

Toxicity of Vinyl Chloride and Poly(vinyl Chloride): A Critical Review

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In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals. Additional research has now demonstrated the carcinogenicity of VC to other organs and at lower concentrations. The target organs for VC now clearly include the liver, brain and the lung, and probably the lymphohematopoietic system.

The evidence for a carcinogenic risk has been extended to jobs associated with poly(vinyl chloride) exposure. Cases of liver angiosarcoma have been reported among individuals employed in PVC fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to PVC dust and the risk of lung cancer mortality. Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly(vinyl chloride) plants.

An association between PVC dust and pneumoconiosis also has been demonstrated. On the basis of findings, prudent control of PVC dust in the industrial setting is indicated.

Laboratory Bioassay

In 1971, 44 years after vinyl chloride was introduced into American commerce (1), 24 years after vinyl chloride was shown to cause cardiac arrhythmia in experimental animals (2), 22 years after vinyl chloride was reported to be associated with hepatic abnormalities in workers in a Russian plastic factory (3), 14 years after toxic angioneuropathy was noted among workers exposed to vinyl chloride below the then Russian maximum allowable concentration of 390 ppm (4), 11 years after the vinyl chloride production process was associated with a severe neurologic disorder in Minamata, Japan (5), 10 years after vinyl chloride at concentrations down to 200 ppm were reported to cause centrilobular granular degeneration of the liver (6) and 5 years after vinyl chloride was shown to induce acro-osteolysis in workers cleaning reactor vessels (7), Viola et al. (8) reported the induction of tumors of the skin, lung and bone in rats exposed by inhalation to 30,000 ppm of vinyl chloride.

These oncogenic findings have been interpreted by some to have elicited little response because

the testing was conducted only at unrealistically high dosages bordering on the lower explosive limit of vinyl chloride (9). In reality, however, such was not the case. In May of 1971, Viola had presented to several U.S. companies unpublished findings of an increased incidence of tumors in rats exposed to vinyl chloride concentrations down to and including 500 ppm (10). Additional ongoing studies involving vinyl chloride exposures of 20,000, 10,000, 5,000, 2,000, 500 and less than 500 ppm were also described to those same companies. In like manner, Maltoni, in 1972, upon noting angiosarcoma of the liver and cancer of other sites in rats exposed by inhalation to vinyl chloride at lower concentrations, also had transmitted his findings to the Manufacturing Chemists Association in the United States and to several chemical companies in Europe (11). Government, labor and the independent research community were first informed of the expanding carcinogenic properties of vinyl chloride in January of 1974, when representatives of industry announced having found liver angiosarcoma in three workers who had cleaned reactor vessels as part of their employment at a single vinyl chloride polymerization facility in the United States. Almost simultaneously, findings of the induction of liver angiosarcoma in rats exposed to vinyl chloride were made public.

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The carcinogenic properties of vinyl chloride were further clarified in 1974, when Caputo et al. (12) reported an increasing incidence of liver angiosarcoma with an increasing dosage of vinyl chloride. Among rats exposed to vinyl chloride by inhalation, the incidence of liver angiosarcoma was 3% at 500, 5% at 1,000, 6% at 5,000, 8% at 10,000 and 12% at 20,000 ppm. Among controls not exposed to vinyl chloride, liver angiosarcoma was not found. In that same year Maltoni and Lefemine (13) also reported the induction of tumors in mice, hamsters and rats exposed to vinyl chloride by inhalation. The spectrum of induced tumors included angiosarcomas of the liver, adenomas and adenocarcinomas of the lung, neuroblastomas of the brain, lymphomas and carcinomas of other sites. Vinyl chloride in that study was shown to induce liver angiosarcoma in rats at 50 ppm of exposure. Keplinger et al. (14) in that same year also reported the induction of liver angiosarcoma in mice exposed to 50 ppm of vinyl chloride by inhalation. Subsequently, Holmberg et al. (15) reported the induction of hepatic and extrahepatic angiosarcoma in mice following inhalation exposure to vinyl chloride at 50 ppm. Shortly thereafter Maltoni (16) extended the carcinogenicity of vinyl chloride to lower levels of exposure. Vinyl chloride administered by inhalation was shown to induce tumors at a variety of sites, including liver angiosarcoma at 25 ppm and mammary carcinomas at 25, 10, 5 and 1 ppm. Recently Maltoni (17) reported the induction of hepatic and extrahepatic angiosarcoma at 10 ppm of vinyl chloride.

