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Ambient Water Quality Criteria for Vinyl Chloride

AMBIENT WATER QUALITY CRITERIA FOR

VINYL CHLORIDE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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TABLE OF CONTENTS

CRITERIA DOCUMENT

VINYL CHLORIDE

CRITERIA

Aquatic Life

No freshwater organisms have been tested with vinyl chloride and no statement can be made concerning acute or chronic toxicity.

No saltwater organisms have been tested with vinyl chloride and no statement can be made concerning acute or chronic toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of vinyl chloride through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 20 µg/l, 2.0 µg/l, and 0.2 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, exluding consumption of water, the levels are 5,246 µg/l, 525 µg/l, and 52.5 µg/l, respectively.

INTRODUCTION

Vinyl chloride has been used for over 40 years in producing polyvinyl chloride (PVC) which in turn is the most widely used material in the manufacture of plastics throughout the world. Of the estimated 18 billion pounds of vinyl chloride produced worldwide in 1972, about 25 percent was manufactured in the United States (Berk, et al. 1976). Production of vinyl chloride in the United States reached slightly over 5 billion pounds in 1978 (U.S. Int. Trade Comm.). Production of vinyl chloride has risen nearly 14 percent annually between 1968 and 1973 as evidenced by the broad dependence of nearly every branch of industry and commercial activity upon products and components fabricated from polyvinyl chloride (U.S. EPA, 1974).

Vinyl chloride and polyvinyl chloride are used in the manufacture of numerous products in building and construction, the automotive industry, for electrical wire insulation and cables, piping, industrial and household equipment, packaging for food products, medical supplies, and is depended upon heavily by the rubber, paper and glass industries (Maltoni, 1976). Polyvinyl chloride and vinyl chloride copolymers are distributed and processed in a variety of forms including dry resins, plastisol (dispersions in plasticizers), organosol (dispersions in plasticizers plus volatile solvent), and latex (colloidal dispersion in water). Latexes are used to coat or impregnant paper, fabric, or leather (Falk, et al. 1974).

As of 1974, approximately 15 plants synthesized the vinyl chloride monomer, 43 facilities were engaged in the polymerization of PVC and over 7,500 plants fabricated products from PVC. About 1,500 workers were employed in monomer synthesis and an additional 5,000 in polymerization operations

(Falk, et al. 1974). As many as 350,000 workers were estimated to be associated with fabrication plants (U.S. EPA, 1974). By 1976, it was estimated that nearly one million persons were associated with manufacturing goods derived from PVC (Maltoni, 1976).

Vinyl chloride (CH_2CHCl; molecular weight 62.5) is a highly flammable chloroolefinic hydrocarbon which emits a sweet or pleasant odor and has a vapor density slightly more than twice that of air (Weast, 1972; Braker and Mossmein, 1971). It has a boiling point of -13.9°C and a melting point of -153.8°C. Its solubility in water at 28°C is 0.11 g/100g water and it is soluble in alcohol and very soluble in ether and carbon tetrachloride (Weast, 1972). Vinyl chloride is volatile and readily passes from solution into the gas phase under most laboratory and ecological conditions. Many salts such as soluble silver and copper salts, ferrous chloride, platinous chloride, iridium dichloride, and mercurous chloride to name a few, have the ability to form complexes with vinyl chloride which results in its increased solubility in water (U.S. EPA, 1975). Conversely, alkali metal salts such as sodium or potassium chloride may decrease the solubility of vinyl chloride in ionic strengths of the aqueous solution (Fox, 1978). Therefore, the amounts of vinyl chloride in water could be influenced significantly by the presence of salts (U.S. EPA, 1975).

Vinyl chloride introduced into aquatic systems will most probably be quickly transferred to the atmosphere through volatilization. In fact, results from model simulations indicate that vinyl chloride should not remain in an aquatic ecosystem under most natural conditions. Once in the troposphere, vinyl chloride reacts at an extremely rapid rate with hydroxyl radicals, exhibiting a half-life on the order of a few hours with the subsequent formation of hydrogen chloride or formyl chloride as possible products.

Formyl chloride, if formed, is reported to decompose thermally at ambient temperatures with a half-life of about 20 minutes, yielding carbon monoxide and hydrogen chloride. As a result, vinyl chloride in the troposphere should be decomposed within a day or two of release.

Based on the information found, it does not appear that oxidation hydrolysis, biodegradation or sorption, are important fate processes for vinyl chloride in the aquatic environment (U.S. EPA, 1979).

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Aquatic Life Toxicology*

EFFECTS

Few data are available for freshwater or saltwater organisms and vinyl chloride. One paper by Brown, et al. (1977) described an acute test using northern pike, but the description of test methods was incomplete and the control organism procedures were quite different from those for the exposed organisms. No difference could be detected between bacterial growth in cultures of five bacterial populations and in test cultures containing up to 900,000 µg/l, indicating that vinyl chloride was not toxic to bacteria at these concentrations (Hill, et al. 1976).

Summary

No appropriate acute or chronic data are available for any freshwater or saltwater organisms and vinyl chloride.

CRITERIA

No freshwater organisms have been tested with vinyl chloride, and no statement can be made concerning acute or chronic toxicity.

No saltwater organisms have been tested with vinyl chloride, and no statement can be made concerning acute or chronic toxicity.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation.

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Brown, E.R., et al. 1977. Chemical pollutants in relation to diseases in fish. Ann. N. Y. Acad. Sci. 298: 535.

Hill, J., IV, et al. 1976. Dynamic behavior of vinyl chloride in aquatic ecosystems. EPA-600/3-76-001. U.S. Environ. Prot. Agency.

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Sufficient evidence has been accumulated in recent years implicating vinyl chloride as a human and animal carcinogen. The first four human cases of liver angiosarcoma in workers employed by a vinyl chloride plant were reported by Creech and Johnson in 1974. The first experimental data on the carcinogenic effects of vinyl chloride in rats were published by Viola, et al. in 1971; a comprehensive report on dose-effect relationship of vinyl chloride in experimental animals by Maltoni, et al. followed in 1974. These initial reports spurred a series of retrospective epidemiologic investigations of workers in the vinyl chloride industry (Creech and Johnson, 1974; Baxter, et al. 1977; Infante, et al. 1976b; Brady, et al. 1977) and supportive experimental studies in animals. The large amount of published literature was summarized in several comprehensive reviews; of note are the two volumes compiled by the New York Academy of Sciences in 1975 and 1976, a review in the Proceedings of the Royal Society of Medicine (1976) and the U.S. EPA Scientific and Technical Assessment Report (STAR) on Vinyl Chloride and Polyvinyl Chloride (1975a).

The purpose of this report is to briefly summarize the published reviews and reports including more recently published data with special attention to research studies concerned with the extent of human exposure to vinyl chloride contaminated public water supplies. Unfortunately, toxicologic or epidemiologic data on this issue are not available, since vinyl chloride appears to escape in gaseous phase from surface waters; only one report was located

indicating the presence of small amounts of vinyl chloride in water supplies of two cities. There is scanty information available on the carcinogenic effects of vinyl chloride due to ingestion of vinyl chloride-contaminated olive oil (Maltoni, 1976).

There is no evidence that vinyl chloride exists in nature per se. A study by Hoffman, et al. (1976) does suggest that vinyl chloride may be released as a combustion product from organic material where inorganic chloride was originally present. Vinyl chloride is synthesized as chlorinated olefinic hydrocarbon monomer derived from petrochemical feedstock and chlorine. In 1974, the U.S. production of PVC was over 4 billion pounds. Emissions from these sources, therefore, present the primary risk of vinyl chloride exposure for workers employed in these industries and populations living in their vicinity; however, additional exposure, even though it is thought to be minimal, can occur via ingestion of contaminated food and water, and through the skin. Vinyl chloride levels from detectable to high have been found in drinking water, beverages, food, cosmetics, and other consumer products. Aerosol products containing vinyl chloride as a propellent have been discontinued. Municipal incinerators may be an additional source of vinyl chloride emissions. Experimental data by Boettner, et al. (1973) have demonstrated that vinyl chloride monomer may be released under certain combustion conditions from some samples of PVC. It is not clear whether this vinyl chloride represents untrapped vinyl chloride monomer in the PVC mixture that was being tested. There are other data (Close, et al. 1977) which indicate that polyvinyl chloride (PVC) does not usually depolymerize into vinyl chloride mono-

mer even under a variety of conditions. Whether these particular processes can occur in municipal incinerators is uncertain at this time. Insufficient published data are available on exposure levels of persons living in the vicinity of PVC fabricating plants, or on the release of the monomer from various plastic products. Yet, all of these are additional potential sources of population exposure.

EXPOSURE

Ingestion from Water

Small amounts of vinyl chloride may be present in public water supplies as a result of vinyl chloride industrial wastewater discharges. Levels of vinyl chloride in wastewater effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of wastewater from seven areas (representing 12 PVC-vinyl chloride plants) ranged from 0.05 ppm to 20 ppm (U.S. EPA, 1974). More typically, levels of 2 to 3 ppm were found. In these studies, values represent vinyl chloride concentrations in three 24-hour composite wastewater samples. The low solubility (0.11 gms/100 gms water) (Weast, 1978) and high volatility of vinyl chloride in water limit the amount present in a given volume; however, the presence of other agents, such as salts, increases the solubility of vinyl chloride. However, it may be speculated that other materials such as fumates, surfactants, and particulates may extend the residence time of vinyl chloride in water and therefore increase its effective concentration for a given exposure situation via water route (U.S. EPA, 1975a).

Polyvinyl chloride pipe used in water distribution systems provides another source of low levels of vinyl chloride in drinking

water. The U.S. EPA's Water Supply Research Division studied five water distribution systems which used PVC pipes (Dressman and McFarren, 1978). Sites chosen were representative of extremes in climatic conditions and of variable age, length, and size of pipe. Low concentrations of vinyl chloride were detected in three of the five water supply systems. Water from the most recently installed and the longest pipe system had the highest vinyl chloride concentration (1.4 µg/l). Traces of vinyl chloride (0.03 and 0.06 µg/l) were still present in the other two systems (which were the oldest), about nine years after installation.

