Air Products and Chemicals INC
ALLENTOWN, PENNSYLVANIA 18105

2 April 1979

Lloyd B. Tepper, M.D.
Corporate Medical Director

Anthony Robbins, M.D.
Director
National Institute for Occupational
Safety and Health
Parklawn Bldg.
Rockville, Maryland 20852

Dear Dr. Robbins:

Recent articles in lay publications report current NIOSH interest in the occurrence of brain tumors among persons with occupational exposure to vinyl chloride and other compounds. In 1974 our company reported to Tabershaw-Cooper Associates, then conducting an industry-wide survey, the case of a vinyl chloride polymerization worker who had died in 1968 with the final pathological diagnosis of astrocytoma, grade IV, of the left cerebral hemisphere. He had been an employee of the Escambia Chemical Company, acquired by Air Products in 1969.

In view of the current focus upon the specific diagnosis of glioblastoma multiforme and the probable similarity of this histological pattern to that of astrocytoma, grade IV, we have obtained a re-assessment of the slides. The consulting pathologist confirms that the pattern in this case conforms to the diagnostic criteria for glioblastoma multiforme.

The worker in question was employed by Escambia from 3 October 1955 until his death on 19 July 1968. During the period of employment he was engaged in the production of ammonia, aliphatic amines, methyl-methacrylate, and polyvinyl chloride. Quantitative exposure data are not available. We do not have at hand an estimate of the numbers of persons at risk in the relevant occupational categories.

It is not entirely clear to us as to how this event might be evaluated so as to shed light on the biological properties of the compounds in question. Nevertheless it is possible that your people engaged in a study of the incidence of brain tumors among certain chemical workers will wish to be informed of this diagnosis.

Very truly yours,

Lloyd B. Tepper, M.D.

LBT:lpf

Air Products

Date 9 January 1977

INTEROFFICE
MEMORANDUM

Subject Retention of Vinyl Chloride in the Body

To L. B. Tepper, M.D. — Personnel
(Location, Organization, or Department)

From J. T. Barr — Plastics R&D
(Location, Organization, or Department)

cc: J. C. Novak
W. Mayo Smith

I talked to N. Wheeler of Union Carbide regarding post-exposure testing for vinyl chloride in the expired air or blood. They have found a little present on occasions, usually after a massive exposure, but have little calibration data or experience to allow use of this method to calculate exposures.

Their practice is to keep a patient quiet after exposure, and unless there are respiratory difficulties, not to accelerate respiration artificially. They believe that normal expiration will remove the vinyl chloride from the blood very quickly, and that acceleration of metabolic processes would be counterproductive. It was Nick's opinion that no detectable vinyl chloride would be found in the breath or blood after "an hour or two."

I have found three literature references which tend to support this position. Withey says, "on removal from vinyl chloride atmospheres, blood levels (of rats at 7,000 ppm) fell rapidly to barely detectable at two hours." Watanabe reports that the amount lost by respiration increases with the dosage. Hefner shows that a monkey absorbs very little through its skin, and that most of the material is expired, although the form (metabolic or original compound) is not given. I have attached my copies of these reports.

J. T. Barr

JTB/sjl
Att.

(320)

AP00002673

PHARMACODYNAMICS AND UPTAKE OF VINYL CHLORIDE MONOMER ADMINISTERED BY VARIOUS ROUTES TO RATS

Jim R. Withey

Toxicology Division, Bureau of Chemical Safety (Foods), Health Protection Branch, Ottawa, Canada

Finding at least 2-3 ppm and occasionally as much as 10-20 ppm of vinyl chloride monomer in a wide range of foodstuffs has prompted concern for a possible human health hazard. The recognition of vinyl chloride as a carcinogen to humans in April 1974, following the discovery of angiosarcoma as the cause of death in at least 25 workers who had been engaged in the manufacture of polyvinyl chloride, enhanced this concern with respect to the presence of vinyl chloride monomer in foods.

