Appendix B
Section S

VINYL CHLORIDE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research
New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Vinyl chloride is synthesized by the halogenation of ethylene. The major use of vinyl chloride is in the production of polyvinyl chloride resins. It is classified as a human carcinogen (EPA Group A) and has been shown to induce liver cancer in rats, mice, hamsters, and humans. Based on a rat bioassay, a quantitative estimate of human cancer hazard was calculated for exposure to this compound in drinking water. A drinking water concentration of 0.08 ug vinyl chloride per liter is associated with a 95% upper confidence limit lifetime excess cancer risk of one in a million.

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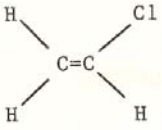
BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical Name	Vinyl Chloride
Synonyms	Chloroethylene, chloroethene, vinyl chloride monomer
CAS #	75-01-4
Chemical formula	$H_2C = CHCl$
Chemical structure	
Molecular weight	62.50
Physical state (room temperature)	colorless gas
Melting point	-153.8 °C
Boiling point	-13.37 °C
Vapor pressure, volatility	2,660 torr at 25 °C
Specific gravity, density	0.9106 at 20 °C
Water solubility	1.1 mg/l at 25 °C
Log octanol/water partition coefficient	0.60
Taste threshold (water)	not available
Odor threshold (water)	3.4 ppm
Odor threshold (air)	1,200-3,000 ppm
Conversion factors	1 ppm = 2.6 mg/m^3

Production and Use

Vinyl chloride is a synthetic chemical with no natural sources. In the U.S., vinyl chloride has been synthesized commercially for over fifty years reaching a production level of 7.5 billion pounds in 1984 (Weber,

1985). Vinyl chloride is used in the production of vinyl chloride polymer (polyvinyl chloride). Polyvinyl chloride is used in the manufacture of piping, and conduit, electrical wire insulation and cables, food packaging materials, floor coverings, and a variety of other industrial products.

Guidelines, Regulations, and Standards

The Occupational Safety and Health Administration (OSHA) standard, a 1 ppm 8-hour time-weighted-average (TWA) with a TWA maximum excursion of 5 ppm over a 15 minute period, was effective as of April 5, 1975.

Ambient Water Quality Criteria were published by the U.S. Environmental Protection Agency (U.S.EPA, 1980). Assuming consumption of 2 L of water and 6.5 g of fish per day by a 70-kg adult, a vinyl chloride level of 2.0 ug/L was estimated to limit excess lifetime cancer risk to one in a million.

Health Advisory drinking water guidance describing non-carcinogenic effects has been developed for vinyl chloride by the Office of Drinking Water (U.S.EPA, 1985a). Assuming that a 10-kg child consumes 1 L of water per day, the ten-day and longer-term Health Advisories are 2,600 ug/L and 13 ug/L, respectively. The longer-term Health Advisory is 46 ug/L for a 70-kg adult with 2 L daily water consumption.

The U.S. Environmental Protection Agency under the Safe Drinking Water Act promulgated final recommended Maximum contaminant levels (RMCLs) and proposed maximum contaminant levels (MCLs) (U.S.EPA, 1985b). The RMCL and MCL for vinyl chloride are zero and 1 ug/L, respectively.

ENVIRONMENTAL EXPOSURE

Fate and Transport

The rapid transfer of vinyl chloride from water to the atmosphere by volatilization is the most significant process affecting environmental distribution. Under experimental conditions, the half-life of aqueous vinyl chloride in a continuously stirred open container was 27 minutes. In contrast, quiescent vinyl chloride at 22 ^{o}C yielded an evaporative half-life of 290 minutes (U.S.EPA, 1984).

Oxidation, hydrolysis, biodegradation, and bioaccumulation are not important transport and fate processes for vinyl chloride.

Ambient Levels

Vinyl chloride in the environment can originate from vinyl chloride synthesis plants, polyvinyl chloride resin production plants, and polyvinyl chloride fabricating plants (U.S. EPA, 1984).