The National Sanitation Foundation (NSF) annually issues a list of PVC pipe and fittings conforming to standard No 14. Those manufactured in 1977-78 and listed will be low in residual monomer. A level of 10 ppm or less of residual monomer in finished pipe and fittings was adopted as a voluntary standard in February, 1977. Three times a year NSF field personnel collect test samples. More than 95 percent of these samples conformed to the standard in 1977. However, in testing samples of water supplies in several cities, vinyl chloride (5.6 µg/l and 0.27 µg/l) was detected in the water supply of at least two American cities (U.S. EPA, 1975b).

Although the vinyl chloride concentrations in public water supplies tested so far are below the minimum levels associated with reported carcinogenic or other toxic responses, confirmation studies with experimental animals are in progress. For example, investigations are being conducted by Professor Cesare Maltoni of Bologna, Italy, to determine the incidence and type of cancer produced by ingestion of low doses of vinyl chloride, including 1.0, 0.3,

and 0.03 mg/kg/day. Because of the long latency of the carcinogenic response, the results of these investigations will not be available for some time (Maltoni, 1976).

The environmental fate of vinyl chloride was evaluated in a closed model aquatic ecosystem by Lu, et al. in 1977. Five organisms, including algae and fish, bioaccumulated small amounts of vinyl chloride and/or metabolites of vinyl chloride. The low tissue values observed in fish as a result of the three day exposure suggest that vinyl chloride is not biomagnified to any great degree.

Ingestion from Food

Small quantities of vinyl chloride are ingested by humans since the entrained monomer migrates into foods packaged in PVC wrappings and containers (U.S. EPA, 1975a). The solubility of vinyl chloride in foods packaged in water is low (0.11 g/100 g water); however, the monomer is soluble in alcohols and mineral oil. In 1973, prior to the recognition of the carcinogenicity of vinyl chloride in man, the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages as a result of studies indicating that levels up to 20 mg/kg were present in liquors so packaged [International Agency for Research on Cancer (IARC), 1974]. The reason for this action was that vinyl chloride migration into the liquor resulted in a discoloration and unpleasant taste. The Food and Drug Administration analyzed a number of PVC packaged products for vinyl chloride content in 1974. Concentrations ranged from "not detectable" to 9,000 ppb. Vegetable oils and apple cider contained the highest concentration.

Table 1 presents some levels of vinyl chloride found in foods and beverages in 1975.

Withey and Collins (1976) have developed a statistical model for use in equating oral dose levels of vinyl chloride to inhalation exposure levels in rats, using vinyl chloride blood level time curves. For example, the authors concluded that "if the total daily liquid intake contained 20 ppm vinyl chloride, then the area generated under the blood level time curve for rats would be equivalent to an inhalation exposure of about 2 ppm for 24 hours."

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

TABLE 1

Levels of Vinyl Chloride in Alcoholic Beverages, Peanut Oil, and Vinegars Contained in PVC Bottles[f]

Sample	Type of PVC Bottle	No. of Samples	Range, µg/ml[a]	Av., µg/ml
Alcoholic beverages				
Gin	A[e]	4	0.21-0.65	0.44
Martini	A	4	0.86-1.60	0.37
Beaujolais	B	4	0.15-0.84	0.60
Cognac	C	4	0.025	-
Sherry	D	6	0.38-0.98	0.66
Vegetable oil				
Peanut	H	10	0.3-3.29[b]	2.16[b]
Vinegars				
Apple cider	E	13	0.56-8.40	3.49
Malt	E	4	0.16-2.28	1.86
Malt	F	7	0,[c] 1.5[d]	-
Malt	G	1	0[c]	-
Salad	G	2	0[c]	-
Red wine	G	1	0[c]	-

[a]Analyzed on column A, average of duplicate injections

[b]Values expressed as ppm

[c]No vinyl chloride detected, detection limit 0.01 µg/ml

[d]Single positive, six negative

[e]Letters designate manufacturing brands of PVC

[f]Source: Williams and Miles, 1975

No measured steady-state BCF is available for vinyl chloride, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol-water partition coefficient (P). Since no measured log P value could be found, a log P value of 1.38 was calculated for vinyl chloride using the method described in Hansch and Leo (1979). Thus, the steady-state bioconcentration factor for vinyl chloride is estimated to be 2.97. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for vinyl chloride and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 2.97 x 0.395 = 1.17.

Inhalation

Inhalation of vinyl chloride is the principal route of exposure to people working in or living near vinyl chloride industries. Vinyl chloride boils at -13.9°C and is a gas at normal atmospheric temperature and pressure. The odor is usually described as sweet or pleasant and those familiar with the odor may first detect it at 1,200 to 2,000 ppm.

Because of its narcotic properties (Patty, et al. 1930), vinyl chloride was considered for use as an anesthetic agent, but reports in 1947 of cardiac arrythmias in dogs following its inhalation resulted in vinyl chloride being dropped from consideration as an anesthetic (Oster, et al. 1947).

Relatively little attention was given in the past to monitoring vinyl chloride in the air of workplaces because toxicologic data at the time indicated there was little hazard. The earliest reports of hepatoxicity in vinyl chloride workers were noted by Tribukh, et al. (1949); however, the effects were attributed to plasticizers added in the manufacturing process. In these studies, the observed concentrations of vinyl chloride ranged from 1 to 470 ppm.

Some data are available concerning airborne vinyl chloride in the workplace prior to 1974. In Russia, Filatova and Gronsberg (1957) observed concentrations of 8 to 16,000 ppm with average exposures ranging from 20 to 300 ppm. Although monitoring of the workplace for vinyl chloride levels was not a common practice in the U.S. prior to 1950, Dow Chemical Co. initiated monitoring about that time. Exposures were generally below 500 ppm; however, peak concentrations of 4,000 ppm were recorded (Ott, et al. 1975). After 1960, Dow Chemical Co. was successful in reducing exposures to workers to about 25 ppm even though levels up to 500 ppm still occurred. After vinyl chloride-induced angiosarcoma of the liver was reported in workers and animals (Creech and Johnson, 1974; Viola, et al. 1971; Maltoni and Lefemine, 1974b) inhalation exposures dropped drastically.

Inhalation of vinyl chloride by the general population occurs in the vicinity of vinyl chloride and PVC industries (Nelson, et al. 1975). This problem currently is receiving increased attention. Prior to 1974, vinyl chloride was widely used as a propellant for many commercially available products such as pesticides,

deodorants, hair sprays, et cetera. Consumers repeatedly using such products in closed rooms were undoubtedly exposed to moderately high concentrations.

Dermal

Absorption of vinyl chloride through the skin is minor. Calculations based on the percutaneous absorption of vinyl chloride by Rhesus monkeys (Hefner, et al. 1975b), indicate that a 6-foot, 90 kg man exposed to 7,000 ppm (dermal) for two hours would absorb the equivalent of a 0.2 ppm, 8-hour inhalation exposure. Therefore, significant percutaneous absorption would not be expected to occur upon exposures to low concentrations of 1 or 5 ppm.

PHARMACOKINETICS

Absorption

Vinyl chloride is rapidly absorbed through the lungs and enters the blood stream (Duprat, et al. 1977). In rats inhaling 20,000 ppm ^{14}C vinyl chloride for five minutes, ^{14}C was found in the liver, bile duct, digestive lumen, and kidneys 10 minutes from the beginning of the inhalation exposure. The amount and distribution of vinyl chloride and its metabolites increased up to three hours post-exposure and in addition to sites of deposition observed 10 minutes from initiation of exposure, ^{14}C activity was found in the urinary tract, salivary, harder and lacrimal glands, skin, and thymus. Watanabe, et al. (1976b) and Bolt, et al. (1977) also observed the rapid uptake and equilibration of atmospheric vinyl chloride with rats via the inhalation route.

The fate and absorption of vinyl chloride following oral administration is consistent with observations derived from inhala-

tion studies (Watanabe, et al. 1976a). Watanabe, et al. (1977) compared the fate of vinyl chloride in rats following repeated versus single inhalation exposures and found that the routes and rates of excretion were the same for both groups. The activity of microsomal enzymes was essentially the same in rats exposed once, repeatedly, and in control rats. Covalent bonding to hepatic macromolecules was greater in repeatedly exposed rats than in those given a single exposure. The hepatic nonprotein sulfhydryl concentration of the repeatedly exposed rats was greater than that of the single exposure rats (79 and 37 percent of control, respectively); the authors concluded that "...repeated exposure to vinyl chloride 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."

Using male Wistar rats, Withey (1976) determined that vinyl chloride migrates rapidly from the gastrointestinal tract to the blood following gastric intubation of aqueous solutions of vinyl chloride (22.6 to 28.2 mg per animal) or gastric intubation of a vegetable oil solution of vinyl chloride (12.55 or 25.1 mg per animal). The nature of the vehicle had little or no effect on the rates of uptake or elimination kinetics. After a 5-hour inhalation exposure at approximately 7,000 ppm, blood levels of vinyl chloride decreased rapidly.

Distribution

The liver of rats (Table 2) retains the greatest percentage of vinyl chloride and/or metabolites of vinyl chloride 72 hours after single oral administration of 0.05, 1.0, or 100 mg/kg of the ^{14}C-labeled compound (Watanabe, et al. 1976a).

Ten minutes after the initiation of a 5-minute 10,000 ppm inhalation exposure to ^{14}C-vinyl chloride, ^{14}C activity is found in the liver, bile duct, stomach, and kidneys of rats (Duprat, et al. 1977).

Bolt, et al. (1976) studied the tissue disposition of ^{14}C-vinyl chloride in rats. Immediately after exposure by inhalation of 50 ppm vinyl chloride for five hours in a closed system, the percent incorporated as ^{14}C-radioactivity per g tissue was highest for kidney (2.13), liver (1.86), and spleen (0.73). Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

Metabolism

Detoxification of vinyl chloride takes place primarily in the liver by oxidation to polar compounds which can be conjugated to glutathione and/or cysteine (Hefner, et al. 1975a). These covalently bound metabolites are then excreted in the urine.

