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I. SUMMARY

Almost 7 billion pounds of vinyl chloride are produced in the United States annually. Most emissions into the environment originate from manufacturing plants which use the compound for the production of polyvinyl chloride resins. The predominant route of exposure to the public living near these plants is through inhalation, while the principal source of vinyl chloride exposure for most Americans is probably from polyvinyl chloride food containers. This source contributes approximately 1 ppb to the diet. Vinyl chloride has also been found in drinking water. Three national surveys of drinking water have demonstrated the presence of vinyl chloride at very low levels (ug/l range) in a small number of supplies.

Upon ingestion, vinyl chloride is rapidly absorbed from the gastrointestinal tract and is distributed to the liver and other organs. Several pathways may be involved in vinyl chloride metabolism, which occurs primarily in the liver. The toxicity of vinyl chloride appears to be attributable to its enzymatic conversion to reactive polar metabolites such as chloroacetaldehyde or chloroethylene oxide. Several of these suspected metabolites are mutagenic, while vinyl chloride itself is not, according to available information. At low doses (e.g., 1 mg/kg) the metabolites of vinyl chloride are primarily excreted in the urine. At high doses (e.g., 100 mg/kg), most of the solvent is expired as vinyl chloride.

Acute and chronic exposure to vinyl chloride can result in toxicity in experimental animals and humans. In animals, an inhalation exposure of approximately 100,000 ppm results in death within several hours, with autopsies revealing congestion and edema of the lungs and hyperemia of the kidneys and liver. Test animals exposed to an inspired air concentration below 100 ppm exhibit no pronounced adverse health effects. Teratogenicity was not observed in rats and rabbits exposed to 2500 ppm vinyl chloride.

Studies on humans working in vinyl chloride plants suggest that systemic toxic effects that are noncarcinogenic in nature can be demonstrated at exposure levels below 50 ppm. Some plant workers may have been exposed to concentrations exceeding 1000 ppm and occasionally approaching 10,000 ppm before OSHA standards were instituted in 1974. At these levels, workers manifested dizziness, headaches, and/or euphoria. Long-term exposure to these levels in vinyl chloride plants have resulted in a number of diseases (i.e., acroosteolysis, pulmonary insufficiency), cardiovascular and gastrointestinal manifestations, and disturbances of the central nervous system. Unfortunately, data regarding dose-response relationships in humans are very scarce because of the virtual absence of air measurements of vinyl chloride in the work environment before 1974.

Vinyl chloride has been implicated as a human and animal carcinogen. Animal studies indicate that vinyl chloride may

produce tumors of different types at different sites, and that the incidence and relative distribution are greatly influenced by dose, age of the animal, and species and strain of animal used. Lifetime studies currently in progress have shown that vinyl chloride inhalation exposures as low as 25 ppm produce liver angiosarcoma in rats, and suggest that mammary cancers in rats may be produced at inhalation concentrations as low as 1 ppm.

Human data have been primarily obtained from workers exposed to vinyl chloride. A number of epidemiologic studies have linked vinyl chloride with angiosarcoma and other forms of neoplasm. The reported frequency of angiosarcoma of the liver is especially noteworthy because this is a very rare type of cancer (25 - 30 cases/yr in the United States), and it is reasonable to infer a causal relationship between exposure to vinyl chloride and the development of this tumor. Through 1977, a total of 64 cases of liver angiosarcoma have been identified worldwide among vinyl chloride-exposed industrial workers. Although rare, the carcinogenicity of vinyl chloride to humans is unambiguous.

The National Academy of Science (NAS) and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water by mathematical extrapolation from high-dose animal studies. Using the risk estimates generated by the NAS (1977-1979) where the multi-stage model was utilized, that range of vinyl chloride concentrations were computed that

would nominally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption at the stated exposure level. From the NAS model it is estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a vinyl chloride concentration of 100 ug/l, 10 ug/l or 1 ug/l would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, respectively. Using the revised CAG approach and thus the "improved" multi-stage model, it can be estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a vinyl chloride concentration of 200 ug/l, 20 ug/l or 2 ug/l would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed respectively. The numerical differences observed after utilizing the NAS and the CAG risk estimates are partly due to the fact that the dose extrapolation model used by the two groups is similar but not identical. The NAS has used the multi-stage model whereas the CAG has used the "improved" version of the multi-stage model recently discussed by Crump (U.S. EPA, 1980). In addition, the selection of the data and other parameters in each model will also result in some differences, especially since the NAS based its calculations on an ingestion study by Maltoni et al. (1975) in which rats were exposed to vinyl chloride by gavage, while the CAG used the same Maltoni et al. (1975) study but based its estimate upon the increased incidence of total tumors in rats exposed to vinyl chloride through inhalation.

Drinking Water Concentrations and Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)*		
	CAG (95% confidence limit)	NAS (95% confidence limit)	NAS (point estimate)
10^{-4}	200	100	170
10^{-5}	20	10	17
10^{-6}	2	1	1.7

*Assume 2 liters of water are consumed per day by a 70 kg adult for a 70 yr lifetime.

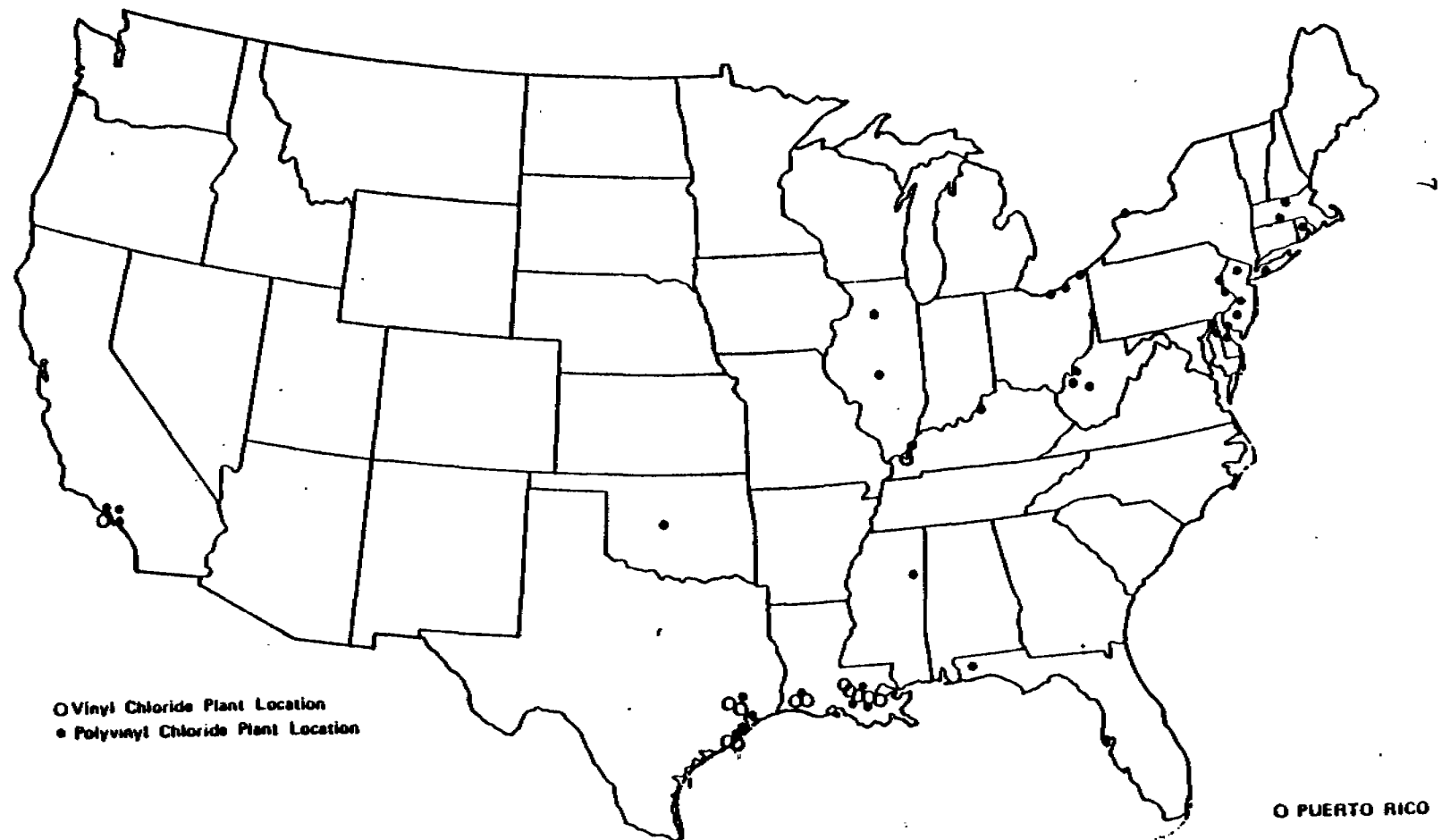
II. INTRODUCTION

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride (PVC), the most widely used material in the manufacture of plastics throughout the world. About 25% of the estimated 18 billion pounds of vinyl chloride produced worldwide in 1972 was manufactured in the United States (Berk, et al., 1976). Between 1968 and 1973, vinyl chloride production in the United States rose 14% annually, reaching a production level of nearly 7 billion pounds in 1978 (U.S. Int. Trade Comm.). This increase in vinyl chloride production was due to the growing dependence of virtually every branch of industry and commerce upon products and components fabricated from polyvinyl chloride (U.S. EPA, 1974). (For the location of vinyl chloride and polyvinyl chloride manufacturing and processing plants in the United States in 1978, refer to Figure 1.)

Vinyl chloride is not known to occur in nature (National Academy of Sciences, 1977). The compound is synthesized as chlorinated olefinic hydrocarbon monomer from petrochemical feedstock and chlorine. In 1975, vinyl chloride emissions in the United States were found to originate from three major sources: (1) 17 plants where vinyl chloride was commercially synthesized (about 11 percent); (2) 41 PVC plants where the vinyl chloride monomer was used in the production of PVC resins for various industrial purposes (about 85 percent); (3) about 8,000 PVC fabricating plants (U.S. EPA, 1975b).

FIGURE 1

Locations of Vinyl Chloride and
Polyvinyl Chloride Plants in the United States
(Milby, 1978)



SOURCE: SRI.

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Vinyl chloride and polyvinyl chloride are used as raw materials in the rubber, paper, glass and automotive industries. In addition, vinyl chloride and polyvinyl chloride are used in the manufacture of electrical wire insulation and cables, piping, industrial and household equipment, medical supplies, food packaging materials and building and construction products. 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 (a colloidal dispersion in water used to coat paper, fabric or leather).

