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Acute Inhalation Toxicity of Vinyl Chloride to Laboratory Animals

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Introduction

FIRST prepared in 1833, vinyl chloride has come into increased use in the last decade in the production of polyvinyl chloride resins. The fire and explosion hazard of the monomer and its narcotic properties on acute exposure are well known. As an industrial material, however, it has been regarded as of moderate toxicity. A Threshold Limit Value of 500 ppm was established by the American Conference of Governmental Industrial Hygienists.

No industrial fatalities associated with its use have previously been reported. It was therefore of special interest when two fatalities occurred in a plant handling vinyl chloride. This plant is engaged in the polymerization of the gaseous monomer with the aid of catalysts. One worker died while cleaning out a polymerization vessel and the other while working in a pit. Details of these two fatalities have been reported by one of the authors.[1]

Published information on the acute toxicity of vinyl chloride to experimental animals proved scanty. Patty, Yant and Waite[2] in 1930 reported on the acute response of guinea pigs to vinyl chloride. They found that exposure to 20 to 40 per cent in air killed guinea pigs in a short time; exposure to ten per cent was endured for several hours. Congestion and edema of the lungs with hyperemia of the liver and kidneys were noted.

Peoples and Leake[3] found the minimal anesthetic range of vinyl chloride in mice exposed for ten minutes was 8 to 12 per cent in air; 25 to 30 per cent was fatal in ten minutes. Dogs and rabbits were anesthetized within one minute when exposed to a concentration of about 18 per cent in air. Recovery was very rapid with no apparent untoward effect even after prolonged anesthesia.

Lehmann and Flury[4] noted that vinyl chloride was highly narcotic but had a wide margin between its narcotic and lethal concentrations. Its local irritating effect and its toxicity were described as very slight. Elimination from the body was very rapid. These authors quoted the work of Schaumann[5] with experimental animals. Mice, rats and dogs were able to endure repeated narcosis without any pathological evidence of liver or kidney damage. According to Schaumann, concentrations of seven to ten per cent in air would be narcotic to humans in a short time and 12 per cent would be dangerous.

Vinyl chloride has been studied as a possible anesthetic agent. Oster and associates[6] noted that incoordinated muscular activity of the extremities and cardiac arrythmias of a serious nature were observed in all six dogs used in their experiment. Carr and others[7] found that vinyl chloride produced sensitization of the myocardium in three of seven dogs in which it was administered as an anesthetic agent.

Two cases of vinyl chloride gassing occurred in a factory in Great Britain where polyvinyl chloride resin was being made. These were reported by the Chief Inspector of Factories.[8] In one case a process worker was standing outside a polymerization vessel and washing it with a water stream. After ten minutes of this he suddenly collapsed across the open manhole. Artificial resuscitation was successfully applied. Subsequent symptoms experienced by this worker were tightness of the chest, nausea, abdominal pain and headache. The second case occurred in a maintenance worker who was overcome while repairing a vinyl chloride leak. Both men were hospitalized. Another worker whose hands were accidentally sprayed with vinyl chloride liquid under pressure developed a burn. This latter case was reported by Harris.[9] Such burns may occur with other highly volatile materials when sprayed onto the hands as a liquid under pressure.

Filatova and Gronsberg[10] in 1957 reported on hygienic conditions in a polyvinyl processing plant in the U.S.S.R. The plant was engaged in the polymerization of vinyl chloride by means of a catalyst. Air sampling was done and the concentration of vinyl chloride was found to vary from about 20 ppm to about 315 ppm. (U.S.S.R. Threshold Limit Value: 1 mg/liter or about 400 ppm). A spastic type blood vessel disorder was described in workers from this plant.

Because of the recent fatalities mentioned above it was decided to undertake acute inhalation studies in laboratory animals with commercially available vinyl chloride. This was done both for comparison with earlier work and to provide information on the acute response and pathological changes in more than one species of laboratory animal.

