III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Vinyl acetate, molecular formula CH3COOCH=CH2, is a colorless flammable liquid at room temperature. It has a vapor pressure of 100 mmHg at 21.5 C [1] and a boiling point of 72.7 C. Its odor is at first pleasant but quickly becomes sharp and irritating [2]. The threshold of odor detection for vinyl acetate has been reported to be as low as 1 mg/cu m (0.284 ppm) [3]. Olfactory fatigue has occurred at 19.5 ppm (68.3 mg/cu m) [4]. Some salient physical and chemical properties of vinyl acetate are listed in Table XI-1 [1,2,5-9]. Vinyl acetate is produced by a vapor-phase reaction between ethylene and acetic acid in the presence of a palladium catalyst or between acetylene and acetic acid in the presence of a zinc acetate catalyst [7]. In the United States, 1,481 and 1,606 million pounds of vinyl acetate were produced in 1976 and 1977, respectively [10,11].

Vinyl acetate is used primarily in polymerization processes, eg, to produce polyvinyl acetate, polyvinyl alcohol, and vinyl chloride-vinyl acetate copolymer [2]. The polymers, usually made as emulsions, suspensions, solutions, or resins, are used to prepare adhesives, paints, paper coatings, and textile finishes [7]. Low-molecular-weight polyvinyl acetate is used as a chewing gum base [12]. Vinyl acetate is extremely flammable and forms explosive mixtures at from 2.6 to 13.4% by volume in air [5].

Occupational exposure to vinyl acetate may occur in any work involving the production, storage, transport, or use of the chemical. Occupations with potential exposure to vinyl acetate are listed in Table XI-2 [2,5,8].

NIOSH estimates that approximately 70,000 workers are potentially exposed to vinyl acetate in the United States.

Historical Reports

The earliest report of vinyl acetate seems to have appeared in 1912 [2]. At that time, it was a minor byproduct formed when acetylene and acetic acid were reacted to produce ethylidene diacetate. During World War I, vinyl acetate was prepared and polymerized in Germany [13]. In the late 1920's, vinyl acetate production was commercialized; acetylene and acetic acid were reacted in the liquid phase using such catalysts as mercuric oxide [13].

The toxicity of vinyl acetate was evaluated in 1949 as part of a range-finding study of 96 chemicals by Carpenter et al [14]. Sherman rats were exposed to the test substances for 4 hours to determine the nominal concentrations necessary to kill two to four of six exposed animals within 14

days. For vinyl acetate, this concentration was 4,000 ppm (14,000 mg/cu m), causing the authors to classify it as a "moderate hazard."

Before 1970, few industrial exposure studies had been conducted on vinyl compounds other than vinyl chloride. Research on the biologic effects of vinyl acetate and other vinyl compounds was accelerated after the carcinogenic hazard of vinyl chloride exposure became recognized.

Effects on Humans

Much of the information on short-term effects of vinyl acetate on humans has come from controlled experimental exposures of volunteers and from one short-term study at a vinyl acetate production plant.

Gofmekler [3] tested vinyl acetate on volunteers to determine threshold concentrations for olfactory perception, changes in light sensitivity of the eye, and ability to produce a conditioned-response change in the electrical activity of the brain. Vinyl acetate concentrations were determined by a colorimetric method reported to have a sensitivity of 0.025 μg/ml of sample.

Odor determinations were made by 77 subjects, ranging from 20 to 65 years old [3]. Each test concentration was administered for 2-3 hours and was repeated at an average interval of 3-5 days with each person during a 2-month period.

Light sensitivity was determined in 15 persons over a 3.5-month period [3]. Subjects were placed in a dark room free of noise and other extraneous stimuli. After their eyes became dark adapted, their ability to perceive a light stimulus from an ADM adaptometer was measured. After 5-7 days of exposure to air to establish baseline data on light sensitivity, subjects were exposed to vinyl acetate at least three times at each concentration tested. Only those concentrations that produced a change in light sensitivity at least twice the mean error of the baseline values were considered effective.

To determine the concentration of vinyl acetate that could produce a conditioned response, two subjects inhaled vinyl acetate while their brain electrical activity was recorded on an electroencephalograph (EEG) [3]. After 10-15 seconds of exposure, the vinyl acetate stimulus was reinforced by light, which caused a desynchronization in the EEG. Through association with the light (unconditioned stimulus), addition of vinyl acetate to the inspired air could become a conditioned stimulus, producing EEG desynchronization before the light was presented [15]. Vinyl acetate exposures were conducted once a day at gradually decreasing concentrations to determine the lowest concentration that could produce this conditioned change in brain electrical activity.

Gofmekler [3] found that the minimum perceptible concentration of vinyl acetate in odor detection tests was 1.0 mg/cu m (0.3 ppm), while 0.7 mg/cu m (0.2 ppm) was the maximum imperceptible concentration. The minimum active and maximum inactive concentrations for affecting light sensitivity of the eye were 0.77 and 0.60 mg/cu m (0.22 and 0.17 ppm), respectively. For production of a conditioned change in brain electrical activity, the minimum active concentration was 0.32 mg/cu m (0.09 ppm) and the maximum inactive concentration was 0.21 mg/cu m (0.06 ppm); apparently, vinyl acetate at these concentrations did not produce any observable unconditioned change in EEG patterns. The author concluded that the maximum acceptable concentration for occupational exposure to vinyl acetate should be 0.20 mg/cu m (0.06 ppm). However, this study presented no evidence that adverse effects resulted from exposure to vinyl acetate at the low concentrations that produced positive responses in these tests.

In 1968, investigators [4] at the Mellon Institute described olfactory perception findings in nine volunteers exposed to vinyl acetate vapor at various concentrations for 2-minute periods. Each concentration was tested twice, and the concentrations were measured by gas chromatography; no other experimental details were provided. The lowest concentration at which all subjects could detect an odor was 1.3 ppm (4.6 mg/cu m), and the highest concentration at which all subjects (with one questionable exception) could not detect an odor was 0.6 ppm (2.1 mg/cu m).