III. PHYSICAL AND CHEMICAL PROPERTIES

The structure of vinyl chloride is as follows:



Vinyl chloride is highly flammable (limits of inflammability: 4.00-21.70%) and in sufficient concentrations (at least 1200-2000 ppm) has a sweet, pleasant odor. The compound has a boiling point of -13.37°C . Thus, at standard temperature and pressure, vinyl chloride exists as a gas. Vinyl chloride is only sparingly soluble in water (0.11 g/100 g water at 28°C), but is soluble in alcohol and very soluble in ether and carbon tetrachloride. The specific gravity of the chemical is 0.91; thus it would tend to rise to the surface of water. The vapor density of vinyl chloride is slightly more than twice that of air (CRC Handbook of Chemistry and Physics, 1978-1979; Braker and Mossman, 1971).

The above information indicates that vinyl chloride is volatile and readily passes from water into the gas phase under most laboratory and environmental conditions. This was confirmed in experiments where 16 mg/l vinyl chloride was added to distilled water in beakers and the concentration determined with time (U.S. EPA, 1974). The data indicate that if first order kinetics are assumed, the volatilization half-life in quiescent water (unstirred) is 290 minutes and in continually stirred water is 25.8 minutes. Dilling, et al., (1975) found similar values for the stirred water. As Dilling, et al., note, predictions of vinyl chloride loss from water at relatively high concentrations (e.g., 1 mg/l) may not reflect the situation at very low concentrations.

Volatilization appears to be the most significant process in the loss of vinyl chloride from the aquatic environment (Hill, et al., 1976). Once in the atmosphere, vinyl chloride undergoes rapid photochemical oxidation (Gay, et al., 1976; Lillian et al., 1975).

IV. SOURCES OF HUMAN EXPOSURE

Vinyl chloride exposure can occur through inhalation of the airborne chemical, ingestion of contaminated food and/or water, and dermal absorption. For persons working in vinyl chloride manufacturing or processing plants or living near such facilities, inhalation is the principal route of vinyl chloride

exposure, while exposure via ingestion appears to be the primary route for the general population. Vinyl chloride has been detected in drinking water, food, beverages, cosmetics, and other consumer products.

A. Inhalation

Some early data are available concerning airborne vinyl chloride in the workplace. In the Soviet Union, Filatova and Gronsberg (1957) reported airborne vinyl chloride concentrations of 8 to 16,000 ppm, with average exposures ranging from 20 to 300 ppm. Monitoring of the workplace for vinyl chloride levels was not a common practice in the U.S. until about 1950, when Dow Chemical Company, an American manufacturer, initiated monitoring of vinyl chloride levels. Exposures were generally below 500 ppm; however peak concentrations of 4,000 ppm were recorded (Ott, et al., 1975). After 1960, Dow Chemical Company reduced exposures of workers to about 25 ppm, 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, 1974), permissible exposure levels were drastically reduced.

Inhalation of vinyl chloride by the general population occurs in the vicinity of vinyl chloride and PVC manufacturing plants. Marcus and Coniglio (American Health Association, 1975) estimated that 4.6 million people in the United States lived within five miles of at least one vinyl chloride plant, and some

of these people lived within five miles of three such plants. Kuzmack and McGaughy (1975) calculated that the population within five miles of uncontrolled vinyl chloride production or polymerization plants is exposed to an average ambient air concentration of about 17 ppb. However, in a sample of ambient air collected at Delaware City, Delaware, a city in which a polyvinyl chloride manufacturing plant is located, 1.5 ppm vinyl chloride was detected (Lillian, et al., 1975). In 1975, the Environmental Protection Agency declared vinyl chloride to be a hazardous pollutant under the Clean Air Act. A vinyl chloride emission limit of 10 ppm at the stack was set, which should reduce emissions by about 95 percent (U.S. EPA, 1975b). Thus, vinyl chloride ambient air values are probably considerably lower today than values measured in the past.

Other sources of vinyl chloride exposure exist in addition to stack emissions. Municipal incinerators may release vinyl chloride after incomplete combustion of PVC products (Boettner et al., 1973). If this situation occurs, the released vinyl chloride would probably reflect unreacted monomer within the PVC rather than any depolymerization of the PVC. This route of exposure is considered minimal. Vinyl chloride has also been detected in the air above covered sanitary landfills containing PVC waste sludge from vinyl chloride/PVC facilities. In a study by Battelle Laboratories (Markle et al., 1976), concentrations in grab air samples ranged from 0.07 to 1.10 ppm. Four additional

grab air samples were collected in residential or public access areas within 0.16 to 1.6 km of one of the landfills (about 150 km from the PVC facility originating the sludge), and vinyl chloride levels ranged from 0.12 to 0.37 ppm. The gas chromatograph analyses, however, were not confirmed by mass spectrograph analyses. More recent data from B.F. Goodrich (Becker, 1979) indicate the average ambient air concentrations above two such sanitary landfills were 25 ppb and 34 ppb (uncovered landfill). Prior to being banned for this use in 1974, another source of inhalation exposure was the vinyl chloride propellant used for dispensing household and cosmetic products.

B. Ingestion from Water

Several recent national surveys of organic compounds in drinking water have reported finding vinyl chloride in potable water. In 1974, the EPA initiated the National Organics Reconnaissance Survey (NORS); an extensive water survey of 80 public water supplies (U.S. EPA, 1975a). As part of this program, the concentration of specific organic chemicals in drinking water supplies in ten cities was determined. Vinyl chloride was found in two of these cities -- Miami (5.6 ug/l) and Philadelphia (0.27 ug/l).

In a subsequent survey, the National Organics Monitoring Survey (NOMS), the EPA investigated 113 community water supplies for a number of organic compounds (U.S. EPA, 1977). Vinyl

chloride was found in two locations -- Des Moines, Iowa (0.18 ug/l) and Waterford Township, New York (0.1 ug/l). The limit of detection in this study was approximately 0.1 ug/l. A third national survey, known as the National Screening Program for Organics in Drinking Water, is currently examining 136 water supplies nationally. This study is not complete. Preliminary data indicate that at least two supplies contain measurable amounts of vinyl chloride. It is apparent from these three surveys that vinyl chloride is present in a small number of water supplies in spite of the chemical's low solubility and high volatility.

Industrial waste water effluent may be one source of the vinyl chloride found in drinking water. Levels of vinyl chloride in waste water effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of waste water from seven areas (representing 13 vinyl chloride/PVC plants) ranged from less than 0.1 ppm to 20 ppm (U.S. EPA, 1974). In these studies, values represent vinyl chloride concentrations in three 24-hour composite waste water samples from each area.

Polyvinyl chloride pipe used in water distribution systems provides another source of vinyl chloride in drinking water. The EPA's Water Supply Research Division studied five water distribution systems which used PVC pipes (Dressman and McFarren, 1978). Trace amounts of vinyl chloride were detected in samples from

three of the five water supply systems. Water samples collected from the most recently installed and the longest pipe system had the highest vinyl chloride concentration (1.4 ug/l). Traces of vinyl chloride (0.03 and 0.06 ug/l) were still present in samples from two other systems 9 years after installation.

The level of residual vinyl chloride in water pipes varies from less than 10 ppm to more than 100 ppm (FDA, 1975). The FDA scientists speculated that very little vinyl chloride migrates into the water from the pipes because of the low solubility of the chemical in water, the short time of contact, the large volume of water in contact with the pipe, and the low temperatures of exposure. No numerical estimates, however, were provided. In 1977, the manufacturers of water pipes adopted a voluntary standard of 10 ppm or less of residual vinyl chloride in finished pipes and fittings.

C. Ingestion from Food

Approximately 300 million pounds of PVC are used in the packaging of food each year (FDA, 1975). PVC packaging and food contact material contain low levels of vinyl chloride monomer, some of which may slowly migrate into food. According to the FDA (1975), in past studies as much as 2000 ppm residual vinyl chloride was found to be present in commercially available PVC. The FDA also cited studies which reported vinyl chloride levels in several foods packaged in PVC material. Cooking oils were reported to contain 1.6 and 6.5 ppm (one study), 74 ppb and 2 ppm

(another study), and 10 to 40 ppb (third study). Fruit squashes contained 10 to 80 ppb and a mouthwash contained 174 ppb. Before the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages, up to 20 ppm was present in so packaged liquors (Anon, 1973). Van Esch and Van Logten (1975) reported that vinyl chloride migration from PVC containers with vinyl chloride residue levels of 30 ppm into water, soft drinks, and blood, produced after 40 days, concentrations of 20-50 ppb, 0.2 ppb and 14-80 ppb, respectively. The extent of migration depends on the initial content of vinyl chloride in PVC, product storage time, and type of industrial process used.

In 1975, the FDA proposed regulations to restrict the uses of vinyl chloride polymers in contact with food. To date (May, 1980) this regulation has not been promulgated. According to the FDA (Drs. T. Troxell and V. Anand, Personal Communications), the reason for this is that great progress has been made by industry since 1975 in reducing vinyl chloride residuals in PVC. Some companies have reduced vinyl chloride levels to 1.2 ppb, which is considerably less than the levels previously found. According to an industry source, Union Carbide Corp., levels of vinyl chloride in PVC products commercially available vary greatly. Plastisol vinyl chloride coatings on food containers have levels of 10-20 ppb, while PVC bottles used for food contain less than 1 ppm residual. Calculations performed by the FDA indicate that if a

PVC container has 1.5 ppb residual, less than 20 ppt (trillion) would migrate into food (50% ethanol) after 6 months at 120°F (Mike Flood, Personal Communications). According to the FDA, the Ethyl Corp. performed an experiment where a 50% ethanol solution was stored at 120°F in a PVC bottle containing a vinyl chloride residual of 1 ppm. After 58 days, 6-9 ppb had migrated into the ethanol solution. These calculations indicate that for commercially available PVC containers, no more than a few ppb's should migrate into the food. The FDA also assumes that about 25% of the food in the U.S. is packaged in PVC containers. Thus, a tentative estimate of the level of vinyl chloride in the diet is 1 ppb.

Another source of vinyl chloride ingestion exposure is through fish and shellfish consumption. However, bioaccumulation of vinyl chloride in fish appears to be very low due to the high volatility of the compound. In one study, ^{14}C -vinyl chloride was added to the water of a closed model aquatic ecosystem which included mosquito fish, green algae, and mosquito larvae. After three days, there did not appear to be an appreciable bioconcentration of extractable radioactivity in the tissues of the organisms (Lu et al., 1977). The low bioaccumulation factor in fish was also suggested by theoretical considerations based on laboratory data (Veith et al., unpublished manuscript).

D. Dermal Absorption

According to a study by Hefner et al. (1975b), absorption of vinyl chloride through the skin is minor. In their investigation, two rhesus monkeys were exposed (whole body, excluding the head) to 7000 and 800 ppm of airborne ^{14}C -vinyl chloride for 2.0 and 2.5 hours, respectively. After sacrifice, the radioactivity in the brain, heart, lung, liver and other tissues was determined. The total amount of vinyl chloride absorbed was between 0.023% and 0.031%, respectively, of the total vinyl chloride available for absorption. Assuming that absorption is related directly to surface area, the investigators calculated that a 6 foot, 90 kg man would absorb 4.75 mg of vinyl chloride if exposed to 7000 ppm for 2 hours. Absorption of this level of vinyl chloride was determined to be equivalent to being exposed to 0.2 ppm via inhalation for 8 hours. Based on these results, the authors concluded that significant percutaneous absorption would not be expected to occur upon exposure to low concentrations (less than 5 ppm) of airborne vinyl chloride.

