December 2, 1958

Dr. A. J. Lehman
Division of Pharmacology
Food and Drug Administration
Department of Health, Education and
Public Welfare
Washington 25, D.C.

Dear Dr. Lehman:

Pursuant to our forthcoming meeting on vinyl chloride toxicity, we attach herewith proposed program of investigation. We believe it to be quite adequate to assess the hazards from inhalation of vinyl chloride when used as a component of an aerosol propellant not exceeding about 35%, but would appreciate your suggestions both as to additional tests which may be needed or tests which may not be necessary in view of previous toxicological investigations of vinyl chloride.

Very truly yours,

W. A. Knapp
Research Consultant

WAK:ncm
enc. 1

VINYL CHLORIDE (PROPELLANT 1140)
TOXICOLOGICAL PROGRAM

I. PURPOSE

The program herein described is designed to determine the physiological and toxicological effects arising from acute and semi-chronic inhalation of gaseous vinyl chloride. The purpose of this study is to assess the hazard, if any, in the use of vinyl chloride as a possible propellant for insecticide aerosols, cosmetic aerosols or various other household aerosol products. This propellant is not visualized for use in oral pharmaceutical aerosols or in food aerosols. Since vinyl chloride of itself is flammable in air it is estimated from preliminary tests that this material cannot constitute greater than 35% of the propellant composition in a liquefied gas aerosol.

II. Literature Background

The pharmacology and toxicology of vinyl chloride is not entirely unknown. In the study of its absorption, distribution and elimination it has been shown to be readily absorbed through the lungs and because of its low solubility in blood and high vapor pressure to be rapidly eliminated by pulmonary ventilation. Like other chlorinated hydrocarbons, vinyl chloride has narcotic properties, the anesthetic concentration in the blood being about 15-17 mg. per 100 ml. of blood (1). The concentrations of the vapor and the times of exposure essential to product this concentration in the blood and thus narcosis have been experimentally investigated in animals. The narcotic concentration for mice is between 8 and 12 per cent; 25-30 per cent is fatal in 10 minutes. In dogs and rabbits 17 per cent of vinyl chloride vapor causes narcosis in 1 minute (2). The limiting concentration for producing narcosis in humans is 7-10 per cent; above 12 per cent is dangerous (3). In guinea pigs deep narcosis was produced by 90 minutes of exposure to 2.5 per cent of vinyl chloride (4).

The recovery from vinyl chloride upon discontinuation of exposure is rapid. Most of the investigators describe the vinyl chloride vapor as having very slight irritating effect and the recovery from narcosis to be without significant general toxic effect or metabolic injuries. However, Patty, et al (4), concluded from their experiment with guinea pigs that vinyl chloride is irritating to the lungs producing congestion and edema of this organ with exposure to narcotic concentrations of the vapors. In fact they report the occurrence of deaths 1 to 8 days after such single exposures. The vinyl chloride used in these experiments was a commercial product whose description indicated the presence of impurities including as much as possibly 0.5 per cent of acetaldehyde. These impurities may explain the more pronounced irritation observed by these investigators as compared with that reported by others.

In considering the application of vinyl chloride to any use other than for producing narcosis, exposure to anesthetic concentrations of the vapor, even for short periods of time, is

obviously objectionable. But even at some concentrations below narcosis producing level, symptoms of intoxication can be reasonably anticipated. Experimental study of the toxicity of vinyl chloride vapors at such levels has been restricted only to single exposures (4). In guinea pigs, while 2.5 per cent of the vapor did not cause anesthesia until an hour or more of exposure, unsteadiness, staggering and other signs of motor ataxia occurr d within 2 to 5 minutes. Concentrations of 0.5 and 1.0 per cent produced little or no symptoms on several hours of exposure.

Exposure of human subjects for about 3 minutes to 2.5 per cent of vinyl chloride vapor caused dizziness, disorientation, a burning sensation in the soles of the feet and slight headache lasting about 30 minutes.

