International Association for the Study of the Liver. Acapulco, Mexico, Oct. 20-22, 1974
- Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ (1978) Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. *Am J Pathol* 92:349-370
- Preston BJ, Jones KL, Grainger RG (1976) Clinical aspects of vinyl chloride disease. *Proc R Soc Med* 69:284-286
- Prodan L, Suciu I, Pislaru V, Ilea E, Pascu L (1975) Experimental acute toxicity of vinyl chloride (monochloroethene). *Ann NY Acad Sci* 246:154-163
- Puech AM, Fournet A, Lauhere L, Faure J, Cau G, Mallion JM (1977) Etude des lésions hépatiques observées chez 5 sujets exposés au chlorure de vinyle dont 3 cas d'angiosarcome hépatique. *Arch Mal Prof* 38:787-795
- Purchase LFH, Williamson KS (1974) Proportional mortality among vinyl-chloride workers. *Lancet* II:591-592
- Purchase LFH, Richardson CR, Anderson D (1975) Chromosomal and dominant lethal effects of vinyl chloride. *Lancet* II:410-411
- Purchase LFH, Richardson C, Anderson D (1976) Chromosomal effects in peripheral lymphocytes. *Proc R Soc Med* 69:290-292
- Pushin GA (1965) On lesions of the liver and the biliary tract in workers engaged in the production of some types of plastics. *Sov Med* 28:132-135 (Russian text)
- Radwan Z (1977) Uptake and rate of metabolism of vinyl chloride by the isolated perfused rat liver preparation. *Int Arch Occup Environ Health* 40:101-110
- Radwan Z, Henschler D (1975) Uptake and metabolism of vinyl chloride in the isolated perfused rat liver preparation. *Naunyn Schmiedebergs Arch Pharmacol (Suppl)* 287:R100
- Ramalingaswami V, Wig KL, Sama SK (1962) Cirrhosis of the liver in northern India - a clinicopathological study. *Arch Intern Med* 110:350-358
- Rannug U, Johansson A, Ramel C, Wachtmeister CA (1974) The mutagenicity of vinyl chloride after metabolic activation. *Ambio* 3/5:194-197
- Rannug U, Göthe R, Wachtmeister CA (1976) The mutagenicity of chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride. *Chem Biol Interact* 12:251-263
- Ravenna P (1940) Banti syndrome (fibrocongestive splenomegaly). Definition, classification and pathogenesis. *Arch Intern Med* 66:879-892
- Ravey M, Klopstock J (1975) Trace analysis of vinyl chloride in PVC and in the atmosphere. *J Chromatogr Sci* 13:552-553
- Ravier E, Diter JM, Pialat J (1975) Un cas d'angiosarcome hépatique chez un ouvrier exposé au chlorure de vinyle monomère. *Arch Mal Prof* 36:171-177
- Regelson W, Kim U, Ospina J, Holland JF (1968) Hemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's solution. *Cancer* 21:514-522
- Reger RB (1977) Vinyl chloride and the polymers. *J Occup Med* 16:772-773

Regnault
ölbilde
Rein FR.
Kollekt
Reinl W (1
des Lu
Reinl W, A
Gewer
Reinl W, V
rid-Kra
Reinl W, V
der Ge
Reinl W, V
der Ge
Reinl W, W
der Ge
Reitz RH.
ing the
Rety J, La
supervi
Arch M
Rety J, Sa
tique
Reynolds I
vinyl ch
Reynolds I
ation of
dase sy
Reynolds I
vinyl ch
18:36
Richards
Nature
Roche J (1
tions, R
Roche J, I
hépatiq
2:669
Ross JM (1
Bacteri
Roth F (1
Berück
Roth F (1
468-5
Roth F (1
Dtsch
Roth F (1