V. PHARMACOKINETICS

A. Absorption and Distribution

An investigation by Duprat et al. (1977) indicates that inhaled vinyl chloride is rapidly absorbed by the lungs and immediately accumulates in the liver. In this study, rats were exposed in a chamber to 20,000 ppm ^{14}C -vinyl chloride for 5 minutes, and then the distribution of radioactive vinyl chloride

in the various body organs was determined. After 10 minutes exposure, radioactivity was found in the liver, bile duct, digestive lumen, and kidneys. With increasing time (up to 3 hours), ^{14}C activity was detected in the urinary system, salivary and lacrimal glands, skin and thymus.

Using male Wistar rats, Withey (1976) determined that vinyl chloride is rapidly absorbed from the gastrointestinal tract following gastric intubation of aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Vinyl chloride uptake by this route was extremely rapid; peak concentrations were found less than 10 minutes after the dose was administered.

In a study by Watanabe et al. (1976a), rats were given single oral doses (gavage) of 0.05, 1, or 100 mg/kg of ^{14}C -vinyl chloride dissolved in corn oil, and the routes and rates of elimination of ^{14}C activity were followed for 72 hours. The percentage of the dose expired as vinyl chloride per se was 1, 2, and 67%, respectively. The disposition of vinyl chloride to various organs and tissues was also determined. The liver was found to retain the greatest percentage of activity at all dose levels, three to five times the percentage found in muscle, lung or fat (Table 1). The investigators concluded that the fate of vinyl chloride following oral administration is a dose-dependent saturable process, with the saturation of the vinyl chloride-metabolizing enzymes occurring at a concentration between 1 and 100 mg/kg.

TABLE 1

Percentage of the Administered ^{14}C Activity
per Gram of Tissue
After Administration of (^{14}C) Vinyl Chloride
by Gavage to Male Sprague-Dawley Rats^a
(Watanabe et al., 1976a)

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

^a Remaining in the body after 72 hr.

^b Mean $\pm$ SE, five rats per dose

^c Not detectable above background

^d Vinyl chloride dissolved in corn oil

In an inhalation study by this group (Watanabe et al., 1976b), rats were exposed to 10 or 1000 ppm ^{14}C -vinyl chloride for 6 hours and the routes and rates of elimination of ^{14}C activity were followed for 72 hours after termination of exposure. Like the gavage study, animals were sacrificed after 72 hours and samples of tissues collected for analysis of ^{14}C activity. Table 2 indicates that, similar to the gavage study, the liver retains the greatest percentage of vinyl chloride (or metabolites) at the dose levels studied. However, no saturation of vinyl chloride metabolism is discernable between 10 ppm and 100 ppm in this study, in contrast to the gavage experiment.

In another report, 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 5 hours in a closed system, the percent incorporated as ^{14}C -radioactivity per g tissue was highest for kidney (2.13) and liver (1.86). The percent of incorporated activity was 0.73 for the spleen and 0.17 for the brain. Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

The percentage absorption of vinyl chloride from the human gastrointestinal tract has not been established. Because of the lack of data on percent absorption from the gastrointestinal tract, the risk calculations in this document will assume a 100% absorption factor.

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TABLE 2

Percentage of ^{14}C Activity
per Gram Tissue 72 hr Following an Inhalation
Exposure to (^{14}C) Vinyl Chloride
for 6 hr in male Sprague-Dawley Rats
(Watanabe et al., 1976b)

Tissue	Percentage ^{14}C activity	
	Exposure concentration	
	10 ppm	1000 ppm
Liver	0.139 ± 0.009^a (0.35) ^a 0.141 ± 0.009^b	0.145 ± 0.003^a (9.63) ^a 0.165 ± 0.009^b
Skin	0.072 ± 0.004 (0.18) 0.073 ± 0.004	0.115 ± 0.010 (7.64) 0.131 ± 0.011
Carcass	0.048 ± 0.004 (0.12) 0.049 ± 0.004	0.049 ± 0.004 (3.26) 0.056 ± 0.005
Plasma	0.051 ± 0.001 (0.13) 0.052 ± 0.001	ND ^c
Muscle	0.052 ± 0.005 (0.13) 0.053 ± 0.005	0.038 ± 0.003 (2.52) 0.043 ± 0.003
Lung	0.065 ± 0.007 (0.16) 0.066 ± 0.007	0.046 ± 0.001 (3.06) 0.052 ± 0.001
Fat	0.026 ± 0.006 (0.07) 0.026 ± 0.006	ND ^c
Kidney	0.079 ± 0.003 (0.20) 0.080 ± 0.003	0.057 ± 0.005 (3.79) 0.065 ± 0.006

^a Expressed as percentage of total ^{14}C activity per gram of tissue.
Uncorrected for expired VC:

$$\frac{\text{dpm per g tissue}}{\text{total dpm recovered}}$$

Mean $\pm$ SE from four rats.

^b Expressed as percentage of metabolized ^{14}C activity per gram of tissue. Corrected for expired VC:

$$\frac{\text{dpm per g of tissue}}{\text{total dpm recovered minus dpm of expired VC}}$$

Mean $\pm$ SE from four rats.

^c Microgram equivalents vinyl chloride per gram of tissue.

^d Not detectable, detection limit for plasma and fat was 3 $\mu\text{g/g}$ of tissue (3 ppm).

B. Metabolism

Metabolism of vinyl chloride occurs primarily in the liver by microsomal enzymes. There is strong evidence that the toxicity of this compound is attributable to its enzymatic oxidation to reactive polar metabolites. Several of these suspected metabolites are strongly mutagenic, while vinyl chloride itself is not (Bartsch and Montesano, 1975). Exposure to vinyl chloride leads to the reduction of non-protein sulfhydryl levels in rat liver, suggesting that the metabolites of vinyl chloride conjugate with glutathione and/or cysteine (Hefner et al., 1975a). Hathway (1977) reported in vitro depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following administration of vinyl chloride to rats in vivo. This suggests that vinyl chloride metabolites may interact with some purine and pyrimidine residues of DNA, providing a possible explanation for the oncogenic properties associated with vinyl chloride.

In a review of the literature, Bartsch and Montesano (1975) report two possible biotransformation schemes -- one involving alcohol dehydrogenase (Scheme I) and the other involving the mixed function oxidase system (Scheme II). These are indicated below:



Evidence for biodegradation involving the alcohol dehydrogenase pathway includes data which demonstrates that pretreatment of rats with either ethanol or pyrazole (an inhibitor of alcohol dehydrogenase) inhibits the metabolism of vinyl chloride (Hefner et al., 1975a).

There is also ample evidence that the mixed function oxidase (MFO) system is 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, which is thought to be formed by the MFO system, may be the primary microsomal metabolite capable of alkylating these intra-cellular macromolecules (Laib and Bolt, 1977).

Several pathways may be involved in vinyl chloride metabolism, the predominant one depending on dose. Hefner et al. (1975) performed an inhalation study in which rats were exposed to vinyl chloride concentrations ranging from 50.5 to 1167.0 ppm for 12 months time. The rate of metabolism, as determined by measuring the declining level of vinyl chloride in the chamber atmosphere, was three times greater for seven separate exposures ranging from 50 to 105 ppm than it was for five separate exposures ranging from 220 to 1167 ppm. This indicated that the predominant pathway at the lower concentrations, probably

involving alcohol dehydrogenase, is saturable between 105 and 220 ppm. This group also found evidence that oxidases in the microsomes may be involved in metabolism at high level exposures. In another study, Bolt et al. (1977) subjected rats to an inspired concentration of ^{14}C -vinyl chloride ranging from 200 to 1200 ppm in a closed system, and measured the rate of decrease of vinyl chloride levels in the chamber atmosphere. This group calculated that saturation of the vinyl chloride-metabolizing enzymes of the rat is achieved at 250 ppm.

C. Excretion

Excretion of ^{14}C activity within 72 hours following a single oral dose of ^{14}C -labeled vinyl chloride (0.05, 1.0, or 100 mg/kg) is shown in Table 3 (Watanabe et al., 1976a). As the dose increases, a markedly greater proportion of vinyl chloride is expired unmetabolized, while the percentage of metabolite in the urine decreases substantially. Again, saturation kinetics are suggested. The table also indicates that metabolites of vinyl chloride are predominantly excreted via the urine.

Administration of vinyl chloride by inhalation produced almost identical results (Watanabe et al., 1976b). Two major metabolites in the urine are identified as indicated in Table 4.

Green and Hathway (1975) measured the excretion of ^{14}C -vinyl chloride administered to rats by intragastric, intravenous (femoral vein), or intraperitoneal routes. Two doses were used: 0.25 mg/kg and 450 mg/kg. The results are shown in Table 5.

TABLE 3

Percentage of Administered ^{14}C Activity Recovered
Following a Single Oral Dose of Vinyl Chloride^a
(Watanabe et al., 1976a)

	Dose (mg/kg)		
	0.05	1.0	100
Expired:			
As VC	1.43 $\pm$ 0.13 ^b	2.13 $\pm$ 0.22	66.64 $\pm$ 0.67
As CO ₂	8.96 $\pm$ 0.59	13.26 $\pm$ 0.47	2.52 $\pm$ 0.13
Urine	68.34 $\pm$ 0.54	59.30 $\pm$ 2.75	10.84 $\pm$ 0.95
Feces	2.39 $\pm$ 0.52	2.20 $\pm$ 0.39	0.47 $\pm$ 0.06
Carcass and tissues	10.13 $\pm$ 1.93	11.10 $\pm$ 0.47	1.83 $\pm$ 0.14
Cage wash ^c	0	0.84 $\pm$ 0.45	0
Total recovery	91.25 $\pm$ 2.47	88.83 $\pm$ 1.98	82.30 $\pm$ 0.43

^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 $\pm$ SE five rats per dose.

^c Distilled water wash of metabolism cage at termination of the study.

TABLE 4

¹⁴C-containing Urinary Metabolites
from Male Sprague-Dawley Rats^a
Given Vinyl Chloride by Gavage^a
(Watanabe et al., 1976a)

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

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

^b () = Number of animals per dose

^c Mean ± SE

TABLE 5

(Green and Hathway, 1975)

EXCRETION OF RADIOACTIVITY IN RATS, GIVEN A SINGLE DOSE OF [^{14}C]VINYL CHLORIDE

4 rats were each dosed i.g. with 250 μg of [^{14}C]vinyl chloride per kg in corn oil solution, and another 4 rats were each dosed similarly with 450 μg of [^{14}C]vinyl chloride per kg. 4 rats were each injected in the femoral vein with 250 μg of [^{14}C]vinyl chloride per kg in *N*-(β -hydroxyethyl) lactamide. Four rats were each injected i.p. with 250 μg of [^{14}C]vinyl chloride per kg in *N*-(β -hydroxyethyl) lactamide, and another 4 animals were each injected similarly with 450 μg of [^{14}C]vinyl chloride.

