REV 8(F)

THE CARCINOGENICITY OF VINYL CHLORIDE

L. Criteria

Vinyl chloride has proved to be carcinogenic in man and in animals. The data on the carcinogenicity of this substance was reviewed by an IARC Working Group in February 1978 and is published in the series of IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans (Vol. 19).

Pathological conditions other than cancer are also related to the toxicity of vinyl chloride. The complex of lesions provoked by vinyl chloride is now considered as a "sclerotic syndrome" (Haley, 1975). Acro-osteolysis, a lesion of the bones which mostly affects terminal phalanges of the fingers, was described in vinyl chloride workers. Extensive liver fibrosis, particularly periportal fibrosis which leads to portal hypertension and enlargement of the spleen, is the most frequent pathological manifestation among those exposed to vinyl chloride. Sclerotic changes of the skin and Raynaud-like syndromes have also been observed. *In vivo* microscopy has shown skin capillary abnormalities among 36-39.5% of workers in polyvinyl chloride production plants (USA-UK data). At the time of examination, most of these changes were asymptomatic (Maricq et al., 1978). Thrombocytopenia is one of the earliest signs of vinyl chloride intoxication. Symptoms of damage to the central nervous system - narcotic and asthenic nervous symptoms - have also been reported in workers (Haley, 1975).

Chronic exposure of laboratory animals to vinyl chloride led to hepatic lesions and bone changes similar to those described in men (IARC, 1978).

The first animal study indicating carcinogenicity of vinyl chloride involved rats exposed to 30,000 ppm vinyl chloride in air, 4 hours a day, 5 days a week, for 9 to 12 months, when the animals were sacrificed 40-54 weeks after the beginning of exposure. Auditory sebaceous gland tumours and osteochondromas were detected (Viola, 1970; Viola et al., 1971).

In subsequent experiments, lower levels in air proved to be carcinogenic to rats, mice, hamsters and rabbits. The tumours induced were angiosarcomas[1] of the liver and other organs, malignant tumours of the lung, intestine, kidney, skin, mammary gland and forestomach (Caputo et al., 1974; Holmberg et al., 1976; Maltoni, 1976; Maltoni & Lefemine, 1974).

---

[1] Malignant tumours affecting blood vessel walls

The Carcinogenicity Of Vinyl Chloride
Environmental Carcinogens, Selected Methods of Analysis, Vol. 2, Methods for the Measurement of Vinyl Chloride in Poly (Vinyl Chloride), Air, Water and Food Stuffs, IARC Scientific Publication No. 22, pages 3-11, 34 references, 19781978

The compound is carcinogenic in rats, mice and hamsters at levels of 50 ppm in air, and in rats at levels of 25 ppm in air. At lower levels (10.5 and 1 ppm in air), no carcinogenic effect was observed in a study which is still incomplete (Maltoni, 1977).

Ingestion of vinyl chloride by application through stomach tubes at levels of 50.0 mg/kg bw[1] and 16.6 mg/kg bw in olive oil once a day for 52 weeks produced some liver angiosarcomas and other tumours in rats, but levels of 3.3 mg/kg bw produced angiosarcomas at sites other than the liver (Maltoni, 1977).

Angiosarcomas have been observed in the offspring of rats exposed to vinyl chloride between the 12th and the 18th day of pregnancy (Maltoni, 1976).

Vinyl chloride has therefore been shown to be carcinogenic in at least four animal species: rats, mice, hamsters and rabbits.

A number of studies have been carried out on the possible mechanism of the carcinogenicity of vinyl chloride. This compound is mutagenic in bacteria (Ames system) (Bartsch & Montesano, 1975; Bartsch et al., 1975) and its mutagenicity is greatly activated by liver tissue homogenates from man, mice and rats. Chloroethylene oxide, which is considered to be the main active carcinogenic metabolite of vinyl chloride, is a strong alkylating agent. It is responsible for the mutagenic effect in bacteria, yeast and Chinese hamster cells (Huberman et al., 1975; Loprieno et al., 1977; Malaveille et al., 1975). Vinyl chloride produces chromosal alterations in human lymphocytes (Funes-Cravioto et al., 1975).

