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TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT

Part B Report

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DRAFT

TABLE OF CONTENTS

DRAFT

DRAFT

LIST OF TABLES

LIST OF FIGURES

DRAFT

1.0 Executive Summary

Vinyl chloride is a short-chain halogenated hydrocarbon used predominantly in the manufacture of polyvinyl chloride and various packaging and construction products. Vinyl chloride has a very low degree of acute toxicity, with two-hour inhalation LD_{50} values ranging from 27,419 ppm in mice to 236,215 ppm in rabbits and guinea pigs. Exposure to high concentrations can lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis and death. Several human deaths have been attributed to occupational exposure to very high levels of vinyl chloride. Autopsies of these patients revealed congestion of the liver, spleen and kidneys. Acute toxicity symptoms are thought to occur above 100 ppm.

Chronic exposure of workers to vinyl chloride has been shown to lead to "vinyl chloride disease", characterized by occupational acro-osteolysis, vasospasm of the hands similar to Raynaud's syndrome, dermatitis, circulatory and central nervous system alterations, thrombocytopenia, splenomegaly and changes in liver function. Eight symptoms commonly reported by workers exposed to vinyl chloride (including dizziness, headaches and nausea) were observed even at dose levels below 50 ppm.

Vinyl chloride has been shown to induce cancer in animals in utero, but has not been shown to cause any other reproductive or

developmental effects in rats, mice and rabbits. Epidemiologic studies of families of vinyl chloride workers or communities having vinyl chloride processing facilities suggested the possibility of an increased incidence of birth defects and spontaneous abortions among people at risk; however, subsequent reviews of these studies have concluded that there is inadequate evidence to link environmental or paternal exposure to vinyl chloride with birth defects or spontaneous abortions in humans.

The noncarcinogenic effects occur at concentrations near or above 10 ppm, which is greater than four orders of magnitude ab ve possible general ambient levels in California (0.5 ppb). The noncarcinogenic effects also occur at concentrations greater than 3 orders of magnitude above the highest concentrations measured near landfills (10 ppb). Consequently, DHS staff do not expect noncarcinogenic adverse health effects to occur from acute or chronic exposures to vinyl chloride in ambient air.

The International Agency for Research on Cancer (IARC), the United States Environmental Protection Agency (EPA) and the California Department of Health Services (CDHS) have identified vinyl chloride as a chemical for which there is sufficient evidence of carcinogenicity in both humans and experimental animals. Chronic inhalation and oral exposures of rats, mice and hamsters t vinyl chloride have been associated with an increased incidence of malignant and benign tumors at several sites including the liver, lung, mammary gland and the nervous system. In humans,

epidemiological studies of occupationally exposed workers have linked vinyl chloride exposure to development of a rare cancer, liver angiosarcoma, and have suggested a relationship between exposure and lung and brain cancers.

Although pharmacokinetic studies in humans exposed to vinyl chloride are rare, limited evidence indicates that, following inhalation of low levels of vinyl chloride (3 to 24 ppm), up to 71% (with a mean value of 42%) of the given dose may be absorbed. Vinyl chloride absorption appears to depend on its metabolism, which is a dose-dependent, saturable process. Due to saturation of the enzyme systems responsible for the metabolism of vinyl chloride (cytochrome P-450 and alcohol dehydrogenase), exposur to concentrations above approximately 250 ppm will not necessarily lead to an increasing incidence of tumor development. Metabolism of vinyl chloride leads to formation of chloroethylene oxide and chloroacetaldehyde, two reactive intermediates which undergo covalent binding to cellular macromolecules and are thought to be responsible for the toxic effects of vinyl chloride. These and other metabolites may be further metabolized and excreted in the urine. Unmetabolized vinyl chloride is eliminated primarily in exhaled air.

Vinyl chloride is mutagenic in both prokaryotic and eukaryotic test systems, with significantly greater genotoxicity seen after metabolic activation. DHS staff have found no evidence of a carcinogenic threshold level and because vinyl chloride is

mutagenic, the staff recommends that vinyl chloride be considered as not having a threshold for carcinogenicity.

Several animal carcinogenicity and human epidemiological studies of occupationally exposed workers have been analyzed for risk assessment purposes. Although actual exposure levels are not known, exposure estimates have been used to evaluate the Waxweiler et al. (1976) study of vinyl chloride workers. Based on these estimates, DHS staff has calculated that a lifetime exposure to 0.485 ppb might result in an incremental individual cancer risk of 1×10^{-6} (assuming liver, brain and lung cancer are all related to vinyl chloride exposure). This yields a risk estimate of 2.1×10^{-6}/ppb. In the case that only liver cancer is assumed to be linked to exposure, a lifetime exposure to 1.0 ppb may be expected to result in a risk of 1.0×10^{-6}. Due to inadequate exposure data, follow-up time and other methodological problems, DHS staff suggest that the human risk estimates be used only for comparative purposes. Evaluation of animal experiments by the linearized multistage model yields a range of human risks spanning from 1.8×10^{-3}/ppb to 3.9×10^{-6}/ppb, with most estimating a risk of between 10^{-4} and 10^{-5}/ppb. Evaluation of animal tumorigenicity data indicates that vinyl chloride's carcinogenic potency is dependent on sex, tumor site and age of exposure. Taking these factors into account, DHS staff believe that the human risk estimates are consistent with those obtained for laboratory animals. The staff of DHS recommends that the animal data be used to evaluate the risks resulting from vinyl chloride exposure. Consequently, the

range of risks estimated from analyses of animal studies and recommended by DHS for regulatory purposes lie between 3.9×10^{-6}/ppb and 1.8×10^{-3}/ppb.

Vinyl chloride has not been detected in the ambient air of California (limit of detection = 0.5 ppb) except at certain "hot spots". Air Resources Board (ARB) staff has monitored vinyl chloride emissions from the BKK hazardous waste site in West Covina and the OII landfill in Monterey Park. Estimates of peak exposure concentrations for maximally exposed receptors range from 2 to 10 ppb at the BKK landfill and from 0.6 to 9 ppb at the OII site. Air Resources Board staff has estimated that between 17,000 and 131,000 individuals may be exposed to 1 ppb at the BKK site. A lifetime exposure of 131,000 residents to 1 ppb would be associated with an upper bound estimate of 0.5 to 236 excess cancer cases. The calculations represent the upper range of plausible excess cancer risk: the actual risk, which cannot be calculated, may be insignificant. Based on the finding of vinyl chloride-induced carcinogenicity and the results of the risk assessment, DHS staff finds that vinyl chloride is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

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1.1 Vinyl Chloride Highlights

I. National and International Evaluation (Other Agencies' Evaluation)

A. International Agency for Research on Cancer (IARC)

1. Short-Term Tests: There exists sufficient evidence of mutagenic activity both with and without an exogenous metabolic activation system.

2. Animal carcinogenicity bioassays: There exists sufficient evidence of animal carcinogenicity by oral administration or inhalation.

3. Human evidence: There exists sufficient evidence of carcinogenicity to humans. Occupational exposure to vinyl chloride has been linked with development of angiosarcoma of the liver, and has been associated with tumors of the brain and lung and of the hematopoietic and lymphatic systems. Vinyl chloride is grouped under IARC category 1, meaning that it is causally associated with cancer in humans.

B. U.S. Environmental Protection Agency (EPA)

1. Short-Term Tests: Sufficient evidence of mutagenic activity exists both with and without an exogenous

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metabolic activation system, for both DNA damage and mutation.

2. Animal carcinogenicity bioassays: There exists sufficient evidence of animal carcinogenicity by administration orally or by inhalation.

3. Human data: A number of epidemiological studies have linked vinyl chloride with angiosarcoma and other forms of neoplasms. Sufficient evidence exists to indicate that vinyl chloride is a human carcinogen by inhalation.

C. Conclusions: Both EPA and IARC have concluded there is ample evidence that vinyl chloride is genotoxic and is carcinogenic in both animals and humans.

II. Exposure Sources

A. Air Levels

1. Ambient levels were monitored in the Los Angeles Basin area in 1983 and 1984 by the South Coast Air Quality Management District. All measurements were below their limit of detection of 0.5 ppb.

2. Ambient levels measured in "hot spots" by ARB staff: Estimates for the maximally exposed receptors downwind from and adjacent to hazardous waste sites ranged from 0-10 ppb.

III. Quantitative Risk Assessment

A. Range of Extrapolation: Animal to human exposures in air for calculated lifetime daily exposure.

1. Experimental to ambient: Vinyl chloride has not been detected in ambient air, except at "hot spots".

2. Experimental to "hot spots": The lowest doses in the animal studies are approximately 10- to 20-fold higher than the highest residential exposures.

B. Range of Risks:

The human risks associated with a continuous, lifetime exposure to vinyl chloride have been estimated using the linearized multistage model from both animal carcinogenicity bioassays and epidemiological studies of exposed workers. Unit risks for humans estimated from animal data range from 1.8×10^{-3}/ppb to 3.9×10^{-6}/ppb, depending on experimental exposure levels, tumor type observed, and sex, species, and age of animal evaluated. A unit risk of 2.1×10^{-6}/ppb for liver, lung, and brain cancer was derived from epidemiological studies for comparative purposes.

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2.0 METABOLISM AND PHARMACOKINETICS

2.1 Summary

Experimental evidence has suggested that vinyl chloride must undergo transformation to a reactive metabolite(s) by the liver to be toxic. Based on this information, the best dose-response data would consider the amount of vinyl chloride actually absorbed and metabolized rather than the reported exposure or administered dose concentrations. Reports of the vinyl chloride metabolism in humans are sparse, but limited evidence indicates that, after inhalation exposure to low concentrations, up to 71% (average = 42%) of a given dose was absorbed (Krajewski et al., 1980). Based on this study it is assumed that 71% of an inhaled vinyl chloride exposure may be absorbed by humans at ambient concentrations. Unmetabolized vinyl chloride is eliminated primarily via the lungs. Unlike in other species, absorption of vinyl chloride at the doses tested was not concentration-dependent in humans. Data from rodent studies suggest that the absorption of vinyl chloride depends on its rate of metabolism and the extent of metabolic saturation. Studies in rats and a single experiment in monkeys indicate that the metabolic pathways of vinyl chloride become saturated at exposure concentrations between 100 and 300 ppm.

Metabolism of vinyl chloride involves the cytochrome P-450 mixed-function oxidase system. The first step is thought to be epoxidation of the double bond to form the reactive epoxide

chloroethylene oxide, which may undergo a number of further reactions, including binding to cellular macromolecules. Intramolecular rearrangement of the chlorine atom may also occur, resulting in the formation of chloroacetaldehyde, another reactive intermediate. In addition, alcohol dehydrogenase has a role in vinyl chloride biotransformation, since inhibitors of this enzyme can significantly reduce the amount of vinyl chloride metabolized. Section 2.3 of this report provides a detailed discussion of vinyl chloride metabolism.

2.2 Absorption, Distribution and Excretion

2.2.1 Inhalation

The pharmacokinetics of vinyl chloride following inhalation has been studied in multiple species of experimental animals. The uptake of vinyl chloride at higher doses appears to depend on its metabolism. The metabolic breakdown of vinyl chloride in rats and monkeys (and perhaps in other species) is a dose-dependent, saturable process (Buchter et al., 1980, Filser and Bolt, 1979). Substantial species differences have been observed in the rates of vinyl chloride clearance, with first-order metabolic clearance rates (in liters/hour/kg body weight) for the elimination of vinyl chloride decreasing in the order of mouse (25.6) > gerbil (12.5) > Wistar rat (11.0) > Rhesus monkey (3.55) > rabbit (2.74) > human (2.02) (Buchter et al., 1980).

Results from inhalation exposure studies in humans, monkeys, and rats using direct and indirect test methods indicate that vinyl chloride is rapidly absorbed and metabolized, quickly distributed throughout the body, and excreted by the kidneys. Unmetabolized vinyl chloride is expired by the lungs and, to a limited extent, expelled in the feces.

Several limited studies have been conducted in humans measuring vinyl chloride absorption following inhalation exposure. Krajewski et al. (1980) observed that five male volunteers exposed to 3, 6, 12, or 24 ppm vinyl chloride for six hours by a "face only" chamber absorbed an average of 42% of the dose regardless of concentration. Large interindividual variation in the degree of vinyl chloride retention was observed, with one individual retaining 71% of the dose at the time exposure was terminated; no other individual retained greater than 45%. This indicates a possible large range of interindividual variability. Concentration of vinyl chloride in expired air, measured for 90 minutes after cessation of exposure, decreased to negligible amounts after only 30 minutes post-exposure. The quantity of unmetabolized vinyl chloride exhaled was considered negligible and constituted roughly 4% of the inhalation concentration of vinyl chloride to which subjects were exposed (Krajewski et al., 1980). Thus, humans metabolized up to 96% of the absorbed vinyl chloride dose.

Buchter et al. (1978) reported that humans exposed to 2.5 ppm vinyl chloride retained 26-28% of the administered dose (Krajewski et

al., 1980). Substantial interindividual differences were reported in this study. These differences appear due to differences in the adipose tissue mass among individuals, although this hypothesis has not been confirmed in follow-up studies (Buchter, 1979: Buchter et al., 1978; Bolt et al., 1981).

Pulmonary absorption of vinyl chloride by rats occurs rapidly. Blood levels of vinyl chloride increase with the dose. Blood concentrations quickly decline after cessation of exposure; unmetabolized vinyl chloride is exhaled (Withey, 1976; Hefner et al., 1975a; 1975b; 1975c).

Evidence from both whole animal and "nose-only" inhalation studies in rats indicates that the rate of pulmonary uptake of vinyl chloride in a closed system is partially dependent on the extent of metabolism (Bolt et al., 1977; Hefner et al., 1975a; 1975b; Withey, 1976). In the "nose-only" exposure system used by Hefner et al. (1975a), pretreatment of rats with either pyrazole (a non-specific inhibitor of alcohol dehydrogenase) or 95% ethanol significantly reduced both the uptake (as calculated from the disappearance of vinyl chloride from the exposure chamber) and metabolism of vinyl chloride. This held true for both exposure levels. Pyrazole-pretreated rats were exposed to either 65 or 1234 ppm, while ethanol-pretreated rats were exposed to 56 or 1034 ppm.

Several groups of investigators have presented additional data concerning the uptake, metabolism and disposition of vinyl chloride

following inhalation exposure (Bolt et al., 1976; 1977; Hefner et al., 1975a; 1975b; Buchter et al., 1977). In an investigation into the disposition of ^{14}C-vinyl chloride, Bolt and co-workers (1976) exposed male Wistar rats to initial concentrations of "less than 100 ppm" vinyl chloride (apparent range 1-50 ppm) in a closed system for six hours. The half-life for vinyl chloride disappearance from the chamber was about 68 minutes. From this study, the authors estimated that approximately 40% of the inspired vinyl chloride was absorbed by the lungs (Bolt et al., 1976). Pulmonary uptake of vinyl chloride by rats was completely blocked following pretreatment with the cytochrome P-450 inhibitors 6-nitro-1,2,3-benzothiadiazole or 3-bromophenyl-4(5)-imidazole (Bolt et al., 1976). Uptake of vinyl chloride appeared to be linked to its metabolism, since 24 hours after pretreatment with the relatively short-lived P-450 inhibitor 3-bromophenyl-4(5)-imidazole the uptake of vinyl chloride had returned to control levels. Following exposure, the liver and kidney contained the highest levels of vinyl chloride metabolites (Bolt et al., 1976). In an attempt to determine the exact minimal concentration of vinyl chloride in air necessary to achieve metabolic saturation, Bolt et al. (1977) exposed groups of rats to a wide range of vinyl chloride concentrations and showed that saturation occurred at 250 ppm. First-order kinetics occurred at exposures less than 250 ppm, while zero-order kinetics predominated at higher exposures.

Hefner and colleagues (1975a; 1975b) exposed male Sprague-Dawley rats to initial vinyl chloride concentrations ranging from 50 to

1,167 ppm in a closed nose-only inhalation system. The rate of uptake of vinyl chloride by the animals (as calculated from the rate of disappearance of vinyl chloride from the chamber atmosphere) was approximately three times greater for doses less than 105 ppm (range 50 to 105 ppm) than for doses greater than 220 ppm (range 220 to 1,167 ppm). After an initial equilibration period and regardless of the administered concentration, vinyl chloride disappearance from the chamber apparently followed first-order kinetics. The half-life for atmospheric vinyl chloride at concentrations below 100 ppm was 86 minutes compared with 261 minutes for concentrations greater than 220 ppm. Hefner et al. (1975b) concluded that the predominant pathway for metabolism of vinyl chloride by rats exposed to 100 ppm or less is saturabl , and that this metabolism was due primarily to alcohol dehydrogenase (based on the inhibitor studies with pyrazole and ethanol).

Studies in rats and monkeys suggest that, after absorption, vinyl chloride is rapidly distributed to all tissues reached by the bloodstream (Duprat et al., 1977; Buchter et al., 1980). Lipids or lipoproteins, rather than proteins, transport vinyl chloride in the blood (Bolt et al., 1977). Studies of the distribution of ^{14}C-labeled vinyl chloride in rats indicated that, immediately after inhalation administration, the liver (predominant site of metabolism) and the kidneys (site of excretion of p lar metabolites) contained the highest concentrations of ^{14}C activity, followed by lungs, spleen, and small intestine (Watanabe et al., 1976a; Bolt et al., 1976). However, ^{14}C counts quickly decreased

after cessation of exposure. In one study, vinyl chloride metabolite concentrations decreased significantly in these tissues 48 hours after a single inhalation exposure (50 ppm for five hours) compared to measurements made immediately after exposure ended (Bolt et al., 1976).

Watanabe and co-workers (1976a) also examined the fate of ^{14}C-vinyl chloride following inhalation exposure in rats. Male Sprague-Dawley rats were exposed to 10 or 1,000 ppm vinyl chloride in whole-body metabolism cages for six hours and were observed for an additional 72 hours. After exposure to 10 ppm vinyl chloride, urinary radioactivity accounted for 68%, expired vinyl chloride for 2%, expired CO_2 for 12%, feces for 4%, and carcass and tissues for 14%, respectively, of the recovered radioactivity. After exposure to 1,000 ppm, urinary radioactivity accounted for 56%, expired vinyl chloride for 12%, expired CO_2 for 12%, feces for 4%, and carcass and tissues for 15% of the recovered radioactivity. The patterns of pulmonary elimination of unmetabolized vinyl chloride following exposure to 10 or 1,000 ppm were similar and could be described by first-order kinetics, with half-lives of 20.4 and 22.4 minutes, respectively. A corresponding biphasic elimination of urinary radioactivity following inhalation exposure to 10 or 1,000 ppm vinyl chloride was observed; the half-lives for the initial phase were 276 and 246 minutes, respectively. The liver and skin contained the highest concentrations of radioactivity 72 hours after exposure to either dose. The authors concluded that since "the rate of elimination of vinyl chloride per se from the lungs or

^{14}C activity in the urine was not different in rats exposed to 10 or 1000 ppm," the dose-dependent fate (the relative amount of vinyl chloride excreted by the two different routes) was not attributable to saturation of the excretion pathways. The results are in agreement with the hypothesis that the metabolism of vinyl chloride becomes saturated at high exposure levels (Watanabe et al., 1976a).

The pharmacokinetics of inhaled vinyl chloride in a closed system has also been examined in Rhesus monkeys (Buchter et al., 1980). Uptake of vinyl chloride appeared to depend on its metabolism and to be a dose-dependent, saturable process. When monkeys were exposed to concentrations up to 200-300 ppm in a closed system, vinyl chloride disappearance from the chamber followed apparent first-order kinetics. At higher exposure levels (up to 800 ppm), zero-order kinetics were observed, implying metabolic saturation. The first-order clearance rate was 3.55 liters/hour/kg. The clearance rate fell by 90% after pretreatment with the alcohol dehydrogenase inhibitor disulfiram (Buchter et al., 1980). Thus, alcohol dehydrogenase appears to have a role in vinyl chloride metabolism along with cytochrome P-450.

Liver microsomal enzyme activities and macromolecular covalent binding in rats following either single or repeated exposures to vinyl chloride were compared by Watanabe et al. (1978a). One group of rats was exposed by inhalation to 5,000 ppm nonlabeled vinyl chloride 6 hours/day, 5 days/week for 7 weeks, and then exposed to ^{14}C-vinyl chloride on the last day. The fate of the ^{14}C-vinyl

chloride from these rats was compared with a separate group exposed for a single 6 hour period to 5,000 ppm of ^{14}C-vinyl chloride. The activities of aniline hydroxylase and p-nitroanisole O-demethylase were the same in rats exposed once or repeatedly or in unexposed control rats. Covalent binding to hepatic macromolecules was greater in rats repeatedly exposed as compared to those given a single exposure. Watanabe et al. (1978a) concluded that this "increase in hepatic macromolecular binding indicates that repeated exposure augments the reaction of electrophilic metabolites with macromolecules, and this may be expected to enhance potential toxicity, including carcinogenicity".

Chronic exposure (28,000 ppm, seven hours/day, five days/week for 2, 4 or 6 weeks) was found to increase glutathione reductase activity, glutathione-S-epoxide transferase activity, glutathione-S-aralkyl transferase activities, and glutathione levels in rat liver and to depress cytochrome P-450 levels (Du et al., 1982). This suggests that a reactive metabolite of vinyl chloride can destroy cytochrome P-450 and disrupt several enzymes that may effect its chronic toxicity.

2.2.2 Intragastric, Intraperitoneal, Intravenous, Dermal, and Oral Administration

Uptake and absorption of vinyl chloride administered by intragastric (IG), intraperitoneal (IP) and intravenous (IV) administration follows the patterns observed in inhalation studies.

It appears from these studies that the quantity of vinyl chloride metabolized by these routes is dependent on the quantity administered.

Green and Hathway (1975) examined the excretion pattern of single doses of 0.25 and 450 mg/kg of radiolabeled ^{14}C-vinyl chloride administered to rats by the IG, IP, and IV routes. More than 90% of the administered dose was excreted within the first 24 hours. Exhalation of unmetabolized vinyl chloride is the predominant route of excretion for each route of exposure at the high dose and for the low-dose intravenous exposure. After IG administration of the high dose, more than 90% of the dose was exhaled as unmetabolized vinyl chloride and less than 1% as CO_2, while 5% of the administered radioactivity was found in the urine. At the low dose, urinary excretion accounted for 72% of the dose, unchanged exhaled vinyl chloride for 4% of the dose, and CO_2 for 13% of the dose. About 100 times more vinyl chloride was metabolized at the higher dose level than at the lower dose (an 1,800-fold difference in dose). These observations suggest that the metabolism of vinyl chloride is saturable by administration of a single dose. In another experiment, chronic IG dosing with unlabeled vinyl chloride at 3, 30, or 300 mg/kg daily for 60 days did not affect the rate or route of elimination of a single dose of radiolabeled vinyl chloride from the body. Based on these results, the authors suggested that vinyl chloride excretion data for a single dose may also apply for chronic exposure to vinyl chloride.

Watanab and associates (1976b) examined the excretion of ^{14}C-labeled vinyl chloride following single oral doses of vinyl chloride in rats. Their results were similar to those of Green and Hathway (1975). After administration of a single oral dose of 0.05, 1, or 100 mg/kg of ^{14}C-vinyl chloride to male rats, urinary metabolites accounted for 68, 59, and 11%, respectively, of the administered dose while the $^{14}CO_2$ in expired air accounted for 9, 13, and 3%, respectively. Pulmonary elimination of unmetabolized vinyl chloride represented only 1 to 3% at the lower dose levels, but 67% at the higher dose level. Pulmonary clearance of the 0.05 and 1 mg/kg doses was monophasic, with half-lives of 53.3 and 57.8 minutes, respectively. Clearance of the 100 mg/kg dose was biphasic, with half-lives of 14.4 and 40.8 minutes for the fast and slow phases, respectively.

Absorption of vinyl chloride after oral administration has been measured in rats, both in diet studies (Feron et al., 1981) and gavage studies (Withey, 1976; Watanabe, 1976b). In these reports, almost 100% of the administered dose was absorbed, suggesting extensive gastrointestinal uptake of vinyl chloride. Maximum blood concentrations of vinyl chloride were observed within 10-20 minutes following dosing with aqueous or vegetable oil solutions (dose range 12.5-28.2 mg per rat (Withey, 1976). Green and Hathway (1975) observed absorption of 98.7% from the gastrointestinal tract following an oral dose of 450 mg/kg.

Limited percutaneous absorption (0.03% of dose) following whole body exposure (excluding the head) to either 800 or 7000 ppm of vinyl chloride has been demonstrated in monkeys (Hefner et al., 1975c). The usefulness of this study is limited, however, since only one monkey was exposed at each dose level. Exposure times were limited to 2.5 hours for the 800 ppm group and 2 hours for the 7000 ppm group. The majority of the absorbed vinyl chloride was eliminated in the expired air (Hefner et al., 1975c).

2.3 Metabolism

Two main routes have been proposed for the metabolism of vinyl chloride. The first involves both microsomal and nonmicrosomal enzymes and results in the conversion of vinyl chloride to 2-chloroethanol and subsequent oxidation to 2-chloroacetaldehyde and monochloroacetic acid. This pathway is believed to operate at low doses ($\leq$ 100 ppm) and is saturable. It leads to the production of polar metabolites, which are predominantly excreted in the urine.

The initial studies of Hefner and colleagues (Hefner et al., 1975a; 1975b), discussed in Section 2.2, provide evidence for the role of alcohol dehydrogenase in the metabolism of vinyl chloride. Following exposure of Sprague-Dawley rats to low concentrations (< 200 ppm), vinyl chloride was metabolized to 2-chloroethanol, chloroacetaldehyde, and monochloroacetic acid by an alcohol dehydrogenase (ADH)-mediated pathway. Pretreatment of rats with pyrazole (an ADH inhibitor) or 95% ethanol significantly reduced

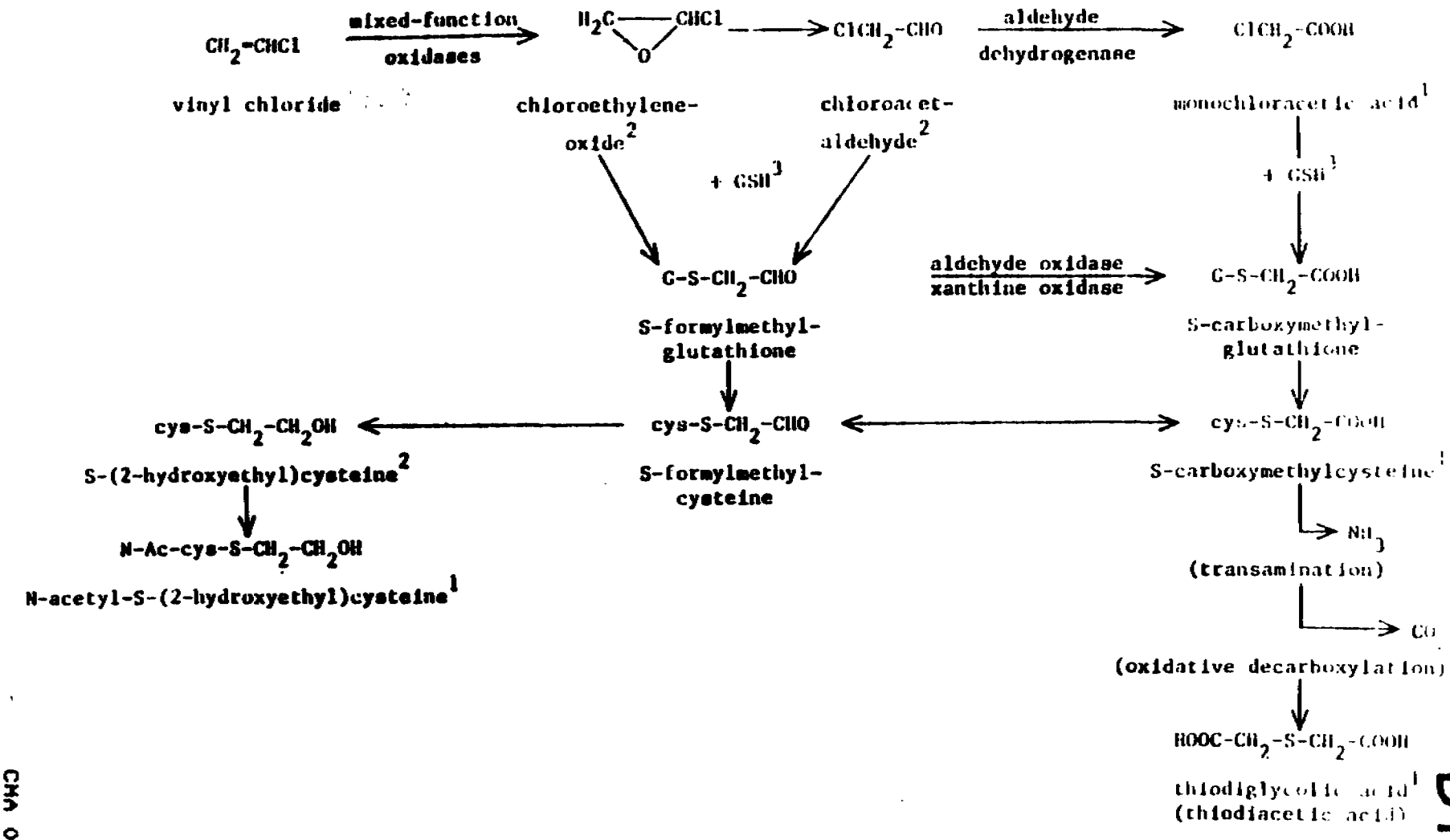
both the uptake and metabolism of inhaled vinyl chloride (Hefner et al., 1975a).

The second proposed pathway involves only microsomal enzymes and is believed to result in the formation of chloroethylene oxide, which may then spontaneously rearrange to form 2-chloroacetaldehyde and, subsequently, monochloroacetic acid (Kilbey, 1981). The epoxide, chloroacetaldehyde, and monochloroacetic acid can then undergo conjugation with glutathione. Further metabolism of these glutathione conjugates can produce a number of compounds, some of which have been identified in the urine of animals treated with vinyl chloride (Figure 2.1). Specifically, monochloroacetic acid, S-(carboxymethyl)cysteine, N-acetyl-S-(2-hydroxyethyl) cysteine, N-acetyl-vinylcysteine, and thiodiglycolic acid have been found in the urine of rats exposed to vinyl chloride by the inhalation and oral routes (Green and Hathway, 1975; 1977; Watanabe et al., 1976a; 1976b). Thiodiglycolic acid and chloroacetic acid have been detected in the urine of workers exposed to atmospheric vinyl chloride (Muller et al., 1978; Heger et al., 1982). The generation of CO_2 from vinyl chloride has been postulated to occur through the tricarboxylic acid cycle or the one- or two-carbon pools, with chloroacetic acid or chloroethylene glycol as the starting intermediate (Woo et al., 1985).

Studies by Bolt and co-workers (1976) indicate that the cytochrome P-450 system is involved in vinyl chloride metabolism. Their results demonstrated that the uptake of 50 ppm vinyl chloride in a

Figure 2.1

Metabolism of Vinyl Chloride



Source: IARC (1979)

1 Detected In vivo

2 Detected In vitro

3 GSH = glutathione

closed system was completely blocked by inhibitors of cytochrome P-450, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiodiazole. Pretreatment with the insecticide dichlorodiphenyl trichloroethane (DDT), an inducer of cytochrome P-450, was effective in enhancing uptake and absorption. However, phenobarbital, another P-450 inducer, has shown no effect on vinyl chloride metabolism (Guengerich and Watanabe, 1979), possibly due to selective induction of different cytochrome P-450 isozymes by the two compounds.

Chronic ethanol treatment has been shown to potentiate the carcinogenic effect of vinyl chloride in male Sprague-Dawley rats (Radike et al., 1981). Animals were exposed by inhalation to 600 ppm vinyl chloride four hours/day, five days/week, for one year. Ingestion of 5% ethanol in water (volume/volume, v/v) ad libitum was begun four weeks prior to vinyl chloride exposure and continued for life or until the termination of the experiment, 2.5 years after the first vinyl chloride exposure and 1.5 years after vinyl chloride exposure was terminated. The incidence of liver angiosarcoma in rats exposed to vinyl chloride and ethanol was 50% (40/80) versus 23% (18/80) in rats exposed to vinyl chloride alone and 0% (0/80) in animals treated only with ethanol. Radike and associates have suggested that this potentiation of tumor formation may be due to the effect of alcohol on vinyl chlorid metabolism and a shared step in the oxidation of ethanol and vinyl chloride. The acetaldehyde product in ethanol metabolism may compete with chloroacetaldehyde for ADH. This would result in

higher levels of chloroacetaldehyde. However, this metabolite may not be the ultimate carcinogen. Chloroacetaldehyde buildup may result in a decrease in epoxide-to-aldehyde conversion, leading to epoxide buildup and increased interaction with cellular macromolecules.

Radiolabeled vinyl chloride has been shown to bind covalently to cellular macromolecules in vivo and in vitro (Watanabe et al., 1978b; Woo et al., 1985; International Agency for Research on Cancer [IARC] 1979). Watanabe et al. (1978b) exposed rats to ^{14}C-vinyl chloride (range 1-5000 ppm) for six hours, and measured covalent binding of radioactivity to hepatic macromolecules, RNA and DNA, along with levels of hepatic glutathione. Binding of vinyl chloride metabolites to liver macromolecules did not increase proportionately with dose, but was instead related to the total amount of vinyl chloride metabolized. Binding appeared to plateau above 500 ppm, while below 100 ppm binding was approximately proportional to the increase in exposure. Depression of hepatic glutathione occurred only at exposure levels of 100 ppm or higher. Covalent binding to RNA or DNA was not detected for any exposure group (Watanabe et al., 1978b). However, a subsequent study found covalently bound vinyl chloride metabolites attached to proteins and nucleic acids isolated from the livers of rats exposed to either 10 or 250 ppm vinyl chloride for two hours. (Guengerich and Watanabe, 1979). Rat liver DNA isolated from the two groups of exposed animals contained 0.04 and 0.9 pg of total bound metabolites per gram of wet liver, respectively. Pretreatment with

phenobarbital had no apparent effect on metabolism or DNA-binding of metabolites, but did increase binding to protein and RNA at the 10-ppm dose level. In vitro binding of ^{14}C-vinyl chloride to proteins and nucleic acids appeared to be dependent on the thiol content of the proteins and the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH), oxygen, and microsomal enzymes (Guengerich and Watanabe, 1979).

Both chloroethylene oxide and chloroacetaldehyde have been studied as possible reactive intermediates that could act as the "ultimate" mutagen or carcinogen formed from vinyl chloride. The epoxide is considered to be the most biologically active metabolite (Bartsch et al., 1975; Laib and Bolt, 1977). Other researchers have proposed that chloroacetaldehyde may be a more effective alkylating agent (Woo et al., 1985). In vivo and in vitro studies by Guengerich and Watanabe (1979) suggest that the mechanism for activation and binding of vinyl chloride involves the release of the chloride atoms as chloride ions, either in the actual activation mechanism or in rearrangment of the metabolite or adduct. However, Guengerich and Strickland (1977) have demonstrated that neither chloroethylene oxide or 2-chloroacetaldehyde appear to be the vinyl chloride metabolite responsible for destruction the heme group of cytochrome P-450, and that other mechanisms (or reactive metabolites) may account for this.

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3.0 ACUTE TOXICITY

The toxic effects of acute exposure to vinyl chloride have been reported by several investigators (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984). Relevant findings are summarized below.