R&S 117160

- R&S 117161 H.J. Marsteller
- Iron Health Per-
- portal hyper-
- Lessons from
- ters exposed
- of biochemical and mor-
- anti syndrome followed
- presented at the Sixth
- the Liver. Acapulco,
- Development of hepatic
- and arsenic. *Am J*
- vinyl chloride disease.
- ental acute toxicity of
- 154-163
- M (1977) Etude des
- ure de vinyle dont 3 cas
- among vinyl-chloride
- omal and dominant lethal
- nal effects in peripheral
- in workers engaged in
- 135 (Russian text)
- ide by the isolated per-
- 40:101-110
- l chloride in the isolated
- Pharmacol (Suppl)
- liver in northern India -
- The mutagenicity of vinyl
- ity of chloroethylene
- ic acid, conceivable
- 263
- galy). Definition, classi-
- in PVC and in the atmo-
- patique chez un ouvrier
- 171-177
- ndothelial sarcoma of
- n. *Cancer* 21:514-522
- fed 16:772-773
- Regnault V (1835) Über die Zusammensetzung des Chlorkohlenwasserstoffs (Oel des ölbildenden Gases). *Liebigs Ann Pharm* 14:22-38
- Rein FR, Huth F (1975) Sechs spontane primäre maligne Gefäßgeschwülste in einem Kollektiv von 30.000 Obduktionen. *Int Arch Arbeitsmed* 34:237-246
- Reinl W (1975) Erkrankungen durch Vinylchlorid. Jahresbericht der Gewerbeaufsicht des Landes Nordrhein-Westfalen, pp 299-316
- Reinl W, Weber H (1974) Erkrankungen durch Vinylchlorid. Jahresbericht der Gewerbeaufsicht des Landes Nordrhein-Westfalen, pp 217-252
- Reinl W, Weber H (1976) Stand der epidemiologischen Forschung über die Vinylchlorid-Krankheit. *Zentralbl Arbeitsmed* 26:97-104
- Reinl W, Weber H, Greiser E (1976) Erkrankungen durch Vinylchlorid. Jahresbericht der Gewerbeaufsicht des Landes Nordrhein-Westfalen, pp 287-295
- Reinl W, Weber H, Greiser E (1977) Erkrankungen durch Vinylchlorid. Jahresbericht der Gewerbeaufsicht des Landes Nordrhein-Westfalen, pp 305-324
- Reinl W, Weber H, Greiser E (1978) Erkrankungen durch Vinylchlorid. Jahresbericht der Gewerbeaufsicht des Landes Nordrhein-Westfalen, pp 347-377
- Reitz RH, Quast JF, Watanabe PG, Gehring PJ (1979) Chemical carcinogens: Estimating the risk. *Science* 205:1206-1208
- Rety J, Lazard P, Berrod J, Schmitt M (1974) Infrared thermography in diagnosis and supervision of morbidity in workers dealing with vinyl chloride polymerisation. *Arch Mal Prof* 35:733-738
