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*Guest Editorial**

Malignant Tumors After Chronic Exposure to Vinyl Chloride

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Summary. Correlations between exposure to vinyl chloride and the development of malignant tumors in the liver have been known since 1974 and have been confirmed by many an experimental investigation.
Based on the evaluation of mortality statistics from nine different countries an increased incidence of malignant tumors of the lung, the gastrointestinal tract, and the central nervous system (CNS), and of malignant lymphomas is documented in connection with exposure to vinyl chloride. Statistically significant increases, however, are only found in the incidence of malignant liver tumors. Metabolism and toxicology of vinyl chloride are discussed in detail.

Key words: Human carcinogenesis – Vinyl chloride – Toxicology – Liver tumors – Metabolism

Introduction

The industrial production of monomeric vinyl chloride (VCM) started some 30 years ago. In 1976, the USA produced 2.58, Western Europe 3.925, and Japan 1.31 million tons. About 95% of this output went into polymerization, the remaining 5% into the production of other chemicals, such as methylchloroform (IARC 1978).

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The very nature of the polymerization process allows for various ways of VC release into the environment. Workers were exposed to particularly high concentrations of VCM during manual autoclave cleansing. Up to the 1960s the health risk of vinyl chloride was thought to be negligible (Lefaux 1966). Concentrations of 1,000 ppm at the individual working place were not uncommon in certain plants. First recommendations for limiting the exposure to 500 ppm were issued in 1961 in the United States. The average concentration levels of that period can be estimated approximately in retrospect:

1945–1955: ± 1,000 ppm
1955–1960: 400–500 ppm
1960–1970: 300–400 ppm
1973: ± 140 ppm
1975: ± 5 ppm (Barnes 1976).

In the Federal Republic of Germany the statutory MAK level [1] was fixed at 500 ppm until 1970, then reduced to 100 ppm until 1974. Today the technical limit concentration at the work place in the FRG is below 5 ppm for older and current working plants, under 2 ppm for new plants under construction. The management soon realized that VCM concentration could be effectively reduced to the statutory levels by technical innovation and financial investments. One Swedish firm was able to reduce mean VCM concentrations from 12.2. ppm (2nd quarter of 1974) to 0.6 ppm (4th quarter of 1975) (Englund and Holmerg 1976).

Due to the physicochemical binding of VCM in PVC products, workers in PVC-processing or -manufactoring industries are equally exposed to a certain concentration of VCM, although at much lower levels than during the process of polymerization. In a 1974 survey of PVC-manufacturing plants levels were below 1 ppm in more than 60% of all firms checked.

The first reports about the potential risk of VCM had been published in 1949. Since 1957 reports had appeared here and there about a certain disease occurring in VCM industrial workers, manifested in scleroderma-like skin changes, Raynaud syndrome, and acro-osteolysis (Juehe and Lange 1972). Some years later, further symptoms of the disease were described as liver damage, splenomegaly, and thrombocytopenia (K. T. Müller et al. 1976). Detailed investigations were carried out on liver changes since the first cases of hemangiosarcoma had been found among VCM workers. These liver changes were graded histologically in five steps, correlating the length of exposure, and the severity of recorded changes (Gedigk et al. 1975; R. Müller et al. 1975). Even in VCM-exposed workers showing no clinical symptoms of liver damage, sequential scintigraphy would reveal RHS changes in liver and spleen (Biersack et al. 1975).

In addition to liver changes a considerable number of workers showed an impairment of pulmonary functions, and roentgenologic changes up to pulmonary fibrosis (Miller et al. 1975; Miller 1975; Lilis et al. 1976). These findings equally reflected a signification correlation between the length of exposure and the severity of changes.

The first reports about tumors induced by VCM were published in 1974, recording the increased incidence of a very rare neoplasm, liver hemangiosarcoma.

