CARCINOGENICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE

SEE VINYLIDENE CHLORIDE (2)

C. C. Lee, J. C. Bhandari, J. M. Winston, W. B. House

Pharmacology and Toxicology, Midwest Research Institute, Kansas City, Missouri

R. L. Dixon, J. S. Woods

Environmental Toxicology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

Exposure of mice to 50, 250, or 1000 ppm of vinyl chloride (VC) in the air for 6 h/d, 5 d/wk, caused a high incidence of bronchioloalveolar adenoma, mammary gland tumors, and hemangiosarcoma. Mammary gland tumors occurred in the females and included ductular adenocarcinoma and squamous and anaplastic cell carcinomas with metastasis to the lung. Hemangiosarcoma occurred in the liver and, to a lesser extent, in various other organs. The incidence and severity of these tumors increased with the concentration of VC and the length of exposure. Malignant lymphoma involving various organs was observed in several mice. Rats were more resistant to the carcinogenic effects of VC. Exposure of rats to 250 or 1000 ppm of VC caused hemangiosarcoma in the liver. Many rats with hepatic hemangiosarcoma also developed hemangiosarcoma in the lung. Extrahepatic hemangiosarcoma also occasionally occurred in other organs. Exposure to 55 ppm of vinylidene chloride (VDC) caused hepatic hemangiosarcoma and probably bronchioloalveolar adenoma in mice. Hemangiosarcoma also occurred in the mesenteric lymph node or subcutaneous tissue in two rats exposed to 55 ppm of VDC.

INTRODUCTION

In 1971, the carcinogenic effect of vinyl chloride (VC) was first reported in animals (Viola et al., 1971). Male Ar/IRE rats exposed to 30,000 ppm of VC, 4 h/d, 5 d/wk, for 12 mo, developed epidermoid

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Requests for reprints should be sent to Cheng-Chun Lee, Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri 64110.

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Vinyl Chloride

Occupational Acroosteolysis

II. An Industrial Hygiene Study

Warren A. Cook; Paul M. Giever, MPH; Bertram D. Dinman, MD, ScD; and Harold J. Magnuson, MD, MPH, Ann Arbor, Mich

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An industrial hygiene survey was conducted in respect to occupational acroosteolysis (AOL) in 32 plants engaged in production and compounding of polyvinyl chloride. This survey was limited to inspection of facilities, interrogation of technical personnel, and statistical analyses. All manufacturing processes and chemicals utilized were explored. A major objective was the identification of variables in processes and chemicals that were peculiar to those plants affording known cases of AOL. No such processes or chemicals were found. The survey brought to light a number of situations suspected of relationship to the precise cause of AOL, some of which require additional exploration. Most positive of these was the finding that essentially all of the persons who developed AOL had served as reactor cleaners using manual methods.

POLYVINYL chloride (PVC) has been in production and widespread use for more than 30 years. An extensive account of the chemistry, methods of production, materials utilized, properties, and uses of the PVC resins was recently published in a series of technical articles by Albright.[1-5] Uses include such diverse products as floor tiles, films for food wrappings, sheeting for shower curtains, phonographic records, and coatings for cables.

As an indication of the magnitude of the PVC industry, the average operating capacity in this country for the year 1969 was about 3 billion lb.[6] Much PVC is produced in other countries. Even with this extensive production involving thousands of operators, the occurrence of occupational acroosteolysis (AOL) among these workers was not recognized until about 1961.[7]

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Reprint requests to School of Public Health, University of Michigan, Ann Arbor, Mich 48104 (Dr. Dinman).

The clinical and epidemiological aspects of this condition are discussed in separate papers in this issue of the ARCHIVES.[8,9]

Industrial Hygiene Survey

Surveys were made of 32 plants by the authors of this paper, most of the plants being visited by a team of one physician and one industrial hygienist. Twenty-six of these were polymer production plants. Vinyl chloride monomer production plants and plants engaged in compounding and fabricating of the polymerized resin were a part of the manufacturing complex at a number of these locations. Five plants conducted compounding and fabricating operations only, and one plant produced only the vinyl chloride monomer. These plants were located throughout the United States and one in Canada.

This survey was designed to obtain information on equipment used, procedures followed, materials involved, extent of exposure to these, and names and descriptions of jobs in order to compare practices in the plants where cases of AOL occurred with those in plants experiencing no cases.

