

Four: EPIDEMIOLOGIC APPROACHES
IN CARCINOGEN DETECTION

TOXICITY OF VINYL CHLORIDE
AND POLYVINYL CHLORIDE AS SEEN
THROUGH EPIDEMIOLOGIC OBSERVATIONS

Joseph K. Wagoner

Environmental Defense Fund, Washington, D.C.

Peter F. Infante, Rosanne B. Apfeldorf

Office of Carcinogen Identification and
Classification, Directorate of Health Standards
Programs, Occupational Safety and Health
Administration, Washington, D.C.

In 1974, vinyl chloride (VC) was first reported in the scientific literature to induce angiosarcoma of the liver in animals and humans. Further research has now demonstrated the carcinogenicity of this agent to other organs. Target organs for VC now include the liver, brain, and lung, and probably the lymphohematopoietic system.

The carcinogenic risk has been extended to jobs associated with polyvinyl chloride (PVC) exposure. This is evidenced by cases of liver angiosarcoma reported among individuals employed in or residing near PVC fabrication facilities and by epidemiologic study demonstrating a significant association between lung cancer and exposure to PVC dust. An association between PVC dust and pneumoconiosis has been demonstrated. On the basis of these findings, experimental bioassays and epidemiologic studies of the carcinogenicity of PVC are clearly in order. Prudent control of PVC in the industrial setting is also clearly indicated.

INTRODUCTION

In 1971, some 40 yr after the introduction of vinyl chloride (VC) into American commerce and 10 yr after acro-osteolysis was shown to be developing in workers exposed to it, Viola et al. first reported the induction of tumors of the skin, lung, and bone in rats exposed by inhalation to 30,000 ppm VC. These oncogenic findings were confirmed in 1972 by Maltoni, who, noting angiosarcoma of the liver and cancers of other sites, transmitted his findings to the Manufacturing Chemists Association in the United States and to chemical companies in Europe (Maltoni, 1976a). Government, labor, and the independent research community were first made aware of this site-specific carcinogenic activity of VC in early 1974, when representatives of industry announced three cases of liver angiosarcoma among workers who had cleaned reactor vessels as part of their employment at a single VC polymerization facility in the United States (Creech and Johnson, 1974).

We thank Ms. Jolie Appel for typing the manuscript.

1101[181]

Copyright © 1980 by Hemisphere Publishing Corporation

ANGIOSARCOMA OF THE LIVER AND VINYL CHLORIDE

Subsequently, several epidemiologic investigations have indicated that occupational exposure to VC is associated with an increased risk of liver cancer (Waxweiler et al., 1976; Byren et al., 1976; Fox and Collier, 1977).

In addition to the results of these epidemiologic studies, several cases of liver angiosarcoma have been reported in association with exposure to VC. Christine et al. (1974) noted six histopathologically confirmed cases of hepatic angiosarcoma in Connecticut. One individual with liver angiosarcoma lived within 2 mi of a plant producing wire coated with polyvinyl chloride (PVC), while a second individual lived within 0.5 mi of a plant producing vinyl sheets. Neither individual was known to have had occupational exposure to VC or arsenic or diagnostic exposure to thorium dioxide. Two additional subjects had been employed in industrial facilities that used PVC. One of these individuals, a 47-yr-old man, had worked for the previous 10 yr as an accountant in a factory producing vinyl sheets and processing PVC resins and had frequently visited the plant's production areas. The other individual, a 61-yr-old man, had spent 25 yr in an electrical plant operating a machine that applied PVC-containing plastic to wires. [With regard to a further observation involving PVC-coated wire, Casterline et al. (1977) reported a case of a healthy 22-yr-old male who developed a squamous cell carcinoma of the buccal mucosa, against which PVC-containing plastic materials were held for prolonged periods of time (6-8 h/d). The person did electrical wiring and held the coated wire in his mouth so that he could strip the coating and expose the base wire. He gave a history of no use of tobacco or alcohol and no prior mouth or lip lesions.]

