DANGEROUS PROPERTIES OF INDUSTRIAL MATERIALS

REPORT

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VNR INFORMATION SERVICES

K-1711-(100)

CHEMICAL REVIEW: VINYL CHLORIDE

CAS RN 75-01-4
NIOSH # KU 9625000
SIC Code 2813

See N.I. Sax. 1984. *Dangerous Properties of Industrial Materials*, 6th ed. New York: Van Nostrand Reinhold, p. 2728.

SYNS Chloroethene (9CI); chloroethylene (8CI); chlorethene; chlorethylene; chloroethene; chlorethylene; chlorure de vinyle (French); cloruro di vinile (Italian); ethylene monochloride; EXON 470; monochloroethene; monochloroethylene; trovidur; vinyl chloride monomer; vinyl chloride, inhibited; vinyl C monomer; vinylchlorid (German); VC; VCM; winylu chlorek (Polish).

STRUCTURAL FORMULA

$ClCH=CH_2$

mf C_2H_3Cl
mw 62.50

SPECIES IN MIXTURE 99.42% pure.

COMMON USES Approximately 96% is used in production of vinyl chloride homopolymer and copolymer resins. It is also used in production of methyl chloroform and as a comonomer with vinylidene chloride in the production of resins. Polyvinyl chloride resins are used in production of plastic piping and conduit. Other uses are in floor covering, consumer goods, electrical applications, and transport applications. Vinyl chloride has been used as a refrigerant, extraction solvent, and aerosol propellant. (R-63)

STORAGE AND HANDLING INFORMATION

TRANSPORT, RAIL (%) 90.0

TRANSPORT, BARGE (%) 2.0.

TRANSPORT, PIPE (%) 8.0

CONTAINERS Pressure cylinders, tank cars, tank barges.

GENERAL STORAGE PROCEDURE Protect against physical damage. Outside or detached storage is preferable. Inside storage should be in a fire resistive storage room, provided with adequate ventilation and free of sources of ignition and heat.

GENERAL HANDLING PROCEDURE Guard against all sources of ignition.

ADDITIVE (%) Phenol.

STANDARD CODES NFPA, 2,4T,1; ICC, flammable gas, red gas label, 300 lbs in an outside container; USCG, liquefied flammable gas; IATA (inhibited) flammable gas, red label, not acceptable passenger, 140 kg cargo, (inhibited) flammable gas, not acceptable.

PRODUCTION

Manufacturer	*Location*	*Year/Volume*	*Ref*
Nine companies	U.S.	1977/2,580 mill kg	R-63
Dow Chemical Co.	Midland, MI		R-63
The B. F. Goodrich Co.	Cleveland, OH		R-63
PPG Industries, Inc.	Guayanilla, PR		R-63
Allied Chemical Corp.	Moundsville, WV		R-47
American Chemical Corp.	Watson, CA		R-47
Cumberland Chemical Corp.	Calvert City, KY Charleston, WV		R-47
Dow Chemical Corp.	Freeport, TX Plaquemine, LA		R-47
Ethyl Corp.	Baton Rouge, LA Houston, TX		R-47
U.S. Tire and Rubber Co.	Ashtabula, OH		R-47
U.S. Rubber Co.	Painesville, OH		R-47
Goodyear Tire and Rubber Co.	Niagara Falls, NY		R-47
Monchem, Inc.	Geisman, LA		R-47
Monsanto Co.	Texas City, TX		R-47
Tenneco Chemical Co.	Houston, TX		R-47
Union Carbide Corp., Chemicals Div.	Texas City, TX		R-47
Goodrich Chemical Co.	Louisville, KY Calvert City, KY Niagara Falls, NY	1969/ 3,735,942 lb (sales measured by U.S. Tariff Comm.	R-70 2,358,741 lb)

HAZARDS Flammable gas. (R-1).Severe explosion risk @ 30,000 ppm. (R-7) When heated to decomp. it emits highly tox fumes of phosgene; can react vigorously with oxidizing materials. (R-9)

WATER: AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA EPA recommends an ambient water conc of zero for maximum protection of human health from potential carcinogenic effects due to exposure to vinyl chloride through ingestion of contaminated water and contaminated aquatic organisms. The levels that may result in incremental increase of cancer risk over the lifetime are estimated at 1E-5, 1E-6, and 1E-7. The corresponding recommended criteria are 20 μg/L, 2.0 μg/L, and 0.2 μg/L. (R-11).

AIR: AGENCY RESTRICTIONS, STANDARDS OR CRITERIA M.E.C. equals 150 mg/m^3 if emission > 3 kg/H. (R-6) Clean Air Act designates that concs of vinyl chloride in all exhaust gases discharged to the atmosphere during ethylene dichloride purification shall not exceed 10 ppm except as provided for in 40 CFR 61.65(a). (R-107) Clean Air Act emission standards for vinyl chloride-producing plants are specified. (R-108)

FOOD: AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA U.S. Treasury Dept. has banned the use of vinyl chloride polymers in packaging of alcoholic beverages. (R-63)

TRANSPORTATION: AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA HMTA designates vinyl chloride as a hazardous material for the purpose of transportation in commerce. Hazard class is flammable gas. A flammable gas label is required. Material is forbidden for transport on passenger-carrying aircraft or railcar. Maximum net quantity permitted in one package is 300 lb for cargo-only aircraft and package must bear a cargo aircraft only label. Material may be stowed on or below deck and away from living quarters on cargo vessels. For passenger vessels, the material is limited to quantities specified in 49 CFR 173.304 (charging of cylinders with liquefied compressed gas), 49 CFR 173.314 (requirements for compressed gases in tank cars), and 49 CFR 173.315 (compressed gases in cargo tanks and portable tank containers) and is also subject to the same stowage requirements as for a cargo vessel for the same material. (R-101) CERCLA designates vinyl chloride waste and heavy ends from the distillation of vinyl chloride in vinyl chloride monomer production as hazardous materials under HMTA. (R-101) WA sections 307(a) and 112 designate vinyl chloride as a hazardous material under HMTA. (R-101) HMTA also designates inhibited vinyl chloride as an optional hazardous material for international shipment. IMCO code is flammable gases and DOT class is flammable gas. A flammable gas label is required. Material may be stowed on or below deck and away from living quarters on cargo vessels but must be stowed on deck and away from living quarters for passenger vessels. (R-102)

OCCUPATIONAL EXPOSURE: AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA OSHA standard for vinyl chloride is 1 ppm averaged over an 8-H period with a short-term ceiling exposure level of 5 ppm averaged over any period of time not to exceed 15 M. No employees may be exposed to vinyl chloride by direct contact with liquid vinyl chloride. (R-109) ACGIH recommends a TLV of 5 ppm. (R-106) The NIOSH recommendation for occupational health standard environmental exposure limit is the minimum detectable level averaged over a 10-H work period with a short-term ceiling exposure of 1 ppm averaged over any period of time not to exceed 15 M. (R-110) Regulated by OSHA as a recognized carcinogen, Appendix Ala. (R-111)

DISPOSAL: AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA RCRA 3001–3004: subjects the heavy ends from the distillation of vinyl dichloride in vinyl chloride monomer production to handling and report/recordkeeping requirements. (R-103) The Act also subjects the waste product, off-specification batches, and spill residues in excess of 1,000 kg to handling and report/recordkeeping requirements. (R-104) The Act also designates vinyl chloride as an Appendix VIII chemical. (R-105)

OTHER AGENCY RESTRICTIONS, STANDARDS, OR CRITERIA OSHA prohibits the use of vinyl chloride in aerosol sprays. (R-7)

STATE Gas. (R-63)

COLOR Colorless. (R-6)

ODOR Mild, sweetish. (R-6)

AUTOIGNITION POINT (C) 472.22.

EXPLOSIVENESS Reactive at high temp or pressure. Polymerizes with evolution of heat, in presence of air, oxygen, sunlight, or heat.

EXPLOSION LIMITS (%) Lower, 4; upper, 22. (R-47)

MELTING CHARACTERISTICS −153.8 C (caution, flash p −78 C). (MERCK* 83/WIN)

■ AQUEOUS SOLUBILITY

Solubility (ppm)	*Temp (C)*	*Meas/Est*	*Method*	*Ref*
60	10			R-118
TEST CONDITIONS No method or test conditions reported.				
1.1	25			R-119
TEST CONDITIONS No method or test conditions reported.				

BOILING POINT (C) −13.37 (ignites).

SOLUBILITY CHARACTERISTICS Slightly soluble.

DENSITY 20/4 C = 0.9106. (R-63) 250/25 C = 0.908. (R-71)

SOLUBILITY: OTHER SOLVENTS Soluble in ethanol; very soluble in ether, carbon tetrachloride, and benzene. (R-63)

FLAMMABILITY Very, flamm. Extreme hazard–do not enter.

FLAMMABILITY LIMIT (%), LOWER 3.6.

FLAMMABILITY LIMIT (%), UPPER 33.

CONVERSION FACTOR: 1 ppm in air = 2.6 mg/m^3. (R-63) 1 mg/L = 391 ppm. (R-112)

N-OCTANOL/WATER COEFFICIENT Log/kow 1.38, est, substituent constant estimation. (R-11)

ODOR THRESHOLD-AIR Air = 25,000 ppm; slight odor @ 4,000 ppm. Odor index @ 20, C = 100. (R-6)

OTHER PHYSICAL/CHEMICAL PROPERTIES Polymerizes in light or in presence of catalyst; on combustion it degrades to HCl, CO, CO_2 with traces of phosgene; on treatment with strong alkalis at high temps it loses HCl. (R-63) Vapor density = 2.2 (air = 1) (R-63) Vinyl chloride is a nonreactive gas that has no tendency to escape. When it escapes, high concs may accumulate and are very dangerous to life. (R-114)

CHEMICAL SYNTHESIS METHODS Direct chlorination of ethylene to form ethylene dichloride (EDC) and subsequent purification. Vinyl chloride is produced by thermal cracking of EDC. (R-70) Vinyl chloride gas

■ VAPOR PRESSURE

Vapor Pressure (mm Hg)	*Temp (C)*	*Meas/Est*	*Method*	*Ref*
2,530	20			R-63
TEST CONDITIONS No method or test conditions reported.				
2,320	20			R-118
TEST CONDITIONS No method or test conditions reported.				
2,660	25			R-120
TEST CONDITIONS No method or test conditions reported.				
2,320	20			R-121
TEST CONDITIONS No method or test conditions reported.				

■ ANIMAL TOXICITY TEXT

Value	*Time*	*Species*	*Param*	*Route*	*Ref*
20 ppm		Hmn	TCLo	Inh	JWPFA5 0017
500		Rat	LD50	Orl	TXAPA9 0031

and vapor is produced during the production of poly vinyl chloride. (R-113)

TOXIC COMBUSTION PRODUCT HCl, phosgene, CO; hazardous, employ self-contained breathing apparatus.

EXTINGUISHING METHOD Stop flow of gas. Use water to keep containers cool. Do not extinguish unless necessary to effect an immediate shutoff of flow. Dry chemical and CO_2 can be used to extinguish vinyl chloride fires.

PERSISTENCY Polymerizes in presence of air, oxygen, sunlight, or heat. Volatilizes and will leave water quite soon.

TOXICITY

CARCINOGENICITY Studies indicate positive development from occupational exposure.

INHALATION LIMIT (Text) *Regulations:* OSHA carcinogen. (29CFR*1910) OSHA PEL (TWA) 1 ppm. (29CFR*1910) OSHA peak 5 ppm/15 M. (29CFR*1910) *Recommendations:* NIOSH ceiling 2.55 mg/m³ 15

■ ACUTE TOXICITY: TERRESTRIAL LIFE—INHALATION LC50

Species	*LC50 (mg/m³)*	*Duration (H)*	*Ref*
Mus	305,500	2	R-11
Mus	68,550	2	R-114

TEST CONDITIONS A total of 536 white mice were tested in Pravdin-type gas chambers. Ten concs were used.

RESULTS The LC50 was found, using the Behren's method, to be 27,419 ppm (1 ppm = 2.5 mg/m³ under test conditions). The LC10 was equal to 139,975 ppm.

Rat	119,100	2	R-114

TEST CONDITIONS A total of 70 rats were tested @ 5 concs of VC in a Pravdin-type gas chamber.

RESULTS The LC50 was determined, using Behren's method, to be 47,640 ppm (1 ppm = 2.5 mg/m³ under test conditions). The LC100 was equal to 208,425 ppm.

Gpg	590,000	2	R-114

TEST CONDITIONS A total of 30 guinea pigs were tested @ 5 concs of VC in a Pravdin-type gas chamber.

RESULTS The LC50 was determined, using Behren's method, to be 236,215 ppm (1 ppm = 2.5 mg/m³ under test conditions). The LC100 was equal to 277,900 ppm.

Rbt	590,000	2	R-114

TEST CONDITIONS A total of 20 rabbits were tested @ 5 concs of vinyl chloride in Pravdin-type gas chambers.

RESULTS The LC50 was determined, using Behren's method, to be 236,215 ppm (1 ppm = 2.5 mg/m³ under test conditions). The LC10 was equal to 277,900 ppm.

Mus	293,750	2	R-117
Rat	390,000	2	R-117
Gpg	595,000	2	R-117
Rbt	595,000	2	R-117

TEST CONDITIONS The experiments were carried out in a 580-L chamber of the Pravdin type. The animals were exposed to various concs of vinyl chloride for 2 H. After the animals were placed in the chamber, the gas was introduced at the beginning at the lower part of the chamber without any ventilation. The gas was measured volumetrically. A total of 536 mice, 70 rats, 30 guinea pigs, and 20 rabbits were used. LD50 values were calculated according to the Behrens method.

M: 1 ppm/15 M. (CRSOE* PB-246619/NIOSH) ACGIH human carcinogen. (TLVADM 83/ACGIH) ACGIH TLV (TWA) 10 mg/m^3 5 ppm. (TLVADM 83/ACGIH)

DIRECT CONTACT Acts as refrigerant under prolonged contact and as such can cause skin burns.

