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U.S. CONSUMER PRODUCT SAFETY COMMISSION

WASHINGTON, D.C. 20207

May 6, 1975

Dr. Theodore R. Torkelson
Corporate Medical Department
The Dow Chemical Company
Bennett Building
2030 Dow Center
Midland, Michigan 48640

Dear Dr. Torkelson:

Thank you for your letter dated April 23, 1975, regarding CPSC's proposed protocol for inhalation studies on vinyl chloride.

As I remember, you have a copy of the original protocol scheduled to be performed at Edgewood Arsenal.

Attached is a copy of the proposed changes. In regard to the schedule, the acute study of 1 hour only with rats and mice and holding for 24 months is now in its second month.

The three generation reproductive studies are now in the 60 day exposure stage.

The sub-acute inhalation stage is entirely new and is just beginning.

If I can be of any further help, do not hesitate to call or write.

Sincerely,

Robert M. Hehir, Ph.D.
Director
Bureau of Biomedical Science

Attachment

RSV 0001500

CONSUMER PRODUCT SAFETY COMMISSION

During a visit to Biomedical Laboratory by Drs. McLaughlin and Wyer on 27 March 1975, it was mutually agreed by the contract project officer, Dr. McLaughlin and Dr. McNamara, Edgewood Arsenal Contract Administrator, that the following technical changes would be made in the toxicological testing of Vinyl Chloride monomer:

1. No biochemical or enzymatic work would be performed in the vinyl chloride studies.

2. The three generation reproductive studies will be changed as follows:

a. The number of animals per dose will be increased from 10 to 25.

b. The exposure concentration and time of exposure will be 50 and 500 ppm, 5 days week/10 weeks.

c. The parent generation will be held and observed for 2 years.

d. No teratology studies will be performed.

3. A sub-acute inhalation study will be added to the acute work. The exposure schedule is as follows:

Sub-Acute Vinyl Chloride Inhalation Study
(Exposure Schedule)

Dose Level	Species (Strain)	Number Exposed	Frequency of Exposure
50	Rat (Fisher)	180	5 dy/wk - 20 wks
	Mouse (A/J)	180	" "
500	Rat (Fisher)	180	5 dy/wk - 2 wks
	Mouse (A/J)	180	" "
Control	Rat 50 ppm	100	- -
	500 ppm	100	- -
	Mouse 50 ppm	100	- -
	500 ppm	100	- -

The observation and sacrifice schedule is as follows:

Sub-Acute Vinyl Chloride Inhalation Study
(Observation and Sacrifice Schedule)

Dose Level (ppm)	Time of Observation & Sacrifice (Months)					
	8		16		24	
	Rat	Mouse	Rat	Mouse	Rat	Mouse
50	20 20	20 20	20 20	20 20	50 50	50 50
500	20 20	20 20	20 20	20 20	50 50	50 50
Controls						
50 ppm level	10 10	10 10	10 10	10 10	30 30	30 30
500 ppm level	10 10	10 10	10 10	10 10	30 30	30 30
Totals	120	120	120	120	320	320

Total Animals: Rats - 560
Mice - 560

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Vinyl Chloride Emission Control

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Vinyl Chloride Exposure in a Controlled Industrial Environment

A Long-Term Mortality Experience in 594 Employees

Marvin Gerald Ott, MS; Ralph R. Langner, PhD; Benjamin B. Holder, MD

Vinyl chloride has been associated recently with findings of angiosarcoma in animals and man. The present study examines the mortality experience of individuals occupationally exposed to vinyl chloride and lesser amounts of vinylidene chloride and other compounds.

Employees were grouped into four exposure categories according to the highest levels of vinyl chloride exposure experienced for at least one month. Although no angiosarcomas were found and there were no deaths due to any liver malignancy, the observed mal[illegible] deaths exceeded the expected among workers in the high-exposure category. Fewer than expected malignancy deaths were observed in the remaining exposure categories.

Vinyl chloride has a 30- to 40-year history of industrial use. Until recently, it was thought to be a relatively benign material and, in fact, was once considered for use as a surgical anesthetic. Reports documenting anesthetic effects in animals and humans and liver injury in animals from chronic exposure were published in 1960 thru 1963 by Mastromatteo et al,[1] Torkelson et al,[2] and Lester et al.[3]

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From the Dow Chemical Company, Midland, Mich.

Reprint requests to the Dow Chemical Company, Corporate Medical Department, 2030 Dow Center, Midland, MI 48640 (Mr. Ott).