Brady et al. (1977) reported the results of a New York State study of 26 confirmed cases of angiosarcoma of the liver and controls comprised of individuals who had an internal malignant tumor other than primary liver cancer. Controls were matched with index cases on the basis of age at diagnosis, race, sex, place of residence, and vital status. This study showed a statistically significant association ($p < 0.02$) between angiosarcoma of the liver and direct occupational exposure to arsenic (two cases), VC (three cases), and diagnostic exposure to thorium dioxide (two cases). In addition, the authors noted that of 10 females with liver angiosarcoma, one lived within 1700 ft of a VC polymerization plant for 62 yr and four lived 500-4500 ft from PVC fabrication plants for 8-27 yr, whereas none of their matched controls did so. This latter observation, according to the authors, lent support to the hypothesis that indirect modes of exposure to VC or PVC might be important in the etiology of liver angiosarcoma. On a voluntary basis, cases of liver angiosarcoma have been reported among workers occupationally exposed to VC in countries throughout the world (Lloyd, 1975).

LIVER CHANGES AND POLYVINYL CHLORIDE POWDER

In 1976, the 90-wk preliminary results from a 2-yr oral toxicity study being conducted by the Central Institute for Nutrition and Food Research in Holland were transmitted to the National Institute for Occupational Safety and Health (NIOSH). This unpublished report indicated that administration of VC monomer (as PVC powder in the diet) to rats at levels of 3 and 9 mg per kilogram of body weight resulted in obvious liver changes that in many cases appeared to be neoplastic. To the best of our knowledge, the final results of this bioassay have not been published or released (E. J. Fairchild, personal communication).

BRAIN CANCER

Consistent with the epidemiologic results of a significant excess of 10 cases of CNS cancer, glioblastoma multiforme, authors noted that this compared to data from intracranial neoplasms studies have also been associated with VC (Equitable et al., 1976). Thus, both the brain and liver are considered as target organs for VC.

PNEUMOCONIOSIS

In 1975, I. J. ... to avoid the inhalation of dust during the handling of the PVC powder. Sinai Hospital reported that workers (Miller et al., 1975) in a toxicology study of guinea pigs, exposed to filling sacks with PVC powder, exhibited granulomatous disorders possibly due to the dust. This might be expected at concentrations ranging from being smaller than 100 mg/m³ to 1000 mg/m³ (communication).

In 1978, Arnat et al. (1978) reported that a worker had been exposed to PVC powder and presented with excretory abnormalities. Electron microscopy of particles in the macrophages of the lung by Szende et al. (1978) showed that the secondary to the inhalation of PVC powder found in the patient.

Results of the etiology of pneumoconiosis in production facilities with these individuals is

BRAIN CANCER AND VINYL CHLORIDE

Consistent with the experimental bioassay results of Maltoni (1977) and with the epidemiologic results of Tabershaw and Gaffey (1974), Waxweiler et al. (1976) reported a significant excess of central nervous system (CNS) cancer among workers exposed to VC. Of 10 cases of CNS cancer observed in the latter study, 9 were histologically classified as glioblastoma multiforme (no histological diagnosis was reported for the tenth case). The authors noted that the distribution of cell types of these intracranial neoplasms was unusual compared to data from the Yale autopsy series, which indicated that only 33% of primary intracranial neoplasms were of the glioblastoma multiforme cell type. Other epidemiologic studies have also demonstrated a significant excess of brain cancer among workers exposed to VC (Equitable Environmental Health, Inc., Rockville, Md., unpublished report; Byren et al., 1976). Thus, both experimental bioassay and epidemiologic study have demonstrated the brain as a target organ for the carcinogenicity of VC.