GENERAL SENSATION Sweet-smelling gas. Proposed limits will be 1 ppm for 8-H working day, 5 ppm for 15-M average; may be anesthetic above 500 ppm. Handling of uninhibited material has caused circulatory and bone changes. (30ZNA5 0001)

PERSONAL SAFETY PRECAUTIONS Gas-tight goggles and breathing apparatus is required in fire areas or where closed environment or poor ventilation causes high vapor conc. Eye goggles and impervious outerwear are recommended for areas where liquid vinyl chloride may be encountered.

ACUTE HAZARD LEVEL Irritant. Moderately tox when inhaled. Should cause no problem in water. Emits tox vapors when heated to decomp.

CHRONIC HAZARD LEVEL Chronic exposure has shown liver injury in rats and rabbits. Chronic irritant.

DEGREE OF HAZARD TO PUBLIC HEALTH Irritant. Moderately tox with inhalation. Emits highly tox vapors when heated to decomp.

ACUTE TOXICITY: TERRESTRIAL LIFE—STUDIES ■ For mice, the smallest conc that is fatal in 10 M is 10–12 mmol/L (about 25–30% volume). The smallest narcotic conc is about 3.5 to 5 mmol/L (8–12% volume). Death occurs due to respiratory paralysis with resultant heart arrest. At a conc of 7 mmol in air, it anesthetizes rabbits and dogs within a minute. Recovery is rapid with no apparent adverse effects even after prolonged anesthetization. (R-115) ■ Single exposure of guinea pigs to vinyl chloride gas @ 10 (250 mg/L) in air resulted in narcosis and death within 30–60 M. Lower concs resulted in ataxia and narcosis. Pathological examination revealed congestion and edema of the lungs and hyperima of the kidneys and liver. (R-11) ■ Vinyl chloride was considered for use as an anesthetic because of its narcotic properties and low acute ihl tox, however studies with dogs found vinyl chloride caused cardiac irregularities at anesthetic concs. (R-106) ■ EEGs in rats were altered following oral administration of vinyl chloride and the alteration varied with sex. Vinyl chloride @ 45 and 135 mg/kg altered learning ability. The compound @ 12 mg/kg had immunosuppressant activity in rabbits. (R-36) ■ Guinea pigs exposed to 5–7% conc of vinyl chloride lived only 1 H following exposure; exposure to 2.5% resulted in an 8-H survival time following exposure. Exposure to 1.5% for 1 H or to 0.5% for 8 H had no effect. (R-114) ■ Five mice, 5 rats, and 5 guinea pigs were exposed to concs @ 10%, 20%, and 30% for 30 M. At 10% concs, the animals became agitated, then had unconscious movements, and some fell, in a state of narcosis. At 20%, the animals' symptoms were salivary secretion, narcosis, and respiratory failure. At 30%, all these symptoms occurred faster. Dead animals showed lung, hepatic, and renal congestion, lung edema, and hepatic degeneration. ■ (R-114) Mice, rats, guinea pigs, and rabbits were tested to determine acute tox levels, symptoms of tox, and the pathological effect on the organs. Exposure was for 2 H in a gas chamber. Animals exposed to vinyl chloride gas without homogenization (no ventilation) died at concs 3 times lower than when the gas was stirred up continuously. The most common symptom in all animals was a state of narcosis, usually attained during the first hour. Narcosis proceeded from excitement to tranquility to falling down. These symptoms included muscular contractions, tanico-clonic convulsions, respiratory disturbances, bradypnea, Cheyne-Stokes type respiration, and finally death by respiratory failure. Circulatory disturbances were also noted. Animals that survived the 2-H exposure rapidly regained a normal appearance. Autopsy revealed congestion of the lungs, liver, kidneys, brain, and spleen. Some animals also showed pulmonary edema, marmorated liver, and slight tumefaction of the kidneys. (R-114)

ACUTE TOXICITY: HUMAN STUDIES ■ Two Canadian workers died following acute exposure to vinyl chloride gas; autopsies discovered congestion of the liver, spleen, and kidneys. (R-11) ■ Workers exposed to vinyl chloride reported symptoms of euphoria and intoxication. Irritation of the respiratory tract, chronic bronchitis, headache, irritability, poor memory, and weight loss were also noted. (R-11) ■ A 3-M exposure to 2.5% vinyl chloride produced dizziness and disorientation in humans. (R-113)

CARCINOGENICITY: IARC DETERMINATION VC is a human carcinogen. VC is carcinogenic in mice, rats, and hamsters by oral and inhalation exposure. (R-63)

CARCINOGENICITY: POSITIVE REFERENCES R-12, R-31, R-41, R-63, R-85, R-86, R-89, R-90, R-93, R-97.

CARCINOGENICITY: OTHER STUDIES ■ This study investigated the possibility that changes in nuclear size of HeLa S3 cells, exposed in vitro, might be used as

(Continued on page 29)

■ ACUTE TOXICITY: AQUATIC LIFE—FRESHWATER STUDIES

Species	*Duration (H)*	*Effect Level (mg/L)*	*Ref*
Northern pike (*Esox lucius*)	240	388	R-67

RESULTS The 10-D LD100 to Northern Pike (*Esox lucius*) was 388 ppm. Fifteen fish were exposed to 388 ppm in 15–20 gal tanks. Within 10 D all had died. First indication of tox was loss of scales. This phenomenon was followed by the appearance of a gray-white ulcerated area surrounded by indurated borders. A lack of neutrophilic response was also noted. Twenty fish from uncontaminated Illinois Benedictine Lake were used as controls. After 120 D, 1 fish died due to mechanical injury. (R-67)

■ SUBACUTE-CHRONIC EFFECTS: TERRESTRIAL LIFE

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
Rat	Ihl	30,000 ppm	4 H/D, 5 D/W for 12 mos	R-12

TEST CONDITIONS Twenty-five rats were sacrificed in lots at 20-D intervals after 12 mos of exposure.

RESULTS After 10 mos, some animals showed a decrease in weight and aggressiveness to outside stimuli and disturbed equilibrium. Thirteen animals died from cardiorespiratory complications. Two animals died from hematoperitoneum. Most of the animals showed pathological degeneration of the brain, liver, kidneys, and thyroid. Six rats showed histopathological alterations of the skeleton. Degeneration of the skeleton and connective tissue was similar to that observed in human acroosteolysis of the hands.

Rbt	Ihl	9–10 mg/L	4 H/D for 5.5 mos	R-17

RESULTS After 5 1/2 mos of exposure to vinyl chloride, altered beta-waves (frequency > 80 Hz) appeared on the electroencephalogram from the anterior hypothalmic nuclei, and the potentials of the anterior and posterior nuclei increased by 18–30% and 70–85%, respectively, over control values. Concommitant changes in the cardiovascular system (bradycardia, arrhythmia, decreased voltage of electrocardiogram peaks or whole complexes, decreased duration of systole, increased arterial pressure, and retarded blood flow) also occurred. The functional changes in the anterior and posterior hypothalmic nuclei may have a role in the pathogenesis of tox angioneurosis due to vinyl chloride.

Rat	Ihl	0.03–5 mos 0.04 mg/L	5 mos	R-18

RESULTS Chronic exposure of rats to vinyl chloride disrupted cardiac work rhythm, induced bradycardia and arrhythmia, and reduced the relative duration of I-II and T-II sound intervals. The relative duration of the Q-T complex did not change significantly. Within 15 D after termination of exposure, the rat cardiac activity rhythm returned to normal, but the duration of I-II and T-II sound intervals remained below the initial levels for another 15 D. Authors concluded that the maximal permissible conc of vinyl chloride is significantly less than 0.03 mg/L.

Rat	Ihl	5,000 ppm	7 H/D, 5 D/W for 52 W	R-23

■ SUBACUTE-CHRONIC EFFECTS: TERRESTRIAL LIFE (*Continued*)

Species	*Route*	*Dose*	*Dosing Schedule*	*Ref*
	TEST CONDITIONS 80 male and female Wistar rats were used. A control group was also used.		RESULTS After 4, 13, 26, and 52 W, 10 rats/sex/group were sacrificed and subjected to extensive examinations as to growth, mortality, hematology, clinical chemistry, and organ weights. Slight growth retardation throughout the experimental period and high mortality in the second half of the study were observed in the vinyl chloride-exposed animals. Some of the hematological parameters and biochemical blood parameters were influenced by vinyl chloride after an experimental period of 52 W only. Blood clotting time was shorter in rats exposed to vinyl chloride monomer (VCM) than in the controls. There were minor indications of increased potassium contents of the blood serum in VCM-exposed animals during the first half of the experimental period. The kidneys were adversely affected by VCM as indicated by increased blood urea nitrogen levels and relative kidney weights. After 52 W, increased weights of heart and spleen and slight signs of anemia were noticed in VCM-exposed rats.	
Mus	NG	NG	Up to 6 mos	R-24
			RESULTS Electron microscopic studies of liver of mice exposed to vinyl chloride monomer for up to 6 mos revealed changes mainly in and around sinusoids and in sinusoidal lining cells, particularly with only mild alterations of hepatocytes. The angiosarcomas that developed in some mice arose from the sinusoidal lining cells.	
Rat	Ihl	5,000 ppm	7 H/D, 5 D/W for 52 W	R-31
	TEST CONDITIONS After exposure to 0 ppm (control) or 5,000 ppm vinyl chloride, 62 male and 62 female Wistar rats were sacrificed (at 4, 13, 26, and 52 W) and subjected to extensive examinations. A description of the morphological changes observed in respiratory tract, ceruminous glands, brain, kidney, heart, and spleen were noted.		RESULTS The vinyl chloride effects included increased degree of tubular nephrosis, mild focal degeneration of the myocardia, and increased hemopoietic activity in the spleen.	
Mus, rat	Ihl	50, 250, or 1,000 ppm	6 H/D, 5 D/W for up to 1 Y	R-41
			RESULTS Exposure of 2-mo-old albino CD-1 mice (36 of each sex) to 1,000 ppm of vinyl chloride (VC) caused some acute deaths with tox hepatitis and marked tubular necrosis of the renal cortex. Starting with the 6th mo, mice exposed to 50 or 250 ppm VC became lethargic, lost weight quickly, and died. Only a few mice exposed to 50 ppm survived for 12 mos. Pulmonary macrophage count was elevated in some mice. In rats (groups of 36 male and 36 female CD) exposure to 1,000 ppm VC sightly depressed body weight of the females. Exposures of 250 or 1,000 ppm caused a number of deaths.	
hat	Ihl	50, 500, and 20,000 ppm	10 mos	R-45
	TEST CONDITIONS The activity of microsomal cytochrome P-450 onooxygenase and ultrastructure of the liver were studied in rats exposed dynamically to 50, 500, and 20,000 ppm VC over 10 mos.		RESULTS After 1 and 3 mos of exposure to 500 and 20,000 ppm VC, the level of cytochrome P-450 was slightly lower than in the control animals. Upon continuation of exposure, it was restored to the original level accompanied by a slight increase of activity of aniline-p-hydroxylase. Liver enlargement, developed in the course of exposure, was accompanied by ultrastructural alterations begin-	

■ SUBACUTE-CHRONIC EFFECTS: TERRESTRIAL LIFE (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
			ning in the 3rd mo of exposure to all concs of VC. Development of hepatic alterations (hypertrophy of smooth and rough endoplasmic reticulum, swelling of mitochondria, accumulation of lipid droplets, focal cytoplasmic degradation) also occurred.	
Rat	Ihl	50, 500, and 20,000 ppm	5 H/D, 5 D/W for 10 mos	R-48
	TEST CONDITIONS 340 male Wistar rats, 180–220 g, were exposed to vinyl chloride (VC) at the concs of 50, 500, and 20,000 ppm, 5 H/D, 5 D/W for 10 mos.		RESULTS Morphological lesions in the liver and testes detected by light and electron microscope intensified with the duration of exposure. After 10 mos of treatment, the difference from the controls was statistically signficant ($p < 0.05$) at all levels of vinyl chloride exposure. At that time, the relative weights of spleen, liver, kidneys, heart, and testes were significantly elevated in some groups of the exposed animals, the difference being most pronounced for the spleen and dose-related for the liver and kidneys. The no-tox-effect level of VC could not be established. The lowest conc of VC (50 ppm) still caused some tox effects in rats, including slight hematological and biochemical changes and fluctuations, and also ultrastructural changes in hepatocytes and a tendency for an increased incidence of histological liver alterations. Statistical analysis involved the Students *t* test.	
Dog	Ihl	10%, 20% volume in air	7 times/3 W, for 3 H each exposure	R-112
			RESULTS At 10% volume dogs showed no considerable changes in liver and kidneys. At 20% volume, respiratory paralysis, strong flow of saliva, and, after narcosis, vomiting occurred.	