- Rety J, Sauvage, Tuailon, Habrard A (1976) Le 3e cas français d'angiosarcome hépatique chez un ouvrier du chlorure de vinyle. *Arch Mal Prof* 37:551-555
- Reynolds ES, Moslen MT, Szabo S, Jaeger RJ, Murphy SD (1975a) Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. *Am J Pathol* 81:219-236
- Reynolds ES, Moslen MT, Szabo S, Jaeger RJ (1975b) Vinyl chloride-induced deactivation of cytochrome P-450 and other components of the liver mixed function oxidase system: an in vivo study. *Res. Comm Chem Pathol Pharmacol* 12:685-694
- Reynolds ES, Moslen MT, Szabo S, Jaeger RJ (1976) Modulation of halothane and vinyl chloride induced acute injury to liver endoplasmic reticulum. *Panminerva Med* 18:367-374
- Richards RJ, Desai R, Hext PM, Rose FA (1975) Biological reactivity of PVC dust. *Nature* 256:664-665
- Roche J (1977) Affections hépatiques et chlorure de vinyle. A propos de 5 observations. *Revue générale de littérature. Thèse, University of Grenoble*
- Roche J, Fournet J, Hostein J, Panh M, Bonnet-Eymard J (1978) Angiosarcome hépatique dû au chlorure de vinyle. Présentation de 4 cas. *Gastroenterol Clin Biol* 2:669-678
- Ross JM (1932) A case illustrating the effect of prolonged action of radium. *J Pathol Bacteriol* 35:899-912
- Roth F (1956) Über die chronische Arsenvergiftung der Moselwinzer mit besonderer Berücksichtigung des Arsenkrebses. *Z Krebsforsch* 61:287-319
- Roth F (1957a) Arsen, Leber, Tumoren (Hämangioendotheliom). *Z Krebsforsch* 61:468-503
- Roth F (1957b) Über die Spätfolgen des chronischen Arsenismus der Moselwinzer. *Dtsch Med Wochenschr* 82:211-217
- Roth F (1959) Zur Pathologie der chronischen Arsenvergiftung. *Zentralbl Allg Pathol Pathol Anat* 100:529-530
- Roubal J (1972) Vinyl, polyvinyl chloride. In: I.L.O. (International Labor Organization) *Encyclopaedia of occupational health and safety*, vol II. Geneva, pp 1467-1468
- Rousselot LM (1940) The late phase of congestive splenomegaly (Banti's syndrome) with hematemesis but without cirrhosis of the liver. Further observations on the etiology of Banti's syndrome and the effect on prognosis of certain variations in the portal venous pattern. *Surgery* 8:34-42