The investigators then determined the reactions of four volunteers exposed to vinyl acetate at higher concentrations for longer periods [4]. In experiments conducted on 4 consecutive days, from one to four of the subjects inhaled air containing vinyl acetate at various concentrations ranging from 19.5 to 71.5 ppm (68.3-250.3 mg/cu m) for 0.5-4 hours in a test chamber. Exposure information and the effects reported by each subject are shown in Table III-1. All subjects agreed that they could not work for 8 hours at the highest concentration tested, 71.5 ppm. Although all subjects developed olfactory fatigue, the investigators noted that they returned to the chamber within 10 minutes after each test and reported that the odor was as strong as it had been at the beginning of the test, indicating rapid recovery from olfactory fatigue.

This report [4] indicates that vinyl acetate can irritate the mucous membranes of the throat at concentrations as low as 19.5 ppm (68.3 mg/cu m) and can produce eye irritation at 71.5 ppm (250.3 mg/cu m). It also shows a wide variation in individual sensitivity; only one (B) of three subjects reported throat irritation at 19.5 ppm and another (C) did not report throat irritation at any concentration, although he did experience throat "dryness" at 71.5 ppm.

In 1969, EI du Pont de Nemours and Company conducted an industrial hygiene survey of the vinyl acetate production area at its Niagara Falls plant [16]. Air was sampled from the breathing zones of the workers with a midget impinger

TABLE III-1

EFFECTS OF SHORT-TERM EXPOSURE OF FOUR VOLUNTEERS TO VINYL ACETATE VAPOR

Concentration (ppm)	Concentration (mg/cu m)	Duration (hr)	Subject and Effects
19.5	68.3	4	A - Complete olfactory fatigue in 71 min; no irritative effects B - Complete olfactory fatigue in 3 min*; slight, persistent throat irritation starting at 1 min C - Complete olfactory fatigue in 116 min; no irritative effects
22.9	80.2	4	A - Complete olfactory fatigue in 92 min; no irritative effects
34.2	119.7	2	A - Olfactory fatigue, never complete; transient nose and throat irritation B - Olfactory fatigue, never complete; throat irritation, no worse than in preceding experiment C - Complete olfactory fatigue in 40 min; no irritative effects
71.5**	250.3	0.5	A - Strong odor; olfactory fatigue, never complete; slight throat irritation at 13 min, lasting 20 min after exposure; transient eye irritation at 20 min B - Nearly complete olfactory fatigue; slight, persistent throat irritation at 4 min, lasting 30 min after exposure C - Strong odor; olfactory fatigue, never complete; reddening of sclera at 10 min, lasting 1 hr after exposure; dryness of throat at 20 min, lasting 2 hr after exposure D - Sharp odor; olfactory fatigue, never complete; slight eye and throat irritation at 1 min, lasting until end of exposure

*Considered questionable by the author
**Consensus: "We could not work at this concentration for 8 hours."

Adapted from reference 4

containing 10 cc of dimethylformamide as the absorbent, and the solution was analyzed by gas chromatography. Samples were collected in both summer and winter. Time-weighted average (TWA) concentrations ranged from 0.4 to 4.9 ppm (1.4-17.2 mg/cu m), with no seasonal variation detected. When workers were questioned about eye or upper respiratory tract irritation experiences, there were no affirmative responses. The only irritation reported was that which had resulted from high concentrations of airborne vinyl acetate during "spills." No spills or leaks occurred during the survey, so that vinyl acetate concentrations capable of producing irritation could not be determined.

According to a Union Carbide Corporation publication [17], plant experience indicated that some persons might react to dermal contact with vinyl acetate with blister formation, particularly on the thin skin of the finger web and the underside of the wrist, and that continued contact, such as that afforded by clothing wet with vinyl acetate, might result in severe irritation or blistering of the skin [17].

Epidemiologic Studies

The only available epidemiologic data on vinyl acetate resulted from a cross-sectional study. In 1969, Deese and Joyner [18] described the effects of long-term exposure of chemical operators to vinyl acetate in three production units of a Gulf Coast chemical plant. The study population consisted of 21 volunteers of the 26 operators then assigned to a vinyl acetate complex. The men ranged in age from 26 to 61 years (average 45.3 years) and had been employed in the vinyl acetate complex for an average of 15.2 years; 3 had been employed for less than 2 years, 12 for 2-20 years, and 6 for over 20 years. The control group, 21 operators from other production units not involved with vinyl acetate, was selected from participants in the company's multiphasic screening program, which included complete physical examinations, chest x-rays films, spirometry, electrocardiograms (ECG's), and analyses of blood and urine. The controls were closely matched in age with the vinyl acetate workers. Medical records were reviewed for the previous 5 years for all participants in the study, and the results of their most recent medical examinations were compared. The 21 exposed workers also answered a supplementary questionnaire designed to elicit their personal opinions regarding effects of exposure to vinyl acetate.

To characterize employee exposure to vinyl acetate, the authors collected 40 air samples at 3-6 sites in each of 3 production units during 2 sampling periods 1 month apart [18]. Both 10-minute and 2-hour samples were collected in order to characterize average exposure and excursions. Samples were analyzed for vinyl acetate by gas chromatography, and TWA exposures were calculated for the operators in each unit.

Results of these analyses showed vinyl acetate concentrations ranging from undetectable to 49.3 ppm (173 mg/cu m), with a mean of 8.6 ppm (30 mg/cu m);

83% of the samples showed concentrations of less than 10 ppm (35 mg/cu m) [18]. TWA exposures for operators in the three process units were 8.2, 7.7, and 5.2 ppm (29, 27, and 18 mg/cu m). The authors assumed that these values were representative of the long-term exposure of workers in the study, since operating conditions, processes, and equipment in the plant had been unchanged for more than 5 years. They noted, however, that these values did not reflect high exposures that might occur during nonroutine operations. Vinyl acetate concentrations of 123.3-326.5 ppm (432-1,143 mg/cu m) were measured during one such operation, the opening of a hopper door to remove material, which required about 3 minutes to complete and was carried out an average of twice a day. The lowest concentrations of vinyl acetate, below 0.8 ppm (2.8 mg/cu m), were found in an "acoustically designed" control room equipped with a positive pressure ventilating system; the mean concentration inside each control room was lower than that of the general plant environs.