■ SUBACUTE-CHRONIC EFFECTS: HUMAN STUDIES

Route	*Doses*	*Dosing Schedule*	*Ref*
NG	NG	Occupational	R-87
	TEST CONDITIONS An epidemiological study was performed covering 5,011 employees with 21,510 man-years experience in various phases of VC and PVC manufacturing in 32 plants throughout the U.S. and Canada.	RESULTS The total number of definitive cases of acroosteolysis (AOL) was 25; 16 other individuals were under suspicion. This condition is clearly associated with the hand cleaning of polymerizers. Workers engaged in other phases of VC or PVC manufacturing do not appear to be at risk of developing AOL. AOL appears to be a systemic rather than local disease. Currently neither the etiological agent nor its portal of entry is known.	
NG	NG	Occupational	R-88
		RESULTS Two cases of acroosteolysis (AOL) occurring in men engaged in the polymerization of VC are described. The bones affected were the terminal phalanges of the fingers and the sacroiliac joints, but in one case the patella and in the other the phalanges of the feet were involved. The condition was accompanied by Raynaud's phenomenon and skin lesions.	
NG	NG	Occupational	R-91

■ SUBACUTE-CHRONIC EFFECTS: HUMAN STUDIES (*Continued*)

Route	*Dose*	*Dosing Schedule*	*Ref*
	TEST CONDITIONS The cohort of workers employed in a Swedish VC/PVC plant since its start in the early 1940s has been followed for mortality and cancer morbidity patterns. Only 21 of the 771 persons could not be traced. Difficulties in establishing exposure levels at different work areas in the past makes an evaluation of dose-effect relationships impossible.	RESULTS A four- to five-fold excess of pancreas/liver tumors was found, including two cases later classified as angiosarcomas of the liver. The number of brain tumors and suicide do not deviate significantly from the expected. Cardiovascular and cerebrovascular diseases, on the other hand, differ significantly from the expected.	
Ihl, dermal	NG	NG	R-8
		RESULTS VC is a skin irritant, and contact with liquid may cause frostbite upon evaporation. VC gas depresses the CNS. Lightheadedness, some nausea, and dulling of visual and auditory responses may develop in acute exposures. Chronic exposure of workers may result in acroosteolysis, Raynaud's phenomenon, and sclerodermatus skin changes. Chronic exposure may also cause hepatic damage.	
NG	NG	Occupational	R-11
		RESULTS There are numerous clinical indications that chronic exposure to VC is tox to humans. Hepatitis-like liver changes, angioneurosis of a spastic character, Raynaud's syndrome, scleroderma-like skin changes, lytic lesions of the terminal phalanges in hand and feet, and pseudoclubbing of the fingers have been reported in many workers in the U.S. and Europe. The latter conditions had been termed occupational acroosteolysis. Other long-term effects include functional disturbances of the CNS with adrenergic sensory polyneuritis, thrombocytopenia, splenomegaly, liver malfunction with marked fibrosis in the portal areas, and pulmonary insufficiency with restrictive changes in the lungs.	
NG	NG	Occupational for 1 Y	R-11
		RESULTS Workers exposed to VC for 1 Y showed a decrease of peroxidase, indophenoloxidase, and glutathione levels. Serum levels of gammaglutamic transpeptidase in exposed workers appear to be the best clinical parameter for detecting abnormalities. Alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, and bilirubin levels were also increased in many cases. Other data are also available that suggest that VC disease is an immune-complex disorder. Immunological and immuno-chemical investigations of workers with the syndrome showed the presence of circulating immune complexes in 19 of 28 patients.	
Ihl	NG	NG	R-43
		RESULTS Liver function tests showed no difference between exposed workers and controls not exposed to VC and no cases of angiosarcoma or florid-VC induced liver disease. However, of 422 exposed workers, 4 had enlarged spleens, compared with none for 202 controls. Liver biopsies of selected cases showed no significant pathological changes, although there was a minimal increase in portal tract and sinusoidal fibrosis in exposed workers.	

■ SUBACUTE-CHRONIC EFFECTS: HUMAN STUDIES (*Continued*)

Route	*Dose*	*Dosing Schedule*	*Ref*
NG	NG	Occupational	R-44

RESULTS Capillary microscopy study showed that 10% or more of workers exposed to VC have capillary abnormalities that were not found in workers without exposure to VC.

Ihl	NG	NG	R-61

RESULTS A cytological examination of the sputa of nearly 4,000 Italian workers in the VC/PVC industry has shown a high incidence of changes in bronchial epithelia, among which squamous dysplasia and atypical adenomatious proliferation were observed.

CARCINOGENICITY: ANIMAL STUDIES

Species	*Route*	*Dose*	*Dosing Schedule*	*Ref*
Rat	Ihl	0 or 5,000 ppm	7 H/D, 5 D/W for 52 W	R-31

TEST CONDITIONS After exposure to 0 ppm (control) or 5,000 ppm vinyl chloride, 2 male and 62 female Wistar rats were sacrificed (at 4, 13, 26, and 52 W) and subjected to extensive examinations. A description of the morphological changes observed in respiratory tract, ceruminous glands, brain, kidney, heart, and spleen were noted.

RESULTS Primary tumors were found in the brain (ependymona), lungs (papillary adenoma and mesenchymal types of tumors), ceruminous glands (mainly keratinized squamous cell tumors), and nasal cavity (carcinomas of the olfactory epithelium, carcino-sarcoma, esthesioneuroepithelioma).

Mus	Ihl	50,250, or 1,000 ppm	6 H/D, 5 D/W	R-41, R-66

TEST CONDITIONS 2-mo-old albino CD-1 mice were divided into 4 groups, each consisting of 36 males and 36 females. Each group received 0, 50, 250, or 1,000 ppm VC. Four animals of each sex and exposure level were terminated for various laboratory tests and gross and histopathologic examinations at the end of 1, 2, 3, 6, and 9 mos; the surviving animals were terminated at the end of 12 mos.

RESULTS Exposure to VC caused a high incidence of bronchioalveolar adenomas, liver hemangiosarcomas, and mammary gland tumors. The incidence of bronchiolar adenomas was: control group, 1/26 males and 0/36 females; 50 ppm group, 8/20 males and 4/34 females; 250 ppm group, 10/29 males and 12/34 females; 1,000 ppm group, 22/33 males and 26/36 females. The incidence of liver hemangiosarcomas was: control group, 0/26 males and 0/36 females; 50 ppm group, 3/29 males and 0/34 females; 250 ppm group, 7/29 males ($p < 0.05$) and 16/34 females ($p < 0.05$); 1,000 ppm group, 13/33 males ($p < 0.05$) and 18/36 females ($p < 0.05$). Mammary gland tumors consisted of adenocarcinomas and squamous and anaplastic cell carcinomas. There was a total of 0/36, 9/34, 3/34, and 13/36 mammary gland tumors in females exposed to 0, 50, 250, and 1,000 ppm, respectively. Metastases in the lung occurred in 0/36, 2/34, 2/34, and 8/36 females in the 0, 50, 250, and 1,000 ppm groups, respectively.

Rat	Ihl	0, 50, 250, or 1,000 ppm	6 H/D, 5 D/W for 1,2,3,6, or 12 mos	R-41, R-86

TEST CONDITIONS 2-mo-old CD rats were divided into 4 groups each consisting of 36 males and 36 females. Each group received 0, 50, 250, or 1,000 ppm VC. Four animals of each sex and exposure level were terminated at the end of 1, 2, 3, 6, and 9 mos; the surviving animals were terminated at the end of 12 mos.

RESULTS The incidence of liver and lung hemangiosarcomas was significantly increased in female rats. An increased incidence of these tumors was also seen in male rats, but this was not significantly ($p < 0.05$) increased. None of the male (0/35) or female (0/35) controls, and none of the 50 ppm dose group (0/36 males, 0/36 females) developed either liver or lung hemangiosarcomas. The incidence of these tumors in the medium and high dose

■ CARCINOGENICITY: ANIMAL STUDIES (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
			groups were as follows: 2/36 males and 10/36 females ($p < 0.05$) from the 250 ppm group developed hemangiosarcomas in the livers; 0/36 males and 3/34 females from the same group developed hemangiosarcomas in the lungs. A total of 6/34 males and 15/36 females ($p < 0.05$) from the 1,000 ppm group developed hemangiosarcomas in the liver; 4/34 males and 9/36 females ($p < 0.05$) developed hemangiosarcomas in the lungs. VC did not cause any other type of tumor in rats.	
Rat	Ihl	30,000 ppm	4 H/D, 5 D/W for 52 W	R-89
	TEST CONDITIONS 30 male and 30 female 17-W-old Sprague-Dawley rats were exposed to 30,000 ppm VC for 1 Y. The animals were then kept under observation until spontaneous death.		RESULTS A total of 31/60 animals had Zymbal gland carcinomas and 17/60 had liver angiosarcomas. No mention of control animals was made.	
Rat	Ihl	50 ppm	4 H/D, 5 D/W for 1 Y	R-89
	TEST CONDITIONS A total of 300 male and female Sprague-Dawley rats (11 W old) were exposed to 50 ppm VC for 1 Y (4 H/D, 5 D/W). A control group consisted of 100 untreated rats. The animals were then kept under observation until spontaneous death.		RESULTS After 100 W there were 55 survivors in the treated group and 28 in the control group. At this time the following results were observed: Of the animals in the treatment group, 6/300 had Zymbal gland carcinomas (0/100 controls), 1/100 had a nephroblastoma (1/100 control), 6/300 had liver angiosarcomas (0/100 controls), 7/300 had angiosarcomas at other sites (0/100 controls), 43/300 had mammary carcinomas (3/100 controls), 2/300 had mammary carcinosarcomas (2/100 controls), 45/300 had mammary fibroadenomas (3/100 controls), and 28/300 had other types of tumors (and/or sites) (7/100 controls).	
Rat	Ihl	1, 5, 10, and 25 ppm	4 H/D, 5 D/W for 1 Y	R-89
	TEST CONDITIONS 13-week-old Sprague-Dawley rats in groups of 120 (males and females combined) were exposed to 0, 1, 5, 10, or 25 ppm VC for 4 H/D, 5 D/W for 1 Y. The animals were then observed until spontaneous death.		RESULTS After 87 W there were 49, 49, 62, 51, and 45 survivors for the 0, 1, 5, 10, and 25 ppm dose groups, respectively. The number of animals with tumors (excluding survivors) at this time follows: within the 25 ppm group, 3 rats had Zymbal gland carcinomas, 3 had liver angiosarcomas, 10 had mammary carcinomas, and 7 had other type and/or site tumors; within the 10 ppm group, 1 had Zymbal gland carcinoma, 11 had mammary carcinomas, and 5 had other type and/or site tumors; within the 1 ppm group, 8 had mammary carcinomas and 4 had other type and/or site tumors; in the control group, 2 had mammary carcinomas and 4 had other type and/or site tumors.	
Rat	Ihl	6,000 or 10,000 ppm	4 H/D, 7 D	R-89
	TEST CONDITIONS 110 pregnant Sprague-Dawley rats were exposed to 6,000 or 10,000 ppm VC for 4 H/D for 7 D, from the 12th to the 18th D of pregnancy. Offspring were examined for tumors to see if VC was transported transplacentally. The animals were examined 143 W post-treatment. Four groups were used: Group I consisted of 30 dams who received 10,000 ppm VC; Group II consisted of 30 dams who received 6,000 ppm VC; Group III consisted of 54 offspring whose mothers received 10,000 ppm VC; Group IV consisted of 32 offspring whose mothers received 6,000 ppm VC. No controls were used.		RESULTS Group I: 1 animal had a Zymbal gland carcinoma, 1 had an intraabdominal angiosarcoma, 1 had a liver fibroangioma, and 1 had a liver angioma. Group II: no tumors were found. Group III: 3 animals had Zymbal gland carcinomas, 1 had a nephroblastoma, 1 had a liver fibroangioma, 1 had a liver angioma, 1 had a Zymbal gland fibrosarcoma, and 1 had an ovarian leiomyosarcoma. Group IV: 1 animal had a Zymbal gland carcinoma, 1 had a subcutaneous angiosarcoma, 1 had an intraabdominal angiosarcoma, 1 had a Zymbal gland adenoma, 1 had a skin carcinoma, 1 had a subcutaneous fibroangioma, and 1 had a mammary carcinoma.	

■ CARCINOGENICITY: ANIMAL STUDIES (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
Rat	Ihl	6,000 or 10,000 ppm	4 H/D, 5 D/W for 5 W	R-89

TEST CONDITIONS 45 female and 44 male Sprague-Dawley rats began treatment at 1 D of age. Animals received 6,000 or 10,000 ppm VC 4 H/D, 5 D/W for 5 W. The animals were then observed until spontaneous death.

RESULTS Of the 46 animals receiving 10,000 ppm VC, there were 10 cases of angiosarcomas and 15 of hepatomas (total of 19 rats with tumors). Of the 43 rats exposed to 6,000 ppm VC, there were 10 cases of angiosarcomas and 13 of hepatomas (total of 17 rats with liver tumors). At W 104 (from start of treatment) there were 5 and 8 survivors in the 6,000 and 10,000 ppm exposure groups, respectively.

Rat	Ihl	6,000 or 10,000 ppm	4 H/D, 5D/W for 5 W	R-89

TEST CONDITIONS Groups of 120 (male and female combined) Sprague-Dawley rats 13 W of age were exposed to 6,000 or 10,000 ppm VC for 5 W. Controls consisted of 249 rats that were untreated. After treatment the animals were observed until spontaneous death.

RESULTS After 104 W there were 55, 15, and 16 animals still alive in the 0, 6,000, and 10,000 ppm dose groups, respectively. The only tumor reported at this time was 1 hepatoma in the high dose groups. The results reported in another reference (R-65) after 135 W were identical to those at 104 W. This study showed that the age of the animals is an important factor in determining the incidence of tumors and their relative distribution. The older rats (13 W) were much less susceptible to tumor incidence than the newborn rats (1 D). In addition, the authors concluded that the shorter exposure period (5 W compared to 17 W) resulted in a sharp reduction in the onset of several types of tumors, especially liver angiosarcomas.

Ham	Ihl	50, 250, 500, 2,500, 6,000, or 10,000 ppm	4 H/D, 5 D/W for 30 W	R-89

TEST CONDITIONS A total of 268 male Golden hamsters were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm VC, 4 H/D, 5 D/W for 30 W. After treatment animals were observed until spontaneous death. Surviving animals were examined after 109 W of treatment.