Vinyl chloride is metabolized extensively by rats in vivo and the metabolic pathway appears to be saturable (Watanabe, et al. 1976a,b; Bolt, et al. 1977; Hefner, et al. 1975a). These investigators postulate that the primary metabolic pathway involves alcohol dehydrogenase because ingested ethanol or pyrazole inhibits the uptake of vinyl chloride. In rats this primary pathway appears to

TABLE 2

Percentage of the Administered ^{14}C Activity per Gram of Tissue After Administration of (^{14}C) Vinyl Chloride[a*]

Tissue	Dose (mg/kg) 0.05	1.0	100
Liver	0.172 ± 0.025[b]	0.182 ± 0.005	0.029 ± 0.002
Skin	0.070 ± 0.023	0.076 ± 0.010	0.010 ± 0.002
Carcass	0.027 ± 0.007	0.046 ± 0.002	0.007 ± 0.001
Plasma	0.041 ± 0.004	0.053 ± 0.007	ND[c]
Muscle	0.028 ± 0.003	0.031 ± 0.003	0.006 ± 0.001
Lung	0.050 ± 0.003	0.061 ± 0.003	0.011 ± 0.001
Fat	0.030 ± 0.004	0.045 ± 0.008	0.006 ± 0.001

*Source: Watanabe, et al. 1976a

[a]Remaining in the body after 72 hr.

[b]Mean ± SE, five rats per dose

[c]Not detectable above background

be saturated by exposures to concentrations exceeding 220 to 250 ppm. In rats exposed to higher concentrations, metabolism of vinyl chloride is postulated to occur via a secondary pathway involving epoxidation and/or peroxidation. Present data indicate that vinyl chloride is metabolized to an activated carcinogen electrophile (Van Duuren, 1975; Montesano and Bartsch, 1976; Kappus, et al. 1976) and is capable of covalently reacting with nucleophilic groups or cellular macromolecules.

There is ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Pretreatment of rats with phenobarbital, which induces the MFO system, also enhances liver toxicity of vinyl chloride (Jaeger, et al. 1974). Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids (Kappus, et al. 1975; 1976); chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules (Laib and Bolt, 1977). Hathway (1977) reports *in vitro* depurination of calf thymus DNA by chloroacetaldehyde is identical to that observed in hepatocyte DNA following administration of vinyl chloride to rats *in vivo*.

Excretion

Excretion of ^{14}C activity within 72 hours following a single oral dose of ^{14}C-labeled vinyl chloride is shown in Table 3. Administration of vinyl chloride by inhalation produced almost identical results (Watanabe, et al. 1976b). Two or three major metabolites are identified as indicated in Table 4; again, the route of administration has no effect.

TABLE 3

Percentage of Administered ^{14}C Activity Recovered Following A Single Oral Dose of Vinyl Chloride[a*]

	Dose (mg/kg)		
	0.05	1.0	100
Expired:			
As VC	1.43 ± 0.13[b]	2.13 ± 0.22	66.64 ± 0.67
As CO_2	8.96 ± 0.59	13.26 ± 0.47	2.52 ± 0.13
Urine	68.34 ± 0.54	59.30 ± 2.75	10.84 ± 0.95
Feces	2.39 ± 0.52	2.20 ± 0.39	0.47 + 0.06
Carcass and tissues	10.13 ± 1.93	11.10 ± 0.47	1.83 ± 0.14
Cage wash[c]	0	0.84 ± 0.45	0
Total recovery	91.25 ± 2.47	88.83 ± 1.98	82.30 ± 0.43

*Source: Watanabe, et al. 1976a

[a]Percentage of dose excreted over 72 hr. Only the ^{14}C activity associated with the expired VC can be attributed to VC per se

[b]Mean ± SE five rats per dose

[c]Distilled water wash of metabolism cage at termination of the study

TABLE 4

Separation of ^{14}C-containing Urinary Metabolites from Rats Given Vinyl Chloride[a*]

Compound	Dose (mg/kg) 0.05(4)[b]	1.0(5)[b]	100(5)[b]
N-acetyl-S-(2-hydroxyethyl)-cysteine	30.4 ± 2.0[c]	36.2 + 3.9	29.1 ± 2.0
Thiodiglycolic acid	25.6 + 1.9	23.7 ± 1.1	25.4 ± 0.9
Unidentified	38.6 + 2.9	34.5 ± 4.6	36.6 ± 2.0
Total	94.6	94.4	91.1

*Source: Watanabe, et al. 1976a

[a]Metabolites were separated and quantitated by high pressure liquid chromatography. Values are expressed as percentage of total urinary radioactivity.

[b]Number in parentheses = Number of animals per dose

[c]Mean ± SE

Green and Hathway (1975) measured the excretion of 250 µg ^{14}C-vinyl chloride per kg body weight administered to rats by intragastric, intravenous (femoral vein), or intraperitoneal routes. Rats given ^{14}C-vinyl chloride by the intragastric route (250 µg/kg in corn oil) exhaled 3.7 percent of this dose as vinyl chloride 24 hours post exposure, 12.6 percent as CO_2, 71.5 percent labeled material in the urine, and 2.8 percent in the feces. Intravenous injections of 250 µg/kg in n-(B-hydroxethyl) lactamide resulted in 99 percent exhaled as vinyl chloride, 0.1 percent CO_2, 0.5 percent of the label excreted in the urine, and 0.1 in the feces.

Intraperitoneal injection of 250 µg/kg resulted in 43.2 percent of the dose exhaled as vinyl chloride, 10.3 percent as CO_2, 41.5 percent in the urine, and 4.8 percent in the feces. At a larger dose, (450 µg/kg) 92 to 96 percent was exhaled as vinyl chloride following intragastric and intraperitoneal routes, respectively.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Acute toxicity tests with vinyl chloride were carried out by Patty, et al. (1930) of the Bureau of Mines, Department of Commerce. Single exposure of guinea pigs to vinyl chloride gas, 10 percent in air, resulted in narcosis and death within 30 to 60 minutes. Lower concentrations resulted in ataxia and narcosis. Pathological findings at necropsy were congestion and edema of the lungs and hyperemia of the kidneys and liver. A number of investigators have made similar observations when examining the acute inhalation toxicity of vinyl chloride in mice, rats, guinea pigs, rabbits, cats, dogs (Peoples and Leake, 1933; Lester, et al. 1963;

Mastromatteo, et al. 1961; Haley, 1975; Prodan, et al. 1975). In animal studies, LD_{50}s at two hours ranged from 117,500 ppm for mice to 230,800 ppm for rabbits. Deaths of two Canadian workers were reported in 1960 (Danziger, 1960) following acute exposures to vinyl chloride gas. At autopsy, there was congestion of the liver, spleen, and kidneys.

The earliest reports of vinyl chloride-associated liver abnormalities were from the USSR (Tribukh, et al. 1949), although the effects were attributed to vinyl chloride and plasticizer resin. In 1957 the USSR set upper limits of industrial exposures to vinyl chloride at 400 ppm. As referenced by Marsteller and Lebach (1975), reports from Romania in 1963 and 1967 described vinyl chloride-associated Raynaud's syndrome, dermatitis, scleroderma, thyroid insufficiency, and hepatomegaly. Cordier, et al. (1966) were the first to describe acro-osteolysis of the distal phalanges combined with a Raynaud-like symptomatology. Subsequently, other cases were reported in the literature. The first cases in the U.S. of occupational vinyl chloride-associated acro-osteolysis were reported by Wilson, et al. 1967. These reports prompted studies of chronic toxicity (Viola, 1970), and to further observations of vinyl chloride-induced neoplasia in rats (Viola, et al. 1971).

Exposure of workers to high concentrations of vinyl chloride produces conditions of euphoria and intoxication. Irritation of the respiratory tract is followed by chronic bronchitis and workers complained of headache, irritability, poor memory, tingling, and weight loss (Suciu, et al. 1975).

There are numerous clinical indications that chronic exposure to vinyl chloride is toxic to humans. Tribukh, et al. (1949) reported hepatitis-like liver changes although the effects were attributed to vinyl chloride and plasticizer resin. Angioneurosis of a spastic character was reported by Filatova, et al. in 1958. Raynaud's syndrome, scleroderma-like skin changes, lytic lesions of the terminal phalanges in hands and feet, and pseudoclubbing of the fingers have been reported in many workers in the U.S. and Europe. This latter condition has been termed occupational acro-osteolysis. Cases of this new occupational disease have been reported from around the world (Wilson, et al. 1967; Dinman, et al. 1971; Wedrychowiez, 1976; Harris and Adams, 1967).

Examination by wide-field capillary microscopy of the hands of PVC workers demonstrated capillary abnormalities in a high percentage of exposed men. This noninvasive technique may be useful as a mass-screening procedure in the early detection and prevention of vinyl chloride-associated diseases (Maricq, et al. 1976).

Other long-term effects include functional disturbances of the central nervous sytem with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with marked fibrosis in the portal areas, and pulmonary insufficiency with restrictive changes in the lungs (Lange, et al. 1974).

In 1972, Kramer and Mutchler studied workers exposed to vinyl chloride and correlated clinical parameters with environmental exposure. Ninety-eight workers were studied who had been exposed to vinyl chloride up to 25 years. Tests indicated there were

slight changes in physiologic and clinical laboratory parameters suggesting some impairment of liver function.

Increased urinary excretion of monochloroacetic acid has been correlated with an increase in the concentration of inhaled vinyl chloride (Grigorescu and Tiba, 1966). One-year exposure to vinyl chloride caused a decrease in blood catalase activity and an increase in peroxidase, indophenoloxidase, and glutathione (Gabor, et al. 1964).

In humans exposed to vinyl chloride, serum levels of gamma-glutamic transpeptidase (GGTP) appear to be the best clinical parameter for detecting liver abnormalities and reflecting the extent of liver lesions by the degree of elevation. Alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, and bilirubin levels were also increased in many cases. Location of the liver lesions affected the elevation of specific enzymes found in the plasma. (Makk, et al. 1976).

Ward, et al. (1976) provided data which suggest that vinyl chloride 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. Abnormalities were also detected in some workers exposed to vinyl chloride who had few or no overt clinical signs. Studies are in progress to investigate all the exposed workers in one factory and also workers in other related industrial plants.