PNEUMOCONIOSIS AND POLYVINYL CHLORIDE

In 1975, I. J. Selikoff wrote to NIOSH suggesting that appropriate precautions be taken to avoid the inhalation of PVC dust, both in the packaging and transport of PVC and in its handling during the manufacture of PVC products. Selikoff based his suggestion on Mount Sinai Hospital reports of radiographic and pulmonary function changes among VC and PVC workers (Miller et al., 1975; Lillis et al., 1975) and on the findings of a PVC inhalation toxicology study by Frongia et al. (1974). This latter investigation showed that rats and guinea pigs, exposed in the same occupational setting as workers who were employed in filling sacks with PVC powder, subsequently developed alveolar reactions and septal thickening. This investigation also showed that 7 mo after their initial exposure both species exhibited granulomatous changes, with fine granules observed intracellularly. Pulmonary disorders possibly associated with exposure to PVC resins produced by the emission process might be expected, as dust samples taken by NIOSH during the bagging of PVC resin showed concentrations ranging from less than 1 up to 19 mg/m³, with about 90% of the particles being smaller than 2.5 μ m and 100% smaller than 7 μ m in diameter (J. J. Finklea, private communication).

In 1978, Arnaud et al. reported a case of pneumoconiosis in a 53-yr-old man who had been exposed to PVC in the bagging area of a VC polymerization plant. This patient presented with exertional dyspnea, pulmonary function changes, and chest radiographic abnormalities. Electron microscopy of lung tissue obtained by drill biopsy showed foreign particles in the macrophages that were identical to PVC powder viewed under the electron microscope. *In vitro* incubation of PVC powder with human lung macrophages showed that the macrophages engulfed the powder to give an appearance similar to that seen *in vivo*. The authors noted that the histological lesions in this patient were identical to those recorded by Szende et al. (1970), who diagnosed advanced pneumoconiosis in a 31-yr-old man secondary to the inhalation of PVC dust. Szende et al. (1970) also reported that microscopic examination of PVC dust particles showed them to be morphologically similar to particles found in the patient's lungs.

Results of more recent epidemiologic study further support the role of PVC in the etiology of pneumoconiosis (Mastrangelo et al., 1979). A total of 1216 employees of a PVC production factory in Italy underwent chest X-ray examinations. Of 731 examined individuals with exposure to PVC dust, 20 were diagnosed as having pneumoconiosis. All of these individuals had worked 5 or more years in departments classified as having PVC dust

R&S
001072

pollution. No cases of pneumoconiosis were observed among the 485 examined individuals who worked in areas free of PVC dust.

LUNG CANCER AND VINYL CHLORIDE AND POLYVINYL CHLORIDE

Jones, in 1978 (unpublished report), gave the results of industrial hygiene surveys conducted by NIOSH in 13 VC-PVC plants during 1974-1975. These surveys indicated that VC exposures, as determined by personal sampling, ranged from 0.01 to 84.77 ppm ($n = 119$) for VC monomer plants, from undetected to 245.0 ppm ($n = 449$) for VC polymerization plants, and from undetected to 2.44 ppm ($n = 268$) for PVC fabrication plants. Polyvinyl chloride personal dust sampling in VC polymerization plants showed that concentrations ranged from 0.38 to 18.62 mg/m³ and were highest for those who worked in the bagger job category. A total of 17 area dust samples taken in PVC fabrication plants showed concentrations ranging from 1.67 to 13.33 mg/m³.

An epidemiologic evaluation designed to assess the spectrum of neoplastic effects among workers exposed to VC in PVC production facilities was reported by Waxweiler et al. in 1976. Excess cancer of the lung and other sites was found. An additional epidemiologic study has also demonstrated a significant excess of lung and respiratory system cancers (Buffler et al., 1979), while other studies have not reported such an excess (Equitable Environmental Health, Inc., unpublished report; Ott et al., 1975; Byren et al., 1976; Tabershaw and Gaffey, 1974).