RESULTS Group I (10,000 ppm): 6/35 had skin trichoepitheliomas and basaliomas, 4/35 had forestomach epithelial tumors, 1 subcutaneous angioma, and 1 gall bladder adenocarcinoma. Group II (6,000 ppm): 1/32 had a liver angiosarcoma, 2/32 had skin trichoepitheliomas and basaliomas, 2/32 had melanomas, 7/32 had forestomach epithelial tumors, 2/32 had hepatomas, 2/32 had liver fibroangiomas, 2/32 had liver angiomas, and 1/32 had a biliducts adenocarcinoma. Group III (2,500 ppm): out of 33 hamsters, 1 had skin trichoepitheliomas and basaliomas, 1 had melanomas, 1 had lymphomas, 11 had forestomach epithelial tumors, 1 had hepatoma, 1 had a liver fibroangioma, and 1 had a liver angioma. Group IV (500 ppm): out of 33 hamsters, 2 had liver angiosarcomas, 4 had skin trichoepitheliomas and basaliomas, 1 had lymphomas, 7 had forestomach epithelial tumors, 1 had a subcutaneous angioma, and 1 had a bronchial carcinoma. Group V (250 ppm): out of 32 hamsters, 3 had skin trichoepitheliomas and basaliomas, 1 had lymphomas, and 2 had forestomach epithelial tumors. Group VI (50 ppm): out of 33 hamsters, 6 had skin trichoepitheliomas and basaliomas, 1 had melanomas, 1 had lymphomas, and 4 had forestomach epithelial tumors. Group VII (0 ppm): out of 70 animals, 2 had skin trichoepitheliomas and basaliomas, 2 had lymphomas, and 2 had forestomach epithelial tumors.

Rat	Ihl	50, 250, 500, 2,500, 6,000, or 10,000 ppm	4 H/D, 5 D/W for 52 W	R-89

TEST CONDITIONS Groups of 64–74 Sprague-Dawley rats (male and female combined), age 13 W, were exposed to the above VC concs for 52 W. Controls consisted of 68

RESULTS After 135 W (end of experiment) increased incidences of liver angiosarcomas, Zymbal gland carcinomas, and nephroblastomas were observed in the treated

■ CARCINOGENICITY: ANIMAL STUDIES (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
		untreated rats. After exposure the animals were observed until spontaneous death.	rats. The following incidences of these tumors were observed in rats that survived until at least 26 W, when the first tumor was observed: for the controls, 50, 250, 500, 2,500, 6,000, and 10,000 ppm dose groups, respectively, liver angiosarcoma occurred in 0/58, 1/59, 4/59, 7/59, 13/59, 13/60, and 9/61; Zymbal gland carcinoma in 0/58, 0/59, 0/59, 4/59, 2/59, 7/60, and 16/61; nephroblastoma in 0/58, 1/59, 6/59; 4/59, 6/59, 4/60, and 5/61.	
Rat	Ihl	100, 150, and 200 ppm	4 H/D, 5 D/W for 52 W	R-89
		TEST CONDITIONS Groups of 120 (male and female combined) Sprague-Dawley rats, age 13 W, were exposed to the above VC concs for 52 W. Controls consisted of 185 untreated rats. After exposure the animals were observed until spontaneous death.	RESULTS The results after 143 W (end of experiment) were given. Liver angiosarcomas and nephroblastomas were observed in the treated but not control animals. The following are the number of animals observed with these tumors for the control, low, medium, and high dose groups, respectively: liver angiosarcomas, 0, 1, 5, and 12; nephroblastomas, 0, 10, 7, and 3.	
Rat	Ihl	50, 250, 500, 2,500, 6,000, and 10,000 ppm	4 H/D, 5 D/W for 17 W	R-89
		TEST CONDITIONS Groups of 60 (male and female combined) Sprague-Dawley rats, age 17 W, were exposed to the above concs of VC. Controls consisted of 190 untreated rats. After exposure the animals were observed until spontaneous death.	RESULTS The results after 155 W (end of experiment) were given. The incidence of Zymbal gland carcinomas and brain euroblastomas were increased in the treated rats. The number of animals with these tumors for the control, 50, 250, 500, 2,500, 6,000, and 10,000 ppm dose groups, respectively, were as follows: Zymbal gland carcinoma, 1, 0, 1, 3, 6, and 7; brain neuroblastoma, 0, 0, 0, 0, 2, 2, and 6. Nephroblastomas and liver angiosarcomas were observed in 0–2 animals per each exposed group, but none were seen in the control animals.	
Mus	Ihl	50, 250, 500, 2,500, 6,000, and 10,000 ppm	4 H/D, 5 D/W for 30 W	R-89
		TEST CONDITIONS Groups of 30 male and 30 female Swiss mice, age 11 W, were exposed to the above VC concs for 30 W. Controls consisted of 80 untreated males and 70 untreated females. After exposure the animals were observed until their spontaneous death.	RESULTS The experiment was terminated after 81 W. Lung tumors, mammary carcinomas, liver angiosarcomas, and epithelial tumors of the skin were increased in the treated mice. The following incidences (males and females combined) of these tumors were noted in animals alive after 16 W when the first tumor was observed: (for the control group followed by lowest through highest dose group were observed) lung tumors: 8/141, 2/57, 33/58, 38/58, 30/53, 8/54 and 35/50; mammary carcinomas: 0/141, 12/57, 11/58, 7/58, 9/53, 8/54 and 13/50; liver angiosarcoma: 0/141, 1/57, 11/58, 1/58, 11/53, 5/54 and 8/50; and skin epithelial tumors: 0/141, 0/57, 2/58, 1/58, 3/53, 6/54 and 3/50.	
Rat	Ihl	50, 250, 500, 2,500, 6,000, and 10,000 ppm	4 H/D, 5 D/W for 52 W	R-89
		TEST CONDITIONS Groups of 30 Wistar rats (males and females combined) were exposed to VC by inhalation for 52 W. Controls consisted of 40 untreated rats. After treatment the animals were observed until spontaneous death.	RESULTS After 136 W there were 3 animals still alive in the control group and none in the treated groups. Treatment with VC caused an increased incidence of liver angiosarcomas. The number of rats with this tumor was, 0, 0, 1, 4, 3, 2, and 8 for the controls, and 50, 250, 500, 2,500, 6,000, and 10,000 ppm dose groups, respectively.	
Rat	Orl	3.33, 16.65, and 50 mg/kg	4–5 D/W for 52 W	R-89

■ CARCINOGENICITY: ANIMAL STUDIES (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
		TEST CONDITIONS Groups of 80 Sprague-Dawley rats were administered VC by gavage, 4–5 D/W for 52 W. A control group of rats received the olive oil vehicle only. After treatment the animals were observed until spontaneous death.	RESULTS After 120 W there were 4, 4, 2, and 2 animals still alive in the control, low, medium, and high dose groups, respectively. Treatment with VC was associated with an increased incidence of liver angiosarcomas. The numbers of animals with this tumor at 120 W were 0, 0, 9, and 16 for the control, low, medium, and high dose groups, respectively.	
Rat	Orl	0.03, 0.3, and 1 mg/kg	4–5 D/W for 104 W	R-89
		TEST CONDITIONS Groups of 158–163 Sprague-Dawley rats were to be given VC by gavage for 104 W. This experiment was still underway at the time of the report. The control group received the olive oil vehicle only.	RESULTS Since this experiment was still underway, conclusions were not made; however, the tumors found in animals that died at the time of the report (57 W) are given in the report.	
Mus	Ihl	50 and 500 ppm	6 H/D, 5 D/W for 52 W 6 H/D, 5 D/W for 26 W	R-90
		TEST CONDITIONS Albino NMRI mice, 12 W old, were used. Twelve male and 12 females were exposed to 50 ppm VC for 6 H/D, 5 D/W for 52 W. The same number of rats were exposed at the same schedule for 26 W to 500 ppm VC. Each experimental group had a control series run parallel to it. Four animals of each sex from all groups were sacrificed and pathologically examined 26 W after start of exposure. Additionally, 4 control animals were sacrificed 1 Y after the start of the experiment. The remaining animals were allowed to live until spontaneous death, or were sacrificed when moribund.	RESULTS The results of the control animals were pooled since no difference between the two groups was found. Out of a total of 48 control animals, 3 were found with tumors (1 mammary adenocarcinoma, 1 ovarian disgerminoma, and 1 reticulum cell sarcoma). In the 50 ppm group, 18/24 animals developed tumors. Alveologenic adenomas were observed in 13/24 animals. Subperitoneal hemangiosarcomas were found in 14/24 animals, and subcutaneous hemangiosarcomas in 5/24 animals. In the 500 ppm group exposure was stopped at 26 W due to the bad condition of most of the animals. All (24/24) exposed animals in this group developed alveologenic adenomas. Subperitoneal hemangiosarcomas were found in 8/24 animals, and mammary carcinomas were observed in 4/24 animals. The primary subcutaneous and subperitoneal hemangiosarcomas found in both the 50 and 500 ppm groups were all located in fat tissue.	
Mus	Ihl	50, 200, or 2,500 ppm	7 H/D, 5 D/W for 9 mos	R-63
		TEST CONDITIONS Groups of 100 male and 100 female CDI Swiss ChR mice (age NG) were exposed to 50, 200, or 2,500 ppm VC in air for 7 H/D, 5 D/W for 9 mos and were observed for an additional 9 mos.	RESULTS After 8 mos exposure, 49 treated animals died with tumors. A total of 42 pulmonary adenomas, 41 liver angiosarcomas, and 11 mammary gland adenocarcinomas were observed. Distribution of these tumors were as follows. Pulmonary adenomas: 2 in the 50 ppm group, 12 in the 200 ppm group, 28 in the 2,500 ppm group, and 0 in the control group. Liver angiosarcomas: 3 in the 50 ppm group, 11 in the 200 ppm group, 28 in the high dose group, and 0 in the controls. Mammary adenocarcinomas: 2 in the low dose group, 3 in the mid dose group, 6 in the high dose group, and 0 in the controls.	
Rat	Ihl	30,000 ppm	4 H/D, 5 D/W for 12 mos	R-12,R-85
		TEST CONDITIONS Three-month-old male Wistar rats were exposed to 30,000 ppm VC (99% purity) vapors for 4 H/D, 5 D/W for 12 mos. Twenty-five rats served as a control group. At the end of treatment surviving animals were sacrificed at 20-D intervals.	RESULTS Of 26 treated rats, 17 developed skin carcinomas (predominately epidermoid carcinomas). No tumors were found in the control animals. Treated animals with lesions of the lungs: 1 adenocanthoma, 3 adenocarcinomas, 1 squamous cell carcinoma, and 1 mucous-producing adenocarcinoma. Treated animals with lesions of the bone: 5 osteochondromas.	

■ CARCINOGENICITY: ANIMAL STUDIES (*Continued*)

Species	*Route*	*Doses*	*Dosing Schedule*	*Ref*
Rat	Ihl	600 ppm or 600 ppm plus 5% ethanol in drinking water	4 H/D, 5 D/W for 1 Y	R-40

TEST CONDITIONS Groups of 80 Sprague-Dawley male rats were used. One group was exposed to 600 ppm VC vapors; a second group received 5% ethanol in the drinking water (ad libitum) 4 W before the beginning of VC inhalation and continued to receive ethanol-water until death; the control group received only the ethanol-treated drinking water; and a fourth group received no treatment.

RESULTS At the time of this preliminary report, 17% of the animals had been autopsied. Histological evidence showed the latent period for angiosarcoma of the liver to appear was 53 W in rats exposed to VC alone and in 38 W in rats exposed to VC and 5% ethanol. Preliminary results of this long-term study indicated synergism between inhaled VC and ingested ethanol in the induction of tumors.

Rat	Ihl	50, 500, 2,000, 5,000, 10,000, and 20,000 ppm	4 H/D, 5 D/W for 12 mos	R-98

TEST CONDITIONS Groups of 150–200 male and female Wistar Ar/IRE rats, 3 mos old, were exposed to the above VC concs for 12 mos. Controls consisted of 200 rats not exposed to VC and kept under the same conditions for 13 mos.

RESULTS Exposure to VC was associated with an increased incidence of liver angiosarcomas, skin squamous cell carcinomas, and lung adenocarcinomas. The following incidence of these tumors were observed in the control group, followed by lowest to highest dose groups, respectively. Liver angiosarcoma: 0/200, 0/200, 4/150, 10/200, 12/200, 16/200, and 18/150. Skin squamous cell carcinoma: 0/200, 0/200, 3/150, 0/200 (6/200 skin cecanlhomas, however @ 2,000 ppm), 20/200, 34/200, and 67/150. Lung adenocarcinomas: 0/200, 0/200, 0/150, 8/200, 4/200, 14/200, and 21/150.

Rbt	Ihl	10,000 ppm	NG	R-98

TEST CONDITIONS Forty rabbits were exposed to 10,000 ppm vinyl chloride. Controls consisted of 20 rabbits not exposed to VC and kept under similar conditions for 15 mos.

RESULTS Skin acanthomas were observed in 12/40 exposed rabbits and 0/20 controls. Lung adenocarcinomas were observed in 6/40 exposed rabbits and 0/20 controls.

■ CARCINOGENICITY: HUMANS.

Route	*Dose*	*Dosing Schedule*	*Ref*
NG	NG	Occupational exposure	R-93

TEST CONDITIONS A retrospective cohort study of workers at four VC facilities (that had been engaged in the polymerization of VC for at least 15 Y and had a sizable work force) was conducted. Employment records were initially obtained of every individual who had ever worked at any of the 4 VC plants. Then individuals for the study were selected from the records; those individuals having achieved 5 or more Y of employment and 10 Y since onset of initial employment. A modified life-table technique was used to obtain the 12,720 person-years at risk of dying, according to 5-Y age group, 5-Y calendar period, years of work experience, and time since onset of exposure to VC. Comparison was made between the observed number of deaths among the study cohort members and that expected on the basis of the U.S. white male death rates specific for age and calendar year and cause.