The tumour observed in workers in the polyvinyl chloride industry is liver angiosarcoma. The first angiosarcoma of the liver in a polymerization worker, employed for 15 years in the same industry (USA), was detected in 1961, but the relation between the development of this tumour and exposure to vinyl chloride was first described in 1974 (Creech & Jonson, 1974). According to Delorme & Thériault (1978), ten liver angiosarcomas have been diagnosed since 1955 in workers in a vinyl chloride polymerizing plant in Canada. Tumours of this kind rarely occur in the general population (0.0014 cases per 100,000 inhabitants, according to USA statistics) and those detected in workers in the polyvinyl chloride industry represent a 400-fold increase over the expected incidence. Since then, 71 tumours have been observed in people previously exposed to vinyl chloride[2] and 65 of them occurred in workers in polymerization plants.

A special panel of pathologists in the UK has reviewed the histological material available from cases considered to be primary angiosarcomas of the liver, detected between 1963 and 1974 (Baxter et al.,

---

[1] Body weight

[2] NIOSH, unpublished data for January 1978

1977). It confirmed the diagnosis of liver angiosarcomas in only 14 out of 41 cases. Occupational histories were available for 12 of the 14. One of the 12 had been exposed for over 20 years to levels of vinyl chloride of more than 200 ppm. In a second case, the occupational history was not known with certainty, but exposure to vinyl chloride could not be ruled out. The third case involving possible vinyl chloride exposure was that of a man who had lived for six years within half a mile of a plant manufacturing polyvinyl chloride. There were no other cases of liver angiosarcomas which could be related to vinyl chloride exposure in the UK, where commercial production of vinyl chloride began in 1941.

The average lapse of time between initial exposure to vinyl chloride and diagnosis of liver angiosarcomas is 20 years. Tumours have been reported mostly during the last few years, which leads one to suspect that more tumours may be anticipated. Meanwhile, working conditions have been changed considerably. Since the 1950's, when the first signs of vinyl chloride toxicity were observed, equipment and manufacturing methods have been altered to give improved ventilation, sensitive analytical methods have been elaborated and low permissible concentrations have been established, with regular monitoring. Exposure levels have therefore been considerably reduced, with a corresponding reduction of risk.

The estimated historical individual exposures to vinyl chloride are (Stafford, 1977a):

1945-1955	1,000 ppm
1955-1960	400-500 ppm
1960-1970	300-400 ppm
mid 1973	150 ppm
1975	5 ppm

European regulations with respect to vinyl chloride are indicated in Table 1 (Thomas, 1977).

Personal monitoring systems, although still not perfect, tend to confirm the 1-5 ppm TWA (monthly average per person)[1].

Obviously, the concentrations at some sites in a plant can be greater than at others. A leakage of vinyl chloride could occur during removal of filters, plant maintenance (such as repair work to the pumps), loading of tankers, etc. At such times, operators are required to wear protective masks. Although individual sensitivity to the toxic effects of vinyl chloride is certainly variable, it is obvious that exposure should be minimized to the full extent possible.

---

[1] Stafford, unpublished data

Table 1. European regulations concerning vinyl chlorice

1. Workers' protection	
Belgium	(5 ppm/week, intervention level 15 ppm, for all factories)[a]
Denmark	No PVC production, 1 ppm/8 hours for transformers
Finland	5 ppm/8 hours (personnel), 10 ppm/10 minutes max.
France	Existing factories (5 ppm/week, intervention level 15 ppm) New factories (1 ppm/week, intervention level 5 ppm) Values above intervention level are excluded for averaging purposes
Germany (Federal Republic)	As of 1.1.77; existing factories (5 ppm/year, 15 ppm/hour, 50 ppm max); factories to be established + transformers (2 ppm/year, 15 ppm/hour)
Italy	Awaiting EC regulations
Netherlands	(Letter to factory inspectors: 10 ppm max) (personnel)
Norway	No regulations, best technical procedures applied, quarterly report to authorities
Spain	(No regulations, self-discipline in industry)
Sweden	1 ppm/8 hours (personnel); max: 5 ppm/15 minutes (personnel)
Switzerland	10 ppm/week (personnel), based on 8 hours/day during 5 days
United Kingdom	(Code of good practice: 10 ppm/8 hours (personnel), 30 ppm max (personnel). Aim for the lowest possible values)
EC	(5 ppm/period to be established, intervention level 15 ppm)

[a] Proposals and regulations in brackets do not have the force of law.