No major differences were found between the group exposed to vinyl acetate and the controls [18]. A comparison of results of their most recent medical examinations showed some differences in mean blood chemistry values, but all mean values were within normal limits. The numbers of individual abnormalities in blood chemistry were similar in the two groups (12 in the vinyl acetate group and 9 in controls). Medical records for the two groups showed that the numbers of days lost due to illness during the last 5 years did not differ significantly; however, the number of episodes of absence was almost twice as high in the control group as in the exposed group. Vinyl acetate workers lost more time due to respiratory illness, but the authors attributed this excess to one worker with a recurrent upper respiratory infection; similarly, excess absenteeism from gastrointestinal illness in the exposed group was attributable to a single individual with an inflamed gall bladder.

In responses to the questionnaire, 13 of 21 vinyl acetate workers (61%) said they had never been bothered by vinyl acetate, 15 (71%) said it did not irritate their eyes, nose, or throat, and 18 (86%) reported no dermatitis [18]. Two were "bothered" by the odor, and three specifically mentioned eye irritation. Two workers reported upper respiratory tract irritation, specifically associated in one case with unplugging the hoppers, and one reported "a hurting in the chest" from breathing vinyl acetate at high concentrations. Skin effects noted by the workers included dryness of hands and irritation between the fingers; two workers reported that they had experienced skin rashes. The authors reported that there was no positive relationship between length of employment and responses to the questionnaire.

During air sampling, five subjects, including Deese and a laboratory analyst and one operator from each production unit, were asked to record the degrees of odor detection and irritation of the eyes and of the upper respiratory tract that they experienced [18]. Data from 12 sampling operations were reported; 1 sample contained vinyl acetate at a concentration of 21.6 ppm (75.6 mg/cu m) and the remainder ranged between 0.4 and 9.9 ppm (1.4-34.7 mg/cu m).

Three of three subjects exposed at 0.4 ppm (1.4 mg/cu m) reported detecting a slight odor of vinyl acetate [18]. One of three subjects exposed at 7.6 ppm (26.6 mg/cu m) was unable to detect an odor, but all subjects detected the odor at higher concentrations; at 21.6 ppm (75.6 mg/cu m), all three exposed subjects agreed that the odor was marked. The authors noted that the three operators tended to be less sensitive to the odor of vinyl acetate than the two persons, one of whom was Deese, who had not been chronically exposed to odors of various chemicals.

Although Deese experienced slight eye irritation at 5.7 and 6.8 ppm (20.0 and 23.8 mg/cu m), no other eye irritation was reported at concentrations below 10 ppm (35 mg/cu m) [18]. However, all three subjects exposed at 21.6 ppm (75.6 mg/cu m) agreed that the eye irritation they experienced would be intolerable over a prolonged period. All three subjects also reported either hoarseness or cough at 21.6 ppm, but only Deese had upper respiratory tract irritation at lower concentrations, experiencing hoarseness at 4.2 and 5.7 ppm (14.7 and 20.0 mg/cu m).

The authors [18] concluded that long-term exposure to vinyl acetate at concentrations of 5-10 ppm (18-35 mg/cu m) produced no serious chronic effects. They noted that some subjects might be sensitive at concentrations of about 6 ppm (21 mg/cu m), but that concentrations up to 10 ppm (35 mg/cu m) were unlikely to produce irritation of the eyes or respiratory tract in most workers; however, concentrations above 20 ppm (70 mg/cu m) appeared to produce irritation in most persons. The authors also concluded that liquid vinyl acetate was not a serious skin or eye injurant provided prompt washing was carried out. Since this study was limited to a cross-sectional population of 21 of 26 vinyl acetate operators, no general conclusions can be drawn with respect to mortality or other chronic effects in human populations occupationally exposed to vinyl acetate.

No long-term (over 20 years) epidemiologic studies on vinyl acetate were found in the literature.

Animal Toxicity

In 1968, the Mellon Institute, in an unpublished report [4], summarized the responses of rats, guinea pigs, mice, rabbits, and beagles to inhalation of various concentrations of vinyl acetate for 4 hours in a chamber monitored by gas chromatography. Exposure concentrations or ranges were not fully reported. The 4-hour LC50's for six male rats, six female rats, six male guinea pigs, six male mice, and four male rabbits were 3,987, 3,987, 6,215, 1,546, and 2,511 ppm (13,955, 13,955, 21,753, 5,411, and 8,789 mg/cu m), respectively; no information was given on sublethal effects on any of these species. The one male dog exposed to vinyl acetate at 3,825 ppm (13,388 mg/cu m) for 4 hours survived. The highest concentration at which no

observable adverse effect was seen in a dog was 106 ppm (371 mg/cu m); exposure at 240 ppm (840 mg/cu m) caused some blinking and reddening of the sclera.

In a similar investigation sponsored by the Union Carbide Corporation [17], three groups of rats were exposed to vinyl acetate at 1,000, 4,000, or 8,000 ppm (3,500, 14,000, or 28,000 mg/cu m) for 4, 2, and 2 hours, respectively. All rats survived the exposure at 1,000 ppm, three of six rats died "in two hours" at 4,000 ppm, and all of the rats exposed at 8,000 ppm died "in two hours." No sublethal effects were described. The authors also reported that the oral LD50 of vinyl acetate in rats was 2.92 g/kg and that the percutaneous LD50 (covered, 24-hour contact) in rabbits was greater than 5 ml/kg. In addition, they found that "undiluted" vinyl acetate caused no reaction on the rabbit abdomen, but that 0.5 ml applied to the rabbit eye caused severe irritation or mild burns. The test material contained hydroquinone as an inhibitor, but in concentrations that the authors thought to be innocuous.