RESULTS A total of 136 deaths occurred among workers exposed to VC as contrasted with 126.3 deaths expected. Only two causes of death were in excess among workers exposed to VC: nonmalignant respiratory disease, and all malignant neoplasms (6 observed vs 3.4 expected, and 35 observed vs 23.5 expected, respectively). The latter excess was statistically significant @ $p < 0.05$. When cancer mortality was analyzed by site, excesses were found for 4 organ systems: brain and CNS (3 observed vs 0.9 expected), respiratory system (12 vs 7.7 expected), hepatic system (7 vs 0.6 expected, $p < 0.01$), and lymphatic and hematoporitic systems (4 vs 2.5 expected). Of the 14 histologically confirmed cases of biliary and liver cancer, 11 cases of angiosarcoma of the liver were diagnosed (this includes 4 cases still alive at the time of the report).

■ CARCINOGENICITY: HUMANS (*Continued*)

Route	*Dose*	*Dosing Schedule*	*Ref*
NG	NG	Occupational exposure	R-93

TEST CONDITIONS Identification particulars were obtained for over 7,000 men who were at some time between 1940 and 1974 exposed to VC monomer in the manufacture of PVC in Great Britain. Approximately 99% of these men have been traced and their mortality experience studied. The number of deaths observed was compared to that expected, using sex and age standardized death rates for England and Wales.

RESULTS The overall standardized mortality ratio, 75.4, shows a significant reduction compared with the national rates. Four cases of liver cancer were found. Two of these have been confirmed by a panel of liver pathologists as angiosarcoma and 2 as not angiosarcoma. There is no evidence to support the hypothesis that cancers other than those of the liver are associated with exposure to VC monomer. The 2 cases of angiosarcoma were found in men who had been exposed to high concs of the monomer although the second man died only 8 Y after first exposure.

NG	5–240 ppm TWA	Occupational exposure	R-97

TEST CONDITIONS A retrospective cohort study of the mortality experience of individuals occupationally exposed to VC between 1942 and 1960 was conducted. Employees were grouped into 4 exposure categories according to the highest levels of VC exposure experiences for at least 1 mo. Departmental census lists were reviewed over the specified years (1942 and 1960) for 5 production units, Unit I: copolymer plant, 1942–1960, Unit II: PVC and copolymer plant, 1953–1960, Unit III: VC monomer plant, 1947–1954, Unit IV: copolymer semiplant, 1946–1955, Unit V: vinyl latexes and polymer plant, 1946–1960. Exposure measurements were available of units I and II but not for the 3 smaller units. To investigate dose-response relationships with respect to VC, industrial hygiene data were reviewed for each job classification and each job was assayed on exposure level of low, intermediate, or high. The three categories were primarily based on estimated TWA concs for an 8-H D. The low level was defined as TWA concs below 25 ppm VC; the intermediate level was defined as 25–200 ppm; and the high level was defined as 200 plus ppm VC. A subjective evaluation of the other 3 units by industrial hygienists indicated that exposures were in the low to intermediate range, with occasional excursions to high levels. The observed mortality of the study population was compared to that of the U.S. white male population.

RESULTS The distribution of the malignant neoplasms with respect to exposure category suggests a possible dose-response relationship. Although the numbers of deaths were small, 9 of the 13 malignancies were observed in the high-exposure group. An approximate statistical evaluation of the difference between observed and expected malignancy deaths in the high-exposure group compared with all other exposure groups combined was performed, based on the conditional distribution of independent Poisson random variables. A Chi-square value of 6.1 ($p < 0.025$) was obtained after adjusting the total expected deaths to the observed number of deaths (high exposure 9 vs 4.64 expected; all other groups 5 vs 9.36 expected). The mortality experience 15 plus Y after initial exposure was examined. Eight of the 9 malignancies ocurred in the high exposure groups. Again, the Chi-square comparison of the distribution of malignancy deaths between the high and all other exposure groups was significant ($p < 0.01$). A comparison within the high exposure group between those individuals with < 1 Y of high exposure versus those with 1 plus Y of high exposure was not significant.

NG	NG	Occupational exposure	R-96

TEST CONDITIONS A retrospective mortality study of 8,384 men from 33 plants who had worked for at least 1 Y in a job involving exposure to VC before 31 December 1972 was conducted. The observed mortality was compared to that of the U.S. male population. Vital status could not be determined for 15% of the study population. Analysis was restricted to the 7,128 workers on whom follow-up was complete.

RESULTS No specific cause of death (cancer or otherwise) was statistically significantly greater than expected in the total group. When the group was analyzed according to duration or level of exposure, again no significant increases in cancer mortality was observed. However, some cancer mortality was increased although not significantly, and may have been related to exposure. According to the authors, mortality from digestive cancer, respiratory cancer, cancer of other unspecified sites, and lymphomas appeared to be related to exposure.

an index of the carcinogenicity of compounds. VC, along with other tested carcinogens, caused an increased nuclear size in exposed cells. These effects were not seen with noncarcinogens. (R-4) ■ 1,047 workers exposed to VC monomer from 3 different VC/PVC plants, and 289 workers from a polyvinyl chloride (PVC) extrusion plant manufacturing a PVC textile product (exposed to much lower concs of VC) were examined. *Results:* The carcinoembryonic antigen (CEA) titers were determined. The investigation demonstrated that occupational exposure in VC/PVC plants can cause elevations in the CEA titers of otherwise healthy individuals. (R-35)

MUTAGENICITY: GENE MUTATION—POSITIVE REFERENCES R-2, R-20, R-22, R-27, R-58, R-59.

MUTAGENICITY: GENE MUTATION—NEGATIVE REFERENCES R-56.

MUTAGENICITY: CHROMOSOMAL EFFECTS—POSITIVE REFERENCES R-3, R-28, R-49, R-60, R-64.

MUTAGENICITY: GENE MUTATION STUDIES

Assay Type	*Species-Cell Type*	*Route*	*Doses*	*Ref*
Bacterial mutation assay	*Escherichia coli* K12		10.6 mmol	R-100
TEST CONDITIONS Mutagenicity of VC was evaluated in *E. coli* K12 at 4 different loci, consisting of three back mutation systems (gal+, arg+, and nad+) and one forward mutation (MTR). The test was performed using liver microsomes from male mice pretreated for 10 D with 0.1% phenobarbital in the drinking water. VC gas (>99.9% purity) was bubbled through the liquid medium to give a conc of 10.6 mM.		RESULTS Mutagenicity was expressed as number of colony forming units (cfu) on selective media per number of cfu on complete media. VC was mutagenic in the presence of a metabolic activation system. The % of spontaneous mutation rate at the different loci was as follows: gal+ 231%; arg+ 663%; MTR 172%; and nad+ 148%.		
Yeast mutation assay	*Schizosaccharomyces pombe*		16 or 48 mmol	R-20
TEST CONDITIONS This haploid strain of *S. pombe* contains a missense mutation in the ade6 locus. Treatment with a mutagen causes forward mutation at 5 genetic loci for the biosynthesis of adenine. These mutations produce a change in the phenotype of the colonies, which can then be scored. VC was bubbled through liquid cell suspensions, producing concs of 16 and 48 mM.		RESULTS Mutagenic activity was found in *S. pombe* only when microsomal preparations (105,000 g) from mouse liver were included with the treatment solution. A dose-effect relationship was linear with mmol concs in treatments of 30 M. The VCM treatment did not produce any detectable decrease in the survival of cells.		
Host mediated microbial mutation	mus. Schizosaccharomyces pombe	Orl	700 mg/kg	R-20
TEST CONDITIONS Swiss albino mice weighing 25 g each were treated orally with 1.85% VCM in 1 mL of olive oil (700 mg/kg body weight). Yeast cells of *S. pombe* (P. strain) were injected into the peritoneum and incubated for various times to measure the forward mutation frequency.		RESULTS VCM was found active at a dose of 700 mg/kg during 12 H of treatment. Data from regression analysis were significant at the 1% level. This demonstrated VCM was genetically active, in vivo.		
Ames assay	*Salmonella typhimurium* TA1530, TA1535, G46		0.2, 2, or 20%	R-22
		RESULTS Exposure of *S. typhimurium* strains to VC increased the number of His+ revertants/plate, 16, 12, or 5 times over the spontaneous mutation rate. After 6 H of exposure to 20% VCM in air, the mutagenic response for TA1530 strain was enhanced 7, 4, or 5-fold when fortified postmitochondrial liver extractions from humans, rats, or mice were added. VC enzyme-mediated mutagenicity was dependent on an NADPH generating system. Highest mutagenic response was seen with TA1530. Exposure of this strain to 20% VC in air, in the absence of any metabolic activation system, caused a linear increasing mutagenic response as a function of incubation time, which was 20 times the spontaneous rate, @ 48 H. Phenobarbitone pre-		

MUTAGENICITY: GENE MUTATION STUDIES (*Continued*)

Assay Type	*Species-Cell Type*	*Route*	*Dose*	*Ref*
			treatment of rats and mice increased the mutagenic response by up to 15–40% as compared to untreated controls.	
Sex-linked recessive lethal	*Drosophila melanogaster*	Ihl	10,000, 100,000, 200,000 ppm	R-27

TEST CONDITIONS Male *D. malanogaster*, wild type strain Karsnas 60, 0–2 D old, were used for treatment with VC. Males were mated individually with 2–3 Muller 5 females for D 6–12 after treatment without any brooding. Heterozygous daughters were individually mated to 2–3 Muller 5 males and the progeny tested for recessive lethals. In induction experiments, males were treated with sodium phenobarbiturate and/or VC (1% solution sodium phenobarbiturate dissolved in sucrose water for 24 H).

RESULTS VC increased the mutagenicity at the lowest exposure tested. There was no indication of an increased effect with higher concs. The experiments with sodium phenobarbiturate (one with 1% VC and one with 10% VC) produced a pronounced effect. The total number of recessive lethals (when 1% VC was used) with sodium phenobarbiturate pretreatment was different from control at 0.1% significance level (using Chi-square and Yates Correction).

Mammalian spot test	Mus	Ihl	4,600 ppm	R-56

TEST CONDITIONS Female mice of inbred C57BL/6J Han (a/a; wild type) were mated to Han rotated-bred males of T-stock strain. On the 10th D of gestation females were exposed to 12,000 mg/m^3 (4,600 ppm) of VCM in air for 5 H. F1 offspring were examined at 3–5 weeks of age for mosaic coat colors. An experiment using cyclophosphamide to test the ability to induce colored spots in the F1 hybrids served as a positive control. Statistical evaluations of the data were done by Chi-square test.

RESULTS The mammalian spot test did not provide evidence that VC induces somatic gene mutations in mammals in vivo. No offspring with abnormal morphology were found in the VCM exposure group. Treatment with 10 mg (scu) CP/kg produced significant differences in the number of white and colored spots in the offspring in comparison with the control or VCM-treated group.

Ames assay	*Salmonella typhimurium* TA1530		20%	R-58

TEST CONDITIONS Liver S-9 fractions from adult female BD-V1 rats and from human patients were used as metabolic activation systems.

RESULTS VC was mutagenic in the presence of both rat and human liver S-9 fractions. The number of his- revertants in *S. typhimurium* mediated by human and rodent liver S-9 exposed to 20% VC (v/v) in air for 4 H and incubated for 48 H @ 37 C was 85 and 100 revertants/plate, respectively. The number of revertants/plate after exposure to VC in the absence of cofactors (NADP-, G 6-P) was subtracted.

Na/K ATPase assay	Chinese ham-V79		5, 10, 20, and 30%	R-2

TEST CONDITIONS The mutagenicity of VC was tested in V79 Chinese hamster cells in the presence and absence of a S-15 liver fraction from phenobarbitone-pretreated rats. The cells were exposed to a vapor conc of 5–30% (v/v) for 5 H. Mutagenicity was measured by the induction of 8-azaguanine and oubain resistance.

RESULTS Vinyl chloride induced both 8-azaguanine and oubain resistant dose-related mutants @ 5–30% VC in air in the presence of the S-15 fraction. At a conc of 30%, mutation frequencies were 10–20 times that of spontaneous reversions. At this conc there were 51 azaguanine and 4 oubain resistant colonies per 100,000 survivors. Neither toxicity nor mutation was induced in the absence of the metabolic activation system.

Ames assay	*Salmonella typhimurium* TA1530		2, 7, 12, and 20%	R-59

TEST CONDITIONS The mutagenicity of VC in *S. typhimurium* TA1530 without metabolic activation at the above concs was evaluated. In tests to evaluate the effect of a metabolic activation system, a 2% VC conc was used. The metabolic activation system consisted of S-9 liver fraction from adult male NMRI mice either left untreated or treated with Aroclor 1254.

RESULTS In the absence of a metabolic activation system, VC increased the number of his- revertants in a dose-related manner. At the highest conc (20%) there were 101 revertants in the treated plate compound to 10 in the controls. The addition of the S-9 fraction enhanced the mutagenicity of VC. This effect was even more pronounced when liver S-9 from pretreated mice was used.

■ MUTAGENICITY: CHROMOSOMAL EFFECTS STUDIES

Assay Type	*Species-Cell Type*	*Route*	*Doses*	*Ref*
In vivo cytogenetics	Chinese ham, bone marrow	Ihl, ipr	2,500 or 5,000 ppm by Ihl followed by 600 and 300 mg/kg ipr	R-3
	Human lymphocytes	Ihl	NG	R-3

TEST CONDITIONS Bone marrow cells from Chinese hamsters treated with VC in the above doses and routes were studies to determine whether chromosomal aberrations in the bone marrow cells were significantly higher in comparison to control groups. A similar analysis of workers from a PVC plant was undertaken, using lymphocytes from 20 workers with symptoms of VC illness, from 10 workers with no symptoms of VC illness, and from 10 controls matched according to age. A total of 100 cells per individual were scored for gaps, breaks, fragments, dicentrics, rings, chromatid and chromosome translocations, and deletions.

RESULTS In humans, only the group consisting of workers with VC illness showed a significant increase in the rate of aberrations in comparison to the control group (statistical information and exact data not given). In the hamsters, chromosomal aberrations were also significantly higher in the treated animals as compared to controls

Dominant lethal	CD-1 mus	Ihl	3,000, 10,000, 30,000 ppm	R-55

RESULTS No mutagenic effects were seen on any maturation stage of spermatogenesis in male CD-1 mice exposed by inhalation to 7.8, 26, or 72 g/m^3 VC in air for 6 H/D for 5 D as compared to controls.