Size of dose	Time (h)	Radioactivity excreted (% of dose) ^a											
		Intragastric					Intravenous			Intraperitoneal			
		Exhaled air		Urine	Faeces	Exhaled air		Urine	Faeces	Exhaled air		Urine	Faeces
		Vinyl chloride	CO ₂			Vinyl chloride	CO ₂			Vinyl chloride	CO ₂		
250 µg/kg	0-24	3.7 ± 1.2	12.6 ± 1.1	71.5 ± 5.0	2.8 ± 2.5	99.0 ± 0.8	0.1	0.5	0.1	43.2 ± 4.6	10.3 ± 2.2	41.5 ± 4.8	1.6
	24-48		0.9	3.3	1.6						0.7	1.6	0.2
	48-72			0.3	0.2								
	Total	3.7 ± 1.2	13.5 ± 1.3	75.1 ± 4.2	4.6 ± 3.0	99.0 ± 0.8	0.1	0.5	0.1	43.2 ± 4.6	11.0 ± 1.2	43.1 ± 5.7	1.8
450 mg/kg	0-24	91.9 ± 2.5	0.6	4.5 ± 2.3	0.4					96.2 ± 4.1	0.7	2.5 ± 0.9	0.1
	24-48		0.1	0.8	0.3							0.1	
	48-72			0.1									
	Total	91.9 ± 2.5	0.7	5.4 ± 2.2	0.7					96.2 ± 4.1	0.7	2.6 ± 0.9	0.1

^a Values shown are the means $\pm$ S.D. of those means.

During the first 24 hours after treatment, more than 90 percent was excreted from the animals for all three routes. Significant differences were noted, however, in the manner of excretion for the 0.25 mg/kg dose. For the intragastric route, 71.5% was excreted in the urine, whereas 99% was exhaled from the lungs when vinyl chloride was administered intravenously. For the intraperitoneal route, 43.2% was exhaled while 41.5% was excreted in the urine. At the higher dose (450 mg/kg), over 90% was exhaled as vinyl chloride in both intragastric and intraperitoneal administered rats. The intragastric values are consistent with the values reported in the oral studies performed by Watanabe et al. (1976a) (see Table 3).

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 blood level time curves. 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." Thus, according to this model, inhalation exposure is ten times more efficient than oral exposure.

VI. Assessment of Human Exposure to Vinyl Chloride

People in the U.S. can be exposed to vinyl chloride in their drinking water, air and food. The relative contribution from each of these sources to the daily environmental dose varies greatly and depends upon many inter-related factors including occupation, diet, and where a person lives. Information presented in this section summarizes available data regarding the occurrence of vinyl chloride in air, food and drinking water for the purpose of assessing the role of drinking water in the daily environmental dose of vinyl chloride being absorbed by people in the U.S. Information presented in this section is not an exposure assessment: a detailed profile of the number of people exposed at different dose levels is not presented, nor are different alternatives presented which would evaluate different regulatory options. Presented below are summaries of occurrence data for vinyl chloride in air, food and water and information on rates of absorption, and the estimated maximum absorbed dose coming from the different media. This discussion is followed by a general discussion of the contribution from each media and the possible effect upon the daily dose of vinyl chloride.

Air

The inhalation of vinyl chloride vapors can introduce a significant dose of this chemical to the bloodstream and thereby to the organs within the body. The amount of vinyl chloride entering the body from respiration depends upon the levels in the air at work, home and play, as well as the time spent in each segment of the environment.

In 1975 nearly 7 billion pounds of vinyl chloride monomer (VCM) were produced in the United States. Polyvinyl chloride (PVC), a resin produced from vinyl chloride monomer, is a plastic used to make thousands of consumer and industrial products. Vinyl chloride monomer is a gas at ambient temperature, therefore it is easily released into the air at manufacturing and processing plants as well as from industrial solid wastes and PVC consumer or industrial products containing the trapped monomer. Thousands of people are exposed to vinyl chloride (VCM) where they work. According to the National Occupational Hazard Survey, vinyl chloride is released into the work environment at 1,400 to 36,000 plant sites across the U.S.

Occurrence in Ambient Air

Using modeling data, EPA estimated that the level of vinyl chloride monomer in ambient air in 1975 would range from 200 to 800 $\mu\text{g}/\text{m}^3$ near manufacturing and processing plants to 5 to 14 $\mu\text{g}/\text{m}^3$ several miles away from these point

sources. EPA's Office of Air Programs estimates that regulations promulgated in 1975 has resulted in reducing ambient air levels of VCM by more than 90 percent (U.S. EPA, 1981). No additional monitoring data have been generated.

Exposure to VCM may also occur near solid waste disposal sites. Markle, et al. (1976) reported that the concentration of VCM was between 0.07 and 1.1 ppm at landfills where PVC waste was buried. Becker (1979) indicated that the average concentration of VCM in the air above two sanitary landfills was between 61 and 87 $\mu\text{g}/\text{m}^3$.

Absorption Through the Lungs.

Duprat, et al. (1977) reported that vinyl chloride was rapidly absorbed through the lungs of rats and distributed throughout the body. However, no data are available to quantitate respiratory absorption of vinyl chloride. For this reason this report will generally deal with intake rather than absorbed dose. However, calculations of relative source contributions are based on 40 percent respiratory absorption (Khanna, 1980).

Estimated Daily Respiratory Intake

The concentration of vinyl chloride in urban ambient air is highly variable and is related to the distance from production, use and disposal sites. Each point of release creates a "Hot Spot" which diffuses into a halo of general exposure for the remainder of the geographic area.

Monitoring data to document levels in the environment are lacking. It is unlikely that people living in rural areas are exposed to ambient air containing vinyl chloride, but people living near production, use and disposal sites could inhale air containing this chemical. The quantity of air taken into the lungs varies widely with age, sex and the amount of physical activity expended by the individual. These factors may combine to produce a wide variation in the daily dose absorbed by individuals living in the same community. Studies conducted in 1975 indicate that nearly 5 million people live within 5 miles of VCM and PVC plants. Assuming that EPA regulations have reduced exposures by 90 percent, the daily intake for individuals near production sites may be between 0.22 to 12.5 ug/kg/day of vinyl chloride monomer.

Food

Living organisms other than man may be exposed to vinyl chloride in the air, water and food they absorb during their lifetime. Since vinyl chloride is soluble in fatty tissue, a portion of the chemical absorbed by these organisms is retained within their tissue and ingested by higher animals as they feed.

Occurrence in the Food Supply

There is presently no data on the level of vinyl chloride in foods consumed by the American public. According to the FDA (1975), approximately 300 million pounds of PVC are used annually in the packaging of 25 percent of the foods consumed

in the U.S. Prior to 1975, as much as 2000 ppm of VCM remained entrapped in commercially available PVC products.

Van Esch and Van Logten reported that vinyl chloride could migrate from PVC containers, producing levels of 0.20 to 80 ppb in both water and soft drinks. This study indicated that the residual of vinyl chloride migrating into food was small, and that the amount varied according to the type of food in the container. In 1973, the U.S. Treasury Department banned the use of PVC bottles for alcoholic beverages because levels of VCM as high as 20 ppm were found in those products.

Prior to 1975, PVC packing materials for foods commonly contained vinyl chloride residues in the ppm range. In 1975, the FDA proposed regulations to restrict PVC contact with foods. Although this regulation has not been promulgated, VCM levels in PVC packaging materials have reportedly been reduced to 1 to 2 ppb.

Absorption from Food

Very little is known about the absorption of vinyl chloride through the gastrointestinal tract. However, the absorption of lipid soluble organic compounds through the intestine is generally very high. This document will, in general, deal with gastrointestinal intake rather than absorbed dose.

Estimated Daily Intake from Foods

The quantity and type of food consumed by people in the United States varies widely with age, ethnic and regional origin, as well as economic status. Since the amount of vinyl chloride entering the body from dietary habits is highly dependent upon what foods are consumed, the range of how much may be absorbed is highly individual. The USDA patterns of U.S. food consumption for people of various ages were used to estimate the range of potential dose being absorbed from foods (USDA, 1965-66). Data on the level of vinyl chloride migrating into food are very limited. However, even if 25 percent of the food contained 0.01 ppb of VCM, it is estimated that the dietary intake for a 70 kg reference man would be less than 2 ug/kg/day.

Drinking Water

Prior to the 1970's the contamination of drinking water by synthetic organic chemicals was viewed as a series of isolated problems caused by the accidental "mishandling" of chemicals. The results of EPA surveys and the efforts of many States are changing the perception of drinking water quality. Since the passage of the Safe Drinking Water Act, EPA has initiated several major national monitoring efforts to gain perspective on the frequency and intensity of organic chemical contamination of drinking water. The surveys include:

- ° National Organics Reconnaissance Survey (NORS)
- ° National Organics Monitoring Survey (NOMS)

- ° National Screening Program for Organics in Drinking Water (NSP)
- ° Community Water Supply Survey (CWSS)
- ° Rural Water Survey (RWS)
- ° Ground Water Supply Survey (GWSS)

Each survey focused on different sources of water, different segments of the population and different chemical pollutants.

Occurrence in Potable Water

As much as 390 ug/l of vinyl chloride has reportedly been found in well water by State agencies (U.S. EPA, Feb. 1980). Vinyl chloride has been found by 4 of 9 States which have tested for its presence in drinking water. In New Jersey, approximately 411 water wells have been tested but none of these wells reportedly contain a measurable quantity of vinyl chloride (U.S. EPA, March/Dec. 1978). For the purpose of performing a national assessment of the level of vinyl chloride in finished drinking water, monitoring data from the NOMS, NSP, and Region V surveys have been blended into a single composite picture as shown in Table B. The accuracy of this picture is unknown and the data are very limited.

A total of 133 cities which draw upon surface streams for potable water have been sampled during federal surveys. It was found that 2.3 percent of the finished waters serving these cities contained VCM. The concentration of VCM in

these water supplies ranged from 0.1 to 9.8 ug/l. The median concentration in finished water from positive supplies was 3.43 ug/l; the mean was 0.4 ug/l (Table A).

A total of 25 cities that get their water from underground sources have been tested by federal surveys for the presence of VCM. Only three of these finished waters were found to contain a detectable level of this chemical.

Absorption from Drinking Water

There are no data available which quantitate the absorption of vinyl chloride from drinking water. Therefore this report will, in general, deal with gastrointestinal intake rather than dose. However, calculations on the relative source contribution for vinyl chloride are based on 100 percent absorption (Khanna, 1980).

Estimated Daily Intake from Drinking Water

The amount of drinking water consumed by a person depends on the climate where he lives, the unique physiological ability of that person to conserve liquid, the basic metabolic rate, degree of activity and other personal habits. Some individuals may consume 10 liters of water each day while others may consume less than 1 liter. For the following calculations, it has been assumed that a 10 kg child consumes 1 liter of water per day while a 70 kg man consumes 2 liters of water per day (ICP Standard Reference Man). Monitoring

data indicates that some adults drawing their drinking water from underground aquifers may intake 11.4 ug/kg/day of VCM, while a child's dose might be as high as 38 ug/kg/day.