Synergism and/or Antagonism

Hefner, et al. (1975a) inhibited the metabolism of vinyl chloride by administering to rats 320 mg/kg of pyrazole one hour prior to inhalation of the gas. Pyrazole is an inhibitor of alcohol dehydrogenase, xanthine oxidase, and other enzymes (Carter and Isselbacher, 1972). Pretreatment of rats with ethanol (5 mg/kg, 95 percent) also inhibited vinyl chloride metabolism.

A study of the effects of ingested ethanol (5 percent in water ad libitum) on the induction of liver tumors in Sprague-Dawley rats by year-long vinyl chloride inhalation indicates that chronic ingestion of alcohol increases the incidence of liver tumors and tumors in other sites (Radike, 1977b). The first animals treated with 5 percent ethanol and 600 ppm vinyl chloride died of angiosarcoma of the liver in 39 weeks; the first treated with vinyl chloride died due to liver tumor proliferation in 53 weeks.

Jaeger (1975) conducted experiments to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this experiment the effects of 4-hour exposures to 200 ppm of vinylidine chloride and 1,000 ppm vinyl chloride were less than if 1,1-DCE was given alone. Simultaneous 4-hour exposures to 200 ppm vinylidene chloride and 1,000 ppm vinyl chloride indicated that vinyl chloride prevented injury caused in rats by the administration of 1,1-DCE alone. Injury was indicated by an elevation in serum alanine α-ketoglutarate transaminase. These two monomers are used together in the production of vinyl copolymers and exposure to both agents was reported by Kramer and Mutchler (1972).

Teratogenicity

Animal studies using three species (mice, rats, and rabbits) indicate that inhalation of vinyl chloride does not induce gross teratogenic abnormalities in offspring of mothers exposed seven hours daily to concentrations ranging from 50 to 2,500 ppm (John, et al. 1977); however, statistically significant excess occurrences of minor skeletal abnormalities were noted (Wilcoxon, $p < 0.05$). Mice and rats were exposed on days 6 through 15 and rabbits on days 6 through 18 of gestation. At high concentrations there was evidence of increased fetal death in all three species. Radike, et al. (1977a) also did not observe gross abnormalities in the offspring of rats exposed four hours daily on the 9th to the 21st day of gestation by inhalation to 600 or 6,000 ppm vinyl chloride; minor skeletal abnormalities did occur in excess.

As to the teratogenic effects, human females are generally not exposed to high concentrations of vinyl chloride; the question arises whether low environmental levels may cause congenital malformations. There are reports of high rates of congenital defects in three small communities in which vinyl chloride polymerization plants are located. Significantly greater numbers of malformations of the central nervous system, upper alimentary tract, genital organs, and feet were reported (Infante, 1976; Infante, et al. 1976; Edmonds, et al. 1975). Results of these studies are not completely unequivocal and further studies are needed. Overall, the evidence suggests that exposure of pregnant women to vinyl chloride at appreciable levels should be avoided.

Mutagenicity

Vinyl chloride is mutagenic in a number of biological systems. The mutagenic action of vinyl chloride appears to be dependent upon its metabolic conversion into chemically reactive metabolites (e.g., chloroethylene oxide, 2-chloroacetaldehyde). The mutagenic effects of vinyl chloride have been demonstrated in: (1) metabolic ally activated systems using Salmonella typhimurium (Bartsch, et al. 1975; Bartsch and Montesano, 1975; McCann, et al. 1975; Elmore, et al. 1976; Rannug, et al. 1974; Garro, et al. 1976) developed by Ames, et al. (1973) in which the genetic indicator organisms revert to histidine prototrophy by base-pair substitutions, or frameshift mutations; (2) Escherichia coli K12 bioauxotrophic strain with back mutation to arginine^{+} (Greim, et al. 1975); (3) several species of yeast inducing forward mutations and gene conversions at specific loci (Loprieno, et al. 1976, 1977); (4) in germ cells of Drosophila (Verbugt, 1977); and (5) Chinese hamster V79 cells (Huberman, et al. 1975).

The mutagenic activity of inhaled vinyl chloride (3,000, 10,000, or 30,000 ppm for six hours a day for five days) was assessed in fertile male CD-1 mice in the dominant lethal assay (Anderson, et al. 1976). At these high concentrations vinyl chloride was not mutagenic as judged by scoring of post-implantation fetal deaths, pre-implantation egg losses and reduction in fertility. Positive control tests indicated that the dominant lethal effect was expressed in the CD-1 mice used in these experiments.

In relation to man, several investigators have observed a significantly higher incidence of chromosomal aberrations in the

lymphocytes of workers chronically exposed to high levels of vinyl chloride (Ducatman, et al. 1975; Purchase, et al. 1975; Funes-Cravioto, et al. 1975). Most of the damage involved gross changes such as fragmentations or rearrangements.

Picciano, et al. (1977) have reported no statistically significant differences in chromatid and chromosome aberrations or proportion of abnormal cells in a group of 209 vinyl chloride-exposed workers. These workers were exposed for periods ranging from 1 to 332 months ($x = 48.5$ mo.) to time-weighted average levels of vinyl chloride ranging from 0.3 to 15.2 ppm. Killian, et al. (1975) have also reported a lack of evidence for excess chromosome breakage in a population of vinyl chloride-exposed workers.

On the other hand, Ducatman, et al. (1975) and Purchase, et al. (1975) have reported increased incidence of chromosomal breakage among their cohorts of vinyl chloride-exposed workers populations.

Heath, et al. (1977) examined cytogenetic effects in three groups of industrial workers: PVC polymerization workers (presumed high exposure), PVC processing workers (presumed low exposure) and rubber and tire manufacture workers (presumed negligible exposure). Chromosome breakage in all three groups was significantly greater than in nonindustrial controls and overall breakage levels were similar in all three groups. These data suggest that other agents in addition to vinyl chloride may cause cytogenetic damage in workers employed in similar occupations.

Waxweiler, et al. (1977) reported cytogenetic studies of vinyl chloride workers, plastics workers, and rubber workers. Vinyl

chloride workers had a slightly higher rate of chromosome breakage than rubber workers and the plastics workers showed the highest rates of breakage. None of the differences between the industrial groups studied was significant; however, all of the industrial groups had higher chromosome breakage rates than nonindustrial controls. Additionally, a significant increase in fetal loss rate was found in wives of workers relative to their husbands' exposure to vinyl chloride.

Carcinogenicity

Inhalation-Animal Studies: (Viola, et al. 1971) reported the carcinogenic response of male rats (Ar/IRE Wistar strain) exposed to vinyl chloride by inhalation (Table 5). After the year-long exposure, animals were killed at 20-day intervals. Skin tumors were first noted at approximately 10 months; tumors in the lungs and bones were observed at about 11 months.

Maltoni, in a series of reports starting in 1973, confirmed the carcinogenicity of inhaled vinyl chloride in experimental animals and listed several types of neoplasms including angiosarcoma of the liver. Confirmation of observations made in animal models came in 1974 with the report of vinyl chloride-associated angiosarcoma of the liver in vinyl chloride polymerization workers at the B.F. Goodrich plant in Louisville, Kentucky (Creech and Johnson, 1974). By December, 1975, similar reports came from 11 different countries culminating in 64 known cases (according to the latest compilation by Spirtas and Kaminski, 1978).

Caputo, et al. (1974) exposed larger numbers of male and female rats (A and IRE Wistar strain) by inhalation to various con-

TABLE 5

Oncogenic Effects of Inhaled Vinyl Chloride*

Conc. VC (ppm) 4 hrs/day, 5 days/wk 12 months	Number Rats	Skin Epidermoid Carcinomas	Lung Adenocarcinomas & Squamous Cell Carcinomas	Bones Osteochondroma	Total
30,000	26	17	6	5	25
No treatment	25	-	-	-	-

*Source: Viola, et al. 1971

centrations of vinyl chloride. Carcinomas and sarcomas were observed in all groups except those exposed to 50 ppm (Table 6). Tumors appeared between eight and 13 months from the beginning of the inhalation treatment. These investigators also exposed rabbits by inhalation to 10,000 ppm vinyl chloride for 15 months (Table 6) and reported incidence of lung and skin carcinomas.

Maltoni and Lefemine (1974a,b; 1975) reported a series of experiments concerning the effects of inhalation exposure on rats, mice, and hamsters to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for varying periods of time. Animals were observed for their lifetime. Angiosarcomas in the liver occurred in all three species as well as tumors at several other sites. The following tables summarize some of their findings (Tables 7-11). Male hamsters and male and female rats and mice were used in these experiments. A differential response of the sexes was not reported.

The most recent publication of Maltoni's ongoing experiments (1976) does not report average latent periods or the total number of animals with tumors per treatment group. For this reason, both Maltoni and Lefemine's (1975) and Maltoni's (1976) data are included in both reports.

Experiments which are not yet completed (Maltoni, 1976) include: (1) inhalation exposure of male and female Sprague-Dawley rats to concentrations of 200, 150, and 100 ppm for 52 weeks (Table 12); (2) inhalation exposure of male and female Sprague-Dawley rats lasting only 17 weeks, observed at last report up to 114 weeks (data not included) (preliminary results indicate that a 17 week

TABLE 6

Incidence of Tumors in Rats and Rabbits Exposed to Vinyl Chloride by Inhalation*

Conc. VC (ppm) 4 hrs/day, 5 days/wk 12 months	Number of Animals	Liver Angiosarcomas Cholangiomas	Lung Adeno-Alveolar Carcinomas	Skin Squamous Cell Carcinoma Acanthoma	Other
	Rats				
20,000	150	31	21	67	7
10,000	200	16	16	34	8
5,000	200	12	4	20	2
2,000	200	10	8	6	6
500	150	4	-	3	-
50	200	-	-	-	-
No treatment	200	-	-	-	-
15 months	Rabbits				
10,000	40	-	6	12	-
No treatment	20	-	-	-	-

*Source: Caputo, et al. 1974

TABLE 7

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 hrs/day, 5 days/wk, 52 weeks
By Inhalation to Various Concentrations of Vinyl Chloride: Results after 135 weeks*