In 1967, the Haskell Laboratory, in an unpublished report [19], noted the effects of vinyl acetate inhalation at 91-186 ppm (319-651 mg/cu m) on four dogs. Dogs inhaled vinyl acetate at 91 ppm (319 mg/cu m) 6 hours/day, 5 days/week, for 6 weeks. Two and one-half weeks after this exposure ended, the same dogs were exposed to vinyl acetate at 79 ppm (277 mg/cu m) for 2 weeks and then at 186 ppm (651 mg/cu m) for 1 week. No circulatory abnormalities or evidence of disturbed metabolism were noted at any of these concentrations, but at 186 ppm eye irritation and tearing were apparent. Microscopic and gross examination at autopsy showed no lesions that the pathologist attributed to vinyl acetate exposure.

In 1970, Gage [20] presented the results of a short-term inhalation study of a number of industrial chemicals including vinyl acetate. Four groups of four male and four female Alderley Park specific-pathogen-free rats, weighing an average of 200 g, were exposed to vinyl acetate at 100, 250, 630, or 2,000 ppm (350, 875, 2,205, or 7,000 mg/cu m) for 6 hours/day, 5 days/week, for 3 weeks in chambers monitored by gas-liquid chromatography. Control rats were exposed to air alone. Throughout the study the animals were observed for changes in body weight, clinical condition, and behavior. Urine samples were collected overnight after the last exposure day, for biochemical tests. The animals were then anesthetized with halothane, and blood was obtained by heart puncture, for hematologic tests. The organs were examined grossly, and fixed lung, liver, kidney, spleen, and adrenal tissues were examined microscopically.

Exposure to vinyl acetate at 2,000 ppm caused eye and nose irritation and respiratory difficulty, and these rats gained less weight than the controls [20]. Microscopic examination showed increased numbers of macrophages in their lungs, but no other microscopic or pathologic changes were reported. Female rats exposed at 630 or 250 ppm showed abnormally low weight gains. The

results of urine and blood tests on rats exposed at 250 ppm were reported as "normal." No signs of adverse effects were seen in rats exposed at 100 ppm. No abnormalities were apparent in the organs of rats exposed at 100, 250, or 630 ppm. Gage commented that vinyl acetate was the only unsaturated ester of a saturated carboxylic acid, among those tested, of sufficient volatility to exhibit what he termed "...typically...low toxicity, high concentrations producing irritation and narcosis." He recommended a "provisional occupational limit" of 50 ppm for vinyl acetate.

In a 1968 abstract, Goldstein et al [21] reported the effects of inhaling vinyl acetate, alone and with acetic acid, on white mice of unspecified number, age, sex, weight, and strain. Gross and microscopic observations were made and toxic and lethal doses and cytochrome oxidase and succinic dehydrogenase activities of the pulmonary tissue were measured by unidentified methods.

Vinyl acetate alone produced a clinical picture of irritation, primarily of the respiratory system [21]. Microscopic examination revealed acute edematous-hemorrhagic or sero-fibrino-hemorrhagic inflammation, with or without foci of edematous or edematous-hemorrhagic pneumonia. Capillaries in the lung parenchyma, septa, and bronchial walls were dilated, and there were interstitial, subpleural, or parenchymal hemorrhagic foci scattered through the lungs. According to the authors, the experiment showed that vinyl acetate was about four times as toxic as acetic acid. They also noted that the risk of intoxication following industrial exposure to vinyl acetate was more than three times that following exposure to acetic acid. No other details were presented. Vinyl acetate acted rapidly after being inhaled by the mice, and most of the mortality from vinyl acetate (number of deaths not reported) occurred during the actual exposure. The activities of succinic dehydrogenase and of cytochrome oxidase in the lungs of animals that had inhaled vinyl acetate were lower than those in control animals; the activities of these two enzymes in the lungs of animals inhaling acetic acid were higher than those in the lungs of control animals. The microscopic lesions and enzyme activities produced by mixtures were similar to those produced by vinyl acetate alone, and the levels of "lethal concentrations" and "absolute toxicity" were reported to be quite similar for vinyl acetate with and without acetic acid. The authors did not define these terms.

The abstract [21] stated that, since the biologic activity of vinyl acetate with acetic acid was greater than that expected from a simple additive effect, the combined action of the two compounds was synergistic. Because this abstract did not contain essential experimental data, its contribution toward establishing an occupational health standard for vinyl acetate is minimal, but the abstract suggested that mixed exposures to vinyl acetate and acetic acid, which could occur readily in the industrial environment, may be more hazardous than exposure to either chemical alone.

Bartenev [22], in 1957, investigated the effects of low concentrations of vinyl acetate on central nervous system (CNS) function and on recorded changes

in reflex activity in the rabbit. The author's purpose was to establish the threshold concentrations that would elicit recordable changes in reflex activity. Using the methods of Lyublina and of Parfenov, the author monitored CNS activity by measuring two indices of the reflex activity of the rabbit foot: (1) the time for muscle tension reflex development to attain a value of 0.7 kg; (2) the muscle tension value when the reflex had been attained.

Six male rabbits, with body weights of 2,020-2,450 g, were exposed to vinyl acetate vapor at 125, 250, or 500 mg/cu m (35.5, 71, or 142 ppm) for 40 minutes. No significant changes were observed at 125 mg/cu m, but five of six rabbits exposed at 250 mg/cu m showed decreased times for development of target reflex muscle tension and decreased reflex strength. Three of the rabbits exposed at 500 mg/cu m exhibited sharp fluctuations in the excitability of the CNS that occurred much earlier than similar changes seen at 250 mg/cu m, accompanied by increased times for development of target reflex muscular tension and decreased reflex strength.