Relative Source Contribution

The quantity of a pollutant absorbed into the body each day from the environment is the result of many personal choices and several factors over which there is little control. Where one works, lives and what one eats help to determine the daily exposure. People living in the same neighborhood or even in the same house can experience vastly different exposure patterns. Persons living immediately downwind from a location where vinyl chloride is being released into ambient air will tend to receive the vast majority of their daily dose of this chemical from inhalation. Similarly, people drinking highly contaminated water who are not directly downwind of a vinyl chloride discharge will receive the vast majority of their dose of vinyl chloride from the drinking water supply. The food supply can be a major route of exposure for other individuals. It is likely that all of these conditions exist somewhere in the United States. Unfortunately, methods have not been developed to measure all sources of exposure simultaneously. Table C presents a view of the relative contribution of vinyl chloride from drinking water that might be encountered in various communities under conditions where the exposure from food remains constant.

Three separate conditions for exposure levels in air and for exposure levels in drinking water are shown in Table 8. The conditions for air relate to an estimated dose for a standard 70 kg man inhaling $23 \text{ m}^3/\text{day}$ from rural air (0.0 ug/kg/day), urban air (0.21 ug/kg/day), and air near a point source (10.0 ug/kg/day). The exposure levels for water of 1 ug/l , 10 ug/l , and 450 ug/l correspond to a dose rate for the consumption of 2 liters/day by a 70 kg man of 0.03 ug/kg/day , 0.30 ug/kg/day , 3.0 ug/kg/day . The information shown in Table 6 is not an exposure assessment but merely relates several different scenarios regarding various exposure levels. For example, assume that a person consumes an average of $<0.07 \text{ ug/kg/day}$ of vinyl chloride in the diet. If that person lived in a rural area and drank water containing 10 ug/l of TCE, drinking water would contribute 81 percent of the daily intake of vinyl chloride. However, if that person lived in an urban area, drinking water would only contribute 51 percent to the daily dose. The values in Table 8 are for illustrative purposes only since exposure to chemicals such as vinyl chloride is greatly variable depending upon occupation, residence, environmental conditions, and personal habits.

Monitoring data shows that most people living in the United States are drinking water and breathing air that is relatively free from contamination with vinyl chloride. However, elevated levels of this chemical are found in the

air and water being used in some communities. An analysis of the number of individuals at each estimated dose level and the national and local benefits to be gained by reducing the level of vinyl chloride in drinking water will be part of future analyses.

TABLE 6
LEVELS OF VINYL CHLORIDE IN THE ENVIRONMENT

AIR

RURAL	UNKNOWN
URBAN	UNKNOWN - IF WITHIN 5 MILES OF PVC PLANT - 0.3 ug/m ³ POSSIBLE
POINT SOURCES	0.3 - 40 ug/m ³ (BASED ON 90% REDUCTION AFTER 1975 REG. NO MEASURE- MENT TO CONFIRM)

FOOD

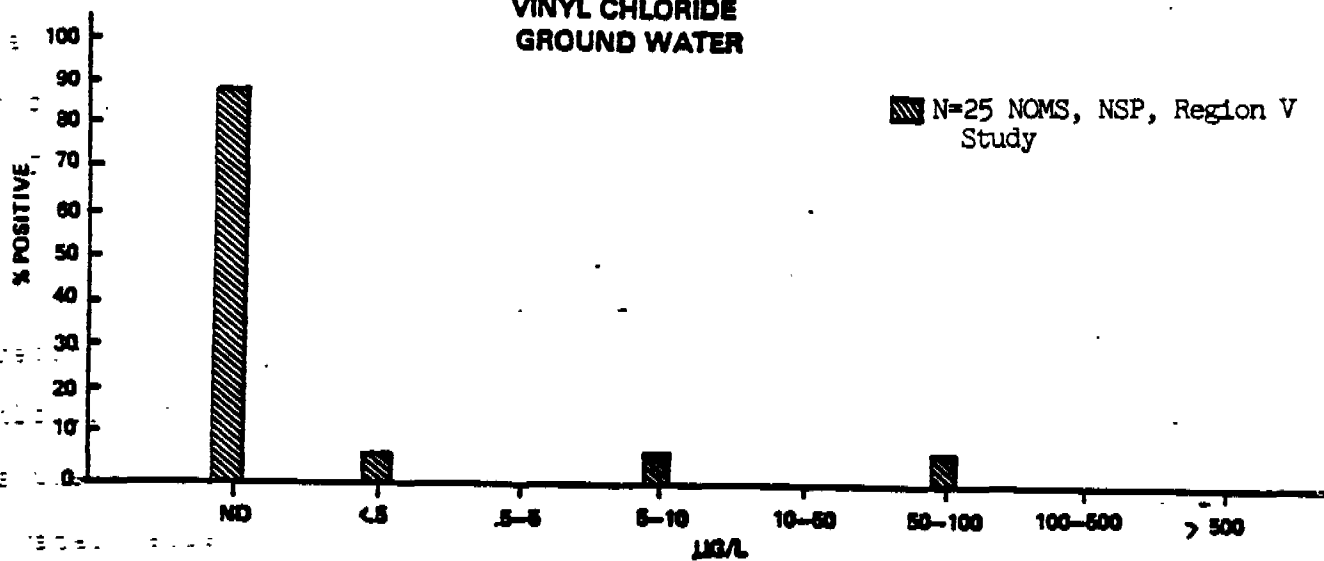
VEGETABLE AND FRUITS	} UNKNOWN
DAIRY PRODUCTS	
MEAT	
BREADS	
	MIGRATION FROM FOOD PACKAGING MATERIAL POSSIBLE, VCM RESIDUES NOW LOW - FOOD RESIDUES PROBABLY 0.01 ppb

WATER

<u>SURVEY</u>	<u># SAMPLED</u>	<u># POSITIVE</u>	<u>RANGE</u>
STATE DATA	1033	73	Tr - 380 ug/l
NOMS*	113	2	Tr - 0.18 ug/l
NOSP**	142	7	TRACE - 78 ug/l

- * Average of phases 1,2,3-quenched and terminal
** GC single column tentative identification, preliminary data.

TABLE 7
VINYL CHLORIDE
GROUND WATER



SURFACE WATER

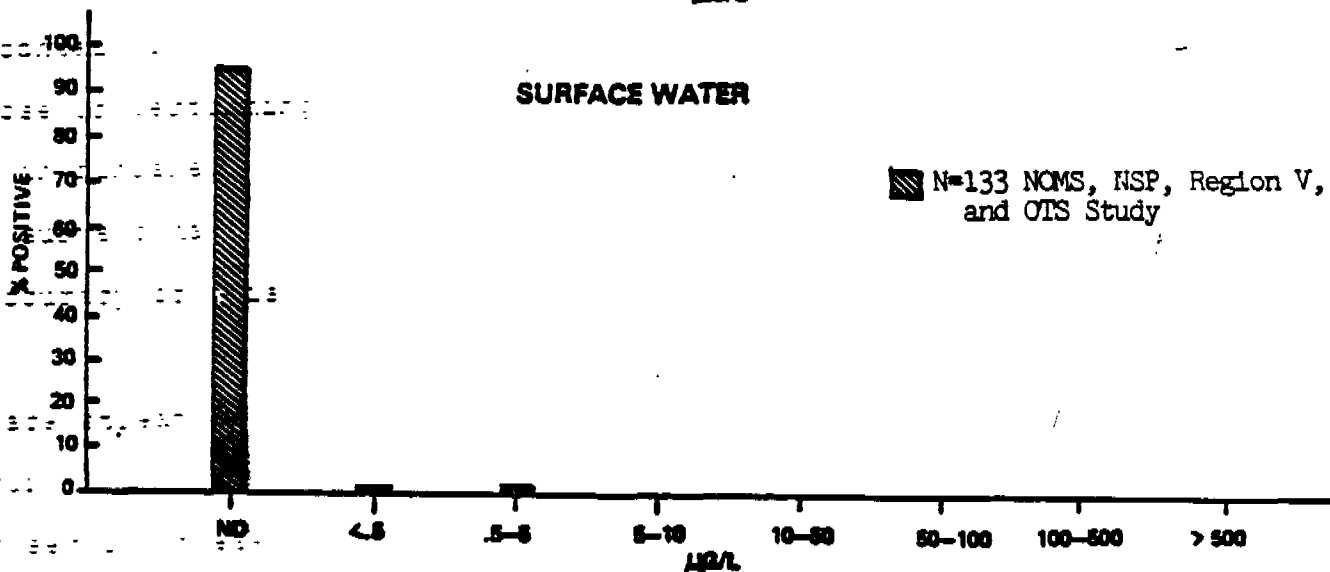


Table 8

Relative Contribution of Drinking Water to
the Environmental Dose of Vinyl Chloride
Being Absorbed in the United States*

Concentration in Drinking Water (ug/l)	Rural Air	High Urban Air	Air Near Point Sources
0	0%	0%	0%
1.0	96	41	0.5
10.0	99	97	5.0
100.0	99	98	35

Dose:

°Water: 4 ug/l: 0.03 ug/kg/day
 45 ug/l: 0.30 ug/kg/day
 450 ug/l: 3.00 ug/kg/day

°Air: Rural: 0.0 ug/kg/day
 Urban: 0.21 ug/kg/day
 Point Source: 10.0 ug/kg/day

°Food: 0.07 ug/kg/day

Assumptions:

°70 kg man
 °23m³ inhaled per day: 40% absorbed.
 °2 liters of water per day: 100% absorbed.

Note:

The above relative source contributions are for illustrative purposes only relating the contributions of air and water based upon specific scenarios of vinyl chloride contamination. The actual relative contributions will vary between communities and within communities depending upon occupation, residence, personal habits, and environmental conditions.

VII. HEALTH EFFECTS IN ANIMALS

A. Acute/Chronic Effects

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 (100,000 ppm), resulted in narcosis and death within 30 to 60 minutes. Inhalation of 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 effects of vinyl chloride in mice, rats, guinea pigs, rabbits, cats, dogs (Peoples and Leake, 1933; Lester et al., 1963; Mastromatteo et al., 1960; Haley, 1975; Prodan et al., 1975). In animal studies, LC50's at 2 hours ranged from 117,500 ppm for mice to 230,800 ppm for rabbits.

Marsteller et al. (1975) has reviewed and summarized the findings of previous studies on vinyl chloride exposure in laboratory animals. Torkelson et al. (1961) exposed test animals to concentrations ranging from 50 to 500 ppm. Rats exposed to 100 ppm (2 hours/day for 6 months) were judged normal on the basis of appearance, mortality, growth, hematological examination and other factors. However, a slight increase in the liver weight was observed. Rats, guinea pigs, rabbits, and dogs exposed to 50 ppm (7 hours/day, 130 times in 189 days) appeared

to be normal in appearance, mortality, and growth, and the increase in weight of the rat livers did not occur at this concentration. Basalaev et al. (1972) administered gaseous vinyl chloride to rats and rabbits at a concentration of 0.03-0.04 mg/l for 4 hours/day for 6 months. Cardiovascular disorders, changes in the bioelectric activity of the hypothalamus, hyperadrenalinemia, osteoporosis and resorption of bone tissue were observed.