3.1 Summary

The acute effects of vinyl chloride are similar for humans and animals: central nervous system depression (anesthesia) and cardiac, circulatory, and respiratory irregularities. Frostbite from contact of skin with liquid vinyl chloride has been reported. Repeated inhalational exposure of humans to high concentrations of vinyl chloride has been associated with narcosis, damage to the liver, spleen, and circulatory system, and a complex of symptoms identified as occupational acro-osteolysis. With the exception of acro-osteolysis, the occurrence of these toxic symptoms has also been confirmed in experimental animals. The exact occupational exposure levels associated with these symptoms are not known, but are thought to be above 100 ppm.

3.2 Acute Toxicity

The doses causing 50% lethality (LD_{50}) in groups of animals exposed to vinyl chloride by inhalation for two hours has been reported to

be 27,419 ppm in mice, 47,640 ppm in rats, 236,215 ppm in guinea pigs, and 263,215 ppm in rabbits, indicating a very low order of acute toxicity. Toxic symptoms following exposure included narcosis accompanied by respiratory and circulatory disturbances. Death was caused by respiratory failure. Microscopic examination of all animals indicated damage to the lungs, liver, and kidneys (Prodan et al., 1975a).

Several human deaths following very high exposure (concentrations unreported) to vinyl chloride have been reported. Autopsies revealed congestion of the liver, spleen, and kidneys (Danziger, 1960, cited in Maltoni et al., 1984). Lester and co-workers (1963) estimated that the short-term (five minutes) exposure limit (STEL) of vinyl chloride to which a human could be exposed without symptoms of acute toxicity was between 8,000 and 13,000 ppm. Suciu et al. (1975) reported that workers exposed to vinyl chloride (levels not given) experienced euphoria, intoxication, and narcosis. They also reported generalized transient contact dermatitis after dermal exposure.

4.0 SUBCHRONIC AND CHRONIC TOXICITY

Several studies on the toxic effects resulting from subchronic and chronic exposure to vinyl chloride have been published (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984). The relevant findings are summarized below.

4.1 Human

Reports on the adverse effects of repeated occupational exposure to vinyl chloride are based mainly on the observations of workers who have been the most heavily exposed. These individuals were involved in occupations such as cleaning autoclaves and centrifuges, or engaged in drying and shifting processes. They experienced a wide range of symptoms: a vasospastic disorder in the hands similar to Raynaud's syndrome; occupational acro-osteolysis, which included clubbing-like swellings and loss of bone from the terminal phalanges, scleroderma-like skin changes, and dermatitis; acrocyanosis, consisting of vascular changes and impaired thermoregulation; positive cold test reactions; capillaroscopic alterations; paresthesias; and central nervous system symptoms. These clinical symptoms (classified as "vinyl chloride disease") were accompanied by circulatory disturbances, thrombocytopenia, splenomegaly, and changes in the liver. The period of exposure before the first sign of symptoms was as short as one month to as long as three years. A year or two after removal from exposure, most of the abnormalities disappeared

(Veltman et al., 1975; Wilson et al., 1967; Harris and Adams, 1967; Lilis et al., 1975).

Several studies have reported hepatotoxicity and impaired liver function in humans resulting from exposure to vinyl chloride at concentrations ranging from 1 to 470 ppm (Marstellar and Lelbach, 1975; Lilis et al., 1975; Thomas and Popper, 1975; Suciu et al., 1975).

Repeated occupational exposure to vinyl chloride has also been noted to result in impaired pulmonary function (Miller et al., 1975; Gamble et al., 1976). Interstitial pulmonary fibrosis has been reported, but these particular workers were also exposed to polyvinyl chloride dust. It has been proposed, but not satisfactorily demonstrated, that interstitial pulmonary fibrosis may be caused by vinyl chloride-altered immune status (Lilis et al., 1975; Ward et al., 1976). In a study of present and past workers affected with vinyl chloride disease, Ward et al. (1976) observed a range of symptoms associated with immune system dysfunction in 19 of the 28 affected workers.

From their study of occupationally exposed workers, Spirtas et al. (1975) concluded that a dose-response relationship existed between exposure to vinyl chloride and certain acute (primarily neurological) symptoms. The investigators examined the frequency of eight symptoms indicative of central nervous system disturbance, peripheral neuromuscular and neurovascular disturbance, and local

irritation. Vinyl chloride doses were estimated from company data describing probable exposure scenarios for different job descriptions. Exposure concentrations appeared to range from 0 to 200 ppm. They observed a statistically significant dose relationship in the occurrence of five of the eight symptoms (dizziness, nausea, headache, tingling sensation in arms and legs, and fatigue). These symptoms occurred after exposures to less than 50 ppm. These data support other observations in humans that indicate vinyl chloride can produce adverse health effects even at levels below 50 ppm (Spirtas et al., 1975).

4.2 Animals

Repeated inhalation exposure to vinyl chloride has been reported to result in osteoporosis and toxicity to the liver, kidney, spleen, lung, and testes in certain animals. The results of some of these studies are reported in Table 4.1.

TABLE 4.1

SUBCHRONIC AND CHRONIC TOXICITY OF VINYL CHLORIDE ADMINISTERED TO ANIMALS BY INHALATION

Species	Dose	Duration (months)	Observations	Reference
Guinea Pig	100,000 ppm 2 hr/day	3	Liver, kidney, spleen toxicity.	Prodan et al., 1975b
Rat	200, 100, 50 ppm 7 hr/day	6	Increase in liver weights; 100 ppm NOAEL.	Torkelson et al., 1961
Rat	100 ppm 2 hr/day	6	No effects observed.	Torkelson et al., 1961
Rat	20,000 ppm 8 hr/day	3	Increased mean liver and spleen weight.	Lester et al., 1963
Rat	5,000 ppm 7 hr/day	12	Growth retardation; shortened blood-clotting time; increased kidney, heart, spleen weight; increased mortality; degenerative and hyperplastic changes in the liver.	Feron et al., 1979a,b
Rat, rabbit	0.03-0.04 mg/L 4 hr/day	6	Cardiovascular disorders, changes in the bioelectric activity of the hypothalamus, hyperadrenalemia, osteoporosis.	Basalaev et al., 1972

Table 4.1 continued

Species	Dose	Duration (months)	Observations	Reference
Rat	20,000, 500, 50 ppm 5 hr/day	10	Liver and testes lesions at exposures of 50 and 500 ppm, respectively; depression of body weight gain at dose levels.	Sokal et al., 1980
Rat	10, 100, 3000 ppm 6 hr/day 60/wk	up to 12	Increased kidney, liver, spleen, and heart weight; decreased testis weight in all within 6 months; testis damage.	Bi et al., 1985
Mice	1,000, 250, 50 ppm 6 hr/day	up to 12	Deaths at high dose caused by hepatitis; at 50 ppm, lethargy, weight loss, rough coat, hepatitis.	Lee et al., 1977
Mice	6,000, 2,500 ppm 5 hr/day	5 to 6	Proliferation and hypertrophy of terminal bronchiolar cells at both dose levels.	Suzuki 1980, 1981

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5.0 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

5.1 Summary

The developmental and reproductive toxicity of vinyl chloride has been investigated in several experimental and epidemiologic studies (Barlow and Sullivan, 1982; Bardin et al., 1982; Hemminki and Vineis, 1985). Vinyl chloride crosses the placenta of experim ntal animals. Some data indicates it may act as a transplacental carcinogen. No teratogenic effects were observed when vinyl chloride was administered by inhalation at maternally toxic doses. A single unconfirmed report disclosed a teratogenic effect in rats after vinyl chloride exposure as low as 2.5 ppm. Evidence that vinyl chloride causes male reproductive damage has been presented in one experimental study and in a few human case studies. Epidemiologic analysis of communities located close to polyvinyl chloride plants have suggested an association between those locations and an increased risk of birth defects, but none of the studies have adequately controlled for all confounding variables, and no positive correlation has been made conclusively linking vinyl chloride exposure with harmful reproductive effects.

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5.2 Teratogenic Effects in Animals

5.2.1 Inhalation Studies

Rats: John et al. (1977) reported that no developmental toxicity or defects occurred when pregnant Sprague-Dawley rats were exposed to either 500 or 2500 ppm vinyl chloride for seven hours daily on days 6 through 15 of gestation. These concentrations proved toxic to the mothers, however. In a separate experiment, pregnant rats exposed to 2500 ppm vinyl chloride by inhalation and 15% ethanol in drinking water experienced greater maternal and fetal toxicity than animals exposed only to vinyl chloride, but no teratogenic response was observed. However, fetal body measurements were lower among those rats that received ethanol and vinyl chloride. These effects on fetuses were similar to those reported following administration of ethanol only (John et al., 1981).

Ungvary et al. (1978) exposed groups of three pregnant CFY rats to 1500 ppm vinyl chloride continuously on days 1 through 9, 8 through 14, or 14 through 21 of gestation. An increased number of resorbed fetuses was found in the group exposed to vinyl chloride during the first 9 days ($p \leq 0.05$), but no significant effects were observed in rats exposed at other stages of gestation.

In a recent study reported in abstract form, Radike et al. (1988) reported that vinyl chloride was a transplacental carcinogen capable of causing perinatal oncogenesis. An increase in the

numbers of liver carcinomas and angiosarcomas in the offspring of pregnant rats exposed to 600 ppm for four hours/day from day 9 to day 21 of gestation was observed. Post-natal exposure of the pups to 600 ppm increased the incidence of liver tumors. Co-administration of 5% ethanol with vinyl chloride did not increase the incidence of treatment-related malignancies.

A single Russian study has reported an association between vinyl chloride exposures of as low as 2.5 ppm during pregnancy and embryo lethality, teratogenicity, and fetotoxicity in rats (Mirkova et al., 1978, cited in Barlow and Sullivan, 1982). The study and its results were reported only qualitatively and no statistical data were published. Adverse effects reported included doubling of embryo mortality, a high incidence of cerebral malformations, and fetotoxicity.

Bi et al. (1985) examined the effects of vinyl chlorid on testicular seminiferous tubules in rats. Groups of 75 rats were exposed by inhalation to either 0, 10, 100 or 3000 ppm vinyl chloride, for six hours/day, six days/week for three, six, nine or twelve months. Eight to thirty rats were sacrificed after ach exposure period, with remaining animals killed 18 months after the initial exposure (i.e., six months after terminating exposure). Incidence of seminiferous tubule damage for the control, 10, 100 and 3000 ppm group were 19, 30, 37 and 56%, respectively. Changes included cytoplasmic vacuolation, nuclear condensation, fusion of spermatids and spermatocytes, and epithelial necrosis and

degeneration. Seminiferous tubule damage in the two higher dose groups was significantly greater than for the control group (Bi et al., 1985).

Mice: Groups of 30 to 40 pregnant CF-1 mice were exposed by inhalation to either 50 or 500 ppm vinyl chloride for seven hours/day on days 6-15 of gestation. Exposure to 500 ppm caused maternal toxicity while no maternally toxic effects were observed at 50 ppm. No developmental defects were reported in fetuses exposed to either concentration. An increased number of resorptions and decreases in litter size and fetal body weight were seen in mice exposed to 500 ppm, but these effects were considered secondary to the toxic effects of vinyl chloride in the mother (John et al., 1977; 1981).

Rabbits: No teratogenic or embryotoxic effects were observed in the offspring of pregnant rabbits (15 to 20 per group) exposed by inhalation to either 500 or 2500 ppm vinyl chloride for seven hours per day on days 6-18 of gestation. The incidence of resorptions was significantly increased in rabbits exposed to 2500 ppm vinyl chloride, a dose that produced other adverse effects in the dam (John et al., 1977; 1981). Simultaneous administration of 15% ethanol in the drinking water and 500 ppm vinyl chloride in air resulted in increased toxicity to the mother and produced defects in the developing embryo not observed in animals exposed to vinyl chloride alone.

5.3 Reproductive Effects in Humans

Several epidemiologic studies have been conducted to assess potential reproductive and developmental effects in the families of vinyl chloride workers (reviewed in Wagoner and Infante, 1980; Clemmesen, 1982). Infante (1976) analyzed birth certificate data obtained from a group of Ohio communities, three of which contained vinyl chloride polymerization plants. Although a statistically significant increase ($p < 0.01$) in birth defects was observed in the towns with vinyl chloride facilities (compared with the birth defect rate for the entire State of Ohio), several other cities without vinyl chloride factories exhibited rates equally high and higher. Spontaneous abortion rates were also elevated in wives of vinyl chloride workers (Infante, 1976). Edmonds et al. (1975; 1978) conducted two case-controlled studies evaluating CNS malformations among offspring of vinyl chloride workers and families living near polyvinyl chloride facilities in Painesville, IN and Kanawha County, WV. More cases than controls lived within three miles of the polyvinyl chloride plants ($p < 0.02$). In reviewing these three studies, Hemminki and Vineis (1985) concluded that there was inadequate evidence linking environmental or paternal exposure to vinyl chloride with birth defects in humans.

Theriault et al. (1983) measured the incidence of birth defects in infants born to residents of Shawinigan, Canada between 1966 and 1979. A vinyl chloride polymerization plant had been operating in the town since 1943. Although the authors stated that some

descriptive data suggested an association between ambient exposure to vinyl chloride and birth defects in the exposed community, no significant increases in either still births or birth defects were observed (Theriault et al., 1983).

6.0 GENOTOXICITY

6.1 Summary

The genotoxicity of vinyl chloride has been reviewed by several authors (IARC, 1979; Duverger et al., 1981; Bartsch et al., 1975; SRI International, 1983; Fabricant and Legator, 1981). Vinyl chloride causes genetic damage in many test systems, including bacteria, fungi, higher plants, and *in vitro* mammalian systems, as well as *in vivo* in *Drosophila* (fruit fly), rodents, and humans. Previous reviews have suggested that a metabolite of vinyl chloride is the major cause of the observed genotoxicity. However, vinyl chloride has been observed to be mutagenic in some *in vitro* test systems without an exogenous activation system. This particular effect may be the result of endogenous cellular metabolizing enzymes, or the molecule itself may be genotoxic. From experiments in laboratory animals vinyl chloride does not appear to cause genetic damage to germ cells, but does transform mammalian cells and enhances virally-induced mammalian cell transformation *in vitro*. This strong evidence of the genotoxicity of vinyl chloride suggests that its reported carcinogenicity proceeds by genotoxic mechanisms. Data that support this suggestion are summarized below.

6.2 Mutagenicity

Vinyl chloride is mutagenic in most major short-term tests. Its activity is enhanced in the presence of exogenous or endogenous

metabolic activation, suggesting that a metabolite may be more mutagenic than the vinyl chloride molecule itself.

6.2.1 Bacterial Assays

Several studies of vinyl chloride have been conducted using the Ames' Salmonella typhimurium (S. typhimurium) assay (McCann et al., 1975; Bartsch and Montesano, 1975; Bartsch et al., 1975; Garro et al., 1976). These studies indicate that vinyl chloride apparently acts as a mutagen whose effect is significantly enhanced in the presence of liver microsomal enzyme preparations from mice, rats, or humans, and NADPH. For example, Bartsch and Montesano (1975) investigated the mutagenicity of vinyl chloride in air at concentrations of 0, 0.2, 2, or 20% in both the absence and the presence of S-9 fraction obtained from livers of uninduced or phenobarbitone-induced rats. In the absence of metabolic activation, a dose-related increase of up to 15 times background was observed in S. typhimurium strains TA1535 and G46. In the presence of S-9 from uninduced rats, the frequency of revertants was increased up to 23 times above background in strain TA1530, and up to 16 and five times above background in strains TA1535 and G46, respectively. The frequency of revertants increas d to approximately 28 times above background in strain TA1530, and to 18 and six times above background in strains TA1535 and G46, respectively, when S-9 from phenobarbitone-induced rats was used. In the same study, chloroacetaldehyde, a metabolite of vinyl chloride, proved mutagenic (15 times above background) in strain

TA1530 in the absence of exogenous metabolic activation. Chloroethylene oxide was less toxic than chloroacetaldehyde, but was also mutagenic (nine times above background) when tested without exogenous metabolic activation. The authors proposed that the increase in revertants in the absence of an exogenous metabolic activation system was either the result of nonenzymatic breakdown products of vinyl chloride or a result of compounds formed by bacterial enzymes. However, the answer to this question was not effectively resolved by this study (Bartsch and Montesano, 1975).

Salmonella typhimurium strains TA1536, TA1537, and TA1538, which are specifically reverted by frameshift mutagens, were unaffected by concentrations of up to 20% vinyl chloride in air, even in the presence of liver fractions from rats or mice (Bartsch et al., 1975). Vinyl chloride in water or methanol was not mutagenic when tested in S. typhimurium strains TA100, TA1530, TA1535 or G46, even with S-9 liver fractions from phenobarbital-induced mice. The authors hypothesized that the inactivity of vinyl chloride might have been caused by the rapid diffusion of vinyl chloride from the solution into the atmosphere (Bartsch et al., 1975).

Other experiments have confirmed the mutagenic activity of vinyl chloride in Salmonella. Vinyl chloride was mutagenic in S. typhimurium strain TA1530, both with and without activation, after incubation in a vinyl chloride/ethanol medium. The mutation rate increased when cells were incubated in the presence of ultraviolet light and decreased when hydroquinone, a radical-trapping agent,

was added to the incubation medium. These results suggest that radical metabolites may be important determinants of mutagenic activity (Duverger-Van Bogaert et al., 1982). The results of other studies support this hypothesis: for example, a free-radical generating system, riboflavin irradiated with ultraviolet light, doubled the number of vinyl chloride-induced revertants in S. typhimurium strain TA1530 (Garro et al., 1976).

In at least one study, the increases in vinyl chloride-induced mutagenicity in S. typhimurium strain TA1530 observed with the addition of liver fractions obtained from untreated or PCB-induced animals were similar, although PCB would be expected to increase the mixed-function oxidase content of the liver and, consequently, the potential number of mutants (Garro et al., 1976). Vinyl chloride was mutagenic in strain TA1530 in the presence of rat or mouse liver S-9 fraction from Aroclor-induced animals. Mutagenicity was observed even in the absence of an NADPH-generating system. Heat-inactivation of the mixed-function oxidase system did not result in decreased mutagenicity of vinyl chloride. These results suggest that the mutagenic activity observed with vinyl chloride in the Ames' test is not necessarily due to enzymatic activation by a mixed-function oxidase system.

Vinyl chloride induced forward and reverse mutations in Escherichia coli (E. coli) strain 343/113 (Mohn, 1981) and forward mutations in E. coli strain K12 with, but required metabolic activation with mouse liver microsomes (Greim et al., 1975, cited in IARC, 1979).

Chloroethylene oxide at concentrations of 2.5 mmol was more cytotoxic and mutagenic than chloroacetaldehyde at concentrations of 100 mmol when tested in E. coli strain K12A (Perrard, 1985). These results are consistent with those obtained in the Salmonella typhimurium assay (Bartsch et al., 1975).

6.2.2 Eukaryotic Systems

Vinyl chloride induced forward mutations in the yeast Schizosaccharomyces pombe following either a host-mediated assay in mice or in vitro after metabolic activation with mouse liver microsomes (Loprieno et al., 1976; Bartsch and Montesano, 1975). Chloroethylene oxide was mutagenic without activation in the same system (Loprieno et al., 1976). In Saccharomyces cerevisiae strain D_4, vinyl chloride (in concentrations of either 16 or 48 mM) induced gene conversion at the adenine-2 and tryptophan-5 loci only in the presence of mouse liver microsomes (Loprieno et al., 1976). Vinyl chloride, both as a gas and as an ethanol solution, was tested for potential mutagenicity in two strains of the fungus Neurospora crassa. There was no detectable mutagenic effect, either with or without metabolic activation. The authors suggested this was because vinyl chloride could not penetrate the conidia (spore) (Drozdowicz and Huang, 1977).

6.2.3 Cultured Mammalian Cell Assays

Vinyl chloride was tested in the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (CHO/HGPRT) system, an assay designed to detect mutations in the gene coding for the HGPRT locus. Vinyl chloride (at concentrations of 10% in air) was mutagenic only in the presence of complete S-9 mixtures from Aroclor-induced rat livers. When various cofactors used to activate the liver enzymes (for example, NADPH) were not included in this test system, vinyl chloride was inactive even at higher concentrations (Krahn, 1979).

Forward mutations were induced in V79 Chinese hamster lung cells in the presence of phenobarbital-pretreated rat liver supernatant (15,000 x g) (Drevon et al., 1977, cited in IARC, 1979). Huberman et al. (1975) reported that at concentrations of 6-13 μm 1 the vinyl chloride metabolites chloroethylene oxide and 2-chloroacetaldehyde caused a dose-dependent induction of 8-azaguanine (four to eight times above background) and ouabain-resistant (up to 23 times above background) mutants in Chinese hamster V79 cells in vitro. Both 2-chloroethanol and monochloroacetic acid (at concentrations of up to 2500 μmol) were found to be inactive (Huberman et al., 1975).

6.2.4 In Vivo Mutagenicity Assays

A significant increase in recessive lethal mutations in Drosophila melanogaster was observed after exposure to 850 ppm vinyl chloride for two days. Exposure to 30 ppm for 17 days also caused an increase in recessive lethal mutations. Although vinyl chloride was tested at concentrations ranging from 30 to 50,000 ppm, the mutation frequency rate reached a plateau at 10,000 ppm, a finding the authors attributed to saturation of metabolizing enzymes (Verburgt and Vogel, 1977). However, vinyl chloride did not cause any significant increase in dominant lethal mutations, translocations, or entire or partial sex-chromosome loss following exposure to 30,000 ppm for 2 days (Verburgt and Vogel, 1977).

6.3 Chromosomal Damage

6.3.1 Dominant Lethal Tests

Vinyl chloride failed to produce dominant lethal mutations in offspring of male CD-1 mice exposed by inhalation to concentrations of 3,000, 10,000, or 30,000 ppm, six hours/day for five days, and then mated with successive pairs of untreated females over an eight-week period (Anderson et al., 1977). There was no evidence that vinyl chloride had any mutagenic effect on any maturation stage of spermatogenesis. In addition, no significant increase in the number of post-implantation early fetal deaths, no evidence of

preimplantation egg loss, and no reduction in fertility were observed in this study (Anderson et al., 1977).

Male rats were exposed to 0, 50, 250, or 1000 ppm vinyl chloride by inhalation for six hours/day, five days/week for 11 weeks (Short et al., 1977). During the eleventh week of exposure, the rats were housed with two untreated females for seven evenings or until matings occurred in both females. Although there was a significant reduction in the number of females who became pregnant when housed with males exposed to 1000 ppm vinyl chloride, there was no significant effect on total implants/female or dead implants/female in those females that became pregnant (Short et al., 1977).

No dominant lethal mutations were produced in Drosophila melanogaster following exposures of up to 30,000 ppm for tw days (Verburgt and Vogel, 1977).

6.3.2 Chromosome Aberration/Sister Chromatid Exchange Studies

6.3.2.1 Experimental Studies

Sister chromatid exchanges (SCE) and aberrant metaphases were increased in chromosomes of bone marrow cells of Chinese hamsters exposed to either 1.25, 2.5 or 5% (v/v) vinyl chloride in air for 6, 12, or 24 hours. The greatest number of SCEs were se n after exposure to 2.5% vinyl chloride for 24 hours. The greatest number

of aberrant metaphases was observed after exposure to 5% vinyl chloride for 24 hours (Basler and Rohrborn, 1980).

The mutagenic potential of vinyl chloride was evaluated in the mammalian spot test. Female C57B1/6J Han mice were mated to male Han/T mice, then exposed to 4600 ppm vinyl chloride in air for five hours on day 10 of gestation. No effect on litter size or coat color was seen in F_1 offspring (Peter and Ungvary, 1980).

No significant increase in any specific genetic effect was observed in bone marrow cells obtained from male Wistar rats exposed to vinyl chloride at 1500 ppm, six hours per day for five days. There was a significant increase in total "abnormalities" (including chromatid gaps, breaks, and fragments) following this exposure scenario; no increases in any of these parameters (including total "abnormalities") were observed when vinyl chloride exposure was extended to three months (Anderson and Richardson, 1981).

6.3.2.2 Human Observations

Several studies of chromosomal abnormalities in the peripheral lymphocytes of workers exposed to vinyl chloride were reported in the IARC monograph (1979). Aberrations most frequently reported were fragments, dicentrics and rings, and breaks and gaps. These earlier studies were of limited value, involving small groups of workers with inadequate controls. For example, Leonard and

associates (1977) examined lymphocytes from seven men working in a vinyl chloride plant and 11 workers in a vinyl chloride polymerization plant. The incidence of such chromosome aberrations as chromatid breaks and gaps were comparable in all groups, but the degree of severity of the abnormalities observed was more severe in ten of the 11 polymerization plant workers than in the seven workers from the other vinyl chloride factory. The lack of controlled conditions greatly reduces the usefulness of this study. Vinyl chloride levels were less than 10 ppm at the time of the study, but were estimated to have been as high as 500 ppm in earlier years. Also, several of the polymerization plant workers had been given X-ray treatment on the hands, but no controls had been exposed to similar X-rays (Leonard et al., 1977).

Another study of 56 workers in the polyvinyl chloride industry suggested that occupational exposure to vinyl chloride could have a measurable effect on the induction of chromosomal aberrations in cultured lymphocytes obtained from these workers (Purchase et al., 1975). Exposure levels were not measured. Workers from both the test and control groups who had been exposed to X-rays or had had prolonged drug treatment or recent viral infections were excluded from the study. However, the results from this study and their significance were not discussed (Purchase et al., 1975). Kucerova and colleagues (1979) found that the frequency of SCE and oth r chromosomal aberrations was significantly higher in workers exposed to 20-150 ppm vinyl chloride in air than in unexposed controls matched for sex and age. Chromatid and chromosome breaks were

detected in the greatest frequency; chromatid and chromosome exchanges occurred only sporadically.

Some subsequent studies have verified these findings. The majority suggest that the frequency of occurrence of aberrations decreased with decreasing occupational exposure levels. For example, polyvinyl chloride workers (N = 52) exposed to mean concentrations of 2.34 ppm vinyl chloride had significantly greater numbers of chromosome breaks and chromosomal aberrations than did unexposed controls (N = 74) (Suskov and Sazonova, 1982). However, in another study, workers exposed to low levels of vinyl chloride showed no differences from controls in the number of SCE or chromosome breaks. Significant differences had been seen in the same population previously when occupational vinyl chloride exposures had been higher (Hansteen et al., 1978).

A study of a large number of polyvinyl chloride workers suggested that vinyl chloride exposures below 15 ppm did not induce chromosomal aberrations (Picciano et al., 1977). When lymphocyte cultures from a group of 109 workers who had worked in the plant (exposure periods ranged from one to 332 months) were compared with cultures from a control group of 295 pre-employment examinees, no significant chromosomal differences were observed. The workers had been exposed to levels of 15.2 ppm vinyl chloride before 1960, 11.4 ppm from 1960 to 1972, and 8.7 ppm between 1973 and 1974. The subjects and controls were not matched for age or for exposure to X-rays, however.

Cytogenetic studies performed on lymphocytes isolated from 39 workers from a polyvinyl chloride plant and 16 control males demonstrated a significant increase in chromosome-breakage frequency for the exposed workers (3.41% versus 1.79%, respectively). This study was repeated for 37 of the 39 workers 2-2.5 years later, during which time the workers had only a minimal exposure to vinyl chloride. More appropriate in-plant matched controls were selected for the follow-up study. In the repeat study no difference was found in mean chromosome-breakage frequency between the workers and their controls (Hansteen et al., 1978).

6.3.3 Micronucleus Tests

In CBA male mice exposed to 5% vinyl chloride in air, nearly a four-fold increase in micronucleated cells was observed (Jenssen and Ramel, 1980).

6.3.4 DNA Damage/Unscheduled DNA Synthesis (UDS) Tests

Vinyl chloride has been reported to induce unscheduled DNA synthesis in adult rat hepatocytes, but no experimental details were provided in the publication (Probst et al., 1981).

Differential killing was induced in the repair-deficient E. coli strain polA$^-$ in assays using the standard disc and liquid suspension methods (Rosenkranz, 1981).

6.4 Mammalian Cell Transformation

Vinyl chloride, 20 to 50% in air, has been reported to transform BHK cells exposed (Styles, 1980). A clear positive transformation response was obtained in BALB/c-3T3 mouse cells exposed to vinyl chloride; in addition, vinyl chloride (chamber concentrations 0-1024 ppm) caused a dose-dependent cytotoxicity (Tu et al., 1985). An increased sensitivity to transformation by SA-7 virus was observed in primary Syrian hamster embryo (SHE) fibroblasts exposed to vinyl chloride concentrations up to 194 $\mu g/cm^3$ (75,781 ppm) (Hatch et al., 1981).

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7.0 CARCINOGENICITY

7.1 Animal Studies

7.1.1 Summary

The evidence for the carcinogenicity of vinyl chloride in laboratory animals has been reviewed by Kalmaz and Kalmaz, 1984, IARC, 1979, SRI, 1983, Kuzmack and McGaughy, 1975, and Purchase et al., 1987. Adequate experimental evidence exists to indicate that vinyl chloride is carcinogenic in mice, rats, and hamsters when given orally and by inhalation. Vinyl chloride has been found to cause tumors in a dose-related manner at several sites, including liver, lung and mammary gland. The oncogenic response appears to be a function of the site, vinyl chloride concentration, tumor type, species of animal, and route of administration.

Although some evidence of vinyl chloride-induced carcinogenesis has been observed by all routes of administration and in all species tested, important discrepancies in the protocols of many studies has limited their usefulness in quantitative risk assessment. These discrepancies include the lack of appropriate control groups, insufficient exposure time, or incomplete histopathology of the animals. Studies that have been used previously in risk assessment include feeding studies (Feron et al., 1981; Til et al., 1983) and a series of inhalation studies (Maltoni et al., 1984). In th Feron studies, liver angiosarcomas and hepatocellular tumors (the

primary site) were produced after chronic oral administration of vinyl chloride. In the studies by Maltoni et al. (1984) a wider variety of tumor types was observed. These studies and others are reviewed below.

7.1.2 Intraperitoneal, Subcutaneous, and Transplacental Administration

Vinyl chloride has been tested in experimental animals by intraperitoneal, subcutaneous, and transplacental administration, but for various reasons all of these studies were deemed inadequate for the evaluation of the carcinogenic risk of vinyl chloride. These reports and the reasons for their inadequacy are described in Appendix A.

7.1.3 Oral Administration

7.1.3.1 Studies by Maltoni and Associates

Rats: Liver angiosarcomas and morphologic alterations of the liver were induced in groups of 40 male and 40 female Sprague-Dawley rats after gastric intubation of 0, 3.33, 16.65, or 50 mg/kg vinyl chloride in olive oil five days/week for 52 weeks. These animals were then observed for the remainder of their lives (Experiment BT11, Maltoni et al., 1984, IARC, 1979). Dose-related increases in the incidence of several types of tumors were observed, including liver angiomas and angiosarcomas, nephroblastomas, and mammary

tumors. In a subsequent experiment, 0, 0.03, 0.3, or 1.0- mg/kg was administered by the same protocol, except that the dose groups contained 75 animals of each sex. Liver angiosarcomas were found in one female in 0.3 mg/kg group and two females and one male in the 1.0 mg/kg group. No such tumors were observed in controls (Experiment BT27, Maltoni et al., 1984). No statistical analyses were reported for any of these experiments.

7.1.3.2 Studies by Feron and Associates

Vinyl chloride in soybean oil was administered by gastric intubation at a dose of 300 mg/kg once daily, five days/week for 83 weeks, to 60 male and 60 female Wistar rats; no vehicle controls were used. Of the 109 animals examined, 56 had angiosarcomas of the liver and 52 had angiosarcomas of the lung (Feron et al., 1981). Although vinyl chloride was clearly demonstrated to be carcinogenic in this study, the data are not suitable for use in quantitative risk assessment because of the lack of vehicle-treated controls.

In conjunction with the above experiment, groups of 60-80 male and 60-80 female five-week old Wistar rats were fed polyvinyl chloride powder (10% of diet) with or without a high vinyl chloride monomer content (0 to 4000 ppm) in the diet for their lifetimes (Feron et al., 1981). The actual doses of vinyl chloride given to rats in the feed were 0, 1.7, 5.0, and 14.1 mg/kg/day. Access to food for controls and treated animals was limited to four hours per day; an

additional control group was fed ad libitum. Gross pathology was performed on all animals that died or were killed; complete histopathology of all organs was performed on only 20 males and 20 females from the controls and 20 males and 20 females from each of the two highest dosage groups. The animals chosen for complete histopathology were those that lived the longest before being killed. Histopathology of all other rats was restricted to the liver, zymbal glands, lungs, kidneys, spleen, pituitary, thyroid, adrenals, grossly visible tumors, and organs containing lesions suspected of bearing tumors. Statistical significance of tumor incidence was determined by the Chi-square test.

Vinyl chloride caused a dose-related increase in the death rate in the 5.0- and 14.1-mg/kg groups; all animals receiving the highest dose were dead by week 134, with females dying earlier than males (Feron et al., 1981). In the low-dose group the mortality of male rats was comparable with that of controls; the death rate in female rats was slightly higher than that in controls. Death of treated animals was attributed to pulmonary or hepatic insufficiency due to neoplastic or nonneoplastic lesions in these organs.

Liver angiosarcomas were reported in 27/59 ($p < 0.001$) and hepatocellular carcinomas in 8/59 ($p < 0.01$) male rats receiving 14.1 mg/kg/day. Incidences of angiosarcomas and hepatocellular carcinomas were 9/59 ($p < 0.01$) and 29/59 ($p < 0.001$), respectively, in females receiving the highest dose (Table 7.1) (Feron et al. 1981). Necrosis, centrilobular degeneration and

mitochondrial damage were also seen in the hepatic parenchyma of rats administered vinyl chloride. The incidence of angiosarcoma of the lung was also significantly increased in high-dose males (19/59, $p < 0.001$) and females (5/57, $p < 0.05$) (Table 7.2). Low-dose males and females showed necrotic damage of the liver and 26/58 low-dose females ($p < 0.01$) had neoplastic nodules of the liver (Table 7.1) (Feron et al., 1981). It is possible that underreporting of tumors at all sites occurred because of the incomplete histopathology performed and the fact that only the longest-surviving high-dose animals were chosen for complete histopathology.

7.1.3.3 Studies by Til and Associates

As a follow-up to the study of Feron and co-workers (1981), groups of 100 male and 100 female Wistar rats (except for the top-dose group, which was composed of 50 animals of each sex) were fed polyvinyl chloride (up to 1% of diet) with a high content of vinyl chloride monomer for up to 149 weeks (Til et al., 1983). Levels of vinyl chloride administered in the powder were 0, 0.017, 0.17, and 1.7 mg/kg/day for 149 weeks. Actual oral exposure to vinyl chloride monomer (calculated by measuring the evaporative loss of vinyl chloride during the four-hour feeding periods, the rate of food intake, and the level of vinyl chloride in the feces) was estimated to be 0.014, 0.13, or 1.3 mg vinyl chloride/kg/day for the low, middle, and high dose groups, respectively. Access to food was limited to four hours per day. An additional control

TABLE 7.1

INCIDENCE OF LIVER TUMORS AND NEOPLASTIC NODULES IN WISTAR RATS EXPOSED ORALLY TO VINYL CHLORIDE (Feron et al., 1981)

Tumor Type/Sex	Incidence[1] Vinyl Chloride (mg/kg/day) 0	1.7	5.0	14.1
Liver Angiosarcoma				
Male	0/55	0/58	6/56*	27/59***[2]
Female	0/57	0/58	2/59	9/57**
Hepatocellular Carcinoma				
Male	0/55	1/58	2/56	8/59**
Female	0/57	4/58	19/59***	29/57***
Neoplastic Nodules				
Male	0/55	1/58	7/56**	23/59***
Female	2/57	26/58**	39/59***	44/57***

[1]Number in denominator = number of animals necropsied.