To assess the hazard presented by the oral ingestion of vinyl chloride monomer, rats that had been surgically prepared with an indwelling jugular cannula were dosed by intragastric intubation with aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Time-concentration curves were obtained from sequential samples of blood. The uptake of vinyl chloride by this route was found to be extremely rapid; peak concentrations were achieved less than 10 min after administration of the dose. Elimination from the blood compartment appeared to be biexponential.

Studies with the same animal model in a single restraint cage that allowed a "head only" exposure to concentrations of vinyl chloride up to 7,000 ppm in the gas phase have shown a similar rapid uptake followed by a plateau blood concentration during several hours of exposure. On removal from the vinyl chloride atmosphere, blood levels fell rapidly to barely detectable concentrations after 2 hr.

The precise kinetic coefficients that describe the distribution and elimination rates of vinyl chloride from the blood compartment were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution.

INTRODUCTION

Prior to the discovery of a connection between the induction of angiosarcoma in humans and the exposure to vinyl chloride monomer (VCM) in January 1974 (Falk et al., 1974; Thomas et al., 1975), the U.S. Food and Drug Administration had already withdrawn their prior sanctioned use of

This paper was presented in part at the 14th Annual Meeting of The Society of Toxicology, Williamsburg, Virginia, March 9-13, 1975.

It is a pleasure to acknowledge the technical assistance of Mr. Peter Collins in this work. The interest, skill, and dedication of Mr. Henry James, who surgically prepared the animals used in this study, is also appreciated.

Requests for reprints should be sent to Jim R. Withey, Toxicology Division, Bureau of Chemical Safety (Foods), Health Protection Branch, Ottawa, Canada.

Journal of Toxicology and Environmental Health, 1:381-394, 1976

FATE OF ^{14}C-VINYL CHLORIDE AFTER SINGLE ORAL ADMINISTRATION IN RATS

P. G. Watanabe, G. R. McGowan, and P. J. Gehring

ABSTRACT

Male rats were given single oral doses of 0.05, 1, and 100 mg/kg of ^{14}C-vinyl chloride (VC), and the routes and rates of elimination of ^{14}C activity followed for 72 hours. Following 0.05 and 1 mg/kg excretion in the urine as nonvolatile metabolites and as $^{14}CO_2$ in expired air accounted for 59-68% and 9-13%, respectively of the administered dose. Only 1-2% of the dose was expired by the lungs as VC. Conversely, after 100 mg/kg, 67% of the dose was eliminated by the lungs as VC, while urinary nonvolatile metabolites and $^{14}CO_2$ comprised 11 and 3%, respectively. Pulmonary elimination after 100 mg/kg showed an apparent biphasic clearance with half-times ($t_{1/2}$) of 14.4 and 40.8 min for the respective fast and slow phases. Following 0.05 and 1 mg/kg the pulmonary clearance of VC was monophasic with $t_{1/2}$ of 53.3 and 57.8 min. The percentage of the dose remaining in the carcass after 72 hr was 10, 11 and 2% for the 0.05-, 1- and 100-mg/kg doses, respectively. The urinary radioactivity was separated by high pressure liquid chromatography into three major metabolites. Two of the three major urinary metabolites have been identified as N-acetyl-S(2-hydroxyethyl)-cysteine and thiodiglycolic acid by gas chromatography-mass spectrometry. The proportions of the urinary metabolites were not influenced by the dose. The fate of VC following an oral dose between 1 and 100 mg/kg was clearly dose-dependent. Consistent with our previous studies on the fate of VC following inhalation exposure in rats, the metabolism of VC appears to be a saturable process.

(Toxicology and Applied Pharmacology, (1976), 36, 339-352).