Jaeger (1975) conducted experiments with rats to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this study, hepatotoxicity was measured by the elevation of serum alanine- -ketoglutarate transaminase (AKT). When fasted rats were exposed to 0.02% (V/V) 1,1-DCE, serum AKT activity was elevated about 50-fold, two hours after the termination of a 4-hour inhalation exposure. No elevation was observed when 0.1% vinyl chloride was administered alone. When the two chemicals were administered simultaneously at the levels indicated, no elevation of serum AKT occurred. Thus, the vinyl chloride was protective. These two monomers are used together in the production of vinyl copolymers, and exposure to both agents in the workplace was reported by Kramer and Mutchler (1972).

B. Teratogenicity

John et al. (1977) examined the effects of vinyl chloride inhalation on the fetuses of mice, rats, and rabbits. The pregnant animals were exposed 7 hours daily to concentrations of 50 or 500 ppm for mice and 500 or 2500 ppm for rats and rabbits.

Mice and rats were exposed on days 6 to 15 of gestation, and rabbits on days 6 to 18. No teratogenic effects were observed at 2500 ppm in rats and rabbits, except that a greater incidence of dilated ureters were noted in rats. Indeed, vinyl chloride exposure at this level actually decreased the incidence of certain skeletal anomalies in rats compared to controls (e.g., delayed ossification of the bones of the skull, and unfused centers of ossification of the skull and sternebrae). Mice were the most sensitive to vinyl chloride. No teratogenic effects were noted in the fetuses of mice exposed to 50 ppm, but a significantly greater incidence of unfused sternebrae and delayed ossification of sternebrae (no. 5) and bones of the skull were observed among litters of mice exposed to 500 ppm compared to unexposed controls. Embryotoxic effects were not generally noted, but some decrease in fetal body weight and crown-rump length was observed in rats and mice.

Radike et al. (1977a) did not observe gross (non-microscopic) abnormalities in the offspring of rats exposed 4 hours daily on the 9th to the 21st day of gestation by inhalation of 600 or 6000 ppm vinyl chloride. A small increase in the incidence of minor skeletal abnormalities, including wavy ribs, extra 14th ribs and delayed calcification of small bones, were observed in the offspring of the exposed animals. However, the investigators concluded that such a small incidence is difficult to distinguish from a sporadic occurrence, and should be considered to be skeletal variants and not malformations.

C. 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 to chemically reactive metabolites (e.g., chloroethylene oxide, 2-chloroacetaldehyde). The mutagenic effects of vinyl chloride have been demonstrated in: (1) metabolically activated systems using Salmonella typhimurium (Bartsch et al., 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 reverts to histidine prototrophy by base-pair substitutions, or by base-pair insertions or deletions; (2) Escherichia coli K12 bioauxotrophic strain with back mutation system 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 (Verburgt and Vogel, 1977) and (5) Chinese hamster V79 cells (Huberman et al., 1975). The literature on the mutagenic effects of vinyl chloride were reviewed by Bartsch and Montesano (1975).

The mutagenic activity of inhaled vinyl chloride (3000, 10,000 or 30,000 ppm for 6 hours a day for 5 days) was assessed in fertile male CD-1 strain mice with the dominant lethal assay (Anderson et al., 1976). At these 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.

D. Carcinogenicity

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; preliminary results of an investigation concerned with the oncogenic potential of vinyl chloride in experimental animals followed (Maltoni and Lefemine, 1974). These initial reports spurred a series of retrospective epidemiologic investigations of workers in the vinyl chloride industry and supportive experimental studies in animals. Several comprehensive reviews and symposium proceedings have been published on the subject (e.g., Selikoff and Hammond, 1975; Proceedings of the Royal Society of Medicine, 1976; U.S. EPA, 1975c; Milby, 1978).

In animal studies, Viola et al. (1971) reported the carcinogenic response of male rats (Ar/IRE Wistar strain) exposed to vinyl chloride by inhalation (Table 7). Skin tumors were first noted at approximately 10 months; tumors in the lungs and bones were observed at about 11 months.

TABLE 9

Oncogenic Effects of Inhaled Vinyl Chloride
(Viola et al., 1971)

Conc. VC (ppm) 4 hrs/day, 5 days/wk 12 months	Number Rats	Skin Epider- moid Car- cinomas	Lung Adenocar- cinomas & Squamous cell Carcinomas	Bones Osteo- chondroma
30,000	26	17	6	5
No treatment	25	-	-	-

Caputo et al. (1974) exposed male and female rats (A and IRE Wistar strain) by inhalation to various concentrations of vinyl chloride. Carcinomas and sarcomas were observed in all groups except those exposed to 50 ppm (Table 8). As can be observed, a dose response relationship exists between exposures of 50 to 20,000 ppm. Tumors appeared between 8 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 8) and reported the occurrence of lung and skin carcinomas.

Recent inhalation studies with albino CD-1 mice and CD rats (Charles River Breeding Lab) confirm the carcinogenicity of vinyl chloride at concentrations as low as 50 ppm (Lee et al., 1977, 1978). Liver angiosarcomas as well as other forms of cancers were found in both species.

TABLE 10

Incidence of Tumors in Rats and Rabbits
Exposed to Vinyl Chloride by Inhalation
(Caputo et al., 1974)

(ppm) 4 hrs/day 5 days/wk 12 months	# of Animals	Liver Angiosarcomas Cholangiomas	Lung Adeno- Alveolar Carcinomas	Skin Squamous Cell Carcinoma Acanthoma	Other
<u>Rats</u>					
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	-	-	-	-
<u>Rabbits</u>					
10,000	40	-	6	12	-
No Treatment	20	-	-	-	-

An extensive examination of vinyl chloride in experimental animals has been conducted by Maltoni (Maltoni, 1977). In one study, Sprague-Dawley rats were exposed by inhalation to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for 52 weeks. Angiosarcoma of the liver as well as other tumors were found to occur (Table 9). In another inhalation study which is currently in progress, rats were exposed to 25, 10, 5, or 1 ppm vinyl chloride. Angiosarcoma of the liver was seen at vinyl chloride levels of 25 ppm, and mammary cancers at exposures as low as 1 ppm (Table 10). An inhalation study in which rats (breeders) were exposed to vinyl chloride at 10,000 ppm and 6,000 ppm, 4 days/week for 1 week (from 12th to 18th day of pregnancy) produced vinyl chloride-dependent tumors in the offspring (Table 11). Two ingestion (gavage) studies are currently in progress and the results for one of the studies after 120 weeks is shown in Table 12. Table 13 indicates the tumor types that have been correlated with vinyl chloride inhalation exposure in experimental animals and man.

Maltoni (1977) concludes from the available data that vinyl chloride may produce tumors of different types at different sites and that the incidence and relative distribution are greatly influenced by dose, age of the animal, and species and strain of animal used.

There is evidence that ingested alcohol promotes the effects of inhaled vinyl chloride. Radike et al. (1977b) exposed male

TABLE 11

Experiment B11 Results after 135 Weeks (End of Experiment)

Group, treatment	Animals with tumors																		total ^d no.
	Animals (S-D rats)		angiosarcomas																
			Zymbal gland carcinomas ^b		nephro- blastomas ^c		livers ^d						sub- cuta- neous an- giomas	skin car- cino- mas	hepa- tomas	brain neuro- blas- tomas	mam- mary car- cino- mas	other sites ^e	
							other sites												
							no.	%	no.	%	no.	%							
total	cor- rected no. ^a	no.	%	latency (weeks)	no.	%	latency (weeks)	no.	%	latency (weeks)	no.	%	latency (weeks)	no.	%	latency (weeks)	no.	%	latency (weeks)
I																			
VA 2500 ppm	96	49	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II																			
VC 10,000 ppm	69	61	16	26	50	5	8	59	9	15	64	3 ^g	4	3	1	7	3	4 ^h	38
III																			
VC 10,000 ppm	72	60	2	12	67	4	7	65	13	22	70	3 ^g	3	1	1	3	—	8 ^h	31
IV																			
VC 2500 ppm	74	59	2	3	33	6	10	74	13	22	78	3 ^g	3	1	2	5	1	3 ^h	32
V																			
VC 500 ppm	67	51	4	7	79	4	7	83	7	12	81	2 ^g	1	1	4	—	1	3 ^h	22
VI																			
VC 250 ppm	61	59	—	—	—	6	10	80	4	7	79	2 ^g	—	4	—	—	1	2 ^h	11
VII																			
VC 50 ppm	61	59	—	—	—	1	2	135	1	2	135	1 ^g	1	1	—	—	2	7 ^h	10
VIII																			
VC 50 ppm	61	59	—	—	—	1	2	135	1	2	135	1 ^g	1	1	—	—	2	7 ^h	10
Total	5	464	20	—	—	20	—	—	47	—	—	14	12	11	8	15	5	—	15

TABLE 11 (continued)

- Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 200, and 50 ppm, 4 hr daily, 5 days weekly, for 52 weeks.
- Animals alive after 26 weeks, when the first tumor (a Zymbal gland adenoma) was observed. The percentages are related to the corrected number.
 - Metastases to lung.
 - Metastases to liver, lung, spleen, and brain.
 - Metastases to lung.
 - One intra-abdominal angiosarcoma (next to liver); 1 angiosarcoma of the lips; 1 angiosarcoma of the nose.
 - One angiosarcoma in subcutaneous fibrosing angioma; 1 ossifying parauricular angiosarcoma; 1 intra-abdominal angiosarcoma (next to liver).
 - One ossifying angiosarcoma of neck; 2 intra-abdominal angiosarcomas (1 next to spleen and 1 next to ovary).
 - One angiosarcoma of uterus; 1 lung angiosarcoma.
 - One intra-abdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.
 - One intra-abdominal diffuse angiosarcoma.
 - Several cases of breast fibroadenomas; adrenal and pituitary tumors (generally adenomas) have not been considered since their distribution in the different groups does not vary significantly.
 - Two Zymbal gland adenomas; 1 ovarian cystadenocarcinoma; 1 neurilemmoma.
 - Four Zymbal gland adenomas; 2 hepatic angiomas; 1 peritoneal angioma; 1 salivary gland adenocarcinoma.
 - One Zymbal gland adenoma; 2 ependymomas.
 - One pulmonary fibrosarcoma; 2 lymphomas.
 - One Zymbal gland adenoma; 1 lymphoma.
 - Three Zymbal gland adenomas; 1 subcutaneous angiopericytoma; 3 uterine adenocarcinomas (1 with sarcomatous component).
 - One invasive acanthoma of Zymbal gland; 1 subcutaneous fibrosarcoma; 2 peritoneal fibroangiomas; 2 uterine adenocarcinomas (1 with sarcomatous component); 1 uterine leiomyosarcoma; 1 ovarian fibrosarcoma; 1 pulmonary adenocarcinoma; 1 lymphoma.
 - Several animals with two or more tumors.