1 MAK = maximale Arbeitsplatz-Konzentration (maximum concentration at work)

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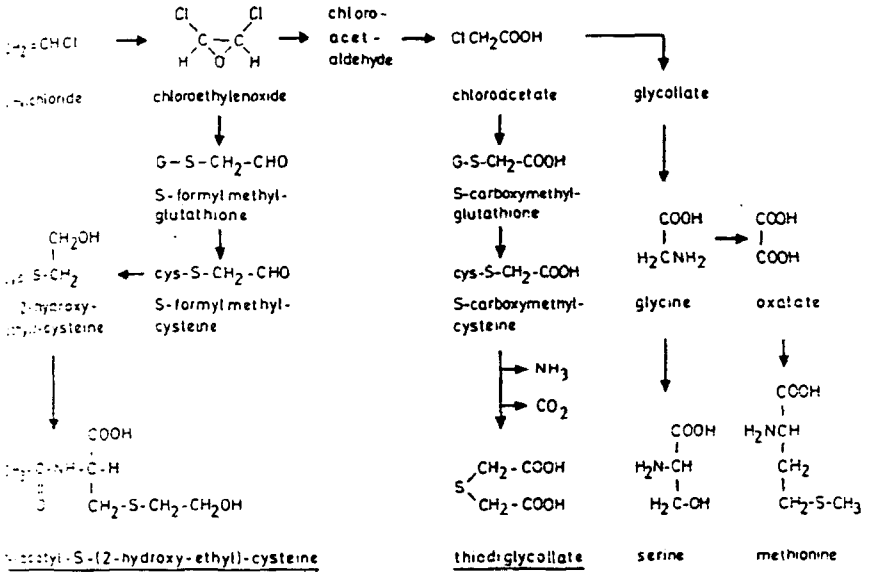

Fig. 1. Major metabolic pathways of vinyl chloride. The main urinary metabolites are underlined

among workers of a PVC-producing firm in the USA (Creech and Johnson 1974). More cases of this uncommon tumor, all among VCM workers, were published in the following years (Lloyd 1974, 1975; Lange et al. 1974, 1975; Byrén and Holmberg 1975). Based on 13 cases of liver hemangiosarcoma reported in the USA, the risk of VCM workers for this rare tumor was determined to be 400 times higher than that of the normal population (Heath et al. 1975). Histological studies of Thomas and Popper (1975) suggested the possibility of multicentric sarcoma development. Until 1978 the cases of liver hemangiosarcoma among VCM workers amounted worldwide to a total of 90 (Stafford 1980).

Sixteen cases of death of liver hemangiosarcoma had been recorded in the FRG until 1978 (Reinl et al. 1979). The cases subjected to detailed investigation until then revealed a longer latency period between first exposure and diagnosis, and a higher age at first diagnosis of hemangiosarcoma. A possible cause for this pattern was seen in the higher initial doses to which workers had been exposed during the first years of VCM production (Spirtas and Kaminski 1978). Environmental studies conducted in the immediate neighborhood of VCM-producing plants failed to assess an increased incidence of hemangiosarcoma in the general population of this area (Saric et al. 1976).

VCM Metabolism and Pharmacokinetics

The metabolism of monomeric vinyl chloride was studied by Green and Hathaway (1975), Watanabe et al. (1976), G. Müller et al. (1976), and many others. Figure 1 presents the major metabolic steps according to current concepts. In the mammalian organism monomeric vinyl chloride undergoes oxidative biotransforma-

tion involving the cytochrome P 450 system. Chlorethylenoxide, an alkylating cancerogen, is the resulting primary metabolite (Malaveille et al. 1975; Greim et al. 1975; Kappus et al. 1975) which is subsequently rearranged to chloracetic aldehyde. Via several, partly unknown metabolic steps, this substance is transformed to S-carboxymethyl-cystein and thiodiacetic acid (Yllner 1971). The latter, a rather stable terminal metabolite, may be excreted via the urine. Quantitative demonstration of thiodiacetic acid is done by GC.MS technique after methylation (G. Müller et al. 1979). Another metabolic pathway, coupling chlorethylenoxide to glutathione, leads to β-hydroxyethyl mercapturic acid (Watanabe et al. 1976). The urinary level of this equally stable end product may be demonstrated by exchange chromatography after hydrolysis, or by the GC.MS test after derivation (G. Müller et al. 1980). It must be emphasized that β-hydroxyethyl mercapturic acid is the main urinary metabolite in the rat (Watanabe et al. 1976), but not in man (G. Müller et al. 1980).

The concept of VCM carcinogenicity being essentially mediated by its metabolite chlorethylenoxide has been substantially verified in recent years. In a mutagenicity test with Salmonella typhimurium TA 1535 the effect of this strongly reacting alkylating agent was 450 times stronger than that of the metabolite chloracetaldehyde (Rannug et al. 1976). Tumor induction in rats with chlorethylenoxide was 100% successful, whereas chloracetaldehyde failed to show any cancerogenic effect in a parallel assay (Zajdela et al. 1980). The role of intracellular chloracetaldehyde, i.e., whether or not it might contribute essentially to VCM cancerogenesis (Guengerich et al. 1979), is still unclear.