Experimental Materials and Procedures

Vinyl Chloride: The vinyl chloride was supplied in a metal cylinder under pressure. A commercial grade with the following specifications was used:

Specific gravity at 20°C	0.963–0.965
Water content	None
Boiling range °C	−11 to −9.5
Hydrogen chloride content	None
Acetylene	10 ppm maximum
Acetaldehyde	20 ppm maximum
Iron	Essentially iron free
Purity (per cent)	99.5 maximum
Impurities (per cent)	0.5 maximum

Pure vinyl chloride is a colorless gas at room temperature; its boiling point is −13.9°C. It has a sweetish odor. Its flash point is given at −78°C and its explosive limits in air from 4 to 22 per cent. It has the molecular formula CH_2:CHCl.

Animals: Mice, rats and guinea pigs were used in the study. Test and control animals were taken from the same laboratory stock. All were fed a standard commercial diet and housed in the same way. All were of the same stage of development.

Equipment: The inhalation chamber capacity was 56.6 liters. It was equipped with a viewing window and an inlet tube. Vinyl chloride was released in gaseous form through an adjustable valve on the top of the containing cylinder, then through connecting rubber tubing and a recalibrated Fisher flow-meter. Fresh air was pumped by motor at an adjustable controlled rate through a meter. The streams of air and vinyl chloride were combined at appropriate rates of flow by a glass Y-tube leading through further rubber tubing to the animal chamber inlet, to deliver a continuing stream in the desired proportions. Calculations and adjustments were made to produce the following flow concentrations of vinyl chloride in air for delivery: 10, 20, 30 and 40 per cent. All concentrations are expressed in this report as per cent by volume in air. No determinations of vinyl chloride concentrations were done in the test chamber during the experiments.

Experimental Procedures: Different groups of five mice, five rats and five guinea pigs were placed in the chamber and exposed for thirty minutes to concentrations of 10, 20 and 30 per cent vinyl chloride in air. Similar groups of control animals were maintained but not exposed to vinyl chloride. At the end of thirty minutes exposure the test animals were immediately removed to fresh air. An additional group of five guinea pigs was exposed to a concentration of 40 per cent vinyl chloride in air. In all 65 experimental animals were involved. Observations were recorded on the animals during and after exposure.

The animals which died either during the exposure or after a delay period were autopsied soon after death. Two weeks after the exposure surviving test animals and controls were sacrificed by a blow to the head with the exception of four control rats which were killed by exsanguination.

All animals were examined for gross pathological changes. Tissues were removed from all animals for microscopic examination. The lungs, liver, kidney and heart were removed in all cases. The brain, adrenal, spleen, trachea, lymph nodes, and the eye were removed from representative animals in each group for study. The tissues were preserved in formalin and sections made for staining with hematoxylin-eosin. Special stains were made where indicated.

Observations

Control Animals: No symptoms were exhibited by the 15 control animals and no deaths occurred.

Ten Per Cent Vinyl Chloride: The response of animals exposed to this concentration is recorded below in summary form:

Exposure Time (minutes)	Response
1	Slight irritation in mice and rats.
5	Increased motor activity first in mice, then rats and guinea pigs.
10	Increased motor activity in all species; twitching of extremities in mice.
15	Pronounced tremor, unsteady gait and muscular incoordination in all species.
20	Mice and rats in side position; muscular incoordination, tremors and twitching of extremities in guinea pigs.
25	Mice and rats unconscious, guinea pigs very unsteady but still standing.
30	Mice and rats in deep narcosis; guinea pigs in side position with tremors—one unconscious.

Exposure was stopped and the animals removed to fresh air. All recovered within five minutes.

Twenty Per Cent Vinyl Chloride: The response

of animals exposed to this concentration is recorded below in summary form:

Exposure Time (minutes)	Response
1	Immediate irritation in mice and rats.
2	Muscular incoordination in mice and rats.
5	Mice and rats on their sides with marked tremors and twitching of the extremities; unsteadiness and muscular incoordination in guinea pigs.
10	Mice and rats unconscious with rapid irregular breathing; guinea pigs unconscious but showing marked twitching.
15	All animals in deep narcosis; respirations irregular and rapid.
20	Deep narcosis; breathing slow and shallow.
25	Breathing ceased in one mouse; frothing at mouth and nostrils in mice and rats.
30	All animals in deep narcosis.

