Ergebnisse der Inneren Medizin und Kinderheilkunde

47

Advances in Internal Medicine and Pediatrics

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

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Vinyl Chloride-Associated Disease

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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

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

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

Ultimately, it was the exceptional character of the three major lesions which occurred in workers exposed to VCM that contributed most to the final appreciation of a causal relationship: (1) the syndrome of acroosteolysis, Raynaud's phenomenon and pseudosleroderma; (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).

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2 Technological Details

2.1 Vinyl Chloride Monomer (VCM)

At standard (ambient) conditions of temperature and pressure, vinyl chloride (CH_2=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 aerosoles. 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:	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 (CH_2=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 *Sawtser* and *Glinsky* (who

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

2.1.2 Production of VCM

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

1) Conversion of acetylene to VCM by hydrochlorination:

$$CH{\equiv}CH + HCl \rightarrow CH_2{=}CHCl$$ (catalyst: $HgCl_2$ on charcoal) (*Austin* 1974)

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

$$CH_2{=}CH_2 + 2HCl + 1/2\ O_2 \rightarrow CH_2Cl{-}CH_2Cl + H_2O;$$

$$CH_2Cl{-}CH_2Cl \xrightarrow[\text{pumice catalyst}]{480^\circ C - 510^\circ C} CH_2{=}CHCl + HCl$$

(pyrolysis: thermal cracking, *Austin* 1974).

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.

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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-isobutyronitride, 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

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

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

2.2.2 Methods of Polymerization

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

Suspension Polymerization. Polymerization is carried out in an aqueous system in which monomer droplets are maintained in suspension by means of protective colloids (such as polyvinyl alcohol, gelatin, substituted celluloses) under heat and pressure in conjuction 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 additon 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.

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Solution Polymerization. This type of precipitation polymerization is carried out in organic solvents such as *n*-butane or cyclohexane. It accounts for only a small percentage of the total amount of all PVC resins produced and it is used for the production of copolymers. Copolymers are mixtures of comonomers (such as vinyl acetate, vinylstearate, 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 (*Smoltić* 1966; *Tola* 1975). Compounding is carried out by hot mixing at fusion temperatures below or within the softening range (120°C–160°C). Diversified compounding and processing technologies were developed about 1950.

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

2.2.4 Sources of Exposure to VCM in PVC Production

Both polymerization of VCM and subsequent processing (centrifuging, drying, screening, bagging) are usually carried out in closed buildings. Exceptions can be found in hot climates (*Aryanpur* 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 prenarcotic symptoms (dizziness etc.)

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

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

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

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

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

(*Patty* 1958)

1 mg/litre	=		391 ppm
1 mg/m³	=		0.391 ppm
1 ppm	=	2.56 mg/m³	= 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

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

2.2.6 The Odour Threshold

Unfortunately, gaseous VCM has no irritating or unpleasant warning properties. Its mild odour is described as faintly pleasant, sweet or ethereal. Some of the PVC workers we interviewed reported that they had even enjoyed 'sniffing the gas', which soon resulted in a feeling of light-headedness. For the early days of PVC production, when appropriately sensitive monitoring equipment was not yet available, workers' reports about perception of the odour of VCM can be taken as circumstantial evidence for a rough estimate of the actual degree of exposure. It should be kept in mind, however, that in chemical production units the presence of other 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 *Hublet* 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

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