In Vivo cytogenetics	Hmn-peripheral blood lymphocytes	Ihl	20–30 ppm	R-28

TEST CONDITIONS Seven occupationally exposed male workers and 3 nonexposed control subjects, all employed in the same PVC factory, were studied for chromosomal effects of VC exposure. In weeks prior to blood sample collection, air conc was approximately 20–30 ppm. Workers who were studied had been exposed to VC for periods ranging from 9 to 29 Y.

RESULTS Investigators found that the average frequency of chromosomal aberrations in this group (9.52%) was significantly ($p < 0.001$) greater than in the controls (1.94%). This was found to be true for chromatid and isochromatid breaks.

In vivo cytogenetics	Chinese ham, bone marrow	Ihl	2.5% or 5.0%	R-49

TEST CONDITIONS Groups of 4 adult (10 to 15 W old) Chinese hamsters weighing 30 g were exposed to 2.5% VC in air for 6, 12, or 24 H. The male-female ratio was 1:1. Another group of 10 hamsters was exposed to 5% VC for 24 H only. Hamsters received ipr injection of 8 mg colchicine/kg body weight 24 H after beginning VC exposure. Bone marrow chromosomes were analyzed for gaps, breaks, fragments, deletions, and exchanges 2 H later.

RESULTS The frequency of chromosome aberrations depended on dose and exposure time. After 6 and 12 H of exposure at the 2.5% level, aberrations (breaks and fragments) were induced in 0.8% of the metaphase. After 24 H the frequency of induced breaks and fragments increased to 4.5%. In 1,400 metaphases of 14 control hamsters only 1 break (0.1%) was found. Gaps including chromosome aberrations increased from 0.6% in controls to 7.3% in group exposed 24 H to 2.5% VC. The highest measured effect was 25.7% metaphases with aberrations when hamsters were exposed to 5% VC for 24 H ($p < 0.02$). Significance of differences in the number of metaphases with aberrations was verified using the Chi-square test.

Micronucleus test	CBA mus	Ihl	15%	R-64

TEST CONDITIONS Three CBA male mice were exposed to 5% VC for 4 H. Controls consisted of 3 untreated mice.

RESULTS Exposure to VC caused a significant increase in the number of polychromatic micronucleated cells as compared to controls. Statistical evaluation was performed with *t* tests and combined probability analysis according to Fisher.

In vivo cytogenetics	Hmn, peripheral blood lymphocyte	Occupational	NG	R-60, R-94

■ MUTAGENICITY: CHROMOSOMAL EFFECTS STUDIES (*Continued*)

Assay Type	*Species-Cell Type*	*Route*	*Doses*	*Ref*
TEST CONDITIONS The 11 subjects were male workers who had received repeated exposure to VC in an Upstate New York PVC polymerization plant. Duration of recurrent occupational exposure in the 11 men ranged from 4 to 28 Y with an average of 15 Y. Of the 10 healthy male controls, 4 were from within the same factory population without known VC exposure. Six controls were also selected from outside the factory environment. The chromosome studies were performed on cultures of peripheral blood lymphocytes. Fifty metaphases from each individual were evaluated.		RESULTS Exposure to VC increased the frequency of chromosomal aberrations. Much of this increased damage was due to cells with unstable chromosome changes such as fragments, dicentrics, and rings.		
In vivo cytogenetics	Hmn-lymphocytes	Ihl	20–150 ppm	R-66
TEST CONDITIONS Lymphocytes from humans who were exposed occupationally to VC for periods ranging from 10 to 27 years to concs most frequently between 20 and 150 ppm were examined.		RESULTS There were 5.2% of the examined lymphocytes from exposed workers that had chromosomal aberrations as compared with 1.8% in the control workers. The aberrations included chromatid and chromatin breaks; chromatid and chromosome exchanges were frequent.		

■ MUTAGENICITY: DNA DAMAGE/REPAIR STUDIES

Assay Type	*Species-Cell Type*	*Route*	*Doses*	*Ref*
Sce	Chinese ham	Ihl	1.25–2.5%	R-49
TEST CONDITIONS Groups of 4 adult Chinese hamsters (10–15 W old) were used in a 1:1 male to female ratio. Hamsters were exposed to VC 6, 12, and 24 H at concs of 1.25 or 2.5% (v/v). The Brd-U-tablet method was used to obtain in vivo induced sister chromatid exchanges (SCE).		RESULTS The number of in vivo-induced SCEs depended on dose and length of exposure to VC. Data were statistically analyzed using the *t* test. The 6-H exposure of the low dose doubled the SCE frequency with 4.41 SCEs/cell in controls, and 8.72 in the experimental group. Lengthening of exposure time increased frequency of SCE. After 12 H, 17.51 SCEs/cell were found and 22.33/cell were found after 24-H exposure. SCE frequency increased in all exposure-time groups after exposure to 2.5% as compared to the lower dose: 12.66 (6 H), 19.80 (12 H). The highest measured effects were 33.25 SCEs/cell after a 24 H exposure to 2.5% VC.		
Sce	Hmn. lymphocytes	Ihl	20–150 ppm	R-66
TEST CONDITIONS Lymphocytes from humans who were exposed occupationally to VC for periods of 10–27 Y (to concs most frequently between 20–150 ppm) were examined.		RESULTS The number of sister chromatid exchanges was increased from 9.41 to 13.30 per lymphocyte.		
Mitotic gene conversion	*Saccharomyces cerevisiae*		16 and 48 mmol mM	R-20
TEST CONDITIONS VC was bubbled through a liquid cell suspension to give concs of 16 and 48 mmol. The assay was performed in the presence and absence of purified mouse liver microsomes. Induction of gene conversion was measured at the ade 2 and trp 5 loci of this strain of yeast.		RESULTS Both gene conversion systems (ade 2 and trp 5) showed a positive response which was dependent on the presence of purified mouse liver microsomes.		

MUTAGENICITY: CHROMOSOMAL EFFECTS—NEGATIVE REFERENCES R-55.

MUTAGENICITY: DNA DAMAGE/REPAIR—POSITIVE REFERENCES R-20, R-49.

MUTAGENICITY: OTHER STUDIES A prophage lambda induction test was conducted using 0.1 mL of 20% VC in DMSO/plate. The test used activated microsomal enzymes (S-9) from livers of rats induced with Aroclor. Results were negative (no other data or statistical analysis given). (R-21)

TERATOGENICITY: MAMMALIAN STUDIES

Species	*Route*	*Doses*	*Dosing Schedules*	*Ref*
Rat	Ihl	2,000, 7,000, 12,000 ppm	2.5 H on D 18	R-26

TEST CONDITIONS Groups of 3 pregnant CFY rats were exposed to VC @ 2,000, 7,000 or 12,000 ppm in air for 2.5 H on the 18th D of pregnance.

RESULTS VC was shown to be present in the fetal and maternal blood as well as in the amniotic fluid, indicating the permeability of the placenta to the agent.

Rat	Ihl	1,500 ppm	24 H/D	R-26

TEST CONDITIONS Pregnant (first trimester) CFY rats (13–28/group) were allocated to experimental groups as follows: Groups IA, IC, IIA, and IIIA inhaled air in an inhalation chamber for 24 H/D on D of pregnancy 1–9, 8–14, and 14–21, respectively; Groups IB, ID, IIB, and IIIB were exposed to VC (4,000 mg/m^3 or approximately 1,500 ppm) for the same length of time during the same periods of gestation as their respective controls. The rats in groups IC and ID were given, subcutaneously, 2 injections (50 mg/kg bw) of trypan blue (1% solution) on the 7th and 8th D of gestation. Group IV was another control. On the 21st D of gestation, the position of fetuses living, dead, or resorbed was noted. Fetuses and placentae were excised and weighed and macroscopic examination was carried out. The *t* test was used for statistical comparison of means. The Mann-Whitney *U* test was used to compare number affected/total fetuses ratio.

RESULTS The maternal liver weight and liver weight/body weight ratio increased in response to trypan blue as well as to VC applied in the 1st or 2nd W of pregnancy ($p < 0.01$ and $p < 0.05$). The number of resorbed fetuses as well as fetal loss (% total implants) was significantly increased in the group exposed to VC during the first 9 D of pregnancy ($p \leq 0.05$). Author concluded that VC in itself has no teratogenic effect on CFY rats, but an embryotoxic effect during the early stages of pregnancy (at 1,500 ppm). Fetal losses and induction of CNS malformations due to trypan blue administration were not potentiated by a combined exposure of pregnant rats to VC and the dye.

Mus	Ihl	50, 500 ppm	7 H/D	R-15
Rat	Ihl	500, 2,500 ppm	7 H/D, D 6–15 of gestation	R-15
Rbt	Ihl	500, 2,500 ppm	7 H/D, D 6–18 of gestation	R-15

TEST CONDITIONS Three groups of each species (CF-1 mice, Sprague-Dawley rats, New Zealand rabbits) were tested: control, inhalation of VC only, and inhalation of VC and ethanol (15%) in drinking water (ethanol blocks metabolism).

RESULTS While maternal tox was observed, VC alone did not produce any significant anomalies when compared to controls ($p > 0.05$). There were significant increases in the number of fetal anomalies in the group that was given 15% ethanol in their drinking water, while receiving 500 ppm VC (mice). Also among mice exposed to VC in combination with 15% ethanol, several skeletal anomalies occurred at an incidence significantly greater than among mice exposed to VC alone (modified Wilcoxon test, $p < 0.05$). Authors concluded that exposure of pregnant mice, rats, and rabbits to VC (ihl) at concs high enough to cause maternal tox was not teratogenic in any of the 3 species. Exposure of VC alone was not consistantly embryotoxic in the 3 species studies. Among mice, @ 2,500 ppm, the incidence of resorptions was significantly higher (13%) than among the concurrent controls (7%). Ingestion of 15% ethanol in the drinking water enhanced the tox effects of the inhaled VC. Maternal tox was enhanced to an extent greater than embryotoxicity.

■ TERATOGENICITY: HUMAN STUDIES

Route	*Dose*	*Dosing Schedule*	*Ref*
Enviromental exposure	NG	NG	R-92

TEST CONDITIONS Three Ohio communities that had polyvinyl production facilities were studied. Since 1968, information for specific congenital malformations in Ohio residents has been recorded on birth certificates. Any information recorded under the congenital anomalies section of the certificate were analyzed. Data for deaths resulting from cancer of the CNS, leukemia, and lymphomas in the adult population aged 45 Y and older were also analyzed.

RESULTS The findings suggest that mothers living in communities with PVC production facilities gave birth to an excess number of children with congenital malformations as compared to the expected based on the state average or based on the experience in the balance of counties in which these cities are located. With regard to specific malformations, anomalies of the CNS appear to be of the greatest concern. Deaths from CNS tumors in adult male residents of two of the cities were also significantly greater than expected. On a community basis, excess deaths from the other cancers were not apparent.

TERATOGENICITY: MAMMALS—NEGATIVE REFERENCES R-15, R-26.

PLACENTAL TRANSFER: POSITIVE REFERENCES R-26.

PHYTOTOXICITY: TERRESTRIAL PLANTS Research was designed to study the effect of VC on the rate of production of excess hydrogen peroxide, which is tox to germinating oat seeds. The effect of the increased H_2O_2 by VC on the sulfhydryl content in germinating seeds and in potatoes was also studied. No apparent increase in the H_2O_2 level was found when germinated seeds were exposed to 50, 100, or 200 ppm VC gas. Results showed that the amount of H_2O_2 gradually increased from 0.35 to 0.45, 0.65, 0.92, and 1.15 mcg H_2O_2/g seed when VC gas was successively increased to 300, 400, 500, and 1,000 ppm. The 2,000 ppm VC gave an effect very similar to that obtained with 1,000 ppm. There was a ten-fold increase in the sulfhydryl content of the seeds after 72 H germination without exposure to VC. The sulfhydryl content was decreased gradually by 5.5, 15.2, 21.7, and 30.4% when VC gas was sucessively increased to 300, 400, 500, and 1,000 ppm. The increased production of H_2O_2 in the germinating seeds exposed to VC gas decreased their sulfhydryl content and thereby produced adverse effects and caused abnormalities in growth. Author concluded threshold levels of VC are > 200 ppm and that saturation level is 1,000 ppm. (R-34)