It is not known whether vinyl chloride induces tumours other than angiosarcomas in man. Such induction is very difficult to establish for tumours which are not as rare as liver angiosarcoma. However, tumours other than angiosarcoma have been induced by vinyl chloride in animals, suggesting that this might also be possible in man. Some preliminary data are in favour of this hypothesis. It has been

suggested that lung cancer and tumours of the brain appear more frequently in workers exposed to vinyl chloride (Equitable Environ. Health, 1978; Monson & Peters, 1974; Monson et al., 1975) and that vinyl chloride could enhance the carcinogenic action of other substances, such as tobacco or benzene (Ott et al., 1975). At the same time, it must be pointed out that other authors have seen no evidence to support the above hypothesis (Fox & Collier, 1977). Further epidemiological studies are essential to establish the facts.

Occupational exposure to vinyl chloride is undoubtedly hazardous. This is important to remember, since the world's vinyl chloride and polyvinyl chloride producing and processing industries employ more than a million workers.

The existence of a dose-response relationship in vinyl chloride carcinogenicity has been established by experiment and by epidemiological observations. Twenty years ago, the concentrations found in polymerization plants may have reached more than 1,000 ppm (Stafford, 1976) and it may be assumed that health hazards have diminished with the reduction of vinyl chloride concentrations in the working environment. The major problem is that no one knows what levels of vinyl chloride can be considered to be safe. Thus, the para-occupational risk and the risk to the general population have also to be considered, together with the problem of hazards to workers handling vinyl chloride.

It can be presumed that the population exposed to the para-occupational risk is larger than the number of plant workers. It includes inhabitants of areas surrounding vinyl chloride processing factories which, in the USA alone, discharged some 110 million kg of vinyl chloride into the atmosphere, prior to 1975. The observation, in the USA, of angiosarcoma of the liver in people who were not exposed to vinyl chloride in industry, but who had lived close to polyvinyl factories, is of great importance (Seymour, 1975). At the present time, it is estimated that the levels of vinyl chloride in the atmosphere up to half a mile from a factory are between 0.01 and 0.03 ppm (Baxter et al., 1977). Such levels were certainly higher in the past. Fortunately, owing to photolysis, vinyl chloride does not accumulate in the atmosphere.

Apart from industrial and para-industrial environments, other more widespread sources of exposure exist, such as residual vinyl chloride in polyvinyl chloride, which, although inevitable, must be diminished. Polyvinyl chloride itself is considered to be non-toxic; it is an established ingredient in our modern way of life, with an average consumption in western Europe of 10 kg *per capita per annum* (Stafford, 1977b). This includes such common items as polyvinyl chloride food containers and bottles. The food in a polyvinyl container can be contaminated by the residual monomer. It has been estimated that the uptake of vinyl chloride from food wrappings can be from 0.1 to 1.0 µg per person per day (CEFIC, 1976), although most food wrapped in polyvinyl chloride film does not contain detectable quantities of vinyl chloride (Thomas, 1977).

Polyvinyl chloride is extensively used in furnishing and in upholstering cars. Seven of eleven new automobile interiors tested in unventilated conditions at interior air temperatures of 50-60°C have been found to contain vinyl chloride in concentrations of 0.4-1.2 ppm (Hedley et al., 1976). According to other data (Environmental Protection Agency, 1976), no vinyl chloride was detected in automobile interiors (sampling was carried out when seat temperatures were 25-45°C).

The use of vinyl chloride as a propellant in aerosol sprays, once a source of exposure, now appears to be prohibited in many countries.

The detection of vinyl chloride in tobacco smoke at levels of 5-27 ng per cigarette (or small cigar) suggests that it may be formed during combustion of any organic material containing inorganic chloride (Hoffmann et al., 1976). Although these levels are very low, they represent an increment in the total carcinogenic load.