- Rowe VK (1975) Experience in industrial exposure control. *Ann NY Acad Sci* 246: 306-310
- Rübsamen H (1976) Vinylchloridkrankheit (VC-Krankheit). *Z. Allgemeinmed* 52: 1551-1555
- Russell RM, Bagheri SA, Boyer JL (1973) The hepatic lesion of hypervitaminosis A - a unique pattern of hepatic fibrosis with portal hypertension and ascites. *Gastroenterology* 65:568
- Russell RM, Boyer JL, Bagheri SA, Hruban Z (1974) Hepatic injury from chronic hypervitaminosis A resulting in portal hypertension and ascites. *N Engl J Med* 291: 435-440
- Sakabe H (1975) Bone lesions among polyvinyl chloride production workers in Japan. *Ann NY Acad Sci* 246:78-79
- Sama SK, Bhargava S, Gopi Nath N, Talwar JR, Nayak NC, Tandon BN, Wig KL (1971) Noncirrhotic portal fibrosis. *Am J Med* 51:160-169
- Šarić M, Kulčar Z, Zorica M, Gelić I (1976) Malignant tumors of the liver and lungs in an area with a PVC industry. *Environ Health Perspect* 17:189-192
- Schaffner F, Popper H, Selikoff IJ (1976) Initial features of vinyl chloride (VC) hepatic injury. *Gastroenterology* 71:928
- Schattenberg PJ, Totović V, Gedigk P, Marsteller HJ (1977) Die Ultrastruktur der Leberschädigung bei der chronischen Vinylchlorid-Intoxikation. *Virchows Archiv (Pathol Anat)* 273:233-247
- Schaumann O (1934) Über die Herzwirkung einiger Inhalationsnarkotika. *Med Chem (Leverkusen Ger)* 2:139-147
- Schaumann O (1938) Monochloräthylen. In: Lehmann KB, Flury F (eds) *Toxikologie und Hygiene der technischen Lösungsmittel*. Springer, Berlin, pp 130-131
- Schlatter C (1976) Gefährdung von Konsument und PVC-Arbeitern durch Vinylchlorid. *Schweiz Med Wochenschr* 106:647-650
- Schmidt H, Schaumann O (1929) Über kombinierte Gasnarkose. *Dtsch Z Chir* 216: 149-157
- Schmidt K, Batora J (1976) Vorkommen des Leberhämangioendothelioms bei Arbeitern, die lang dauernd dem Vinylchlorid ausgesetzt waren. *Z ärztl Fortbild* 70: 1020-1022
- Schnack H, Stockinger L, Wewalka F (1967) Adventitious connective tissue cells in the space of Disse and their relation to fibre formation. *Rev Int Hepatol* 17:855-860
- Schneiderman MA (1979) Chemical carcinogens. *Science* 203:603
- Schneiderman MA, Mantel N, Brown CC (1975) From mouse to man - or how to get from the Laboratory to Park Avenue and 59th street. *Ann NY Acad Sci* 246:237-248
- Schottek W (1969) Zur Toxikologie des Vinylchlorids. *Chem Techn (Leipzig)* 21: 708-711
- Schütz A, Wolf D (1977) Gefährdung durch Vinylchlorid bei der PVC-Weiterverarbeitung. *Berufsgenossenschaften* 1:7-13
- Schwarzweiler F (1957) Verlaufsuntersuchungen bei einem osteolytischen Krankheitsbild. *Z Orthop* 88:404-413
- Schweitzer GE (1975) Environmental concerns beyond the workplace. Presentation to the Working Group on Toxicity of Vinyl Chloride-Polyvinyl Chloride. *Ann NY Acad Sci* 246:296-302
- Sehrt-Bachner U, Etzel F (1977) Haemostaseologische Befunde bei Vinylchloridschäden. In: Gutacker HW, Leibach WK (eds) *Leberschäden durch Vinylchlorid*. Witzstrock. Baden-Baden Brüssel Köln New York, pp 89-91
- Seki K (1965) Histometrical studies of the spleen in Banti's syndrome with reference to clinico-pathologic correlations. *Tohoku J Exp Med* 87:222-243
- Selikoff IJ (1976) Discussion remark to Barnes: Vinyl chloride and the production of PVC. *Proc R Soc Med* 69:281