Falk (1976) reported further on the histopathology of the lung cancer cases in the VC-PVC industry as studied by Waxweiler et al. (1976). Of 22 lung cancer cases reviewed microscopically, 27% were adenocarcinoma and 46% were of the large-cell undifferentiated type. Particular mention was made of cells having a typical adenomatous proliferation. The findings of Waxweiler et al. (1976) and of Falk (1976) are of interest in view of experimental bioassays demonstrating the induction of adenomas in Swiss mice (Maltoni, 1977) and in view of abnormal sputum cytology observed among workers in the Italian VC-PVC industry (Maltoni, 1976b). In the latter study, the incidence of abnormal cells in the sputum of workers in the VC-PVC industry (Table 1) was higher than expected when compared to sputum cells of heavy smokers and workers in the chemical industry.

TABLE 1. Frequency of Cellular Changes in the Respiratory Tract among Workers in the Chromium, VC-PVC, and General Chemical Industry as Detected by Sputum Cytology^a

Occupation	No. of workers	Cytologic class (Papanicolaou)					
		I	II	II-III	III and III-IV	IV	V
Chromium industry	116 (100) ^b	—	62 (53.4)	24 (20.7)	30 (25.9)	—	—
VC-PVC industry	267 (100)	75 (28.1)	138 (51.7)	38 (14.2)	16 (6.0)	—	—
Chemical industry in general	371 (100)	112 (30.2)	196 (52.8)	57 (15.4)	6 (1.6)	—	—
Control (heavy smokers)	1000 (100)	335 (33.5)	556 (55.6)	103 (10.3)	6 (0.6)	—	—

^aFrom Maltoni (1976b).

^bPercentages are given in parentheses.

TABLE 2. Histological

Type of cancer
Total
Epidermoid
Small cell
Adenocarcinoma
Large-cell undifferentiated

^aFrom Waxweiler et al.

^b27 cases reviewed

^c $D = (A \times 27) - (i)$

^d45 total cases.

^e $E = (A \times 45) - (i)$

In 1978, Waxweiler et al. reported on the risk of lung cancer in a VC-PVC facility. Of 22 lung cancer cases reviewed microscopically, 27% were adenocarcinoma and 46% were of the large-cell undifferentiated type. Particular mention was made of cells having a typical adenomatous proliferation. The findings of Waxweiler et al. (1976) and of Falk (1976) are of interest in view of experimental bioassays demonstrating the induction of adenomas in Swiss mice (Maltoni, 1977) and in view of abnormal sputum cytology observed among workers in the Italian VC-PVC industry (Maltoni, 1976b). In the latter study, the incidence of abnormal cells in the sputum of workers in the VC-PVC industry (Table 1) was higher than expected when compared to sputum cells of heavy smokers and workers in the chemical industry.

A further study of the chemicals used at the VC-PVC facility or for the excess of sensitivity and specificity between angiosarcoma and 19 chemicals used statistically significantly differentiated lung cancer.

The studies on the VC monomer industry is related to the fact that VC monomer is a fat-soluble substance. Almost all PVC particles are known to settle in the lung. Thus it is also possible that VC monomer is a fat-soluble substance.

TABLE 2. Histological Specific Lung Cancer Risk among Plant Personnel^a

Type of cancer	Histological distribution (%)		Histological specific standardized mortality ratio (SMR) (C) = $149 \times A/B$	Excess cases among those pathologically reviewed ^b (D) ^c	Total excess cases ^d (E) ^e
	Observed (A)	Expected (B)			
Total	100	98	149	8.9	14.8
Epidermoid	22.2	30	110	0.6	0.9
Small cell	22.2	30	110	0.6	0.9
Adenocarcinoma	25.9	28	138	1.9	3.2
Large-cell undifferentiated	29.6	10	441	6.2	10.3

^aFrom Waxweiler et al. (1978).^b27 cases reviewed pathologically.^c $D = (A \times 27) - (B \times 27 \times 100/149)$.^d45 total cases.^e $E = (A \times 45) - (B \times 45 \times 100/149)$.