TABLE 12

Experiment BT. : Results after 87 Weeks

Group, treatment	No. of animals with tumors							
	Animals (S-D rats)		Zymbal gland car- cinomas	ne- piro- blasto- mas	angiosarcomas liver	other sites	mam- mary car- cinoma	other type
	total	sur- vivors						
I 5 ppm	120	43	3	—	3	—	10	7
II 10 ppm	120	5	1	—	—	—	11	5
III 50 ppm	120	12	—	—	—	—	13	5
IV VC ppm	120	49	—	—	—	—	8	—
V No treatment	120	49	—	—	—	—	2	4
Total	600	256	4	—	3	—	44	25

Exposure by inhalation to VC in air at 25, 10, 5, and 1 ppm, 4 hr daily, 5 days a week, for 52 weeks.

TABLE 13

Experiment B-5: Results after 143 Weeks (End of Experiment)

Group, treatment	No. of animals with tumors						
	Animals (S-D rats)		Zymbal gland car- cinomas	he- phro- car- blasto- mas	angio- sarcoma		other type and/ or site
	total	cor- rected no.			liver	site	
I VC 10,000 ppm breeders	30	30	1	—	—	1*	2*
II VC 6000 ppm breeders		30	—	—	—	—	—
III VC 10,000 ppm offspring	54	51	3	1	—	2*	2*
IV VC 6000 ppm offspring	32	32	1	—	—	—	4*
Total	146	143	5	1	—	5	6

* Exposure by inhalation to VC in air at 10,000 and 6000 ppm of breeders, 4 hr per day for 1 week (from 12th to 18th day of pregnancy).

* Animals alive after 22 weeks, when the first tumor (a subcutaneous angiosarcoma) was found in an offspring.

* One intra-abdominal angiosarcoma.

* One subcutaneous angiosarcoma; 1 angiosarcoma of the leg.

* One subcutaneous angiosarcoma; 1 intra-abdominal angiosarcoma.

* One liver fibroangioma; 1 liver angioma.

* One Zymbal gland fibrosarcoma; 1 ovarian leiomyosarcoma.

* One Zymbal gland adenoma; 1 skin carcinoma; 1 subcutaneous fibroangioma; 1 urinary carcinoma.

* One animal with two tumors.

TABLE 14

Experiment B¹¹: Results after 120 Weeks

Group, treatment	No. of animals with tumors							
	Animals (S-I) rats		Zyrtal gland car- cinomas	nephro- blastoma	angiosarcomas		mam- mary car- cinomas	other type and/ or site
	total	sur- vivors			liver	other sites		
VC 50.00 mg/kg I	80	2	1	2	16	2 ^a	5	7 ^a
VC 16.65 mg/kg II	80	2	2	3	9	—	6	3 ^a
VC 3.33 mg/kg III	80	4	—	—	—	2 ^b	4	3 ^a
Control: olive oil IV	80	4	1	—	—	—	4	5 ^c
Total	320	12	4	5	25	4	19	18

Exposure by ingestion (stomach tube) to VC in olive oil, at 50.00, 16.65, and 3.33 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.

^a One thymus angiosarcoma; 1 intra-abdominal angiosarcoma (next to spleen).

^b One lung angiosarcoma; 1 intra-abdominal angiosarcoma (next to kidney).

^c One skin sebaceous carcinoma; 1 papilloma of the liver; 2 forestomach papillomas; 1 intestinal adenocarcinoma; 1 lymphoma.

^d One liver angiosarcoma; 1 adrenal carcinoma; 1 fibrosarcoma.

^e One subcutaneous sarcoma with angioblastic component; 1 intra-abdominal ossifying sarcoma with angioblastic component; 1 bladder papilloma.

^f One skin carcinoma; 1 papilloma of the liver; 1 papilloma of the forestomach; 1 adenocarcinoma of the kidney.

TABLE 15

Tumors Presently Correlated to VC Exposure (by Inhalation) on Experimental Rodents and Man

Species	Angio- sarcomas of liver	Tumors of brain	Tumors of lung	Lym- phomas and leu- kemias	Hepa- tomas	Angio- sarcomas	Nephro- blastomas	Schro- eous cuta- neous car- cinomas	Other cuta- neous epi- thelial tumors	Mam- mary car- cinomas	Fore stomach papillomas and acan- thomas
Rat	+	+			+	+	+	+	+	(+)	+
Mouse	+		+			+		+	+	+	(+)
Hamster	+		(+)	+		(+)			+		+
Man	+	(+)	(+)	(+)	(+)						

Sprague-Dawley rats to 600 ppm vinyl chloride by inhalation. Half of the group received 5% ethanol in their drinking water starting four weeks before the beginning of vinyl chloride exposure. Based on histological evidence, the latent period for liver angiosarcoma was 38 weeks in rats exposed to the combined effects of vinyl chloride and ethanol, and 53 weeks in rats exposed to vinyl chloride alone.

VIII. HUMAN HEALTH EFFECTS

A. Non-Carcinogenic Effects

Vinyl chloride can produce a number of pathological consequences in humans in addition to its carcinogenic effect. These effects can be from acute or chronic exposure to vinyl chloride. Unfortunately, data regarding dose-response relationships in humans are very scarce because of the virtual absence of air measurements of vinyl chloride in the work environment of vinyl chloride manufacturing and polymerization plants before 1975 (Mancuso, 1975). According to OSHA (39 FR 12342, April 5, 1974), several facilities revealed vinyl chloride concentrations for some job classifications as high as 229 ppm. Rowe (1975) commented that before 1960, a few jobs resulted in exposures in the range of 100 to 385 ppm, but these measurements could be high because the method of quantification measured total halogens rather than vinyl chloride alone. Nicholson et al. (1975) reported that vinyl chloride in polymerization reactors may often have exceeded 1000 ppm and occasionally may have approached

10,000 ppm before OSHA standards were instituted. At these levels, workers experienced dizziness, headaches and/or euphoria during work periods.

Several instances of acute exposure have occurred in vinyl chloride plants. Deaths of two Canadian workers were reported by Danziger in 1960 following acute exposures to vinyl chloride gas. At autopsy, there was congestion of the liver, spleen and kidneys. In another study reported by Suciu et al. (1975), exposure of workers to high concentrations of vinyl chloride produced euphoria, intoxication and narcosis. In this study, the investigators found a dose-response relationship for acute and subacute cases of "occupational disease" from air concentrations ranging from 2,298 mg/m³ (about 900 ppm) to about 100 mg/m³ (about 40 ppm).

In another investigation, Spirtas et al. (1975) conducted a survey of 200 vinyl chloride workers and 89 rubber plant workers (controls) where information was sought on the frequency of eight symptoms, including dizziness, loss of consciousness, headaches, etc. The vinyl chloride workers were categorized into low and high exposure groups. Because the exposure limits had been markedly decreased a short time before the survey, the high exposure group consisted of workers who were exposed to vinyl chloride concentrations of over 200 ppm before the standard, and 20-30 ppm subsequently. The low exposure group consisted of workers who were exposed to 0-50 ppm before the standard and 0-10 ppm

subsequent to it. Examination of the differences among the three groups indicated a statistically significant dose-response relationship for five of the eight symptoms (i.e., frequency of symptoms in the high exposure group > low exposure group > rubber workers), and a similar but non-significant trend in two of the remaining symptom categories. Thus there appears to be a dose-response relationship between certain acute symptoms (predominantly neurological) and level of vinyl chloride exposure. The data also suggest that vinyl chloride levels below 50 ppm can produce health effects.

The earliest reports of hepatotoxicity in vinyl chloride workers were noted by Tribukh et al. (1949); however, the effects were attributed to plasticizers added in the manufacturing process. The observed concentrations of vinyl chloride ranged from 1 to 470 ppm. Since that time, impaired liver function has been noted by other investigators (Marsteller et al., 1975; Lillis et al., 1975; Popper and Thomas, 1975; Jaeger, 1975).

Another effect from chronic vinyl chloride exposure is a condition known as acroosteolysis, which involves bone lesions in the distal phalanges of the hands and feet and scleroderma-like skin lesions. Also associated with this condition are Raynaud's syndrome, pseudoclubbing of fingers, and numerous other symptoms. Many cases of acroosteolysis have been reported and characterized and most involve autoclave workers in vinyl chloride plants (Wilson et al., 1967; Dinman et al., 1971; Harris and Adams, 1967; Lillis et al., 1975).

Other long-term effects include disturbances of the central nervous system, pulmonary insufficiency, cardiovascular manifestations, and several gastrointestinal symptoms (Miller et al., 1975; Suci et al., 1975). These and other vinyl chloride-induced health effects are reviewed in the New York Academy of Sciences report "Toxicity of Vinyl Chloride - Polyvinyl Chloride" (Selikoff and Hammond, 1975).

Reproductive effects have also been noted. According to a study by Infante (Infante, 1976; Infante et al., 1976a), the incidence of birth defects for three small communities in Ohio in which vinyl chloride polymerization plants are located were significantly higher ($P < 0.001$) than those in either the counties in which these communities are located or the State of Ohio in general. Significant excesses were observed for clubfoot and defects of the central nervous system, upper alimentary tract, and genital organs. A follow-up study by Edmonds et al. (1975) identified a moderate increase in central nervous system malformations, but no association could be found with vinyl chloride exposure. In another epidemiologic study by Infante et al. (1976b), there was a significant excess fetal loss ($P < 0.05$) in wives whose husbands were vinyl chloride polymerization workers compared to controls (wives of polyvinyl chloride fabrication and rubber workers). The Infante studies suggest an association between vinyl chloride and birth defects/fetal loss, but they are not yet supported by animal data.

Cytogenetic studies have also been conducted. Picciano et al. (1977) reported no statistically significant differences in chromatid and chromosomal 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 to time-weighted average (TWA) 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. In contrast, Ducatman et al. (1975) and Purchase et al. (1975) have reported increased incidence of chromosomal breakage among vinyl chloride exposed workers.

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). Actual vinyl chloride levels were not measured. Chromosome breakage in all three groups was significantly greater than in non-industrial controls, and overall breakage levels were similar in all three groups. The authors concluded that other agents in addition to vinyl chloride may cause cytogenetic damage in workers employed in the rubber/plastics industry.

B. Carcinogenic Effects

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. Human data have been obtained primarily from occupational exposure of workers to vinyl chloride.

Epidemiologic studies of vinyl chloride exposed workers have focused on cases of angiosarcoma of the liver, a type of cancer which occurs infrequently in the general population, about 25-30 cases per year in the United States (Heath et al., 1975). Because of its rare occurrence, it is possible to infer a causal relationship between exposure to vinyl chloride and the development of this tumor. The epidemiologic evidence linking vinyl chloride to other types of cancers is more tenuous.