Conc. VC (ppm)	Number of Animals		Liver		Kidney		Zymbal Gland		Other	Total Number of Rats with One or More Tumors
	Total	Corrected	Angio sarcomas	Average Latency (wk)	Nephro blastomas	Average Latency (wk)	Carcinomas	Average Latency (wk)		
10,000	69	61	9	64	5	59	16	50	25	38
6,000	72	60	13	70	4	65	7	62	19	31
2,500	74	59	13	78	6	74	2	33	18	32
500	67	59	7	81	4	83	4	79	11	22
250	67	59	4	79	6	80	-	-	9	16
50	64	59	1	135	1	135	-	-	12	10
No treatment	68	58	-	-	-	-	-	-	10	6

*Source: Maltoni and Lefemine, 1975

TABLE 8

Incidence of Tumors in Swiss Mice Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results after 41 weeks*

Conc. VC (ppm)	Number of Animals		Liver Angiosarcomas	Pulmonary Tumors		Mammary Carcinomas		Other	Total Number of Mice One or More Tumors
	Total	Corrected		No.	Average (wks)	No.	Average (wks)		
10,000	60	50	4	27	34	9	28	9	28
6,000	60	54	2	22	33	8	33	5	27
2,500	60	53	4	12	35	4	32	3	13
500	60	58	4	16	34	2	33	2	17
250	60	58	3	11	34	6	30	1	15
50	60	57	-	-	-	7	35	4	8
No treatment	150	141	-	1	39	-	-	-	1

*Source: Maltoni and Lefemine, 1975

TABLE 9

Incidence of Tumors in Swiss Mice Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results after 81 weeks*

Conc. VC (ppm)	Number of Animals (Male and Female)	Number of Animals with Tumors		
		Liver Angiosarcomas	Pulmonary Tumors	Other
10,000	60	8	35	26
6,000	60	5	38	24
2,500	60	11	30	25
500	60	11	38	26
250	60	11	33	35
50	60	1	2	25
No treatment	150	-	8	1

*Source: Maltoni, 1976

TABLE 10

Incidence of Tumors in Golden Hamsters Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results after 48 weeks[a]

Conc. VC (ppm)	Number of Animals		Liver Angiosarcomas	Other	Total Number of Animals with One or more Tumors
	Total	Survivors			
10,000	35	19	-	3	3
6,000	32	21	-	8	5
2,500	33	19	-	5	4
500	33	23	1[b]	4	4
250	32	18	-	2	2
50	33	23	-	5	5
No treatment	70	49	-	2	2

[a]Source: Maltoni and Lefemine, 1975

[b]More than 18 weeks post-exposure

TABLE 11

Incidence of Tumors in Golden Hamsters Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results after 76 weeks[a]

Conc. VC (ppm)	Number of Animals		Liver Tumors Angiosarcoma Angiomas Hepatomas	Other
	Total	Survivors		
10,000	35	1	-	13
6,000	32	3	3	10
2,500	33	4	4	10
500	33	4	2[b]	8
250	32	4	-	4
50	33	5	-	10
No treatment	70	14	-	4

[a]Source: Maltoni, 1976

[b]Angiosarcomas

TABLE 12

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 hrs/day, 5 days/week, 52 weeks by Inhalation to Vinyl Chloride: Results after 89 weeks*

Conc. VC (ppm)	Number of Animals		Liver Angiosarcoma	Nephro Blastomas	Zymbal Gland Carcinomas	Angiosarcomas Other Sites
	Total	Survivors				
200	120	41	7	2	-	1
150	120	45	3	4	-	1
100	120	49	1	8	1	-
No treatment	185	76	-	-	1	1

*Source: Maltoni, 1976

exposure produces the same kinds of lesions observed following a 52-week exposure); (3) 52-week exposure of male Wistar rats observed for 88 weeks with preliminary results in general confirming results with Sprague-Dawley rats; and (4) exposure of newborn rats by inhalation to high concentrations of vinyl chloride for five weeks results after 48 weeks, indicating that angiosarcomas in the liver and hepatomas had developed.

Maltoni (1976) also observed four subcutaneous angiosarcomas, four Zymbal's gland carcinomas, and one nephroblastoma in 66 offspring of 60 Sprague-Dawley rats exposed by inhalation 4 hrs/day to 10,000 or 6,000 ppm vinyl chloride from the 12th to the 18th day of gestation (21-day gestation). At the time of Maltoni's publication (1976), 20 offspring were living at 115 weeks' post-exposure.

Recent inhalation studies with albino CD-1 mice and CD rats (Charles River Breeding Lab) confirm the carcinogenicity of vinyl chloride (Lee, et al. 1977). This study was designed to define biochemical changes relating to histological and neoplastic lesions. For each species 360 animals were divided into five groups, each consisting of 36 males and 36 females. Each group of both species was exposed to 50, 250, or 1,000 ppm vinyl chloride for 6 hrs/day, 5 days/wk. Four animals of each species, sex, and exposure level were terminated at the end of 1, 2, 3, 6, and 9 months and the surviving animals terminated at 12 months. After 12 months, bronchioalveolar adenomas, mammary gland tumors, and angiosarcomas in the liver and other sites developed in mice exposed by inhalation to 50, 250, or 1,000 ppm vinyl chloride. Rats exposed to 250 or 1,000 ppm vinyl chloride developed angiosarcoma in the liver, lungs, and other sites (Lee, et al. 1978).

There is evidence that ingested alcohol makes rats more susceptible to the carcinogenic action of inhaled vinyl chloride (Radike, et al. 1977b). Three hundred and twenty male Sprague-Dawley rats were divided into four groups; two groups received 5 percent ethanol in water four weeks prior to vinyl chloride inhalation (600 ppm 4 hrs/day, 5 days/wk, 12 months). The first death from liver angiosarcoma in rats exposed to vinyl chloride was at 53 weeks from the first exposure; in rats ingesting 5 percent ethanol and inhaling vinyl chloride the first death from angiosarcoma in the liver was at 39 weeks from the first exposure. Cancerous lesions were identified in only 13 rats (Table 13).

Maltoni, et al. (1975, Maltoni, 1976) claim that vinyl chloride is also carcinogenic via gastrointestinal ingestion. Vinyl chloride dissolved in olive oil was administered by stomach tube five times per week to 13-week-old Sprague-Dawley rats (40 males and 40 females) in concentrations equivalent to 50.00, 16.65, and 3.33 mg/kg body weight (Table 14). After 50 weeks, one angiosarcoma of the liver was observed in one male animal in the group given 16.6 mg/kg. This is equivalent to 863 mg total over a 52-week period. One angiosarcoma of the thymus gland was observed in a female animal receiving 50 mg/kg, which is equivalent to three times that given to the male animal. This oral dosage is comparable to the inhalation dose that induces both liver angiosarcomas and renal nephroblastomas, i.e., 800 mg (Maltoni and Lefemine, 1975). The data are preliminary in nature, since the study is not yet completed and/or reported. These studies are now in progress; they will determine the incidence and type of cancer produced by ingestion of

TABLE 13

Tumors in 13 Rats Exposed to Vinyl Chloride or to 5 Percent Ethanol and Vinyl Chloride[a]

Group Treatment	Number of Animals with Tumors	Liver		Lung Angiosarcoma	Kidney Angiosarcoma Fibrosarcoma
		Angio-sarcoma	Hepatocellular Carcinoma		
600 ppm VC[b]	6	2	1	-	-
600 ppm VC[b] 5% Ethanol	7	5	2	1	1 (each)

[a]Source: Radike, et al. 1977b

[b]4 hrs/day, 5 days/wk

TABLE 14

Incidence of Tumors in Sprague-Dawley Rats Ingesting Vinyl Chloride in Olive Oil: Results after 55 weeks*

Conc. VC (mg/kg)	Number of Animals		Liver Angiosarcomas	Angiosarcomas Other Sites
	Total	Survivors		
50.00	80	57	-	1
16.65	80	66	1	-
3.33	80	62	-	-
Olive Oil Alone	80	68	-	-

*Source: Maltoni, et al. 1975

low doses of vinyl chloride, i.e., 1.0, 0.3, and 0.03 mg/kg/day (Maltoni, 1976, 1980).

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organ systems including angiosarcoma of the liver. Liver angiosarcoma is an extremely rare liver cancer in humans with 26 cases reported annually in the U.S. [National Cancer Institute (NCI), 1975]. Human data of carcinogenic effects of vinyl chloride have been obtained primarily from cases of occupational exposures of workers. The latent period has been estimated to be 15 to 20 years following onset of exposure; however, recent case reports indicate a longer average latent period (Spirtas and Kaminski, 1978).

Epidemiological studies of vinyl chloride exposed workers have primarily focused on cases of angiosarcoma of the liver. The basis for this emphasis is clear; a primary problem in all epidemiological investigations is the establishment of a cause/effect relationship between a harmful agent and a population under study. Hemangiosarcoma of the liver is a type of cancer rarely occurring in the general population. Because of this rare occurrence of hemangiosarcoma in man, it is much easier to draw a casual relationship between exposure to vinyl chloride and the development of this tumor. The linking of vinyl chloride to other types of cancers through epidemiological evidence is more tenuous.

The work of Maltoni, et al. (1974) among others was of primary importance in focusing attention on the potential for liver angiosarcoma in workers exposed to vinyl chloride. He demonstrated liver angiosarcoma as a specific lesion in rats following vinyl

chloride inhalation exposures. Subsequently, the first four cases of liver angiosarcoma in vinyl chloride exposed workers were reported (Creech and Johnson, 1974).

Tabershaw/Cooper Associates (1974) conducted a mortality study of vinyl chloride workers. Mortality calculations included only those workers which could be traced in the followup study, i.e., 7,129 of 8,384 workers. These individuals were from 33 different plants and all had been exposed to vinyl chloride for at least one year. The mean employment duration for the group of workers under study was 80 months (in contrast to 44 months for those not located), but the traced workers entered employment about 10 years later. Among the 7,129 workers which were located there were 854 with exposures of 20 years or longer and 1,640 exposed 15 or more years.

Compared to the general male U.S. population the overall mortality rate was found to be lower, i.e., 75 percent that of expected rate. Specific causes of death were no greater than expected and no deaths seemed attributable to angiosarcoma. Standardized mortality ratios (SMR) for malignant neoplasms in general increased with increasing exposure level and/or duration. In the group identified as the high exposure group there were increases in liver cancer (primarily angiosarcoma), respiratory system cancers, and brain cancers. These differences were not statistically significant (Tabershaw/Cooper Assoc., Inc. 1974; Tabershaw and Gaffey, 1974).