Exposure was stopped and the animals removed to fresh air. Mice and rats recovered faster than the guinea pigs and appeared normal within five minutes except for one mouse which was dead. The guinea pigs continued to show muscular incoordination, unsteadiness on their feet until 20 minutes after removal from exposure.

Thirty Per Cent Vinyl Chloride: The response of animals exposed to this concentration is recorded below in summary form:

Exposure Time (minutes)	Response
—	Mice showed irritation immediately and the rats showed irritation quickly thereafter.
1	Muscular incoordination in mice and rats.
2	Mice and rats in side position with marked tremors and twitching of the extremities; muscular incoordination in guinea pigs with developing paralysis of the extremities.
5	All animals unconscious; rapid irregular respirations in mice and rats with frothing about nose and mouth; twitching of extremities still occurred occasionally in guinea pigs.
10	Respirations stopped in mice; breathing slow and shallow in rats; guinea pigs still exhibited occasional twitching movements of the extremities.
15	Breathing stopped in rats; respirations slow and shallow in guinea pigs; twitching of extremities still present in guinea pigs.
30	Mice and rats still; guinea pigs in deep narcosis with slow shallow breathing

Exposure was stopped and the animals removed to fresh air. The mice and rats were dead. The guinea pigs took 25 minutes to return to their normal appearance and activity. One guinea pig from this group died within 24 hours following exposure.

TABLE I

Number of Deaths in Different Groups of Five Mice, Rats and Guinea Pigs Exposed for Thirty Minutes to Varying Concentrations of Vinyl Chloride in Air

Vinyl chloride concentration (per cent by volume in air)	Laboratory animal			Total
	Mice	Rats	Guinea pigs	
10	0/5	0/5	0/5	0/15
20	1/5	0/5	0/5	1/15
30	5/5	5/5	1/5*	11/15
40	—	—	2/5*	2/5
Total	6/15	5/15	3/20	14/50

* A delayed death occurred within 24 hours following exposure.

Forty Per Cent Vinyl Chloride: Only five guinea pigs were exposed to this concentration. Signs of irritation were immediately apparent. Muscular incoordination appeared within seconds. After five minutes all the guinea pigs were unconscious with slow shallow breathing. At the end of the exposure period one guinea pig was dead and the remaining four were in deep narcosis. These survivors took 30 minutes to return to their normal appearance and activity, but one died within the following 24 hours.

The number of deaths occurring in different groups of five laboratory animals exposed for thirty minutes to varying concentrations of vinyl chloride in air is shown in Table I.

Pathological Findings

Gross pathological and histological studies were carried out. The findings are summarized below.

Control Animals: These animals showed no gross or microscopic evidence of damage.

Ten Per Cent Vinyl Chloride: All test animals survived this exposure. They were sacrificed two weeks later. On gross examination there was evidence in mice of slight hyperemia of the lungs. This was less marked in rats. Guinea pigs showed no difference from control animals. On histologic examination the mice showed very slight engorgement of the pulmonary vessels. One mouse showed degenerative changes in the tubular epithelium of the kidney with hydropic swelling. The rats showed slight congestion of the capillaries in the lung. Lungs in the guinea pig were also slightly more hyperemic than those of the control animals.

Twenty Per Cent Vinyl Chloride: One mouse died as a result of 30 minutes exposure to this concentration. Pulmonary congestion was evident on gross examination. Microscopically, there was engorgement of the blood vessels in the lung with patchy areas of atelectasis and minimal edema. The kidneys showed minimal degenerative changes in the epithelium of the convoluted tubules.