[2]Values marked with asterisks differ significantly from controls according to the Chi-square test:

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

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TABLE 7.2

INCIDENCE OF LUNG ANGIOSARCOMAS, ABDOMINAL MESOTHELIOMAS AND MAMMARY TUMORS IN WISTAR RATS EXPOSED ORALLY TO VINYL CHLORIDE (Feron et al., 1981)

	Incidence[1] Vinyl Chloride (mg/kg/day)			
Tumor Type/Sex	0	1.7	5.0	14.1
Lung Angiosarcoma				
Male	0/55	0/58	4/56*[2]	19/59***
Female	0/57	0/58	1/59	5/57*
Abdominal Mesotheliomas				
Male	3/55	1/58	7/56	8/59
Female	1/57	6/58*	3/59	3/57
Mammary Adenoma or Adenocarcinoma or Anaplastic carcinoma				
Female	3/57	2/58	5/59	9/57

[1]Number in denominator = number of animals necropsied.

[2]Values marked with asterisks differ significantly from controls according to the Chi-square test:

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

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group. comprised of 100 rats of each sex, received food ad libitum and were housed in a separate room. Gross pathology was performed on all animals and was restricted to the liver, all grossly visible tumors or presumable tumors in the abdominal cavity, zymbal gland, and mammary glands. No clinical signs of toxicity attributable to vinyl chloride were observed. In the lowest- and mid-dose group, body weight and survival of treated rats were not significantly different from those of controls. In the high-dose group, mortality was slightly increased.

The results of this study demonstrated significant increases in the incidences of hepatic foci of cellular alteration, neoplastic nodules, hepatocellular carcinomas, liver-cell polymorphism, and cysts in the highest dose group. Two females and one male in this group developed liver angiosarcomas. Females, but not males, of the low- and mid-dose groups developed a higher incidence of hepatic basophilic foci of cellular alteration. No pathologic effects in other organ systems were attributed to vinyl chloride exposure (Table 7.3) (Til et al., 1983).

Til and co-workers reported that a threshold of 0.17 mg vinyl chloride/kg/day for the induction of tumors in rats was obs rved. In fact, a threshold cannot be demonstrated. Vinyl chloride induced hepatocellular alterations at all concentrations tested. Histopathology of all organs was not performed on all animals; therefore, tumors not grossly observable or palpable could have

been missed. Because of the shortcomings of the study, its utility for the evaluation of carcinogenic risk is limited.

7.1.4 Inhalation Exposure

Several researchers have investigated the potential carcinogenicity of vinyl chloride administered by inhalation (Viola, 1977; Caputo et al., 1974; Keplinger et al., 1975; Lee et al., 1977; Hong et al., 1981; Suzuki, 1981; Groth et al., 1981; Drew et al., 1983; Maltoni et al., 1984). All experiments confirm the carcinogenicity of vinyl chloride, although only a few of the studies are adequate for a quantitative evaluation of carcinogenic risk.

7.1.4.1 Studies in Rats

The earliest information on the experimental carcinogenicity of vinyl chloride administered by inhalation was reported by Viola (1971). Wistar rats were exposed to 30,000 ppm by inhalation (four hours/day, five days/week) for twelve months. At the end of the treatment period, the surviving animals were killed at 20-day intervals and "the most important tissues and organs examined histologically by standard methods". The primary tumors observed were located in the zymbal gland (found only in rodents), with metastases to the skin, bone, and lung.

Caputo and associates (1974) exposed Wistar rats to 50-20,000 ppm vinyl chloride four hours/day, five days/week for 12 months. Liver

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TABLE 7.3

LIVER TUMOR INCIDENCE IN MALE AND FEMALE WISTAR RATS EXPOSED TO VINYL CHLORIDE BY ORAL ADMINISTRATION FOR 149 WEEKS (Til et al., 1983)

	Incidence[1]			
	Vinyl Chloride (mg/kg/day)			
Tumor Type/Sex	0	0.014	0.13	1.3
Liver Angiosarcoma				
Male	0/99	0/99	0/99	1/49
Female	0/98	0/99	0/96	2/49
Hepatocellular Carcinoma				
Male	0/99	0/99	0/99	3/49
Female	1/98	0/99	1/96	3/49
Neoplastic Nodules				
Male	0/99	0/99	0/99	1/49
Female	0/99	1/99	0/99	9/49

[1]Number in denominator = number of animals necropsied.

Vinyl chloride intake data was adjusted to compensate for loss of vinyl chloride during the four-hour feeding periods. The initial levels of vinyl chloride administered in the diet were 0, 0.017, 0.17, and 1.7 mg/kg/day.

angiosarcomas and skin carcinomas were observed in animals exposed to 500 ppm or greater and lung adenomas in those exposed to 2,000 ppm or more.

Bi et al. (1985) evaluated the tumorigenic potential of vinyl chloride in rats following inhalation exposure to 0, 10, 100 or 3000 ppm (six hours/day, six days/week). The incidence of liver angiosarcomas was 0/19, 0/20, 7/19 and 17/19 for the four exposure groups, and 0/19, 0/20, 2/19 and 9/20 for lung angiosarcomas, respectively. The authors failed to discuss the specific types of tumors or their significance, focusing instead on the testicular effects of vinyl chloride (discussed in Section 5 of this document) (Bi et al., 1985).

7.1.4.2 Studies in Mice

In a preliminary paper reviewed by IARC (1979), Keplinger and co-workers (1975) reported results from ongoing tests on mice, rats, and hamsters. Vinyl chloride was carcinogenic in all three species; the female mouse was the most sensitive of the animals tested. CD1 Swiss mice were exposed to 0, 50, 200, or 2,500 ppm vinyl chloride seven hours/day, five days/week for nine months, then observed for another nine months. Primary tumors found in animals that died included liver angiosarcomas, lung adenomas, and mammary adenocarcinomas. At the time of the IARC report, histological evaluation had been carried out only on grossly visible tumors, but no final report has been published.

Consequently, we cannot accurately quantify tumor incidence in the study.

Lee and co-workers (Lee et al., 1977; IARC, 1979) reported that female mice were more responsive to vinyl chloride exposure than rats. Two month-old male and female CD-1 mice were exposed by inhalation to 0, 50, 250, or 1,000 ppm vinyl chloride for six hours/day, five days/week for 52 weeks (end of experiment). Vinyl chloride induced primary tumors in mice at multiple sites after exposure to 50 ppm or more. Liver cell angiosarcomas, bronchiolo-alveolar adenomas, mammary ductular adenocarcinomas, and squamous and anaplastic cell carcinomas (with metastases to the lung) were observed in treated animals. Vinyl chloride induced tumors at all dose levels, with the incidence and severity of the tumors increasing with dose. The total tumor incidence may have been underestimated because of the short duration of the study.

Hong and colleagues (Hong et al., 1981), as a follow-up of the studies of Lee and associates (Lee et al., 1977), examined the development and incidence of vinyl chloride-related carcinogenic effects during a post-exposure follow-up period. Groups of eight to 28 two month-old male and female CD-1 mice were exposed to 0, 50, 250, or 1,000 ppm for one, three or six months and subsequently observed for 12 months before being sacrificed. Although the number of animals used in the experiment was inadequate for risk assessment purposes, four of sixteen female mice exposed to 50 ppm vinyl chloride for one month (and autopsied

one year later) exhibited mammary gland adenocarcinomas or carcinomas. In mice, the combined (male and female) incidences of hemangiosarcomas for the 250 and 1,000 ppm groups were significantly higher than in controls ($p = 0.05$). Tumor incidence was related to dose and duration of exposure. Bronchiolo-alveolar tumors were also significantly increased in the high-dose group ($p = 0.05$), but no clear trend for the other dose levels was observed (Hong et al., 1981).

In rats, tumor incidence rates following exposure for one or three months did not differ significantly from control values. After a six or ten month exposure, the combined (male and female) cumulative incidences of hemangiosarcomas, hepatocellular carcinomas, and neoplastic liver nodules in rats exposed to 250 or 1,000 ppm differed significantly from those in combined male and female control animals (statistics not reported) (Hong et al., 1981).

Suzuki (1981a) exposed male CD-1 mice (between 30 and 40 per group) to 1, 10, 100, 300, or 600 ppm vinyl chloride six hours/day, five days/week for four weeks. The animals were then observed for up to 41 weeks after cessation of exposures. One mouse in the 10 ppm group had a subcutaneous hemangiosarcoma in the left ear 29 weeks after exposure; one mouse in the 600 ppm group developed a hepatic hemangiosarcoma 65 weeks after exposure. In a separate study, Suzuki (1981b) exposed 27 mice to either 2500 or 6000 ppm vinyl chloride for five or six months. Additional mice were exposed to

0, 1, 10 or 100 ppm for four weeks, and sacrificed forty weeks after exposure. All animals were evaluated for pulmonary tumors. Twenty-six of the 27 high dose animals possessed "alveologenic" tumors. Animals in the lower dose groups exhibited a dose-related trend for pulmonary tumor formation (Suzuki, 1981b). Although this study cannot be used to quantify risk due to study design (for example, inadequate number of test animals), it did demonstrate a carcinogenic response to vinyl chloride after exposure to relatively low concentrations for short durations.

7.1.4.3 Studies on the Potential Effects of Age at Time of Exposure

Groth et al. (1981) exposed groups of 110-128 male and female Sprague-Dawley rats to 948 ppm vinyl chloride in air seven hours/day, five days/week for 29 weeks, beginning at ages varying from six weeks to 52 weeks. Animals were sacrificed after termination of exposure. On the basis of this testing regime, those researchers concluded that vinyl chloride-induced liver angiosarcomas occurred with the greatest frequency in rats whose exposure period began at 52 weeks of age, with females more susceptible than males. The data and study methodology are inadequate for making this conclusion, however. If liver angiosarcomas are expressed at a later age in the rat's life cycle, animals exposed at an early age and sacrificed early in their life cycles would not have had time to express the same tumor incidence as they would if they had lived their full lifetimes. The animals

exposed later in their life cycles would then seem to have the highest tumor incidence.

Drew et al., (1983) looked at the effect of age and exposure duration on vinyl chloride oncogenicity in females of several different species of rodents. Groups of female CD-1 Swiss mice, B6C3F1 mice, Fischer 344 rats, and Golden Syrian hamsters (N = 54 for mice, N = 56 for rats and hamsters) were exposed to vinyl chloride for six hours/day, five days/week for six, 12, 18, or 24 months, beginning at eight weeks of age, and observed for their lifespans. Other groups were held until six or 12 months of age, exposed for six or 12 months, and then observed for the remainder of their lifespans. The exposures were conducted at a single dose level for each species; mice, rats and hamsters were administered 50, 100, and 200 ppm, respectively. All animals exposed to vinyl chloride at age eight weeks (the start of the experiment) exhibited decreased survival relative to controls (Drew et al., 1983). B6C3F1 mice experienced the most significant life-shortening regardless of the age at which exposure was begun. No significant decrease in survival was observed in rats, hamsters, or Swiss mice initially exposed after six months of age. Other clinical signs of vinyl chloride toxicity were not evident and liver necrosis was not observed.

In rats, exposure to vinyl chloride was associated with hemangiosarcomas, mammary gland adenocarcinomas and adenomas, and hepatocellular carcinomas (Table 7.4) (Drew et al., 1983). The

incidence of hemangiosarcomas was a function of the duration of exposure: the longer the exposure period the greater the incidence of hemangiosarcomas. A six-month exposure produced a low incidence of hemangiosarcomas and hepatocellular carcinomas only if begun early in life. One-year exposures produced a significant incidence of tumors, especially if begun early in life. The incidence of mammary gland adenocarcinomas and fibroadenomas was not always related to exposure duration, but the incidence was higher in rats whose exposure began at eight weeks of age. Hepatocellular carcinomas were induced in a dose-related manner in rats when exposures began at eight weeks.

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with vinyl chloride exposure (Table 7.4) (Drew et al. 1983). The highest incidence of hemangiosarcomas and stomach adenomas occurred in animals exposed early in life for only six months. The highest incidence of mammary gland carcinomas was seen in animals exposed at an early age for up to twelve months. Exposure beginning at or after eight months of age resulted in a markedly lower tumor incidence, possibly because the lifespans of chronically exposed hamsters were significantly reduced to the point that late-appearing tumors would not be expressed.

Mice, especially the B6C3F1 strain, appeared to be the species most sensitive to the carcinogenic effects of vinyl chloride (Table 7.4) (Drew et al., 1983). Hemangiosarcomas and mammary gland carcinomas

in both strains and lung carcinomas in Swiss mice were associated with vinyl chloride exposure. In B6C3F1 mice, exposure to vinyl chloride for six months resulted in 60-70% incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in B6C3F1 mice was greatest when the animals were exposed early in life. Lower incidences of this tumor were seen when initial exposure occurred at a later age. In Swiss mice, exposure to vinyl chloride at an early age resulted in the highest incidence of hemangiosarcomas, mammary gland carcinomas, and lung carcinomas, regardless of duration of exposure. Lower incidences of all tumors were observed in animals exposed later in life.

The patterns of tumorigenicity produced by vinyl chloride in the study by Drew et al. (1983) are consistent with patterns reported in other inhalation studies. However, the results reported by these investigators apparently contradict those of Groth et al. (1981). This apparent contradiction can be explained by the fact that Groth et al. reported only the incidence of hemangiosarcomas, a tumor shown in the Drew study to be a relatively late-appearing tumor that developed regardless of either the age at initial exposure or the duration of exposure. In the Groth et al. study, animals exposed at a young age were also sacrificed at a young age, thereby decreasing the probability of hemangiosarcoma development relative to the older exposed animals who were allowed to live.

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TABLE 7.4

TUMOR INCIDENCE FOLLOWING VINYL CHLORIDE EXPOSURE IN

FEMALE RATS, HAMSTERS AND MICE FROM THE STUDY OF DREW ET AL. (1983)

Tumor Type	Length of Exposure (Months)	LDE (ppm)[1]	Tumor Frequency (%)
Female Fisher 344 Rat:	**Experimental Exposure 100 ppm**		
Liver	control	0	0.9 (1/112)
Hemangiosarcomas	6	4.46	5.3 (4/76)
	12	8.93	20.0 (11/55)
	18	13.40	23.6 (13/55)
	24	17.86	34.7 (19/55)
Mammary Gland	control	0	4.5 (5/112)
Adenocarcinoma	6	4.46	7.9 (6/76)
	12	8.93	19.6 (11/56)
	18	13.40	16.4 (9/55)
	24	17.86	9.1 (5/55)
Hepatocellular	control	0	0.9 (1/112)
Carcinoma	6	4.46	4.0 (3/75)
	12	8.93	7.1 (4/56)
	18	13.40	14.8 (8/54)
	29	17.86	16.4 (9/55)
Female B6C3F1 Mice:	**Experimental Exposure 50 ppm**		
Hemangiosarcoma	control	0	5.8 (4/69)
(all sites)	6	2.23	68.7 (46/67)
	12	4.46	76.7 (69/90)
	18	--	--
Mammary Gland	control	0	4.3 (3/69)
Carcinoma	6	2.23	43.2 (29/67)
	12	4.46	41.1 (37/90)
	18	--	--

TABLE 7.- continued

Tumor Type	Length of Exposure (Months)	LDE (ppm)[1]	Tumor Frequency (%)
Female CD-1 Swiss Mice:	**Experimental Exposure 50 ppm**		
Hemangiosarcoma (all sites)	control	0	1.4 (1/71)
	6	2.23	43.3 (29/67)
	12	4.46	63.8 (30/47)
	18	6.69	44.4 (20/45)
Mammary Gland Carcinoma	control	0	2.8 (2/71)
	6	2.23	49.3 (33/67)
	12	4.46	46.8 (22/47)
	18	6.69	48.9 (22/45)
Lung Carcinoma	control	0	12.7 (9/71)
	6	2.23	27.7 (18/65)
	12	4.46	31.9 (15/47)
	18	6.69	24.4 (11/45)
Female Golden Syrian Hamster:	**Experimental Exposure 200 ppm**		
Hemangiosarcoma (all sites)	control	0	0.0 (0/143)
	6	8.93	14.8 (13/88)
	12	17.86	7.7 (4/52)
	18	26.79	1.9 (2/103)
Mammary Gland Carcinoma	0	0	0.0 (0/143)
	6	8.93	32.2 (28/87)
	12	17.86	59.6 (31/52)
	18	26.79	46.1 (47/102)
Skin Carcinoma	0	0	0 (0/133)
	6	8.93	2.5 (2/80)
	12	17.86	18.8 (9/47)
	18	26.79	3.3 (3/90)

[1]LDE = Lifetime Daily Exposure (in ppm)

7.1.4.4 Studies by Maltoni and Associates

Maltoni and co-workers performed a series of chronic inhalation studies on rats, mice, and hamsters in the Bentivoglio Laboratories (BT) or the Bologna Institute of Oncology (Maltoni et al., 1984). The investigators studied the effects of exposure to 14 concentrations of vinyl chloride (1-30,000 ppm) in male and female rats and six concentrations of vinyl chloride in male and female mice and male hamsters. A summary of some of these experiments are included both in this section and in Appendix A. In each experiment, animals were exposed to vinyl chloride for four hours daily, five days per week for various durations, and observed for the rest of their lives. A number of the experimental procedures were not described or were inadequately described in the report by Maltoni et al. (1984). A full necropsy was performed on each animal and the following tissues reportedly were routinely excised for histopathology: brain, zymbal glands, interscapular brown fat, salivary glands, tongue, thymus, lungs, liver, kidneys, adrenal glands, spleen, pancreas, esophagus, stomach, intestine, bladder, uterus, gonads, and any organ in which pathologic lesions were observed. Details of the experimental protocol for the BT experiments are provided in Table 7.5 (Maltoni et al., 1984).

Data on noncarcinogenic toxic effects of vinyl chloride were sparsely reported in the Maltoni BT experiments. Vinyl chloride appeared to be toxic at the higher concentrations, but reportedly the high mortality at these dose levels was due to a high incidence

of vinyl chloride-induced tumors. The available information on survival, including Kaplan-Meier survival curves, indicates that vinyl chloride decreased survival in a dose-dependent manner.

In the Maltoni experiments, exposure to vinyl chloride was associated with an increased incidence of malignant tumors at a variety of tissue sites in all of the species tested. A summary of these tumor sites is provided in Table 7.6 (Maltoni et al., 1984). A direct relationship between exposure levels and tumor incidence was apparently demonstrated, although no statistical tests for trends were performed. Results of experiments on Sprague-Dawley rats exposed to vinyl chloride for 52 weeks were statistically analyzed using the Fischer exact probability test. Correspondence analysis was also performed on the relationship of the incidence of liver angiosarcomas, zymbal gland carcinomas, nephroblastomas, and forestomach papillomas and acanthomas to vinyl chloride exposure (Tassignon, 1980, cited in Maltoni et al., 1984). The results of this analysis were not discussed by Maltoni et al. (1984). A summary of the lowest concentrations at which a statistically significant excess of tumors was observed is given in Table 7.7.

Experiment BT1. Most previous risk assessments have been based on the data from experiment BT1 (Maltoni et al., 1984). In this study, 30 Sprague-Dawley rats of each sex were exposed to concentrations of vinyl chloride ranging from 50 to 10,000 ppm for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age. A positive control group received 2,500 ppm of vinyl

acetate. After treatment the animals were observed for their lifespans up to 135 weeks. Survival of both males and females decreased in a dose-related manner, especially at concentrations above 500 ppm. Vinyl chloride appeared more toxic to females than to males in this experiment. Vinyl chloride was associated with an increased incidence of liver angiosarcomas in a dose-related fashion. These results are presented in Table 7.8 (Maltoni et al., 1984). In addition to liver angiosarcomas, vinyl chloride (at concentrations above 2500 ppm) caused an increased incidence of zymbal gland carcinomas, nephroblastomas, hepatomas, and neuroblastomas. The incidence of liver angiosarcomas was probably underestimated at the higher exposure levels due to mortality resulting from tumors at other sites.

Experiment BT15. Groups of 60 male and 60 female Sprague-Dawley rats were exposed to 0, 1, 5, 10, or 25 ppm of vinyl chloride for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age (Maltoni et al., 1984). Following exp sure the animals were observed for the remainder of their lives (up to 147 weeks). Available data, including Kaplan-Meier survival curves, indicated that vinyl chloride did not affect survival at the concentrations tested. No statistical analyses of mortality and body weight data were reported. Mortality was greater in the mal control group than in the treated groups: the time at which 50% of the male control group had died was week 72, compared with week 100 in the 25-ppm vinyl chloride group. No explanation was given for this decreased survival.

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TABLE 7.5

EXPERIMENTAL PROTOCOL FOR INHALATION STUDIES
MALTONI AND CO-WORKERS (1984)

Experiment Number	Dose (ppm)	Exposure Duration[1] (weeks)	Species/ Strain	Age at Start of Exposure (weeks)	Number of Animals per[2] Dose Level
BT1	0, 50, 250, 500, 2,500, 6,000, 10,000	52	Rat/SD	13	30 M, 30 F (30 M, 30 F)
BT2	1, 100, 150, 200	52	Rat/SD	13	60 M, 60 F (85 M, 100 F)
BT6	30,000	52	Rat/SD	17	30 M, 30 F (no controls)
BT9	0, 50	52	Rat/SD	13	150 M, 150 F (50 M, 50 F)
BT15	0, 1, 5, 10, 25	52	Rat/SD	13	60 M, 60 F (60 M, 60 F)
BT3	0, 50, 250, 500, 2,500, 6,000, 10,000	17	Rat/SD	12	30 M, 30 F (30 M, 30 F)
BT14	6,000, 10,000	5	Rat/SD	21 (parents)	6 F (no controls)
		5		1 day (offspring)	21-22 M, F (no controls)
BT4001	0, 2,500	76	Rat/SD	13	54 F (60 F)
		69		1 day	68 M, 64 F (158 M, 149 F)
BT4006	0, 2,500	15	Rat/SD	1 day	60 M, 60 F (60 M, 60 F)
BT5	6,000, 10,000	1	Rat/SD	19 (fetus)	30 F 13-29 M, F (no controls)
BT7	0, 50, 250, 500, 2,500, 6,000, 10,000	52	Rat/Wistar	11	30 M (40 M)
BT17	0, 1	52	Rat/Wistar	13	120 M (130 M)

Table 7.5 continued

Experiment Number	Dose (ppm)	Exposure Duration (weeks)[1]	Species/ Strain	Age at Start of Exposure (weeks)	Number of Animals per Dose Level[2]
BT4	0, 50, 250, 500, 2,500, 6,000, 10,000	30	Mouse/Swiss	11	30 M, 30 F (80 M, 70 F)
BT8	0, 50, 250 500, 2,000, 6,000, 10,000	30	Hamster/ Syrian golden	11	30 M (62 M)

[1]Exposures were for four-hours daily, five days per week.

[2]Number in parentheses = number of control animals for experiment.

TABLE 7.6

TUMORS CORRELATED TO INHALATION EXPOSURE TO VINYL CHLORIDE IN RATS, MICE, AND HAMSTERS IN THE BT EXPERIMENTS[1]

Tumors	Rat	Mouse	Hamster
Liver angiosarcomas	+	+	+
Hepatomas	+	(+)	
Encephalic neuroblastomas	+		
Lung adenomas		+	
Lymphomas/leukemias			(+)
Angiosarcomas at other sites	+	+	(+)
Zymbal gland epithelial tumors	+		
Nephroblastomas	+		
Cutaneous epithelial tumors	(+)	(+)	(+)
Mammary adenocarcinomas	+	+	
Forestomach papillomas, acanthomas	+	(+)	+

[1]Data from Maltoni et al., 1984

\+ = Tumor incidence was statistically significant ($p < 0.05$) by the Fisher exact test.

(+) = Association was not statistically significant, but was considered biologically significant.

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TABLE 7.7

LOWEST CONCENTRATION AT WHICH A SIGNIFICANT ($p < 0.05$) EXCESS OF TUMORS WAS REPORTED BY MALTONI AND ASSOCIATES[1] IN INHALATION STUDIES AT SPECIFIC SITES IN SPRAGUE-DAWLEY RATS[2]

Tumor	Vinyl Chloride Concentration (ppm)
Forestomach papilloma	30,000 (male, female)
Zymbal gland carcinoma	10,000 (male, female)
Neuroblastoma	10,000 (female)
Nephroblastoma	250 (female)
	100 (male)
Liver angiosarcoma	200 (male)
	25 (female)[2]
Mammary adenocarcinoma	5 (female)

[1]Data are from Maltoni et al., 1984.

[2]Significant at this dose level when specific corrected tumor incidence is used, $p = 0.047$. Analysis by Fisher exact probability test.

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TABLE 7.8

INCIDENCE OF LIVER ANGIOSARCOMAS (LAS) IN MALE AND FEMALE SPRAGUE-DAWLEY RATS EXPOSED FOR 52 WEEKS TO VINYL CHLORIDE (Maltoni et al., 1984)

Study	Experimental Dose Level (ppm)	LAS Incidence[1]		Corrected LAS Incidence[2]	
		Male	Female	Male	Female
BT1	0	0/30	0/30	0/22	0/29
	50	0/30	1/30	0/26	1/29
	250	1/30	2/30	1/28	2/26
	500	0/30	6/30	0/22	6/28
	2,500	6/30	7/30	6/26	7/24
	6,000	3/30	10/30	3/17	10/25
	10,000	3/30	4/30	3/21	4/25
BT2	0	0/85	0/100	0/61	0/68
	100	0/60	1/60	0/37	1/43
	150	1/60	5/60	1/36	5/46
	200	7/60	5/60	7/42	5/44
BT6	30,000	5/30	13/30	5/22	13/24
BT9	0	0/50	0/50	0/29	0/38
	50	1/150	12/150	2/70	12/110
BT15	0	0/60	0/60	0/25	0/44
	1	0/60	0/60	0/48	0/55
	5	0/60	0/60	0/43	0/47
	10	0/60	1/60	0/42	1/46
	25	1/60	4/60	1/41	4/40
LAS Incidence in Historical Controls:					
		1/1179	2/1202	1/364	2/541

[1]Number in denominator = number of animals necropsied.

[2]Number in denominator = number of animals alive when first liver angiosarcoma was observed.

CMA 010426

The incidence of mammary gland carcinomas in treated females was higher than in controls at all concentrations of vinyl chloride exposure. However, the differences from control values were statistically significant only at concentrations above 1 ppm. The mammary gland adenocarcinoma incidence for this and the other relevant BT experiments are presented in Table 7.9 (Maltoni et al., 1984).

Experiment BT4. Thirty male and 30 female Swiss mice were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm of vinyl chloride four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age (Maltoni et al., 1984). The study was terminated 81 weeks after the exposure period began. Vinyl chloride was highly toxic to both males and females, but males appeared more sensitive than females to the toxic effects of vinyl chloride. Survival decreased in a dose-related manner, although statistical analysis apparently was not performed on the data presented.

A very high incidence of lung adenomas was observed in vinyl chloride-treated male and female mice. A statistically significant increase in the incidence of liver angiosarcomas was seen in mal and female mice exposed to vinyl chloride, but a dose response was not seen in the male animals. In addition, a high incidenc of mammary gland adenocarcinomas occurred in treated female mice. These results are presented in Table 7.10 (data from Maltoni et al., 1984).

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TABLE 7.9

INCIDENCE OF MAMMARY GLAND CARCINOMAS IN FEMALE SPRAGUE-DAWLEY RATS AND SWISS MICE EXPOSED BY INHALATION TO VINYL CHLORIDE (Maltoni et al., 1984)

Study No.	Experimental Dose Level (ppm)	Tumor Incidence[1]	Corrected Tumor Incidence[2]
BT1	0	0/30	0/29
(Rat)	50	2/30	2/30
	250	2/30	2/27
	500	1/30	1/28
	2,500	2/30	2/25
	6,000	0/30	0/28
	10,000	3/30	3/29
BT2	0	2/60	2/100
(Rat)	100	4/60	4/60
	150	6/60	6/60
	200	5/60	5/60
BT6	30,000	2/30	2/30
(Rat)			
BT9	0	9/50	9/43
(Rat)	50	59/150	59/142
BT15	0	6/60	6/60
(Rat)	1	14/60	14/60
	5	22/60	22/60
	10	21/60	21/60
	25	16/60	16/60
Tumor Incidence in Historical Controls		100/1202	100/1202
BT4	0	1/80	1/67[3]
(Mice)	50	12/30	12/30[3]
	250	13/30	13/29[3]
	500	10/30	10/28[3]
	2,500	9/30	9/30[3]
	6,000	9/30	9/28[3]
	10,000	14/30	14/28[3]
Tumor Incidence in Historical Controls		21/554	21/554[3]

[1] Number in denominator = number of animals examined.

[2] Number in denominator = number of animals alive when first malignant mammary tumor was observed (type unspecified).

[3] Number in denominator = number of animals alive when first mammary tumor was observed (type unspecified).

CMA 010428

TABLE 7.10

INCIDENCE OF PULMONARY ADENOMAS, MAMMARY CARCINOMAS, AND LIVER ANGIOSARCOMAS IN MALE AND FEMALE SWISS MICE EXPOSED TO VINYL CHLORIDE BY INHALATION (EXPERIMENT BT4)[1]

	Cancer Incidence Vinyl Chloride (ppm)							
Organ/Sex	0	50	250	500	2,500	6,000	10,000	Historical Controls
Pulmonary (lung) adenomas[2]								
Males	8/75	3/27	24/29	24/29	18/25	23/27	20/24	34/491
Females	7/67	3/30	17/29	26/29	22/30	24/29	26/28	27/533
Liver angiosarcomas[3]								
Males	0/62	1/18	9/23	6/17	6/13	2/12	1/9	0/545
Females	0/62	0/26	9/21	8/26	10/24	11/21	9/20	0/554
Mammary adenocarcinomas[4]								
Males	0/74	0/27	0/29	1/28	0/23	0/24	0/22	1/521
Females	1/67	12/30	13/29	10/28	9/30	9/28	14/28	22/545

[1] Data from Maltoni et al., 1984.

[2] Number in denominator = number of animals alive when first pulmonary (lung) adenoma was observed (11 weeks).

[3] Number in denominator = number of animals reportedly alive when first liver angiosarcoma was observed (32 weeks).

[4] Number in denominator = number of animals reportedly alive when first lung mammary tumor (type unspecified) was observed (16 weeks).

7.2 Human Studies on the Carcinogenic Effects of Vinyl Chloride

7.2.1 Introduction

In 1974, Creech and Johnson described three cases of angiosarcoma of the liver (LAS) among workers at the B.F. Goodrich Tire and Rubber Co. in Louisville, Kentucky. Because LAS is a very rare cancer (20-25 cases per year in the United States), the clustering of three cases in one vinyl chloride polymerization facility indicated an abnormally high incidence of this cancer. Based on this report, as well as data indicating that vinyl chloride is carcinogenic in laboratory animals, multiple studies of workers exposed to this agent were conducted. By 1985, at least 17 epidemiologic studies relating vinyl chloride exposure to the incidence of various cancers had been completed.

7.2.2 General Design of Epidemiologic Studies

Most of the epidemiologic studies have been retrospective cohort designs. Groups of workers in the vinyl chloride industry were selected by reviewing employment records. Few baseline data other than age, job classification, and length of employment were obtained. The concentrations of vinyl chloride to which these workers were exposed were generally not available, since ambient levels of vinyl chloride were not routinely measured before 1975. Almost all of the investigators estimated vinyl chloride exposure

based on some combination of job classification and length of exposure.

Exposure information included measured levels of vinyl chloride in only two studies (Ott et al., 1975; Buffler et al., 1979). In all reports, workers were traced to determine the number of deaths that had occurred in the defined cohort. The cause of death was based on information available from death certificates. In the studies from Swedan and Norway, national cancer registries also provided data to assess incidence of cancer (Byren et al., 1976; Heldaas et al., 1984). The expected numbers of deaths were estimated using population-based mortality statistics. Finally, a standardized mortality ratio (SMR) was calculated from the proportion of observed to expected deaths from each cause and the statistical significance of these ratios tested.

7.2.3 Difficulties in Interpreting the Epidemiologic Evidence

There are several problems involved in the interpretation of these studies:

1. Inadequate information on worker outcome. In several of the studies reviewed, outcome data on approximately 10% of the original workers were not obtained (Duck et al., 1979). Since the tumor incidence in humans exposed to vinyl chloride is relatively low, the loss of 10% of the data base could have a

significant effect on the observed tumor rate, and possibly allow for an underestimation of risk.

2. Inadequate exposure data. Specific exposure data did not exist in any of the studies reviewed with the exception of Ott et al. (1975) and Buffler et al. (1979). In some cases, no attempt was made to evaluate exposure. In most studies, exposure was estimated from odor levels, acute toxicity levels, job classification, or length of exposure - methods all considered unreliable for accurate exposure estimation. However, gross differences in exposure levels based on the type of job and length of exposure may have occurred, particularly before 1975, when very high levels of vinyl chloride were common in the industry (up to 500 ppm with rare excursions up to 4,000 ppm) (Ott et al. 1975). After 1975, ambient workplace levels were drastically reduced to an average of about 1 ppm, so that differences in dose estimated by job classification became small.

3. Inadequate follow-up time. In this review, "follow-up time" is the time period between the onset of exposure and the point at which evaluation is completed. The average latency period for LAS among vinyl chloride workers worldwide was determined to be 22.1 years (Stafford, 1983). Several of the epidemiologic studies either do not report length of follow-up or include a large number of subjects who had recently become employed in the vinyl chloride industry and who, therefore, had very short

follow-up time periods. Inclusion of subjects with shorter average follow-up time tends to obscure an exposure-response relationship.

4. Use of death certificates to determine outcome. Cancer is often not listed as a cause of death on death certificates. Even when cancer is reported, the type of cancer may not be given and may not be verified.

5. Healthy worker effect. In retrospective cohort studies of mortality among occupational groups, the number of deaths ar compared to general population rates. A disproportionate number of newly hired employees demonstrating self-selection for good health, or selected for better general health through pre-employment examinations, skews the mortality experience of the worker population. Ott and co-workers (1975) have estimated that the average mortality rate for workers in the plastics industry is about 80% of population-based rates. Since observed deaths in the study cohorts are compared to estimates based on the incidence of death in the general population (not in healthy workers), the SMR becomes an underestimate of risk. Unfortunately, only one of the epidemiologic studies reviewed used a control group of workers not exposed to vinyl chloride (Theriault and Allard, 1981). The failure of more epidemiologic studies to use a proper control cohort increases the difficulty in interpreting the effects of vinyl chloride on the exposed worker.

6. Inadequate statistical power. The term "statistical power" represents the probability of detecting an association or an excess risk if that association really exists. For example, if the power of a study to detect a specified change in risk is 80%, there is an 80% chance that the study will show an increased risk if that risk really exists. Negative findings may have two explanations: there may actually be no increased risk, or the study may have had inadequate power to show a risk that really exists. Power depends on the level of statistical significance used (usually $p < 0.05$), the number of outcomes expected (in these studies cause-specific deaths), and the strength of the association being investigated (effect size).

7.2.4 Mortality Studies

A summary of the important characteristics of individual epidemiologic studies is given in Tables 7-11 and 7-12. Each study should be evaluated keeping in mind the difficulties noted above.

