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VINYL CHLORIDE

CH_2=CHCl

APPENDIX A1c

Since vinyl chloride (chloroethene, CH_2=CHCl) is a gas at room temperature and pressure, the common route of toxic exposure is by inhalation. As with many liquified gases, contact of the skin or eyes with escaping compressed vinyl chloride can produce freezing and frostbite(1).

Vinyl chloride has long been considered to be very low in toxicity by acute inhalation. Lehmann and Flury(2) summarized the literature and reported work by Schauman who considered vinyl chloride to be a candidate surgical anesthetic. Schauman reported little pathological change even after repeated exposure to anesthetic concentrations. Further work on the anesthetic potential of vinyl chloride indicated that vinyl chloride was unsafe for use as a surgical anesthetic in dogs and that because of its flammability, poor efficacy and its ability to cause cardiac irregularities at anesthetic concentrations vinyl chloride was not suitable for use as an anesthetic in humans.

Despite the early reports ascribing low toxicity to vinyl chloride, injury during the production of polyvinyl chloride (PVC) resins was reported as early as 1949. Significantly this report came from Europe where production of PVC in Europe preceded U.S. production by several years and today the quantity produced in Europe still exceeds U.S. production by about two fold. In 1949, Tribuhk et al.(3) reported numerous effects in PVC workers in what by today's standards must be considered as primitive production facilities. These authors found a "considerable number of cases of hepatitis among workers" but were more concerned with other hepatotoxic chemicals such as chlorinated diphenyl and chlorinated naphthylene (Holowax (sic)) than they were with vinyl chloride.

As a result of two deaths in Canada, the acute inhalation toxicity of vinyl chloride was studied by Mastromatteo et al.(4) who reported that exposure of mice, rats, and guinea pigs to 10, 20, and 30 volume percent vinyl chloride caused the following mortality:

NUMBER OF DEATHS IN DIFFERENT GROUPS OF FIVE MICE, RATS AND GUINEA PIGS EXPOSED FOR THIRTY MINUTES TO VARYING CONCENTRATIONS OF VINYL CHLORIDE IN AIR

Vinyl Chloride concentration (percent by volume in air)	Laboratory animal			TOTAL
	Mice	Rats	Guinea pigs	
10	0/5	0/5	0/5	0/15
20	1/5	0/5	0/5	1/15
30	5/5	5/5	1/5*	11/15
40	—	—	2/5*	2/5

*A delayed death occurred within 24 hours following exposure.

Some pulmonary hyperemia and engorgement was observed by these investigators, but liver and kidney injury were remarkably low. Deaths were due to narcosis.

The first report of studies to determine the effect of long-term repeated exposure (6 months) were summarized by Torkelson, Oyen and Rowe(1) as follows:

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"Repeated exposures of laboratory animals at several concentrations of vinyl chloride in air were conducted to determine the chronic toxicity of this material towards animals in order to assess the hazard to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for six months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats, but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, the other species were not affected. All species studied tolerated repeated daily 7-hour exposures at 50 ppm for six months with no detectable injury.

"Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect, longer exposures caused a slight increase in liver weight.

"The standard for evaluating regular daily 7- to 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm."

Lester, Greenberg, and Adams(5) took exception to the conclusion of Torkelson et al. (1961) that 50 ppm should be a maximum time weighted average exposure for workers. On the basis of 3 months exposure of rats to 2 volume percent and 19 days to 5 volume percent, they concluded that 500 ppm was acceptable as a TLV despite minor changes which they observed in rat livers and which they considered "were within the normal range and were not pathologic in nature."

Since 1949 numerous articles describing conditions and problems in PVC production plants have appeared particularly in the Eastern European literature. Filatova and Gronsberg(6), Gabor et al.(7), Suciu et al.(8), Gabor et al.(9), Grigorescu and Toba(10), Antonyuzhenko(11), and Kudryavtseva(12), have all described the effects of apparently gross chronic exposure. These papers and abstracts are difficult to interpret since there are generally inadequate descriptions of the exposure conditions and analysis of the workroom air, so no dose-response relationship can be determined. The injuries and effects described by the authors are not consistent with the levels of exposures claimed by the authors nor are the levels of exposure consistent with past or even present-day chemical technology. Furthermore, mixtures of chemicals are involved making it possible to ascribe the effect to any one of them.