Ott, et al. (1975) have re-examined much of the mortality data reported by Tabershaw and Gaffey (1974) and have included more

clearly defined exposure levels and followup of former company employees. The basic findings remain unchanged: no increase over expected in malignant neoplasms was found in the low exposure group (time-weighted average from 10 to 100 ppm) and an increase in deaths due to malignant neoplasms was observed in the high exposure group (time-weighted average was greater than 200 ppm).

Dow Chemical Co. (Holder, 1974) conducted a mortality study of 594 workers exposed to vinyl chloride between 1942 and 1960. Workers were assigned to exposure groups based on the highest level of exposure for at least one month (low group - time-weighted average less than 25 ppm vinyl chloride, intermediate - time-weighted average 25 to 200 ppm; high - time-weighted average 200 to 300 ppm). Also included in the high group were workers from the intermediate group frequently exposed to 1,000 ppm for short time periods.

Total mortality was 91 percent of expected among the vinyl chloride exposed workers. No deaths due to liver cancer were reported and only a total of 13 cases of neoplasms were reported as opposed to 15.4 expected. However, nine of these malignancies occurred in the high exposure group as compared to 5.1 expected (due to small number of deaths, this difference was not tested for significance). Eight of these malignancies were in workers with 15 or more years of exposure.

Monson, et al. (1974) conducted a proportional mortality study of vinyl chloride workers (two plants) who died from 1947 to 1973. Death certificates were obtained for 142 out of 161 workers who died within this time period. Deaths attributable to cancer were 50 percent higher than expected (a statistically significant dif-

ference). A 900 percent increase in cancers of the liver and biliary tract was noted (five angiosarcomas). Excluding angiosarcoma, a 275 percent excess was observed in the remaining forms of cancer. Two brain tumors (320 percent excess) and 13 lung cancers (60 percent excess) were observed. In addition the cancer death rate increased during the period.

Nicholson, et al. (1975) studied a group of 257 workers (of whom 255 were traced) exposed to vinyl chloride for at least five years prior to 1946. Their mortality status was evaluated beginning 10 years after start of employment until 1974. Exposures were estimated to often exceed 10,000 ppm. Among the 24 deaths were three cases of angiosarcoma of the liver. Preliminary findings indicated a 25 percent increase over expected in all deaths and a 131 percent increase in all cancer deaths although neither of these increases was statistically significant.

The National Institute for Occupational Safety and Health (NIOSH) conducted a study which involved 950 individuals who were exposed for at least five years and for whom at least 10 years had elapsed since initial employment. Of these individuals, 285 were located. A total of 109 deaths was reported versus 105 expected (not a significant difference). A 57 percent increase over the expected for cancer deaths was noted - statistically significant. Cancerous lesions were noted in the respiratory system, blood forming tissues, brain, and central nervous system. Liver cancer deaths were 12-fold greater than expected and brain cancer deaths were 5-fold higher (both statistically significant differences) (Wagoner, 1974).

Chiazze, et al. (1977) have reported a cross-sectional mortality study of 4,341 employees from 17 PVC plants who died between 1964 and 1973. No angiosarcoma deaths were identified. Total cancer deaths increased in white employees (especially due to cancer of the digestive system). In white women employees deaths from cancer of the breast and urinary organs were greater than expected.

On the other hand, in a mortality study of 7,000 British workers exposed to vinyl chloride between 1940 and 1974, the authors found no evidence of increased cancer mortality other than from liver cancer. In this study, four cases of malignant liver tumor were diagnosed and two of these were confirmed to be angiosarcoma. Both cases were in men exposed to high levels of vinyl chloride (Fox and Collier, 1977).

In addition, Byren, et al. (1976) studied 771 Swedish vinyl chloride plant workers, of which only 21 could not be traced. A four-to fivefold increase over expected in pancreas and liver tumors was found and two cases were diagnosed as angiosarcoma. Numbers of other tumors did not deviate significantly from expected.

Ten cases of hepatic angiosarcoma have been found among the relatively small work force employed at a vinyl chloride polymerization plant in Quebec, this being the largest number of cases to be diagnosed in a single plant (Makk, et al. 1976). As a result of this unusually large number of occurrences, Delorme and Theriault (1978) have retrieved more detailed information on these employees. The authors suggest that the cases of hepatic angiosarcoma appear to be associated with high vinyl chloride exposure levels and over-

time work hours. No correlation was found between occurrence of this tumor and alcohol or cigarette use.

In the workers engaged in the polymerization of vinyl chloride who were studied (Popper and Thomas, 1975), a characteristic hepatic fibrosis was present in all cases of angiosarcoma. Although the relation of fibrotic lesions to the development of angiosarcomas requires further study, a transition from the fibrotic stage to angiosarcoma is suggested by the focal proliferation of the sinusoidal lining cells and of the hepatocytes that are seen in the fibrotic stage but become even more pronounced in the initial stages of angiosarcoma development. These findings suggest that the fibrotic lesions without angiosarcomas, frequently described in the workers exposed to vinyl chloride (Lilis, et al. 1975), might be only the pre-stage of developing neoplastic lesions. The diagnosis of the fibrotic lesions in these workers may imply a longer latency period for tumor appearance based on a possibly lower exposure level. The series of changes observed in the liver appear to represent a multicentric development of angiosarcoma and are similar to the changes induced by thorotrast and inorganic arsenicals (Berk, 1976).

In the most recent update of the NIOSH register (Spritas and Kaminski, 1978) a total of 64 cases of hepatic angiosarcoma has been identified worldwide among vinyl chloride-exposed industrial workers (Figure 1). A listing of all documented cases by country is presented in Table 15.

Of the 64 cases, 23 have been reported in the U.S., representing more than one third of all diagnosed cases. Six of these cases have been documented since 1975.

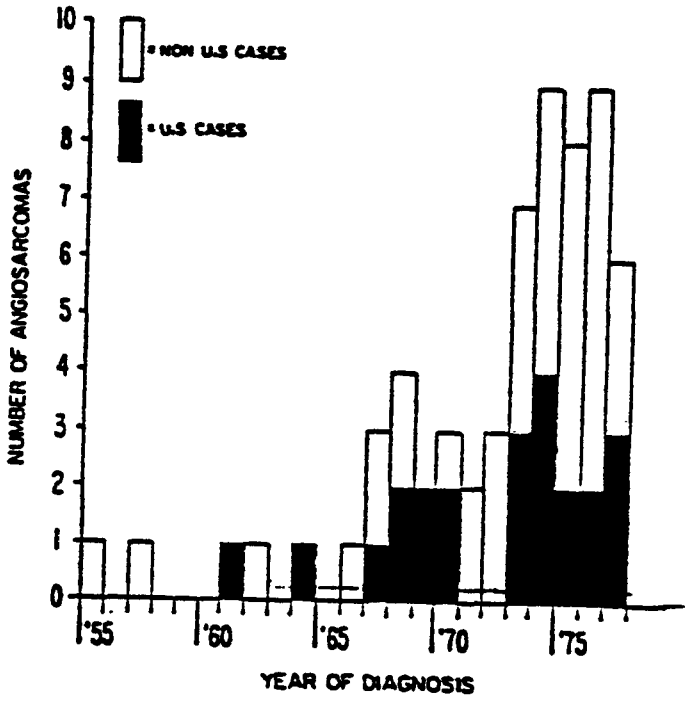

FIGURE 1

Number of cases of vinyl chloride/PVC related angiosarcomas reported to NIOSH by year of diagnosis (representing only 63 of the 64 cases known to NIOSH since information on diagnosis is missing for one case).

Source: Spirtas and Kaminski, 1978

TABLE 15

Angiosarcoma of the Liver in Vinyl Chloride/PVC Workers[+]

Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Belgium	01	00-00-00	00-00-00	00-00-00	00	00	00	06-29-76
Canada	01*	12-15-13	00-00-44	00-00-55	41	11	11	09-02-55
Canada	02*	03-06-14	00-00-43	00-00-57	43	14	14	12-21-57
Canada	03*	08-26-19	00-00-41	00-00-62	42	21	20	03-22-62
Canada	04*	04-05-19	00-00-45	00-00-67	48	22	22	01-21-68
Canada	05*	05-07-11	00-00-44	00-00-68	57	24	05	07-05-68
Canada	06*	12-15-19	00-00-47	00-00-71	51	24	23	04-10-71
Canada	07*	11-09-19	00-00-46	00-00-72	53	26	25	12-24-72
Canada	08	05-13-20	00-00-61	00-00-73	53	12	05	06-12-73
Canada	09	07-19-21	00-00-46	00-00-74	53	28	26	09-04-74
Canada	10	05-16-15	00-00-53	00-00-76	61	23	14	04-00-77
Czechoslovakia	01*	00-00-28	00-00-57	00-00-73	46	16	16	00-00-74
Czechoslovakia	02*	00-00-26	00-00-51	00-00-66	40	15	15	00-00-66
Fed Rep Germany	01*	06-04-30	10-01-56	09-19-68	38	12	12	01-25-69
Fed Rep Germany	02*	07-26-31	10-14-57	09-25-70	39	13	12	12-14-71
Fed Rep Germany	04	09-04-30	04-16-57	00-00-74	44	17	17	11-25-74
Fed Rep Germany	05*	01-01-32	12-16-62	00-00-75	43	13	12	01-09-75
Fed Rep Germany	07*	09-29-26	04-15-54	00-00-75	49	21	12	11-13-75
Fed Rep Germany	08*	10-19-17	04-19-54	00-00-75	58	22	21	12-25-75
Fed Rep Germany	09*	12-13-34	12-02-59	06-16-76	42	17	15	Alive
Fed Rep Germany	10*	07-25-29	10-10-55	06-28-77	47	22	22	06-28-77
Fed Rep Germany	11*	12-29-36	01-02-61	00-00-77	41	16	10	03-07-77
France	01*	04-15-24	01-00-46	02-18-67	43	21	19	02-19-67
France	02	06-03-11	07-06-59	01-08-75	63	15	12	01-24-75
France	03*	00-00-19	00-00-46	01-00-75	55	29	29	06-29-75
France	04*	01-27-27	10-19-49	01-04-76	49	26	26	01-04-76
France	05*	01-29-38	00-00-65	04-00-76	38	11	10	05-13-76
France	06*	04-14-34	00-00-58	09-00-76	42	18	17	09-12-76
France	07	00-00-27	07-01-50	07-00-76	49	26	23	07-02-76
France	08*	04-01-34	05-23-57	12-03-76	42	19	19	01-30-77
Great Britain	01*	04-20-01	00-00-44	12-00-72	71	28	22	12-00-72
Great Britain	03	06-02-37	02-00-66	12-00-74	37	09	04	12-24-74