Soon after the initial case reports by Creech and Johnson (1974), describing the identification of liver angiosarcomas in vinyl chloride workers, Monson et al. (1974) published a proportionate mortality analysis of the deaths of 161 vinyl chloride workers at two plants in the United States. A statistically significant 50% excess mortality for all cancers and an 11-fold increase in mortality from cancer of the digestive system, including five angiosarcomas of the liver (LAS), were observed. In addition,

TABLE 7-11

A SUMMARY OF EPIDEMIOLOGIC DATA FOR
OCCUPATIONALLY EXPOSED VINYL CHLORIDE WORKERS

	STUDY	COHORT	F/U(%)	DEATHS(%)	EXPOSURE(YRS)	F/U TIMES(YRS)	DOSE	SMR DEATH	SMR ALL SITES	SMR LIVER(LAS)	SMR BRAIN	SMR LUNG	SMR LYMPHOMA
1.	Tabershaw & Gaffey[1] USA (1974)	8,384	1258(15%)	352(4.7%)	>1 10.2%>20yrs	>1	EST	75	110	94[3](6)	155[4]	112	106
2.	Duck et al. U.K. (1975)	2,122	7(0.3%)	152(7.2%)	>0	27%>19yrs	EST	96	96	99[3](0)	--	103	
3.	Nicholson et al. USA (1975)	257	2(0.8%)	24(9.3%)	>5	>10	EST	126	231	- (3)	--	--	--
4.	Ott et al.[2] USA(1975)	594	0(0%)	79(13.3%)	>0	> 0	measured	89	81	- (0)	--	77	--
5.	Byren et al. Sweden (1976)	771	21(2.7%)	58(75%)	>0	55%>10yrs	EST			413[a](2)	612[a]	168	--
6.	Maxweiler et al. USA (1976)	1,294	13(1%)	136(10.5%)	>5	>10 >15	EST	108	149[a] 189[b]	1155[b](11) 1606[b]	329[a5] 498[a]	156 194[d]	159 176
7.	Fox and Collier U K (1977)	7,717	393(5.1%)	409(5.3%)	>0 8%>20yrs	> 0	EST	75.4	90.7	1408[a](2)	54.6	89.8	90.9
8.	EEN USA (1975)	10,173	496(4.8%)	707(6.9%)	>1 19.3%>20yrs	32%>20yrs	EST	89	104	75[3](5)	203[a]	107	112
9.	Buffler et al. Texas (1979)	464	0(0%)	28(0%)	>0	> 0	measured	87	138	- (0)	--	208[a]	--
10.	Bertazzi et al. Italy (1979)	4,777	659(13.8%)	62(1.3%)	>0.5	>0.5	EST	44	97	800[a](3)	125	81	133
11.	Masuda et al. Japan (1979)	304	1(0.3%)	26(8.5%)	>1	>1	EST	--	138	500[a](0)	--	125	

TABLE 7-11 (con't)

	STUDY	COHORT	F/U(%)	DEATHS(%)	EXPOSURE(YRS)	F/U TIMES(YRS)	DOSE	SMR DEATH	SMR ALL SITES	SMR LIVER(LAS)	SMR BRAIN	SMR LUNG	SMR LYMPHOMA
12.	Weber, Reinl, Greiser Germany (1981)												
	production	7,021	700(4.4%)	414(5.9%)	>0	>0	EST	95	112	1523[b]	162	--	214[a]
	processing	4,007		368(9%)	>0	>0	EST	95	85	434[a]	535[a]	--	34
	unexposed	4,910		417(8.5%)	>0	>0	EST	78	83	401[a]	184	--	77
13.	Cooper[1] USA (1981)	10,173	496(4.8%)	707(6.9%)	>1	33.4%	EST	89	104	75[3](8)	203[a]	107	112
14.	Nakamura Japan (1983)	4,524	29(0.6%)	209(4.6%)	>1	mean 16.3yrs	EST	87	138[a]	236[a](3)	--	86	--
15.	Heldass et al. Norway (1984)	454	0(0%)	50(11%)	>1	>1	EST	84	114	(1)	--	180	--
								---------- Relative Risk ----------					
16.	Theriault & Allard Canada (1981)												
	exposed	451	0(0%)	59(2.6%)	>5	81%115yrs	EST	1.07	1.48	6.25[a](10)	--	.36	--
	unexposed	871		233(26.8%)	-	--							

1. The studies of Cooper and EEH are reanalyses of the Tabershaw and Gaffey Cohort
2. SMR subjects also in the Tabershaw and Gaffey Cohort
3. SMR is for "digestive system cancer", not liver cancer
4. SMR is for "other and unspecified cancer", 40% of which were brain cancer
5. SMR is for cancer of CNS, not Brain

F/U = Follow up time (years)
EST = Estimated dose
[a] $p < 0.05$
[b] $p < 0.01$

TABLE 7-12

A SUMMARY OF TUMOR INCIDENCES AND STANDARDIZED MORTALITY RATIOS (SMR)
FOR OCCUPATIONALLY EXPOSED VINYL CHLORIDE WORKERS

STUDY	DEATH O E SMR	ALL CANCER O E SMR	LIVER CANCER O E SMR	BRAIN CANCER O E SMR	LUNG CANCER O E SMR	LYMPHOMA O E SMR
1. Monson et al.	161-161-100	41-27.9-150	8--0.7-1100	5--1.2--420	13-7.9--160	5--3.4--150
2. Taberahau & Gaffey	352-467-75[a]	79-77--110	19-21.7-94	17-11.78-155	25-23.9-112	6--6.1-106
3. Duck et al.	136-142.2-96	35-36.4-96	11-11.1-99	----------	16-15.5-103	----------
4. Nicholson et al.	24--19--126	9--3.9-----	31---------	11---------	----------	21---------
5. Ott et al.	79--89.1-89	13--16--81	----------	----------	4--5.2--77	----------
6. Byren et al.	----------	----------	4--.97--413	2--.38--612[a]	3--1.8-108	----------
7. Waxweiler et al.	136-126.3-108	35-23.5-149[a]	7-0.6-1155[b]	3-0.9-329[a]	12-7.7-156	4-2.5-159
15 year		31-16.9-184[b]	7-0.4-1606[b]	3-0.6-498[a]	11-5.7-194[a]	3-1.7-176
8. Fox & Collier	393-521:2-75.4	115-126.8-90.7	1-.71-140.8	2-3.66-54.6	46-51.2-90	9-9.0-99.9
9. EEN	707-795--89[b]	139-141.4-104	29-40.8-75	12-5.9-203[a]	45-44.3-107	11-10.4-112
10. Buffler et al.		8--5.2--154	0--.2-----	1--0.1----	5--1.7--289[a]	0--0.5-----
11. Bertazzi et al.		30-30.9-97	8--1--800[b]	1-0.8-125	7--7.7--91	4---3---133
12. Nasuda et al.		8--5.8--138	1-.6--167	0--.15----	1--.8--125	0--.5------
13. Weber et al.						
Production	414------95	94------112	12------1523[b]	2-------162	----------	15-----214[b]
Processing	360------95	62------85	31------434	51------535[a]	----------	2-------34
Control	417------78	83------83	41------401[a]	2-------184	----------	6-------77
14. Cooper	707-795-89[a]	139-141-104	29-40.8-75	12-5.9-203[b]	45-44.3-107	11-10.4-112
15. Waldaas	----------	23-20.2-110	----------	----------	5--2.8--180	----------
16. Theriault and Allard	----------	20-16.4-122.2	14-5.4-259.3[b]	0--0.6-----	2--5.8--34.6	----------
17. Nakamura	128-147.6-87	37-26.85-138[a]	6--2.54-236[a]	----------	2-2.3-0.86	----------

[a] $p < 0.05$

[b] $p < 0.01$ o = observed e = expected SMR = standardized mortality ratio

increases in the proportionate mortality ratios (PMR) for brain cancer, lung cancer, and lymphoma were noted. Proportionate mortality ratios do not represent a specific measure of risk, but the consistent PMR excesses for neoplasms found in this study suggests that vinyl chloride may operate as a multisystem carcinogen.

Tabershaw and Gaffey (1974) published a large cohort study of 8,384 vinyl chloride workers at 33 plants in the United States, which demonstrated a statistically significant increase in angiosarcoma of the liver and a nonsignificant positive trend correlating vinyl chloride exposure with lymphoma and cancers of the buccal cavity and pharynx, CNS (primarily brain), and lung. The SMRs for all these tumor types were greater in the high exposure groups after the cohort was stratified by high and low exposure indices (estimates based on job classification and length of exposure), but the differences in SMRs for the high- and low-exposure groups were not statistically significant. Follow-up in this study was only 85% complete. The workers for whom follow-up was incomplete were mostly older workers, and Tabershaw and Gaffey (1974) suggested that these workers, who experienced a long latent period after exposure, might show a somewhat different mortality pattern from workers who were followed up. Another significant problem is that the authors reported only digestive system cancer and did not distinguish cancer of the liver from other cancers in this classification. Information on this cohort has been updated and

reanalyzed by Cooper (1981). The final report included 10,173 vinyl chloride workers from 37 plants in the United States (Cooper, 1981). Follow-up had increased to 95.1% of the cohort and extended more than 20 years for 33.4% of the cohort. Statistically significant excess mortality was shown for LAS and for CNS cancers (primarily brain). Again, SMRs for lung cancer and lymphoma were elevated but not statistically significant.

Duck and co-workers published an analysis of 2,122 vinyl chloride workers in Great Britain (1975). In this study, no excess of total or cause-specific mortality occurred. There were no cases of LAS, although one was recorded in the cohort after the study period ended. Only 16% of the cohort in this study was followed more than 15 years from the time of initial exposure, which undermines the reliability of the negative results of this study.

Nicholson and colleagues reported on 257 workers in th United States who were exposed to vinyl chloride for at least five years and whose initial exposure occurred more than ten years before the end of the study (1975). These inclusion criteria are important because this is the first study that attempted to limit the cohort to workers who had significant vinyl chloride exposure and follow-up time. Three cases of LAS were observed and the SMRs for all deaths and deaths due to cancer were elevated. Because LAS is otherwise exceedingly rare, the increased incidence of this tumor was statistically significant, but the study lacked power to detect significant increases in other classifications of malignancy.

A larger cohort based on similar criteria was assembled by Waxweiler et al. (1976) for the National Institute for Occupational Safety and Health (NIOSH). This study followed an adequate number of workers (1,294) for more than 10 years, with all having had more than five years of exposure. Separate analyses were also performed for those workers with more than 15 years of follow-up time. Significant excesses in the SMR of exposed workers were found for all deaths due to cancer, liver cancer (11 cases of LAS), and CNS cancers. Standard mortality ratios for lung cancer and lymphoma were elevated, but were not significant at the $p < 0.05$ level. Workers with more than 15 years of follow-up time showed higher mortality rates compared to those with ten years of follow-up time. The SMR for lung cancer reached statistical significance in the group with a 15-year follow-up. This cohort provides the strongest evidence for the association between length of time since exposure to vinyl chloride and the subsequent development of cancers of the liver, CNS, and lung (Waxweiler et al., 1976).

Ott and associates completed a study of 594 Dow Chemical workers in Michigan (1975). Many of these workers were also included in the study by Tabershaw and Gaffey (1974). The best available vinyl chloride exposure data are included in this study. Automated sampling of air levels began in one plant as early as 1959. Unfortunately, a large number of workers had less than one year of vinyl chloride exposure at the time of this report. Stratifying the cohort into low, medium, and high exposure groups resulted in less than 200 subjects per group, with only 20, 18, and 22 deaths per

group, respectively. No cases of LAS and no significant increase in mortality from any cause for the entire cohort were noted. However, total deaths and deaths due to cancer were significantly higher in the high vinyl chloride exposure group compared to all other dose groups. These data are insufficient to develop any human dose-response relationship.

The only other study providing quantified human exposure data is by Buffler and co-workers (1979). Area sampling began after 1971 for 464 Dow Chemical vinyl chloride workers in Texas, but data on exposure levels were not available for those workers (the majority) exposed before monitoring began. No cases of LAS were observed among these subjects. There was a statistically significant excess only for lung cancer in exposed workers. The number of deaths (N = 28) in this cohort was very small, making it impossible to perform statistical assessment of many of the causes of death. Buffler and associates have published the only information on the smoking habits of vinyl chloride workers. Even after adjustment for smoking habits, the excess of lung cancers in this group remained significant.

Byren et al. (1976) and Heldaas et al. (1984) reported on Swedish and Norwegian vinyl chloride workers, respectively. Although these studies included all vinyl chloride workers in the respective countries and had the advantage of access to excellent cancer registries, the total number of workers in both studies was still quite small. Nevertheless, both studies show a significant excess

of LAS in exposed workers. The Swedish study indicates a significantly increased mortality for CNS cancers. Both reports also demonstrate a trend toward increased mortality due to lung cancer.

Fox and Collier (1977) studied all 7,717 workers in Britain who may have been occupationally exposed to vinyl chloride between 1940 and 1974. Four cases of liver cancer were found; two of these were angiosarcomas. No other tumor type showed a significant increase (statistical methods not reported). Because workers were added to this cohort as they entered the industry, the study included a large proportion of workers with brief exposure and short follow-up time. Approximately 75% of the subjects had been employed in the vinyl chloride industry for less than ten years and only 8% of the workers had been employed for more than 20 years. Inadequate length of exposure and follow-up make this study's negative results of questionable validity.

Bertazzi et al. (1979) examined the mortality rates among 5,441 Italian vinyl chloride workers. This study showed a significant increase in mortality among exposed workers only for liver cancer (three cases of LAS). Follow-up was less than optimal (14% of the total remained untraced), and person-years at risk were calculated as if the workers unavailable to follow-up were all alive and well, which contributed to the very low SMR for all causes of death.

Masuda and co-workers studied 304 Japanese vinyl chloride workers (1979). This cohort was too small to determine statistical significance for any cause of death.

Weber, Reinl, and Greiser (1981) reported on mortality information from three cohorts of German chemical industry workers: 7,021 vinyl chloride and polyvinyl chloride production workers (usually considered a high exposure area), 4,007 polyvinyl chloride processing workers (a lower exposure area), and 4,910 chemical workers not exposed to vinyl chloride (1981). The SMRs w re determined for causes of death in each of the three groups but no statistical comparisons were made. A significant increase in mortality from liver cancer was observed in all three of the groups evaluated, most notably for the vinyl chloride processing workers (SMR = 1523). A significant increase in malignancies of the lymphatic and hematopoietic tissues was noted among the production workers, while a significant increase in brain tumors was observed among the processing personnel.

Analysis of the mortality experience of 4,524 Japanes vinyl chloride workers by Nakamura (1983) revealed a significant increase in the mortality ratio for death from all cancers and from liver cancer alone (three cases of LAS). Cancer of the lung was not elevated; cancers of the CNS and lymphoma were not reported in this study.

Theriault and Allard (1981) studied Canadian vinyl chloride workers in the only cohort to employ an occupational control group for evaluation of relative risk in workers exposed to vinyl chloride. The control cohort consisted of 870 chemical workers not exposed to vinyl chloride, while the study group comprised 585 vinyl chloride-exposed workers, with 454 of these workers exposed for more than five years. Exposure levels were not quantified. Very few deaths (59 cases) occurred in the exposed group, compared with 233 in the control group. The only significantly increased relative risk was for liver cancer (eight cases of LAS). The SMR for digestive cancer (which includes liver cancer) among workers exposed for greater than five years was 259, significantly greater ($p < 0.01$) than for the general population. The authors suggested that the small size of the study reduced the power of the study with respect to finding an excess of CNS cancer or lymphoma that may have been present. Theriault (1983) published an extended follow-up on this same cohort in 1983 with no significant changes in the initial findings.

Heldaas and co-workers reported a study of cancer incidence and mortality in a cohort of 454 male workers exposed to vinyl chloride and polyvinyl chloride between 1950 and 1969 (Heldaas et al. 1984). This cohort was divided into three exposure groups, as estimated from job classification, and the study population followed for 27 years. The investigation demonstrated an increased incidence of malignant melanoma, and cancer of the lung, colon, and thyroid

in the exposed cohort. This study reported cancer incidence, as well as mortality, unlike most other studies.

The observation of an increased incidence of malignant melanoma is the first reported in humans (Heldaas et al., 1984). Four malignant melanomas of the skin were identified in the study population where only 0.8 were expected. Three of four cases of malignant melanomas occurred in the high exposure group, where 0.5 cases were expected. The fourth case was in the medium exposure group with 0.18 cases expected. After the observation period, one more case was diagnosed in the medium exposure group. The authors noted one additional case of incipient malignant melanoma in the medium exposure level group that was diagnosed in 1977 but not included in the study (Heldaas et al. 1984).

Dahar et al. (1988) recently published an update to the vinyl chloride mortality study of Ott et al. (1975). There was no statistically significant excess for any neoplasm or disease of interest among the exposed cohort. Rinsky et al. (1988) evaluated the mortality rate and cause of death for a cohort of chemical workers in West Virginia. A statistically significant increase in liver cancer and lympho- and reticulo-sarcoma was seen among the workers. The mortality rate of the 29,319 male workers studied was similar to that of the U.S. white male population (Rinsky et al., 1988). Smulevich et al. (1988) reported that mortality resulting from tumors of the digestive organs, respiratory system, bone and connective tissues, brain and skin was higher in workers exposed to

vinyl chloride than for the general population (USSR). No cases of liver angiosarcoma were reported in the study cohort during the follow-up period (Smulevich et al., 1988).

7.2.5 Cancer Risks Associated with Exposure to Vinyl Chloride

7.2.5.1 Liver Cancer

Between 1961 and 1977, 23 cases of LAS were reported among approximately 20,000 vinyl chloride workers in the United States (Lelbach and Marsteller, 1981; Spirtas and Kaminski, 1978). The expected incidence of LAS is 0.014 cases per 100,000 per year in the general population in the United States (Heath et al., 1975). Based on analysis of these data, the relative risk for developing LAS following vinyl chloride exposure among this country's vinyl chloride workers is 483.

The epidemiologic studies also demonstrate a strong and consistent association between vinyl chloride exposure and primary cancer of the liver. All eight of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMR). The average relative risk for liver cancer among vinyl chloride workers is five to six times greater than the incidence of that seen in the general population. Strong evidence suggests that exposure to vinyl chloride can cause liver cancer. All reports published to date indicate that the standardized mortality ratios of exposed workers are elevated, and

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TABLE 7-13

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND PRIMARY CANCERS OF THE LIVER

STUDY	SMR	RESULT	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	413[a]	Significant	---	Yes
Waxweiler et al.	1155[b]	Significant	---	Yes
Fox & Collier	141[a]	Significant	Yes	---
Bertazzi et al.	800[a]	Significant	---	---
Masuda	500[a]	Significant	---	---
Weber et al.	1523[b]	Significant	Yes	Yes
Theriault & Allard[3]	6.25[a]	Significant	---	No
Nakamura	236[a]	Significant	Yes	Yes

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Relative risk, not SMR

[a] $p < 0.05$

[b] $p < 0.01$

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TABLE 7-14

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND BRAIN CANCER

STUDY	SMR	RESULT	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	612[a]	Significant	---	---
Waxweiler et al.	329[a]	Significant	---	Yes
Fox & Collier	55	-	Yes	---
Bertazzi et al.	125	+	---	---
Weber et al.	535[a]	Significant	No	No
Cooper[3]	203[a]	Significant	---	---

1 - Does risk increase with higher estimated dose?
2 - F/U Time = Follow up time (years)
Does risk increase with longer latency?
3 - Cooper's data are used in the most recent reevaluation of the Tabershaw, Gaffey and EEH cohort.

[a] $p < 0.05$

+ = non-significant positive trend for increased risk ($p < 0.05$)

risk of liver cancer was seen to increase with both increased dose and a longer follow-up time (Table 7-13).

7.2.5.2 Other Cancers

The association between vinyl chloride exposure and increased risk for other cancers is not as clear as that for liver cancer. Some evidence associates exposure to vinyl chloride with increased mortality ratios for brain cancer, lung cancer, and lymphoma. Since these cancers appear more commonly in the general population than LAS and primary liver cancer, it becomes more difficult to show increased risk.

7.2.5.2.1 Brain Cancer

Workers exposed to vinyl chloride appear to be at greater risk for brain cancer than do non-exposed populations. Of the six studies that assessed the risk of brain cancer, five showed a positive trend for increased risk of this cancer type following exposure to vinyl chloride, with four demonstrating statistical significance ($p < 0.05$) (Table 7-14). Cancer risk increased an average of four times above that expected in the general population in those studies that exhibited a significantly increased risk. Of the two studies not showing a significant increase in risk for brain cancer, statistical power in the Bertazzi and associates study was only about 35% (Bertazzi et

al., 1979), while that of Fox and Collier (1977) was approximately 80% (Beaumont and Breslow, 1981). In the Fox and Collier study, the number of deaths overall was low and, most importantly, a large percentage of workers in the cohort was very recently employed in the vinyl chloride industry and thus had a short follow-up time. These factors may partially explain why this study failed to detect an association between vinyl chloride exposure and brain cancer.

7.2.5.2.2 Lung Cancer

The evidence linking vinyl chloride exposure with lung cancer remains inconclusive. Analyses of SMRs for cancer of the lung were performed in 12 studies (Table 7-15). Of these, seven studies showed an increased risk for lung cancer, but only one was statistically significant at the 5% level (Buffler et al., 1979). This increased risk persisted after adjusting for personal smoking habits (for this particular cohort). However, this cohort was small and the study was unable to demonstrate an increased risk for any other cancer. The Waxweiler et al. cohort (which had a follow-up period greater than 15 years) also used a small group (1976). Of all the studies that examined the risk for lung cancer, only those of Fox and Collier (1977) and Cooper (1981) have greater than 80% power to detect increased relative risks (of 1.5 or 2) for lung cancer following exposure to vinyl chloride. Both of these studies found no statistically significant increased risk for lung cancer.

7.2.5.2.3 Lymphoma

An association between vinyl chloride exposure and lymphoma has not been established. Five studies evaluated the risk of lymphoma development among workers occupationally exposed to vinyl chloride (Table 7-16). Four of the studies showed a positive trend for lymphoma among vinyl chloride workers, but statistical significance was noted only by Weber et al. (1981). However, the statistical power in all of these studies was less than 80% to demonstrate a relative risk of two, and less than 40% to show a relative risk of 1.5.

7.2.6 Exposure Information

Most of the published epidemiologic studies did not present quantified exposure data. Levels of exposure were estimated by job classification and length of employment. Only the studies by Ott and co-workers (1975) and Buffler and associates (1979) contain measured industrial hygiene data. After the workers were classified according to exposure levels, the cohorts were too small to yield any statistically significant correlations. A dose-response relationship cannot be constructed based on these kinds of human data. This conclusion was also reached by the United States Environmental Protection Agency (1986).

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TABLE 7-15

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND LUNG CANCER

STUDY	SMR	RESULT	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Duck et al.	103	+	---	No
Ott et al.	77	-	---	---
Byren et al.	168	+	---	---
Waxweiler et al.	156	+	---	Yes
Fox & Collier	90	-	No	---
Buffler et al.	268[a]	Significant	---	---
Bertazzi et al.	91	-	---	---
Masuda et al.	125	+	---	---
Cooper[3]	107	+	Yes	No
Heldass et al.	180	+	---	---
Theriault & Allard[4]	.36	-	---	---
Nakamura	86	-	---	---

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Cooper's data is used in the most recent revaluation of the Tabershaw, Gaffey and EEH cohorts.

4 - Relative risk, not SMR

+ = non-significant positive trend for increased risk ($p < 0.05$)

[a] $p < 0.05$

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TABLE 7-16

A SUMMARY OF EPIDEMIOLOGIC STUDIES WHICH EXAMINED POSSIBLE CORRELATIONS BETWEEN OCCUPATIONAL VINYL CHLORIDE EXPOSURE AND LYMPHOMA

STUDY	SMR	RESULT	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Waxweiler et al.	159	+	---	Yes
Fox & Collier	100	-	---	---
Bertazzi et al.	133	+	---	---
Weber et al.	214[a]	Significant	+	---
Cooper[3]	112	+	---	---

1 - Does risk increase with higher estimated dose?
2 - F/U time = Follow-up time (years)
Does risk increase with longer latency?
3 - Cooper's data are used in the most recent revaluation of the Tabershaw, Gaffey and EEH cohorts.

[a] $p < 0.05$

+ = non-significant positive trend for increased risk ($p < 0.05$)

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7.2.7 Conclusions

Epidemiologic studies of workers exposed to high levels of vinyl chloride indicate that this chemical is a human carcinogen. Strong evidence suggests that vinyl chloride causes an increased risk for angiosarcoma of the liver. Vinyl chloride appears to be associated with a moderately increased risk for brain cancer, but current epidemiologic evidence does not demonstrate a significant correlation between vinyl chloride exposure and subsequent development of lung cancer or lymphoma. Exposure data in humans are inadequate to construct a dose-response curve for any of the cancers studied. However, exposure levels can be estimated, and appendices B and C discuss the potential human health risk for vinyl chloride using exposure estimates for the Waxweiler et al. (1976) study of occupationally-exposed workers.

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8.0 QUANTITATIVE CARCINOGENIC RISK ASSESSMENT

8.1 Introduction

Vinyl chloride has been demonstrated to be a carcinogen in multiple species of laboratory animals, including rats, mice and hamsters. Inhalation exposure of rats to low doses of vinyl chloride (<250 ppm) led predominantly to formation of hepatocellular carcinomas, neoplastic nodules of the liver, mammary tumors and nephroblastomas, while higher exposures were associated with liver and lung angiosarcomas, neuroblastomas, and zymbal gland carcinomas. Feeding studies have confirmed these results. Vinyl chloride has also been identified as a human carcinogen by IARC (1979), the EPA (1984b); and the State of California (CDHS, 1985). Epidemiologic evidence has linked occupational exposure to vinyl chloride with the development of liver angiosarcomas in chronically exposed workers.

Several aspects of vinyl chloride metabolism (reviewed in Section 2 of this document) are relevant to its carcinogenicity. First, the oncogenicity of vinyl chloride appears to be due to one or more reactive metabolites, rather than the parent molecule; and secondly, the metabolism of vinyl chloride is a saturable, dose-dependent process. The rate of formation of the carcinogenic metabolites is limited by the metabolism of the parent compound, and once the enzyme systems responsible (alcohol dehydrogenase and cytochrome P-450) become saturated, administering a larger dose of vinyl chloride may not necessarily result in a significantly greater tumor incidence.

Exposure concentrations above 250 ppm may exceed the metabolic capacity of these enzymes, and thus exposures to higher concentrations have to be evaluated with this caveat in mind.

There are many inherent difficulties and uncertainties involved in using animal data to determine human risk. Because of this, risk estimates have been calculated from different species, sexes, experiments and tumor types. Several adjustments need to be made to the experimental exposure data to calculate the lifetime daily exposure (LDE) levels.

Thus, for inhalation exposures, the reported dose must be multiplied by:

H/24: where H is the hours of exposure per day. This converts the exposure period to a time weighted average for 24 hours daily continuous exposure.

D/7: where D is the number of days exposed per week. This converts the dosing schedule to a time-weighted average for a seven day/week continuous exposure.

Le/L: where Le is the length of the experiment and L is the lifespan of the animal (the longer of Le or 24 months). This converts the experimental protocol to a continuous lifetime exposure.

The staff of DHS has used the linearized multistage computer program GLOBAL86 to calculate potential risks associated with vinyl chloride exposure. The multistage model may be expressed as:

$$P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)}$$

where P(d) is the lifetime probability of cancer for a given dose d of carcinogen, q_0 is a constant that accounts for the background incidence of cancer occurring in the absence of carcinogen, and q_1, q_2, ... q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen to obtain the best fit of the model to the data.

8.2 Analysis of Data from Maltoni et al.

The most sensitive site, sex and species in which a significant increase in tumor formation was observed following exposure to vinyl chloride appear to be the mammary gland in female Sprague-Dawley rats from the Maltoni et al. BT15 experiment (Table 7-8). A statistically significant increase in malignant mammary gland tumors was observed following a one year exposure to levels as low as 5 ppm. This experiment (BT15) has several potential problems associated with it: 1) the observed mammary tumor incidence in both treated and control animals was elevated compared to the results obtained from other Maltoni et al. vinyl chloride experiments (Table 7.8); and 2) there is no observable dose-response trend over the entire dose range of the experiment (0-25 ppm); tumor incidence at the 5 ppm dose level was greater than at the 25 ppm level. Risk estimates can be calculated by the linearized multistage model for both the entire dose range as well as for the first three doses (0, 1, and 5 ppm) where the tumor incidence increases with the dose. The 95% upper confidence interval of the cancer potency slope for mammary tumors for the entire exposure protocol in BT15 suggests a lifetime risk of

2.4 x 10^{-4}/ppb; analyzing just the 0, 1, and 5 ppm dose levels yields a risk estimate of 1.9 x 10^{-3}/ppb. However, there do not appear to be any scientifically justifiable reasons for dropping the two upper doses from the analysis; DHS staff therefore recommends that the value of 2.4 x 10^{-4}/ppb derived from the incidence of mammary gland carcinomas in female rats for the entire exposure range from the BT15 experiment be used as an estimate of risk from vinyl chloride exposure. Risk estimates for mammary gland carcinomas for other Maltoni et al. experiments which demonstrated a significant increase in tumor formation are lower than that derived from the BT15 data (Table 8.1).

Maltoni et al. also observed significant increases in the induction of liver angiosarcomas (LAS) following a one-year exposure of rats to vinyl chloride (Table 7.7). Although there is substantial variability in the different data sets, all experiments show a clear trend towards an increased incidence of LAS, a relatively rare tumor response in laboratory animals. The incidence of LAS in control groups of the experiments evaluated herein is consistent with the low historical control value of 2/541 claimed by Maltoni et al. (1984). These tumors were observed in female rats at experimental exp sures as low as 10 ppm (1/46). Female rats were more sensitive than males to the oncogenic effects of vinyl chloride in all Maltoni et al. experiments (Table 7.7). This increased sensitivity is reflected in the risk estimates (Table 8.1). Risk values for LAS range from 9.0 x 10^{-7}/ppb for male rats in the BT1 experiment to 7.4 x 10^{-5}/ppb for female rats from the BT15 experiment.

For some of the inhalation experiments, exposures greatly exceeded the metabolic capability of the enzyme systems involved. Based on the studies of Bolt et al. (1977) and Hefner et al. (1975b), it appears that metabolic saturation is reached at vinyl chloride concentrations of approximately 250 ppm. Maltoni et al. exposed animals to doses as high as 30,000 ppm. Exposure levels in the Bi et al. study reached 3,000 ppm. Tumor incidence and risk estimates derived from the groups exposed to concentrations greater than 250 ppm may not accurately reflect the oncogenic potential of vinyl chloride. Thus, although risk estimates for the entire range of exposures from the Maltoni et al. BT1 experiment and the Bi et al. study have been calculated, DHS staff recommends that only the risk estimates based on exposures of less than 250 ppm be considered valid estimates of cancer risk. This choice preempts the need to adjust for saturation in the risk calculations since many experimental results using animals exposed to concentrations below 250 ppm are available. Table 8.1 gives risk estimates calculated by the linearized multistage model for LAS and other tumor types from both male and female rats for inhalation experiments done by Maltoni et al., Bi et al., and Drew et al. for the entire exposure range, as well as for exposures of less than 250 ppm.

8.3 Analysis of Data from Bi et al.

Bi et al. (1985) measured liver and lung angiosarcomas in rats following an 18-month exposure to either 0, 10, 100, or 3000 ppm vinyl chloride. A significant increase in tumor induction at both

sites was observed, especially for the high-dose group. The vinyl chloride concentration in the high-dose group would almost certainly have saturated the metabolizing enzymes involved. Since lung cancers have been linked to vinyl chloride in occupationally exposed workers, risk estimates for lung angiosarcomas have been estimated using the data of Bi et al. (1985). Risk estimates for liver and lung angiosarcomas for exposure scenarios of 0 to 100 ppm and 0 to 3000 ppm have been calculated, and are included in Table 8.1. Risks based on the 0 to 100 ppm exposure range are substantially greater. The risk for liver angiosarcomas calculated from the 0 to 100 ppm data was 3.6×10^{-5}/ppb, while the risk for lung angiosarcoma for the same group was 1.6×10^{-6}/ppb.

8.4 Analysis of Data from Drew et al.

Drew et al. evaluated the effects of age and length of exposure on vinyl chloride-induced carcinogenicity in female rats, mice and hamsters (Drew et al., 1983). Female Golden Syrian hamsters, F-344 rats, CD-1 Swiss mice, and B6C3F1 mice were exposed to 200, 100, 50 and 50 ppm vinyl chloride, respectively, six hours/day, five days/week for 6, 12 and 18 months. These doses are established carcinogenic levels of vinyl chloride for each species. The rats and hamsters also underwent exposure periods of up to 24 months. The risk assessments were based on those exposure durations demonstrating the greatest tumorigenic response in each species. Because exposure scenarios were limited to a single concentration per species, lifetime daily exposure equivalents were calculated using the

different exposure lengths as the primary variable (instead of the dose, as is more customary).

Hemangiosarcoma was the most sensitive tumor type, and the most sensitive sex and species were female B6C3F1 mice. Except for female F-344 rats, the authors made no distinction between liver hemangiosarcomas and hemangiosarcomas found at other sites. Hemangiosarcomas in B6C3F1 mice yielded a risk estimate of 4.2×10^{-4}/ppb. The 95% upper confidence interval for mammary gland carcinomas in female CD-1 Swiss mice suggest a risk of 6.1×10^{-4}/ppb. The most sensitive tumor site in female F-344 rats was the liver hemangiosarcoma, with an estimated risk value of 3.7×10^{-5}/ppb; for female Syrian golden hamsters, mammary gland carcinoma was the most sensitive site, with a risk value of 5.3×10^{-5}/ppb. The risk estimates for these and the remainder of the Drew et al. study are found in Table 8.1.

8.5 Human Studies

The prior review of the epidemiological studies (Section 7.2 of this document) strongly suggests a causal association between vinyl chloride and several different types of cancer, including liver, lung, and brain. Although exposure data from the occupational cohort studies were inadequate to derive a dose-response curve, other historical industrial hygiene data can be used to reconstruct a range of likely exposures from which risk estimates can be derived (Appendix B). Using this approach the exposure level associated with

a one in a million risk for these carcinogenic endpoints was estimated as 0.485 ppb and the estimated risk per ppb as 2.1×10^{-6}/ppb (Appendix B, Table D). If the assumption is made that just liver cancer (the tumor type for which the epidemiologic evidence is strongest) is associated with vinyl chloride exposure, the risk per ppb is estimated to be 1.0×10^{-6}/ppb. In a more recent study of vinyl chloride workers, Heldaas et al. (1984) linked vinyl chloride exposure with malignant melanomas of the skin, lung cancer, colon cancer, and thyroid cancer, strengthening the association between vinyl chloride exposure and the development of human cancers.