PERCUTANEOUS ABSORPTION OF VINYL CHLORIDE (VCM) GAS IN THE RHESUS MONKEY

By: R. Hefner, P. Watanabe, P. Gehring
Dow Chemical U.S.A. - Midland, Michigan

The experiments described herein were designed to determine the degree to which vinyl chloride monomer (VCM) gas (Matheson Gas Products, Joliet, Ill., 99.9% purity) may be percutaneously absorbed. A male Rhesus monkey (Macaca mulatta) weighing 5 kg was used in the experiment. Prior to exposure, 30 mg/kg sodium pentobarbital was administered intravenously. An endotracheal catheter with an inflatable collar was inserted into and the trachea connected to a Harvard respiratory pump adjusted to deliver a volume of 20 ml of air at a rate of 28 to 38 cycles per minute. A catheter was placed in the saphenous vein of the left leg so that additional sodium pentobarbital could be administered during exposure. The body of the monkey was placed in a 191.5L plexiglas chamber with the head protruding from the chamber through a silastic rubber membrane. After the hair around the neck had been carefully removed with clippers the membrane was fitted around the neck and secured to the skin with tape, to provide an adequate seal. The body of the monkey rested on 3 large glass bell jars in the chamber. A slight vacuum was pulled on the chamber, and 1.5L of VCM gas was metered in to establish a VCM concentration of approximately 7000 ppm in the chamber. Chamber concentrations were periodically monitored by infrared analysis (10.9 μ).

To trap VCM in the expired air, a polyethylene tube filled with 0.5g of carbon made from saran beads was placed in the exhaust port of the respiratory pump. A similar tube placed on the intake port filtered any VCM from the air pumped into the monkey. The expired air traps were changed at 1/2 or 1 hour intervals while the intake traps were changed every 2 hours. The VCM from these traps was eluted with carbon disulfide at dry ice temperature and analyzed by gas chromatography. Additionally, a sample of control saran carbon was checked for VCM.

It was found that the VCM concentration in the exposure chamber declined more rapidly when a monkey was present than if empty, however, it was not possible to attribute this difference solely to percutaneous absorption. Comparison would be valid only if identical chamber conditions could be obtained. This is not possible since an empty chamber could not be made to simulate the leakage characteristics, adsorption to fur, and thermal mixing characteristics in the test solution.

A monkey was exposed to approximately 7000 ppm ^{14}C-VCM (specific activity 0.180 μCi/mg) for 2 hours. Immediately post-exposure the monkey was sacrificed and tissues (brain, heart, lung, liver, muscle, stomach, duodemum, thymus, spleen, mesenteric fat, testes, kidney) were sampled and homogenized. Urine was taken from the urinary bladder and bile

from the gall bladder. Aliquots of the tissue homogenates were combusted and the ^{14}C-CO_2 trapped in 2-methoxyethanol-monoethanolamine solution. The resulting CO_2-2-methoxyethanol-monoethanolamine solutions, as well as aliquots of urine and bile were counted in scintillation cocktails using a Mark II liquid scintillation counter. ^{14}C activity in excess of twice background was detected in only the bile, kidneys, and liver. 1792 DPM of ^{14}C activity was in the bile, 11,352 DPM in the kidneys, and 105,821 DPM in the liver, for a total of 118,965 DPM. Expired air samples contained a total of 182,709 DPM for the 2 hour exposure period, thus a total of 314,818 DPM or 0.024% of the VCM (3.28 g or 1,316,987,916 DPM) in the chamber was absorbed percutaneously over the 2-hour period. Of the total dose absorbed percutaneously, 39.4% was in the tissue, while 60.6% was in the expired air. The aforementioned experimental results demonstrate that small amounts of VCM are percutaneously absorbed by a monkey maintained under the described experimental conditions.

Assuming that the percutaneous absorption of VCM is proportional to the surface area of the body, extrapolating the amount absorbed by the monkey under the specified conditions to that which would be absorbed by a 6 ft, 90 kg

man yields 4.76 mg of VCM. Possible influence of fur and clothing was not determined and, therefore, not considered in making this extrapolation. However, this data indicates that the amount of VCM a man would absorb through the skin in an atmosphere containing 7000 ppm in two hours would be equivalent to the man breathing an atmosphere containing 0.186 ppm VCM for an eight hour working day. This theoretical calculation assumes that a 10 m^3 volume of air was breathed over eight hours and all VCM was assimilated.