Bartenev [22] also evaluated cerebral cortical activity in three rabbits by recording changes in the respiratory component of their reactions to electrical stimulation of the paw. Two positive conditioned stimuli, the sound of a metronome and light from two flashlights, and a negative one, a dim light from another pair of flashlights, were presented to the rabbits twice before exposure, with 5 minutes between presentations, and twice during the 37 minutes when vinyl acetate vapor was being inhaled.

Exposure to vinyl acetate vapor at 25 mg/cu m (7.1 ppm) usually caused no marked effect on higher CNS activity, but, although it did not disturb differentiation, it clearly enhanced the reaction to the metronome when the stimuli were presented to one rabbit three times during an exposure. This rabbit exhibited the same phenomenon at higher concentrations. 50 mg/cu m (14.2 ppm) caused different changes in the nervous activity of each rabbit, manifested particularly by uncertain differentiation between the two light stimuli. More profound changes occurred during exposure to vinyl acetate at 100 mg/cu m. In this situation, the rabbits failed to respond to the sound stimulus after 20-26 minutes of exposure and to the strong light at the end of the exposure period. At that time, a paradoxical response to the weak light was present. Complete recovery of normal responsiveness to the various stimuli required 2-6 days.

Bartenev [22] concluded that (1) the minimum (threshold) concentration of vinyl acetate vapor that affected the CNS of rabbits, determined by flexor reflex changes, was between 125 and 250 mg/cu m, (2) the threshold concentration of vinyl acetate vapor during a 37-minute exposure that altered the ability of rabbits to differentiate between qualitatively similar but quantitatively different visual stimuli was between 25 and 50 mg/cu m, and (3) inhalation of vinyl acetate at a concentration one-fifth of that causing changes in unconditioned reflex activity induced disturbances in conditioned reflex activity.

Goeva [23], in 1966, studied the acute and long-term effects of ingested vinyl acetate on mice and rats, including its influence on conditioned reflex development in rats. In the first series of acute experiments, the oral median lethal dose, or LD50, of vinyl acetate for 50 white mice was determined to be 1,613 mg/kg; a majority of the mice died within 3-5 days. In the second short-term test, 20 mice were given oral doses of vinyl acetate of 300 mg/kg (about 0.2 of the median lethal dose) daily for 3 weeks. Each mouse received a total of about 6,000 mg of vinyl acetate. Two animals died during the experiment. At the end of the experiment, all surviving mice were given the median lethal dose (about 1,600 mg/kg), and 8 of the remaining 18 died; on these bases, the author concluded that vinyl acetate had moderate cumulative properties.

The long-term experiment on 30 albino rats lasted for 7 months and included one group of control rats and two experimental groups [23]. Rats ingested vinyl acetate in doses of 0.01 or 0.1 mg/kg with their drinking water. No information was given on the stability of vinyl acetate in water. The rats were observed or examined for: general appearance; body and organ weight changes; peripheral red blood cell counts and hemoglobin values; external gas exchange; liver function by Quick's test (excretion of hippuric acid after ingestion of sodium benzoate) and prothrombin time; blood cholinesterase activity; urinary protein, sugar, urobilin, and acetone; and, microscopically, for changes in the lungs, liver, kidneys, heart, spleen, and gastric and intestinal mucosa. Experimental and control animals showed no appreciable differences in any of the parameters measured, ie, oral administration of vinyl acetate at 0.01 and 0.1 mg/kg produced no toxic effects in rats. It should be noted, however, that the acid environment of the stomach results in the rather rapid hydrolysis of vinyl acetate to acetic acid and acetaldehyde.

Goeva [23] also determined the time required for acquisition of conditioned reflexes in rats that had previously ingested vinyl acetate at 0.01 or 0.1 mg/kg in their drinking water for 7 months. Rats that ingested vinyl acetate at 0.1 mg/kg exhibited fewer positive responses to the conditioned stimulus and took longer to acquire conditioned reflexes than controls; thus, the author considered this the threshold dose. No significant differences were observed in the acquisition of conditioned reflexes between control and experimental rats fed vinyl acetate at 0.01 mg/kg.

Maltoni and Lefemine [24], in 1974, and Maltoni [25], in 1976, reported the results of a study involving 96 13-week-old Sprague-Dawley rats exposed to vinyl acetate vapor at 2,500 ppm (8,750 mg/cu m). The authors said this concentration appeared to be the "maximum possible dose for a chronic exposure" [24]. The rats were exposed for 4 hours/day, 5 days/week, for 52 weeks and observed for up to 83 weeks after exposure for tumorigenic effects. None of the rats exposed to vinyl acetate developed tumors; however, six controls developed a variety of tumors [25]. No toxic effects from exposure to vinyl acetate were reported, but only 49 of 96 exposed animals (51%)

survived at 26 weeks; 58 of 68 controls (85%) were alive at that time. The authors did not discuss the reasons for this increased mortality in the rats exposed to vinyl acetate.

In 1976, Bartsch et al [26] reported data comparing the mutagenicity of several olefinic compounds on two strains of Salmonella typhimurium, TA1530 and TA100, in a modified Ames test. Vinyl acetate served as the control substance. Vinyl acetate was combined with mouse liver fractions, with and without an NADPH-generating system, and S. typhimurium in a soft agar layer. No mutagenic effect was detectable with vinyl acetate.

Metabolism

Filov [27], in 1959, discussed the fate of inhaled vinyl acetate in rabbits. The concentrations of inspired and expired vinyl acetate were measured polarographically, but the author did not specify the concentrations used. Blood was removed from the carotid artery periodically during exposure for polarographic analysis for vinyl acetate. Filov reported that vinyl acetate tended to remain in the body after it was inhaled; 70% of the vinyl acetate administered was retained, and an equilibrium was established in the first few minutes after exposure began. Filov found no vinyl acetate in the blood, either during or after its inhalation, which suggested to him that vinyl acetate is rapidly metabolized when it enters the body through the lungs.