The Federal Reporting Data Systems survey on people served by primary water supply systems was used by the U.S. Environmental Protection Agency to estimate exposure to vinyl chloride through drinking water. An estimated 1,922,000 individuals were exposed to levels of vinyl chloride in drinking water at or above 1.0 ug/L (Table I) (U.S.EPA, 1984).

The Office of Science and Research, New Jersey Department of Environmental Protection, sampled public water supplies statewide for over 100 substances during the period 1978 through 1981. Vinyl chloride was detected in one sample at a level of 0.8 ug/L.

Potable water purveyors in New Jersey recently monitored listed chemicals listed in the New Jersey Assembly Bill A-280. Vinyl chloride was found by one purveyor at 1.1 ug/L.

Table I.
Estimated Drinking Water Intake of Vinyl Chloride

Exposure Level (ug/l)	Population	Intake* (ug/kg/day)
$\geq$ 1.0	1,922,000	>0.028
> 5.0	591,000	>0.14
> 10	118,000	>0.29
> 50	118,000	>1.4

*Assumes 70 kg man consumes 2 L of water per day.
(U.S.EPA, 1984)

METABOLISM AND PHARMACOKINETICS

Absorption

Vinyl chloride administered by gastric intubation of aqueous solution is rapidly absorbed from the gastrointestinal tract of male Wistar rats (Withey, 1976).

Tissue Distribution

Inhaled vinyl chloride was rapidly absorbed by the lungs and immediately accumulated in the liver (Duprat et al., 1977). Rats were exposed to 20,000 ppm (^{14}C)vinyl chloride for 5 minutes. Ten minutes post-exposure, radioactivity was found in the liver, bile duct, digestive lumen, and kidneys. Within 3 hours radioactivity was also detected in the urinary system, salivary and lacrimal glands, skin, and thymus.

The liver was found to retain orally administered vinyl chloride (Watanabe et al., 1976a). Male Sprague-Dawley rats were given single oral doses by gavage of 0.05, 1, or 100 mg/kg of (^{14}C)vinyl chloride dissolved in corn oil. The percentage of the dose expired as unchanged vinyl chloride was 1, 2, and 67%, respectively. After 72 hours, the liver was found to retain the highest percentage of radioactivity at all dose levels.

Metabolism

Two metabolic pathways for vinyl chloride have been described (Bartsch and Montesano, 1975). One involves alcohol dehydrogenase and the other, the mixed function oxidase.

It has been suggested that vinyl chloride metabolism is saturable, that other metabolic pathways may be involved, and that predominance of a given pathway depends on the level of expsoure (Bolt et al., 1977; Watanabe et al., 1976).

Excretion

As acute oral or inhalation vinyl chloride exposure in rats increased, a greater percentage of vinyl chloride was expired unchanged, and a lesser percentage of metabolite was excreted in the urine. In rats, urinary metabolites included N-acetyl-5-(2-hydroxyethylcysteine) and thiodiglycolic acid (Watanabe et al., 1976a, b).

Human Exposure and Body Burden

Vinyl chloride does not bioaccumulate to a significant extent in animals or humans.

HEALTH EFFECTS

Overview

Vinyl chloride is an established human carcinogen: IARC Category 1 and U.S.EPA Group A. Increased occurrence of liver, brain, lung, and hemolymphopoietic system tumors has been associated with occupational vinyl chloride exposure (Beaumont and Breslow, 1981; IARC, 1979). Regardless of exposure route, vinyl chloride induced angiosarcomas in mice, rats and hamsters (Maltoni et al., 1984; Feron et al., 1981). Chronic inhalation symptoms in humans include hepatotoxicity, pulmonary insufficiency, central nervous system (CNS) disturbances, and cardiovascular manifestations (Selikoff and Hammond, 1975).

Human

Acute. Two deaths were reported at a Canadian vinyl chloride plant following acute exposure to vinyl chloride. Congestion of the liver, spleen, and kidney was noted at autopsy (IARC, 1979).

Acute and subacute occupational vinyl chloride exposure (100 to 2,298 mg/m^3) produced euphoria, intoxication and narcosis.