Selmg
79
Severs
enc
As
Shah
the
Sherie
of
Sider
stru
Da Sil
effe
n. ca

R&S 117162

Smith
pro
Smith
rid
Smole
for
Smyt
17
Somme
Scat
Sorens
Spirtas
chie
429
Spirtas
ride
Stein
pha
Stein
nar
Stewar
ride
Stutte
all
Suciul
clat
Suciul
Med

- Lead Sci 246:
- Unmed 52:
- Leukemia A —
ites. Gastro-
- Chronic
Am J Med 291:
- Workers in Japan.
- Wig KL (1971)
- er and lungs in
- ide (VC) hepa-
- Struktur der
Archiv
- ka. Med Chem
- Toxikologie
- R&S 117163
- 5:
- bei-
- n the
- 60
- get
- 7 -
- ipzig) 21.
- Weiterverarbei-
- hen Krankheits-
- Presentation
ide. Ann NY
- ylchloridschä-
chlorid.
- with reference
- production of
- Selinger M, Koff RS (1975) Thorotrast and the liver: a reminder. *Gastroenterology* 68: 799-803
- Severs LW, Skory LK (1975) Monitoring personnel exposure to vinyl chloride, vinylidene chloride and methyl chloride in an industrial work environment. *Am Ind Hyg Assoc J* 36:669-676
- Shahin MM (1976) The non-mutagenicity and -recombinogenicity of vinyl chloride in the absence of metabolic activation. *Mutat Res* 40:269-272
- Sherlock S, Feldman CA, Moran B, Scheuer PJ (1966) Partial nodular transformation of the liver with portal hypertension. *Am J Med* 40:195-203
- Siderys H, Vellios F (1964) Portal hypertension without cirrhosis or extrahepatic obstruction. *Am J Surg* 108:785-789
- Da Silva Horta J (1967) Late effects of thorotrast on the liver and spleen, and their efferent lymph nodes. *Ann NY Acad Sci* 145:676-699
- Da Silva Horta J, da Motta LC (1967) Follow-up study of thorium dioxide patients in Portugal. *Ann NY Acad Sci* 145:830-842
- Simpson HM, Baggenstoss AH, Stauffer MH (1955) Primary sarcoma of the liver: a report of three cases. *South Med J* 48:1177-1182
- Slater TF (1972) Free radical mechanisms in tissue injury. Pion, London
- Smirnova NA (1954) Paper presented at the conference of young scientists, Gor'kii. 1954, pp 10-11 (Russian text)
- Smirnova NA (1959) Clinics of chronic intoxication by olefins and vinyl chloride. Dissertation Gor'kii (Russian text)
- Smirnova NA (1961) On the question of bone lesions due to chronic intoxication by olefins and vinyl chloride. *Vestn Rentgenol Radiol* 36:63-66 (Russian text)
- Smith PM, Williams DMJ (1974) Vinyl chloride and cirrhosis. *Digestion* 10:321
- Smith PM, Williams DMJ, Crossley IR (1975) Portal hypertension induced by vinyl chloride. *Gut* 16:402-403
- Smith PM, Crossley IR, Williams DMJ (1976a) Portal hypertension in vinyl chloride production workers. *Lancet* II:602-604
- Smith PM, Williams DMJ, Evans DMD (1976b) Hepatic angiosarcoma in a vinyl chloride worker. *Bull NY Acad Med* 52:447-452
- Smolčić V (1966) Assessment of lead exposure in PVC manufactories and suggestions for control measures. *Arh Hig Rada Toksikol* 17:309-316 (Serbo-Croatian text)
- Smyth HF Jr (1956) Hygienic standards for daily inhalation. *Am Ind Hyg Assoc J* 17:129-185
- Sommerschield H, Kluge T (1971) Some observations on hepatic sinusoids. *Acta Chir Scand* 137:257-263
- Sorenson WR (1976) Polyvinyl chloride in fires. *JAMA* 236:1449
- Spirtas R, Kaminski R (1977) Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. — 1977 Update on the NIOSH Register. *J Occup Med* 20:427-429
- Spirtas R, McMichael AJ, Gamble J, van Ert M (1975) The association of vinyl chloride exposures with morbidity symptoms. *Am Ind Hyg Assoc J* 36:779-789
- Stein G, Jühe S, Lange CE, Veltman G (1973a) Bandförmige Osteolysen in den Endphalangen des Handskeletts. *ROEFO* 118:60-63
- Stein G, Jühe S, Lange CE, Veltman G (1973b) Skelettveränderungen bei der sogenannten Vinylchloridkrankheit. *Roentgenblaetter* 26:350-355
- Stewart JD, Williams DMJ, McLachlan MSF (1975) Acro-osteolysis in a polyvinyl chloride worker with an atypical industrial history. *J Soc Occup Med* 25:103-109
- Stutte HJ, Heusermann U (1978) Die Milz bei der Vinylchlorid-Krankheit. *Zentralblatt allg Pathol Pathol Anat* 122:284
- Suciu I, Drejman I, Valaskai M (1963) Contribuții la studiul îmbolnăvirilor produse de clorura de vinil. *Med Internă* 15:967-978
- Suciu I, Drejman I, Valaskai M (1967) Etude des maladies dues au chlorure de vinyle. *Med Lav* 58:261-271