The test animals surviving this exposure were sacrificed in two weeks. On gross examination, congestion of the lungs was present in all species, but it was more marked in the mice and rats than in the guinea pigs. Histologically, there was evidence of pulmonary congestion in exposed animals. Some fatty infiltration was present in the liver of one rat. All other tissues studied appeared normal.

Thirty Per Cent Vinyl Chloride: Gross examination of the animals which died as a result of this exposure revealed congestion of the lungs with hemorrhagic areas. The mice and rats in addition showed congestion of the liver and kidney. The one guinea pig death was delayed. In this animal there was marked congestion of the lungs with hemorrhages and the liver was distended and very friable. The microscopic changes in the animals which died included marked engorgement of the pulmonary blood vessels with edema and hemorrhages in the lungs. The trachea of one rat showed superficial desquamation of the epithelium. Congestion was also evident in the liver and kidney of the mice and rats. The liver of the guinea pig which had the delayed death showed severe fatty degeneration of the liver confirmed with frozen sections stained with Sudan III.

The four surviving guinea pigs were sacrificed two weeks later. Marked pulmonary congestion was present with hemorrhagic areas and edema. In one case there was evidence of secondary bacterial infiltration. The liver in these guinea pigs gave the appearance of fatty infiltration but no fat was demonstrated on frozen section.

Forty Per Cent Vinyl Chloride: One of five guinea pigs exposed to this concentration died during the exposure and another died within 24 hours. The two which died showed marked congestion of the lungs with hemorrhages on gross examination. This was also evident on microscopic examination. The liver of one of these gave the appearance of fatty infiltration, but no fat could be demonstrated on frozen section.

The three surviving guinea pigs were sacrificed two weeks later. Marked congestion of the lungs with hemorrhage was evident on both the gross and microscopic examination. In one guinea pig, the tracheal epithelium was completely absent.

Pathological studies which were made of the brain, heart, spleen, adrenals, lymph nodes and the eyes showed no difference between controls and animals dying as a result of exposure or between controls and the surviving animals sacrificed two weeks after exposure. There was a tendency for the blood to remain unclotted in the animals dying during exposure. This feature was noted in the two human fatalities mentioned earlier but it is not a specific characteristic of vinyl chloride.

Discussion

The response of guinea pigs to inhalation of vinyl chloride was similar to that reported by Patty, Yant and Waite. The guinea pigs in our study, however, tolerated a greater exposure during the experimental period than either the mice or rats. The results in mice agreed closely with those reported by Peoples and Leake. Rats were similar to mice in their response.

The pathological changes in animals which died as a result of exposure were mainly those of vascular engorgement of the lungs with hemorrhages and edema. The severity of these changes varied with the severity of exposure. In the higher concentrations, pulmonary change was marked with severe damage to the tracheal epithelium. Congestion of the liver and kidneys also occurred in test animals. These changes are similar to those reported by Patty and associates.

Evidence of pulmonary congestion was still present in surviving animals sacrificed two weeks after exposure. Patty and associates reported that such changes had disappeared in about eight days.

Degenerative changes in the tubular epithelium of the kidney were noted in one mouse dying as a result of exposure and in one mouse sacrificed two weeks after being exposed. Such changes, however, were minimal and not shown by other animals in the group.

One of the guinea pigs with delayed death following exposure showed severe fatty infiltration of the liver. Changes suggestive of fatty infiltration were observed in other exposed animals but not confirmed by frozen sections stained with Sudan III.

Summary

Separate groups of laboratory animals comprising five mice, five rats and five guinea pigs were exposed in an inhalation chamber to concentrations of 10, 20 and 30 per cent vinyl chloride in air for 30 minutes. An additional five guinea pigs were exposed to a 40 per cent concentration for a similar period of time. The response by each of the three species to these concentrations is noted.

Inhalation of these relatively high concentrations produced narcosis and death. Mice were the most susceptible with guinea pigs considerably more resistant. Rats were similar to mice in their

response. Exposure to ten per cent vinyl chloride in air produced deep narcosis in mice and rats but no deaths; 30 per cent concentrations killed mice and rats. Exposure of guinea pigs to 20 per cent produced deep narcosis; but three of five guinea pigs survived exposure to 40 per cent concentration.