A new clinical entity associated with vinyl chloride exposure, acroosteolysis, was reported in the United States by Wilson et al in 1967.[4] This was elaborated by Cook et al,[5] Dodson et al,[6] and Dinman et al.[7]

In 1972, an environmental study of vinyl chloride workers by Kramer and Mutchler[8] revealed laboratory indications of liver disease in workers exposed to a time-weighted average concentration for an eight-hour day (TWA) of 300 ppm or above. [illegible] of other effects associated with exposure to high levels of vinyl chloride were summarized by Marstellar and Juhe[9] in the European literature.

Neoplasia was first associated with vinyl chloride in 1971 by Viola et al.[10] Maltoni[11] later reported malignant changes in animals, including angiosarcoma of the liver. Creech and Johnson[12] supported this observation by their report of angiosarcoma of the liver in vinyl chloride workers. In May 1974, Tabershaw and Gaffey[13] released their industry-wide epidemiological study of vinyl chloride workers that suggested increased numbers of malignant neoplasms at other body sites.

This report summarizes the mortality experience of an industrial population exposed to vinyl chloride in an environment for which many years of monitoring data are available. Many of the employees were also included in the Tabershaw and Gaffey report; however, in the present study the mortality experience was combined with more clearly defined levels of exposure and follow-up of former company employees.

HISTORY

Research involving vinyl chloride started at this company location in the mid-1930s. In 1941, a small copolymer plant was constructed that employed four operators, two miller-packagers, one foreman, and one superintendent. In the late 1940s, the plant capacity was enlarged and two assistant operators joined the work force. The [illegible] mer plant continued to grow and other types of copolymer were developed, which resulted in a larger department with a new group of operating, clerical, and supervisory personnel. A small production unit to produce vinyl chloride monomer and a copolymer semiplant also were operated during this period.

Continued research resulted in a new outdoor homopolymer (PVC) and copolymer unit being constructed in 1952. The rapid development of the market for PVC resin in the 1950s outstripped the new plant capacity. In response, PVC production was begun in a portion of a third copolymer unit that had previously used only limited quantities of vinyl chloride. Thus, besides the research efforts and monomer production, three polymer units were in operation. The PVC was produced until 1969, when the decision was made to discontinue production of homopolymer and use the facilities to modernize copolymer production. The modernization allowed the closing of the plant built in 1941.

GJS

W. M. Smith

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COMPARISON BETWEEN *IN VITRO* TOXICITY OF POLYMER AND MINERAL DUSTS AND THEIR FIBROGENICITY

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Abstract—The cytotoxicity of a variety of polymer dusts to suspensions of rat alveolar and peritoneal macrophages in culture was measured using trypan blue as an indicator of cell death. Suspensions of the same dusts were administered to rats by intraperitoneal injection and the tissue reaction examined at 1 month and 3 months. A good correlation was found between the cytotoxicity of the dusts to macrophages in culture and the degree of fibrosis caused by them in the animals.

INTRODUCTION

The relationship between cytotoxicity of mineral dusts to macrophages *in vitro* and their fibrogenic activity *in vivo* was examined by Marks *et al.* (1956) using a quantitative *in vitro* technique (Marks and Mason, 1956). Further work was carried out by Conning *et al.* (1971) who compared the ability of several mineral and polymer dusts to produce progressive or persistent fibrosis after intraperitoneal or intratracheal injection in rats, and their cytotoxic activity in rat alveolar and peritoneal macrophages in culture. They were able to distinguish three distinct levels of cytotoxicity *in vitro* which related directly to the degree of fibrogenicity of the dusts *in vivo*. The dusts of low cytotoxicity did not cause persistent fibrosis; those of intermediate cytotoxicity were comparable to silica in their ability to cause progressive fibrosis. Only asbestos was placed in the third category of cytotoxicity and this produced the most fibrosis.

The results of these investigations suggest that there is a direct relationship between cytotoxicity of a dust to macrophages in culture and fibrogenicity in the living animal. With the limited material available they were unable to elucidate the effects of changes in particle size and configuration. Marks *et al.* (1956) examined only mineral dusts, and Conning *et al.* (1971) examined two mineral and two polymer dusts. The present study examines the relation between cytotoxicity to macrophages in culture and the fibrogenic activity *in vivo* of a much wider range of polymer and mineral dusts allowing more general conclusions to be drawn.

MATERIALS AND METHODS

Animals

Specific pathogen free albino Wistar rats (Alderley Park strain) of both sexes and of a weight range 200–250 g were used.

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