In 1978, Waxweiler et al. reported the results of a study of lung cancer at a single VC-PVC facility. One objective of this study was to determine whether there was an excess risk of lung cancer of a particular histological type at the plant. A case control study showed a clear excess of type 3 (adenocarcinoma) and type 4 (large-cell undifferentiated) lung cancers in cases occurring among plant employees as compared to other lung cancer cases from the same hospital of diagnosis, matched for age and calendar period of diagnosis. These data are shown in Table 2. The authors noted that adenocarcinomas of the lung, accounting for a minor proportion of this excess risk, have been shown to be at most only weakly related to cigarette smoking; some studies have shown no association at all. The authors also noted that large-cell undifferentiated carcinoma of the lung, accounting for the vast majority of the excess lung cancer risk, is the only major histological type that has never been related to cigarette smoking by epidemiologic study. Thus, they concluded that cigarette smoking was not a major confounding variable in the study.

A further study was made by Waxweiler et al. (1978) to test whether one or more chemicals used at the plant were responsible for the excess of lung cancer of types 3 and 4 or for the excess of only type 4. A model was specifically developed for this purpose. The sensitivity and specificity of the model was demonstrated by its confirmation of the relationship between angiosarcoma of the liver and direct VC exposure. The authors reported that of all 19 chemicals used at the plant, PVC dust was the only chemical for which they found a statistically significant association with lung cancer mortality and specifically with large-cell undifferentiated lung cancer.

The studies mentioned above suggest that the excess lung cancer risk in the VC-PVC industry is related to exposure to PVC dust. That the dust itself or as a carrier of residual VC monomer is a factor in the etiology of lung cancer seems biologically plausible. PVC dust particles are known to be often in the respirable range—that is, less than 10 μm in diameter. Almost all PVC particles produced by the emulsion system, one of the systems at the facility studied by Waxweiler et al. (1978), are in the respirable range. These particles could easily settle in the lung and conceivably by themselves cause lung cancer. However, it is known that VC monomer becomes entrapped in PVC dust and can be released slowly over time. Thus it is also possible that PVC dust particles in the lung could slowly release VC

monomer to small adjacent areas of the tissue, prolonging the contact time of that chemical with tissue.

LYMPHATIC SYSTEM CANCERS AND VINYL CHLORIDE

Experimental study has demonstrated the induction of lymphatic cancer in golden hamsters exposed to VC (Maltoni, 1977). Several epidemiologic investigations have reported a nonstatistically significant excess of mortality from lymphatic system cancer among workers exposed to VC (Tabershaw and Gaffey, 1974; Equitable Environmental Health, Inc., unpublished report; Waxweiler et al., 1976). More data are needed to demonstrate this site as a target for VC-induced disease.