OTHER ADVERSE EFFECTS ■ Male CD-1 mice were exposed to 10, 100, or 1,000 ppm VC for 2–8 W @ 6 H/D, 5 D/W. A slight increase in the spleen weight of mice was noted at the highest level. Spleens were obtained from these animals (4 mice/group after 2, 4, and 8 W exposure) and their lymphocytes cultured in vitro with or without the presence of phytomitogens, phytohemagglutinin (PHA), and pokeweed mitogen (PWM). Relative blast formation and the DNA synthesis was measured by the incorporation of 3H-thymidine in the cultured cells. The response to splenic lymphocytes to the phytomitogens was increased several fold by VC exposure. The effects were apparent @ 1,000 ppm VC after 2 W of exposure and at all levels of VC exposure after 4–8 W. The effects were generally more pronounced at 100 ppm VC exposure than those @ 1,000 ppm. In vitro culture of splenic lymphoctves from control or VC-exposed mice in the VC atmosphere did not show exhancement of blast formation. Alteration of VC metabolism during the VC exposure in vivo yielded results that indicated that metabolites of VC may be responsible for the stimulation of lymphocyte transformation observed in splenic cultures. (R-50) ■ Male, but not female, rats were susceptible to the acute hepatotoxic effects of inhaled VC. In phenobarbital-pretreated male rats, pyrazole, and SKF-525A, inhibitors of ethanol metabolism and mixed function oxidase system (MFO) activity, protected against tox. When disulfiram and ethanol were given acutely, a slightly increased tox effect of VC was observed. Ethanol given in drinking water (10% for 7 D or an equivalent dose of 10 mL/kg/D) did not, by itself, enhance VC hepatotoxicity in male rats, even though this dose regimen did slightly increase mixed function oxidase system activity. Apparently, inhibition of either liver alcohol dehydrogenase or microsomal oxidase protects rats from acute hepatotoxicity of VC. But, since pyrazole also has some inhibitory action on microsomal oxidases, it is possible that inhibition of reactions catalyzed by the mixed function oxidase system alone could account for protection against VC. (R-52) ■ Single exposure to VC induced acute liver injury in rats whose mixed function oxidase system was stimulated by pretreatment with Aroclor 1254 or phenobarbital. The endoplasmic reticulum

was involved in the primary morphological injury, with denaturation of the smooth membranes. The increased hepatotoxicity of VC may involve their metabolic activation via free radical or epoxide intermediates. (R-53) ■ Male rats were pretreated by gavage with the PCB mixture Aroclor 1254 (300 μmol of PCB/kg) for 3 consecutive D. On D 4, these rats were exposed by inhalation (4 H) to 24,000 ppm VC. Animals were sacrificed 24 H later and acute hepatic responses were estimated by measurement of serum-alamine alpha-ketoglutarate transaminase (SAKT) and by light microscopy. VC caused significant elevations of (SAKT) and produced severe degeneration and necrosis of liver. SAKT elevations (mg pyruvate/mL serum-H) were as follows. Untreated controls: 0.17 ± 0.01. PCB pre-treated, not exposed: 0.19 ± 0.02. PCB plus VC: 2.58 ± 1.25. (R-5) ■ Absorption through the skin is minor. Calculations based on the percutaneous absorption of VC by Rhesus monkeys, indicate that a 6-ft, 90 kg man exposed to 7,000 ppm (dermal) for 2 H would absorb the equivalent of a 0.2 ppm, 8-H inhalation exposure. (R-11) ■ VC reacted to a greater extent with denatured than with native herring sperm DNA, in vitro, in aqueous soln. However, VC failed to react with previously acylated calf thymus DNA in vitro in citrate buffer. (R-38) ■ VC may be anaesthetic above 500 ppm. Handling of material has caused circulatory and bone changes. (R-47) ■ [14C] VC, 0.5 mmole/kg in 0.5 mL/kg methanol, was given ipr for 1–6 D to male Sprague-Dawley rats. After administration of the VC, hepatic P-450 was not significantly decreased after 1 dose, but progressively decreased after repeated doses. Hepatic glutathione and SGPT activity were unchanged and histologic examination of liver specimens obtained after 1, 3, or 6 doses showed no liver necrosis. The amount of [14C]-material irreversibly bound to proteins increased in various tissues during administration of the first 3 doses but then tended to decrease in the liver and in the kidney. (R-68)

PHARMACOKINETICS/METABOLISM In rats inhaling 20,000 ppm [14C]-VC for 5 M_7, [14C] was found in the liver, bile duct, digestive lumen, and kidneys 10 M from the beginning of the inhalation exposure. The amount of VC and its metabolites increased up to 3 H postexposure. Additional deposition sites showing [14C] activity included urinary tract, salivary glands, lacrimal glands, skin, and thymus. (R-11) ■ The tissue deposition of [14C]-vinyl chloride has been studied. Immediately after exposure by inhalation of 50 ppm VC for 5 H in a closed system, the % incorporated as [14C]-radioactivity per gram tissue was highest for kidney (2.13%), liver (1.86%), and spleen (0.73%). Forty-eight H after the beginning of exposure, labeled material could still be found in these tissues. (R-11) ■ Present data indicate that VC is metabolized to an activated carcinogen electrophile that is capable of covalently reacting with nucleophilic groups or cellular macromolecules. There is also ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids. Chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules. (R-11) ■ The metabolism of VC may be inhibited by administering to rats, 320 mg/kg of pyrazole, 1 H prior to inhalation of the gas. Pyrazole is an inhibitor of alcohol dehydrogenase and xanthine oxidase. Pretreatment of rats with ethanol, 5 mg/kg, 95%, also inhibited vinyl chloride metabolism. (R-11) ■ When a mixture of VC/oxygen (1:1 v/v) was passed through a medium consisting of liver microsomes from phenobarbitone-pretreated mice, and an NADPH-generating system, a volatile metabolite was formed; this was trapped by its reaction with 4-(4-nitrobenzyl)pyridine, in ethylene glycol. (R-13) ■ Radioactivity from [14C]-labeled VC was covalently bound to protein and nucleic acids in vivo and in vitro, in the presence of rat liver microsomal fractions of highly purified cytochrome P-450 and NADPH-cytochrome P-450 reductase preparations. The ratio of bound to total nonvolatile metabolites increased from the in vivo to the microsomal to the purified system. In vivo, total metabolism of [14C]-labeled VC was not induced by phenobarbital pretreatment (0.1% in drinking water for 5 D) in rats exposed to either 10 ppm or 250 ppm of the [14C]-VC; however, binding to protein and RNA was enhanced but only at the lower exposure level. In vitro, phenobarbital pretreatment increased microsomal conversion of [14C]-VC to both total and bound metabolites. The metabolites of [14C]-VC metabolism in an in vitro liver microsomal fraction were distributed among many microsomal proteins and not localized to cytochrome P-450. (R-25) ■ [14C]-Labeled VC was studied in rats. Rats exposed to 10 ppm VC for 6 H eliminated 68% of the absorbed radioactivity in their urine and 2% (as VC) in the expired air over 72 H. Six-H exposures to 1,000 ppm resulted in 56% of the dose appearing in the urine, with 12% in the expired air as VC. The pulmonary excretion of VC followed first order kinetics with similar half lives at both treatment levels: 20.4 M @ 10 ppm and 22.4 M @ 1,000 ppm. (R-29) ■ The mechanisms responsible for and protecting against metabolic activation of VC were investigated in male Sprague-Dawley rats. Inhalation of 5% VC for 18 H was utilized. When [14C]-VC was incubated with hepatic microsomes, a [14C]-labeled material be-

came irreversibly bound to microsomal proteins. Binding required NADPH; was decreased by CO, SKF-525A (2-diethylaminoethyl 2,2-diphenylvalerate hydrochloride, 75 mg/kg, ipr), or glutathione; and was increased by 1,1,1-trichloropropene-2,3-oxide (TCPO). Inhalation of a 5% VC atmosphere decreased hepatic cytochrome P-450 and glutathione. Pretreatment of the animals with DDT or phenobarbital had the following effects: increased in vitro irreversible binding to microsomal proteins measured in the presence but not in the absence of TCPO, and increased the in vivo loss of cytochrome P-450 during inhalation of the VC; and decreased the in vitro irreversible binding to 10,000 g supernatant proteins and the in vitro loss of glutathione during inhalation of VC. (R-32) ■ In rats exposed to 400 ppm VC for 6 H and then treated ipr with 20 mg 3,4-dichlorobenzenethiol, and again exposed to 400 ppm VC for 12 H, S-2-(3,4-dichlorothiophenyl)acetic acid was detected in the urine. Authors concluded that the formation of nucleophilic carcinogens from nonelectrophilic precursors can be proven by the use of nucleophilic reagents, in vitro as well as in vivo. (R-33) ■ Rats were exposed to 5,000 ppm of VC, via inhalation, 6 H/D, 5 D/W for 7 W. This VC was nonlabeled. On the last day of repeated exposure, [14C]-VC was used. The fate of the [14C]-VC was compared in a group of rats exposed repeatedly, to a group exposed simultaneously for a single 6-H period to 5,000 ppm of [14C]-VC. The routes and rates of excretion of [14C]-activity were the same for the two experimental groups. The activity of microsomal enzymes, as reflected by aniline hydroxylase and p-nitroanisole-o-demethylase derived from 9,000 g liver supernatants, was essentially the same in rats exposed repeatedly or in nonexposed control rats. Covalent binding to hepatic macromolecules was greater in rats repeatedly exposed as compared to those subjected to a single exposure. Thus, repeated exposure to VC does not induce its biotransformation. However, the increase in hepatic macromolecular binding indicates that repeated exposure augments the reaction of electrophilic metabolites with macromolecules, and this may be expected to enhance potential toxicity including carcinogenicity. (R-37) ■ After a 5-H inhalation exposure, rats metabolized [14C]-labeled VC much faster than carbon tetrachloride (CCl_4). The half-life was found to be 1.1 H. [14C]-VC bound covalently to tissue proteins, particularly in the liver. In kidney, small intestine, and other organs much less radioactivity was observed. (R-39) ■ VC uptake rate and proportion metabolized by isolated perfused rat livers remained constant for VC concs of 50–25,000 ppm. The overall VC conversion was 14.6% of the offered conc. ETOH, pyrazole, and 6-bromobenzothiazole inhibited VC metabolism by 12.7, 31.6, and 48.9%, respectively. Phenobarbital and fasting increased VC metabolism by 20.9 and 31.2%, respectively. VC had no effect on marker enzymes, but slight liver damage occurred after increased metabolic VC transformation. Mixed function oxygenation was apparently involved in VC metabolism. (R-42) ■ The metabolic elimination of VC in Rhesus monkeys is a dose-dependent, saturable process, as in rats. Below 200–300 ppm of VC in atm, elimination obeys a first-order law; the clearance rate is much closer to that found in man than that for rats, mice, or gerbils. The maximal velocity of metabolic elimination of VC at high concs in Rhesus monkeys is only about half that of rats when related to kg body weight. Thus, the Rhesus monkeys mimic the quantitative aspects of VC metabolism better than rats or mice do. (R-46) ■ In the presence of hepatic microsomes, VC produced a Type I difference spectrum and stimulated coinhibitable NADPH consumption. A comparison of the binding and Michaelis parameters for the interaction of VC with uninduced phenobarbitol-, and 3-methylcholanthrene-induced microsomes, indicates that the binding and metabolism of VC was catalyzed by > 1 type P-450 cytochrome, but predominately by cytochrome P-450. Metabolites of VC from this enzyme system decreased the levels of cytochrome P-450 and microsomal heme, but not cytochrome 65 or NADPH-cytochrome c reductase, in vitro. (R-51) ■ Thiodiacetic acid and S-(carboxy-methyl) cysteine were found in the urine of rats after a 48-H exposure to 1,000 ppm VC. The structures of both compounds were clarified by means of gas chromatography/mass spectroscopy. Chloroethylene oxide, chloroacetaldehyde, and chloroacetic acid are assumed to be intermediates in VC metabolism. Compounds that can be transformed to one of these alkylating agents in vivo may also lead to renal excretion of thiodiacetic acid and S-(carboxy-methyl)cysteine. (R-54) ■ Strong evidence has been obtained that the biotransformation of VC involves microsomal mixed-function oxidase, i.e., the metabolic activation of VC by a liver microsomal system from rats, mice, or humans, and depends on the presence of necessary cofactors for a NADPH generating system and oxygen. Cloroethylene oxide rearranges to 2-chloroacetaldehyde spontaneously. In aqueous soln @ pH 7.4 and 37 C, the epoxy compound has a half-life of 1.6 M. Chloroethylene oxide is capable of reacting with glutathione and with nucleophilic groups of macromolecules. N-acetyl-S-(2-hydroxyethyl)cysteine (a major metabolite), S-(carboxymethyl)cysteine and N-acetyl-S-vinyl cysteine are metabolites of VC after inhalation or oral administration in rats. Chloroethylyene oxide and chloroacetaldehyde alkylate to 4-(4-nitrobenzyl)pyridine and adenosine. Rat liver microsomes catalyze the co-

valent binding of [14C]-VC to proteins and nucleic acids. (R-57) ■ Ethylene and its analogues (i.e., VC, vinyl bromide) are converted to the corresponding ethylene oxides by cell-free preparations from mature cotyledons of the broad bean (*Vicia faba*). VC acts as a competitive inhibitor in the first-order oxidation of ethylene. The measured Ki where Ki (gas) = 3.19E-6 M; Ki (liquid) = 1.5E-6M. (R-73) ■ Postmitochondrial supernatants of liver, kidney, and lung tissue from rats and mice that had been exposed to 20% VCM were assayed for their capacity to generate VCM metabolites mutagenic for *Salmonella typhimurium* TA1530. Data indicate that the liver efficiently converted VCM into mutagenic metabolites. (R-60) ■ After oral administration of VC to rats and rabbits, maximum blood level peaks occurred 4–5 H after high dose and 3–4 after lower doses. No VC was observed in blood 24 H later. Liver cytochrome P-450 was elevated by higher VC doses. EEGs in rats were altered following oral administration of VC and the alteration varied with sex. VC @ 45 and 135 mg/kg altered learning ability. The compound @ 12 mg/kg had immunosuppressant activity in rabbits. (R-36)

ENVIROMENTAL IMPACT

AIR POLLUTION High.

ACTION LEVELS Evacuate area. Enter from upwind side after gas levels have subsided. Notify fire and air authority. Remove ignition sources.

IN SITU AMELIORATION Use carbon or peat on dissolved portion. Seek professional environmental engineering assistance through EPA's Environmental Response Team (ERT), Edison, NJ, 24-H No. (201)321-6660.

AVAILABILITY OF COUNTERMEASURE MATERIAL Carbon: water treatment plants, sugar refineries. Peat: nurseries, floral shops.

DISPOSAL METHOD Dilute to 1% soln and remove phenol inhibitor as NaI. (1) Pour onto vermiculite, sodium bicarbonate, or a sand-soda ash mixture (90/10). (Add slaked lime if fluoride is present.) Mix in paper boxes, place in incinerator, cover with scrap wood and paper, ignite with excelsior train. Stay upwind. Or dump in closed incinerator with afterburner. (2) Dissolve in flammable solvent and spray in incinerator firebox equipped with afterburner and alkali scrubber.

DISPOSAL NOTIFICATION Local air authority.

MAJOR WATER USE THREATENED Recreation.