Epidemiology

Occupational Exposure: Vinyl Chloride Production or Polymerization

In 1974, the same year that the public was first informed that vinyl chloride induced liver angiosarcoma and cancers of other sites by way of experimental bioassay, epidemiological studies also were reported demonstrating an excess of cancer of multiple organs among workers occupationally exposed to vinyl chloride. Tabershaw and Gaffey (18) reported that cancers of the buccal cavity and pharynx, digestive tract (primarily liver angiosarcoma), respiratory tract, central nervous system (primarily brain) and the lymphatic system were excessive among workers in the United States having been employed for at least one year in plants producing and/or polymerizing vinyl chloride. Monson et al. (19) in that same year reported the results of a proportionate

mortality analysis of 161 deceased workers having been employed at one of two plants in the United States producing and polymerizing vinyl chloride. The specific sites of cancer with the greatest excess were the liver and biliary tract, with an 11-fold excess; the brain, with a 4-fold excess; the digestive tract and the lung.

In 1975, Nicholson et al. (20) published a study of cancer mortality among 257 individuals occupationally exposed to vinyl chloride for at least 5 years, with the initial exposure having occurred more than 10 years in the past during employment in a U.S. plant polymerizing vinyl chloride. A 2.3-fold excess in deaths from cancer of all sites combined was demonstrated with three deaths due to hemangiosarcoma of the liver. In that same year, Ott et al. (21) reported the mortality experience of 549 individuals occupationally exposed to vinyl chloride-poly(vinyl chloride). Whereas no angiosarcomas of the liver were found, an excess of all malignancies combined was reported among those workers classified as having been highly exposed when contrasted with workers of all other exposure intensities. Among the nine cancer deaths in the highly exposed group of workers, four were due to lung cancer. In a discussion of the limitations of the study, the investigators noted that the majority of workers in the category "other than highly exposed" had less than one year of work experience in departments with exposure to vinyl chloride-polyvinyl chloride.

Duck et al. (22) in 1975 reported that a study of 2100 employees of a vinyl chloride polymerization plant in the United Kingdom revealed no excess of total or cause-specific mortality. In addition to reporting no excess of cancer mortality. The investigators reported an inverse relation between vinyl chloride exposure and cancer mortality, i.e., as the duration of exposure to vinyl chloride-poly(vinyl chloride) increased, the risk of cancer decreased. The results and conclusions of that study were adjudged by Wagoner et al. (23) to be spurious and due to the use of faulty analytical methodology. Upon reanalysis of the data in that study, Duck and Carter (24) reported an increased risk of cancer of the digestive system among workers observed 15 years or more after onset of exposure to vinyl chloride-poly(vinyl chloride).

Subsequently, Waxweiler et al. (25) reported the results of a retrospective study of mortality among a cohort of 1294 workers occupationally exposed to vinyl chloride in the United States. Since occupationally induced cancers often take years to become clinically manifest following exposure to carcinogens, the study was restricted to

those individuals with 5 years or more of employment in departments and jobs directly involving vinyl chloride exposure and with 10 years or more elapsed time since onset of initial exposure. Specific jobs and departments with vinyl chloride exposure were determined following a walk-through survey and review of the manufacturing process, engineering controls and air-sampling data for the plants studied. When analyses were based on the total study cohort, only two major causes of death were in excess: nonneoplastic respiratory disease (6 observed vs. 3.4 expected) and all malignant neoplasms combined (35 observed vs. 23.4 expected). The latter excess was statistically significant at $p = 0.05$. When analyses were made according to site of malignancy and latency (interval since onset of exposure), an excess cancer mortality was found for four organ systems, i.e., central nervous system, respiratory system, hepatic system and lymphatic and hematopoietic system. The excessive mortality was statistically significant for three of the four organ systems, i.e., cancer of the central nervous, the respiratory and the hepatic systems, among workers who had been observed 15 years or more since onset of exposure. During the course of the study by Waxweiler et al., an evaluation was made of the pathologic data underlying each neoplasm identified. Of the 14 cases of liver cancer identified, 11 were diagnosed as angiosarcoma. Of ten cases of brain cancer identified, nine were shown to be glioblastoma multiforme in type. Furthermore, of eight lung cancer cases histologically confirmed, all were large cell undifferentiated or adenocarcinoma in type.

Byren et al. (26) in 1976 also reported a statistically significant excess of liver-pancreatic and brain cancer deaths among 771 workers employed in a Swedish vinyl chloride/poly(vinyl chloride) production plant. These investigators reported that this excess appeared within the first 5 years after onset of exposure to vinyl chloride.