8.6 Choice of Appropriate Risk Estimates

Table 8.1 has identified a range of human and animal cancer potency values (q_1^*) from vinyl chloride inhalation carcinogenicity studies in laboratory animals. These potency values can be converted to risk estimates by the equation: dose x potency = risk. Therefore,

$$1 \text{ ppb} \times \left[3.9 \times 10^{-6} \text{ (ppb)}^{-1}\right] = \text{a risk of } 3.9 \times 10^{-6}$$

for a lifetime exposure to 1 ppb vinyl chloride. Human risk was estimated from rodent data as follows:

$$\text{Estimated Human Risk} = \text{Rodent Risk} \left[(I_R/I_H) \times (W_H)^{2/3}/(W_R)^{2/3}\right]^{-1}$$

where I_R and I_H are the inhalation rates of rodents and humans, respectively, and W_R and W_H are the body weights of rodents and humans, respectively. Humans are assumed to weigh 70 kg and inhale 20 m^3/day. The inhalation rates (I) for mice and rats were estimated using the following formulas (EPA, 1985):

$$\text{For mice: } I = 0.0345 \left[\text{wt (kg)}/0.025 \text{ (kg)}\right]^{2/3} \text{ m}^3/\text{day}$$

$$\text{For rats: } I = 0.0105 \left[\text{wt (kg)}/0.113 \text{ (kg)}\right]^{2/3} \text{ m}^3/\text{day}$$

The inhalation rate for hamsters was assumed to be 0.086 m^3/day (Biology Data Book, 1974). Rodent bodyweight values for the studies of Maltoni et al. (1984) and Bi et al. (1985) were derived from data provided in the respective publications. Rodent bodyweights were not given for the Drew et al. (1983) study, and were estimated to be 300 g for rats, 30 g for mice, and 92 g for hamsters.

Human risks associated with vinyl chloride exposure as estimated from the animal data range from 2.4 x 10^{-6}/ppb to 5.0 x 10^{-3}/ppb, as shown in Table 8.2. Due to reasons previously discussed (which include metabolic saturation and experimental variability), the staff of DHS believes that a more appropriate range of risks lies between 3.9 x 10^{-6}/ppb and 1.8 x 10^{-3}/ppb (Table 8.3). Using data from Maltoni and Lefemine (1975), the EPA (1984) calculated a unit risk of 6.8 x 10^{-6} $(ppb)^{-1}$. This was converted to a human q_1^* of 2.5 x 10^{-2} $(mg/kg/day)^{-1}$, equivalent to a q_1^* of 1.8 x 10^{-5} $(ppb)^{-1}$. The human q_1^*'s from the analysis herein range from 3.9 x 10^{-6} $(ppb)^{-1}$ to 1.8 x

$10^{-3}(ppb)^{-1}$, a range which includes the EPA's potency value of $1.8 \times 10^{-5}(ppb)^{-1}$.

Appendices B and C detail the calculation of human risk from estimates of occupational vinyl chloride exposure, determined to be 2.1×10^{-6}/ppb. Considering the potential differences in exposure duration, oncogenic sensitivity of different species, age of exposure, sex, and levels of exposure, the estimated unit risk values for the human epidemiologic data and those calculated from animal data are consistent with one another. Since many of the tumors associated with vinyl chloride exposure (particularly LAS) exhibit a long latency period, exposure at an early age would produce a greater risk. The average latency period for the development of LAS in occupationally exposed vinyl chloride workers was determined to be 22.1 years (Stafford, 1983). Drew et al. (1983) demonstrated that in rats, mice and hamsters, the highest incidence of neoplasms was observed when vinyl chloride exposure was started early in life. Exposures early in life may produce up to a 10-fold greater incidence in tumors compared to exposures late in life. The BT15 experiment by Maltoni et al. (1984) suggests that mammary gland carcinoma may be a more sensitive indicator of vinyl chloride exposure than LAS, with risk estimates of 6.3×10^{-4}/ppb and 1.9×10^{-4}/ppb for the tw tumor types, respectively. Also, examination of the Drew et al. data (Table 8.3) indicates that the mammary gland is a more sensitive endpoint than LAS. Thus, it is possible that an epidemiologic study of adult males measuring the incidence of LAS may underestimate the actual risk associated with vinyl chloride exposure. Although there

are significant difficulties associated with extrapolating between animals and humans, the animal studies have the benefit of examining both sexes for a greater proportion of their lifetimes. The human epidemiology studies have been conducted primarily in adult male vinyl chloride workers, which may not adequately estimate risks for the general population.

TABLE 8.1. RANGE OF CANCER POTENCY VALUES FOR
VINYL CHLORIDE CALCULATED FROM ANIMAL CARCINOGENICITY STUDIES

Experiment	Species and Sex	Tumor Type	Experimental Exposures (ppm)	LDE (ppm)[1]	q_1^* animal[2] $(ppb)^{-1}$
Maltoni et al.					
BT1	rat, male	LAS[3]	0-10,000	0-595	9.0×10^{-7}
	rat, female	LAS	0-10,000	0-595	2.7×10^{-6}
	rat, female	LAS	0-250	0-14.9	1.5×10^{-6}
BT2	rat, female	LAS	0-200	0-11.9	1.5×10^{-5}
	rat, female	mammary gland	0-200	0-11.9	1.3×10^{-5}
BT9	rat, male	LAS	0-50	0-3	2.6×10^{-5}
	rat, female	LAS	0-50	0-3	6.0×10^{-5}
	rat, female	mammary gland	0-50	0-3	1.6×10^{-4}
BT15	rat, male	LAS	0-25	0-1.5	2.9×10^{-5}
	rat, female	LAS	0-25	0-1.5	7.4×10^{-5}
	rat, female	mammary gland	0-25	0-1.5	2.4×10^{-4}
	rat, female	mammary gland	0-5	0-0.3	1.9×10^{-3}
Bi et al.	rat, male	LAS	0-3000	0-482.1	8.1×10^{-6}
	rat, male	LAS	0-100	0-16.1	3.6×10^{-5}
	rat, male	lung angiosarcoma	0-3000	0-482.1	2.3×10^{-6}
	rat, male	lung angiosarcoma	0-100	0-16.1	1.6×10^{-5}
Drew et al.	rat, female	LAS	0-100	0-17.9	3.7×10^{-5}
	rat, female	mammary gland	0-100	0-8.9	3.1×10^{-5}
	rat, female	hepatocellular carcinoma	0-100	0-17.9	1.7×10^{-5}
B6C3F1	mouse, female	hemangiosarcoma	0-50	0-4.5	4.2×10^{-5}
B6C3F1	mouse, female	mammary gland	0-50	0-2.2	2.5×10^{-4}
CD-1	Swiss mouse, female	hemangiosarcoma	0-50	0-4.5	1.5×10^{-4}
CD-1	Swiss mouse, female	mammary gland	0-50	0-2.2	6.1×10^{-4}
CD-1	Swiss mouse, female	lung carcinoma	0-50	0-4.5	1.2×10^{-4}
	hamster, female	hemangiosarcoma	0-200	0-2.2	2.5×10^{-5}
	hamster, f male	skin carcinoma	0-200	0-17.9	2.0×10^{-5}
	hamster, female	mammary gland	0-200	0-17.9	5.3×10^{-5}

[1]LDE - Lifetime Daily Exposure (in ppm) [2]95% Upper Confidence Interval [3]LAS - Liver Angiosarcoma

TABLE 8.2. RANGE OF HUMAN RISKS FOR VINYL CHLORIDE EXPOSURE ESTIMATED FROM ANIMAL CARCINOGENICITY STUDIES

Experiment	Species and Sex	Estimated Weight (kg)	Estimated Inhalation Rate (m^3/day)	Estimated Human Risk/ppb
Maltoni et al.				
BT1	rat, male	.425	.254	2.4×10^{-6}
	rat, female	.275	.190	7.1×10^{-6}
	rat, female	.275	.190	3.9×10^{-5}
BT2	rat, female	.275	.190	3.9×10^{-5}
	rat, female	.275	.190	3.4×10^{-5}
BT9	rat, male	.600	.320	6.8×10^{-4}
	rat, female	.400	.244	1.6×10^{-5}
	rat, female	.400	.244	4.2×10^{-5}
BT15	rat, male	.600	.320	7.6×10^{-5}
	rat, female	.400	.244	1.9×10^{-4}
	rat, female	.400	.244	6.3×10^{-4}
	rat, female	.400	.244	5.0×10^{-3}
Bi et al.	rat, male	.300	.201	2.1×10^{-5}
	rat, male	.300	.201	9.5×10^{-5}
	rat, male	.300	.201	6.0×10^{-6}
	rat, male	.300	.201	4.2×10^{-6}
Drew et al.	rat, female	.300	.201	9.7×10^{-5}
	rat, female	.300	.201	8.1×10^{-5}
	rat, female	.300	.201	4.5×10^{-5}
B6C3F1	mouse, female	.030	.039	1.2×10^{-4}
B6C3F1	mouse, female	.030	.039	7.3×10^{-5}
CD-1	Swiss mouse, female	.030	.039	4.4×10^{-4}
CD-1	Swiss mouse, female	.030	.039	1.8×10^{-3}
CD-1	Swiss mouse, female	.030	.039	3.5×10^{-4}
	hamster, female	.092	.086	7.0×10^{-5}
	hamster, female	.092	.086	5.6×10^{-5}
	hamster, female	.092	.086	1.5×10^{-4}

Se text for discussion of estimating the inhalation rat and human risk.

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TABLE 8.3. SELECTED HUMAN RISK ESTIMATES
FOR LIFETIME EXPOSURE TO 1 PPB VINYL CHLORIDE[1]

Experiment	Species and Sex	Most Sensitive Tumor Site	95% Upper Confidence Interval (risk/ppb)
Maltoni et al.			
BT1	rat, female	LAS[2]	3.9×10^{-6}
BT2	rat, female	LAS	3.9×10^{-5}
BT9	rat, female	LAS	1.6×10^{-4}
	rat, male	LAS	6.8×10^{-5}
BT15	rat, female	mammary gland	6.3×10^{-4}
	rat, female	LAS	5.0×10^{-3}
Bi et al.	rat, male	LAS	9.5×10^{-5}
	rat, male	lung angiosarcoma	4.2×10^{-6}
Drew et al.	rat, female	LAS	9.7×10^{-5}
B6C3F1	mouse, female	hemangiosarcoma	1.2×10^{-4}
CD-1	Swiss mouse, female	mammary gland	1.8×10^{-3}
	hamster, female	mammary gland	1.5×10^{-4}
Appendices B and C	human, male	liver	1.0×10^{-6}
	human, male	liver, lung and brain	2.1×10^{-6}

[1]Estimates were selected on the basis of the most sensitive species, sex, and tumor site for experimental exposure scenarios of less than 250 ppm

[2]LAS = Liver Angiosarcoma

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9.0. CONCLUSIONS

9.1 Acute Toxicity

Vinyl chloride has a relatively low degree of acute toxicity in experimental animals; two-hour inhalation LD_{50} values are greater than 200,000 ppm in several species. Exposure to high concentrations can lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis and death. Several human deaths have been attributed to occupational exposure to very high levels of vinyl chloride. Autopsies of these patients revealed congestion of the liver, spleen and kidneys.

9.2 Subchronic and Chronic Toxicity

Chronic exposure of workers to vinyl chloride has been shown to lead to "vinyl chloride disease", characterized by occupational acro-osteolysis, vasospasm of the hands similar to Raynaud's syndrome, dermatitis, circulatory and central nervous system alterations, thrombocytopenia, splenomegaly and changes in liver function (Veltman et al., 1975). Spirtas et al. (1975) measured the frequency of eight symptoms commonly reported by workers exposed to vinyl chloride (including dizziness, headaches and nausea) and observed a dose-response relationship using exposure levels estimated from job classifications. These symptoms were observed even at dose levels below 50 ppm.

9.3 Pharmacokinetics

Approximately 42% (but up to 71%) of an inhaled dose of vinyl chloride was absorbed by both man and rats. Oral exposure results in more complete absorption. Radiolabeled vinyl chloride metabolites have been detected in a range of tissues, suggesting thorough distribution. Most of the metabolized vinyl chloride is excreted by the kidney, often as glutathione conjugates. Unmetabolized vinyl chloride is eliminated primarily by pulmonary excretion.

Both alcohol dehydrogenase and cytochrome P-450 are involved in the metabolism of vinyl chloride. The evidence suggests that reactive metabolites may be responsible for the toxic effects of vinyl chloride, with the most likely candidates thought to be chloroethylene oxide and chloroacetaldehyde.

The metabolism of vinyl chloride appears to be dose-dependent and saturable, with higher doses incompletely metabolized. It has been suggested that saturation of the metabolizing enzymes occurs at exposure scenarios between 100 and 300 ppm, with 250 ppm chosen herein as the concentration necessary to achieve metabolic saturation.

9.4 Reproductive Toxicity

No teratogenic or embryotoxic effects were observed in mice, rats or rabbits exposed to vinyl chloride at maternally toxic doses during gestation. A recent study has suggested that vinyl chloride can cross the placental barrier of exposed pregnant female rats and cause liver cancer and angiosarcoma in the offspring. Epidemiologic studies have suggested a possible increased rate of fetal deaths in women whose husbands were occupationally exposed to vinyl chloride. However, additional studies have concluded that there was no association between vinyl chloride exposure and fetal deaths or birth defects.

9.5 Mutagenicity

Vinyl chloride has been identified as a mutagen in bacteria, yeast and animal systems, both with and without addition of an exogenous metabolic activation system. Chloroacetaldehyde and chloroethylene oxide, the putative toxic metabolites of vinyl chloride, were also mutagenic. Levels of chromosomal aberrations and sister chromatid exchanges were higher in workers exposed to vinyl chloride (20 to 150 ppm) than for unexposed control groups. Workers exposed to less than 15 ppm showed no differences in chromosome breaks or aberrations from controls.

9.6 Carcinogenicity

Both experimental animal studies and epidemiological studies of worker populations have demonstrated that vinyl chloride is carcinogenic. The International Agency for Research on Cancer (IARC) reviewed the literature on vinyl chloride mutagenicity and carcinogenicity and concluded that vinyl chloride is a proven human carcinogen (IARC, 1979) and placed vinyl chloride in its carcinogenicity group 1. Substances assigned to this category have demonstrated sufficient evidence to support a causal association between exposure and cancer in humans.

IARC also noted that, "...several independent but mutually confirmatory studies have shown that exposure to vinyl chloride results in an increased carcinogenic risk in humans, involving the liver, brain, lung and hemolymphopoietic systems in man." They also noted in "two proportionate mortality studies ... there appeared to be an increased proportion of cancer of the digestive system in both sexes and possibly of the urinary system and of the breast in woman," and "there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans" (IARC, 1979).

The Environmental Protection Agency (EPA, 1984b) has likewise reviewed the data and also concluded that vinyl chloride is a proven human carcinogen. The EPA placed vinyl chloride in its group A as a proven human carcinogen.

Although both EPA and the National Academy of Science have concluded that there were insufficient data to base a quantitative carcinogenic risk assessment from epidemiological studies, DHS staff have included a human risk assessment using an estimation of exposure made by Barnes (1976) and Paddle (1986) (see Appendices B and C). The estimated incremental lifetime risk of liver, lung, and brain tumors as a result of vinyl chloride exposure is 2.1 x 10^{-6}/ppb. This risk is several orders of magnitude lower than that calculated from data for female mouse liver angiosarcomas or mammary gland carcinomas (Drew et al., 1983).

The animal studies demonstrated a relationship between tumor formation and the sex and age of the animal at first exposure. Fetuses, newborns, younger animals, and females exhibited the highest carcinogenic sensitivity (Drew et al., 1983). In the epidemiological studies of vinyl chloride workers, who were predominantly male, the average age at first exposure was 29.7 years. Thus, to protect all members of the general population, it is more appropriate to base risk assessment calculations on the animal inhalation studies, which were based on a more representative portion of the population actually at risk.

The staff of the Department of Health Services conclude that:

1. Vinyl chloride is mutagenic and a proven animal and human carcinogen.

2. Since vinyl chloride is genotoxic and there is no experimental evidence that vinyl chloride has a carcinogenic threshold, it should not be considered to have one. Animal evidence has demonstrated that vinyl chloride is carcinogenic at a lifetime daily exposure of 0.06 ppm. Potential human residential exposures may be only from six to 60-fold lower than those in the animal studies.

3. Vinyl chloride has been demonstrated to cause a number of malignant tumor types in animals, including angiosarcoma of both the liver and lung, hepatocellular carcinomas, several different lung tumors, brain tumors, and other types of cancers. Vinyl chloride has been shown to cause liver angiosarcoma in humans and epidemiological evidence suggests that vinyl chloride may induce lung, breast, and brain tumors. Vinyl chloride has been demonstrated to be multisite carcinogen, and the risk analysis performed by the staff of DHS reflects this finding.

4. Quantitative risk assessments of the relevant animal inhalation studies of vinyl chloride using the linearized multistage model have suggested a range of potential human risks from 1.8×10^{-3}/ppb to 3.9×10^{-6}/ppb (Table 8.2). The human risk from occupational vinyl chloride exposure has been estimated herein to be 2.1×10^{-6}/ppb (Appendices B and C). Thus, alth ugh the human risk estimate is based on a historical reconstruction of occupational exposures, it is close to the range estimated from animal studies. Vinyl chloride has not been detected in

the ambient air of California (limit of detection = 0.5 ppb). The California Air Resources Board has monitored vinyl chloride emissions from the BKK landfill in West Covina and the OII landfill in Monterey Park. Estimates of peak exposure concentrations for maximally exposed receptors range from 2 to 10 ppb at the BKK landfill and 0.6 to 9 ppb at the OII site. The Air Resources Board has estimated that between 17,000 and 131,000 individuals may be exposed to 1 ppb at the BKK site. A lifetime exposure of 131,000 residents to 1 ppb would be associated with an upper bound estimate of 0.5 to 236 excess cancer cases. These calculations represent an upper range of plausible excess cancer risk: the actual risk, which cannot be calculated, may be insignificant.

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Appendix A

Abstracts of Maltoni et al. (1984)

Bioassays

Intraperitoneal Administration

Rats: Groups of 30 male and 30 female 13-week-old Sprague-Dawley rats received an intraperitoneal injection of 4.25 mg vinyl chloride in oliv oil on 1, 2, 3, or 4 occasions over a two-month period and observed for the duration of their lives (145 weeks). One nephroblastoma and one subcutaneous angiosarcoma were found. No difference in survival or body weight was observed between test animals and controls. This experiment was considered inadequate for the determination of the carcinogenic potential of vinyl chloride because of the unconventional dosing protocol used (Experiment BT12, Maltoni et al., 1984).

Subcutaneous Administration

Rats: In a separate study, a group of 75 male and female Sprague-Dawley rats was administered a single subcutaneous injection of 4.5 mg vinyl chloride in 1 ml olive oil at 21 weeks of age and observed for the remainder of their lifetime (145 weeks after injection). Body weight and survival were not significantly different between controls and treated animals. One nephroblastoma in a treated male was observed (Experiment BT13, Malt ni et al., [redacted] ufficient protocol prevents any assessment f the carci[redacted] chloride from this experiment.

Transplacental Exposure

Rats: Groups of pregnant female Sprague-Dawley rats were exposed from day 12 to day 18 of gestation to 6,000 or 10,000 ppm vinyl chloride. The

females and offspring were observed for their lifetimes (143 weeks after start of experiment). Survival of the offspring was poor after week 95 of the experiment. Several animals from both groups exposed in utero had mammary tumors, zymbal gland carcinoma, leukemias and nephroblastomas; no hepatic angiosarcomas or hepatomas were reported. No results from control animals were reported, thus statistical evaluation of these results is not possible. Only a few tumors were found in the female breeders (Experiment BT5, Maltoni et al., 1984; IARC, 1979).

Transplacental-Inhalation Exposure

Rats: Groups of 12-week-old pregnant Sprague-Dawley rats were exposed to either 0 or 2,500 ppm vinyl chloride four hours/day, five days/week for seven weeks, then seven hours/day for 69 weeks, after which time all animals died. One group of offspring was first exposed transplacentally from day 12 of gestation, then exposed by inhalation after birth using the same protocol. A second group of offspring was also exposed transplacentally from day 12 of gestation but was exposed by inhalation four hours/day, five days/week for seven weeks, then seven hours/day, five days/week for eight weeks. Vinyl chloride was toxic at all concentrations tested: all animals exposed to vinyl chloride for 76 weeks died by that time, whereas the control animals survived for up to 150 weeks. The poor survival of treated animals certainly diminished the number of observed tumors, especially tumors with long latency periods, such as liver angiosarcomas. An increased incidence of zymbal gland tumors (8/54), liver angiosarcomas (27/54), hepatomas (5/54), and neuroblastomas (32/54) were reported for the

breeding females exposed to vinyl chloride, compared to 1/60, 0,60, 0/60, 1/60, respectively, in the controls.

In the male offspring exposed to vinyl chloride for 76 weeks, 9/63 had zymbal gland carcinomas, 36/63 had liver angiosarcomas, 27/63 had hepatomas, and 31/63 had neuroblastomas, compared to 2/158, 0/158, 1/158, and 0/158, respectively, in the controls. In the female offspring exposed to vinyl chloride for 76 weeks, 6/64, 28/64, 38/63, and 28/64 were reported for these above tumors respectively compared to zero tumor incidence in the controls. The incidence of these same tumors in the male offspring exposed t vinyl chloride for only 15 weeks was 7/59, 24/59, 42/59, and 7/59 for the same tumors respectively, compared to 2/158, 0/158, 1/158, and 0/158, respectively, in the controls. In female offspring exposed for only 15 weeks, the incidence was 2/60, 28/60, 43/60, and 11/60 for the same tumors, respectively, compared to a zero incidence of these tumors in c ntrols. These studies (BT4001, BT4006) were cited by Maltoni and colleagues (1984) as an example of transplacentally-induced-tumorigenesis, but was, in effect, an investigation of the increased sensitivity of young experimental animals to the toxic effects of vinyl chloride. The tumor incidence in breeders and offspring exposed to vinyl chloride for 76 weeks did not appear to differ signifi[redacted]he increased tumor incidence in offspring exposed to vinyl[redacted] weeks appear to differ substantially from the tumor incid[redacted] breeders. However, no explicit statistical comparison of these parameters was made in the report (Maltoni et al., 1984; Experiments BT4001, BT4006).

Inhalation Exposure

Hamsters: Groups of 30 male Syrian golden hamsters were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm vinyl chloride, four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age. The hamsters were then observed for their lifespan (109 weeks). Two liver angiosarcomas were observed in the group exposed to 500 ppm vinyl chloride and one liver angiosarcoma was observed in the group exposed to 6,000 ppm. The increased incidence of forestomach epithelial tumors in hamsters exposed to 500 ppm or more of vinyl chloride appeared to be biologically significant but no statistics were reported (Experiment BT8, Maltoni et al., 1984).

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Appendix B

Cancer Risk Assessment for Vinyl Chloride Based On Human Data

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Introduction

The main problem with using epidemiological data for health risk assessment is the frequent lack of suitable quantitative exposure data. Exposure data from animal bioassays are, by comparison, markedly more accurate. However, a major source of potential error in using animal data for human health risk assessment is the animal-to-human extrapolation of risk. It follows that the decision to use epidemiological data in health-based risk assessments should not be based solely on contrasting the quality of exposure dat available for humans with that for animal studies, but should also take into account other important variables such as the observed tumor type and the latency period of the tumors under study.

In fact, the decision concerning use of human versus animal data in a health-based risk assessment should take into account the main source of error from each approach: the exposure data for human studies and the animal-to-human extrapolation for animal studies. In the latter cas , one would hope that the error in extrapolation to humans was within one order of magnitude. However, the adjustments made to correct for body surface area differences (when extrapolating from animal bioassays to humans) can in itself [redacted] of magnitude difference in estimates when compared to estim[redacted] a simple dose per body weight extrapolation. Since other [redacted] of error exist, the uncertainty of animal-to-human extrapolation probably lies within one or two orders of magnitude, except in the case where there may be no effect in an animal model but an effect in humans (or vice versa). In this case, the error would be infinite.

When human studies show a clear relationship between an outcome and an exposure, the question concerning their use in risk assessment should therefore be whether or not one can estimate exposure within one to two orders of magnitude. If sound human studies that enable exposure estimation within one to two orders of magnitude are available, then these studies should be utilized in addition to animal studies in evaluating the human health risk.

In the case of vinyl chloride, there are unequivocal epidemiological data that identify vinyl chloride as a human carcinogen. Although detailed exposure data for the relevant time periods are lacking, estimates can be made that should be well within one order of magnitude of error. While the methods for estimating past exposure are crude, the true exposure rates are considered unlikely to be more than five times higher or lower than estimated. It follows that the human data may be appropriate for vinyl chloride cancer risk assessment.

Identifying the Most Appropriate Study for Use in Vinyl Chloride Risk Assessment

A literature review was undertaken to assess available information regarding the [redacted] caused by exposure to vinyl chloride. The results of this review, presented in Tables B-1 and B-2, suggest that the cohort study reported by Waxweiler and co-workers contains the most thoroughly documented information for risk assessment purposes (Waxweiler et al., 1976). Eleven cases of angiosarcoma of the liver were identified among the 1,294 exposed workers. Three additional cases of biliary cancer were seen. Significant

excesses of both brain cancer and lung cancer were also observed. The Waxweiler report gives SMRs for liver cancer, brain cancer, and lung cancer. It is apparent from Table B-2 that the SMRs from Waxweiler et al. are consistent with some of the other studies. The cumulative risk of liver, lung and brain cancer following vinyl chloride exposure is greatest in the Waxweiler et al. (1976) report. Thus cancer risks to vinyl chloride workers are unlikely to be substantially underestimated by a risk assessment based on this study.

The results reported for the Waxweiler cohort of polyvinyl chloride (PVC) workers involved a subset who had worked for at least five years between 1942 and 1973 and who had commenced work at least ten years before follow-up was completed. Follow-up for mortality was to the end of 1973. This subset of the cohort was comprised of 1294 workers. There were 136 deaths during the follow-up period of which 35 were due to cancer. The SMR for biliary and liver cancer was 1155, for brain cancer, 329, and for lung cancer, 156.

The remainder of this appendix discusses the risk of liver, lung, and brain cancer for the workers in the Waxweiler et al. (1976) cohort. In addition, assessments evaluating the risks for each cancer have been recalculated, using [redacted] exposure estimations and assumptions described herein.

[redacted]

As in many retrospective cohorts, individual exposure data were not available (Waxweiler et al., 1976). However, several reports have attempted to reconstruct the magnitude of exposure among vinyl chloride workers since

the 1940's (Ott et al., 1976; Jones, 1974; Paddle, 1986). Table B-3 summarizes proposed estimates of exposure for several countries.

Most of the data available for specific United States exposure levels utilize measurements determined at a single plant operated by Dow Chemical Company (Jones, 1974). Although some job class exposures were quite high, most exposures were less than proposed international levels during commensurate time periods. However, Dow Chemical Company responded to early reports of vinyl chloride toxicity in animal studies by creating an in-house standard of 50 ppm (Ott et al., 1974; Paddle, 1986). This was well below the acceptable limit during the 1960's and early 1970's and probably does not represent the average exposure at other vinyl chloride polymerization plants. Dow Chemical Company had not reported any cases of angiosarcoma of the liver to 1985 (Forman et al., 1985).

Other exposure estimates, such as those presented by Barnes and summarized in Tables B-3 and B-5 of this appendix, may better describe average exposure for the Waxweiler et al. cohort (Barnes, 1976). Data were not given by Barnes to substantiate his exposure estimates, but rather he qualifies his estimates by stating: "the general consensus of opinion throughout the world [redacted] average atmospheric exposure for polymerization work[redacted] and 1970 might have been of the following order" (Table B-5) (Barnes, 1976). The Barnes estimates approach the existing standards during these time periods. Additionally, the exposure experience among cohorts with angiosarcoma of the liver should be higher when compared to exposure levels in cohorts reporting no angiosarcomas. Consequently, exposure estimates provided by Barnes are used to quantify cumulative vinyl

chloride exposure for the risk assessment since the group studied by Waxweiler et al. (1976) was presumably one of the most heavily exposed cohorts and therefore, unlikely to involve exposures lower than th se given by Barnes.

The employment dates of the Waxweiler et al. cohort span 1942-1973. Thus, some work histories fell below the boundary of the first time period provided by Barnes (January 1, 1945). These particular histories were counted separately and assigned an exposure level of 1000 ppm. This practice assumes exposure during early process days (pre-1945) t be the same as that during the 1945-1955 exposure period.

Methods For Using Average Cohort Exposure Data

Data for individual exposure estimates for the Waxweiler et al. occupational cohort do not exist. However, Appendix C of this document gives a meth d for incorporating average exposure data into a risk assessment analysis used in the following manner. Deaths due to angiosarcoma of the liver occurred between 1964 and 1979. The latency period between vinyl chloride exp sure and death due to angiosarcoma of the liver ranged from five t twe[redacted] et al., 1980). More recently, Stafford (1983) has calcu[redacted] latency period for angiosarcoma of the liver among vinyl chlorid[redacted] workers worldwide to be 22.1 years. The work histories for the cohort were analyzed to identify the person-time in each calendar year for the subset who had at least five years of employment and who began work (and thus vinyl chloride exposure) prior to 1964. These restrictions were incorporated to correspond to the same restrictions used by Waxweiler and

co-workers (1976) in generating their SMR values. Thus, the SMR values correspond to those workers with at least five years of exposure and at least a ten-year latency period from first exposure.

The analysis herein assumes that the average worktime cohort exposure for the period 1942 to 1964 was a time-weighted average of 647 ppm of vinyl chloride. The plant had begun operations in 1942. The year 1964 was chosen as an endpoint since 1969 was the midpoint of diagnosis of liver angiosarcoma cases and since exposures in the last five years preceding diagnosis were probably not relevant to etiology (Smith et al., 1980). It is assumed that this exposure rate was experienced for eight hours per day, five days per week, 46 weeks per year, and that, outside these times, the exposure to vinyl chloride was the same as for the general population. Thus, the average excess exposure per day is the average worktime exposure multiplied by (1/3) x (5/7) x (46/52) which equals 0.211. The average overall exposure rate above background for vinyl chloride workers was estimated to be 0.211 x 647 ppm or 136 ppm of vinyl chloride.

Lifetime Exposure Estimations and Risk of Liver Cancer

The [redacted] relate to workplace exposures occurring over a relat[redacted] period of time. The SMR for liver cancer was 1155. The avera[redacted] of employment for this cohort between 1942 and 1964 was 11.6 years and the average age at first exposure was 29.7 years. Based on the assumptions stated in Appendix C, the adjustment used to extrapolate to lifetime exposure is duration of employment/(age + duration of employment),

or 11.6/(29.7 + 11.6). Therefore, the average lifetime exposure estimated to result in a liver cancer SMR of 1155 is [(136 ppm)(0.281)] or 38.3 ppm.

Between 1960 and 1979, 67,782 deaths from liver cancer occurred among white males in the United States (International Classification of Diseases (ICD) codes 155,156). The total number of deaths among the same group was approximately 18,297,297. Thus, one in approximately 270 deaths was from liver cancer.

Since the workers under discussion in the Waxweiler et al. cohort had an SMR of 1155, their lifetime risk of dying from liver cancer would increase above the background rate of one in 270. An SMR of 1155 is equivalent to a relative risk of 11.55 (Symons and Taulbee, 1981). The lifetime risk of dying from liver cancer calculated herein for workers exposed to vinyl chloride is thus the relative risk multiplied by the background lifetime risk or 11.55 x 1/270. The added lifetime risk would be the excess relative risk times the background lifetime risk, or 10.55 x 1/270 = 1/25.6. Thus, the added lifetime risk of liver cancer attributable to an exposure rate causing an SMR of 1155 would be one in 25.6 on that lifetime exposure to 38.3 ppm of vinyl chloride would cause a 39,062 in a million increase in the [redacted] from liver cancer.

Cancer [redacted] Including Brain and Lung Cancer as Well as Liver Cancer

The same approach can be adopted for brain cancer and lung cancer. Evidence for their relationship to vinyl chloride exposure is discussed in th next

sections. In the absence of evidence to the contrary, it is assumed that the latency period is the same as for angiosarcoma of the liver. The number of deaths from brain cancer (ICD codes 191 & 192) between 1960 and 1979 in the United States was 79,847 (1/229 of deaths), and for lung cancer (ICD codes 160-163, 165) 978,504 (1/18.7 of deaths). Applying the same procedure indicated above, the added brain cancer lifetime risk was one in 100 and, for lung cancer, was one in 39.4, assuming the average exposure rate of 38.3 ppm.

Brain and Lung Cancer and Vinyl Chloride Exposure

While it is clear that exposure to vinyl chloride causes angiosarcoma of the liver, the causal relationship to brain and lung cancer is not so well-defined. One review suggested that there was a consistent relationship with brain cancer in occupational studies, but not with lung cancer (Beaumont and Breslow, 1981). However, it would seem appropriate to consider lung cancer in the risk assessment along with liver and brain cancer, since this is consistent with a conservative approach and the relationship with lung cancer cannot be rejected out of hand. In fact, the report referenced above focused on statistical power independent of the degree of exposure experienced by the various cohorts reviewed. The lung cancer findings become significant when considered in conjunction with the liver cancer excesses experienced by each cohort. Since excesses of liver cancer can be used as a surrogate indicator of exposure, this suggests that some studies not finding an excess of lung cancer may have been a result of relatively low exposures.

However, a more recent large study presents evidence against a relationship between lung cancer and vinyl chloride exposure (EHA, 1985). This study considered deaths between 1942 and 1982 inclusive for a cohort of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride. The SMR for liver cancer was 641, for brain cancer was 180, but for lung cancer was only 95.8. Most of the liver and brain cancer excess was in two of the 37 plants forming the cohort. Unfortunately, lung cancer SMRs were not presented for these two plants. In spite of this, the study provides evidence against a vinyl chloride-lung cancer association. However, without lung cancer data for the two plants with the highest liver and brain cancer excesses, it would seem inadvisable to completely exclude lung cancer from the risk assessment.

Confidence Limits for the Lifetime Risk Estimates

Confidence limits for the risk estimates are calculated by combining the risks for tumor development for each site (by summing observed and expected values for each site) and then calculating the 95% confidence limits of that single point estimate assuming a Poisson distribution. The 95% confidence interval for the liver cancer SMR is (467-2404). To estimate the upper 95% confi[redacted] the excess risk estimate, the upper limit f excess risk [redacted] 04) is multiplied by the lifetime risk for the average perso[redacted] from liver cancer (1/270). Therefore, the upper 95% confidance limit for the added risk due to vinyl chloride exposure is 23.04 x 1/270 = 0.085 or 1/11.7.

The same calculation is used to estimate the upper 95% confidence limit based on liver cancer and brain cancer combined. In this case, the combined observed and expected values for liver and brain cancer (7+3)/(0.6+0.9) results in 95% confidence interval for the SMR of (319 - 1226). Thus, the upper 95% confidence limit for the excess risk estimate is (12.26-1)(1/270+1/229), or 1/11.0.

For liver cancer, brain cancer, and lung cancer combined, the observed to expected ratio is 22/9.2 and the 95% confidence interval for the SMR is (149 - 362). Using the same strategy, the upper 95% confidence limit for the estimate of added risk is (3.62 - 1)(1/270 + 1/229 + 1/18.7), or 1/6.20.

Extrapolation of Risk to Low Dose Exposure

There are many models for extrapolating risks to low dose exposure. The method of analysis employed here gives only one exposure point and therefore limits the models that may be used. A linear extrapolation of excess risk was chosen as the most appropriate for this analysis. This approach is very close to a one-hit model extrapolation. In fact, the one-hit model extrapolation is very close to a multistage extrapolation with linearization as [redacted] U.S. Environmental Protection Agency (EPA) Carcinogen Assessment [redacted] for use with animal data. Thus, a simple linear extrapolation would provide similar results to the more complex multistage model approach that could have been used with more extensive data.

As indicated in the above section entitled "Lifetime Exposure Estimations and Risk of Liver Cancer", lifetime exposure to 38.3 ppm of vinyl chloride

is calculated to increase lifetime liver cancer risk by one in 25.6, or 39,062 in a million. The corresponding unit risk estimate for one in a million added risk is 0.98 ppb. Table B-4 gives corresponding results for the addition of brain cancer and lung cancer and the 95% confidence limits on unit risk exposures.