Filov [27] also suggested that on hydrolysis vinyl acetate yields acetic acid, a normal body constituent, and vinyl alcohol, which should rapidly tautomerize to yield acetaldehyde, another normal body constituent. The rate of vinyl acetate hydrolysis in blood was investigated by determining its hydrolysis products in body fluids and the mode of their formation. Aqueous and physiologic solutions containing 380 μg of vinyl acetate were added to 2 ml samples of rat and human blood. The mixtures were then analyzed spectrophotometrically at various time intervals for acetaldehyde. Amounts of acetaldehyde in 2 ml of blood ranged from 84 μg immediately after addition of vinyl acetate to 174 μg 4.5 minutes after addition. Filov calculated a theoretical yield of 194 μg of acetaldehyde with complete hydrolysis and concluded that vinyl acetate hydrolyzes rapidly in the blood in vitro to produce acetaldehyde.

To identify the sites of hydrolysis of vinyl acetate in the blood, the author added 380 μg of vinyl acetate in physiologic solution to 2 ml samples of human or rat whole blood, plasma, or washed erythrocytes; the mixtures were held for 3 minutes and analyzed for acetaldehyde [27]. Whole human blood produced 175 μg of acetaldehyde, while plasma produced 178 μg, and washed cells produced none. In rat blood, 158-165 μg of acetaldehyde were produced; 162-165 μg were produced in plasma, and washed rat erythrocytes produced about 70 μg of acetaldehyde, showing that hydrolysis occurred primarily due to

plasma proteins and partially due to red cells. Incubation of blood plasmas from humans and rats at 62 C for 1 hour destroyed their abilities to hydrolyze vinyl acetate.

Acetaldehyde was detected in the blood of rats that had inhaled vinyl acetate vapor [27]. Because of this finding, and because vinyl acetate was not detected in the blood, the true concentrations of acetaldehyde were measured in the blood of rats that had inhaled vinyl acetate or acetaldehyde until they assumed what was described as the lateral position; they were then decapitated, and blood was collected for acetaldehyde analysis. The mean concentration of acetaldehyde in whole blood of seven rats inhaling vinyl acetate was 45.8 μg%; for seven rats inhaling acetaldehyde it was 30.4 μg%, indicating that vinyl acetate is hydrolyzed rapidly in the blood, with formation of acetaldehyde.

Rostovskii et al [28] reported that the rate constant for hydrolysis of vinyl acetate in aqueous alkali, 2.15 x 10*5 (* means to the power of), is 370 times as high as that for its acid hydrolysis; the concentrations of acid or alkali studied were not reported. Filov's [27] conclusion, that vinyl acetate is metabolized rapidly by enzymatic hydrolysis to acetaldehyde, is consistent with the information showing that vinyl acetate was rapidly hydrolyzed in aqueous alkali. No information was presented in the Filov paper on the concentration of vinyl acetate inhaled or on the distribution of vinyl acetate and its metabolites in the organism, however.

The existence of nonspecific esterases in mammalian blood is well established [29-31]. It is reasonable to assume that they are the probable basis for the hydrolysis of vinyl acetate observed by Filov [27]. These enzymes have not been characterized with vinyl acetate as a substrate; however, Oi and Satomura [32], in 1967, found that vinyl acetate was the most easily hydrolyzed of the acetic acid esters tested with acetylesterase from the fungus Sclerotinia libertiana. Although Oi and Satomura primarily investigated the structure, function, and inhibition of acetylesterase, their results also were consistent with the finding of Filov [27] that vinyl acetate may be rapidly hydrolyzed enzymatically.

In 1970, Boyland and Chasseaud [33] reported the effect of vinyl acetate on glutathione (GSH) levels in rat liver. Liquid vinyl acetate was administered intraperitoneally (ip) at a dose of 0.8 ml/kg (selected as about one-fourth the published LD50) to female Chester Beatty rats weighing 200-380 g. Forty-four control rats, weighing about the same as the experimental rats, were given arachis oil or 0.1 M orthophosphate buffer. GSH assays were performed on homogenized liver samples from three and two experimental rats killed after 30 minutes and 2 hours, respectively; three control animals were killed after 2 hours for GSH assays.

The mean GSH level in control rat livers was 155 mg/100 g of liver [33]. Mean GSH levels of the experimental rat livers, expressed as percentages of control values, were 77% after 30 minutes and 149% after 2 hours, ie, vinyl

acetate produced an initial depression followed by an apparent elevation of rat liver GSH levels. The authors stated that a previous study [34] had shown that vinyl acetate was a slowly reacting substrate for enzyme-catalyzed conjugation with GSH. Chasseaud [35], in 1973, also reported that vinyl acetate underwent enzyme-catalyzed conjugation with GSH. Boyland and Chasseaud [33] concluded that if a compound is a good substrate for glutathione S-transferases, it will lower glutathione levels soon after administration to rats. Although the experiments of Filov [27] indicate that vinyl acetate is rapidly hydrolyzed in blood, the experiments of Boyland and Chasseaud [33] suggest that, following ip administration, vinyl acetate or its metabolites influence the metabolic activity of the liver.

Tiunova and Rumyantsev [36], in 1975, published the results of a study of the inhalation exposure of male albino rats to vinyl acetate. Changes in the synchrony of the activity cycles of liver alanine-aminotransferase and aspartate-aminotransferase (transaminases) were determined over 5 months. The purpose of the study was to test the authors' hypothesis that the desynchronization of fluctuations in enzyme activity during chronic exposures to a chemical stimulus would result in toxic effects, whereas maintenance of synchronization would result in compensation and adaptation.

Three groups of 10 rats each, weighing 120 g, kept in 0.47-cu m metal chambers, inhaled vinyl acetate at 2.4 ±0.2, 13.2 ±0.6, or 68.0 ±2.1 mg/cu m (0.68, 3.75, or 19.3 ppm) 24 hours/day for 4 months. The concentrations of vinyl acetate in the chambers were determined by gas chromatography. Two unexposed groups, one maintained under colony conditions and one kept in chambers similar to those used for exposures, served as controls. The activities of liver alanine- and aspartate-aminotranferase were determined (presumably in serum samples) in all five groups periodically throughout the 5 months (March-July).

