ANESTHESIA XXVII. NARCOSIS WITH VINYL CHLORIDE *†

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IN our studies on various volatile organic compounds available as inhalation anesthetics, our attention was directed to vinyl chloride. Vinyl chloride is an industrial chemical used in the synthesis of many organic compounds. The substance is a gas which boils at −18 C. It is soluble in the etherial solvents and its vapors are combustible.

Vinyl chloride was suggested as an anesthetic by Patty, et al. (1) and tried on human subjects by Schaumann (2). Patty's experiments on guinea pigs revealed that the action of vinyl chloride was similar to that of ethyl chloride and less harmful than either chloroform or carbon tetrachloride. According to Schaumann the narcotic limiting concentration for man is 7 to 10 per cent; 12 per cent is dangerous. In our studies, planned to give a first approximation of the anesthetic syndrome of vinyl chloride, we suggest that this compound not be used as an anesthetic in man.

Chemotherapeutic Considerations: There is a dictum in pharmacology (3) that potency and unsaturation parallel each other among analogous organic compounds. This holds for ethane and its more potent analogue, ethylene. It is also true for ethyl ether and its more potent analogue, divinyl ether. Therefore, one might expect that vinyl chloride would be a more potent anesthetic than its analogue, ethyl chloride. This relationship, however, appears not to obtain between these two chlorinated hydrocarbons. With ethyl chloride, 3.6 to 4.5 volumes per cent (4) are required for anesthesia with 20 mg. per cent in the blood. Schaumann (2) used 7 to 10 volumes per cent of vinyl chloride to produce anesthesia and found 17 to 20 mg. per cent in the blood. Our observations in dogs conform well to the indication of these data, namely, that there is little difference in potency between the saturated and the unsaturated analogues, and actually ethyl chloride appears to be the more potent.

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Observation Anesthesias in Dogs: Two dogs were anesthetized with vinyl chloride * using mixtures of the gas and oxygen. For induction the concentration of the gas momentarily was allowed to run to 50 volumes per cent and then reduced to 7 volumes per cent. Induction was rapid. There was continuous "crowing" even under deep anesthesia. There was much salivation. Abdominal relaxation was good, but the legs showed rigidity and incoordinated leg movements throughout the anesthesia. The recovery period was prompt but accompanied by violent excitation.

In a third dog anesthesia was produced using 25 volumes per cent momentarily, and a similar syndrome ensued.

Blood Pressure in Dogs: Four dogs were prepared for blood pressure tracings by cannulating the femoral artery. The operation was performed under monocaine hydrochloride local anesthesia. After a normal blood pressure tracing had been obtained, the animals were anesthetized with vinyl chloride-oxygen mixtures, using 10 volumes per cent of the former. In all 4 cases the magnitude of the blood pressure remained within normal limits during anesthesia. There was definite evidence of cardiac irregularity, however, such as intermittent tachycardia, extraventricular systoles and vagal beats. These irregularities disappeared upon changing the anesthetic to ethyl ether. These cardiac disturbances confirmed our stethoscopic observations on the unoperated dogs.

Electrocardiographic Studies in Dogs: Six dogs were anesthetized with vinyl chloride-oxygen mixtures, using 10 volumes per cent of the former. Electrocardiographic records, lead II, were made at light surgical anesthesia, surgical anesthesia and threatened respiratory collapse. All of the animals manifested marked changes in cardiac rhythm in surgical anesthesia. Marked tachycardia followed by bradycardia was typical. In 2 of the 6 animals the R-spike was inverted during surgical anesthesia and in 1, evidence of incipient ventricular fibrillation obtained. Inversion of the R-spike with bradycardia is shown in the record from dog 6, lead II, chart 1.

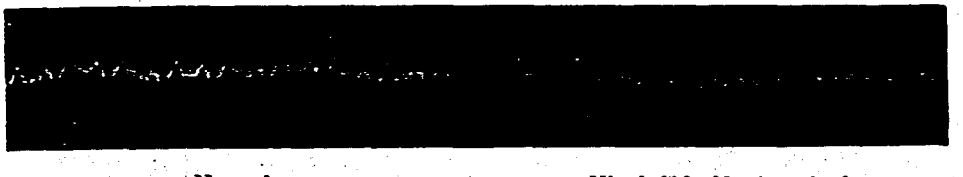
Abnormalities in the QRS complex were found in all 6 dogs varying from sinus arrhythmia and transitory extreme left axis deviation to very serious conditions including auriculoventricular block, ventricular