Chronic. Several systemic disorders are associated with occupational exposure to vinyl chloride. Vinyl chloride associated diseases include acro-osteolysis, Raymand's syndrome, hepatomegaly, liver fibrosis, splenomegaly, thrombocytopenia, and angiosarcoma (Selikoff and Hammond, 1975).

Animal

Acute. The 2-hour LC_{50} of vinyl chloride gas was 113,000 ppm for mice and 150,000 ppm for rats (IARC, 1979). Animals exhibited excitement, convulsions, accelerated respiration and respiratory failure. Internal organ congestion was found at necropsy.

Behavioral and Central Nervous System

At high inhalation exposure levels, workers have experienced dizziness, headaches, euphoria and narcosis.

Reproductive, Embryotoxic, and Teratogenic

Animal laboratory investigations of fertility, endocrine, and gonadal effects were inadequate for evaluation. Vinyl chloride was not teratogenic or embryotoxic in rats at doses below those causing maternal toxicity (John et al., 1977). Vinyl chloride has, however, been shown to be a transplacental carcinogen in rats (Maltoni et al., 1984).

Genetic

The mutagenic activity of vinyl chloride is summarized in Table II. Vinyl chloride metabolites induced point mutations in bacterial and mammalian systems, gene conversion in yeast, and chromosomal aberrations in male rats.

Carcinogenicity

Human Epidemiology. The National Institute for Occupational Safety and Health (NIOSH) conducted a retrospective occupational cohort mortality investigation at four facilities that engaged in the polymerization of vinyl chloride (Waxweiler et al., 1976). The cohort, consisting of 1,294 male workers with a minimum of 5 years of cumulative exposure and 10 years following initial exposure, was observed through December 31, 1973. One hundred thirty-six (136) deaths were reported and 7 individuals were lost to follow-up. With a minimum 15 year latency period, statistically significant excesses of malignant neoplasms were noted in the brain and CNS, respiratory system, and biliary and liver specific sites (Table III). The predominant histologic of the liver cancers was angiosarcoma.

Table II.

Genetic Toxcity of Vinyl Chloride

Process	End Point	Test System	Conclusion	References
Gene Mutation	Base-pair substitution	Ames *Salmonella typhimurium* histidine reversion with metabolic activation	Positive	Bartsch et al., 1975 McCann et al., 1975
		E. coli K-12 arginine reversion with metabolic activation	Positive	Greim et al., 1975
		Chinese hamster V79 cells ouabain resistance with metabolic activation	Positive	Huberman et al., 1975 Drevon et al., 1977
Chromosomal Rearrangement Homologous recombination	Gene conversion	*Saccharomyces cerevisiae* (yeast)	Positive	Loprieno et al., 1976 Loprieno et al., 1975
Chromosomal Rearrangement Non-homologous recombination	Chromosomal aberrations	Alderley Park male rats *in vivo*	Positive	Anderson and Richarson, 1981

Table III.

Mortality by Cause for Vinyl Chloride Workers

Cause of Death (7th ICDA)	Time Since First Exposure 10-14 years Obs.	SMR	15 years Obs.	SMR
All Malignant Neoplasms (140-205)	4	61	31	184**
Brain and CNS (193)	0	0	3	498*
Respiratory System (160-164)	1	50	11	194*
Biliary and Liver (155-156A)	0	0	7	1,606**
Lymphatic and Hematopoietic System (200-205)	1	125	3	176

* Significant at $p<0.05$.
** Significant at $p<0.01$.

Table IV.
Mortality by Cause for Male Workers in the Manufacture of Polyvinyl Chloride in Great Britain, 1940 to 1974

Cause of Death (ICD No. 8)	Observed	Expected	SMR
All deaths (1-999)	393	521.22	75.4
All cancers (140-239)	115	126.77	90.7
Cancer of stomach (151)	14	15.33	91.3
Primary cancer of liver (155)	1	0.71	140.8
Cancer of lung (162-163)	46	51.23	89.8
Cancer of brain (191)	2	3.66	54.6
Other liver cancers (197.7, 197.8, etc.)	3	0.93	322.6
Lymphatic and hematopoietic tissues (200-207)	9	9.01	99.9
Liver disease (570-573)	1	2.68	37.3