The extent of exposures was estimated on the basis of general observation, a knowledge of the physical, chemical, and physiological prop-

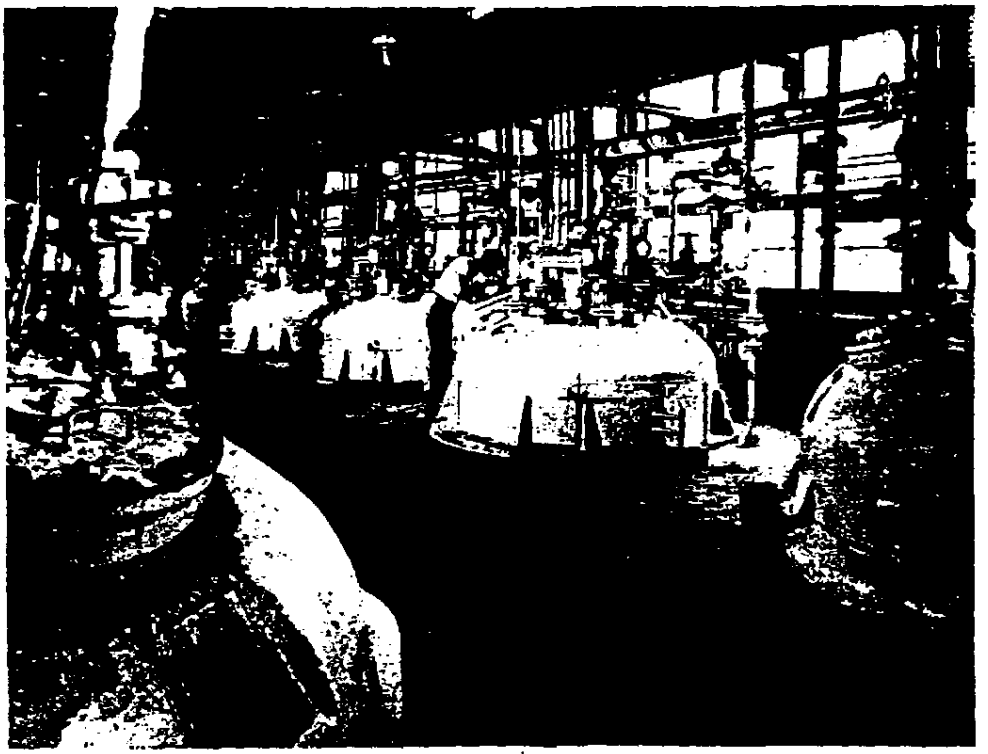

Fig 2.—Charging floor of PVC production plant showing top portion of reactors.

in Fig 2. The reactors extend for ten feet or so down to the floor below.

The polymer slurry is pumped to blend tanks, then to centrifuges for removal of much of the water. The dewatered polymer is passed through a rotary dryer with heated air, the temperature of the polymer being kept below 140 F to avoid degradation. The dried granular polymer is pneumatically conveyed into a cyclone separator, with finer particles being removed from the air stream by means of a filter-type collector. The polymer particles are sized by vibrating screens, then bagged for transfer to compounding and fabricating plants or shipped in bulk. In some plants, the polymer is stored in bins prior to being shipped.

In the emulsion process, the equipment and process is essentially the same as in the suspension process up to the drying operations. In order to produce the finer polymer particles characteristic of the emulsion process, a wide variety of emulsifying agents is used. These may be soaps such as ammonium or sodium laurate, surfactants such as salts of naphthalene sulfonic acid, or various synthetic detergents. Water-soluble initiators such as ammonium persulfate and hydrogen peroxide are used as catalysts. Since the fine polymer particles cannot be readily separated from the emulsion by centrifuging or filtering, a spray dryer is employed in this process.

The bulk process is similar to suspension polymerization but is characterized by the precipitation of the polymer from the liquid phase, as about 10% of the vinyl chloride becomes polymerized.

Solution polymerization is much the same as suspension polymerization, but no water is introduced. Instead, the polymerization is conducted in such solvents as cyclohexane, acetone, or *n*-butane.