The use of vinyl chloride and its release in the environment is difficult to restrain. The main objective of those responsible for industrial and general hygiene is the promotion of technology which will reduce vinyl chloride pollution. Much progress has been made in the last few years. An essential step in this direction is to organize the monitoring of vinyl chloride in different environments. For this reason, it is important to have reliable analytical methods.

REFERENCES

Bartsch, H. & Montesano, R. (1975) Mutagenic and carcinogenic effects of vinyl chloride. *Mutat. Res., 32*, 93-114

Bartsch, H., Malaveille, C. & Montesano, R. (1975) Human, rat and mouse liver-mediated mutagenicity of vinyl chloride in *S. typhimurium* strains. *Int. J. Cancer, 15*, 429-437

Baxter, P.J., Anthony, P.P., MacSween, R.N.M. & Scheuer, P.J. (1977) Angiosarcoma of the liver in Great Britain, 1963-1973. *Br. Med. J., 2*, 919-929

Caputo, A., Viola, P.L. & Bigotti, A. (1974) Oncogenicity of vinyl chloride at low concentrations in rats and rabbits. *IRCS, 2*, 1582

CEFIC (1976) *Vinyl chloride toxicity and the use of PVC for packaging foodstuffs.* CEFIC Committee for the Toxicity of Vinyl Chloride, Brussels

Creech, J.L. & Jonson, M.N. (1974) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *J. Occup. Med.*, *16*, 150

Delorme, F. & Thériault, G. (1978) Ten cases of angiosarcoma of the liver in Shawinigan, Quebec. *J. Occup. Med.*, *20*, 338-340

Environmental Protection Agency (1976) Sampling and analysis of selected toxic substances. Task III: Vinyl chloride, secondary sources. *Environ. Prot. Agency (U.S.)*[1]

Equitable Environmental Health Inc. (1978) *Epidemiological Study of Vinyl Chloride Workers*, Final Report, January 1978, Rockville, MD, USA

Fox, A.J. & Collier, P.F. (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

Funes-Cravioto, F., Lambert, B., Lindsten, J., Ehrenberg, L., Natarajan, A.T. & Osterman-Golkar, S. (1975) Chromosome aberrations in workers exposed to vinyl chloride. *Lancet*, 459

Haley, T.J. (1975) Vinyl chloride - How many unknown problems? *J. Toxicol. Environ. Health*, *1*, 47-73

Heath, C.W., Jr, Dumont, C.R., Gamble, J. & Waxweiler, R.J. (1977) Chromosomal damage in men occupationally exposed to vinyl chloride monomer and other chemicals. *Environ. Res.*, *14*, 68-72

Hedley, W.H., Cheng, J.T., McCormick, R.J. & Lewis, W.A. (1976) Sampling of automobile interiors for vinyl chloride monomer. *Environ. Prot. Agency (U.S.)*

Hoffmann, D., Patrianakos, C., Brunnemann, K.D. & Gori, G.B. (1976) Chromatographic determination of vinyl chloride in tobacco smoke. *Anal. Chem.*, *48*, 47-50

Holmberg, B., Kronevi, T. & Winell, M. (1976) The pathology of vinyl chloride exposed mice. *Acta Vet. Scand.*, *17*, 328-342

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

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 19 (1978) *Plastics and synthetic elastomers - Some monomers, homopolymers and copolymers*, Lyon, International Agency for Research on Cancer

---

[1] U.S. Environmental Protection Agency Publications may be obtained from U.S. Department of Commerce, National Technical Information Service, Springfield, Va, 22161, USA

Loprieno, N., Barale, R., Baroncelli, S., Bartsch, H., Bronzetti, G., Cammellini, A., Corsi, C., Frezza, D., Nieri, R., Leporini, C., Rosellini, D. & Rossi, A.M. (1977) Induction of gene mutations and gene conversions by vinyl chloride metabolites in yeast. *Cancer Res.*, *36*, 253-257

Malaveille, C., Bartsch, H., Barbin, A., Camus, A.M. & Montesano, R. (1975) Mutagenicity of vinyl chloride, chloroethyleneoxide, chloroacetaldehyde and chloroethanol. *Biochem. Biophys. Res. Commun.*, *63*, 363-370