* The vinyl chloride used in these studies was prepared for us especially purified by H. B. Smith of Petroleum Chemicals, Inc., Baltimore, Md. It was stabilized with 0.5 per cent of p-tertiary butyl catechol. The compound was purified as follows:

"Vinyl chloride of 97.4% by weight purity containing 2.6% by weight trichlorethylene, 3.5 ppm. of acetylene, and no free acidity was carefully distilled to remove trichlorethylene. The distilled vinyl chloride was washed with cuprous ammonium chloride, phosphoric acid, and dried over pelleted potassium hydroxide. The purified vinyl chloride was found to have the following specifications:

Acetylene: None by cuprous ammonium chloride test.
Free Acidity: None.
Ammonia: None.
Trichlorethylene: Trace."

tachycardia, ventricular multifocal extra systoles, and inversion of the T-wave with elevated ST segments in lead II. As anesthesia progressed toward respiratory failure, most of the QRS abnormalities disappeared but the R amplitude was greatly reduced.



Normal
Lead II

Vinyl Chloride Anesthesia
Lead II

CHART 1

Two dogs under ethyl chloride anesthesia and the same experimental conditions showed a lowering of blood pressure and progressive bradycardia without arrhythmias. In 1 animal a brief period of left axis deviation appeared during the induction phase.

SUMMARY AND CONCLUSIONS

1. Vinyl chloride has been studied as an anesthetic in the dog.
2. The anesthetic syndrome is marked by incoordinated muscular activity in the extremities.
3. In 6 dogs cardiac arrhythmias of a serious nature were observed.

It is our opinion that, as an anesthetic in the dog, vinyl chloride is unsafe and that its use in man is unwarranted.

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THE SCIENTIFIC ASSEMBLY OF THE AMERICAN MEDICAL ASSOCIATION will be held in Chicago in 1948. Anyone who wishes to appear on the Program of the Section on Anesthesiology should submit titles of papers to the Secretary, Dr. John S. Lundy, 102 Second Avenue Southwest, Rochester, Minn., as soon as possible.

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The professional group conforms more nearly to the average for the entire population considered. Few conditions are found to have excessive rates; but on the other hand, there are not very many with particularly low rates.

The business group approximates the average for the entire population considered in nearly every respect.

The skilled trade group stands out distinctly from the others in a number of respects. Its rates of impairments are excessively high for eye and ear, teeth, heart and pulse, and many miscellaneous conditions. The desirability of a study of the rates of impairments in the specific occupations making up this group is suggested.

Again, it should be emphasized that one could not expect in this study to find very marked differences, since the lower social levels are but slightly represented in the data.

ACKNOWLEDGMENTS

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ACUTE RESPONSE OF GUINEA PIGS TO VAPORS OF SOME NEW COMMERCIAL OI GANIC COMPOUNDS

V. VINYL CI LORIDE[1]

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

This report on the acute respons of guinea pigs to vinyl chloride gas is the fifth of a series of simila reports which deal with studies pertinent to evaluating the hazard involved in exposure to some chemical products which have recen y reached, or promise to reach, important domestic and industrial u . The first report of the series dealt with ethylene dichloride,[3] e second with ethyl benzene vapor,[4] the third with "Cellosolv (ethylene glycol monoethyl ether),[5] and the fourth with ethylen oxide.[6]

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

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

SCOPE OF ORK

The scope of the work included study of the toxicity of vinyl chloride and the physiological respo e to its vapors as determined by exposure of guinea pigs. Only ute effects as produced by a single exposure were studied. The e eriments were planned to give information relative to the concentr ions and periods of exposure which produce but slight response, oderate response, and serious response.

[1] This report represents work done under cooperative a ement between the Bureau of Mines, Depart ment of Commerce, and the Carbide & Carbon Chemi s Corporation. Published by permission of the Director, U. S. Bureau of Mines.

[2] Assistant surgeon, United States Public Health Servic letailed to the Bureau of Mines.

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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.[5] Briefly, the method was to subject the vinyl chloride to combustion with oxygen (explosion method using electrolytic gas to "energize" the combusiton), 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.[5]

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.
[6] See previous footnote 6.
[7] Jones, G. W., U. S. Bureau of Mines, unpublished data.

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.

