THE TOXICITY OF VINYL CHLORIDE VAPOR
A Brief Summary of the Published Literature
February 7, 1974

Woody might like to see again

The following articles and abstracts, compiled by The Dow Chemical Company, are believed to include most of the significant scientific information on the toxicology of vinyl chloride in man and animals. The articles and abstracts are arranged in chronological order. Articles published in the last half of 1973 may not be included if they have not been abstracted by Chemical Abstracts or Biological Abstracts.

Important review articles which summarise much of the old literature have been used to cover the literature prior to 1961-1962. Therefore, copies of certain articles and abstracts described in these early reviews are not included in this compilation.

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. (Torkelson et al, 1961).

Vinyl chloride has long been considered to be very low in toxicity by acute inhalation. Lehmann and Flury (1938) summarized the literature and reported work by Schauman who considered vinyl chloride to be a candidate surgical anesthetic. Schauman reported little pathological changes even after repeated exposure to anesthetic concentrations.

W. F. von Oettingen (1955) of the U. S. Public Health Service summarized the available toxicity data on many halogenated hydrocarbons in an excellent monograph.

According to von Oettingen, several authors had reported vinyl chloride to be rapidly absorbed and excreted through the lungs and to cause anesthesia. The following is von Oettingen's summary of the toxicity of vinyl chloride in animals and man:

"As to the *toxicity* of vinyl chloride, Patty, Yant, and Waite (1930) studied this in guinea pigs. They found that exposure to 20 to 40 vol. percent kills the animals in a very short time, that concentrations of 10 vol. percent are dangerous to life with exposures for 30 to 60 minutes, and that 0.5 vol. percent is the maximum allowable concentration for several hours' exposure without causing acute disturbances of severe nature. Animals exposed in this way showed some edema of the lungs and hyperemia of liver and kidneys. They considered vinyl chloride less harmful than chloroform or carbon tetrachloride and of a similar order of toxicity as ethyl chloride. Schaumann (1938) found that mice and rats tolerate repeated light narcosis for 4 hours daily on 5 to 8 consecutive days and for 1 hour daily for 4 weeks without showing kidney or liver injuries. Dogs which had been narcotized for 3 hours with 10 vol. percent on 7 occasions in the course of several weeks showed no considerable changes in kidney and liver. Higher concentrations (20 vol. percent) caused in dogs marked salivation, respiratory arrest, and vomiting after narcosis. Peoples and Lehr (1933) determined the lethal range for mice with 10 minutes' exposure as 10 to 12 ml per liter, and Schaumann (1934) determined the vinyl chloride level in the blood at the time of cardiac arrest as 40 mg percent and at the time of respiratory arrest as 27 to 30 mg percent, the same value for chloroform being 60 to 70 mg percent.

Regarding the *toxicity* of vinyl chloride *for man*, Patty, Yant, and Waite (1930) expressed the opinion that the gas does not possess adequate warning properties because of its odor or irritant action, but that it gives warning by producing symptoms of dizziness and disorientation in advance of harm, except when present in exceedingly high concentrations which would cause almost immediately helplessness and unconsciousness. Inhalation of 2.5 percent will soon cause dizziness, disorientation, and a burning sensation in the soles of the feet, which symptoms disappear immediately after discontinuation of the exposure except for a slight headache which may last 30 minutes. These authors suggested the use of vinyl chloride for narcosis in man."

As a result of two deaths in Canada, the acute inhalation toxicity of vinyl chloride was studied by Mastromatteo et al (1960) 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
Total	6/15	5/15	3/15	14/30

* A delayed death occurred within 24 hours following exposure.

Some pulmanary 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 (1961) as follows:

"Repeated exposures of laboratory animals to 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 to 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 (1963) took strong 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."

Because of these conflicting reports, the TLV Committee of the ACGIH in 1963 chose to change their TLV from 500 ppm as a maximum time-weighted average for industrial exposure to 500 ppm as a ceiling value. (American Conference Governmental Industrial Hygiene, 1963).

Since 1962, numerous European articles on vinyl chloride have appeared, particularly in the Russian literature. For several reasons, these articles are difficult in interpret in terms of chronic toxicity since the reported exposures were to mixtures or were otherwise ill-defined, the exposures are often acute, or the criteria of effect was a minimal change in physiology or behavior, such as a subtle change in a conditioned response.

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 (1967) reported on two cases in Europe. Wilson et al (1967), reported on 37 cases in the B. F. Goodrich Company. Basalaev (1970) described the use of large frame photofluorography for diagnosis of acroosteolysis in Russia. Basalaev et al (1972) described studies in rats and rabbits and claimed to have produced the disease in these species. Fethiere and Kerzner (1972) discussed the disease as did Jühe et al of the University of Bonn (1973). Jühe et al (1973) described a syndrome consisting of (arranged in decreasing order of occurrence) thrombopenia, splenomegaly, liver damage, obstruction of ventillation, 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 this disease in sponsoring American companies. The results of a large scale epidemiological study of workers then currently employed in vinyl chloride and polyvinyl chloride production ware reported in three publications by this group (Dinman et al, (1971) Cook et al, (1971) and Dodson et al, (1971)).

Dinman et al 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 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 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."

The MCA sponsored studies by Dinman et al and Mutchler and Kramer appear to be the only two significant epidemiological studies on vinyl chloride reported in the literature.

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. (Viola, March, 1970). 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, (Viola, 1970), and subsequently in May, 1971, Viola, Bigotti and Caputo (1971) reported tumors of the skin, lungs and bones occurring first after 10 months of exposure. The authors summarized this work as follows:

"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 recognised 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 higher number of rats, a benign proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metaphyseal and diaphyseal regions of the four limbs.

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