For example, Suciu et al.(8) (through translation) described nervous disorders including euphoria with whistling and laughing, incoordination and dizziness similar to alcohol intoxication. However, Suciu et al. ascribes these results to exposure of the order of 5.5 mg/m^3 (2 ppm v/v) which is not consistent with other publications which indicate these effects will be apparent only if concentrations greatly exceed 10,000 to 20,000 ppm v/v. Therefore, the following conclusions by the authors can be construed as being the result of massive and apparently repeated exposures:

1. Vinyl chloride and the vinyl monomers possess a narcotic action and produce, depending upon concentration, in addition to characteristic neurologic manifestation, a state of euphoria (12%), followed by a state of inebriation similar to that of alcohol intoxication. In certain cases narcosis can appear.

   After leaving the working environment, a state of somnolence (45%) persists, with hypersomnia. Vinyl chloride acts on the skin and produces a sensation of formication and of heat.

2. After repeated exposure, a neurologic asthenia sets in in which somnolence predominates.

3. After a variable period of time, dyspeptic disturbances are added to the neurologic manifestations; these are at first not characteristic; they are in the form of epigastric pains (16%), swelling, discomfort, feeling of heaviness in the right hypochondrium (7%) or the left (5%) with anorexia, particularly for fats.

   In 30.2% of the cases, congestive hepatomegaly appears, which may mimic toxic hepatitis without jaundice; some cases may become chronic.

   In 6% of the cases, the hepatomegaly is accompanied by splenomegaly. The proteinogram and the aldolases are the most sensitive tests and show changes similar to those of acute hepatitis: increase in α-globulins and of the β- and γ-globulins; and thymol test, Greenstedt's reaction and the zinc sulfate test are positive only in few of the cases.

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4. After 3 years of exposure in 9% of the cases a syndrome typical of ulcer without radiologic changes becomes manifest.

5. In 6% of the cases the Raynaud syndrome has appeared, particularly among the young men. Plethysmography shows in half of the cases an inhibition of the vasomotor centers.

6. In addition, allergic dermatitis in 4.4% of the cases, and scleroderma in 3.6%, has been observed.

7. The clinical and laboratory findings are of great importance in occupational pathology because in numerous cases diseases appear in man that cannot be reproduced in the animal (Raynaud's syndrome and scleroderma).

The sudden and frequent appearance of these manifestations in the PVC division of several plants, and in certain divisions in normal individuals who are still relatively young, and their disappearance in the majority of the cases after the institution of protective measures and change of work, have shown us decisively that vinyl chloride and the vinyl monomers have played a part in the production of these manifestations. (End of author's summary).

In 1967, reports appeared in the literature describing a condition known as acroosteolysis in workmen engaged in polymerization of vinyl chloride to polyvinyl chloride. Harris and Adams(13) reported on two cases in Europe. Wilson et al.(14), reported on 37 cases in the B. F. Goodrich Company. Jühe et al.(15) described a syndrome consisting of (arranged in decreasing order of occurrence) thrombopenia, splenomegaly, liver damage, obstruction of ventilation, circulatory obstruction, and skin and bone alteration.

As a result of this problem, the University of Michigan in 1967 was retained by the Manufacturing Chemists Association to investigate acroosteolysis in sponsoring American companies. The results of a large scale epidemiological study of workers then currently employed in vinyl chloride and polyvinyl chloride production were reported in three publications by this group Dinman et al.(16), Cook et al.(17), and Dodson et al.(18).

Dinman et al.(16) summarized the study as follows:

"An epidemiological study was performed covering 5,011 employees with 21,510 man-years experience in various phases of vinyl chloride (VC) and polyvinyl chloride (PVC) manufacturing in 32 plants throughout the United States and Canada. The total number of definitive cases of acroosteolysis (AOL) was 25; 16 other individuals were under suspicion. This condition is clearly associated with the hand cleaning of polymerizers. Workers engaged in other phases of VC or PVC manufacturing do not appear to be at risk of developing AOL. The importance of Raynaud's phenomenon as a concomitant of AOL is emphasized. Several statistical approaches for rapid medical survey are suggested. Acroosteolysis appears to be a systemic rather than local disease. Presently, neither the etiological agent nor its portal of entry is known."

Cook et al.(17) describes the polyvinyl chloride production process in considerable detail. They concluded that although no etiological agent could be identified, "There appeared to be a correlation between the extent of degassing prior to entry into the reactor" and the incidence of acroosteolysis.

Mutchler and Kramer(19) presented a paper at the 1968 Gordon Research Conference which was subsequently published (1972), which reported on "The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride." The authors drew the following conclusion:

"Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone."