PROBABLE LOCATION AND STATE OF MATERIAL Colorless gas. Heavy vapors will cling near ground. Some will dissolve. Polymerizes readily in air or sunlight.

WATER CHEMISTRY Subject to polymerization.

COLOR IN WATER Colorless.

ENVIRONMENTAL FATE: TRANSPORT PROCESSES—SORPTION Sorption measurements of VC by four basic food constituents (water, corn oil, casein, and sucrose) were conducted. For water, oil/water emulsions, and casein, it was found that the partition coefficient values (defined as the equilibrium conc of VCM sorbed over the equilibrium VCM in headspace) were fairly constant within the sorbate (VCM) concs studied. At 24 C, the partition coefficient values for oil, casein, and water were 23.7E3, 11.7E3, and 2.1E3, respectively. Sucrose did not sorb detectable amounts of VCM under the experimental conditions employed. (R-75)

ENVIROMENTAL FATE: MICROBIAL EFFECTS Serum bottles (125 mL) were used in the anaerobic toxicity assay (ATA). This allowed gas production to be measured periodically with a syringe and analyzed. The bottles were purged with 70% N_2 and 30% CO_2, and then the following were added: 30 mL of a nutrient and buffer soln ($NaHCO_3$, 5.7 g/L, and $FeCl_2$, 0.37 g/L); 20 mL of sludge from a laboratory digester to serve as a "seed" of anaerobic microorganisms; and 0.100 mL of ethanol to serve as a substrate. VC was added to the ethanol in various concs prior to its addition. The bottles were incubated @ 35 C, and a reduction in the rate or extent of gas production in chemical-containing samples in comparison with controls served as an indicator of inhibition. Inhibition was quantified approximately by determining the conc of VC that causes a 50% reduction in total gas production over a fixed period of time (50% inhibition). Semicontinuous bioassays were conducted using continuously stirred 1.5-L digesters, operated at a 15-D dentention time, and a temperature of 35 C ± 1 C. The digesters were initially seeded with digested municipal sludge. Primary sludge was used as feed. Each day 100 mL of digested sludge was removed, and an equal amount of feed sludge was added. 4, 16, or 64 mg/L of VC were added to ethanol and 0.1 mL of the mixture was added each day prior to feeding. Digester performance was evaluated from daily gas production and routine analysis of COD, total and volatile solids, volatile acids, pH, alkalinity, and gas composition. Batch

results for VC indicate that 5.4 mg/L was marginally inhibitory and 32 mg/L was strongly inhibitory, although some acclimation did occur. A conc of approximately 40 mg/L was required for 50% inhibition of 3.5 D. Semicontinuous digestion with VC did not result in adverse digester performance, even at the highest conc of 64 mg/L. Volatile acids were slightly higher with VC @ 16 and 64 mg/L than in the controls, but no significant signs of stress were apparent. (R-99)

ENVIROMENTAL FATE: OTHER PROCESSES The level of VC found in potable water as a result of PVC piping is directly proportional to the level of residual VC in the pipe. Pipe containing < 1.0 ppm residual showed no VC in the water with a test sensitive to 2 ppb.

TOXICOLOGIAL DATA

MUTAGEN DATA	CODEN
mmo-sat 2,000 ppm/48H	BBRCA9 63,363,75
mma-sat 2 pph	ATSUDG (4),63,80
nma-esc 10,600 μmol/L	BCPCA6 24,9013,75
dnr-esc 100 μg/plate	MUREAV 54,101,78
sln-dmg-ihl 1 pph	MUREAV 57,307,78
sln-dmg-orl 850 ppm	EVSRBT 24,175,81
mma-smc 25,000 ppm	MUREAV 91,381,81
mrc-smc 48 mmol/L/3H	MUREAV 40,85,76
mmo-ssp 130 ppm	CMMUAG 5,25,78
mma-ssp 16 mmol/L/30M	MUREAV 40,85,76
mrc-ssp 48 mmol/L	IARCCD 12,505,76
cyt-man-unr 25 ppm/10Y	MUREAV 51,271,78
cyt-hmn:hla 10 mmol/L	TXCYAC 9,21,78
otr-rat-ihl 2,000 ppm/14W-I	ARTODN 47,71,81
dnd-rat-orl 18 g/kg/2Y-C	CBINA8 22,211,78
oms-rat:lvr 1 nmol	NATUAS 257,134,75
dnd-rat-ihl 2,000 ppm	JCROD7 94,139,79
dnd-rat-ihl 205 ppm/5H	CBINA8 37,219,81
dns-rat:lvr 2,100 μmol/L	CRNGDP 5,1629,84
dni-rat-ivn 9,500 μg/kg	CBINA8 17,239,77
cyt-rat-ihl 150μg/m³/14W-C	GISAAA 43(7),111,78
hma-rat/smc 1 pph/24H-C	MUREAV 91,381,81
mnt-mus-ihl 5 pph/4H	MUREAV 75,191,80
hma-mus/ssp 700 mg/kg	MUREAV 40,85,76
hma-mus/smc 700 mg/kg	TOERD9 3,131,81
mma-ham:lng 20 pph/5H	MUREAV 67,173,79
cyt-ham-ihl 12,500 ppm/6H	ARTODN 45,1,80
cyt-ham-mul 600 mg/kg	MUREAV 53,187,78
sce-ham-ihl 12,500 ppm/6H	ARTODN 45,1,80
msc-ham:ovr 10 pph	EVSRBT 25,91,82

TERATOGENIC DATA	CODEN
ihl-man TCLo:30 mg/m³ (5Y male)	GTPZAB 24(5),28,80
ihl-rat TCLo:1,000 ppm/6H (55D male)	JTEHD6 3,965,77
ihl-rat TCLo:500 ppm/7H (6-15D preg)	TXAPA9 33,134,75
ihl-rat TCLo:1,500 ppm/24H (1-9D preg)	TXCYAC 11,45,78
ihl-rat TCLo:500 ppm/7H (6-15D preg)	EVHPAZ 41,171,81
ihl-rat TCLo:2,500 ppm/7H (6-15D preg)	EVHPAZ 41,171,81
ihl-rat TCLo:250 ppm/6H (55D preg)	JTEHD6 3,965,77
ihl-mus TCLo:30,000 ppm/6H (5D male)	EVHPAZ 21,71,77
ihl-mus TCLo:500 ppm/7H (6-15D preg)	EVHPAZ 41,171,81
ihl-rbt TCLo:500 ppm/7H (6-18D preg)	EVHPAZ 41,171,81

TUMORIGENIC DATA	CODEN
ihl-man TDLo:200 ppm/14Y-I	VAPHDQ 372,195,76
orl-rat TDLo:3,463 mg/kg/52W-I	EVHPAZ 41,3,81
ihl-rat TCLo:1 ppm/4H/52W-I	EVHPAZ 41,3,81
ihl-rat TCLo:10,000 ppm/4H (12-18D preg)	CSHCAL 4,119,77
irp-rat TDLo:21 mg/kg/65W-I	APDCDT 3,216,76
scu-rat TDLo:21 mg/kg/67W-I	APDCDT 3,216,76
ihl-mus TCLo:50 ppm/30W-I	ANYAA9 271,431,76
ihl-ham TCLo:50 ppm/4H/30W-I	APDCDT 3,216,76
ihl-rat TC:50 ppm/7H/26W-C	TXAPA9 68,120,83
ihl-rat TC:100 ppm/7H/26W-C	TXAPA9 68,120,83
ihl mus TC:50 ppm/47W-I	JTEHD6 4,15,78
orl-rat TD:34 gm/kg/3Y-I	EVHPAZ 21,1,77
ihl-mus TC:50 ppm/6H/4W-I	JTEHD6 7,909,81
ihl-mus TC:50 ppm/4H/30W-I	CSHCAL 4,119,77
ihl-rat TC:250 ppm/2Y-I	AANLAW 56,1,74
ihl-hmn TC:300 mg/m³/W-C	GTPZAB 26(1),28,82
ihl-rat TC:5 ppm/4H/52W-I	EVHPAZ 41,3,81
ihl-rat TC:50 ppm/6H/43W-I	JTEHD6 7,909,81

TOXICITY DATA	CODEN
orl-rat LD50:500 mg/kg	DOWCC*
ihl-gpg LCLo:20 ppm/30M	85DVA7 -,1160,38

DATA REFERENCES	CODEN
Agricultural Chemical	
Tumorigen	
Mutagen	
Teratogen	
Toxicology Review	FAZMAE 18,365,74
Toxicology Review	JTEHD6 1(1),47,75

Toxicology Review	CMTVAS 10(3),49,73
Toxicology Review	CHWEAP 70,5,74
Toxicology Review	CANCAR 39,1792,77
Toxicology Review	MUREAV 32(2),93,76
Toxicology Review	ZHPMAT 166,113,78
Toxicology Review	BNYMAM 54,413,78
Toxicology Review	ABMHAM 35, 585,77
Toxicology Review	CBINA8 22,117,78
Toxicology Review	GTPZAB 20(4),46,76
Toxicology Review	VHTODE 22,31,80
Toxicology Review	MUREAV 41,131,7
Carcinogenic Review: Human Positive	IARC** 19,377,7
Carcinogenic Review: Animal Positive	IARC** 7,291,74
Carcinogenic Review: Human Suspected	IARC** 7,291,74
Carcinogenic Review: Animal Positive	IARC** 19,377,79
TLV: Human Carcinogen	DTLVS* 4,427,80
TLV: TWA 5 ppm	DTLVS* 4,427,80
OSHA: Cancer Suspect Agent	CFRGBR 29,1910.1017,81
OSHA Standard:air:TWA 1 ppm; CL 5 ppm/15M	FEREAC 40,23073,75
DOT:Hazard:Flammable Gas; Label:Flammable Gas	CFRGBR 49,172.101,84
Occupational Exposure to Vinyl Chloride Recommended Standard:Air:TWA 1 ppm; CL 5 ppm/15M	
NTP Fourth Annual Report on Carcinogens, 1985	
NIOSH Manual of Analytical Methods, 3rd Ed. See: Method 1007	
NIOSH Current Intelligence Bulletin 28, 1978	
Reported in EPA TSCA Inventory, 1983	
EPA Genetic Toxicology Program, January 1984	
EPA TSCA Section 8(e) Status Report 8EHQ-0680-0345;8EHQ-0982-0457;8EHQ-0378-0104	
Meets Criteria for Proposed OSHA Medical Records Rule	FEREAC 47,30420,82

RECENT FEDERAL REGISTER CITATIONS

CITATION NUMBER 48.207.1088 (48FR49408ff, 10-25-83)

PROPOSED RULE Revision of 40CFR415, Environmental Protection Agency, Clean Water Act; inorganic chemicals manufacturing point source category; effluent limitation guideline, pretreatment standard, New Stationary Source Performance Standard; comments solicited by 12-27-83; toxic pollutant.

CITATION NUMBER 48.209.1088 (48FR49808ff, 10-27-83)

FINAL RULE, PROPOSED RULE Revision of 40CFR439, Environmental Protection Agency, Clean Water Act; two documents, pharmaceutical manufacturing point source category; effluent limitation guideline, pretreatment standard, New Stationary Source Performance Standard; effective date 12-12-83 with exceptions; comments solicited by 12-27-83 for proposed rule. (41FR50676, 42FR6814, 47FR53584, 44FR4450, 44FR50732, 47FR49176)

CITATION NUMBER 48.223.1088 (48FR52380ff, 11-17-83)

FINAL RULE Revison of 40CFR465, Environmental Protection Agency, Clean Water Act; effluent limitation guideline, pretreatment standard, New Stationary Source Performance Standard, coil coating point source category, canmaking subcategory; effective date 1-2-84. (48FR6268)

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NIOSH/CIS, RTECS: KU 9625000
CIS CTCP, Chem Toxicology of Commerical Products: 352
CIS/NCI, CCRIS
CIS, THERMO: NBS TN-270 Series
CIS FRSS (Federal Register Search System)

NON-CIS REFERENCES
EPA, TSCA Inventory List
Merck Index: 9645
EPA, Chemical Spills
EPA, AEROS SOTDAT: 3860
EPA, Pesticides—Registered Inert Ingredients
NBS/NIH, Ionization Potential
NFPA, Hazardous Chemicals: 49300

U.S. International Trade Commission P&I Statistics: PROD/T15-77,PROD/T15-79
European Economic Community Inventory: 9019
EPA, Effluent Guidelines Priority Pollutants
EPA, Organic Chemical Producers: 3520
IPC, Chemical Product: 8612867576445
IPC, Chemical Plant: 867576445
NSF, Hazardous Chemicals List: A4,65
EROICA, Organic Properties
PHS-149 Carcinogenic Activity: G129,J45
NIOSH, NOHS: 76445
ORNL, EMIC
ORNL, ETIC
USCG, CHRIS (Chemical Hazards Response Info System): VSF
Japan, Chem. Sub. Control Law, Existing Chem. Sub.: 2-117
EPA/IERL, Non-Criteria Pollutant Emissions
EPA, Chemical Indicators, Industrial Contamination
EPA, Selected Organic Air Pollutants
Clean Air Act—Section 112
EPA, Carcinogen Assessment Group List of Chemicals
API/TRC, Thermodynamics and Spectroscopy
NTP, Annual Report on Carcinogens. 1:69
EPA/NCTR, Industrial Carcinogen and Mutagen Study
EPA, Environmental Carcinogen Assessment Program
DHEW/NIH, Laboratory Chemicals Monographs
ITII, Toxic and Hazard Indust. Chem Safety Manual
EPA/NSF, Econ. & Tox. Data—Selected Comm. Chem.
IARC, Monographs (Carcinogenicity Reviews): 7:291, 19:377
EPA, Expanded Potential Industrial Car. & Mut.
NLM, Tox Tips: 9:9,1:10,1:13,1:8,1:3,5:5,16:45,1:6
NLM, CHEMLINE: TOXLINE,TDB,TOXBACK
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