Assumptions and Uncertainties

The confidence limits that were calculated for the risk estimates measure only the uncertainty related to the SMR statistics for workers and do not measure the uncertainty of the risk assessment process overall. This risk assessment is based on specific assumptions which, if incorrect, affect the assessment by either overstating or understating the true risk. The assumptions are listed below.

1. Assumptions are made concerning the exposure estimates. This can affect the accuracy of the risk estimates in either direction.

2. The relationship between cancer relative risk and lifetime average exposure is assumed to be linear. If the relationship is better described by a supralinear curve, then a linear assumption will [redacted] Conversely, if the relationship is better described by a sublinear curve, then a linear assumption will overstate the risk.

3. It was assumed that cancer risks were dependent on cumulative exposure and not on exposure rate. A given cumulative exposure achieved as an

adult is assumed to carry the cancer risk equal to the same cumulative exposure starting at birth.

4. It was assumed that relative risk was dependent only on cumulative exposure and not on age.

5. Based on the pattern of excess exposure for this cohort (Smith et al., 1980), it was assumed that the dose accumulated five years prior to death was not relevant to causation of cancer.

6. The SMRs used were calculated using United States general population cancer rates. If national cancer rates were higher than local rates, the value of the SMR is underestimated, and vice versa.

7. It is assumed that lung cancer and brain cancer are causally associated with vinyl chloride exposure and that the dose accumulated in the five years immediately prior to death was not relevant to causation of cancer. If these cancers are not associated with exposure to vinyl chloride, then the true risk is overstated by including them in the analysis.

8. [redacted] the effect of a given cumulative exposure is th same [redacted]

Conclusions

This risk assessment analysis suggests that an average exposure to 38.3 ppm of vinyl chloride may result in an added lifetime cancer risk of 1/25.6 for

liver cancer, 1/100 for brain cancer, and 1/33.4 for lung cancer, assuming each cancer is related to vinyl chloride exposure.

If one adopts a linear extrapolation approach, one would conclude that an exposure to 0.485 ppb for a lifetime might result in a cancer risk of one in a million, if all these cancers are related to exposure. In the most likely case that only liver and brain cancer are related to exposure, an exposure to 0.781 ppb might result in a one in a million lifetime cancer risk.

TABLE B-1

COHORT CHARACTERISTICS OF SELECTED VINYL CHLORIDE STUDIES

Author	Cohort Size	Total No. of Deaths	Number of Cancer Deaths	Range of Exposure Duration Minimum	Maximum	Length of Longest Follow-up	Notes on Follow-up	Place of Company Involved
Byren et al., 1976	750		11	>0 yr 15% > 10 yrs		1940's - 1974	97%	Sweden
Cooper, 1981++	10173		139	> 1 yr	23 yrs	1948's - 1972	95%	37 Plants in United States
Duck et al., 1975	2120		36	>0 yr	> 15 yrs	1948 - 1974	99.6%	South Wales
Fox et al., 1977	7561		112	>0 yr 23% > 10 yrs, 8% > 20 yrs		1940 - 1975	99.1%	Great Britain
Heldaas et al., 1984	456	50	22	> 1 yr 35% > 5 yrs		1953 - 1979		
Monson et al., 1975++	6	161+	41			1946 - 1976	99.2%	Louisville, Kentucky
Nicholson et al., 1975	257	24	9	----------(not given)----------		1947 - 1975		New York
Tabershaw et al., 1976++	6384	352	79	> 1 yr	> 30 yrs	1930's - 1972	85%	33 Plants in United States
Takamura, 1983	4584	280	37	> 1 yr	> 15 yrs	1950 - 1975		Japan
Theriault et al., 1981	451	59	20	> 5 yrs	> 30 yrs	1963 - 1974	81% > 15 yrs, 23% > 29 yrs	Canada
Waxweiler et al., 1976++	1287	136	25	> 5 yrs	27 yrs	1940's - 1973	99.5%	4 Plants in United States
Weber et al., 1981	7821	414	94	30 yr	> 10 yrs	1940's - 1974	90%	West Germany
Wong et al., 1986++	10173	1536	359	>1 yr	30 yrs	1942 - 1982	92%	United States

*Proportional mortality study

++Overlapping cohorts of Goodrich company workers

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TABLE 5-2

STANDARD MORTALITY RATIOS (AND 90% CONFIDENCE INTERVALS)
FOR SELECTED VINYL CHLORIDE STUDIES

Author	Liver O	Liver E	Liver SMR	Liver 90% C.I.	Number of Liver Angiosarcomas	Lung O	Lung E	Lung SMR	Lung 90% C.I.	Brain (CNS) O	Brain (CNS) E	Brain (CNS) SMR	Brain (CNS) 90% C.I.
Byren et al., 1976	liver and [illegible] 4	0.97	[illegible]	[illegible], 843.9)	2	3	1.78	168	(45.5, 435.1)	2	0.33	612	(104.4, 1904.5)
Cooper, 1981*	digestive 29	40.8	[illegible]	[illegible], 88.9)	0	respiratory 25	23.9	107	(72.7, 146.1)	12	5.9	203	(117.3, 329.5)
Duck et al., 1975	digestive 11	11.09	99	(55.6, 164.2)	0	16	15.5	103	(64.7, 156.8)	-	-	-	-
Fox et al., 1977	4				2	46	51.23	89.8	(69.2, 114.8)	2	3.66	54.6	(9.4, 171.7)
Heldaas et al., 1984	1	1			1	5	2.84	180	(69.2, 370.8)	-	-	-	-
Monson et al., 1975#	biliary and liver 8	0.7	1100	(560.3, 2061.5)	5	13	7.9	160	(97.3, 261.6)	5	1.2	420	(163.8, 875.6)
Nicholson et al., 1975	3	0.12	2500	(675.2, 6454.2)	3	0	1.1	0		1	0.1	1000	(39.5, 4728.4)
Tabershaw et al., 1974*	digestive 19	21.67	94	(57.4, 128.6)	6	respiratory 25	23.93	112	(72.6, 165.9)	-	-	-	-
Takamura, 1983	6	2.54	236	(102.7, 466.0)	1	2	2.33	86	(14.8, 268.3)	-	-	-	-
Theriault et al., 1981	digestive 14	5.4	259	(156.7, 405.3)	8	respiratory 2	5.78	34.6	(6.0, 108.7)	0	0.6	0	
Waxweiler et al., 1976*	biliary & liver 7	0.6	1455	(569.0, [illegible])	[illegible]	respiratory 12	7.7	156	(89.9, 252.5)	3	0.9	329	(90.0, 860.6)
Weber et al., 1981	12	0.79	1523	(876.3, 2460.7)	4	-	-	-	-	2	1.23	162	(28.1, 511.0)
Wong et al., 1986*	liver and biliary 37	5.77	641.2	(478.2, 843.6)	[15]	185	[illegible]	4.2	(80.3, 110)	23	12.76	180	(123.2, 255.4)

*Overlapping cohorts of Goodrich company workers.

++[illegible] confirmed cases, irrespective of meeting the five-year exposure and ten-year latency criteria of this cohort study

90[illegible]. - 90% confidence interval

TABLE 8-3

HISTORIC EXPOSURE LEVELS (ppm): VINYL CHLORIDE

Standards	U.K. Borneo	Location Author Year	USA Barreto et al	USA Kramer & Hutchler	USA Cook et al	USSR Filatova & Gromberg	Lefevre et al	Romania Suciu et al	Hungary Anghelescu et al	Greece Gitsios	Sweden Byren & Holmberg
	1000	1950		Avg TWA in 1950-155 ppm							
		1951									
		1952									
MAC = 500 ppm		1953									
		1954				(Pub.1957) reactor area avg: 58-310 ppm					
		1955		TWA range for 1950-1965: 10-300 ppm		range: 15 ppm-16,000 ppm (16K-peak)					
	400-500	1956				precip. & centrifuge: 8 - 3850 ppm					
		1957				drying ovens: 4 - 15 ppm					
		1958									
		1959									
		1960									
		1961									
		1962									
		1963									
ACGIH = 100 ppm	300-400	1964		Avg. TWA in 1965-30 ppm		1965: highest measure = 115 ppm and 75% measures were > MAC of 12 ppm	500 ppm @ scrapers' hands				
		1965									
		1966									
		1967									
		1968	(Pub.1969) TWA range: 5-300 ppm peaks > 1000 ppm		(Pub.1970) resp.area: 50-100 ppm peaks: 600-1000 ppm @ scrapers' hands			(Pub. 1967) "levels ranged as high as 2.2 ppm"	(Pub. 1969) 43-213 ppm	(Pub. 1971) peak value= 10,000 ppm	(Pub. 1974) range in reactor area: 18-20 ppm
OSHA = 500		1969									
OSHA = 100		1970									
		1971									
	50	1972									
OSHA = 50		1973									
OSHA = 1	5	1974									
		1975									

MAC = Maximum Allowable Concentration
ACGIH = American Conference of Governmental Industrial Hygienists
OSHA = Occupational Safety and Health Administration
TWA = time weighted average (in ppm) based on an eight-hour day
ppm = part per million
range TWA = highest and lowest TWA reported
avg TWA = average TWA for that period
peaks = highest concentration reported (ppm). There is little documentation regarding frequency or duration of peaks
reactor area = work area around and within the vessel where polymerization took place
scraper' hands = after polymerization; workers entered vessel to scrape any buildup of polymer off the reactor vessel walls; measurements represented this exposure
precipitor, centrifuge and drying ovens = post polymerization work areas

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CMA 010512

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TABLE B-4

EXPOSURE LEVELS ASSOCIATED WITH
ONE IN A MILLION LIFETIME CANCER RISKS

Cancer Site	Most Likely	Upper 95% Limit	Lower 95% Limit
Liver	0.981 ppb	2.82 ppb	0.448 ppb
Liver and Brain	0.781 ppb	2.17 ppb	0.421 ppb
Liver, Lung and Brain	0.485 ppb	1.27 ppb	0.238 ppb

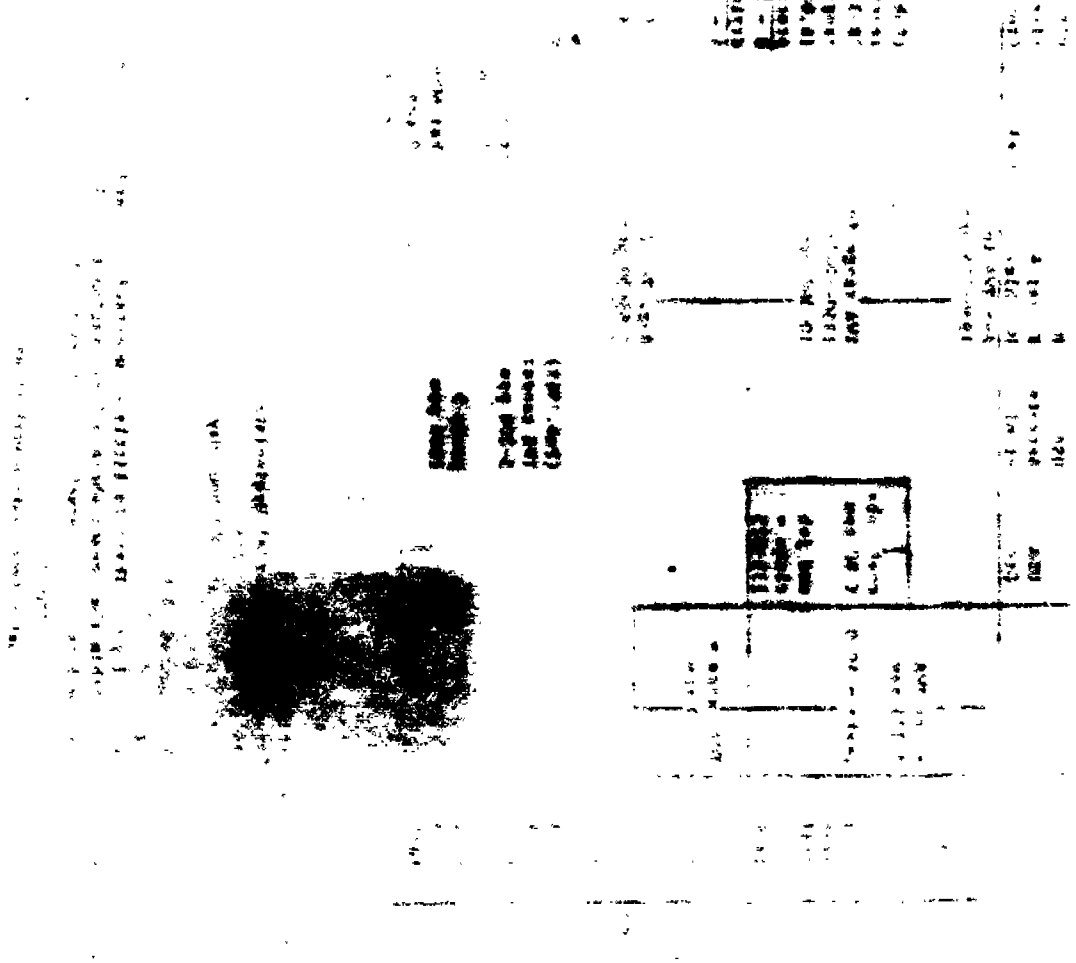

TABLE B-5

BARNES' EXPOSURE ESTIMATES[1]

Time Period	Exposure Estimate (ppm)
1945-1955	1000
1955-1960	400-500
1960-1970	300-400
Mid 1973	150
1975	5

[1]Barnes, 1976.

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TABLE B-6: HISTORICAL EVOLUTION OF OCCUPATIONAL EXPOSURE LIMITS[1, 2]

Year	Authority	Vinyl Chloride Limit (ppm)
1954	MAC [3]	500
1962	ACGIH[3]	500
1971	OSHA[3]	500
1972	OSHA	200
1974	OSHA	50 - temporary emergency standard over an eight hour period
Late 1974	OSHA	Proposed non-detectable limit
April 1975	OSHA	1 - averaged over eight hour period with a maximum of five for 15 minutes

[1]From Paddle Correspondence (1986)

[2]As a point of interest, Table F presents a summary of historical occupational standards for vinyl chloride.

[3]MAC - Maximum Allowable Concentration;
ACGIH - American Conference of Government Industrial Hygienists;
OSHA - Occupational Safety and Health Administration

CMA 010515

DRAFT

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CMA 010516

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CMA 010517

DRAFT

Appendix C

Using The Average Exposure Rate of a Cohort In Risk Assessment Analysis

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Introduction

Individual exposure data that could be used for health risk assessment are frequently not recorded in occupational health cohort studies. However, a reasonable estimate of health risk may be found in the average exposure that the cohort experienced in certain time periods. This appendix presents a method for using such data for risk assessment by employing certain assumptions.

Objectives in Risk Assessment

The primary objective behind health risk assessment is to contribute to risk management decision-making, including regulating permissible exposur levels. Workplace exposures and general environmental exposures are two major areas considered.

In the case of general environmental exposures, the underlying goal is to establish levels of exposure, which, if experienced over a lifetime, would result in levels of risk acceptable for the public.

The f[redacted]would thus involve lifetime exposure measurements at a serie[redacted] of exposure, the establishment of a dose-resp nse relationship, and the extrapolation of the data to low levels of exposure. Such human studies for vinyl chloride are not available. Animal studies of this agent may produce relevant information, but the extrapolation t humans may include large potential errors. The purpose of this paper is t present one approach to establishing exposure levels by using relevant human

information which, in the case of chemical exposures, usually involves occupational settings.

The Model

Consider a cohort of a number (N) of individuals who are exposed at constant rates to a particular chemical. The rates of exposure differ among the individuals, but each individual has a constant lifetime rate of exposure.

The model assumes a linear relationship between excess relative risk and the exposure rate:

$$RR - 1 = bE$$

where RR refers to relative risk, b is a constant, and E is an exposure rate (lifetime).

Strictly speaking, E is the difference in exposure between the study population and the comparison population used in calculating relative risk. However, the [redacted] of the comparison population is usually negligible when [redacted] that of the exposed study population. The exposed study popula[redacted] usually experiences the background population exposure. In the case of occupational exposures, estimation of workplace exposures effectively gives an estimate of the difference in the worker cohort exposure and that of the comparison population.

DRAFT

Assumption Concerning Age

The model assumes that a constant rate of exposure to the chemical over a lifetime results in a relative risk for a particular disease outcome that does not vary by age. This implies that exposure would have a multiplicative effect on background incidence rates. Such an assumption would follow from a multistage model situation in which the exposure of concern affected particular stages, while the background exposures predominantly affected other stages.

Variation in Exposure Rates

The model considers a cohort with a variety of exposure rates, but in which all individuals are of the same age. It includes a subcohort "i" within it that experiences exposure rate E_i, composed of individuals of the same age. For this subcohort:

$$RR_i - 1 = bE_i$$

If one uses an indirect standardization measure of relative risk such as the

[redacted]

where o_i is the observed number of cases with the disease in the subcohort and e_i is the expected number of cases based on some external "standard"

population. Hence,

$$\frac{o_i}{e_i} - 1 = bE_i.$$

Now for any one particular age group,

$$e_i = n_i e$$

where e is the expected number of deaths per person in the subcohort and n_i is the number of persons in subcohort i. Hence,

$$o_i = n_i e(1 + bE_i).$$

Summing overall exposure levels,

$$\Sigma o_i = \Sigma n_i e(1 + bE_i)$$

$$= Ne = \Sigma n_i ebE_i.$$

[redacted] number in the cohort [redacted] particular age [redacted]

$$= Ne + eb\Sigma n_i E_i$$

DRAFT

However,

$$\dot{E} = \frac{\Sigma n_i E_i}{N}$$

Hence,

$$\Sigma o_i = Ne + ebN\dot{E}$$

$$= Ne(1 + b\dot{E})$$

Now,

$$Ne = \Sigma e_i$$

Therefore,

$$\frac{\Sigma o_i}{\Sigma e_i} = 1 + b\dot{E}$$

and hence,

$$\hat{b} = \frac{\frac{\Sigma o_i}{\Sigma e_i} - 1}{\dot{E}}$$

gives an estimate of b.

Combining Age Groups

In each [redacted] can obtain an estimate of b as shown in the previous [redacted] average exposure rate. If one expands the summation over [redacted] we get the familiar standardized mortality ratio.

(SMR):

$$SMR = \frac{\Sigma o_i}{\Sigma e_i}$$

Assuming that the SMR is not age dependent, then the following equati n,

$$\hat{b} = \frac{(SMR-1)}{\dot{E}}$$

will provide an estimate of b, where Ė is now the average exposure rate for everyone in the cohort.

This estimate is based on the assumption that each individual experiences a constant exposure rate. It also implies that the constant exposure rate has been experienced for a lifetime, since no distinction has been made according to age.

Variation in Exposure Rates, Duration, and Age at Exposure

Most chemical risk assessments are based on occupational studies in which workers experience variation in exposure rates, variable exposure duration, and different ages at exposure. In the case of cancer, the risk assessment is also complicated by cancer latency.

To deal with the variable exposure rate, it will be assumed that the effect of exposure is related to the average exposure rate during relevant etiologic time periods. (This assumption is analogous to the assumption that risk is related to cumulative exposure independent of the pattern f exposure, for example the peaks or troughs of the exposure rate.)

To [redacted], the assessment of exposure rate will focus on relevant time periods in relation to dates of diagnosis. For example, the assessment of average exposure rate could be assessed up to a point in time 5 years before the mid-year of diagnosis of the cases.

DRAFT

Finally, to deal with lifetime exposure risks, an adjustment will be made for the age at first exposure. A linear relationship will be assumed between risk and duration of exposure. If the average duration of exposure up to 5 years before the mid-year of diagnosis is d, and if the average age at first exposure is a, then the calculated average rate of exposure will be corrected by multiplying by d/(d+a). (It should be noted that most carcinogen animal bioassays do not commence dosing until the animals are fully grown, so this correction is a conservative element in using human data).

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TECHNICAL SUPPORT DOCUMENT

PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT

Part A Report

State of California
Air Resources Board
Stationary Source Division

July 1989

[redacted]

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PRELIMINARY DRAFT

TECHNICAL SUPPORT DOCUMENT

PART A

PUBLIC EXPOSURE TO, SOURCES, AND EMISSIONS OF VINYL CHLORIDE IN CALIFORNIA

REPORT TO THE AIR RESOURCES BOARD ON VINYL CHLORIDE

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July 1989

(This report has been reviewed by the staff of the California Air Resources Board and approved for publication. Approval does not signify that the contents necessarily reflects the views and policies of the Air Resources Board, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.)

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PRELIMINARY DRAFT

PUBLIC EXPOSURE TO, AND SOURCES OF ATMOSPHERIC VINYL CHLORIDE IN CALIFORNIA

Table of Contents

DRAFT

LIST OF APPENDICES

DRAFT

LIST OF TABLES AND FIGURES

TABLES

FIGURES

CMA 010531

DRAFT

I.

INTRODUCTION

Part A of this report is an evaluation of vinyl chloride's uses, emission sources, ambient and indoor air concentrations, and population exposure in California. Also included are discussions of the physical properties and atmospheric persistence of vinyl chloride. California Health and Safety Code Section 39655 states that substances listed by the U.S. Environmental Protection Agency (EPA) as hazardous air pollutants (Section 112 of the Clean Air Act) shall be identified as toxic air contaminants (TACs) by the Air Resources Board (ARB). Therefore, because the EPA has listed vinyl chloride as a hazardous air pollutant, the ARB is directed by statute to identify vinyl chloride as a TAC.

The ARB is the state agency responsible for the identification of TACs in their non-pesticidal uses. The California Health and Safety Code Section 39655 defines a TAC as "an air pollutant which may causa or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health." The findings of the Part A report are considered with the health effects findings (Part B report) of the Department of Health Services (DHS) to determine if a compound should be identified as a TAC by the ARB.

In 1978, the ARB adopted an ambient air quality standard for vinyl chloride of 10 ppb for a 24-hour average. The standard represented the limit of detection for vinyl chloride at the time it was adopted.

Vinyl chloride is an extremely volatile compound that is primarily used for the production of polyvinyl chloride (PVC). PVC is fabricated for use in several products of which many are used by the

construction industry. In California, the identified sources of vinyl chloride emissions are landfills, PVC production and fabrication facilities, and sewage treatment plants.

Available information indicates that landfills are the largest source category of vinyl chloride emissions in California. Vinyl chloride has been measured in the ambient air near hazardous waste and municipal waste landfills. Numerous studies have documented the presence of vinyl chloride in the landfill gas of these and other landfills, and have shown that vinyl chloride can be formed in landfills where chlorinated organic compounds have been disposed. Therefore, because disposal of such chlorinated compounds is prevalent, the staff recommends that all landfills (hazardous and municipal) in the state be regarded as potential vinyl chloride emission sources.

In this report, ambient monitoring data and meteorological data are used with an atmospheric dispersion model to estimate population exposure to vinyl chloride near two California landfills. The modeling results show that people living near these landfills are exposed to elevated levels of vinyl chloride. The results also imply that people residing near other landfills in the state may be exposed to elevated levels of vinyl chloride. In addition to estimating ambient air exposure, this report also evaluates indoor air exposure to vinyl chloride.

Based on limited monitoring data, indoor air exposure to vinyl chloride is probably not significant for the majority of the population. However, for people residing near landfills, inhalation of indoor air may represent the most significant source of vinyl chloride exposure. This is because vinyl chloride can migrate underground from landfills and accumulate in nearby structures. The concentrations of vinyl chloride measured in homes located near landfills have been reported to be several times greater than the corresponding ambient concentrations.

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II.

EXPOSURE TO VINYL CHLORIDE

A. AMBIENT MONITORING IN CALIFORNIA

Vinyl chloride is frequently detected in the ambient air of California. However, detectable levels are limited to locations near identified emission sources. Previous monitoring throughout the South Coast Air Basin (SCAB), as part of the ARB's ambient monitoring network, has failed to detect vinyl chloride above the ARB's limit of detection (LOD) of 0.5 ppb. In recent years, the only known emission sources in California near which vinyl chloride has been frequently detected in the ambient air are two landfills in the SCAB: BKK and Operating Industries Inc. (OII). For both of these landfills, the South Coast Air Quality Management District (SCAQMD) has frequently measured ambient vinyl chloride concentrations above the SCAQMD's LOD of 2 ppb. The analysis in this report estimates ambient concentrations and population exposure to vinyl chloride near BKK and OII because they are the only landfills in the state where vinyl chloride has been routinely monitored on a long-term basis.

In response to the lack of monitoring data for other landfills, Health and Safety Code Section 41805.5 requires hazardous and municipal landfills throughout the state to conduct monitoring for several [redacted] include vinyl chloride. As these monitoring results are [redacted] will be helpful in identifying which landfills could be [redacted] to emit vinyl chloride and warrant further monitoring [redacted] mitigation measures. A more detailed description of the [redacted] of Health and Safety Code Section 41805.5 is provided on page A-31.

The SCAQMD's monitoring program for vinyl chloride at BKK and OII has consisted of six monitoring stations. Three stations have been

located on the southern borders of each landfill. Previous monitoring around both landfills has indicated that the southern borders are generally where the highest concentrations are detected. All samples are collected in Tedlar bags over 24-hour periods and subsequently analyzed by gas chromatography employing a flame ionization detector. Details of the SCAQMD's sampling and analysis procedures are provided in Appendix I.

Topographical maps of the BKK and OII landfills are provided respectively in Figures II-1 and II-2. These figures show the approximate perimeter of the landfills, the approximate locations of the monitoring sites, and proximity of streets to the landfills. As indicated by the maps, the southern borders of BKK and OII are adjacent to a network of streets. However, the maps do not show that the area served by these streets consists of single-family residential housing.

Ambient air samples used to estimate population exposure near BKK and OII were collected from January through December 1987 and January through December 1986, respectively. When the exposure analysis was performed, these sampling periods represented the most recent calendar years of monitoring data that were available. For BKK, 337 to 340 samples were taken at each of the monitoring sites; of those sites, a range of 88 to 90 percent of the samples are below the LOD of 2 ppb. For OII, 128 to 264 samples were taken at each of the monitoring sites; of those sites, 32 to 100 percent of the samples are below the LOD.

The ambient vinyl chloride monitoring data for BKK and OII are summarized in Tables II-1 and II-2, respectively. Each table provides the number of samples taken at each site, the percent of samples below the LOD, an estimate for the values below the LOD, the estimated mean concentration, and the maximum 24-hour concentration that was measured.

Calculation of mean concentrations for stations is complicated by the presence of concentrations below the LOD. The concentrations below the LOD must be somehow included in the calculation although their exact values are not known.

[illegible] used a method proposed by Gleit (1985) to calculate the [illegible] method assumes that the sample of concentrations is [illegible] a normal distribution. Data that are judged not to be [illegible] may be transformed to approximate normality. [illegible] vinyl chloride data suggested that they were [illegible] log-normally distributed, and Gleit's method was applied to the [illegible] data. The calculated means were then transformed back to the original units.

Gleit's method accounts for the concentrations below the LOD by setting them equal to the "below-LOD mean," the mean of the portion of

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FIGURE II-1

BKK LANDFILL AND THE SURROUNDING AREA

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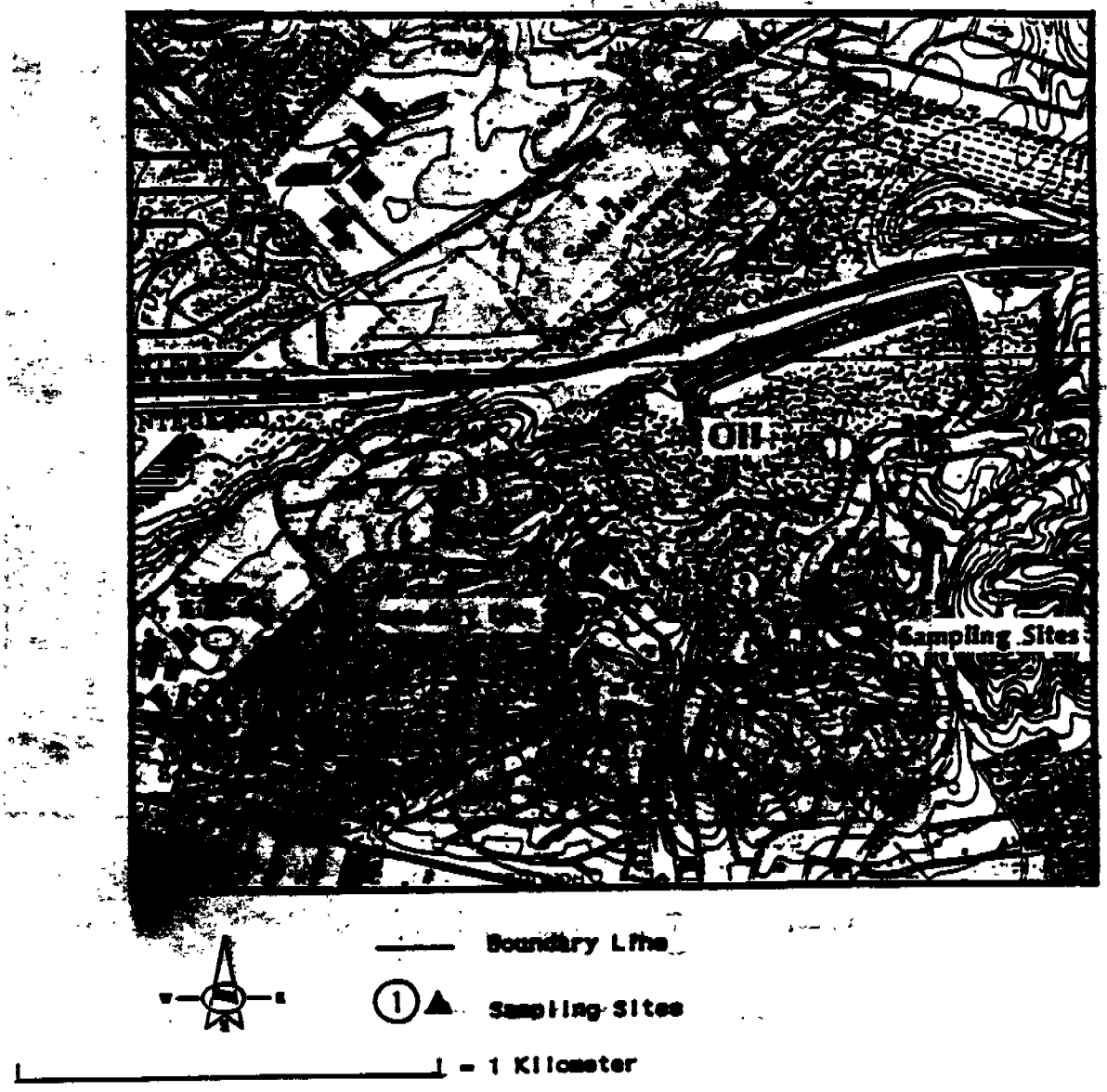
FIGURE II-2

OII LANDFILL AND THE SURROUNDING AREA



CMA 010538

the normal distribution below the LOD. Setting the unknown concentrations to their average value seems intuitively reasonable, and the simulations reported in Gleit's paper show that his method is more accurate than other commonly used approximations. A detailed description of the method used to estimate the concentration of data below the LOD is provided on Appendix II.

The estimated values for samples below the LOD range from 1.0 ppb to 1.1 ppb for BKK and from 1.0 ppb to 1.2 ppb for OII. As previously indicated, the specific value for each station is shown in Table II-1 for BKK and II-2 for OII. Because all samples for site 1 of OII are below the LOD, Gleit's method could not be used to estimate their concentration. Therefore, a value of one-half the LOD (1.0 ppb) is assumed for these samples.

TABLE II-1

SUMMARY STATISTICS FOR THE JANUARY 1987 THROUGH DECEMBER 1987 MONITORING DATA FOR VINYL CHLORIDE NEAR BKK LANDFILL
(Concentrations reported in parts per billion (ppb))

	Station 1	Station 2	Station 3
Number of Samples	337	337	345
Percent of Samples Below the LOD[a]	73	90	55
Estimated Concentration for Samples Below the LOD[b]	1.0	1.0	1.1
Estimated Mean Concentration[b]	1.7	1.2	2.6
Maximum 24-Hour Concentration[c]	7	8	15

a - The limit of detection (LOD) for vinyl chloride is 2 ppb.
b - Gleit's method was used to estimate the concentration of samples below the LOD.
c - California's Ambient Air Quality Standard for vinyl chloride is 10 ppb for a 24-hour averaging period.

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The estimated mean vinyl chloride concentrations, as provided in Tables II-1 and II-2 range from 1.2 ppb to 2.6 ppb for the monitoring stations at BKK, and 1.0 ppb to 2.0 ppb for the monitoring stations at OII. For all stations, except station 3 of BKK, the estimated annual mean concentration is equal to or less than the SCAQMD's LOD for vinyl chloride.

Tables II-1 and II-2 also list the maximum 24-hour concentration of vinyl chloride for each monitoring station at BKK and OII, respectively. For BKK, the maximum 24-hour concentration is 15 ppb (measured at station 3); for OII the maximum concentration is 9.8 ppb (measured at station 3). These concentrations can be compared to ARB's ambient air quality standard for vinyl chloride of 10 ppb for a 24-hour averaging period. The standard was

TABLE II-2

SUMMARY STATISTICS FOR THE JANUARY 1986 THROUGH DECEMBER 1986 MONITORING DATA FOR VINYL CHLORIDE NEAR OII LANDFILL

(Concentrations reported in parts per billion (ppb))

	Station 1	Station 2	Station 3
Number of Samples	264	220	128
Percent of Samples Below the LOD[a]	100	[illegible]	32
Estimated Concentration for[b] Samples Below the LOD	[illegible]	[illegible]	1.2
Estimated Mean[b] Concentration	[illegible]	2.0	2.0
Maximum 24-Hour Concentration[c]	d	[illegible]	9.8

a - [illegible]mit of detection (LOD) for vinyl chloride is 2 ppb.
b - [illegible]was used to estimate the concentration of samples below
c - [illegible]Ambient Air Quality Standard for vinyl chloride is 10 ppb [illegible] average.
d - All samples are below the LOD

adopted in 1978 in response to information which associated vinyl chloride with the development of cancer in humans. However, the standard is not necessarily health protective; it simply represented the LOD at the time it was adopted. For the monitoring periods presented in this report, BKK exceeded the state standard for vinyl chloride 11 times (all exceedances occurred at site 3) while OII did not exceed the standard. Based on previous years of monitoring data, the number of exceedances at BKK and OII has decreased substantially. In fact, due to the lack of exceedances of the standard, the SCAQMD discontinued monitoring for vinyl chloride at OII in early 1987. The reduction in ambient concentrations of vinyl chloride near BKK and OII has been attributed to the installation of gas collection and flare systems.

In an effort to represent the uncertainties associated with the estimated mean concentrations of vinyl chloride, the staff developed a statistical treatment for calculating upper and lower bound estimates of the mean concentration at each monitoring station. This method takes into account factors such as sample size, variance of the data, and an estimate of the uncertainty associated with the sampling and analysis method. Table II-3 shows the estimated mean concentration as well as the upper and lower bound estimate of the mean concentration for each monitoring station at BKK and OII.