P. L. Viola, in an attempt to produce acroosteolysis in animals, exposed rats 4 hours per day, 5 days per week to 30,000 ppm (3%) vinyl chloride vapor. In his first report on the results of 12 months exposure, he described metaplastic changes in the bones which he considered similar to the human disease acroosteolysis. He made no mention of having observed cancer in these animals until the Tenth International Cancer Congress in May, 1970. In the abstracts of this meeting, and subsequently in May, 1971, Viola, Bigotti and Caputo(21) reported tumors of the skin, lungs and bones occurring first after 10 months of exposure. The authors summarized this work as follows:

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"Rats (Ar/IRE Wistar strain) exposed for 12 months to vapors of vinyl chloride developed tumors of the skin, lungs, and bones. The cutaneous tumors, which always appeared in the area in which submaxillary and parotid glands are located, have been histologically recognized as epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas. The morphological characteristics of lung tumors, which occurred in a lower percentage, were mainly of the adenocarcinoma type, with the exception of a single epidermoid tumor originating from the epithelial covering cells. In a minor number of rats, a large proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metacarpal and metatarsal regions of the four limbs."

The report by Viola et al.(21) is apparently the earliest publication in which carcinogenic activity has been ascribed to vinyl chloride in man or animals. Although there were obvious deficiencies in Viola's study, such as his very impure sample, the presence of food and bedding in the exposure chamber, the excessive exposure concentration as well as in the statistical evaluation and interpretation of the lesions, the report was of serious concern and resulted in additional animal and epidemiological studies which are currently underway in Italy Maltoni(22). Maltoni and and Lefemine(23,24) and the U.S., Keplinger et al.(25).

On January 22-23, 1974, the B. F. Goodrich Company notified its employees, NIOSH, the Kentucky State Department of Labor, and the public, that three workers had died of angiosarcomas of the liver. The case reports of the first subject has been published by Creech and Johnson(26). The subject, a 36 year old male, was hospitalized January 5, 1970 and subsequently succumbed September 27, 1971. He had worked in PVC production from November 1955 until his illness. The history, clinical course and pathologic findings are consistent with the others who died of angiosarcoma.

The work of Maltoni and Lefemine(23,24) has been reported publicly at the OSHA hearing, Washington, D.C., February 15, 1974, and included in the 1974 publication of the Second International Symposium on Cancer Detection and Prevention, Bologna, Italy, April 9-12, 1973. In these studies groups of rats as well as mice and hamsters have been exposed at concentrations of 10,000 to 50 ppm vinyl chloride vapor. Maltoni and Lefemine (1974) reported carcinomas of the Zymbal glands, nephroblastoma and angiosarcomas of the livers of rats at concentrations of 250 ppm to 10,000 ppm but not at 50 ppm. Subsequent unpublished information (August 31, 1974) reported "1 liver angiosarcoma, 1 extrahepatic angiosarcoma and 1 nephroblastoma, in three animals of the first experiment, exposed at 50 ppm of VC for 1 year, and surviving 135 weeks from the beginning of the treatment." The authors conclude that "a dose-response relationship clearly emerges, as far as angiosarcomas and nephroblastomas are concerned, in the lower dose ranges: from 500 ppm to 50 ppm for angiosarcomas, and from 250 ppm to 50 ppm for nephroblastomas. A comparison of the results available at the present moment in rats exposed for 12 months and 4 months (BT1 and BT3 experiments) shows that the neoplastic response, as far as angiosarcomas and nephroblastomas are concerned, is affected by the length of exposure to VC."

In their experiment BT3 Maltoni and Lefemine reported possible in utero production of angiosarcomas in offspring of pregnant rats exposed at 10,000 and 6,000 ppm.

Keplinger et al.(25) in a study sponsored by American companies have confirmed the findings of Maltoni and Lefemine. In this study groups of 100 rats, mice and hamsters of each sex are being exposed seven hours per day, five days per week to either 2,500, 200 to 50 ppm vinyl chloride monomer. After seven months of exposure angiosarcoma and lung adenomas have been observed in mice at all exposure levels. Although the data are preliminary in nature and require confirmation, angiosarcomas were apparently also observed in rats at 2,500 and 200 ppm and in a single hamster at 2,500 ppm. This study is still in progress and will not be completed until 1976 or 1977.

Epidemiological studies on U.S. workers have been conducted by Tabershaw-Cooper Associates for the Manufacturing Chemists Association(27). The summary of this study is as follows:

1. This historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride before December 31, 1972, demonstrated that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. The explanation for the latter finding is not apparent.

The other major findings of the study are: (1) The overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; (2) No cause

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of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and (3) No deaths identified as angiosarcoma of the liver were found other than those previously identified.

This is the first epidemiological study which suggests that in humans vinyl chloride may also be associated with cancer of multiple sites.

Vinyl chloride is tentatively assigned to Appendix A1c, "Substances awaiting reassignment of TLV because of recently discovered carcinogenicity."

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