Maltoni, C. (1976) *Occupational chemical carcinogenesis: new facts, priorities and perspectives.* In: Rosenfeld, C. & Davis, W., eds, *Environmental Pollution and Carcinogenic Risks*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications No. 13, INSERM Symposium Series Vol. 32*), pp. 127-134

Maltoni, C. (1977) *Vinyl chloride carcinogenicity: an experimental model for carcinogenesis studies.* In: Hiatt, H.H., Watson, J.D. & Winsten, J.A., eds, *Origins of Human Cancer*, Cold Spring Harbor Conferences on Cell Proliferation, Vol. 4, pp. 119-146

Maltoni, C. & Lefemine, S. (1974) Carcinogenicity bioassays of vinyl chloride. I: Research plan and early results. *Environ. Res.*, *7*, 387

Maricq, H.R., Darke, C.S., Archibald, R.M.L. & Leroy, E.C. (1978) *In vivo* observation of skin capillaries in workers exposed to vinyl chloride. An English-American comparison. *Br. J. Ind. Med.*, *35*, 1-7

Monson, R.R. & Peters, J.M. (1974) Proportional morbidity among vinyl chloride workers. *Lancet*, *1*, 397

Monson, R.R., Peters, J.M. & Johnson, M.N. (1975) Proportional mortality among vinyl chloride workers. *Environ. Health Perspect.*, *11*, 75-77

Ott, M.G., Langner, R.R. & Holder, B.B. (1975) Vinyl chloride exposure in a controlled industrial environment. *Arch. Environ. Health*, *30*, 333-339

Seymour, R.B. (1975) The VCM-PVC syndrome. *Aust. Plast. Rubber*, 9-11

Stafford, J. (1976) The vinyl chloride monomer health problem. *Chem. & Ind.*, 466-470

Stafford, J. (1977a) Case study for Science Policy Foundation Conference - Vinyl chloride monomer. *Sci. & Public Policy*, *4*, 134-142

Stafford, J. (1977b) Vinyl chloride monomer. *Tijdschr. Soc. Geneeskd.*, *55*, 574-578

Thomas, J.C. (1977) PVC et sécurité, règlementations européennes. *Caoutch. Plast.*, *571*, 33-38

Viola, P.L. (1970) Pathology of vinyl chloride. *Med. Lav.*, *61*, 174-180

Viola, P.L., Bigotti, A. & Caputo, A. (1971) Oncogenic response of rat skin, lungs and bones to vinyl chloride. *Cancer Res.*, *31*, 516-522

SI - NIOSH/00149574
AU - Griciute L
TI - The Carcinogenicity Of Vinyl Chloride
SO - Environmental Carcinogens, Selected Methods of Analysis, Vol. 2, Methods for the Measurement of Vinyl Chloride in Poly (Vinyl Chloride), Air, Water and Food Stuffs, IARC Scientific Publication No. 22, pages 3-11, 34 references, 19781978
AB - The carcinogenicity of vinyl-chloride (75014) is reviewed. Vinyl-chloride is carcinogenic in humans and animals. Pathological conditions are outlined; chronic exposures in animals cause hepatic lesions and bone changes. Tumors induced by vinyl-chloride in animal liver, lung, intestine, kidney, skin, mammary gland, and forestomach are discussed. Tumors observed in workers in the polyvinyl-chloride (9002862) industry are generally liver angiosarcomas. Histological studies made by British scientists on the primary angiosarcomas of the liver are described. Estimated individual exposures to vinyl-chloride are presented. The European standards for concentrations of vinyl-chloride in the workplace environment are between 1 to 5 parts per million, time weighted average. The concentrations at some sites in an industrial facility can be greater than at others. Hazardous conditions may result from leakage of vinyl-chloride, caused by mechanical breakdown or malfunction of manufacturing equipment. The regulations set by 13 European countries for pollution of the workplace environment by vinyl-chloride are discussed. The author concludes that to reduce vinyl-chloride concentrations in the workplace, the use of modern technology to promote industrial and general hygiene is crucial.
KW - DCN-136178 ; Environmental factors ; Carcinogens ; Toxins ; Industrial environment ; Industrial exposures ; Cancer ; Analytical instruments ; Cancer rate ; Animal studies ; Analytical models ; Humans
RN - 75-01-4; 9002-86-2
EM - 9003