Copolymer and Terpolymer Production.—In addition to the production of the homopolymer PVC, many of the plants also produce copolymer and terpolymers, including vinyl chloride. The greater percentage of the monomer tends to be the vinyl chloride in all of these. The copolymer vinyl chloride-vinyl acetate is in highest production

Table 3.—*Magnitude of Dosage Expressed as Single Concept*

Magnitude* of Dosage	Severity/Duration Exposure Parameters†		
	Less Than 1 hr/Week	1-8 hr/Week	More Than 8 hr/Week
Slight			
1	Negligible	None	None
2		Negligible	None
3			Negligible
4	Moderate	None	None
5	Moderate	Negligible	None
6	Moderate		Negligible
Intermediate			
7	Appreciable	None	None
8	Appreciable	Negligible	None
9	Appreciable		Negligible
10		Moderate	None
11		Moderate	Negligible
12			Moderate
Major			
13	Appreciable	Moderate	None
14	Appreciable		Moderate
15		Appreciable	None
16		Appreciable	Negligible
17		Appreciable	Moderate
18			Appreciable

* Expressed in order of increasing dosage received from exposure, which is the summation of the three columns to the right.
† Severity of exposure is estimated as none, negligible, moderate, or appreciable for indicated durations.

pounding consists of mixing PVC with a multiplicity of plasticizers, antioxidants, pigments, emulsifiers, stabilizers, and other special compounds in ribbon blenders and mills. The mixtures are then passed through roll mills or mixers, such as are used in the rubber industry, where the temperature may rise sufficiently to vaporize some of the plasticizer and other volatile constituents. The compounded polymer is then extruded through rolls or dies to form sheets, films, or pellets. These are used in fabricating operations.

Job Classification

Many variables were introduced in the plants surveyed and even in different units of the same plant in regard to nearly every phase of the operations. Investigation of unit jobs in the plants disclosed a wide assortment of job titles. In fact, a job title as used by the technical supervisors often differed from that for the same job in the same plant as listed by the personnel department.

Furthermore, a job assignment in one plant might include a different group of unit operations than in another plant. Also, the proportion of time devoted to the several unit operations often differed. To compound the difficulties of classification, workers would frequently rotate through several jobs at a weekly, monthly, or other period.

A classification of 26 job titles for the statistical purposes of this study was prepared (Table 1). These job titles corresponded to comparable operations in all the plants and to a common group of types of exposures to production materials. Every job in each of the plants was given its fraction of time related to the job title as defined for the study. Details of the manner in which this was done are discussed in the accompanying paper on epidemiological aspects of AOL.[8]

Job Progression.—Often the first job assignment of the new employee is that of reactor cleaner. Unless there are many reactors, this work does not require the entire time of the employee. Part of his time may be spent in bagging or shipping finished polymer or in the handling of catalysts and other additives.

As job openings arise and with accretion of seniority, this employee may progress to higher skilled jobs such as reactor, monomer recovery or dryer operator, or any combination of these at any one time.

In plants producing other products in addition to vinyl chloride polymers, employees may transfer between these product areas either as full time for a period of months or dividing their time within a given week or even day. The latter occurs particularly among maintenance personnel.

Where production of vinyl chloride is part of the operation, operators may rotate between jobs in the production of the monomer and those associated with the production of the polymer.

The length of time spent at various jobs is a function of production needs, economic conditions, plant growth rates, and activity of other product lines.

Occupational Exposures to Materials

Extent of Exposures.—Information was obtained not only on each of the materials

Table 5.—Reactor Cleaning Procedures

Plant Code	Hand Scraping: After Every Batch	Hand Scraping: Less Than Every Cycle	Cleaning by Water Jet	Cleaning by Solvent
Plants with AOL cases				
B	X			
E	X			
F	X			
K	X (through 1964)		From 1965	
R	X			
U		Every 5-12 cycles (building A)	From 1962 (building B)	
EE	X			
Plants with possible AOL cases				
BB		Every "several" cycles		On glass-lined, intermittently in 1966, entirely by December 1966
Plants with no AOL cases				
A	X (to September 1964)			From September 1964
C	X			
D			From 1962	
H	X			
J		Every 2½ cycles		
L		Every 4-8 days		
N	X			
P		Weekly through 1964, every 2 weeks 1965-1966	From 1965	
Q	X			
S	X			
T	X (emulsion)	Every 1-3 cycles (suspension)		
V		Every 10 cycles		
Z	X			
AA		Every 4 or more cycles		
DD	X			
GG				From start of operations

vinyl chloride to prevent spontaneous polymerization in storage. An inhibitor may also be added to the vinyl chloride recovered from the reactor. The phenol is removed by treatment with caustic soda prior to its transfer to the reactor. The practice over the years covered by the study is presented in Table 3. The use of the inhibitor in the virgin vinyl chloride at two of the positive plants and three of the negative plants, with inhibitor being added in the vinyl chloride recovery operation in two positive plants and four negative plants, leads to the conclusion that inhibitors probably are not a factor in AOL causation.