- Suciu I, Prodan L, Ilea E, Paduraru A, Pascu L (1975) Clinical manifestations in vinyl chloride poisoning. *Ann NY Acad Sci* 246:53-69
- Szende B, Lapis K, Nemes A, Pinter A (1970) Pneumoconiosis caused by the inhalation of polyvinylchloride dust. *Med Lav* 61:433-436
- Tabershaw IR, Gaffey WR (1974) Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 16:509-518
- Takeuchi Y, Mabuchi C (1973) A case of occupational acroosteolysis, presumably caused by vinyl chloride. *Jpn J Ind Health* 15:385-394
- Tamburro CH (1978) The hepatic role in the carcinogenesis and in early detection - the vinyl chloride model. *Yale J Biol Med* 51:67-80
- Tamburro CH, Creech JL, Makk L, Whelan JG (1978a) Alcohol vinyl chloride: a causal relationship in the development of primary hepatocellular carcinoma. Paper presented at the Meeting of the International Association for the Study of the Liver, Fuengirola, Spain, October 20-21, 1978
- Tamburro CH, Creech JL, Davis A, Greenberg RA (1978b) Indocyanine green clearance as the prospective indicator of hepatocellular chemical toxicity. Paper presented to the American Association for the Study of Liver Diseases at the 29th Annual Meeting, Chicago, Ill, Nov 6-8, 1978
- Tandon BN, Lakshminarayanan R, Bhargava S, Nayak NC, Sama SK (1970) Ultrastructure of the liver in non-cirrhotic portal fibrosis with portal hypertension. *Gut* 11:905-910
- Tassignon JP (1979) Log normal distribution of the incubation period of liver angiosarcoma in vinyl chloride polymerization workers. *J Occup Med* 21:10
- Taylor KJW, Barrett JJ, Williams DMJ, Smith PM, Duck BW (1976) Preliminary results of grey-scale ultrasonography in the detection of vinyl chloride related liver and spleen disease. *Proc R Soc Med* 69:292-295
- Thiess AM, Versen P (1974) Arbeitsmedizinische Gedanken zur sogenannten „Vinylchloriderkrankung“. *Arbeitsmed Sozialmed Praeventivmed* 9:146-148
- Thomas LB, Popper H (1975) Pathology of angiosarcoma of the liver among vinyl chloride - polyvinyl chloride workers. *Ann NY Acad Sci* 246:268-277
- Thomas LB, Popper H, Berk PD, Selikoff I, Falk H (1975) Vinyl-chloride-induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to angiosarcomas. *N Engl J Med* 292:17-22
- Tisdale WA, Klatskin G, Glenn WWL (1959) Portal hypertension and bleeding esophageal varices. Their occurrence in the absence of both intrahepatic and extrahepatic obstruction of the portal vein. *N Engl J Med* 261:209-218
- Tola S (1975) Occupational lead exposure in Finland. IV. The polyvinyl chloride plastic industry. *Scand J Work Environ Health* 1:173-177
- Torkelson TR, Oyen F, Rowe VK (1961) The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. *Am Ind Hyg Assoc J* 22:354-361
- Trapp JT, Lummus FL, Hilbun BM (1974) Acro-osteolysis: a case report. *J Miss State Med Assoc* 15:246-248
- Tribukh SL, Tikhomirova NP, Levina SV, Kozlov LA (1949) Conditions of work and measures of industrial hygiene in the production of, and manufacture from, vinyl chloride plastics. *Gig Sanit* 10:38-44 (Russian text)
- Triche T, Nanba K, Ishak K, Wolkoff A, Berk PD (1975) Hepatic ultrastructural changes in vinyl chloride (VC) workers. *Clin Res* 23:259A
- Truell JE, Peck SD, Reiquam CW (1973) Hemangiosarcoma of the liver complicated by disseminated intravascular coagulation. *Gastroenterology* 65:936-942
- Vainio H (1978) Vinyl chloride and vinyl benzene (styrene)-metabolism, mutagenicity and carcinogenicity. *Chem Biol Interact* 22:117-124
- Vale PT, Kipling MD, Walker AE (1976) Miscellaneous symptoms occurring in workers engaged in the manufacture of PVC. *J Soc Occup Med* 26:95-97
- Vazin AN, Plokhova ET (1968) On the pathogenesis of disease due to chronic exposure to vinyl chloride. *Farmakol Toksikol* 3:369-372 (Russian text)

