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INDUSTRIAL HYGIENE FOUNDATION OF AMERICA, INC.

MELLON INSTITUTE 4400 FIFTH AVENUE

PITTSBURGH 13, PA.



Report on A COMPARISON OF THE SUBACUTE INHALATION
TOXICITY OF ETHYLENE DICHLORIDE,
TRICHLOROETHYLENE, AND A Mixture OF THE TWO

Done PITTSBURGH PLATE GLASS COMPANY

Done MARGUERITE CORP.

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Report on

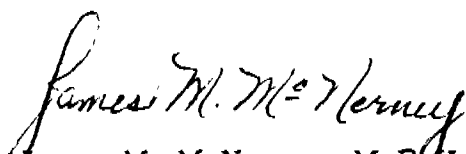
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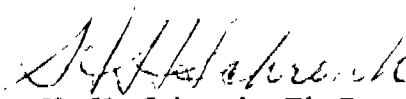
PITTSBURGH PLATE GLASS COMPANY

March-June 1961

by


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INTRODUCTION

This report presents data and conclusions on the subacute inhalation toxicity of a mixture of trichloroethylene (67%) and ethylene dichloride (33%) containing a stabilizing system. The objective of the study was to determine if there is significant synergistic action, as revealed by behavioral, growth, mortality, and pathological data, on laboratory animals exposed to the vapors of the mixture. The effects were evaluated by comparing the response on a group of rats subjected to the vapors of the mixture during daily exposures with the effect on rats similarly exposed to trichloroethylene and ethylene dichloride vapors, alone.

Adams, Spencer, et al^(1,2) reported that rats exposed to 400 ppm of ethylene dichloride for three, daily, seven-hour exposures had a mortality of 60%, a rapid loss in body weight, a slight increase in liver and kidney weights, and upon histopathological examination revealed slight cloudy swelling of the liver with a few large fat vacuoles but no kidney damage. Rats exposed to 200 ppm of ethylene dichloride tolerated 151 exposures in 212 days and showed no evidence of adverse effects as judged by general appearance and behavior, growth, mortality, or histopathological examination. In exposures to trichloroethylene groups of rats tolerated 400 ppm for as many as 173 exposures in 243 days without evidence of adverse effects as judged by mortality or general appearance and behavior. Growth curves were slightly depressed, liver and kidney weights were increased, but no

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significant changes were observed in any tissue upon histopathological examination. Rats exposed to 200 ppm of trichloroethylene tolerated as many as 151 exposures in 205 days without adverse effects as judged by general appearance and behavior, mortality, growth, organ weights, and histopathological examination of tissues.

On the basis of these studies it was decided to employ the effects on rats exposed to ethylene dichloride, the more toxic of the two solvents, as the point of reference in this study. Since at the 400 ppm concentration level the trichloroethylene rats exhibited a greater increase in liver and kidney weights than the ethylene dichloride but upon histopathological examination showed no lesions while the ethylene dichloride did, organ weights were considered irrelevant to this study. The effects considered of prime significance in this study are growth, mortality, and pathological. A concentration and length of daily exposure of ethylene dichloride was chosen so as to produce a response severe enough to cause some mortality by three weeks and sufficient data to terminate the study after approximately one month. The length of daily exposures were to be increased if effects were not adequate. The same volume of liquid as was evaporated to yield the ethylene dichloride concentration was used for trichloroethylene and the mixtures of ethylene dichloride and trichloroethylene so that the exposures were comparable on the basis of liquid vaporized. Each group of rats was thus exposed to the same liquid volume of its respective solvent for equal periods of time.

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MATERIALS AND METHODS

A five gallon drum each of the Trichloroethylene-Ethylene Dichloride Mixture, Reference No. 61701-3-213-231, hereafter referred to as the mixture; of Trichloroethylene, Reference No. 61701-3-213-230, hereafter referred to as TCE; and of Ethylene Dichloride, Reference No. 61712-3-213-232, hereafter referred to as EDC was received for testing.

The apparatus consisted of three, seven-cubic-foot, stainless steel chambers, three vapor generating units, and analytical chemical equipment. Each chamber contained five animal cages, had a glass-windowed door for observation of the animals during exposure, and was constructed to maintain the animals twenty-four hours per day. Each vapor-generating unit was composed of a monodrum mechanism,⁽³⁾ a single syringe feeder,⁽⁴⁾ a glass Graham condenser, and glass and tygon tubing connections. The monodrum mechanism drove the single syringe feeder, which contained the solvent, at a calculated, constant rate, delivering the required amount of chemical into the condenser. Hot water was passed through the outer jacket of the condenser and as the solvent was dropped into its spiral, tubular center, it was evaporated, mixed with air, and drawn through the chamber. The calculated vapor concentrations were in good agreement with the results of analysis by combustion and determination of total halogen colorimetrically using mercuric chloranilate.⁽⁵⁾

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Twenty-five male, albino rats were exposed to each compound. They were fed ad libitum on Purina Lab Chow except during the exposure when water and feed were withheld. The rats were weighed each morning before the exposure. Animals that died during the testing period and those sacrificed terminally were subjected to autopsy and the lungs, livers, and kidneys were dissected for histopathological preparation and examination.

The experimental conditions are presented in Table 1. As sub-noted in the table, the length of exposure was increased during the study from five hours per day to eventually seven hours per day in order to produce more significant effects within the proposed one-month period. The EDC concentration, upon which the concentrations of the other solvents were based, was held constant during the study at 300 ppm, midway between the 200 ppm no effect level and the 400 ppm, 60% mortality level.

Table 1 -- Exposure Conditions

Solvent	Concentration		<i>vol. basis</i> ↓ ppm	Length of Exposure		
	ml./l.	mg./l.		Daily (hrs)	Actual Exposure (days)	Overall Period (days)
EDC	0.000951	1.194	301	5-7*	24	32
TCE	0.0009502	1.392	260	5-7	24	32
Mixture	0.000952	(EDC 0.395 TCE 0.934)	100 174	5-7	24	32

* See text for explanation of variation.

convert to gas volume using $PV = nRT$

$$V_{\text{liters}} = \frac{n \times 0.0283}{1}$$

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then ppm = $\frac{\text{liters of organic, etc. to ppm}}{1 \text{ liter}}$

RESULTS

The mortality data are presented in Table 2.

Table 2 -- Exposure Results

Solvent	Weight Data		PPM	Mortality Data (out of 25)			
	Original Average (gms.)	Final Average (gms.)		Extraneous		Experimental	
				No.	%	No.	%
EDC	200	278	201	1	4	12	48
TCE	200	312	260	0	0	2	8
Mixture	200	307	180 174	1	4	0	0

The striking lethal effect of the EDC (48%) is shown in contrast to the lower mortality of TCE (8%) and the absence of experimental death for the mixture. The extraneous deaths occurred during the second week of exposure and were of probable bacterial origin showing signs of severe pneumonia and slight empyema. The experimental TCE deaths occurred during the third and final weeks of the test period. Five of the experimental EDC deaths occurred during the third week and seven during the final week. Table 2 also shows that the increase in weight of the TCE and mixture exposed rats significantly exceeds that of the EDC exposed rats. The difference in growth effect is graphically presented in Figure 1. The following points should be noted: The three curves were distinct following the third day of exposure but even after three weeks their difference was not of a high level

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of significance. After increasing the exposure periods to seven hours there was a definite effect on growth. Concern over the possible killing of all of the EDC exposed rats brought about trials with different lengths of exposure periods during the third week. However, it was finally decided to continue the exposure length at seven hours during the remainder of the study. The sharp dips in the EDC growth curve (mean weight) are due to acute weight losses in a number of severely affected rats. The subsequent sharp rises in the curve are due to the removal of the animals from subsequent calculation of the mean weight after their deaths.

The kidneys and livers of five of the EDC fatalities were examined microscopically. All showed severe renal tubular necrosis, enough to account for the death of the animals. One animal showed, in addition, hepatic necrosis.

Ten of the surviving animals were also similarly examined. All three groups were represented and no significant or constant renal or hepatic lesions were found.

The lungs of the surviving animals, however, showed minor degrees of focal chronic interstitial pneumonitis, characterized by cellular proliferation and desquamation.

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CONCLUSIONS

Rats exposed for the same period of time and to the same vaporized volume of a TCE (67%)-EDC(33%) mixture as those exposed to EDC and TCE alone, exhibited a lower mortality rate than either and a growth rate intermediate between the two. Volume for volume, the mixture was less toxic than EDC alone, and was similar in toxicity to TCE, the major constituent of the mixture.

Hence, the toxicity of the mixture was essentially that which would be expected from a simple summation of the toxicities of the constituents. These results are in general agreement with other studies^(6, 7) of toxicities of mixtures of halogenated and other organic solvents.

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Figure 1 -- Growth Effects