In 1977, von Reinl et al. (27) reported the results of a study of cancer mortality among 7021 males employed in the production and polymerization of vinyl chloride. When compared to the mortality experience of the West German male population, vinyl chloride-poly(vinyl chloride) exposed workers experienced an excess of cancer of multiple organs, i.e., liver, lung, brain and the lymphatic and hematopoietic system. Fox and Collier (28) in 1977 also reported the results of the study of cancer mortality patterns among 7561 males who, at some time between 1940 and 1974, were employed at one of four plants producing poly(vinyl chloride). An excess mortality from

liver cancer was shown for each group of workers whether exposure to vinyl chloride was judged to have been high, medium or low. The authors commented that, although there were no data from the study to support an excess mortality from cancers other than of the liver, the period of follow-up of the workers was too short to permit a clear evaluation of those carcinogenic effects at that time.

Epidemiological investigations have now clearly demonstrated that laboratory bioassay findings were predictive not only for the carcinogenicity of vinyl chloride, but also for several of the target organs. On the basis of these results, the IARC (29) in 1979 concluded "Vinyl chloride is a human carcinogen. Its target organs are the liver, brain, lung and haemo-lymphopoietic system."

Occupational Exposure: Poly(vinyl Chloride) Packing and Fabricating

Christine et al. in 1974 reported (30) two histopathologically confirmed cases of hepatic angiosarcoma in Connecticut among individuals who had been employed in industrial facilities that used poly(vinyl chloride). One of these individuals, a 47-year-old man, had worked for the previous 10 years as an accountant in a factory producing vinyl sheets and processing poly(vinyl chloride) resins. This individual had frequently visited the plant's production area. The second individual, a 61-year-old man, had spent 25 years in an electrical plant operating a machine that applied poly(vinyl chloride)-containing plastic to wires. In 1977, Baxter et al. (31), in a review of 14 cases of hepatic angiosarcoma diagnosed in Great Britain during 1963-73, noted one case who had worked on a process which used poly(vinyl chloride) as a raw material.

In 1975, Selikoff wrote to NIOSH suggesting that appropriate precautions be taken to avoid the inhalation of poly(vinyl chloride) dust, both in the packaging and transport and in its handling during the manufacture of poly(vinyl chloride) products. Selikoff based his suggestion on the results of studies by Lilis et al. (32) and Miller et al. (33) showing radiographic and pulmonary function changes among vinyl chlorides-poly(vinyl chloride) workers and on the findings of a poly(vinyl chloride) inhalation toxicologic study by Frongia et al. (34). This latter investigation showed that rats and guinea pigs, exposed in the same occupational setting as workers who were employed in filling sacks with poly(vinyl chloride) powder, subsequently developed alveolar reactions and septal thickening. This investigation

also showed that 7 months after their initial exposure, both species exhibited granulomatous changes, with fine granules observed intracellularly. Agarwal et al. (35) in 1978 demonstrated that intratracheal administration of poly(vinyl chloride) dust in rats resulted in an increase in the activity of lysosomal enzymes, interstitial fibrosis and granulomatous lesions surrounded by fibroblasts, reticulin and collagen fibers. Pulmonary disorders possibly associated with exposure to poly(vinyl chloride) resins produced by the emission process might be expected, as dust samples taken by NIOSH during the bagging of poly(vinyl chloride) resin have shown 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.

In 1978, Arnaud et al. (36) reported a case of pneumoconiosis in a 53-year-old man who had been exposed to poly(vinyl chloride) 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 poly(vinyl chloride) powder viewed under the electron microscope. *In vitro* incubation of poly(vinyl chloride) 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. (37), who diagnosed advanced pneumoconiosis in a 31-year-old man secondary to the inhalation of poly(vinyl chloride) dust. Szende et al. also reported that microscopic examination of poly(vinyl chloride) dust particles showed them to be morphologically similar to particles found in the patient's lungs.

Results of epidemiologic studies by Vertkin and Hamontov (38) and by Mastrangelo et al. (39) further support the role of poly(vinyl chloride) in the etiology of pneumoconiosis. A total of 1216 employees of a poly(vinyl chloride) production factory in Italy underwent chest X-ray examinations. Of 731 examined individuals with exposure to poly(vinyl chloride) dust, 20 were diagnosed as having pneumoconiosis. All of these individuals had worked 5 years or more in departments classified as having poly(vinyl chloride) dust pollution. No cases of pneumoconiosis were observed among the 485 examined individuals who worked in areas free of poly(vinyl chloride) dust.

The effects of vinyl chloride-poly(vinyl chloride) exposure on the respiratory system of ex-

posed workers seem to indicate a pattern of non-neoplastic effects, a granulomatous reaction to poly(vinyl chloride) dust, with inclusion of poly(vinyl chloride) particles in macrophages and histiocytes, and associated interstitial fibrosis.