Table V.
Liver Cancer Deaths by Exposure to Vinyl Chloride

Cause of Death	Constant Exposure Observed	Expected	SMR	High Exposure Observed	Expected	SMR
All cancers	28	39.70	70.5	9	9.59	93.8
Liver cancer	2	0.54	370.5	2	0.13	1538.5

A study of mortality patterns in the manufacturing industry in Great Britain was coordinated by the Employment Medical Advisory Service (Fox and Collier, 1977). 7,717 workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride between the period 1940 and 1974 were identified. A total of 409 deaths (393 men and 16 women) were recorded; 148 workers emigrated, 85 workers could not been traced, and 72 workers were excluded because of inadequate work history. The male mortality pattern is displayed in Table IV. Two of the 4 liver cancer deaths were confirmed by a panel of histopathologists as due to angiosarcoma of the liver. Both men were exposed to constant (most of the time) and high (maximum time- weighted-average greater than 200 ppm) levels of vinyl chloride for an average of 10.5 years. The standardized mortality ratio (SMR) for liver cancer according to exposure is 370.4 for constant exposure and 1,538.5 for high exposure (Table V).

Animal Laboratory Bioassays. A comprehensive evaluation of the carcinogenic potential of vinyl chloride was undertaken by Maltoni et al. (1984). Vinyl chloride was administered to experimental animals of different species, strains, sexes, and ages in separate experiments employing oral or inhalation routes of exposure. A complete autopsy and histopathological examination was performed for each animal. Only data pertaining to the oral route of exposure will be presented in this document.

In the experiment designated BT11, 13-week old Sprague-Dawley rats were treated with 3.33, 16.65, or 50 mg vinyl chloride/kg body weight, in olive oil, by gavage. Controls received olive oil by gavage. Animals were treated 5 times per week for 52 weeks. There were 40 animals of each sex and treatment group. Animals were kept until their natural death. The rate of angiosarcoma of the liver among treated animals was significantly higher than the rate among controls (Table VI).

In the experiment designated BT27, 10-week old Sprague-Dawley rats received 0.03, 0.3, or 1 mg vinyl chloride/kg body weight, in olive oil, 5 times per week for 52 or 59 weeks. Controls received olive oil according to the same schedule. There were 75 animals of each sex and treatment group. Animals were maintained until their natural death (week 136). Angiosarcoma occurred slightly more frequently among the mid- and high-dose groups of both sexes, but the elevation in incidence was not statistically significant (Table VI).

The Netherlands Organization for Applied Scientific Research conducted two carcinogenicity studies of vinyl chloride (Feron et al., 1981; Til et al., 1983). Vinyl chloride monomer orally administered to rats induced hepatic tumors (angiosarcomas, hepatocellular carcinomas, and neoplastic nodules).

Table VI
Incidence of Liver and Lung Tumors in Rats
Induced by Vinyl Chloride[a]

Dose Levels[b]		Responses (# animals with tumor/# animals at risk		
Experimental ppm	Adjusted mg/kg/day	Male	Female	Combined
	Maltoni (BT11) - Liver Angiosarcoma[c]			
0	0			0/76
3.33	1.19			0/71
16.65	5.95			10/73
50	17.86			17/71
	Maltoni (BT27) - Liver Angiosarcoma[c]			
0	0			0/34
0.03	0.011			0/33
0.3	0.107			1/34
1.0	0.357			3/50
mg/kg/day				
	Feron - Liver Hepatocellular Carcinoma[d]			
0	0	0/55	0/57	
1.7	1.7	1/58	4/58	
5.0	5.0	2/56	19/59	
14.1	14.1	8/59	29/57	
	Feron - Liver Angiosarcoma[d]			
0	0	0/55	0/57	
1.7	1.7	0/58	0/58	
5.0	5.0	6/56	2/59	
14.1	14.1	27/59	9/57	
	Feron - Lung Angiosarcoma[d]			
0	0	0/55	0/57	
1.7	1.7	0/58	0/58	
5.0	5.0	4/56	1/59	
14.1	14.1	19/59	5/57	

a Data are taken from Maltoni (1984) gavage study and Feron (1981) diet study.
b Dose levels for the Maltoni study are converted from mg/kg to mg/kg/day by multiplying by a factor of 5/7 to account for the fact that vinyl chloride was administered 5 days per week. Doses are further multiplied by a factor of 52/104 = 1/2. No adjustment was necessary for the Feron et al. (1981) study.
c Number of animals at risk is the number of animals alive at the time of the first response (46 weeks for BT11 and 92 weeks for BT27).
d Number of animals at risk is the number of animals examined.