In the colony controls, the activities of the two enzymes fluctuated synchronously; control animals placed in the chamber environment showed an altered rhythm of fluctuation, but the enzyme activities were still highly synchronous [36]. Rank correlation coefficients for the activity of the two enzymes were 0.87 in the colony controls (P=0.01) and 0.81 in the chamber controls (P=0.05). Rats exposed to vinyl acetate at 2.4 mg/cu m also showed a change in the rhythm of fluctuation of enzyme activity, although synchrony was maintained. However, marked and unsynchronized changes developed in the activities of the two enzymes in rats exposed at 13.2 mg/cu m, and especially at 68 mg/cu m; other, undescribed, signs of intoxication were also reported in animals exposed at the latter concentration. Correlation coefficients were not given for the activities of the two enzymes in exposed animals. The authors regarded the modification of the rhythm of fluctuation without loss of synchronization as an indication of adaptive change. They concluded that these biologic rhythms could be used to distinguish adaptive from pathologic changes.

Correlation of Exposure and Effect

Occupational exposure to vinyl acetate occurs primarily via inhalation of the vapor and contact of the liquid or vapor with the skin and eyes. In humans, exposure to vinyl acetate vapor at lower concentrations (68.3-75.6 mg/cu m) has resulted in reversible eye and upper respiratory irritation [4,18]. Dermal exposure to the liquid may result in irritation of the skin [17,18].

Vinyl acetate was lethal to all (presumably six) rats exposed for 2 hours at 28,000 mg/cu m [17], and 4-hour LC50's for exposed rats, guinea pigs, mice, and rabbits ranged from 5,411 to 21,753 mg/cu m [4,14]. No pathologic data were reported for the animals that died from these exposures [4,14,17]. The one beagle exposed to vinyl acetate at 13,388 mg/cu m [4] and all of the rats exposed at 3,500 mg/cu m [17] survived. Upper respiratory difficulty, eye and nose irritation, and increased macrophages in the lungs were noted in rats exposed at 7,000 mg/cu m periodically for 3 weeks [20].

Deese and Joyner [18] found that each of three persons exposed to vinyl acetate at 75.6 mg/cu m experienced hoarseness or coughing and eye irritation; one person became hoarse when exposed at about 15 mg/cu m (14.7).

Ocular effects have also been reported from contact with airborne vinyl acetate. Exposure to vinyl acetate at 840 mg/cu m caused some eye blinking and reddening of the sclerae in a dog [4]; 651 mg/cu m caused eye irritation and tearing in dogs [19]; and 0.5 ml of vinyl acetate caused severe irritation or mild burns when applied to a rabbit's eye [17]. The lowest concentration that caused eye irritation in humans (one of three subjects) was 20.0 mg/cu m [18].

Two reports [17,18] suggested that skin irritation can result in humans after dermal contact with (presumably liquid) vinyl acetate. One report [17] noted that this irritation might result in blisters. Deese and Joyner [18] reported that skin irritation or rash was noted by 3 of 21 vinyl acetate workers. Union Carbide investigators [17] reported that the dermal LD50 in rabbits was greater than 5 ml/kg in a 24-hour covered-skin contact test with liquid vinyl acetate, but they also stated that undiluted vinyl acetate on the skin of the shaved abdomen of a rabbit caused no reaction.

Vinyl acetate has not been characterized as a substrate for mammalian enzymes; however, it was the most easily hydrolyzed of the acetic acid esters tested with acetylesterase from the fungus Sclerotinia libertiana [32]. This was consistent with the finding of Filov [27] that vinyl acetate undergoes rapid enzymatic hydrolysis in vivo, producing end-products that are normal body constituents.

Evidence of possible adverse effects of vinyl acetate on the human nervous system is sparse. Gofmekler [3] found that 0.32 mg/cu m was the minimum concentration of vinyl acetate capable of inducing EEG desynchronization as a

conditioned response; 0.21 mg/cu m did not produce this effect. Goeva [23] found that rats given vinyl acetate in oral doses of 0.1 mg/kg for 7 months exhibited fewer positive responses to a conditioned stimulus and took longer to develop conditioned reflexes than either controls or rats fed 0.01 mg/kg of vinyl acetate. It is questionable whether these particular studies [3,23] demonstrated adverse changes; so it does not now seem appropriate to conclude that vinyl acetate exposure in the work environment at these concentrations will induce biologically significant effects on the nervous system.

The readily identifiable odor of vinyl acetate appears to be one means by which workers are warned of its presence in the work environment. Determinations of the threshold of odor detection have given varying results. For example, Deese and Joyner [18] reported that three of three subjects detected a marked odor of vinyl acetate at 75.6 mg/cu m; a "slight" odor was reported by all of three or four exposed at 14.7 and 1.4 mg/cu m. In an experimental study [4], all of nine volunteers detected the odor of vinyl acetate at 4.6 mg/cu m, but, with one questionable exception, they did not detect its odor at 2.1 mg/cu m. Minimum perceptible (threshold) and maximum imperceptible concentrations for odor detection were determined by Gofmekler [3] to be 1.0 and 0.7 mg/cu m, respectively. These findings indicate that the odor threshold of vinyl acetate probably ranges from 1.0 to 3.3 mg/cu m; their variability probably reflects differences in methods of determination, and possibly in the development by the test subjects of adaptation to the odor. While a noticeable odor of vinyl acetate may indicate a potential hazard, it is not quantitatively reliable.

Olfactory fatigue has also been observed during exposure to vinyl acetate. Vinyl acetate at 68.3-250.3 mg/cu m produced olfactory fatigue in all exposed volunteers [4]. Olfactory fatigue was complete in three of three persons exposed at 68.3 mg/cu m and in one of three at 119.7 mg/cu m after 3-116 minutes; two of three subjects at the latter concentration and four of four at 250.3 mg/cu m experienced partial olfactory fatigue.