TABLE 15 (Continued)

Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Italy	02*	11-13-29	00-00-57	12-13-72	43	15	06	12-00-72
Italy	03*	03-14-20	00-00-53	07-10-75	55	22	21	07-10-75
Japan	01	08-01-22	04-00-53	08-21-74	52	22	22	10-24-75
Norway	01*	12-23-15	03-00-50	12-20-71	56	22	21	01-04-72
Sweden	01*	06-23-27	08-14-51	08-00-74	43	19	18	10-20-70
Sweden	03*	06-10-10	05-00-47	03-19-76	65	29	21	03-19-76
Sweden	04*	11-16-14	00-00-46	05-12-77	62	31	31	05-12-77
U.S.A.	01*	10-17-23	12-09-48	03-03-73	49	24	21	03-03-73
U.S.A.	02*	08-19-33	11-15-55	05-00-70	37	14	13	09-28-71
U.S.A.	03*	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
U.S.A.	04*	01-15-24	07-06-52	08-19-67	43	15	15	01-07-68
U.S.A.	05*	01-25-12	06-19-44	04-09-64	52	20	20	04-09-64
U.S.A.	06*	11-23-28	01-17-62	02-00-74	46	12	12	07-24-75
U.S.A.	07*	05-03-22	08-27-44	00-00-68	45	24	17	03-23-68
U.S.A.	08*	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
U.S.A.	09*	11-08-31	05-28-45	03-01-74	43	29	24	03-00-75
U.S.A.	10*	08-16-13	06-12-51	05-00-68	55	17	17	05-10-68
U.S.A.	11*	05-27-09	10-14-46	03-00-70	61	23	23	03-16-70
U.S.A.	12*	11-17-18	09-13-49	05-02-69	50	20	19	05-02-69
U.S.A.	13*	12-01-21	12-11-42	05-00-74	52	32	26	07-04-74
U.S.A.	16*	11-04-27	05-08-50	00-00-69	41	19	04	03-27-69
U.S.A.	17*	05-06-31	06-23-55	10-11-74	43	19	19	Alive
U.S.A.	18*	04-22-28	09-15-54	00-00-75	46	21	11	11-02-75
U.S.A.	19*	00-00-15	00-00-43	06-19-75	60	32	22	04-06-76
U.S.A.	20*	08-31-17	00-00-55	01-30-76	58	21	18	01-30-77
U.S.A.	21*	09-02-09	12-00-46	00-00-77	67	30	21	01-02-77
U.S.A.	22*	10-02-23	07-11-47	01-00-76	52	29	28	12-04-76
U.S.A.	23*	00-00-23	09-00-58	04-06-73	50	15	14	04-06-73
U.S.A.	24*	05-07-17	00-00-39	05-27-77	60	38	26	05-27-77
U.S.A.	25*	08-07-10	02-00-47	03-10-77	67	30	20	03-10-77
Yugoslavia	01*	04-05-14	00-00-53	04-08-73	59	20	20	04-08-73
Yugoslavia	02*	11-15-31	00-00-50	07-12-73	42	23	18	07-12-73
Total Reported Cases	64							

†Spirtas and Kaminski, 1978
*Diagnosis was microscopically confirmed
00 indicates unknown data

It is apparent from Table 15 that both the age at diagnosis and the latency period for cancer induction appear to be increasing. The authors suggest three explanations for this phenomena: (1) early cases may have had heavier exposure; (2) the initial cases were more biologically susceptible; (3) random fluctuation. Should the first of these hypotheses prove to be correct, it would have a profound impact upon risk assessment related to low level exposures of vinyl chloride in the next 10 to 20 years.

In addition to the large numbers of workers occupationally exposed to vinyl chloride, individuals residing near PVC processing plants may also be at risk (Baxter, et al. 1977). It has been estimated that 4.6 million people live within five miles of PVC or vinyl chloride production plants in the United States. Prior to restriction of plant emissions the average exposure level for this population has been estimated to be 17 ppm (Kuzmak and McGaughy, 1975).

Brady, et al. (1977) have examined annual rates of hepatic angiosarcoma from 1970 through 1975 in residents of the State of New York (excluding New York City). Direct exposures to arsenic, vinyl chloride, or thorium dioxide were suggested to be significant factors in the etiology of these tumors. Direct exposures to these agents could not be demonstrated for 19 of the 26 study cases. Five of the 19 patients lived closer to vinyl chloride plants than did their matched controls. This may lend some support to the idea that "indirect modes of exposure, not specifically related to occupation might be important in the etiology of this disorder" (Brady, et al. 1977).

It should be noted that a relatively short time period elapsed since the large scale development of the vinyl chloride-PVC industries. If the trend of increased age at diagnosis and the longer latent period for hepatic angiosarcoma induction are indeed related to lower levels of occupational exposure, then the latent period for cancer induction as a result of these very low levels of environmental exposure may be much longer than previously anticipated, i.e., it would be many years before the ultimate outcome of these exposures will be known.

CRITERION FORMULATION

Existing Guidelines and Standards

In the 1950's an upper limit of 500 ppm of VC at the work place was recommended in the United States; for comparison, in the USSR, the upper limit was set at 400 ppm. Exposures in the USA were mostly below the time-weighted average (TWA) of 500 ppm; however, peak exposures as high as 4,000 ppm were recorded in some work areas (Ott, et al. 1975). About 1960, Dow Chemical Company established a company standard for a limit of 50 ppm (TWA). They were successful in reducing exposures to workers to about 25 ppm vinyl chloride, however, excursions up to 500 ppm did occur. Dow Chemical also initiated continuous sampling and analysis using a multi-point remote sampler and gas chromatography.

In 1962, a Threshold Limit Value (TLV) of 500 ppm was set by the American Conference of Government Industrial Hygienists which was later adopted after its establishment by the Occupational Safety and Health Administration (Table 16).

Inhalation exposures dropped drastically after the carcinogenicity of vinyl chloride was reported (Viola, et al. 1971; Maltoni and Lefemine, 1974a; and Creech and Johnson, 1974). The Occupational Safety and Health Administration set an emergency temporary standard of 50 ppm (TWA) on April 5, 1974. A flurry of epidemiological studies was performed. Based on all of the information available at the time, a permanent standard of 1 ppm (TWA) with a maximum excursion of 5 ppm for a period of no longer than 15 minutes in one day was promulgated for the workplace (39 FR 35890). The U.S. EPA and other government agencies [Food and Drug Administra-

TABLE 16

Regulations Concerning Vinyl Chloride (Compiled by J.F. Stara)

Year	Agency or Organization	Air Standard (ppm)	Other Action
1962	ACGIH*	500 (TLV)	
1971	OSHA**	500 (TLV)	
1974 (4/5)	OSHA	50 (Max. TLV)	Emergency temp. standard
1974	EPA***	--	Banned as propellant in pesticide aerosols
1974	FDA+	--	Banned as propellant in cosmetics and drug aerosols
1974	CPSC++	--	Banned as propellent in all aerosols for household use
1974 (10/4)	OSHA	1 (8 hr TWA)	5 ppm max. for 15 min.
1974	U.S. Coast Guard	--	Amended carriage on tank vessels
1975	EPA	--	Declared a hazardous pollutant (under Sec. 112, Clean Air Act), and proposed fugitive emission standard at the outlet not to exceed 10 ppm (acc. to BAT)
1976	EPA	--	Clarified proposed emission standard for various industrial processes including discharges in waste water.

* American Conference of Governmental Industrial Hygienists

** Occupational Safety and Health Administration

*** U.S. Environmental Protection Agency

\+ Food and Drug Administration

++ Consumer Product Safety Commission

tion (FDA), Consum. Prod. Safety Comm.] have begun to investigate vinyl chloride inhalation exposures of humans in the general environment. Because of reports that 41 pesticide spray products contained vinyl chloride as a propellant, there was published (39 FR 14753) a notice of intent to cancel registrations of all such products. Other aerosol products such as hair spray, also found to utilize vinyl chloride as a propellant, were banned from the market in the U.S. and some other countries shortly thereafter (IARC, 1974). In 1975, the U.S. EPA declared vinyl chloride to be a hazardous substance under Sec. 112 of the Clean Air Act. Further, it promulgated in 1975 and 1976 emission standards of total emissions with a limit of 10 ppm at the stack. Other government agencies have published new control measures during this time, or have new standards under consideration, e.g., FDA concerning packaging of food substances containing oil in PVC containers. Since 1975, when EPA published its intent to issue new standards for total emissions at the stack, the proposal has been litigated in court action initiated by the Environmental Defense Fund and questioned by industry.

In support of the proposed regulations, the U.S. EPA evaluated the risk to populations living in the vicinity of vinyl chloride and PVC plants in a document entitled "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride" by Kuzmack and McGaughy in 1975. A number of factors influenced the estimate of risk to this population, i.e., the number of persons living at distances up to five miles from vinyl chloride and PVC plants (Table 17).

The total number of persons at risk was estimated at 4.6 million. Using standard diffusion models, the annual average ambient

TABLE 17

Estimate of Exposed Population in the Vicinity of Vinyl Chloride and PVC Plants*

Distance (mi)	Population
0-½	47,000
½-1	203,000
1-3	1,491,000
3-5	2,838,000
Total	4,579,000

*Source: American Public Health Association, 1975

concentrations of vinyl chloride were calculated for distances 0-0.5; 0.5-1.0; 1.0-3.0; and 3.0-5.0 miles from the plants (Table 18). The average exposure of a person chosen at random living in the 5-mile radius was calculated to be 17 ppb.