VCM pharmacokinetics in rats and in man were extensively studies by Heinze et al. (1975), Whitey (1976), Bolt et al. (1976, 1977), Bolt (1978), Buchter et al. (1978), and Filser and Bolt (1979). According to them, man reacts to VCM levels around 2 ppm by establishing within a few minutes an equilibrium between environmental (air) and intracorporeal concentration. The constants of this equilibrium depend on the individual constitution, being approximately 0.8 in persons of normal weight. Overweight individuals will absorb a higher amount in proportion to their weight, and so the constant rises above 1.0, possibly due to the higher proportion of fatty tissue (Buchter et al. 1978). Experimental studies with rats have shown that the speed constant of VCM uptake and clearance after stopping the exposure ($k = 0.216\ \text{min}^{-1}$) is always much higher than the constant of metabolization ($k = 0.0037 \cdot \text{min}^{-1}$) and of urinary metabolite excretion ($k = 0.0032 \cdot \text{min}^{-1}$). Assuming human conditions to be similar, we may deduce that physiologic variations of ventilation levels will have either no or only minor influence on the VCM uptake by inhalation.

From data on the dose dependency of VCM biotransformation (G. Müller et al. 1976; Gehring et al. 1978, 1979) we may infer that reactive cancerogenic VCM metabolites will not increase in linear correlation with exposure, but rather follow the Michaelis-Menten function. Tumor incidence in rats (Gehring et al. 1978) and even in man (Gehring et al. 1979) is most adequately demonstrated in a probate model of frequency percentage correlated with exposure (Gehring et al. 1979). Functional correlation may be complicated if experimental exposure is under 50 ppm, by the glutathione-mediated detoxication of chlorethylenoxide, which is an effective protection mechanism at lower levels of exposure. Gehring et al. (1979) had even

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cussed the possibility of a veritable threshold dose of VCM, below which the tumor latency period would be longer than the normal life expectancy of the exposed person.

VCM Genotoxicity and Embryotoxicity

The mutagenicity of monomeric vinyl chloride on salmonella typhimurium strain in vitro was studied by Rannug et al. (1974), Bartsch et al. (1975). Greim et al. (1975), McCann et al. (1975), Andrews et al. (1976), and Garro et al. (1976). In a recent paper De Meester et al. (1980), though confirming the often cited mutagenic effect, reported that its action was considerably enhanced by the addition of an oxigenase-enriched preparation of mammalian liver tissue (S9 Mix). Hubermann et al. (1975) described the mutagenic effect of VCM on cultures mammalian cells. In studies of *Drosophila melanogatser* Magnusson and Ramel (1978) recorded an increase of lethal dominants under VCM exposure. Pretreatment with phenobarbitol for 24 h would enhance the mutagenicity of VCM, probably via the induction of mixed-function oxidases which enhance the biotransformation of VCM to chlorethylenoxide.

In contrast to in vitro evidence of VCM mutagenicity, Short et al. (1977) and Peter and Ungvary (1980) were unable to register increased lethal dominants after VCM exposure in rats or mice. On the other hand, Basler and Röhrborn (1980) reported a time-dependent increase in sister-chromatid exchanges and structural chromosome aberrations in the bone marrow of Chinese hamsters after forced aspiration of high doese VCM. Fleig and Thies (1978) had already registered an increasing number of chromosomal aberrations in humans and animals with VCM disease, and an increased proportion of chromosomal aberrations was also found by Ducatman et al. (1975) among VCM-exposed workers in the USA, and in Sweden by Funes-Cravioto et al. (1975). Szentesi et al. (1976) recorded a rise of chromatid aberrations and instable chromosomal aberrations among VCM-exposed workers as compared to non-exposed controls. In his cytogenetic studies repeated at 30-month intervals, Hansteen et al. (1978) found a high proportion of chromosome fractures in lymphocyte cultures from workers exposed to high levels of VCM, which would return to lower values when doses were reduced. Purchase et al. (1978) in similar studies also registered a significant rise of chromosomal anomalies in VCM-exposed workers as compared to non-exposed control collectives. Heath et al. (1977) pointed out that cytogenetic damage might be due to other agents besides VCM. Finally, Infante et al. (1976) reported an increased rate of miscarriages among the wives of workers exposed to high VCM levels. According to them, an increasing rate of malformations was found even among the neonates of the general population of towns with VCM-processing factories.