In the study conducted by Til et al. (1983), 32-day old Wistar SPF rats of both sexes were exposed to vinyl chloride monomer (VCM) by incorporating varying proportions of VCM-containing (4,600 ppm) polyvinyl chloride (PVC) and VCM-free PVC powder into the diet to comprise a total of 1% dietary PVC. The control groups received 1% VCM-free PVC, and the high-dose groups received 1% VCM-containing PVC. The low- and mid-dose groups received an appropriate mixture of the two PVC powders. This diet was administered for 4 consecutive hours each day for life with drinking water provided ad libitum. Food intake and evaporation loss of VCM was quantitatively determined. The delivered VCM dose was assessed by subtracting the amount of VCM excreted in the feces from the previous quantity. Delivered VCM was at a level of 0, 0.014, 0.13, or 1.3 mg/kg body weight per day.

One hundred (100) animals were randomly assigned to each treatment and sex group, except for the high-dose group which consisted of 50 animals of each sex. Male rats surviving to week 149 and females surviving to week 150 of the study were sacrificed. Complete autopsies and histopathological examinations were performed on all animals. The elevated incidence of neoplastic liver nodules in high-dose males and females over controls was statistically significant ($p < 0.05$). There were no statistically significant increases of hepatocellular carcinoma or angiosarcoma of the liver in treated animals over controls.

In the study by Feron et al. (1981), weanling Wistar SPF rats were subjected to the same basic protocol as employed by Til et al. (1983). The dietary concentration of PVC was 10% and the concentration of VCM in the VCM-containing PVC was 4,000 ppm. The VCM delivered dose was calculated as 0, 1.7, 5.0, or 14.1 mg VCM/kg body weight per day.

Animals were randomly assigned with 80 animals per sex in the control and high-dose groups and 60 animals per sex in the low- and mid-dose groups. Terminal sacrifices were performed when the mortality in the control groups had reached 75% (males, week 135; females, week 144). In addition, interim sacrifices at 26 and 52 weeks were performed on groups of 10 animals per sex from the control and high-dose groups. The frequency of angiosarcoma of both the liver and the lung was statistically elevated in the high-dose groups of both sexes. Hepatocellular carcinoma was increased in all dose groups reaching statistical significance among the high-dose males and mid- and high-dose females. The elevation in the incidence of neoplastic liver nodules in all dose groups except the low-dose males was statistically significant (Table VI).

QUANTITATIVE RISK ESTIMATION

Studies Useful for Risk Assessment

Epidemiologic studies can provide appropriate information for quantitative risk assessment. Presently, vinyl chloride exposure information is missing in several of the occupational studies. This deficiency prevents the use of epidemiologic studies for vinyl chloride

risk assessment.

Animal bioassay data will be employed for vinyl chloride risk assessment. The rationale applied for the selection of animal studies to be used for quantitative risk assessment was based on the guidelines set forth in Crump and Howe (1980). Experimental designs judged to be most suitable involved treatment of animals for at least 85% of their expected life span and observation of animals for at least 90% of their expected life span. The oral exposure route was considered relevant to drinking water quality criteria. The highest dose should maximize malignant responses without causing overt chronic toxicity. The Feron et al. (1981) study satisfied these guidelines. Liver cancer is the response of interest in both rats and humans.