Data published by Maltoni and Lefemine in 1975 which reported liver hemangiosarcoma induction in rats due to vinyl chloride inhalation, were used for calculation of the probability of angiosarcoma cases in highly-exposed populations of workers. This prediction was tested using epidemiological studies of workers and projecting the results to ambient air concentrations of vinyl chloride in the vicinity of the plants. Incidence rates of hemangiosarcoma in rats were compared to incidence rates in exposed workers with the assumption that a long-term exposure of rats would produce the same incidence of effects as a long-term exposure of humans. In this instance, the incidence rate following 1-year exposure of rats would compare to the incidence rate of 30 years of human exposure.

Maltoni's rat liver angiosarcoma data (Rat Experiment BT-1) were analyzed using a linear-dose response model to calculate the probability of incidence of liver angiosarcoma in high level exposed workers during each year of continuous exposure to vinyl chloride. Such treatment of the data resulted in an estimate of 71 cases per year of uninterrupted exposure to 1 ppm of vinyl chloride per million persons exposed. Using the same technique, the probability of cancer in all body organs was approximately doubled, i.e., 150 cases per year of continuous exposure to 1 ppm of vinyl chloride per million persons (Kuzmack and McGaughy, 1978).

TABLE 18

Annual Average Concentrations (ppb) of Vinyl Chloride in the Vicinity of a Vinyl Chloride and PVC Plant*

Distance (mi)	Vinyl Chloride Concentration (ppb)	
	PVC Plant	VC Plant
0-½	323	113
½-1	57	20
1-3	15	5.2
3-5	5.7	2.0

*Source: Kuzmack and McGaughy, 1975

Four epidemiological studies in workers (Ott, et al. 1975; Tabershaw and Gaffey, 1974; Nicholson, et al. 1975; Heath and Falk, 1975) were used to estimate the hemangiosarcoma incidence rate based on human experience, and to compare the results with the incidence rates derived from animal data. From the epidemiological data the probability that a vinyl chloride worker would suffer from angiosarcoma of the liver at some point in his life was calculated to be 0.0031 per year of exposure. If the animal derived-data are converted to a standard work exposure time (7 hrs, 5 days/wk, an exposure to 350 ppm of vinyl chloride), the probability was calculated to be 0.0052. Since such estimates contain a number of inherent errors, the authors concluded that "the slope of the linear animal dose-response relationship for angiosarcomas is consistent with human data."

The results of this analysis were used in estimating the risk to the 4.6 million persons living in the vicinity of the vinyl chloride and PVC plants employing the animal dose-response estimates, which were applied to the 17 ppb of vinyl chloride (the average estimated concentration in the 5-mile radius of the plants). Both mathematical probability models were used. The results are tabulated in Table 19.

Based on the linear model it was estimated that an incidence of 5.5 cases of liver angiosarcoma per year can be expected in the exposed population living in the vicinity of vinyl chloride and PVC plants. The calculation using the log-probit model predicted an incidence rate which is 10 to 100 times lower. The estimates for all cancers were about twice as great in both cases. The uncer-

TABLE 19

Estimated Incidence of Cancer in Populations Living in the Vicinity of Vinyl Chloride-PVC Plants*

Type of Effect	Cases per Year of Exposure	
	Linear Model	Log-Probit Model
All Cancer	11	0.1 - 1.0
Liver Angiosarcoma	5.5	0.05 - 0.5

*Source: Kuzmack and McGaughy, 1975

tainties in extrapolation process to low doses are reflected in this wide range of estimated effects.

The vinyl chloride-related cancer incidence probability calculations by Kuzmack and McGaughy (1975) provide the best available quantitative estimate of the risk resulting from vinyl chloride inhalation exposure of a large segment of U.S. human population living in the vicinity of vinyl chloride-polymerization and fabrication plants. Recently published epidemiological studies indirectly support their conclusions. Brady, et al. (1977) investigated the annual incidence rate for angiosarcoma of the liver among residents of New York State (excluding New York City). The study lends support to the hypothesis that direct exposure to vinyl chloride, arsenic, and thorium dioxide was a significant factor in the etiology of this type of cancer ($P = < 0.02$); and that it resulted in its increased incidence by a factor of 2 over the expected annual incidence for the U.S. (0.25 per million for New York State vs. 0.14 per million for the U.S.). The important finding in this study was the diagnosis of five new cases of angiosarcoma of the liver in persons living in the vicinity of vinyl chloride polymerization and fabrication plants for 8 to 62 years prior to diagnosis of the disease.

The most recent report on this subject is a worldwide review of all cases of liver angiosarcoma in workers published by Spirtas and Kaminski in June, 1978. The conclusions concerning the workers' age at diagnosis of the disease and the latency period, both of which appear to be increasing in recent years, are most important. Lloyd reported in 1975 that the median age at diagnosis was

44 years and the latency period from first exposure to diagnosis averaged 17 years. Spirtas and Kaminski (1978) reported 49 as the median age at diagnosis and a latency period of 21 years. It is probable that the initial cases may have had higher exposures of vinyl chloride and that the recent cases are due to more moderate exposures. It is also possible some variation is caused by statistical uncertainty in the age and latency parameter.

Insufficient information is available on the exposure levels and associated risk to man from vinyl chloride-contaminated water supplies. Toxicologic or epidemiologic data are not available in the current literature. However, from the available data, it is thought that the hazard is small in comparison to the inhalation route of exposure.

There are some published hard data available on the vinyl chloride exposure levels of persons living in the vicinity of vinyl chloride/PVC fabricating plants and on the amount of the vinyl chloride monomer released in time from various plastic products. In addition there are some initial data on vinyl chloride concentration in food packaged in PVC containers. The food oils require a special attention; toxicologic data support this evidence.

Recent epidemiologic reports indicate that the median latency period for hemangiosarcoma occurrence in vinyl chloride-exposed workers is shifting to the right; and suggest that the recently diagnosed cases may have been due to lower exposures than the initial cases. This is an observation which, if confirmed, may have important consequences regarding the estimation of future risk for the population living in the vicinity of vinyl chloride/PVC plants, in addition to the workers.

Special Groups at Risk

Other than those that work in or live near vinyl chloride plants, special risk groups have not been identified.

Basis and Derivation of Criterion

Vinyl chloride is a well-known human and animal carcinogen. Several occupational epidemiology studies in highly exposed workers have reported excess rates of liver angiosarcoma and tumors at other organ sites. Animal experiments using both inhalation and oral routes of exposure have shown induced liver angiosarcoma.

The recommended water quality criterion is calculated using the tumor incidence data from chronic rat inhalation studies. The validity of these incidence rates for humans was established by evaluating the cancer incidence in workers after accounting for their exposure.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Vinyl chloride is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of vinyl chloride in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of vinyl chloride corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk

level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish (2)	0.2 µg/l	2.0 µg/l	20 µg/l
Consumption of fish and shellfish only.	52.5 µg/l	525 µg/l	5,246 µg/l

(1) Calculated by applying a linearized multistage model as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document to the animal bioassay data summarized in the Appendix. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Zero point four percent of the vinyl chloride exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration factor of 1.17-fold. The remaining 99.6 percent of vinyl chloride exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of vinyl chloride, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding vinyl chloride concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding vinyl chloride concentrations.

Although total exposure information for vinyl chloride is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality cirteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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APPENDIX

Summary of Pertinent Data for Vinyl Chloride

The rat inhalation experiments of Maltoni and Lefemine (1975) with vinyl chloride resulted in an incidence of total tumors as given in the following table.

Vinyl Chloride Concentration (ppm)	Tumor Incidence
0	6/58
50	10/59
250	16/59
500	22/59
2,500	32/59
6,000	31/60
10,000	38/61

The slope parameter corresponding to this data is 4.05×10^{-4} $(ppm)^{-1}$. All the other polynominal coefficients are zero. In the process of fitting this data to the linearized multistage model the highest two doses were not used.

Since the animals were exposed for four hours per day, five days per week for 52 weeks and then held to two years for observation, the lifetime average concentration was $4/24 \times 5/7 \times 52/104 = 0.060$ times the concentration administered. Therefore, based on the animal slope parameter from inhalation, $q_1(I)$, is:

$$q_1(I) = 4.05 \times 10^{-4}/0.06 = 6.80 \times 10^{-3} \ (ppm)^{-1}.$$

The vinyl chloride uptake study by Withey and Collins (1976) stated that for 200 gm rats the same blood concentration of vinyl chloride is produced by either breathing 1.97 ppm or by ingesting 4.5 mg/kg/day by gavage. This relationship was true over a range of gavage doses from 2 to 25 mg/kg. Although the linear relationship between administered dose and the blood concentration did not hold true for the 400 gm rats, the above data do at least give a rough estimate of the relation between inhalation and ingestion.

Assuming this equivalence to be true, then 1 ppm inhaled equals 2.28 mg/kg/day (i.e., 4.5/1.97). Therefore, the slope of the dose-response curve for rats after oral gavage, $q_1(O)$, is estimated by:

$$q_1(O) = q_1(I)/2.28,$$
$$= 6.8 \times 10^{-3}/2.28,$$
$$= 3.0 \times 10^{-3} \text{ (mg/kg/day)}^{-1}.$$

The equivalent slope for humans after oral ingestion, q_1^*, is estimated by:

$$q_1^* = q_1(O) \times \sqrt[3]{\frac{70}{0.350}},$$

$$= 3.0 \times 10^{-3} \times \sqrt[3]{\frac{70}{0.350}},$$

$$= 1.74 \times 10^{-2} \text{ (mg/kg/day)}^{-1}.$$

The water quality criterion for vinyl chloride is now a straightforward calculation:

$$C = \frac{70 \times 10^{-5}}{q_1^* \times (2 + 0.0065 \times BCF)},$$

where 70×10^{-5} is the human cancer lifetime risk of interest, 2 and 0.0065 represent the daily water (in liters) and fish (in kg) consumption, respectively, and BCF is the bioconcentration factor for vinyl chloride. Therefore,

$$C = \frac{70 \times 10^{-5}}{1.74 \times 10^{-2} \times (2 + 0.0065 \times 1.17)},$$

$$= 20 \text{ mg/l}.$$

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