The following text discusses the statistical treatment that is used:

a) After reviewing the ambient vinyl chloride monitoring data for BKK and OII, the staff observed that the data appear to be lognormally distributed. Because available software analyze data that are only normally distributed, vinyl chloride monitoring data were first converted from a lognormal distribution to a normal distribution. This was done by using the logarithms of the data for the analysis. The statistical analysis system (SAS, 1982) was used to calculate the standard error about the mean. The standard error calculated from the logarithms of the data is then converted back into concentration units by taking the antilogarithms.

b) The upper and lower bound estimates reported for the mean represent two standard errors. For the error associated with sampling and analysis, ARB staff used an overall uncertainty factor of ± 20 percent to calculate the upper and lower bound estimates of the mean. This is in agreement with the actual error which is estimated to be ± 1 ppb in the range of 1 ppb to 50 ppb. The lower bound estimate represents two standard errors for the data with each sample concentration reduced by 20 percent. The upper bound estimate represents two standard errors for the data with each sample concentration increased by

20 percent. Upper and lower bound estimates for each station are shown in Table II-3. Because all values for station 1 of OII are below the LOD, the upper and lower bound estimates represent ± 20 percent of one-half the LOD.

B. ESTIMATING AMBIENT CONCENTRATIONS

Annual average vinyl chloride concentrations were estimated for a 41 x 41 grid of one square kilometer cells surrounding each landfill with the use of the Industrial Source Complex Short Term (ISCST) Gaussian model. In order to predict the annual average concentration of vinyl chloride in each of the 1681 square kilometer cells, the ISCST model required the emission rates for each landfill as input. Emission rates were estimated for BKK and OII using the range of estimated annual mean concentrations at each of the monitoring stations.

The estimated emission rates were derived by ratioing estimated annual mean concentrations over modeled concentrations for each station.

TABLE II-3

UPPER AND LOWER BOUND ESTIMATES OF THE ANNUAL MEAN CONCENTRATIONS OF VINYL CHLORIDE AT BKK AND OII LANDFILLS

	Lower bound Estimate	Annual Mean Concentration	Upper Bound Estimate
BKK Landfill			
Station 1	1.2	1.7	2.1
Station 2	0.8	1.1	1.4
Station 3	2.5	2.9	3.4
OII Landfill			
Station 1	0.8	1.0	1.2
Station 2	1.4	2.0	2.8
Station 3	1.4	2.0	2.6

* - All samples are below the LOD of 2 ppb.

The modeled concentrations were determined by assuming a landfill emission rate of 1 gram per square meter per second (gram meter^{-2} second^{-1}) in conjunction with historical meteorological data. Each landfill was represented as an area source. Based on review of topographical maps as well as information concerning the landfills disposal history, BKK was assumed to emit vinyl chloride from an area of approximately 1,700,000 meters^2 while OII was assumed to emit vinyl chloride from an area of approximately 330,000 meters^2. These assumed areas approximate the area where wastes have been disposed. Meteorological data for 1981 at the SCAQMD's Walnut and Upland stations were used for BKK and OII, respectively. Meteorological data from these stations were used for this study because Walnut was considered the most representative station for BKK where processed data were available while Upland was considered the most representative station for OII where processed data were available. These data were entered into the ISCST model to calculate the annual average modeled concentration at each monitoring station. Because one year of meteorological data is used, one modeled concentration is obtained for each monitoring station at BKK and OII. For each site at BKK and OII the modeled concentration was divided into the estimated mean concentration (from Table II-3) of its respective monitoring station. The resulting factors or ratios were then multiplied by the assumed emission rate (1 gram meter^{-2} second^{-1}) to estimate a landfill emission rate for each monitoring station that will result in an exact match between estimated and modeled concentrations. Equation (1) illustrates the procedure that was used:

$$\text{Estimated Emission Rate} = \text{Assumed Emission Rate} \times \left(\frac{\text{Estimated Concentration}}{\text{Modeled Concentration}}\right) \quad (1)$$

The estimated landfill emission rates for each monitoring station at BKK and OII are given in Table II-4. The emission rate derived from the estimated mean concentration for each monitoring station and the emission rates derived from the upper and lower bound estimates of the mean concentration for each monitoring station are listed. The greatest range of estimated emission rates for BKK is from 0.75 micrograms meter^{-2} second^{-1} (lower bound at station 2) to 3.32 micrograms meter^{-2} second^{-1} (upper bound at station 3). For OII, the estimated emission rate [illegible] micrograms meter^{-2} second^{-1} (lower bound at station [illegible] micrograms meter^{-2} second^{-1} (upper bound at station 3).

Using the full range of emission rate estimates (0.75 to 3.32 micrograms meter^{-2} second^{-1} for BKK and 0.31 to 4.42 micrograms meter^{-2} second^{-1} for OII), a range of estimated annual average vinyl chloride concentrations was derived for the 41 by 41 grid of one square kilometer

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TABLE II-4

ESTIMATED EMISSION RATES OF VINYL CHLORIDE
FROM BKK AND OII LANDFILLS
(micrograms meters^{-2} second^{-1})

	Lower Bound[a]	Average[b]	Upper Bound[c]
BKK Landfill			
Station 1	1.36	[illegible]	2.30
Station 2	0.75	0.97	1.20
Station 3	1.88	2.60	3.32
OII Landfill			
Station 1	0.31	0.39	0.48
Station 2	0.52	0.74	1.04
Station 3	2.69	3.46	4.42

a - These emission rates were derived from the lower-bound annual mean concentration
b - These emission rates were derived from the annual mean concentration
c - These emission rates were derived from the upper-bound annual mean concentration

cells. Each landfill was located in the center of the grid and was represented as an area source. As previously stated, BKK was assumed to emit vinyl chloride from an area of approximately 1,700,000 meters^2 while OII was assumed to emit vinyl chloride from an area of approximately 1,000,000 meters^2. These areas approximate the area where wastes were disposed at each landfill. However, because subsurface migration of landfill gases has been observed at BKK and OII, it is possible that emissions of vinyl chloride occur over an area substantially greater than where wastes have actually been disposed. The ISCST model used the range of estimated emission rates assuming no plume rise in conjunction with historical meteorological data to predict

a range of annual average concentrations for each of the 1681 one square kilometer cells. The annual average concentrations of vinyl chloride predicted for the one square kilometer cells within the grid centered on BKK, range from less than 0.1 ppb to approximately 22 ppb. For OII, the range is from less than 0.1 ppb to approximately 3.8 ppb.

In order to obtain these modeling results, several assumptions are made. These assumptions may act to elevate or reduce the estimated annual average concentrations of vinyl chloride predicted for the cells surrounding BKK and OII. The primary assumptions are as follows:

1) Vinyl chloride is assumed to be emitted from an area of approximately 1,700,000 meters^2 for BKK and 330,000 meters^2 for OII. Although these areas approximate the area where wastes have been disposed, data are not available to demonstrate that these areas actually represent where vinyl chloride emissions occur. Emissions of vinyl chloride may occur over an area which is either larger or smaller than that assumed.

2) Emissions of vinyl chloride are assumed to occur continuously and uniformly over a given area of each landfill. In reality, vinyl chloride is not likely to emanate uniformly over the surface of the landfills. However, the data required by the model to take this into consideration are not available. If emissions of vinyl chloride vary over the surface of the landfills, the annual concentrations estimated for some cells would be expected to be underestimated while others would be overestimated.

3) This study does not use meteorology for the same year as the vinyl chloride measurements. Because there is not a great deal of variation in meteorological data from year to year, the degree of error from using a meteorological year different than the vinyl chloride measurement year is estimated to be less than 50 percent.

Because the emission rates were derived by model calibration to known vinyl chloride concentrations, the uncertainty is at a minimum [redacted] sites. Alternatively, as the distance from each [redacted] increases, the uncertainty associated with the [redacted] concentration increases.

C[redacted] EXPOSURE

The population exposure to vinyl chloride near BKK and OII was estimated by using the grid cell concentrations estimated from the ISCST model in conjunction with 1985 updated census data. Estimates of the

cumulative population exposed to various concentration levels of vinyl chloride near BKK and OII landfills are shown in Tables II-5 and II-6. The 1986 residential population estimates were determined for each 1 kilometer grid cell with the concentration determined at the center of each cell by the ISCST model. The 1,681 grid cells, with their associated populations, were sorted from high to low by concentration. The grid cell populations were then summed to determine the cumulative population exposed to a certain level of vinyl chloride. For Tables II-5 and II-6, a lower bound of exposure is estimated. The range of

RANGE OF CUMULATIVE POPULATION EXPOSED TO VINYL CHLORIDE NEAR BKK

Vinyl Chloride Concentration (ppb)	Range of Cumulative Population Exposed	
	Lower-Bound Estimate	Upper-Bound Estimate
0.01[b]	2,028,000	2,154,000
0.08	732,000	1,970,000
0.1	330,000	1,431,000
1.0	17,000 -	131,000
2.3		54,000
3.2		28,000
4.0		20,000
5.0		14,000
[redacted]		7,000
		2,500

a - The exposure estimate is based on a vinyl chloride emission rate of 0.75 micrograms meter^{-2} sec^{-1}.

b - The exposure estimate is based on a vinyl chloride emission rate of 3.32 micrograms meter^{-2} sec^{-1}.

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TABLE II-6

RANGE OF CUMULATIVE POPULATION EXPOSED
TO VINYL CHLORIDE NEAR OII

Vinyl Chloride Concentration (ppb)	Range of Cumulative Population Exposure	
	Lower-Bound Estimate[a]	Upper-Bound Estimate[b]
0.01	272,000 -	3,111,000
0.05	33,000 -	1,073,000
0.10	12,000 -	445,000
1.0	6,000 -	22,000
1.5	6,000 -	12,000
2.0	2,000 -	6,000
3.0	0 -	6,000

a - The exposure estimate is based on an emission rate of 0.31 micrograms meter^{-2} sec^{-1}.

b - The exposure estimate is based on an emission rate of 4.42 micrograms meter^{-2} sec^{-1}.

exposure represents the range and upper bound of concentrations predicted for each of the one-square-kilometer cells. Table II-5 shows that approximately 272,000 to 878,000 people are exposed to an annual average concentration of at least 0.01 ppb of vinyl chloride from the [redacted]. Approximately 17,000 to 101,000 of these people are exposed to an annual average concentration of at least 1.0 ppb from this facility. Table II-6 shows that approximately 33,000 to 1,073,000 people are exposed to an annual average concentration of at least 0.05 ppb of vinyl chloride from the OII landfill. Additionally, Table II-6 shows that a range from 0 to 12,700 people are exposed to an annual average concentration of at least 1.0 ppb vinyl chloride near OII.

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In addition to estimating the cumulative population exposure to vinyl chloride for people living near BKK and OII, the population-weighted exposure results were calculated. The population-weighted exposure is calculated by multiplying the estimated annual average concentration for each cell by the population represented by the cell. The exposure results for the 1681 cells are subsequently summed and divided by the total population represented by the 1681 cells. For BKK, the population-weighted exposure results show that 2,154,000 people are exposed to an annual average vinyl chloride concentration ranging from 0.08 ppb to 0.34 ppb. For OII the population-weighted exposure results show that 4,287,000 people are exposed to an annual average vinyl chloride concentration ranging from 0.004 ppb to 0.06 ppb.

The model was also used to estimate the annual average concentrations for the maximum exposed individual at each landfill. For BKK, the maximum exposed individual is estimated to be exposed to an annual average concentration ranging from 2.3 ppb to 10.3 ppb. For OII, the maximum exposed individual is estimated to be exposed to an annual average concentration ranging from 0.6 to 8.7 ppb.

The population exposure results for BKK and OII suggest that other landfills in California that emit vinyl chloride may expose the nearby population to elevated concentrations. However, because monitoring data for other landfills is limited, we are unable to estimate population exposure near other landfills in the State. Chapter III of this report discusses other vinyl chloride monitoring data that are available as well as existing programs intended to provide more information concerning vinyl chloride emissions and exposure resulting from other landfills in California.

D. INDOOR EXPOSURE TO VINYL CHLORIDE

With the exception of some homes located near landfills, indoor concentrations of vinyl chloride are not expected to be substantially greater than outdoor concentrations. Although data are limited, the above statement is supported by the following facts: 1) few indoor sources of vinyl chloride have been identified, and 2) most studies that have monitored for indoor concentrations of vinyl chloride fail to detect it. Landfills have been identified as a source of emissions that contribute to elevated indoor concentrations of vinyl chloride in homes. However, landfills can accumulate vinyl chloride resulting in indoor concentrations that may be several times greater than general outdoor concentrations. In some houses located near landfills, vinyl chloride has been detected at concentrations up to 100 ppb.

We estimate that people living near landfills may be inhaling up to 2600 micrograms of vinyl chloride a day (see Appendix for III

assumptions). For these individuals, inhalation of vinyl chloride indoors is expected to represent the most significant source of exposure. A more detailed discussion of indoor exposure to air contaminants is presented in Appendix III.

1. Potential Sources of Indoor Vinyl Chloride

There are several potential sources that can contribute to elevated indoor concentrations of vinyl chloride. These sources include landfills, polyvinyl chloride (PVC) products containing residues of vinyl chloride, water that contains residues of vinyl chloride and cigarette smoke. For most homes, these sources are not expected to result in substantially elevated indoor levels of vinyl chloride. However, for some homes located near landfills, staff believe that landfills may represent the most significant contribution to indoor levels of vinyl chloride.

Vinyl Chloride From Landfill Gas. There are at least two ways that vinyl chloride emissions from landfills may contribute to indoor concentrations of vinyl chloride in nearby residences: 1) homes that are located downwind from landfills can receive vinyl chloride through direct outdoor air influx into indoor environments; and 2) landfill gases containing vinyl chloride can migrate underground and enter homes through substructures. The rate of accumulation of vinyl chloride indoors depends on several factors including soil permeability, source strength, air exchange rate, and structure of the home. In addition, higher indoor concentrations may occur because vinyl chloride is more rapidly destroyed in outdoor air than indoor air because of direct exposure to sunlight.

Plastic Materials and Consumer Products. Plastic products made of PVC and other vinyl chloride polymers are ubiquitous in most homes. Because vinyl chloride monomer can remain in the PVC resin for an extended period of time, an indirect source of indoor vinyl chloride emissions may come from the release of unreacted vinyl chloride monomer from these plastic products.

Emissions of unreacted vinyl chloride monomer have been substantially reduced due to improvements in monomer stripping [redacted] 1981). In the past, residual vinyl chloride [redacted] resins at the time of shipment, were as high as [redacted]. PVC resins contain about 10 ppm residual vinyl [redacted] of shipment and may lose vinyl chloride at a rate of [redacted] percent per month during storage. In addition, most of the vinyl chloride will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products. Thus, consumer products made of PVC resins no longer contain elevated

residual levels of vinyl chloride monomer and, therefore, are not expected to be an important contributor of indoor levels of vinyl chloride.

Vaporization from Water Sources. Because activities such as using water for cooking, heating and showering can promote rapid vaporization of vinyl chloride from water, contaminated surface or ground water may increase indoor vinyl chloride levels.

In California, surface water is generally free of vinyl chloride (Sharrp, 1987). In assessing ground water quality, the California Department of Health Services reported, based on a limit of detection of 0.5 micrograms/liter, that one out of the 2087 wells for large public water systems that were sampled had detectable levels of vinyl chloride (DHS, 1986). The maximum concentration found in that well was 23 micrograms/liter with a median value of 20 micrograms/liter. Vinyl chloride has not been detected in wells used for small public water systems (DHS, 1987). Therefore, vinyl chloride in the water supply is not believed to significantly impact indoor air concentrations of vinyl chloride.

Cigarette Smoke. A minute amount of vinyl chloride has been identified in the smoke of cigarettes (1.3 to 16 nanograms/cigarette) and of little cigars (14 to 27 nanograms/cigar) (IARC, 1985; Hoffmann, Patrianakos and Brunnemann, 1976). The vinyl chloride level in the mainstream smoke may be estimated by the total inorganic chloride content of the tobacco. However, the contribution from tobacco smoke does not appear to have a significant impact on the indoor concentration of vinyl chloride.

2. Indoor Monitoring Data

Indoor air data can be obtained either by personal air sampling or by fixed-site air sampling. In personal sampling, the sampling equipment is carried by an individual and the samples are taken wherever the individual may be. In contrast, fixed-site air sampling refers to air samples taken at fixed locations. Personal air sampling data generally provide more realistic estimates of individual exposure. Because people spend 80 to 90 percent of their time in indoor environments, personal air sampling data are strongly weighted by indoor air

Personal Sampling Data. Based on limited personal sampling data, it appears that indoor air exposure to vinyl chloride is apparently low. In monitoring nine subjects in New Jersey and three from North Carolina for several days on three separate occasions, all of the 138 air samples taken were below the LOD (Wallace et al., 1984). The LOD was reported to range from 0.25 ppb to 1.11 ppb (0.63 to 2.84 micrograms meter^{-3}).

Fixed-Site Sampling Data. For a study conducted in California, fixed-site monitoring stations were installed to monitor indoor and outdoor air concentrations of vinyl chloride. Based on the analysis of 32 indoor samples taken in eight homes during summer season for two twelve-hour sampling periods (daytime and nighttime), concentrations of vinyl chloride are all below the LOD. The samples were analyzed by two analytical methods with LODs ranging from about 0.21 ppb to 55 ppb (0.55 and 140 micrograms meter^{-3}) (Pellizzari, 1989).

A similar study was conducted in Baltimore where indoor air concentrations of vinyl chloride in about 160 homes were monitored by fixed-site sampling stations. Based on partially analyzed results, vinyl chloride was not detected in indoor air environments. The LOD was reported to range from 10.2 ppb to 15.7 ppb (26 to 40 micrograms meter^{-3}) (Pellizzari, 1987).

Special Situation Air Monitoring. In 1981, the SCAQMD collected 24-hour bag samples in the vicinity of BKK landfill. Over 500 air samples were taken at two outdoor sites and at four indoor sites downwind of the landfill (SCAQMD, 1982). All of the samples (approximately 120 samples) that equaled or exceeded the state vinyl chloride standard of 10 ppb (26 micrograms meter^{-3}) were taken inside the residences. The highest recorded indoor vinyl chloride concentration was 50 ppb (130 micrograms/meter^{-3}). The LOD was reported to be 2 ppb (5.2 micrograms meter^{-3}).

In 1988, the SCAQMD collected grab-samples inside some residences adjacent to OII. The sampling study was prompted by the SCAQMD's finding of elevated levels of vinyl chloride in several water meter boxes in homes adjacent to OII. Indoor sampling results show vinyl chloride concentrations ranging from 0 to 100 ppb (20.8-260 micrograms meter^{-3}) (SCAQMD, 1988). Presently, indoor concentrations of vinyl chloride in these residences are believed to be substantially lower because routine monitoring of water meter boxes has not detected significant levels of landfill gases. This has been attributed to improvements in the OII landfill gas collection system (Coy, 1987).

E. EXPOSURE THROUGH OTHER ROUTES

[redacted] objective of this report is to estimate exposure thr[redacted]osure to vinyl chloride may also occur from the ing[redacted] water that contain residues of vinyl chloride. The [redacted] and Safety Code specifies that the ARB shall identify the rel[redacted] contribution to total exposure to the contaminant from indoor concentrations, taking into account both ambient and indoor environments (California Health and Safety Code, 1989). The inclusion of these data provide a useful perspective of the overall exposure to vinyl chloride through environmental media. The estimated daily dose of vinyl chloride

from different environmental media are presented in Table II-7. From the table, exposure to vinyl chloride from the indoor air of homes not located near landfills, food, and water appears to be minor. However, for people living in houses located near landfills, indoor exposure to vinyl chloride may represent the major source of total vinyl chloride exposure. The need for total exposure assessment and some of the issues and concepts involved in total exposure estimates are discussed in Appendix III.

ESTIMATED VINYL CHLORIDE EXPOSURE THROUGH DIFFERENT MEDIA[a]

Media	Daily Dose	Reference
AIR		
Ambient Air	< 104 to 700 ug[b]	Table II-1
Indoor Air		
Homes not near landfills		Wallace et al., 1984
Homes near landfills	up to [redacted]	SCAQMD, 1982
INGESTION		
Drinking water		
Surface/Ground water		EMA, 1986; 1987
Food including beverages	< 0.025 ug	FDA, 1986

[redacted]

a [redacted] that were used for Table II-7 are provided in

b [redacted]

1. Water Ingestion

The major source of drinking water for California is surface water which, because of vinyl chloride's high volatility, is not expected to have detectable levels of vinyl chloride. Ground water used for public water systems is also relatively free of vinyl chloride with concentrations typically below 0.5 ug liter^{-1} (DHS, 1987, 1986). Based on this information, staff believe that exposure to vinyl chloride through drinking water is not important under ordinary situations.

2. Food Ingestion

Vinyl chloride is not routinely monitored for in U.S. food products. However, before 1973, vinyl chloride was found in food and beverages packaged in vinyl chloride polymer materials (IARC, 1979). kg^{-1} (ppm) of vinyl chloride monomer were present in alcoholic beverages packaged in this material. Vinyl chloride was also found in edible oils, butter and margarine at concentrations ranging from 0.05-14.8 mg kg^{-1}. When cleaner PVC resins became available after 1975, vinyl chloride polymer containers typically contained less than 10 ppb of residual vinyl chloride monomer. In its recent rule-making proposal, the Food and Drug Administration (FDA) estimated lifetime-averaged individual exposure to vinyl chloride from food and beverages packaged with vinyl chloride polymer materials would not exceed 25 nanograms per day.

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III.

PRODUCTION, USES AND EMISSIONS

Although vinyl chloride is not produced in California, several thousand tons are used each year in the State for the production of polyvinyl chloride (PVC). The PVC which is produced is primarily used by fabricators for the production of materials used by the construction, packaging, electrical, and transportation industries.

Based on the emission estimates for two landfills in California (BKK and OII), landfills are the largest identified source category of vinyl chloride emissions in the state. The information necessary to estimate vinyl chloride emissions for the hundreds of other landfills in California is not available. However, without monitoring data which shows otherwise, all of the state's landfills should be regarded as potential vinyl chloride emission sources. Other known emission sources of vinyl chloride in the state include PVC production and fabrication facilities, and sewage treatment plants.

A. PRODUCTION

Commercial production of vinyl chloride in the United States began in 1936. During the first year of production, two thousand tons were produced (CEN, 1987). With a reported annual U.S. production of 3.8 million tons, vinyl chloride ranked 21st on a list of the most produced chemicals in the United States in 1984 (CEN, 1985a). Figure III-1 shows the production, imports, exports, and use of vinyl chloride from 1974 through 1984 (CEN, 1985a; US DOC, 1985a; and US DOC, 1985b). During this 10-year period, vinyl chloride production increased at an average annual rate of 3% (CEN, 1985a). More recent estimates for U.S. vinyl chloride production are 4.7 million tons and 4.2 million tons for 1985 and 1986, respectively (CEN, 1987).

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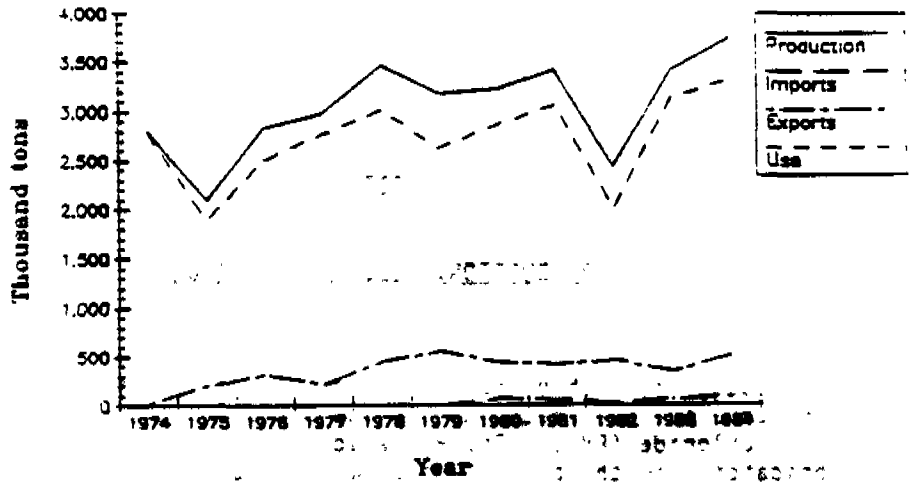
FIGURE III-1

NATIONAL VINYL CHLORIDE PRODUCTION, IMPORTS, EXPORTS, AND USE



Two facilities in California currently use vinyl chloride to produce PVC. Two other facilities in the State that were producing PVC ceased production, one in 1982 and the other in 1985 (Personal Communication, 1985a, 1985b, 1985c; and Zwiacher, W., et al., 1983).

B. CURRENT AND PROJECTED USES

About 96 percent of the vinyl chloride produced in the U.S. is used to manufacture PVC. The remainder is either exported or used to manufacture 1,1,1-trichloroethane (methyl chloroform) (SRI, 1978; and McPherson, M., 1979). Sixty percent of the PVC is used for fabricating various plastic materials used by the construction industry. Specifically, PVC is used by the construction industry for pipe, fittings, flooring, panelling, and roofing. PVC is also used by the packaging, furnishings, transportation, recreation, apparel, and [redacted] industries.

[redacted] of the vinyl chloride industry is closely tied to PVC use. Historical data for California show the number of housing units in the construction industry increased from approximately 1.0 million units in 1981 to 1.8 million units in 1986 (U.S. DOC, 1987). If this growth

in the construction industry continues, the PVC use by this industry is also expected to increase. Data are not available to forecast the use of PVC in other sectors. However, the total United States demand for PVC has been forecasted to increase by approximately 3 to 5 percent annually from 1985 to 1990 (CMR, 1985).

C. LANDFILLS: A MAJOR EMISSION SOURCE

Landfills are estimated to be the largest source category of vinyl chloride emissions in California. However, because landfills vary in the amount and composition of wastes they accept as well as the waste disposal methods used, estimating total vinyl chloride emissions for the state's hundreds of landfills is not possible. To better understand why all landfills are potential vinyl chloride emission sources, this section presents information on the types and number of landfills in California, the disposal methods employed, the causes of vinyl chloride emissions from landfills, vinyl chloride emission estimates for landfills, and some methods used to control landfill emissions.

1. Types of Landfills

There are three types of landfills in California: Class I sites (e.g., BKK, located in West Covina) which accept all types of wastes including hazardous materials; Class II sites (e.g., Operating Industries Inc. (OII), located in Monterey Park) which normally accept only "non-hazardous" wastes but can accept certain types of hazardous wastes (ARB, 1982b); and Class III (municipal or sanitary landfills) sites which can accept only household wastes. In California, there are fourteen Class I sites (includes two open and twelve closed facilities), 210 Class II sites, and approximately 200 Class III sites (ARB, 1982b; WRQCB, 1987).

2. Land Disposal Methods

Landfarming, surface impoundments, and landcovering are often used as waste disposal methods in California. These disposal methods may b practiced by [illegible] of the three types of landfills mentioned above as disposal method. However, OII, a Class I and II facility, has only surface impoundments. In addition, landfills may employ more than one disposal method. For example, [illegible] is then cultivated into the soil at frequent intervals. This cultivating process ensures a better aerobic decomposition of the wastes (Thibodeaux and Hwang, 1982). Surface impoundments, often called evaporation ponds or lagoons, are used to dispose of certain types of liquid wastes. As the name implies, surface impoundments allow the wastes to be evaporated into the atmosphere.

Landcovering is most often used at Class III sites or municipal landfills. In landcovering, wastes are spread over the land. At the end of each day, the wastes are covered with approximately six inches to 12 inches of cover. Ultimately, the wastes are covered with a layer of cover material that is at least four feet deep.

3. Landfill Emissions

Emissions of vinyl chloride from landfills mainly occur by two mechanisms: 1) direct vinyl chloride emissions from disposed wastes which contain vinyl chloride; and 2) the formation of vinyl chloride from the biodegradation of chlorinated hydrocarbons. Other minor mechanisms by which vinyl chloride emissions may occur include chemical reactions such as pyrolysis, surface photolysis, and hydrolysis of trichloroethylene and other chlorinated hydrocarbons, and off-gassing of PVC (Molton et al., 1987).

Direct Emissions. Direct emissions of vinyl chloride can only occur at landfill sites where vinyl chloride containing wastes were previously disposed. Because vinyl chloride containing wastes cannot be legally disposed in Class II or Class III landfills, Class I landfills (e.g., BKK) at which vinyl chloride has been disposed are probably the largest source of direct emissions of vinyl chloride. However, because vinyl chloride containing wastes may have been illegally disposed, Class II and Class III landfills may also emit vinyl chloride directly.

Formation of Vinyl Chloride. Because vinyl chloride can be formed from the biodegradation of chlorinated wastes, emissions of vinyl chloride may occur from any landfill site including Class II and Class III sites where no vinyl chloride has been disposed. Of the three landfill disposal methods, it appears that landcovering and landfarming are most likely to produce the conditions necessary for the formation of vinyl chloride.

Results of an AGA sponsored study demonstrated the formation of vinyl chloride when soil samples from two different landfills were incubated with chlorinated hydrocarbons (Molton et al., 1987). Similar results were obtained when sludge samples were incubated with chlorinated hydrocarbons. The evaluation of the biological mechanism showed that vinyl chloride production occurred predominently under anaerobic (oxygen) conditions. Subsequent experimentation with carbon-labeled chloroethanes and chloroethenes yielded carbon-13 labeled vinyl chloride as well as other biodegradation products. These results are in agreement with other studies which evaluated the biodegradation of chlorinated hydrocarbons to produce vinyl chloride (Kleopfer, 1985; Beeman, et al., 1978; Wood et al., 1980; and Parsons et al., 1984). Figure III-2 illustrates the pathways by which vinyl chloride is formed from the dehalogenation (chlorine removal) of

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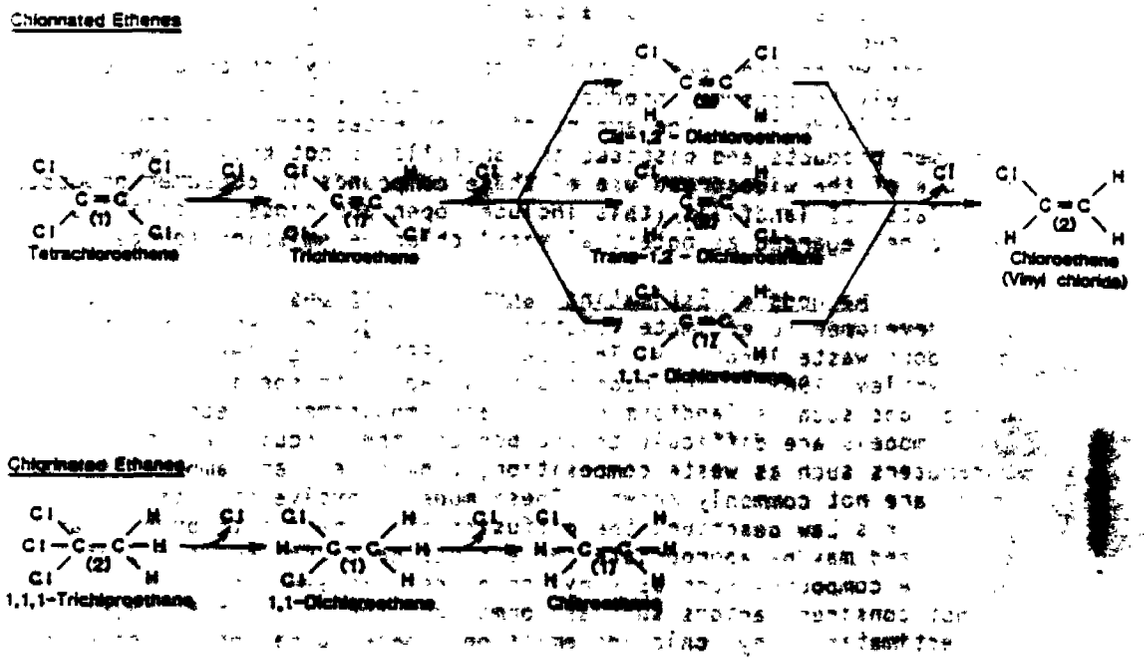
FIGURE III-2

ANAEROBIC BREAKDOWN SEQUENCE VIA REDUCTIVE DEHALOGENATION



Source: Cline and Viste, 1985

chlorinated ethanes and ethenes. In addition, the figure illustrates the relative rate by which the various compounds are degraded. Not all of the compounds presented in this scheme have necessarily been unequivocally demonstrated to form vinyl chloride. However, given the current state of knowledge, they should be considered as [illegible] chloride precursors.

[illegible] disposal of halogenated wastes [illegible] substantially restricted, for decades these materials were [illegible] Class I landfills as well as some Class II landfills throughout the state. The halogenated wastes are composed of many of the chlorinated compounds which can lead to the formation of vinyl chloride. However, the amount of halogenated wastes previously disposed in these facilities is unknown. Therefore, without monitoring data that

shows otherwise, all Class I and Class II facilities (this includes open and closed facilities) should be regarded as potential vinyl chloride emission sources.

Industrially generated halogenated wastes were never permitted to be disposed in Class III facilities. However, many of the chlorinated compounds which can lead to the formation of vinyl chloride are used extensively in consumer products, which after use typically end up in Class III landfills. The amount of chlorinated compounds remaining in consumer products and disposed in landfills is not known. However, because of the widespread use of these compounds in consumer products, all Class III landfills (this includes open and closed facilities) should be regarded as potential vinyl chloride emission sources.

Methods of Estimating Landfill Emissions. Several models have been developed to estimate volatile organic gaseous emissions from hazardous waste landfills (Thidobeaux, 1981; Hwang, 1982; Shen, 1981; and Hartley, 1969). The models usually apply to specific landfill operations such as landfarming, surface impoundments, etc. However, these models are difficult to use because they require a number of input parameters such as waste composition, wind speed, and ambient conditions which are not commonly known. These models involve the use of Fick's law (Fick's Law describes the diffusion of a species through a layer of fluid) and may be appropriate for estimating direct emissions of volatile compounds such as vinyl chloride. However, because the models do not consider factors such as formation, they may not be appropriate for estimating vinyl chloride emissions where formation is occurring.

A method to estimate vinyl chloride emissions where formation may be occurring is to establish monitoring stations around landfill sites to measure the ambient concentrations of the compounds of interest. The ambient concentrations along with appropriate meteorological data can then be used in dispersion models to back-calculate the emission rate from the landfill site. This is the method that was used to estimate vinyl chloride emissions from BKK and OII.

Landfill Emission Estimates. As previously stated, the largest source category of vinyl chloride emissions in California is landfills. Table I-1 summarizes vinyl chloride emission estimates for the [redacted]. As indicated in the table, vinyl chloride emissions were estimated for BKK and OII landfills. Although other landfills (Class II, and III) throughout the state may emit vinyl chloride, the information necessary to estimate emissions is not available. Therefore, total vinyl chloride emissions from landfills may be significantly greater than estimated in this report.

The vinyl chloride emission estimates for BKK and OII make several assumptions. These assumptions are: 1) vinyl chloride is emitted from

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TABLE III-1

VINYL CHLORIDE LANDFILL EMISSION ESTIMATES*

Source	Source Type	Emissions (tons/year)	Inventory Year	Ref.
Class I Landfills				
BKK, West Covina	Area	44-197	1987	ARB, 1988b
Other Sites	Area	NA		
Class II Landfills				
OII, Los Angeles	Area	4-51	1986	ARB, 1988b
Other Sites	Area	NA		
Class III Landfills	Area	NA		

* - These emission estimates assume that the vinyl chloride emission rates are uniform throughout the year over the area of the landfill that is estimated to emit vinyl chloride.
NA - Not Available

an area of approximately [redacted] meters^2 for BKK and 330,000 meters^2 for OII; 2) annual average emission rates of vinyl chloride from BKK and OII are within the ranges estimated in Table II-4; and 3) emissions of vinyl chloride are uniform over the entire area of the landfill that is estimated to emit vinyl chloride. Although these assumptions add uncertainty to the emission estimates for BKK and OII, ARB staff believe that [redacted] to infer that landfills represent the largest identified category of vinyl chloride emissions in California.