TABLE 1.—*Symptoms produced in guinea pigs during exposure to vapors of vinyl chloride*

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	½ [2] (10)	1 [2] (29)	2 [2] (360)	[2] (360)	[2] (480)	[2] (480)	[2] (480)
Unsteadiness on feet; motor ataxia				2	5	[2] (480)	[2] (480)
Apparent unconsciousness; deep narcosis; no twitching of extremities; quiet	[2] (10)	16–20	60	50	90	[2] (480)	[2] (480)
Jerky, rapid respiration	¼–½	2	(3)	240	[2] (480)	[2] (480)	[2] (480)
Slow, shallow respiration	[2] (10)	20	120–360	360	360–480	[2] (480)	[2] (480)
Respirations ceased	10–20	18–55	[2] (360)	[2] (360)	[2] (480)	[2] (480)	[2] (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-

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

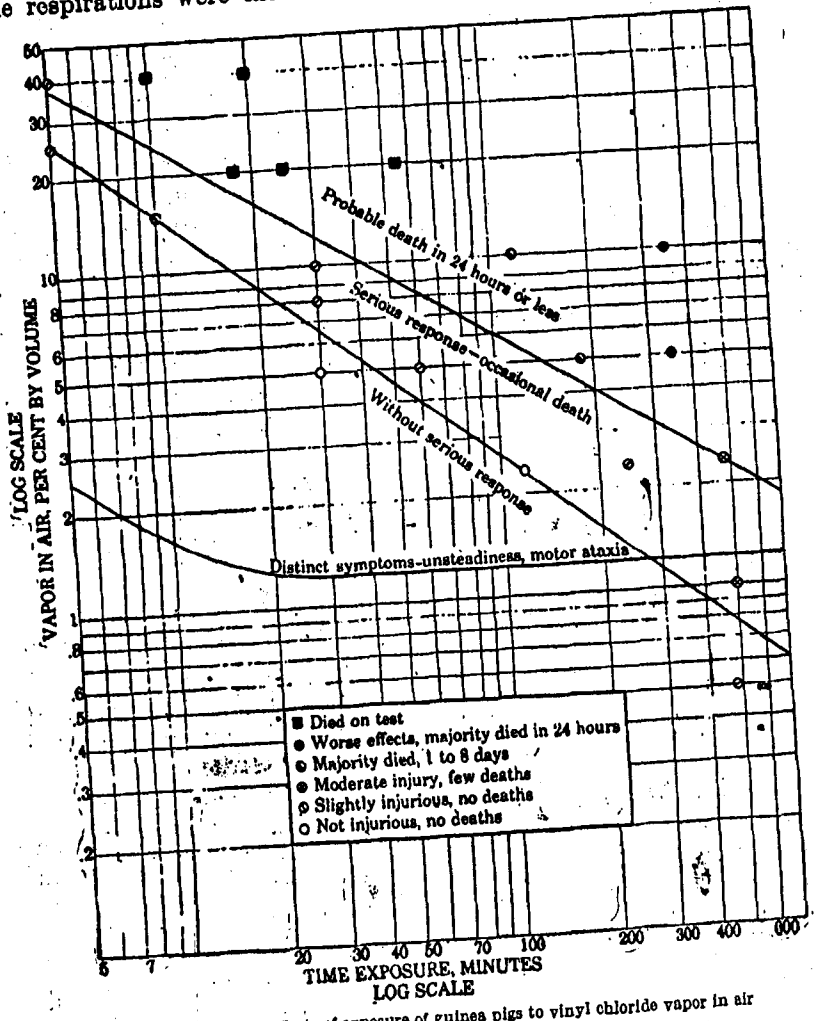

FIGURE 1.—Acute effects of exposure of guinea pigs to vinyl chloride vapor in air

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.

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

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.

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.[3 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.

[3 4 5 6] See previous footnotes 3, 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.

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.

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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, complete 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.

[8] See previous footnote 8.

DEATH RATES IN A GROUP OF INSURED PERSONS

Rates for Principal Causes of Death for June and First Six Months of 1930

The accompanying tables are taken from the Statistical Bulletin for July, 1930, issued by the Metropolitan Life Insurance Co. They present the mortality record of the industrial insurance department of the company for June, 1930, as compared with the preceding month and with the corresponding month of last year, and also give the rates, by white and colored policyholders, for the first six months of the years 1928, 1929, and 1930. Death rates are given for the principal causes of death, and are based on a strength of approximately 19,000,000 insured persons.

It should be remembered that these rates apply to a more or less selected group of persons. In recent years the general death rate for this group has been approximately 73 per cent of the rate for the registration area of the United States.

JUNE, 1930

The death rate for June among these persons was 8.3 per 1,000, the same as for June of last year, and the lowest rate for the month in the mortality records of the company.

As compared with June of last year, improvement is noted for diphtheria, influenza, tuberculosis, pneumonia, accidents, and homi-

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