Vazin
foll
(R)
Vazin
exp
VKE
ban
Veltm
Ber
Veltm
In:
chl
Veltm
cou
Veltm
197
Vertkir
in w
29-
Villene
Vial
Viola F
Viola P
Viola P
Viola P
to v
Wagon
194
Walker
enk
Walker
346
Walker
286
Wallno
Me
Ward
Pro
Ward
nisi
Watan
siba
Watan

R&S 117164

ions in vinyl
the inhala-
manufacture of
presumably
detection -
chloride: a causal
Paper pre-
of the Liver,
green clearance
er presented to
Annual Meet-
970) Ultra-
extension. Gut
liver angio-
to
liminary results
liver and
inten „Vinyl-
ong vinyl
duced
angio-
ing eso-
and extra-
londe
determined
54-361
Miss State
work and
from vinyl
structural
omplified
942
mutagenicity
ing in workers
chronic expo-

- Vazin AN, Plokhova ET (1969a) Changes in adrenalin-like substances in rabbit blood following chronic exposure to vinyl chloride vapour. *Gig Tr Prof Zabol* 13:46-47 (Russian text)
- Vazin AN, Plokhova ET (1969b) Changes of cardiac activity in rats following chronic exposure to vinyl chloride vapour. *Farmakol Toksikol* 32:220-222 (Russian text)
- VKE (1974, 1975) VC/PVC: Beispiel einer Problemlösung. Herausgegeben vom Verband der kunststoffherzeugenden Industrie e.V. (VKE). Frankfurt)
- Veltman G, Lange CE (1977a) Arbeitsmedizinische Aspekte der Vinylchloridschäden. *Berufsdermatosen* 25:67-77
- Veltman G, Lange CE (1977b) Arbeitsmedizinische Aspekte der Vinylchloridschäden. In: Gutacker HW, Leibach WK (eds) *Leberschäden durch Vinylchlorid - Vinylchlorid-Krankheit*. Witzstrock, Baden-Baden Brüssel Köln New York, pp 95-101
- Veltman G, Lange CE, Jühe S, Stein G, Bachner U (1975) Clinical manifestations and course of vinyl chloride disease. *Ann NY Acad Sci* 246:6-17
- Veltman G, Lange CE, Stein G (1978) Die Vinylchlorid-Krankheit. *Hautarzt* 29: 1977-1982
- Vertkin YI, Mamontov YR (1970) On the condition of the broncho-pulmonary system in workers employed in the manufacture of PVC articles. *Gig Tr Prof Zabol* 14: 29-32 (Russian text)
- Villeneuve JP, Huet PM, Joly JG, Marleau D, Cote J, Legare A, Lafortune M, Lavoie P, Viallet A (1976) Idiopathic portal hypertension. *Am J Med* 61:459-464
- Viola PL (1970a) Cancerogenic effect of vinyl chloride. *Int Cancer Congr, Abstr* 29
- Viola PL (1970b) Pathology of vinyl chloride. *Med Lav* 61:174-180
- Viola PL (1974) La malattia da cloruro di vinile. *Med Lav* 65:81-99
- Viola PL, Bigotti A, Caputo A (1971) Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res* 31:516-519
- Wagoner JK, Infante PF, Saracci R (1976) Vinyl chloride and mortality? *Lancet* II: 194-195
- Walker AE (1974) A preliminary report of a vascular abnormality occurring in men engaged in the manufacture of polyvinyl chloride. *Br J Dermatol* 1974: 22-23
- Walker AE (1975) Occupational acro-osteolysis (two cases). *Proc R Soc Med* 68:343-346
- Walker AE (1976) Clinical aspects of vinyl chloride disease: Skin. *Proc R Soc Med* 69: 286-289
- Wallnöfer H, Zinnagl N (1977) Hämangiosarkomatose nach Polyvinylchloridexposition. *Med Klin* 72:410-413
- Ward AM (1976) Evidence of an immune complex disorder in vinyl chloride workers. *Proc R Soc Med* 69:289-290
- Ward M, Udnoon S, Watkins J, Walker AE, Darke CS (1976) Immunological mechanisms in the pathogenesis of vinyl chloride disease. *Br Med J* 1:936-938
- Watanabe PG, Gehring PJ (1976) Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. *Environ Health Perspect* 17:145-152
- Watanabe PG, McGowan GR, Madrid EO, Gehring PJ (1976a) Fate of ¹⁴C-vinylchloride following inhalation exposure in rats. *Toxicol Appl Pharmacol* 37:49-59
- Watanabe PG, Hefner RE Jr, Gehring PJ (1976b) Vinyl chloride-induced depression of hepatic non-protein sulfhydryl content and effects on bromosulphalein (BSP) clearance in rats. *Toxicology* 6:1-8
- Watanabe PG, McGowan GR, Gehring PJ (1976c) Fate of ¹⁴C vinyl chloride after single oral administration in rats. *Toxicol Appl Pharmacol* 36:339-352
- Watanabe PG, Zempel JA, Gehring PJ (1978a) Comparison of the fate of vinyl chloride following single and repeated exposure in rats. *Toxicol Appl Pharmacol* 44: 391-399
- Watanabe PG, Zempel JA, Pegg DG, Gehring PJ (1978b) Hepatic macromolecular binding following exposure to vinyl chloride. *Toxicol Appl Pharmacol* 44:571-579
- Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C (1976) Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 271:40-48