Catalyst Exposures.—Since the catalysts are all active compounds, they were suspect as a possible factor in the causation of AOL. Contact with these inorganic and organic peroxides occurs as they are handled prior to their introduction into the reactor and also during reactor cleaning if any unreacted catalyst remains in the residue. Twenty-two of the 26 plants used lauroyl peroxide. Eight of these were plants with AOL cases or possible AOL cases, and 14 were plants without AOL cases. The next most common organic peroxide was the IPP, and it, too, was in use in both the positive and the negative plants, in four of the former and in eight of the latter. No catalyst or group of catalysts was used in all positive plants and in no negative plants.

Constituents of Scrapings.—Other suspect materials are constituents of scrapings removed from the reactors during manual cleaning. These are believed to include some partially polymerized resins, along with some unreacted catalysts and additives, and unpolymerized vinyl chloride. Little specific information is currently available concerning these constituents. It has been reported that lauroyl peroxide is definitely associated with residual PVC particles, whereas little of the IPP remains unreacted in the polymer.[4]

Further investigation of the scrapings from the reactor may be expected to furnish information that may lead to a better understanding of the factors involved in causation of AOL. A difficulty in such investigation is that the composition of the scrapings is continually changing from the time they are removed from the surfaces of the reactor. It is obvious that comparatively small molecules of partially polymerized vinyl chloride are increasing in size with passage of time, and active constituents such as residual cat-

figure derives from the paper on epidemiological aspects of AOL[8] which reports the prevalence of AOL or possible AOL as one case per 37 reactor cleaners at risk.

Of the negative plants with an AP-T value of 10 or more, none of those in operation earlier than 1965 had enough reactor cleaners at risk to expect an AOL case, whereas two of the four plants with an AP-T value under 10 have enough workers to expect cases. Cases would be expected from the total population of reactor cleaners in the entire group of the seven negative plants with AP-T values of 10 or more, but the total number would be 3.6, as compared with 5.3 expected cases from the entire group of four negative plants with an AP-T value of less than 10. This contrasts with expected cases in the group of positive plants with an AP-T value of less than 10 as 1.7, compared with 11.8 in such plants with an AP-T value of 10 or more.

The proportion of the number of reactor cleaners in the negative plants with an AP-T value of less than 10 to the total number in such plants was 193 to 325. This proportion for the positive plants was 63 to 499. A χ^2 test demonstrated that the probability of this difference between the negative and the positive plants occurring by chance is less than 0.001.

In order to make this comparison between the positive and negative plants with AP-T values below and above 10, it was necessary to oversimplify a multiplicity of varying details of operational procedures from the time the polymerization is completed to the time the cleaner enters the reactor. Accordingly, any interpretation of the findings that reduction of the AP-T value below 10 by reducing the absolute pressure or keeping the reactor at reduced pressure for a longer time or both may results in reduction in development of AOL cases should be approached with great caution.

Preventive Measures

The present knowledge as to AOL is such that categoric statements as to preventive measures are not justified. However, on a somewhat speculative basis, some measures are indicated that may be conducive to AOL prevention:

1. Although some manual removal of residue from reactor surfaces may be required when solvents or high-pressure water jets are used for cleaning, the more extensive employment of these methods would greatly reduce the number of man hours required for conducting this operation by manual methods.

2. The adequacy of ventilation of reactors prior to entry should be checked with flammable vapor indicator equipped with a scale of greater sensitivity than 1% of the lower explosive limit of vinyl chloride or with other instruments of such sensitivity.

3. Further investigation of the constituency of the scrapings from the reactor surfaces should be considered, as such information might disclose the factor responsible for the causation of the disease.

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