The first study associating vinyl chloride exposure in humans with cancer was conducted by Creech and Johnson, 1974. Three cases of angiosarcoma in workers at a polymerization plant in Louisville, Kentucky, were described. The remaining portion of this section describes some of the epidemiologic studies linking vinyl chloride with angiosarcoma and other types of cancer.

Tabershaw and Gaffey (1974) conducted a mortality study of vinyl chloride workers. Mortality calculations included only those workers who could be traced, i.e., 7,128 of 8,384 workers. These individuals were from 33 different facilities and all had been exposed to vinyl chloride for at least 1 year. The mean employment duration for the group of workers under study was 80 months. Among the workers, 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 among vinyl chloride workers was found to be lower, i.e., 75 percent of the expected rate. The favorable overall mortality rate is a phenomenon commonly observed in working populations. Standardized mortality ratios (the ratio of the number of observed deaths in the study population to the number of deaths expected in a comparable population) for malignant neoplasms increased with increasing exposure level and/or longer 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.

Dow Chemical Co. (Holder, 1974) conducted a mortality study of 594 workers in a single plant exposed to vinyl chloride between 1942 and 1960. Workers were assigned to exposure groups based on the highest level of exposure for at least 1 month (low group - TWA less than 25 ppm vinyl chloride, intermediate - 25 to 200 ppm TWA, high - 200 to 300 ppm TWA). Also included in the high group were workers normally exposed to 25 to 200 ppm TWA who were also frequently exposed to excursions of 1000 ppm. Total mortality was 91 percent of expected among the vinyl chloride exposed workers. No deaths due to liver cancer were reported, and only 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 (the author

stated that due to the 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. (1975) conducted a proportional mortality study of workers from two vinyl chloride plants who died between 1947 and 1973. Death certificates were obtained for 142 out of 161 workers (88%) who died within this time period. Deaths attributable to cancer were 50 percent higher than expected (a statistically significant difference). A 900 percent increase in cancers of the liver and biliary tract was noted (five angiosarcomas). Excluding angiosarcoma, a 275 percent excess in numbers of cancers was observed. Two brain tumors (320 percent excess) and 13 lung cancers (60 percent excess) were observed. In addition, the overall 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 5 years 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 in deaths over the expected number 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 1,294 individuals who

were exposed to vinyl chloride for at least 5 years, and for whom at least 10 years had elapsed since initial employment. A total of 136 deaths were reported versus 126.3 expected (not a significant difference). A 49 percent increase over the expected number of cancer deaths was noted, a statistically significant factor. A statistically significant excess number of deaths occurred for brain and CNS cancer, respiratory system cancer, and biliary and liver cancer (Waxweiler et al., 1976).

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 follow-up of former company employees. The basic findings remain unchanged; no increase over expected in malignant neoplasms was found in the low exposure group (TWA from 10 to 100 ppm) and an increase in deaths due to malignant neoplasms was observed in the high exposure group (TWA of greater than 200 ppm).

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.

In contrast, in a mortality study of 7,000 British workers exposed to vinyl chloride between 1940 and 1974, the investigators 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) traced 750 of 771 Swedish vinyl chloride plant workers. A four- to five-fold increase over expected in pancreas and liver tumors was found, and two cases were diagnosed as angiosarcoma. The 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 is the largest number of cases to be diagnosed in a single plant (Makk et al., 1976). As a result, 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 overtime work hours. No correlation was found between occurrence of this tumor and alcohol consumption or cigarette smoking.

In workers engaged in the polymerization of vinyl chloride who were studied by Popper and Thomas (1975), the 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 which becomes even more pronounced in the initial stages of angiosarcoma development. These findings suggest that the fibrotic lesions without angiosarcomas, frequently observed in workers exposed to vinyl chloride (Lilis et al., 1975), might be the pre-stage of developing neoplastic lesions. The diagnosis of the fibrotic lesions in these workers may imply a longer latency period for tumor initiation based on a lower exposure level. The series of changes observed in the liver appear to represent a multi-centric development of angiosarcoma and are similar to the changes induced by Thorotrast and inorganic arsenicals (Berk et al., 1976).

In the most recent update of the NIOSH register (Spirtas and Kaminski, 1978) a total of 64 cases of hepatic angiosarcoma have been identified worldwide among vinyl chloride exposed industrial workers. A listing of all documented cases by country is presented in Table 15. The number of cases by year is depicted in Figure 2. Of the 64 cases, 23 have been reported in the United States. The authors report that both the age at diagnosis and the latency period for cancer induction appear to be increasing. They suggest three explanations for these phenomena: (1) early cases may have heavier exposures; (2) the initial cases represented more biologically susceptible individuals; and (3) random fluctuation. If the trend of increased age at diagnosis and the

TABLE 16

Angiosarcoma of the Liver in Vinyl Chloride/PVC Worker
(Spirtas and Kaminski, 1978)

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 R p 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 R p 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

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TABLE 16 (Continued)

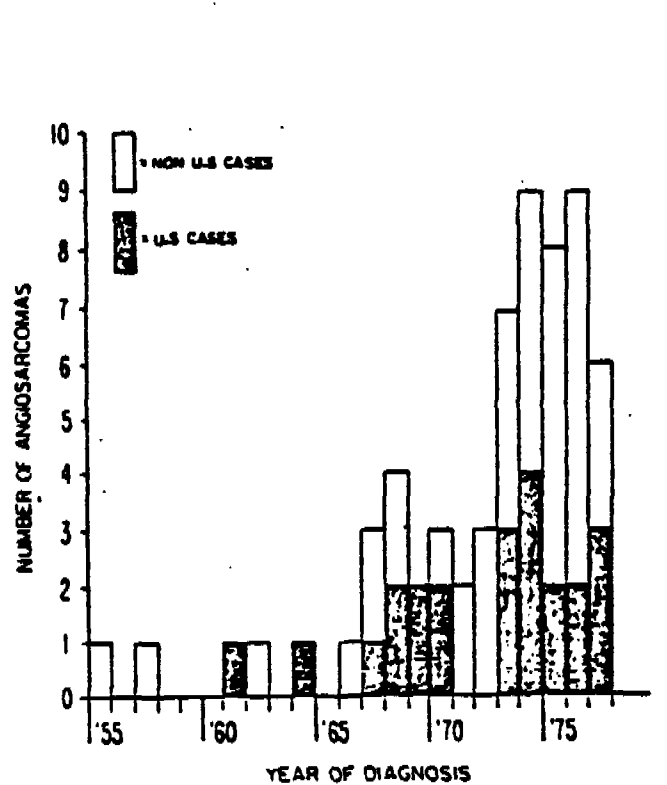
Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Italy	02*	11-13-29	00-00-57	12-13-72	43	15	06	12-00-72
Italy	03*	03-14-20	00-00-53	07-10-75	55	22	21	07-10-75
Japan	01	08-01-22	04-00-53	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	04-08-78	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						

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*Diagnosis was microscopically confirmed
 00 indicates unknown data

Figure 2
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) (Spirtas and Kaminski, 1978).



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 low levels of exposure may be longer than previously anticipated, i.e., it would be many years before the ultimate outcome of these exposures will be known.

It has been hypothesized that inhalation of low levels of vinyl chloride by the general public in the vicinity of vinyl chloride/PVC manufacturing plants could be responsible for an increased risk of angiosarcoma of the liver development. Brady et al. (1977) examined annual rates of hepatic angiosarcoma from 1970 through 1975 in residents of the State of New York (excluding New York City). Exposures to arsenic, vinyl chloride, or thorium dioxide were suggested to be significant factors in the etiology of these tumors. Direct exposure to these agents could not be demonstrated in 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).

IX. MECHANISM OF TOXICITY

The mechanisms of non-carcinogenic injury and carcinogenic action of vinyl chloride are not known. It is theorized that the

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toxicity of this compound is attributable to its enzymatic oxidation to reactive polar metabolites, possibly chloroethylene oxide or chloroacetaldehyde (see Pharmacokinetics section).

Ward et al. (1976) hypothesized that an immunological mechanism is responsible for the non-carcinogenic pathological effects of vinyl chloride exposure. According to this model, a metabolite of vinyl chloride binds to plasma protein, producing an antibody response. The antigen and resulting immunoglobulin interact to produce a soluble complex which causes vascular occlusion, platelet aggregation, and other adverse effects which explain the observed symptoms of the disease. An investigation of workers with "vinyl chloride disease" 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.

X. Risk Assessment

Because vinyl chloride rarely occurs in nature, virtually all of the compound found in the aquatic environment appears to be in discharge water from vinyl chloride production and polymerization plants, and leachates from disposal sites. Up to 20 ppm has been found in samples of discharge water (U.S. EPA, 1974). Because of its low solubility in water and high volatility, vinyl chloride would not be expected to persist in the aquatic environment (Hill et al., 1976). It nevertheless has been detected in the potable water of several cities and towns in

two national surveys (U.S. EPA, 1975a and 1977), and tentatively identified in the drinking water of a number of locations in an investigation currently in progress. It is interesting to note that the highest value so far detected in raw and finished drinking water is in Miami, which, according to Figure 1, is not located near a vinyl chloride plant.

Animal studies and epidemiologic studies collectively confirm that vinyl chloride is carcinogenic. Numerous non-carcinogenic effects have also been noted. The presence of vinyl chloride in drinking water, therefore, is of concern. The NAS and EPA's CAG have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water by mathematical extrapolation from high-dose animal studies. Using the risk estimates generated by the NAS (1977-1979) where the multi-stage model was utilized, that range of vinyl chloride concentrations were computed that would nominally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime assuming daily consumption at the stated exposure level. From the NAS model, it is estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a vinyl chloride concentration of 100 ug/l, 10 ug/l or 1 ug/l would increase the risk of one excess cancer per 10,000; 100,000 or 1,000,000 people exposed, respectively. Using the revised CAG approach and thus the "improved" multi-stage

model, it can be estimated at the 95% confidence limit that consuming two liters per day over a lifetime having a vinyl chloride concentration of 200 ug/l, 20 ug/l or 2 ug/l would increase the risk of one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, respectively. The numerical differences observed after utilizing the NAS and the CAG risk estimates are partly due to the fact that the dose extrapolation model used by the two groups is similar but not identical. The NAS has used the multi-stage model whereas the CAG has used the "improved" version of the multi-stage model recently discussed by Crump (U.S. EPA, 1980). In addition, the selection of the data and other parameters in each model will also result in some differences, especially since the NAS based its calculations on an ingestion study in which rats were exposed to vinyl chloride by gavage, while the CAG used an inhalation study.

XI. MCL (To be developed later)

Drinking Water Concentrations and Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)*		
	CAG (95% confidence limit)	NAS (95% confidence limit)	NAS (point estimate)
10^{-4}	200	100	170
10^{-5}	20	10	17
10^{-6}	2	1	1.7

*Assume 2 liters of water are consumed per day by a 70 kg adult for a 70 yr lifetime.

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