Experimental Studies of VCM Carcinogenicity

The first experimental investigations of VCM-induced carcinogenesis were performed by Viola et al. (1971) who exposed Wistar rats to high doses of VCM (30,000 ppm) for 20 h each week over a whole year. Under this extreme exposure the animals developed tumors of skin, lungs, and bone. Subsequent animal studies

Table 1. Standardized mortality rates for tumor disease among VCM workers

Authors	Period	No.	SMR
Byrén et al. 1976	1958–1974	771	–
Chiazze et al. 1977	1964–1973	65.000	1.19 1.31
Duck et al. 1975	1955–1975	2.120	0.96
Fox and Collier 1977	1940–1974	7.717	0.75
Monson et al. 1974	1947–1973	(161 deaths)	1.50
Nicholson et al. 1975	1946–1974	255	3.90
Reinl et al. 1979	1946–1974	7,021	1.03
Tabershaw and Gaffey 1974	1946–1972	8.384	1.10
Waxweiler et al. 1976	1941–1973	1.294	1.49

revealed that the cancerogenic effect of low doses (50 ppm) would depend on the duration of the exposure. Extensive serial studies recorded VCM-induced tumors in all reodent species, such as rats, mice, and hamsters. Besides angiosarcoma mice were found to develop mammary carcinomas, pulmonary adenomas, and skin tumors. Apart from angiosarcomas rats would develop malignant neoplasms of the skin and zymbal gland, nephroblastomas, heptomas, angiomas, and neuroblastomas. In hamsters, VCM induced liver hemangiosarcomas, trichoepithelomas, and lymphomas (Maltoni and Lefemine 1975). Suzuki (1978) induced pulmonary tumors in mice by exposing them to VCM doses of 2,500 and 6,000 ppm for 5–6 months.

On the whole, these experimental results suggest that VCM exposure is likely to induce neoplastic changes also in other organs than the liver.

Epidemiological Data

Reports about angiosarcoma incidence among VCM workers, and also the results of experimental studies, have stimulated a survey of mortality statistics and proportional VCM mortality among former and present workers in VCM-processing factories. These studies attempted to determine the particular risk of VCM workers to acquire certain diseases, compared with the average normal population. Risks were assessed quantitatively by comparison with the standardized mortality (SMR), but the studies are based on a wide variety of collectives and observation periods (Table 1).

The only Swedish VCM factory registered an increased incidence of liver tumors (SMR = 4.5) and an accumulation of cardiovascular diseases among 58 workers dying between 1958 and 1974. The problem of a general increase in the overall SMR of tumors was not discussed by the authors of this report (Byrén et al. 1976).

An extensive study was conducted between 1965 and 1975 in some 65,000 people working in the American VCM production (Chiazze et al. 1977). Cancer mortality was generally increased (SMR in males = 1.19, females = 1.31). It showed an increased incidence of gastrointestinal tumors (SMR = 1.34), liver tumors (SMR = 1.43), pulmonary tumors (SMR = 1.17) tumors of the CNS (=) and of the lymphatic system (= 1.30). Women showed a particular increase in

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Table 2. Standardized mortality rates of malignancies among VCM workers according to different organ sites

Authors		Gastroint.	Liver	Lung	CNS	Lymph.	Others
Byrén et al. 1976		–	4.13	1.68	6.12	–	–
Chiazze et al. 1977	M	1.34	1.43	1.17	1.15	1.30	1.09
	F	1.66	0.0	1.07	1.14	1.18	2.42
Duck et al. 1975		0.99	–	1.03	–	–	
Fox and Collier 1977		0.91	3.22	0.89	0.54	0.99	
Monson et al. 1974		–	11.00	1.60	4.20	1.50	
Reinl et al. 1979		1.30	15.23	0.96	1.62	2.14	
Tabershaw and Gaffey 1974		0.94	–	1.12	–	1.06	1.89
Waxweiler et al. 1976		>1	11.55	1.56	3.29	1.59	1.55

incidence of urogenital tumors (SMR = 2.42); tumors of the gastrointestinal tract had a SMR of 1.66, that of pulmonary tumors was only slightly elevated (= 1.07) and so were the SMR of CNS (= 1.14) and lymphatic tumors (= 1.18).