- Wegener K, Wesch H, Kämpfmann H (1971) Reticuloendotheliales System und Thorotrastose nach diagnostischer Angiographie. *Arch Med Wochenschr* 96:1977-1981
- Wegman DH (1975) (Discussion reprinted in *Ann NY Acad Sci* 246:20-21
- Wegman DH (1976) Public Health rounds at the Harvard School of Public Health. *N Engl J Med* 294:632
- Weigert FJ (1979) Chemical carcinogenesis. *Science* 203:603
- Weinbrek K (1976) Health effects of liver disorders associated with exposure to vinyl chloride monomer. *J Soc Occup Med* 26:98-99
- Whelan JG Jr, Gellera JF, Smith PM (1975) A comparison and a summary of characteristics of liver diseases in vinyl chloride monomer workers. *Radiology* 115:549-557
- Williams DMJ, McCachlan AS (1977) Healing of phalangeal defects in acro-osteolysis. *J Soc Occup Med* 26:98-99
- Williams DMJ, Taylor KJW, Crossley IR, Smith PM (1975a) Screening vinyl chloride monomer workers for liver disease. *Gut* 16:839
- Williams DMJ, Taylor KJW, Crossley IR, Smith PM, Duck BW (1975b) Pre-symptomatic detection of liver changes in vinyl chloride monomer workers. *Digestion* 12:362
- Williams DMJ, Smith PM, Taylor KJW, Crossley IR (1976) Monitoring liver disorders in vinyl chloride monomer workers using greyscale ultrasonography. *Br J Ind Med* 33:152-157
- Williams DMJ, Roberts E, Evans KT (1977) An assessment of hand thermography in vinyl chloride workers. *J Soc Occup Med* 27:57-62
- Williamson DG, Cvetanović RJ (1968) Rates of reactions of ozone with chlorinated and conjugated olefines. *J Am Chem Soc* 90:4248
- Wilson RH, McCormick WE, Tatum CF, Creech JL (1967) Occupational acroosteolysis. Report of 31 cases. *JAMA* 201:577-581
- Winell M, Holmberg B, Kronevi T (1976) Biological effects of vinyl chloride: an experimental study. *Environ Health Perspect* 17:211-216
- Woods JS (1979) Epidemiologic considerations in the design of toxicologic studies: an approach to risk assessment in humans. *Fed Proc* 38:1891-1896
- Wyatt RH, Kotchen JM, Hochstrasser DL, Buchanan JW Jr, Campbell DR, Slaughter JC, Doll AH (1975) An epidemiologic study of blood screening tests and illness histories among chemical workers involved in the manufacture of polyvinyl chloride. *Ann NY Acad Sci* 246:80-87
- Yamamoto K (1978) Morphological studies of the spleen in splenomegalic liver cirrhosis comparing with the spleen in idiopathic portal hypertension (so-called Banti's syndrome with liver cirrhosis). *Acta Pathol Jpn* 28:891-905
- Yamamoto K (1979) Morphological studies of the spleen in idiopathic portal hypertension (so-called Banti's syndrome without liver cirrhosis) using light microscopy, scanning electron microscopy and histometry. *Acta Pathol Jpn* 29:1-19
- Zapp JA (1964) Vinyl chloride. *Am Ind Hyg Assoc J* 25:421-423
- Zeegen R, Stansfeld AG, Dawson AM, Hunt AH (1970) Prolonged survival after portal decompression of patients with non-cirrhotic intrahepatic portal hypertension. *Gut* 11:610-617
- Zielhuis RL (1974) Permissible limits for occupational exposure to toxic agents. A discussion in approach between US and USSR. *Int Arch Arbeitsmed* 33:1-13
- Zimmermann H, Eck H (1975) Zur Pathologischen Anatomie der Vinylchlorid-Krankheit. *Virchows Arch (Pathol Anat)* 368:51-59
- Zonca M, Sarić M, Konstantinović M, Kovač I (1975) Two cases of angiosarcoma of the liver following exposure to vinyl chloride. *Arch Hig Rada Toksikol* 26:275-281 (Serbo-Croatian text)

- 1 Einleit.
2 Gesch.
3 Allgem.
3.1 D.
3.2 D.
3.3 D.
3.4 D.
3.5 D.
3.6
3.7
3.8
4 Manon
4.1 B.
4.2
4.3
4.4
4.5
4.6
5 Klinisc
5.1 E.
5.2 P.
5
5

* Herrn F
1 Medizin
renstra: