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TO VAPORS OF SOME NEW COMMERCIAL
ORGANIC COMPOUNDS

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BY

F. A. PATTY

Assistant Physiological Chemist

W. P. YANT

Supervising Chemist

Pittsburgh Experiment Station

United States Bureau of Mines

AND

C. P. WAITE

Assistant Surgeon

United States Public Health Service

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ACUTE RESPONSE OF GUINEA PIGS TO VAPORS OF SOME NEW COMMERCIAL ORGANIC COMPOUNDS

V. VINYL CHLORIDE¹

By F. A. PATTY, *Assistant Physiological Chemist*, W. P. YANT, *Supervising Chemist*, and C. P. WAITE, *Assistant Surgeon,² Health Laboratory Section, Pittsburgh Experiment Station, Bureau of Mines*

This report on the acute response of guinea pigs to vinyl chloride gas is the fifth of a series of similar reports which deal with studies pertinent to evaluating the hazards involved in exposure to some chemical products which have recently reached, or promise to reach, important domestic and industrial use. The first report of the series dealt with ethylene dichloride,³ the second with ethyl benzene vapor,⁴ the third with "Cellosolve" (ethylene glycol monoethyl ether),⁵ and the fourth with ethylene oxide.⁶

Vinyl chloride is used at present only in the synthesis of organic compounds, principally resins.

The investigation described herein was undertaken at the request of the Carbide & Carbon Chemicals Corporation, and the work was conducted jointly by that corporation and the United States Bureau of Mines at the Pittsburgh Experiment Station of the Bureau of Mines.

SCOPE OF WORK

The scope of the work included a study of the toxicity of vinyl chloride and the physiological response to its vapors as determined by exposure of guinea pigs. Only acute effects as produced by a single exposure were studied. The experiments were planned to give information relative to the concentrations and periods of exposure which produce but slight response, moderate response, and serious response.

¹ This report represents work done under cooperative agreement between the Bureau of Mines, Department of Commerce, and the Carbide & Carbon Chemicals Corporation. Published by permission of the Director, U. S. Bureau of Mines.

² Assistant surgeon, United States Public Health Service, detailed to the Bureau of Mines.

³ Sayers, R. R., Yant, W. P., Waite, C. P., and Patty, F. A.: Acute response of guinea pigs to vapors of some new commercial organic compounds. I. Ethylene dichloride. Pub. Health Rep., vol. 45, No. 5, Jan. 31, 1930, pp. 225-239. (Reprint No. 1349.)

⁴ Yant, W. P., Schrenk, H. H., Waite, C. P., and Patty, F. A.: Acute response of guinea pigs to vapors of some new commercial organic compounds. II. Ethyl benzene. Pub. Health Rep., vol. 45, No. 22, May 30, 1930, pp. 1241-1250. (Reprint No. 1379.)

⁵ Waite, C. P., Patty, F. A., and Yant, W. P.: Acute response of guinea pigs to vapors of some new commercial organic compounds. III. "Cellosolve." Pub. Health Rep., vol. 45, No. 26, June 27, 1930, pp. 1459-1466. (Reprint No. 1399.)

⁶ Waite, C. P., Patty, F. A., and Yant, W. P.: Acute response of guinea pigs to vapors of some new commercial organic compounds. IV. Ethylene oxide. Pub. Health Rep., vol. 45, No. 32, Aug. 5, 1930, [pp. 1832-1843. (Reprint No. 1401.)]

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DESCRIPTION OF MATERIAL USED FOR TESTS

Vinyl chloride (CH_2CHCl) is a colorless gas at room temperatures (boiling point, -13.9°C). The gas has a pleasant ethereal odor and is slightly soluble in water. Its limits of inflammability are 4.0 to 21.7 per cent by volume in air.⁷

The vinyl chloride used in experiments described in this report was a commercial product having the following plant specifications: Boiling range, 95 per cent or more below -10°C . at 760 mm.; acetaldehyde, not more than 0.5 per cent; residue, not more than 0.5 per cent.

TEST APPARATUS

The test apparatus was the same as that described in a previous report dealing with ethylene oxide.⁶

COMPUTATION AND ANALYSIS OF GAS-AIR MIXTURES

The vinyl chloride-air mixtures were created by adjusting calibrated flowmeters (Venturi type) to give the desired proportions of gas and air. The vinyl chloride content was then checked by analysis.

The apparatus used was the same as that used for determining ethylene dichloride in air.⁶ Briefly, the method was to subject the vinyl chloride to combustion with oxygen (explosion method using electrolytic gas to "energize" the combustion), and absorption of the products of combustion. For mixtures containing insufficient oxygen for complete combustion, a known amount of additional air or pure oxygen was mixed with the sample before adding the electrolytic gas. A minimum amount of stopcock grease was used in the apparatus to reduce error through solubility of the gas. For the same reason rubber tubing was not used except for making joints of glass tubing, caution being taken to have the ends butt together.

TEST PROCEDURE, DESCRIPTION AND CARE OF ANIMALS

The test procedure, and the animals and their care were the same as described in the published report dealing with ethylene dichloride.⁶

RESULTS OF TESTS

The detailed test data are too voluminous to be presented in this report and only summarized results pertinent to symptoms, gross pathology, and fatality are given. Specimens of tissue were taken for microscopic examination, a report of which will be made later.

⁶ See previous footnote 5.

⁷ See previous footnote 5.

⁸ Jones, G. W., U. S. Bureau of Mines, unpublished data.

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SYMPTOMS OF ANIMALS

Control animals.—No symptoms were exhibited by the 18 control guinea pigs used in these tests or by the stock animals from which all of the test animals were taken. Also, no deaths occurred.

Exposed animals.—Table 1 gives the symptoms shown by the animals exposed to vapors of vinyl chloride and also the average period of exposure required to produce these symptoms by various concentrations of vapor in air. The reader should note that the figures in parentheses indicate that the particular symptom did not occur in the maximum period of test as given.

The highest concentration of vinyl chloride in air used in the exposures (40 per cent) exerted an almost immediate narcotic effect on the animals. Within one-fourth minute the animals fell to their sides in an apparent unconscious or narcose state, with convulsive twitchings of the trunk and extremities and jerky rapid respirations. The pigs remained in this state until death or termination of the test.

Type of symptoms	Concentration of vapor and period of exposure producing symptoms ¹						
	40	15 to 25	10	5	2.5	1.0	0.5
Dropping to sides; incomplete narcosis; nervous phenomena; irregular twitching of extremities.....	14 * (10)	1 * (20)	2 * (360)	3 * (360)	5 * (480)	5 * (480)	5 * (480)
Unsteadiness on feet; motor ataxia.....							
Apparent unconsciousness; deep narcosis; no twitching of extremities; quiet.....	1 (10)	16-20	60	50	90	1 (480)	1 (480)
Jerky, rapid respiration.....	14-16	2	(?)	240	1 (480)	1 (480)	1 (480)
Slow, shallow respiration.....	1 (10)	20	120-360	360	360-480	1 (480)	1 (480)
Respirations ceased.....	10-20	18-55	1 (360)	1 (360)	1 (480)	1 (480)	1 (480)

¹ Concentrations of vapor in per cent by volume; time in minutes.
² Not observed during maximum exposure period as given in parentheses.
³ Not determined.

Concentrations of 10 to 25 per cent caused the animals to fall on their sides with convulsions and with jerky, rapid respirations in 1 to 2 minutes. Following this the pigs lapsed into a state of apparently deep narcosis in which the convulsive twitchings and all movements ceased, the pigs being quiet and relaxed. This occurred within 16 to 20 minutes at concentrations of 15 to 25 per cent and within 60 minutes at concentrations of 10 per cent. Slow, shallow respirations occurred with 20 minutes' exposure to 15 to 25 per cent and with 120 to 360 minutes' exposure to 10 per cent. The pigs remained in this state until death or termination of the exposure.

Concentrations of 5 and 2.5 per cent did not produce the initial symptom of "dropping to their sides and unconsciousness with convulsive twitching of the extremities." These concentrations produced first an unsteadiness in the animals, a staggering on attempt-

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ing to move about, with signs of motor ataxia. This occurred within 2 to 5 minutes, and lasted 50 to 90 minutes, at the end of which time the pigs fell on their sides in an apparent profound narcosis, being entirely relaxed with no convulsions or movements of any kind. The respirations were increased in rate and amplitude, becoming

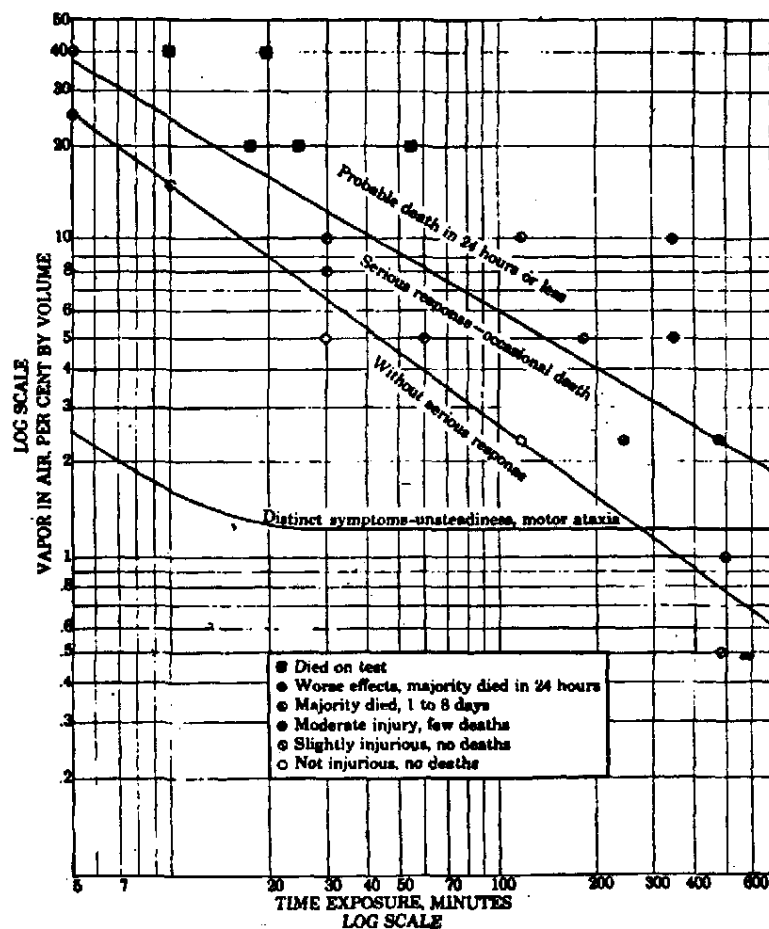


FIGURE 1.—Acute effects of exposure of guinea pigs to vinyl chloride vapor in air

rapid and jerky in character at the end of 240 minutes' exposure to 5 per cent, and slowed and became shallower at the end of 360 minutes, remaining in the latter condition until death or termination of the exposure.

Concentrations of 0.5 and 1.0 per cent did not produce any symptoms.

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The general symptom of narcosis was manifested in three degrees, increasing in severity with increasing concentrations of vinyl chloride: (1) Unsteadiness, staggering, and motor ataxia; (2) incomplete narcosis in which convulsions affecting the trunk and extremities persist; (3) a state of profound or deep narcosis in which the animals are quiet, on their sides, relaxed, and without movement.

Observation showed that animals after being removed from the exposure chamber recovered from the most profound narcosis within 12 minutes.

No signs of eye or nasal irritation were observed.

SYMPTOMS EXPERIENCED BY MEN

Two of the experimenters were exposed to 2.5 per cent vinyl chloride in air for a period of approximately three minutes. They reported that the gas had a fairly pleasant odor. They soon began to feel dizzy and disoriented as to space and size of surrounding objects, and complained of a burning sensation in the soles of the feet. They immediately recovered on leaving the chamber and complained only of a slight headache, which lasted about 30 minutes.

GROSS PATHOLOGY

Control animals.—A total of 18 control animals were killed for autopsy. No gross pathology resembling that found in the exposed animals was found. Also no deaths occurred among the control animals.

Exposed animals.—The gross pathological changes found in the animals that died during exposure (see fig. 1 for conditions of exposure causing death on test) were intense congestion and edema of the lungs and a hyperemia of the kidneys and liver. The lungs were light pink in color; the cut section was uniformly light red, and bled freely. A frothy exudate was present in the large bronchi, and squeezing of the lung tissue covered the cut surface with a frothy, bloody fluid. The kidneys and liver were deep red to purple in color and the cut sections were moist and dripped blood.

The animals that died within 1 to 8 days following exposure showed a congestion and edema of the lungs, with a swelling and hyperemia of the kidneys. The findings in animals of these same groups which were killed for autopsy immediately after exposure showed a hyperemia and edema of the lungs, with a congestion of the liver and kidneys. Animals that were killed for autopsy 4 days following exposure still showed a hyperemia with areas of congestion throughout the lungs, whereas those killed for autopsy 8 days following exposure showed atelectatic and emphysematous patches throughout the lungs.

The findings in those animals that were killed immediately after exposure to conditions that did not cause death, but which caused

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a mild degree of pathological change, were principally congestion and slight edema of the lungs, and hyperemia of the liver. The findings in the lungs were not as severe as noted in the exposures previously described. These changes cleared up in most of the animals within 8 days after exposure.

A clouding and thickening of the cortex of the kidneys was noted in those animals killed immediately after exposure to 25 per cent for 5 minutes and 5 per cent for 1 hour. This change was not noted in members of those groups killed 4 days and 8 days later.

No significant gross pathological changes were found in animals exposed to 15 per cent for 10 minutes, 5 per cent for 30 minutes, and 2.5 per cent for 2 hours.

DISCUSSION OF PATHOLOGY

Vinyl chloride is irritating to the lungs. Congestion and edema of the lungs are the most constant and prominent observations for exposure to conditions which caused death during or following exposure. Accompanying the lung changes was a passive congestion of the liver and kidneys.

The signs of lung irritation which were found immediately after exposure to conditions which did not cause death, practically disappeared within 8 days. A clouding and thickening of the cortex of the kidney was noted immediately after exposure to 25 per cent for 5 minutes and 5 per cent for 1 hour. These kidney changes were not present in animals of the same groups after 4 days.

FATALITY AND SUMMARY OF PHYSIOLOGICAL RESPONSE

A summary of the fatality and response of guinea pigs exposed to various concentrations of vinyl chloride in air is shown graphically in Figure 1, and given in conventional degrees of response in Table 2. The results of each experiment are designated by a symbol which represents one of six different degrees of severity. With the exception of concentrations causing death during exposure for which the results obtained for individual animals are given, the selected symbol describes the results obtained for at least one-half the individual animals, and in most cases the results are for the majority of a group (at least three and usually six animals) exposed to a given condition.

It will be noted from the legend on Figure 1 that the six degrees of response are—

1. Died on test.
2. Majority died within 24 hours.
3. Majority died, 1 to 8 days.
4. Moderate injury, few deaths.
5. Slightly injurious, no deaths.
6. Not injurious, no deaths.

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In addition to representing the response of each group by symbols, the latter have been separated into four general fields or zones of probable response, namely,

1. Probable death, 24 hours or less.
2. Serious response, occasional death.
3. Without serious response.
4. Distinct symptoms.

Table 2 gives the concentrations which produce the degrees of response generally reported in the literature dealing with noxious gases. These data may be compared with toxicological data for other compounds. ^{2 4 5 6 8 9 10 11}

TABLE 2.—Acute effects of exposure of guinea pigs to vinyl chloride in air

Effects of exposure after various periods of time	Concentration, per cent by volume
1. Kills in a very short time.....	20 to 40
2. Serious symptoms in a very short time.....	10
3. Moderate symptoms in a very short time.....	2.5 to 5
4. Dangerous to life in 30 to 60 minutes.....	10
5. Marked symptoms in 30 to 60 minutes.....	5
6. Maximum amount for 60 minutes without serious disturbances leading to death.....	5 to 7
7. Maximum amount for 60 minutes without marked symptoms.....	1.0 to 1.5
8. Maximum amount for several hours without serious disturbances.....	0.5
9. Maximum amount for several hours with but slight or no symptoms.....	1.0

CAUSE OF DEATH DURING AND FOLLOWING EXPOSURE

The animals exposed to 20 to 40 per cent vinyl chloride entered a state of profound narcosis which terminated in death. Recovery was rapid and without fatality following exposure for periods less than those causing death during exposure. This indicated that the degree of lung irritation acquired in these relatively short periods was insufficient to cause death. With concentrations in the range of 5 to 10 per cent the period between a profound but nonfatal narcose state and death was much longer, and permits considerable lung irritation to take place. Also, there was a probable action of vinyl chloride or products of its decomposition on the liver and kidneys. With 2.5 per cent, profound narcosis was present after 90 minutes and irritation of the lungs occurred after several hours, but death was exceptional.

^{2 4 5 6} See previous footnotes 2, 4, 5, 6.
⁸ Cotton, R. T., and Young, H. D.: The use of carbon dioxide to increase the insecticidal efficiency of fumigants. Proc. Entomological Soc. of Washington, vol. 31 (1929), pp. 97-102.
⁹ Sayers, R. R., Yant, W. P., Thomas, B. G. H., and Berger, L. B.: Physiological response attending exposure to vapors of methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride. Pub. Health Bul. No. 185 (1929), 56 pp.
¹⁰ International Critical Tables, first edition (1927), vol. 2, p. 318. Also see errata sheet, vol. 2.
¹¹ Henderson, Yandell, and Haggard, Howard W.: Noxious gases. American Chemical Society Monograph No. 35, 1927. Chemical Catalogue Co., New York.

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HEALTH HAZARDS FROM VINYL CHLORIDE

With regard to symptoms and pathology, as well as the effecting concentrations, the response of guinea pigs to vinyl chloride appears to be similar to their response to ethyl chloride.⁸ In equal concentrations and for single exposures, vinyl chloride is less harmful than gasoline, benzene, chloroform, and carbon tetrachloride.

The comparatively harmless response to concentrations of vinyl chloride that will maintain a narcose state, together with its rather pleasant odor, suggests a possible use for producing surgical anaesthesia. This could be produced quickly by high concentrations and maintained with lower concentrations. Much additional work is necessary, however, to ascertain the practicability of its use.

Vinyl chloride does not possess adequate warning properties of the odor or irritation type. With concentrations of 5 per cent or less, however, it gives warning by producing symptoms of dizziness and disorientation in advance of harm. With higher concentrations the narcotic action is very rapid and persons would have little time to heed the warning symptoms before helplessness would ensue.

Vinyl chloride boils at less than ordinary room temperatures. As a rule, it is contained in cylinders under pressure. This is conducive to escape of the gas; on the other hand, the high concentrations required to produce physiological harm minimize the danger from leakage. There is, in fact, more danger from explosion than from harm to health from exposure.

ACKNOWLEDGMENTS

The writers desire to give acknowledgment to J. G. Davidson, manager of chemical sales for the corporation mentioned, and E. W. Reid, senior fellow of this firm's fellowship at the Mellon Institute, Pittsburgh, Pa., for sponsoring the investigation, to R. R. Sayers, chief surgeon, Bureau of Mines, for suggestions and advice, and to H. F. Brubach, laboratory assistant, Bureau of Mines, for assistance in performing the experimental work.

SUMMARY AND CONCLUSIONS

The acute physiological response of guinea pigs to air containing vinyl chloride was determined. The concentrations of vapor and periods of exposure ranged from those which produced death to those which caused no apparent effect after several hours' exposure. The symptoms, gross pathology, and fatality are given with a discussion of potential hazards.

1. The symptoms are principally those of narcosis. They range from unsteadiness and motor ataxia to incomplete and, finally, com-

⁸ See previous footnote 8.

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plete narcosis. The respirations vary from a rapid, jerky type accompanying the beginning of narcosis to a later, slow, shallow type.

2. The principal gross pathological findings were congestion and edema of the lungs, with hyperemia of the kidneys and liver.

3. Exposure to 20 to 40 per cent kills guinea pigs in a very short time; 10 per cent is dangerous to their lives after 30 to 60 minutes' exposure; and 0.5 per cent is the maximum allowable amount for several hours without acute disturbances of a serious nature.

4. With regard to relative toxicity (concentrations causing acute harm), vinyl chloride is less harmful than carbon tetrachloride and chloroform, and is similar to ethyl chloride.

5. The danger from explosion exceeds the health hazard from exposure.

6. Vinyl chloride does not possess adequate warning properties of the odor or irritation type. It gives warning, however, by producing symptoms of dizziness and disorientation in advance of harm, except when present in exceedingly high concentrations which would cause almost immediate helplessness and unconsciousness.

7. The narcotic action of vinyl chloride and its comparatively low toxicity suggest its possible use for surgical anaesthesia.

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