REFERENCES

- Arnaud, A., Pommier de Santi, P., Garbe, L., Payan, H., and Charpin, J. 1978. Polyvinyl chloride pneumoconiosis. *Thorax* 33:19-25.
- Brady, J. S., Liberatore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J. N. P., Bishop, M., Polan, A., and Vianna, N. 1977. Angiosarcoma of the liver: An epidemiologic study. *J. Natl. Cancer Inst.* 59:1383-1385.
- Buffler, P. A., Wood, S., Eifler, M. A., Suarez, L., and Kilian, D. J. 1979. Mortality experience of workers in a vinyl chloride monomer production plant. *J. Occup. Med.* 21:195-203.
- Cyren, D., Engholm, G., Englund, A., and Westerholm, P. 1976. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. *Environ. Health Perspect.* 17:167-170.
- Casterline, C. L., Casterline, P. F., and Jaques, D. A. 1977. Squamous cell carcinoma of the buccal mucosa associated with chronic oral polyvinyl chloride exposure. *Cancer* 39:1686-1688.
- Christine, B. W., Barrett, H. S., and Lloyd, D. S. 1974. Epidemiologic notes and reports. Angiosarcoma of the liver—Connecticut. *Morbid. Mortal. Weekly Rep.* 23:210-211.
- Creech, J. L. and Johnson, M. N. 1974. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *J. Occup. Med.* 16:150-151.
- Falk, H. 1976. Discussion of part II: Chemical carcinogenesis. *Ann. N.Y. Acad. Sci.* 271:473-480.
- Fox, A. J. and 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.
- Frongia, N., Spinazzola, A., and Bucarelli, A. 1974. Lesioni polmonari sperimentali da inalazione prolungata di polveri di PVC in ambiente di lavoro. (Experimental lung damage from prolonged inhalation of airborne PVC dust.) *Med. Lav.* 65:321-342.
- Lilis, R., Anderson, H., Nicholson, W. J., Daum, S., Fishbein, A. S., and Selikoff, I. J. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann. N.Y. Acad. Sci.* 246:22-40.
- Lloyd, J. W. 1975. Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J. Occup. Med.* 17:333-334.
- Maltoni, C. 1976a. Predictive value of carcinogenesis bioassays. *Ann. N.Y. Acad. Sci.* 271:431-443.
- Maltoni, C. 1976b. Precursor lesions in exposed populations as indicators of occupational cancer risk. *Ann. N.Y. Acad. Sci.* 271:444-447.
- Maltoni, C. 1977. Vinyl chloride carcinogenicity: An experimental model for carcinogenesis studies. In *Origins of Human Cancer*, eds. H. H. Hiatt, J. D. Watson, and J. A. Winsten, book A, pp. 119-146. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.
- Mastrangelo, G., Manno, M., Marcer, G., Bartolucci, G. B., Gemignani, C., Saladino, G., Simonato, L., and Sala, B. 1979. Polyvinyl chloride pneumoconiosis: Epidemiological study of exposed workers. *J. Occup. Med.* 21:540-542.
- Miller, A., Teirstein, A. S., Chuang, M., Selikoff, I. J., and Warshaw, R. 1975. Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. *Ann. N.Y. Acad. Sci.* 246:42-52.
- Ott, M. G., Langner, R. R., and Holder, B. B. 1975. Vinyl chloride exposure in a controlled industrial environment. A long-term mortality experience in 594 employees. *Arch. Environ. Health* 30:333-339.
- Szende, B., Lapis, K., Nemes, A., and Pinter, A. 1970. Pneumoconiosis caused by the inhalation of polyvinyl chloride dust. *Med. Lav.* 61:433-436.

Tabershaw, I. R. and Gaffey, J. 1974. Polyvinyl chloride and its polymer. *Cancer Res.* 34:1-10.

Viola, P. L., Bigotti, A., and Gaffey, J. 1974. Polyvinyl chloride. *Cancer Res.* 34:1-10.

Waxweiler, R. J., Stringer, R. L., and Smith, A. 1976. Excess lung cancer risk among workers exposed to vinyl chloride. *Occupational Health* 15:1-10.

- Tabershaw, I. R. and Gaffey, W. R. 1974. Mortality studies of workers in the manufacture of vinyl chloride and its polymers. *J. Occup. Med.* 16:509-518.
- Viola, P. L., Bigotti, A., and Caputo, A. 1971. Oncogenic response of rat skin, lungs and bones to vinyl chloride. *Cancer Res.* 31:516-522.
- Waxweiler, R. J., Stringer, W., Wagoner, J. K., Jones, J., Falk, H., and Carter, C. 1976. Neoplastic risk among workers exposed to vinyl chloride. *Ann. N.Y. Acad. Sci.* 271:40-48.
- Waxweiler, R. J., Smith, A. H., Tyroler, H. A., and Falk, H. 1978. An epidemiologic investigation of an excess lung cancer risk in a synthetic chemicals plant. Paper presented at the International Congress on Occupational Health, Dubrovnik, Yugoslavia, Sept. 25-30.

R&S 001076