While possible effects of repeated vinyl chloride narcosis have been investigated somewhat, there has been no study of repeated long daily exposure to less than acutely toxic concentrations of the vapor. In the former investigations (4) mice and rats tolerated 4 hours daily narcosis on 5 to 8 consecutive days and 1 hour of daily narcosis for 4 weeks without injury. Dogs likewise tolerated 3 hour periods of narcosis on 7 occasions during several weeks without injury. While this does suggest that repeated exposure to less than intoxicating concentrations of vinyl chloride might be without harm, direct evidence is lacking.

III. Program of Study

A. Human screening tests

On the assumption that any concentration of vapor which on acute exposure causes any symptoms of intoxication will not be acceptable for human exposure it is proposed that the highest concentration producing no toxic symptoms in short exposures be bracketed in tests with human subjects.

B. Preliminary animal screening tests

The purpose of these tests on small groups of animals is to determine the maximum concentration of vapor which on eight-hour exposure produces no visible signs of intoxication and with a week of such repeated daily exposures causes no apparent indications of ill health. Obviously, maximum concentration must not exceed the maximum concentration producing no acute symptoms in man.

ASI 000015797

C. Chronic inhalation study

Using the maximum concentration which in the preliminary tests caused no toxic symptoms, we would then proceed with the large chronic animal study. This study will be made with albino rats. Altogether, 60 animals will be used - 30 experimental and 30 control animals. The daily exposures will be carried out in a large steel gassing chamber. The desired concentrations

of vinyl chloride vapor in air will be maintained by a continuous appropriat flow of vapor and air into th chamber. Mixture of the gases in the chamber will be assured by an explosion-proof fan. A larg glass window in the chamber will enable observation of the animals. The concentration of vinyl chloride vapor in the chamber will be monitored by a thermal conductivity apparatus.

The 30 experimental animals will be exposed 8 hours daily, 5 days per week for a period of 3 months. During the remaining 16 hours daily the animals will be kept in cages with food and water available. The 30 control animals will also be placed in the gassing chamber 8 hours daily, 5 days per week and for 3 months, but without vinyl chloride vapor. Thus, both groups will be treated identically except for the exposure to vinyl chloride.

Young animals will be used in these tests (about 70 grams) in order to observe any effects of exposure on growth as a sensitive index of toxicity. The animals will all be weighed initially and weekly thereafter.

Another index of possible injury due to the exposures will be sought in a battery of hematological tests. These will consist of red and while cell and differential counts, prothrombin time, hemoglobin and transaminase tests. The cell counts will reveal any abnormalities in the formed elements of the blood; the hemaglobin test will detect any possible anemic process; the prothrombin time will reflect any changes in clotting time and its implications. The transaminase test is a more recently developed test that offers a sensitive indication of any abnormal tissue destruction in the body.

Some of these blood tests require a small and readily obtainable quantity of blood; others require larger quantities whose taking from the small animal is more complicated and is itself threatening to the health or life of the animal. The prothrombin-time and transaminase tests belong to the latter category and will be performed only at the end of the study. The following plan will therefore be followed in our study. All of the animals will undergo blood hemoglobin tests at the start of the study and at 2-week intervals thereafter. This will provide a continuous indication of any blood dyscrasia in either the control or experimental animals. The other tests will be made at the end when the animals are sacrificed. Any effect of the vinyl chloride exposures on these will be fully apparent in a comparison with the control animals.

If the experimental animals run the full 3-month course of exposure without apparent and significant health disturbance, they and the control animals will be sacrificed. All of the blood tests enumerated above will be made on each. All of the animals will be examined grossly and microscopic sections of the following tissues from twenty animals (10 test animals and 10 controls) will be prepared and studied;

heart, liver, lung, kidney, spleen and small intestine. Organs of the remaining animals will be retained for possible section pending any inconclusive results from animals examined histopathologically.

REFERENCES

(1) Shaumann, O., Medizin u. Chemie, 2; 139, 1934

(2) Peoples, S. A. and Leake, C. D., J. Pharm. Exptl. Ther., 48, 284, 1933

(3) Shaumann, O., Toxicology and Hygiene of Industrial Solvents, Lehman and Flury, Williams and Wilkins, 1943, pg. 171.

(4) Patty, F. A., Yant, W. P. and Waite, C. P., Pub. Health Report, 45, 1963, 1930.

ASI 000015799