Calculation of a Health-Based Maximum Contaminant Level

The dose-response relationships obtained from the Feron et al. (1981) study are modeled by using regression techniques. The multistage model and multistage Weibull model are used in this analysis for low dose extrapolation with quantal and time-to-tumor data, respectively. The multistage model is given by

$P(d) = 1 - \exp(-q_0 - q_1 d - \ldots - q_k d^k)$, $q_i \geq 0$, $i = 0, 1, \ldots k$, where $P(d)$ is the lifetime probability of cancer at dose d. In practice, k is set equal to the number of dose groups less one.

The multistage Weibull model is given by

$P(d,t) = 1 - \exp[(-q_0 - q_1 d - \ldots - q_k d^k)(t-)^B]$, $q_i \geq 0$, $i = 0, 1, \ldots, k$, where $P(d,t)$ is the lifetime probability of cancer at dose d and time t. Likewise, k is set equal to the number of dose groups less one. The multistage model is implemented using an updated version of the computer program GLOBAL82 and the multistage Weibull model is implemented by using the computer program WEIBULL85. All calculations were provided by K.S. Crump and Company (Crump, 1986).

Risk has been defined as "extra risk", i.e.,

$[P(d) - P(0)]/[1-P(0)]$, where $P(d)$ is the lifetime probability of dying of liver cancer when exposed to vinyl chloride dose d, and $P(0)$ is the lifetime probability of dying of liver cancer when not exposed to vinyl chloride.

A risk level of one in a million was selected for a lifetime exposure scenario. The 95% upper confidence limit on risk is linear at low doses and will be considered a plausible upper bound on risk.

Animal-to-human extrapolation is based on the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when dose is measured in the same unit for both species (Crump and Howe, 1980). The units of mg/m^2 body surface area per day will be used for animal-to-human extrapolation. If D_A represents animal dose in mg/kg/day, then the human dose (D_H) is given by

$$D_H = D_A \ (W_A/W_H)^{1/3},$$

where W_A and W_H are the weights of animals and humans, respectively. The standard assumption is that a 70 kg adult consumes 2 L of water per day.

The results of fitting the multistage model to female hepatocellular carcinoma and male liver angiosarcoma, and the multistage Weibull model to male angiosarcoma at all sites are listed in Table VII. Female hepatocellular carcinoma is the most sensitive response and will be used in calculating vinyl chloride cancer risk.

The human dose in micrograms per liter

= human dose (mg/kg/day) x (1000 ug/mg) x (70 kg)/(2 L/day),
= animal dose (mg/kg/day) x $(W_A/W_H)^{1/3}$ x 35000,
= animal dose (mg/kg/day) x $(0.35 \text{ kg}/70 \text{ kg})^{1/3}$ x 35000,
= animal dose (mg/kg/day) x 35000/5.8.
= (1.4×10^{-5}) (35000)/5.8
= 0.08 ug/L.

A drinking water level of 0.08 ug vinyl chloride per liter is associated with a lifetime excess cancer risk of one in a million.

Table VII.

Vinyl Chloride Quantitative Risk Assessment

Sex	Organ	History	Animal Dose (mg/kg/day)
Female	Liver	Hepatocellular Carcinoma	1.40×10^{-5}
Male	Liver	Angiosarcoma	4.52×10^{-5}
Male	All	Angiosarcoma	3.62×10^{-5}

Assumptions and Uncertainty

The extrapolation of cancer risk from animal bioassay data to human cancer risk is carried out by assuming that animals and humans are equally sensitive relative to a particular measure of dose. The interspecies conversion factor used is mg/m^2 surface area per day. This is equivalent to $(\text{rat weight/human weight})^{1/3}$. Rat and human weights are taken as 0.35 and 70 kg, respectively.

In deriving maximum drinking water levels, a 70-kg adult is assumed to consume 2 L of water per day for life. The risk level applied is the 95% upper confidence level on one in a million extra risk. This is considered a plausible upper bound on risk.

Conclusions

Vinyl chloride is classified as a human carcinogen (IARC Category 1; EPA Group A). Vinyl chloride induces liver cancer in humans, rats, mice, and hamsters. The quantitative estimation of hazard was based on a rat bioassay. A drinking water concentration of 0.08 ug vinyl chloride per liter is associated with a lifetime excess cancer risk of one in a million.

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