Animals dying as a result of exposure were autopsied shortly after death. Survivors and control animals were sacrificed two weeks later. Gross pathological and microscopic studies were done and these findings are described.

The principal pathological changes in animals dying from exposure were congestion of the lungs with pulmonary edema and hemorrhages in some, and congestion of the liver and kidneys. Failure of the blood to clot was also observed. One of the three guinea pigs which died following exposure showed severe fatty infiltration of the liver.

Survivors sacrificed two weeks after exposure showed little difference from the control animals. Pulmonary congestion was still evident but liver and kidney congestion was not.

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Acute and Sub-acute Toxicity Studies of Thallium Compounds

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Introduction

THE element thallium was discovered by Crookes in 1861 by spectroscopic techniques and isolated chemically one year later by A. Lamy. There are no large industrial uses for thallium and its production has been limited. The principal uses of thallium have been related to its rodenticidal properties and it was formerly used as a depilating agent. Thallium salts are also used in the production of certain types of optical glass and in the manufacture of scintillation counters.

An examination of the literature reveals a number of published reports and reviews[1, 2, 3] of thallium toxicity following ingestion of rodenticides containing thallium compounds. A considerable amount of work has been reported on the depilating action of thallium compounds on laboratory animals and man.[4, 5, 6, 7] The distribution and excretion of isotopic thallium (Tl^{204}) has been reported by a number of investigators.[8, 9, 10] Recently, Stavinoha and co-workers[11] have demonstrated that certain compounds containing sulfur act as protective agents against acute thallium poisoning in mice.

The work reported below is concerned with the acute toxicity of thallous acetate (TA) and thallic oxide (TO) following the administration of these compounds to several species of animals by several routes. The ingestion toxicity of these compounds was also investigated for periods up to three months.

Experimental Methods and Materials

The two thallium compounds studied were obtained from the American Smelting and Refining Co., Denver, Colorado (thallic oxide) and Chemical Commerce, Newark, New Jersey (thallous acetate). The purity of these compounds was relatively high (99.5–99.8% Tl).

This paper is based on work performed under contract with the United States Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York.

The thallous acetate was prepared as an aqueous solution at concentrations of 1, 2 or 5 per cent. The thallic oxide was suspended (5%) in distilled water containing 0.8 per cent carboxy methylcellulose.

Young adult, female and male albino rats, originally of the Wistar strain (1923) and bred in the Project Colony were used. The rabbits were young, mature albinos obtained from local breeders. Guinea pigs were young mature animals of mixed sex and obtained from local breeders. The dogs were beagle-type mongrels obtained from local sources.

Single doses of thallous acetate and thallic oxide were administered by intravenous injection to rabbits, by intraperitoneal injection to rabbits, guinea pigs and rats, and orally to rabbits, guinea pigs, rats and dogs. Groups of 2 to 5 rats received single oral or intraperitoneal doses of the compounds. Generally only one rabbit, guinea pig or dog was treated at each dose level. The LD_{50} values, their confidence limits, and the slope function of the regression line, were calculated by the method of Litchfield and Wilcoxon.[12] All animals were held for a 14-day period of observation following injection.

The ingestion studies were conducted using weanling (50–80 gm) albino rats. The basal diet was Purina Fox Chow Meal. The rats were kept in basket-type cages and were permitted to take food and water *ad lib.* The experimental diets were prepared by the admixture of the thallium compounds to the basal diet using an electric mixer. Body weights and clinical data were recorded.

At termination of the ingestion study all of the surviving rats were sacrificed by decapitation. The rats were examined grossly and the heart, liver, kidneys, lungs, spleen, testes and femurs were removed and their weights recorded. Sections of the liver, kidney, brain, lung, spleen, heart, stomach, testes, skin, and adrenals were fixed in Bouins and stained with hematoxylin and eosin for histological study. Portions of the