The known effects of vinyl acetate on humans and animals are summarized in Tables III-2 and III-3.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No specific data on the teratogenic or reproductive effects of vinyl acetate were found in the available literature. No mutagenic effects were detectable in S. typhimurium strains TA1530 and TA100 exposed to vinyl acetate [26]. In the single study [24,25] on its carcinogenicity, 96 rats were exposed to vinyl acetate at 8,750 mg/cu m for 1 year and observed until the end of their lives. No evidence was found that vinyl acetate influenced tumor incidence. Several compounds having structures similar to that of vinyl acetate, eg, vinyl chloride, vinyl bromide, vinylidene chloride, vinyl cyanide (acrylonitrile), and vinyl carbamate, have been shown to be carcinogenic or mutagenic [37-48], but there is no evidence to suggest that vinyl acetate

induces similar irreversible processes. No other reports on the carcinogenic or mutagenic potential of vinyl acetate in humans or animals were found in the literature. Vinyl acetate administered ip to rats at a dose of 0.8 ml/kg reduced liver glutathione levels initially [33]. This suggests that a fraction of the dose reached the liver and disturbed glutathione metabolism, perhaps by acting as a substrate for glutathione conjugase. No evidence from either in vitro or in vivo experiments indicates that an oxirane intermediate plays any role in vinyl acetate metabolism, although intermediates containing oxirane rings seem to be important in the metabolism of vinyl halides [44]. Without further research, these aspects of vinyl acetate toxicity cannot be settled.

TABLE III-2

SUMMARY OF EFFECTS OF VINYL ACETATE EXPOSURE ON HUMANS

No. of Persons	Type of Work	Exposure*		Effects	Reference
		Concentration (mg/cu m)	Duration		
4	Volunteers	68.3-250.3	0.5-4 hr	Olfactory fatigue, and/or upper respiratory tract irritation	4
21	Production	ND**-172.6; mean, 30.1	Mean of 15.2 yr	Upper respiratory tract or eye irritation in 6	18
3	Production and sampling	75.6	Short-term	Severe eye irritation, slight cough, hoarseness in 3, marked odor	18
4	"	19.9-23.8	"	Slight eye irritation in 1	18
5	"	14.7-19.9	"	Hoarseness in 1	18
-	"	1.4-17.2	"	No effects	16
3	"	1.4	"	Slight odor detected by 3	18
9	Volunteers	4.6	2 min	Odor detected by 9	4
9	"	2.1	"	Odor detected by 1	4
77	"	1.0	2-3 hr	Threshold of olfactory perception	3
15	"	0.8	"	Threshold of light sensitivity of eye	3
2	"	0.3	"	Threshold of conditioned-reflex desynchronization of brain electrical activity	3

*All exposures were to vinyl acetate vapor.
**ND=not detectable

TABLE III-3

SUMMARY OF EFFECTS OF VINYL ACETATE EXPOSURE ON ANIMALS

Route of Exposure	Species	Exposure		Effects	Reference
		Concentration/ Dose	Length/ Frequency		
Inhalation	Rat	28,000 mg/cu m	2 hr	Death of all	17
"	"	14,000 mg/cu m	"	Death of half	17
"	"	"	4 hr	Death of about half	14
"	"	13,955 mg/cu m	"	Death of half	4
"	"	8,750 mg/cu m	1 yr	No tumors observed by 135 wk	24
"	"	7,000 mg/cu m	3 wk	Eye and nose irritation, low weight gain, increased macrophages in lungs	20
"	"	3,500 mg/cu m	4 hr	No deaths	17
"	"	2,205 mg/cu m	3 wk	Decreased weight gain in females	20
"	"	875 mg/cu m	"	"	20
"	"	350 mg/cu m	"	No effects	20
"	Rabbit	8,789 mg/cu m	4 hr	Death of half	4
"	"	500 mg/cu m	40 min	Changes in reflex strength and development time	22
"	"	250 mg/cu m	"	"	22
"	"	125 mg/cu m	"	No effects	22

TABLE III-3 (CONTINUED)

SUMMARY OF EFFECTS OF VINYL ACETATE EXPOSURE ON ANIMALS

Route of Exposure	Species	Exposure		Effects	Reference
		Concentration/ Dose	Length/ Frequency		
Inhalation	Rabbit	100 mg/cu m	37 min	Conditioned reflexes impaired	22
"	"	25 mg/cu m	"	No effect	22
"	Mouse	5,411 mg/cu m	4 hr	Death of half	4
"	Guinea pig	21,753 mg/cu m	"	"	4
"	Dog	13,388 mg/cu m	"	Nonlethal	4
"	"	840 mg/cu m	"	Blinking, reddened sclera	4
"	"	651 mg/cu m	1 wk	Eye irritation, lacrimation	19
"	"	371 mg/cu m	4 hr	No effect	4
Oral	Rat	2,920 mg/kg	Once	Death of half	17
"	"	0.1 mg/kg in drinking water	7 mo	Slowed formation of conditioned reflexes; no other effects	23
"	"	0.01 mg/kg in drinking water	"	Normal acquisition of conditioned reflexes	23
"	Mouse	300 mg/kg/d, 6,000 mg/kg total	3 wk	Death in 2 of 20	23
"	"	1,600 mg/kg*	Once	Death in 8 of 18	23

TABLE III-3 (CONTINUED)

SUMMARY OF EFFECTS OF VINYL ACETATE EXPOSURE ON ANIMALS

Route of Exposure	Species	Exposure		Effects	Reference
		Concentration/ Dose	Length/ Frequency		
Oral	Mouse	1,613 mg/kg	Once	Death of half	23
Ocular	Rabbit	0.5 ml	"	Severe irritation, mild corneal burns	17
Dermal	"	>5 ml/kg	24 hr	Death of half	17

*Administered to survivors of 6,000 mg/kg experiment