PUBLISHED REFERENCES TO THE BIOLOGICAL EFFECTS OF VINYL CHLORIDE INCLUDING CHEMICAL ABSTRACTS 1907-JANUARY 14, 1974 AND BIOLOGICAL ABSTRACTS 1962-1973

Assembled in chronological order by:

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Although this compilation contains most of the references to the biological effects of vinyl chloride as related to mammalian toxicity, the compilation should not be considered as exhaustive.

THE TOXICITY OF VINYL CHLORIDE VAPOR

A Brief Summary of the Published Literature

June 20, 1974

The following articles and abstracts are believed to include most of the significant toxicological and medical references to the toxicology of vinyl chloride monomer in man and animals. The articles and abstracts are arranged in chronological order. Articles published in the last half of 1973 and in 1974 may not be included if they have not been abstracted by Chemical Abstracts or Biological Abstracts.

Important review articles which summarize 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. Translations of some articles are included.

Since vinyl chloride (chlorocthene, 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 (1934, 1936) who considered vinyl chloride to be a candidate surgical anesthetic. Schauman reported little pathological changes even after repeated exposure to anesthetic concentrations. Further work on the anesthetic potential of vinyl chloride was reported by Krantz et al, 1936, Oster et al, 1947 and Carr et al, 1949, who concluded that vinyl chloride was unsafe for use as a surgical anesthetic in dogs and that its use in man is unwarranted.

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 Leake (1933) determined the lethal range for mice with 10 minutes' exposure as 10 to 12 mM 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."

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 (Russia). 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 reported numerous effects in PVC workers in what by today's standards must be considered as primitive production facilities. These authors recognized that in addition to vinyl chloride numerous other materials, (plasticizers, stabilizers, breakdown products, etc.) were probably involved. The authors findings are as follows:

"1. The volatile substances formed when vinyl chloride resin and plasticized resins are subjected to heat treatment in production include organic chlorine compounds, hydrocarbons, vapors of free hydrochloric acid, and carbon monoxide.

2. The action of these volatile substances is manifested in irritation of the mucous membrane chiefly of the upper respiratory passage; protracted action by the highly dispersed dust and vapors of vinyl chloride resin additionally causes dryness and atrophy of the mucous membrane of the upper respiratory passages, and also contributes towards the development of chronic bronchitis.

3. The considerable number of cases of hepatitis among the workers examined, as well as the changes in the upper respiratory passages, raise the question of the need for further close observation of the state of health of workers and the taking of a number of therapeutic and prophylactic measures, particularly organization of warm humid (alkaline) inhalation of medicinal substances for workers.

4. With chlorinated diphenyl used as a vinyl chloride plasticizer, cutaneous affections such as acne, with predominant localization on the face and neck, were observed in the majority of the workers.

5. The following array of sanitation measures is required to prevent skin diseases during work with chlorinated diphenyl: 1) provision of protective underwear and outer clothing for the workers; 2) insulation of a shower room of the sanitation control station type, with individual dressing rooms for street clothing and work clothing. The sanitation control station should be outfitted with a steam room for steaming these protective underwear and clothing at a temperature of 110-120° for an hour. The shop should be provided with wash stands with hot and cold water.

6. In order to sanitize the ambient air it is necessary to decrease as much as possible the extent of decomposition of the vinyl chloride resin when subjected to heat treatment. This can be achieved by standardizing its thermal stability, and also by regulating the temperatures to which the rollers, presses, and other equipment are heated, so as to prevent the temperature from exceeding 120-130°.

Of extremely great importance is efficient organization of the ventilation system with the aim of achieving maximum coverage of the sources of liberation of gases, vapors and dust.

In view of the fact that cases of ignition of the condensate form in the ventilation exhaust pipes on contact with open

flame have been observed at some plants, in the designing of exhaust systems the specifications given in legislation governing construction for systems designed for the transmission of combustible gaseous mixtures must be complied with."

As a result of two deaths in Canada, Danziger (1960), 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

* 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 (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).

Kuebler (1964) reported that repeated 2-hour daily exposures to 0.5, 1.5 or 5.0 volume percent (5,000, 15,000 and 50,000 ppm) caused no histological injury in rats, mice or guinea pigs.

Since 1949 numerous articles describing conditions and problems in PVC production plants have appeared particularly in the Eastern European literature. Filatova and Gronsberg (1957), Gabor et al (1962), Suciu et al (1963), Gabor et al (1964), Grigorescu and Toba (1964), Antonyuzhenko (1968), and Rudryavtseva (1970), 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 impossible to ascribe the effect to any one of them.

For example, Suciu et al (1963) (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 (Lehmann and Flury (1938), von Oettingen (1955), Lester et al (1963). 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 manifestations, 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 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 (5%) with anorexia, particularly for fats.

   In 30.2% of the cases, congentive hepatomegaly appe which may mimic toxic hepatitis without jaundice; cases may become chronic.

   In 6% of the cases, the hepatomegaly is accompa splenomegaly. The proteinogram and the aldolases are the most sensitive tests and show changes sim those of acute hepatitis: increase in α-globulins of the β- and γ-globulins; the thymol test, Gre reaction and the zinc sulfate test are pos few of the cases.

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 (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 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 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, ""here 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 study by Dinman et al, together with the study by Mutchler and Kramer, appear to be the only two significant epidemiological studies on vinyl chloride workers reported in the literature prior to 1974, but neither study was designed to evaluate the incidence of cancer.

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 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."

This report by Viola et al 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, 1974; Maltoni and Lefemine, 1974) and the U. S. (Keplinger et al, 1974).

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 (1974). 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 (1974) 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 to 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 information not yet published but presented at the New York Academy of Science May 10, 1974 indicated an angiosarcoma was observed in a very old rat which had been exposed to 50 ppm for one year and kept for over 20 months following exposure. Mice were also reported by Maltoni and Lefemine to have developed tumors at 50 ppm and higher (Experiment BT_3 of the 1974 report). Tumors of other organs were also reported in rats exposed to 250 ppm and higher.

In their experiment BT_3 Maltoni and Lefemine reported possible *in utero* production of angiosarcomas in offspring of pregnant rats exposed to 10,000 and 6,000 ppm.

Keplinger *et al* (1974) 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 or 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. The data were presented May 10 at the New York Academy of Science and a copy of the final report is included (Tabershaw-Cooper Associates, 1974). The summary of this report is as follows:

1. The overall mortality of the study population was approximately 75 percent of what would be expected in a comparable population of U. S. males.

2. No cause of death showed a statistically significant excess over what would be expected in a comparable U. S. male population.

3. No new deaths identified as angiosarcoma of the liver were found.

4. All previously known angiosarcoma deaths in the study population during the study period were found as part of the routine study procedure.

5. Cancers of the liver (primarily angiosarcoma), respiratory system, brain, and cancers of unknown primary site,

as well as lymphosarcoma, occurred more often than expected in those members of the study population with the greatest exposure. Even though the excesses were not statistically significant, the findings warrant further study.

6. Other cancers occurred at lower levels than in the general male population, with the exception of cancers of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to exposure. The explanation for this finding is not apparent.

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