The long-term carcinogenic effect, with a significant increase in lung cancer also is of concern. In 1978, Waxweiler et al. (40) reported the results of a study of lung cancer at a single vinyl chloride-poly(vinyl chloride) 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. 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 differentiated 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. 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 vinyl chloride exposure. The authors reported that of all 19 chemicals used at the plant, poly(vinyl chloride) 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 vinyl chloride-poly(vinyl chloride) industry is related to exposure to poly(vinyl chloride) dust. That the dust itself or as a carrier of residual vinyl chloride monomer is a factor in the etiology of lung cancer seems biologically plausible. Poly(vinyl chloride) dust particles are known to be often in the respirable range—that is, less than 10 μ m in diameter. Almost all poly(vinyl chloride) particles produced by the emulsion system, one of the systems

at the facility studied by Waxweiler et al., 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 vinyl chloride monomer becomes entrapped in poly(vinyl chloride) dust and can be released slowly over time. Thus it is also possible that poly(vinyl chloride) dust particles in the lung could slowly release vinyl chloride monomer to small adjacent areas of the tissue, prolonging the contact time of that chemical with tissue.

On the basis of these findings, one must seriously question the safety of the current OSHA standard for poly(vinyl chloride) dust, i.e., a standard which treats poly(vinyl chloride) as a nuisance dust.

Community Exposure to Vinyl Chloride

Christine et al. (30) reported two cases of hepatic angiosarcoma in Connecticut having a probable residential exposure to vinyl chloride. One individual with hepatic angiosarcoma lived within 2 miles of the plant producing poly(vinyl chloride)-coated wire, while the second individual lived within 0.5 miles of a plant producing vinyl sheets. Each of these two plants also had a case of hepatic angiosarcoma among its labor force. Neither of these residential cases was known to have had occupational exposure to vinyl chloride or arsenic or diagnostic exposure to thorium dioxide, the only three agents known to cause hepatic angiosarcoma in humans. Baxter et al. (31), in 1977 reported another case of liver angiosarcoma in Great Britain who had lived for 6 years within half a mile of a plant manufacturing poly(vinyl chloride). On the basis of these observations, Brady et al. (41) in 1977 undertook a study in New York State of 26 confirmed cases of hepatic angiosarcoma. Controls comprised of individuals who had an internal malignant tumor other than primary liver cancer 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 between angiosarcoma of the liver and direct occupational or therapeutic exposure to arsenic (two cases), vinyl chloride (three cases) and thorium dioxide (two cases). In addition, this study demonstrated that of ten female cases of liver angiosarcoma (no direct occupational or therapeutic exposure to vinyl chloride, arsenic or thorium dioxide) one lived within 1700 ft of a vinyl chloride polymerization plant and four lived from 500 to 4500 ft of a poly(vinyl chloride) fabrication plant. In contrast, none of their matched controls lived

within 1 mile of any facility polymerizing vinyl chloride or fabricating poly(vinyl chloride). These study findings are supportive of the role of indirect modes of vinyl chloride exposure in the etiology of liver angiosarcoma.

Summary

Adenomas and adenocarcinomas of the lung, angiosarcomas of the liver and of other sites, lymphomas, mammary carcinomas, neuroblastomas of the brain, in addition to various other tumors have been induced in mice, rats and hamsters exposed by inhalation to vinyl chloride. In addition vinyl chloride when administered by inhalation has been found to induce hepatic and extrahepatic angiosarcomas at concentrations as low as 10 ppm and mammary carcinomas at even lower concentrations, i.e., 5 and 1 ppm.

Several mutually confirmatory studies, using the retrospective cohort method, have shown an increased risk of liver angiosarcoma and cancer of other sites among employees of vinyl chloride polymerization facilities. The full magnitude of this site-specific cancer risk among employees of vinyl chloride polymerization plants will only be determined following full lifetime observation. Nevertheless, studies already have shown that for liver angiosarcoma the excess risk is approximately 11 to 16 times that of the general population. For brain cancer the excess risk is 4-fold.

The role of indirect modes of exposure to vinyl chloride has now been shown to be associated with an excess risk of cancer. Several cases of liver angiosarcoma have been reported among individuals living in close proximity (less than 2 miles) to facilities polymerizing vinyl chloride or fabricating poly(vinyl chloride). A recent epidemiological study has demonstrated that 50% of females with liver angiosarcoma (5/10) lived within 1 mile of such industrial facilities, whereas none of their matched control did so.

Experimental bioassay and epidemiological studies have shown a high concordance for the carcinogenicity of vinyl chloride, specifically for liver angiosarcoma. This excess of liver angiosarcoma has been shown to persist from the polymerization of vinyl chloride to the residence in near proximity to such facilities.

Both experimental and epidemiological data indicate that PVC dust is probably associated with respiratory effects, both neoplastic and non-neoplastic in nature.

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