An age-standardized survey of 2,100 workers of a VCM-processing factory in England failed to reveal an increased SMR for tumors, with the exception of cerebrovascular disease (SMR = 1.41) (Duck et al. 1975). Fox and Collier (1977) had been unable to detect an increasing SMR for tumors in general among 7,717 workers of PVC-producing industries in Great Britain, except for malignant liver disease with a distinctly elevated SMR of 3.22. Nevertheless, the general tumor SMR was relatively higher than that of cardiovascular disease. The possibility of cancerogenic action on organs other than the liver was refused by these authors.

Another study analyzed 161 deaths recorded among the workers of two PVC-producing factories in the USA between 1954 and 1973. SMR for tumors in general was 1.5 in this period; a striking increase was found in liver tumors (= 11.0) and in tumors of the CNS (= 4.2). A minor rise was seen in pulmonary tumors (= 1.6) and malignant lymphatic disease (= 1.5) (Monson et al. 1974). A smaller study of 255 VCM-exposed workers (Nicholson et al. 1975) recorded a generally increased mortality risk (= 1.27) and a markes increase in tumor SMR (= 3.9).

A recent epidemiologic survey of 7,021 VCM-exposed workers in the Federal Republic of Germany (Reinl et al. 1979) revealed no significant overall increase in malignant tumors (SMR = 1.03), but the rates for individual organ tumors were markedly elevated: gastrointestinal tumor = 1.30, liver tumors = 15.23(!), CNS tumors = 1.62, tumors of the lymphatic system = 2.14. Tabershaw and Gaffey (1974) has assessed standardized mortality rates in 8,384 VCM-exposed workers employed in 33 different factories in the USA. The rate for tumors in general was only slightly elevated (1.10), but organ tumor rates were more distinct: 1.89 for tumors of the oral cavity and pharynx, 1.55 for cancer with unknown primary. There was also the case report of a 22-year-old man who, after 14 years of habitually chewing PVC-coated cables, developed a keratinizing squamous carcinoma of the buccal mucosa (Casterline et al. 1977).

A survey of 1,294 VCM-exposed workers from 1941 to 1973) Waxweiler et al. recorded an increase in the SMR of tumors in general (1.49) with a distinct

Table 3. Increased standard mortality rates for non-neoplastic disease in VCM workers

Authors	SMR	Disease
Byrén et al. 1976	1.52	Cardiovascular
Chiazze et al. 1977	1.05	Cardiovascular (males)
Duck et al. 1975	1.41	Cerebrovascular
Reinl et al. 1979	1.27	Cardiovascular
Waxweiler et al. 1976	1.04	Cardiovascular
	1.76	Pulmonary

rise in liver tumors (11.55) and CNS tumors (3.29), and lesser elevations in pulmonary tumors (1.56), lymphatic malignancies (1.59); tumors of the gastrointestinal tract are registered with the rate "greater than one".

Increasing standardized mortality rates for other diseases are not considered in the same way by all these authors. Some of them did mention rising SM rates for certain diseases, but the latter are not confirmed by other authors. Table 3 compares the rates registered by different authors for nonneoplastic disease occurring in different organs.

Conclusions

Various surveys of standardized mortality rates in workers under chronic exposure to VCM have assessed the risk of developing fatal tumor disease to be distinctly higher in these workers than in the normal population, with the exception of several studies conducted in Great Britain. Besides a very striking elevation in the risk of liver tumors, nearly all these studies revealed an increasing incidence of gastrointestinal, pulmonary, CNS, and lymphatic malignancies. Although the SMR for malignant neoplasms in general was only slightly higher than 1, exposed workers were found to have an increased risk of dying of these tumors. This may be due to the high VCM concentrations registered in factories during the first years of VCM production and processing to PVC, i.e., at levels that were subsequently found to be positively cancerogenic in experimental studies.

Recent years brought a worldwide endeavour to reduce VCM concentrations in the factories to minimize the risk for the exposed workers. Although the levels have been effectively lowered, the potential latency period of 20 years for the induction of VCM tumors in man is a strong point in favor of keeping a close watch on occupational tumor development in the next decades. Ten of fifteen years are a period of risk especially in VCM or PVC workers, because the dangerously high concentrations had been recorded in some factories until 1974. The effectivity of specially closely knit surveillance systems in the early detection of VCM tumors in the exposed group is hard to predict. It is equally undecided whether CEA tests (proposed by Anderson et al. 1978) or alkaline phosphatase tests (Lilis et al. 1979) might help to detect liver damage at an early stage. A practicable way may be found in coordinating biological monitoring of individual exposure, with the analytical monitoring of concentration limits in the occupational environment.

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