[redacted] on 1987 monitoring data for BKK, ARB staff estimate a vinyl chloride emission rate ranging from 0.75 to 3.32 micrograms meter^{-2} second^{-1} (see Table II-4). For BKK landfill, this translates to estimated vinyl chloride emissions ranging from 44 and 197 tons per year. Over BKK's history it is not known how much vinyl chloride containing or halogenated wastes were disposed at the landfill. However, in 1984, BKK received approximately 136,000 tons of volatile or toxic wastes. An unknown portion of these wastes were halogenated solvents (ARB, 1982b). For OII, ARB staff estimated a vinyl chloride emission rate ranging from 0.31 to 4.42 micrograms meter^{-2} second^{-1}

(Table II-4). For the OII landfill, this translates to estimated vinyl chloride emissions ranging from 4 and 51 tons per year. The amount of halogenated wastes disposed at OII over its history is unknown. However, in 1982, OII received 9,200 tons of volatile or toxic wastes. As with BKK, an unknown portion of these wastes were halogenated solvents (ARB, 1982a).

Other than for BKK and OII, vinyl chloride emissions have not been estimated for any of the state's landfill sites. However, based on test results from several Class II and Class III landfills, it is expected that many other landfills in California are vinyl chloride emission sources.

Monitoring results available for several other landfills are as follows: Flux measurements on the surface of the Schell Canyon sanitary landfill (a former Class II landfill located in Glendale, California) showed vinyl chloride concentrations ranging from non-detectible to 180 ppbv (parts per billion by volume) at various locations (Todd and Propper, 1985). In addition, tests conducted by the SCAQMD at several other Class II landfill sites from 1981 to 1985 confirmed the presence of vinyl chloride in landfill surface gas or gas collection system (Coy, 1985).

To partially address the lack of monitoring data from other landfills throughout in the state, Health and Safety Code Section 41805.5 (AB 3525 and subsequent amendments by AB 3374) requires the development and implementation of landfill monitoring guidelines and the reporting of monitoring results. The law requires the ARB to establish guidelines to monitor gas migration, gas constituency, and the ambient air at many of the hazardous and municipal waste landfills in California (ARB, 1986; ARB, 1987). The testing guidelines identify vinyl chloride as one of the compounds requiring monitoring. Landfill operators were required to report their results by July 1, 1987 with provisions for an extension of not later than January 1, 1988. Presently, results for 386 municipal and hazardous waste landfills have been received by the ARB. Of these 386 landfills, 288 performed landfill gas testing with vinyl chloride detected in the gas of [illegible] sites. Concentrations of vinyl chloride in the landfill gas at the testing sites ranged from below detectable [illegible]. As these monitoring results are evaluated, they will [illegible] identifying which landfills could be expected to emit vinyl [illegible] warrant further monitoring studies or mitigation measures.

[illegible] Collection Systems

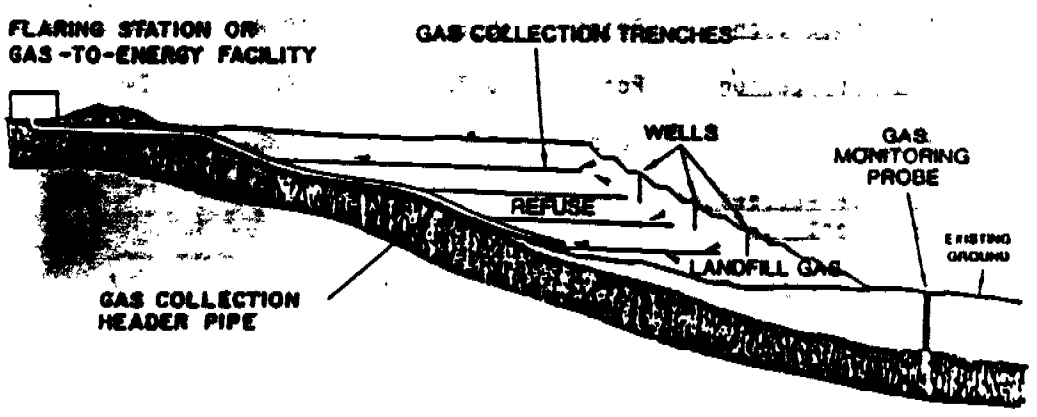
For many landfills emissions are required to be controlled to reduce odors as well as emissions of methane and toxicants. However,

gas control systems have been installed at some landfills as a resource recovery and/or energy conservation measure. For example, BKK transmits collected landfill gases to either one of two flare stations and/or to a five megawatt gas turbine for use as a fuel in generating electricity. Both well (vertical piping) and trench systems (horizontal piping) are used to collect landfill gases. In 1983, BKK installed a number of wells and gas collection lines to help control gaseous emissions. Although there are still potential sources of gaseous emissions such as cracks at the landfill surface, pipe connections and valves, and burner exhaust, ambient concentrations of vinyl chloride near BKK have been declining. Since installing their gas collection system, BKK has continued to expand the system by adding wells and trenches. Since installing a gas collection system at OII, ambient concentrations at the perimeter of the facility have continued to decline. Due to the lack of violations of the state standard for vinyl chloride (10 ppb), ambient monitoring at the perimeter of OII was discontinued by the SCAQMD in early 1987.

A well system consists of a network of wells drilled vertically into the refuse to collect the generated gases. These wells are connected to collection pipelines where gases are withdrawn from the buried layers of waste. In general, a vertical gas well is constructed by drilling a 30-inch diameter hole 50 to 100 feet deep into the waste. Perforated PVC pipes are then placed inside the hole. The space between the pipe and the hole is backfilled with uncrushed gravel (Sanitation Districts of Los Angeles County, 1984). A typical gas control system showing both well and trench systems is shown in Figure III-3.

FIGURE III-3

LANDFILL GAS COLLECTION SYSTEM



Source: Sanitation Districts of Los Angeles, 1984

In the trench system, a network of perforated pipelines is laid in trenches within the waste at approximately 200-foot intervals horizontally and 80-foot intervals vertically. To support the pipes and to allow the migration of the generated gases, approximately 2 feet of uncrushed gravel are packed around the pipelines. These pipelines are then connected to a main collection pipe where gases are withdrawn (Sanitation Districts of Los Angeles County, 1984).

D. OTHER KNOWN EMISSION SOURCES

Other than landfills, emissions of vinyl chloride emissions occur from: PVC production and fabrication, publicly-owned treatment works (POTWs), ethylene dichloride production, vinyl chloride production, methyl chloroform production, caprolactam production, and incomplete incineration of chlorine containing materials (Stitt, M., 1981; Zwiacher et al., 1983; and Lamorte, M., 1978). In California, the identified sources of vinyl chloride emissions that can be quantified are PVC production, PVC fabrication, and POTWs. Table III-2 provides estimates of vinyl chloride emissions for identified sources. Currently, there are no known vinyl chloride, ethylene dichloride, methyl chloroform (TCA) or caprolactam production facilities operating in the State.

TABLE III-2

SUMMARY OF VINYL CHLORIDE EMISSION ESTIMATES FOR OTHER SOURCES

Source	Source Type	Emissions Tons/Year	Inventory Year	Reference
PVC Production	[illegible]	[illegible]	[illegible]	[illegible]
PVC Fabrication	Point	0.78	1982	Zwiacher, et al., 1983
[illegible]	Point	1.7*	[illegible]	[illegible] et al., 1987
[illegible]	Point	NA		
[illegible]	Point	NA		
Transportation and Accidental Spillage Area		NA		

NA - Not Available

1. Polyvinyl Chloride (PVC) Production

Three PVC producers reported emitting a cumulative total of 3 tons of vinyl chloride in 1984 (Personal Communication, 1985a, 1985b, and 1985c). In 1982, vinyl chloride emissions from these producers were estimated to be 1.4 tons (Zwiacher, W. et al., 1983). All three producers reported that they were in compliance with South Coast Air Quality Managment District's (SCAQMD's) Rule 1163. This rule requires that vinyl chloride emissions from desfgnated plants not cause ambient vinyl chloride levels to exceed 10 ppbv (parts per billion by volume) during any 24-hour period when measured beyond the plant's property line (Personal Communication, 1985a, 1985b, 1985c; and ARB, 1980). Rule 1163 was adopted by SCAQMD as part of their program to control vinyl chloride emissions to 10 ppbv.

In 1984, the PVC producers operating in the State reported using closed systems, incineration, routine leak surveys, and maintenance programs as control technologies to comply with existing standards for vinyl chloride emissions (Personal Communication, 1985a, 1985b, and 1985c). The primary control method used by the two PVC producers currently operating in California is incineration. One facility (facility A) uses an afterburner with an operating temperature of approximately 2000°F while the other facility (facility B) uses a catalytic type incinerator. Both facilities have a monitoring system that continuously measures the vinyl chloride concentration within various areas of the plant. Portable hydrocarbon (HC) detectors are used to pinpoint leaks detected by the area monitoring system. These plants are also inspected at least once a year by the SCAQMD Enforcement Division to ensure compliance with district rules (Personal Communication, 1985d).

The SCAQMD periodically conducts ambient monitoring for vinyl chloride near the two PVC producers in California. In addition to the SCAQMD's monitoring program, the SCAQMD required one of the PVC producers (facility A) to monitor the ambient air for vinyl chloride at the perimeter of their facility on a daily basis. The other PVC producer (facility B) is not required by the SCAQMD to conduct ongoing offsite ambient monitoring for vinyl chloride. This is because: 1) historically, the facility has complied with Ambient Air Quality [redacted] chloride; and 2) the process that is used to [redacted] missions is not expected to result in vinyl chloride [redacted] as those associated with the other facility which [redacted] Generally, 24-hour average concentrations near the facilities are below the 10 ppb standard. However, in October of 1985, the SCAQMD reported concentrations as high as 20 ppb for facility A (Melita, 1985). As a result, the SCAQMD plans to conduct ambient monitoring more frequently at this facility to ensure compliance with the ambient air quality standard for vinyl chloride. The SCAQMD's

monitoring results indicate that this PVC producer may contribute to the public's exposure to vinyl chloride. Therefore, this facility should be investigated in more detail when considering control measures to reduce the public's exposure to vinyl chloride.

Table III-2 lists the cumulative vinyl chloride emissions estimates from the two PVC producers in California at less than 0.5 tons for 1987. This estimate is substantially lower than the 1984 estimate of 3 tons when three PVC producers were operating in California (Personal Communication, 1985a, 1985b, 1985c).

2. Polyvinyl Chloride Fabrication

Polyvinyl chloride (PVC) can be fabricated into several products such as PVC pipes, pipe fittings, plastics, etc. Some major fabrication processes are extrusion (to shape by forcing through a die), calendering, molding, and bonding. PVC contains the vinyl chloride monomer as a residual from the PVC production processes. Residual vinyl chloride (RVC) in PVC ranges from 0.002 ppmw (parts-per-million by weight) to 10 ppmw (U.S. EPA, 1982). When PVC is fabricated into final products, vinyl chloride is emitted.

The SCAQMD identified 33 PVC handling and fabrication facilities under its jurisdiction with an estimated usage of 75,000 tons of PVC in 1982. The SCAQMD staff assumed that all vinyl chloride is emitted from the fabrication processes. Using this assumption and a maximum RVC of 10 ppmw in PVC, the SCAQMD estimated that these handling and fabrication facilities emitted approximately 0.75 ton of vinyl chloride in 1982 (Zwiacher, 1983). This estimate represents an upper bound condition because the maximum RVC was used to estimate emissions, and because all RVC from the incoming PVC was assumed to be emitted from the fabrication processes. The vinyl chloride migration studies conducted by the Environmental Protection Agency (EPA) indicated a much smaller percentage of monomer is released during fabrication (U.S. EPA, 1982). A typical release of vinyl chloride in the extrusion process was only 10 percent of the

3. Publicly Owned Treatment Works

Publicly owned treatment works (POTWs) are wastewater treatment plants owned by public entities, and which consist of wastewater collection systems, wastewater and sludge treatment facilities, and effluent and sludge disposal systems. Users that discharge wastewater into POTWs are normally classified as commercial, industrial, and residential. The two primary mechanisms that result in emissions of organic gases are volatilization and biodegradation. Because POTWs treat wastewater which can contain vinyl chloride and

halogenated compounds from industries, vinyl chloride can be volatilized during the treatment processes. In addition, chlorinated hydrocarbons such as trichloroethylene and 1,2-dichloroethane could be biodegraded to vinyl chloride.

Halogenated hydrocarbons including vinyl chloride have been measured at wastewater treatment plants throughout the nation, including California (U.S. EPA, 1980). A preliminary study of two wastewater treatment plants, one in Los Angeles and another in the Sacramento Valley, indicated that vinyl chloride is present in the anaerobic digester tanks. Concentrations of [illegible] have been measured (ARB, 1985). These digester tanks are equipped with pressure/vacuum (P/V) valves to equilibrate the inside and outside pressure of the tanks. These P/V valves are potential sources of vinyl chloride emissions along with fugitive emissions associated with pipe fittings and valves.

In a study performed by the University of California at Davis (UCD), researchers used a mass balance approach to estimate that approximately 4.7 tons of vinyl chloride were emitted by POTWs in California in 1988 (Chang et al., 1987). Specifically, the difference between the concentration of vinyl chloride in the POTW influent and effluent was assumed to be emitted to the atmosphere. This approach may be useful in assessing which POTWs constitute a threat to public health. However, because this approach does not take into account the formation or degradation of vinyl chloride within POTWs, the resulting emission estimates should only be considered rough approximations. In response to the need for more information concerning emissions of toxicants from POTWs, ARB is currently funding a research contract. When the research is complete, the resulting report will contain the most recent information concerning the estimation of emissions of toxicants from POTWs and POTW collection lines. The report will also address the efficacy of POTW odor control systems on reducing emissions of toxic compounds.

E. OTHER POTENTIAL EMISSION SOURCES

Along with the sources discussed in Section B, there are several other [illegible] sources of vinyl chloride emissions in California. [illegible] wastewater treatment plants, incineration of PVC [illegible] transportation of vinyl chloride.

[illegible] Wastewater Treatment Plants

As presented in the discussion on POTWs, wastewater treatment facilities are sources of vinyl chloride emissions. At several industrial facilities such as oil refineries, chemical manufacturers,

etc., industrial wastewater is normally treated before being discharged. These wastewater treatment plants are also potential sources of vinyl chloride emissions.

2. Waste Incinerators

Vinyl chloride has been identified as a combustion product in the flue gas of an incinerator burning plastics (Boettner et al., 1973). It has also been hypothesized to form upon the combustion of PVC materials (Ahling et al., 1978). PVC materials are used extensively in automobile's upholstery, bumper parts and floor mats; when these materials are incinerated, vinyl chloride is a likely pollutant in the incinerator exhaust. Hospital waste incinerators are another potential source of vinyl chloride emissions since much of the hospital waste such as syringes and plastic bags are PVC-containing materials.

3. Transportation and Accidental Spillage

Another potential source of emissions is the accidental spillage and/or leakage of vinyl chloride that is being transported either by rail car, tank car, or marine vessel. Vinyl chloride is transported by rail cars to the two PVC producers currently operating in California. As far back as records are available, there have been no reported accidents involving vinyl chloride in the State (Office Of Emergency Services, 1985; California Highway Patrol, 1985).

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IV.

PERSISTENCE IN THE ATMOSPHERE

A. PHYSICAL PROPERTIES

The chemical structure of vinyl chloride (chloroethene, chloroethylene) is CH_2=CHCl. Vinyl chloride is a sweet smelling, colorless gas at ambient temperature and pressure. It polymerizes in light or in the presence of a catalyst. Vinyl chloride is readily flammable and forms explosive mixtures in air. Upon combustion, it is degraded mainly to hydrogen chloride gas, carbon monoxide, carbon dioxide and traces of phosgene. Vinyl chloride is expected to volatilize rapidly from water systems. Experimental data indicate that for an initial concentration of 1 ppm at a solution depth of 6.5 cm and a stirring rate of 200 rpm, the average evaporative half-life of vinyl chloride at a temperature of approximately 25°C is 27.6 minutes (Dilling, 1977). Another study determined that distilled water spiked with 16 ppm vinyl chloride lost 90 percent of the vinyl chloride within two hours (U.S. EPA, 1974). Although it is soluble in ethanol, industrial solvents, and a number of organic liquids, vinyl chloride is only slightly soluble in water. Vinyl chloride's physical properties are shown in Table IV-1.

[redacted] hydroxyl radical is its dominant mechanism removing [redacted] the troposphere (1980; Atkinson, 1986a). Estimates of [redacted] tropospheric lifetime range from 0.5 to 5.8 days. [redacted] for reasons provided later in this section, ARB staff believe that a tropospheric lifetime ranging from 1.6 to 3.9 days is representative of typical atmospheric conditions. The rate at which this reaction proceeds depends on the temperature and the tropospheric

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TABLE IV-1

PHYSICAL PROPERTIES OF VINYL CHLORIDE

Properties	Value	Reference
Boiling point, 1 Atm	-13.37 °C	Merck Index, 1983
Molecular weight	62.5	Merck Index, 1983
Vapor Pressure, 20 °C	2530 mmHg	Merck Index, 1983
Sol. in water, 25 °C	0.11g/100g H20	Kirk-Othmer, 1980
Partition Coeff. H_2O/air 10°C	0.02	McConnell,G., et al., 1975
Octanol/H_2O Partition Coeff.	20.7	Withey, 1976
Specific gravity, 20/4 °C	0.912	Kirk-Othmer, 1980
Flash pt. open cup	-77.8 °C	Kirk-Othmer, 1980
Liq. Dens. -14.2 °C g/cm^3	0.969	Kirk-Othmer, 1980
Heat capacity, 27°C	16.1	CRC Handbook, 1985

concentration of both vinyl chloride and hydroxyl radicals. The temperature dependence of the reaction rate is incorporated in the rate constant for reaction of vinyl chloride with hydroxyl radicals. The product of the rate constant and both species concentrations gives the rate at which vinyl chloride is being degraded (Finlayson-Pitts and Pitts, 1986).

The tropospheric lifetime of a compound is an estimate of the time required for a given amount of the compound to decrease to 1/e (0.368)

of its original concentration (at time zero). The tropospheric lifetime (τ) of vinyl chloride is related to the rate constant (k) and the hydroxyl radical concentration ([.OH]) by the equation (1):

$$\tau = (k[.OH])^{-1} \qquad (1)$$

In deriving the above equation, it is assumed that hydroxyl radicals are at a constant or steady state concentration in the troposphere.

Estimates have been made for the rate constant resulting from vinyl chloride's reaction with hydroxyl radicals. Perry et al. (1977) estimated the absolute rate constants over the temperature range of 299 Kelvin (^{o}K) to 426^{o}K. The limiting high pressure rate constant for a temperature of 299^{o}K is estimated to be 6.60 [illegible] x 10^{-12} cm^{3} molecule^{-1} second^{-1}. Howard determined rate constants for the reaction of vinyl chloride with hydroxyl radicals at 296^{o}K over a range of pressure where the highest pressure employed had not reached the limiting high pressure regime (Howard et al., 1976). However, when data obtained by Howard are extrapolated to the high pressure limit, the resulting rate constant is approximately 7 x 10^{-12} cm^{3} molecules^{-1} second^{-1} (Perry et al., 1976). This is in good agreement with the value reported by Perry et al. Table IV-2 summarizes the rate constant estimates, atmospheric lifetime estimates, average temperature assumed, and the method used to estimate the rate constant for the reaction of vinyl chloride with hydroxyl radicals and ozone (O_3).

The 24-hour average hydroxyl radical concentration in the troposphere has been estimated to range from 3 x 10^{5} to 3 x 10^{6} molecules cm^{-3} (Hewitt & Harrison, 1985). Because hydroxyl radicals are only present during daylight, the actual range for daytime concentrations is twice the 24-hour averages given above while nighttime concentrations are essentially zero. Daytime hydroxyl radical concentrations vary depending on many factors including photolytic activity and the concentration of ozone as well as other pollutants in the troposphere.

Using the rate constant determined by Perry et al. for an average tropospheric temperature of 299^{o}K and a range of hydroxyl radical concentrations ranging from 3 x 10^{5} to 3 x 10^{6} molecules cm^{-3}, the estimated tropospheric lifetime for vinyl chloride ranges from:

0.6 days for [.OH] = 3 x 10^{6} molecules cm^{-3}

to

5.8 days for [.OH] = 3 x 10^{5} molecules cm^{-3}

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TABLE IV-2

ATMOSPHERIC LIFETIME AND REACTION
RATE CONSTANT ESTIMATES FOR VINYL CHLORIDE

Reactant	Rate Constant[a]	Temperature (Kelvin)	Method	Atmospheric Lifetime[b]	References
OH	6.6 ± 0.66 x 10^{-12}	298	FP-RF[c]	1.6 - 3.9[d]	Perry et al., 1977
O_3	2.35 ± 0.23 x 10^{-19}	298	S-FTIR[e]	47[f]	Zhang et al., 1983
O_3	2.3 x 10^{-19}	NR	S-FTIR[e]	50	Gay et al., 1976
O_3	6.5 x 10^{-21}	296	S-UV[g]	4.9 years	Sanhueza et al. 1976

a - Rate constant units are cm^3 $molecule^{-1}$ $second^{-1}$.

b - The atmospheric lifetime is defined as the time required for a given amount of the compound to decrease to 1/e (0.368) of its original concentration (at time zero).

c - FP-RF = Flash photolysis, resonance flourescence.

d - Assumes a 24-hour average hydroxyl radical concentration ranging from 0.5 x 10^5 to 1 x 10^6 molecules cm^{-3} (Cupitt, 1980).

e - S-FTIR = Static system, Fourier transform infrared absorption spectroscopy.

f - Assumes a 24-hour average O_3 concentration of 1 x 10^{12} molecules cm^{-3} (Singh et al., 1978).

g - S-UV = Static system, ultraviolet absorption.

NR- Not Reported

As previously indicated, the concentration of hydroxyl radicals in the troposphere can vary considerably. However, several researchers recommend 24-hour average hydroxyl radical concentrations which are between 0.5×10^6 and 1×10^6 molecules cm^{-3} (Prinn et al., 1987; Winer, 1987; Singh et al., 1983; Cupitt, 1980; Cox et al., 1976; Davis et al., 1976). By using this range of 24-hour average hydroxyl radical concentrations (0.5×10^6 to 1×10^6 molecules cm^{-3}) in conjunction with the rate constants determined from Perry's rate constant at 299°K, the resulting range in atmospheric lifetimes is from 1.6 to 3.9 days. Using Howard's adjusted rate constant derived by extrapolation to the high pressure limit, and the same range of hydroxyl radical concentrations (0.5×10^6 to 1×10^6 molecules cm^{-3}), the atmospheric lifetime estimates for vinyl chloride ranges from 1.6 to 3.9 days.

The initial step in the reaction of vinyl chloride with hydroxyl radicals proceeds by the addition of hydroxyl radical to the carbon-carbon double bond. Although subsequent steps in the reaction mechanism are unknown, reaction products have been identified (Atkinson, 1986b). The major product resulting from hydroxyl radical attack on vinyl chloride is formyl chloride. An API sponsored study demonstrated that the yield of formyl chloride from the reaction of hydroxyl radicals with vinyl chloride is unity (one molecule of formyl chloride for each molecule of vinyl chloride) within the experimental error of the study (Pitts et al., 1984). The observed unit yield of formyl chloride implies a corresponding unit yield of formaldehyde and shows that the reaction of vinyl chloride with hydroxyl radicals proceeds by essentially 100 percent cleavage of the double bond. Equations (2) through (6) summarize the overall reaction scheme which seems most likely (Pitts et al., 1984).

$$\cdot OH + CH_2{=}CHCl \longrightarrow HOCH_2\dot{C}HCl \qquad (2)$$

$$HOCH_2\dot{C}HCl \xrightarrow{O_2} HOCH_2\dot{C}H(O\text{-}O\cdot)Cl \qquad (3)$$

$$HOCH_2\dot{C}H(O\text{-}O\cdot)Cl + NO \longrightarrow HOCH_2\dot{C}H(O\cdot)Cl + NO_2 \qquad (4)$$

$$HOCH_2\dot{C}H(O\cdot)Cl \longrightarrow \cdot CH_2OH + HCOCl \qquad (5)$$

(formyl chloride)

$$\cdot CH_2OH + O_2 \longrightarrow HCHO + \cdot HO_2 \qquad (6)$$

(formaldehyde)

Under atmospheric conditions, the reaction of vinyl chloride with ozone is not expected to be important compared to its reaction with hydroxyl radicals (Atkinson, 1986a; Atkinson and Carter, 1984). Several rate constant estimates have been made for the reaction of vinyl chloride with ozone. Based on these rate constants, atmospheric lifetime estimates range from about 47 days to approximately 5 years (Zhang et al., 1983; Sanhueza et al., 1976). Table IV-2 summarizes the atmospheric lifetime and rate constant estimates along with other pertinent information for vinyl chloride's reaction with ozone. Due to the variability among the estimated rate constants, a review publication made no recommendations as to the rate constant for the reaction of vinyl chloride with ozone (Atkinson and Carter, 1984). Furthermore, because the reaction of O_3 with vinyl chloride can be complicated by secondary reactions, the rate constants provided in Table IV-2 should be considered to be upper bound limits.

Products resulting from the reaction of ozone with vinyl chloride in the absence of scavengers are formyl chloride and formic acid (Zhang et. al., 1983). Other products resulting from the reaction of ozone with vinyl chloride include carbon monoxide, carbon dioxide, formaldehyde, and hydrochloric acid (Gay et al., 1976; Zhang et al., 1983).

As stated, the most important atmospheric removal mechanism for vinyl chloride is its daytime reaction with hydroxyl radicals. Vinyl chloride does not absorb in the actinic ultraviolet region, hence photolysis need not be considered. Reaction with nitrate radicals ($.NO_3$) may participate in the atmospheric removal of vinyl chloride. However, no kinetic data for $.NO_3$ are available, and studies of $.NO_3$ reactions are not yet sufficiently advanced that lifetime estimates can be made (Finlayson-Pitts and Pitts, 1986).

Little is known about the formation of vinyl chloride in the atmosphere. However, under experimental conditions, vinyl chloride has been shown to be a photodissociation product of 1,2-dichloroethane (Yano and Tschulkaw-Roux, 1980). In the study, 1,2-dichloroethane photodissociated when irradiated with ultraviolet light at 147 nanometers (nm) under pressure and in the presence of NO and CF_4 additives. Although it was not the purpose of the study to identify vinyl chloride formation pathways, vinyl chloride was one of the photodissociation products. Since wavelengths of ultraviolet light below 290 nm do not reach the troposphere, this formation pathway is not important for vinyl chloride in the atmosphere.

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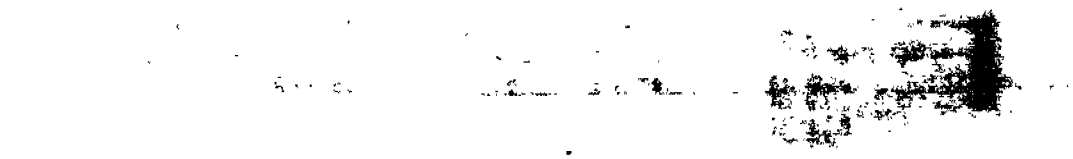

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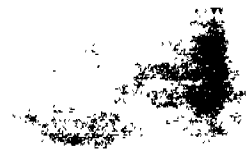
APPENDICES

June 1989

APPENDIX I

SCAQMD'S ANALYTICAL METHOD FOR SAMPLING AND ANALYSIS OF ATMOSPHERIC VINYL CHLORIDE



AMBIENT AIR SAMPLES AT LANDFILL PARIMETER

(REQUIRED BY SUBPARAGRAPH (c)(4)(D) OF RULE 1150.1)

SAMPLING FREQUENCY

Once per month or at less frequent intervals to be determined by the Executive Officer. The landfill owner/operator must file a written request with the Executive Officer if he wants to sample at intervals less frequent than monthly. Such a request must be supported with previous sampling results and other documentation. In determining if the requested sampling frequency is appropriate, the Executive Officer will consider previous ambient air sampling results, landfill surface sampling results, landfill gas composition and other pertinent data. The Executive Officer will notify the landfill owner/operator of his decision in writing.

NUMBER OF SAMPLES

The number of ambient air samples required will depend upon the topography and the size of the landfill. At a minimum, samplers will be sited to provide good meteorological exposure to the predominant offshore (drainage land breeze) and onshore (sea breeze) wind flow patterns. In areas with significant slopes,

local nightly drainage patterns will also be sampled. All sampling locations must be approved by the Executive Officer prior to sampling.

SAMPLING CONDITIONS

Ambient air sampling will be conducted on days when stable (offshore drainage) and unstable (onshore sea breeze) meteorological conditions are representative for the season. Preferable sampling conditions are characterized by the following meteorological conditions:

1. Clear cool nights with wind speeds two (2) miles per hour or less.
2. Onshore sea breezes with wind speeds 10 miles per hour or less.

No sampling will be conducted if the following adverse meteorological conditions exist:

1. Rain
2. Average wind speeds greater than 15 miles per hour for any 30 minute period.
3. Instantaneous wind speeds greater than 25 miles per hour.

Continuously recorded on site wind speed and direction measurements will characterize the micrometeorology of the site and serve to verify that the meteorological criteria have been

met during sampling.

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EQUIPMENT DESCRIPTION

An ambient air sampling unit consists of a [redacted] Tedlar (Dupont trade name for polyvinyl fluoride) [redacted] DC operated pump, stainless steel capillary tubing to control the sample rate to the bag, a bypass valve to control the sample flow rate (and mimimize back pressure on the pump), a rotameter for flow indication to aid in setting the flow, a 24-hour clock timer to shut off the sampler at the end of the 24-hour sampling period, and associated tubing and connections (made of stainless steel, teflon, or borosilicate glass to minimize contamination and reactivity). The physical layout of the sampler is shown in Figure 5 (see Appendix A).

EQUIPMENT SPECIFICATIONS

A. Power -- one 12V DC marine battery

The marine battery provides 12V DC to the pump and the clock.

B. Pump -- one 12V DC pump

The diaphragm is made of non-lubricated Viton (Dupont trade name for co-polymer of hexafluoropropylene and vinylidene fluoride) rubber. The maximum pump unloaded flow rate is

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4.5 liters per minute.

C. Bag -- one 10-liter Tedlar bag with a valve

TEDLAR BAG IS ENCLOSED IN A LIGHT-SEALED CARDBOARD BOX TO PREVENT PHOTOCHEMICAL REACTIONS FROM OCCURING DURING SAMPLING AND TRANSPORTATION. The valve is a push-pull type constructed of aluminum and stainless steel, with a vi[illegible] ring seal.

D. Rotameter

Rotameter is made of borosilicate glass and has a flow range of 3 to 50 cubic centimeters per minute. The scale is in millimeters with major graduations (labeled) every 5 mm and minor graduations every 1 mm.

E. Air flow control orifice -- 316 stainless steel capillary tubing

F. Bypass valve

G. Fittings, tubing, and connectors -- 316 stainless steel or teflon

H. Clock timer

Accuracy should be better than 1%.

I. Wind speed and direction monitor with continuous recorder

1. Wind speed -- 3 cup assembly, range 0 - 50 miles per hour with a threshold of 0.75 mile per hour or less.
2. Wind direction -- Vane, range 0 - 540 degrees with a threshold of 0.75 mile per hour or less.

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SAMPLING PROCEDURES

Ambient air samples will be collected at the perimeter of the landfill over a 24-hour period beginning between 10 A.M. and 11 A.M. using the above described self-contained portable sampling units. The samplers will be placed at the approved locations as described previously. One or more wind speed and direction monitors with continuous recorders will be installed and operated in areas approved by the Executive Officer to measure wind speed and direction throughout the entire sampling period. The wind direction transmitter must be oriented to true north using a compass.

QUALITY CONTROL PROCEDURE

The following quality control procedure is required for the ambient air sampling operation:

A. Assign an identification number to each sampling bag.

B. Clearly mark sampling locations on a landfill topographic map which is drawn to scale.

C. Document the date and time that the bag was put into operation, the sampling location, and the date and time that it was pulled from service.

D. Check the clock timer. The clock time and the actual time should agree within ± 3 minutes.

E. Check whether or not the pump is running.

F. Check the rotameter reading. The float (measured at the middle) should be within +3 and -6 minor graduations of the marked setting for 6.0 cubic centimeters per minute. If the rotameter setting exceeds the above limits adjust the bypass valve to correct the flow rate. Make sure that the flow has stabilized (at least [illegible] minutes at constant flow) since there may be a lag time between the adjustment and final flow.

G. Check whether the bag valve is in the open position. If the valve is in the closed position open the valve and and record the time on the quality control sheet.

H. Remove the bag for analyses at the end of the 24-hour period. KEEP THE BAG IN A LIGHT-SEALED CONTAINER AT ALL TIMES.

Data for each sample collected must be entered on a quality control sheet as shown in Figure 3 (see Appendix A). Prior to use, the Tedlar bags should be evacuated and filled with purified nitrogen three times to flush out the old sample. Before sending the bags into the field, they should be checked to make sure that the vacuum has been maintained. Remove from service any bag that has experienced any leakage.

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ANALYTICAL PROCEDURES

Bag samples collected must be analyzed within 72 hours of collection, or shorter period if notified by the Executive Officer, for total organic compounds and toxic air contaminants using analytical methods identified in Table 1 (see Appendix A) or equivalent methods approved by the Executive Officer. NOTE THAT ALL BAG SAMPLES MUST BE KEPT IN LIGHT-SHIELD CONTAINERS TO AVOID PHOTOCHEMICAL REACTIONS.

REPORTING OF THE RESULTS

The following data must be submitted to the Director of Engineering within 45 days after the end of the quarterly reporting period for the landfill or 45 days after the analytical results are available whichever is sooner. A different submittal time may be implemented upon approval of the Executive Officer.

A. Volume concentration of total organic compounds (reported as methane and total non-methane hydrocarbons).

B. Volume concentration of toxic air contaminants identified in these guidelines.

C. Barometric sea level pressure (inches of mercury) on the d the samples were collected. If a barometer is not availab at the landfill site, use the National Weather Service dat at the nearest station.

D. Wind speed and direction data.

E. A drawn to scale landfill topographic map with sampling locations clearly marked and numbered.

F. Quality control data sheets.

VINYL CHLORIDE ANALYSIS -- METHOD A DRAFT

Instrument: Hewlett Packard 5700A Gas Chromatograph

Detector: Flame Ionization

Injection System: Two Carle valves, [redacted] and a 4-port, are plumbed to contain a 4 ml, 1/4" stainless steel sample loop with pre-column, back-flush and pressure balance. See Figure D for valve plumbing.

GC Conditions:

Detector Temp. -	200°C
Oven Temp. -	60°C
Analytical Column -	6' x 1/4" ss, Chromosil 310, 60/80 mesh
Pre-Column -	6' x 1/8" ss, Durapack n-octane/Porasil 100/120 mesh
Carrier Gas -	80/100 ml/min nitrogen

Data Gathering: A Hewlett Packard 3388A Integrator is used to calculate concentration by peak area comparison to an external standard.

Valve Timing: Timing and switching events are performed by the integrator. 1.4 minutes after injection both valves are switched to the back-flush or initial position

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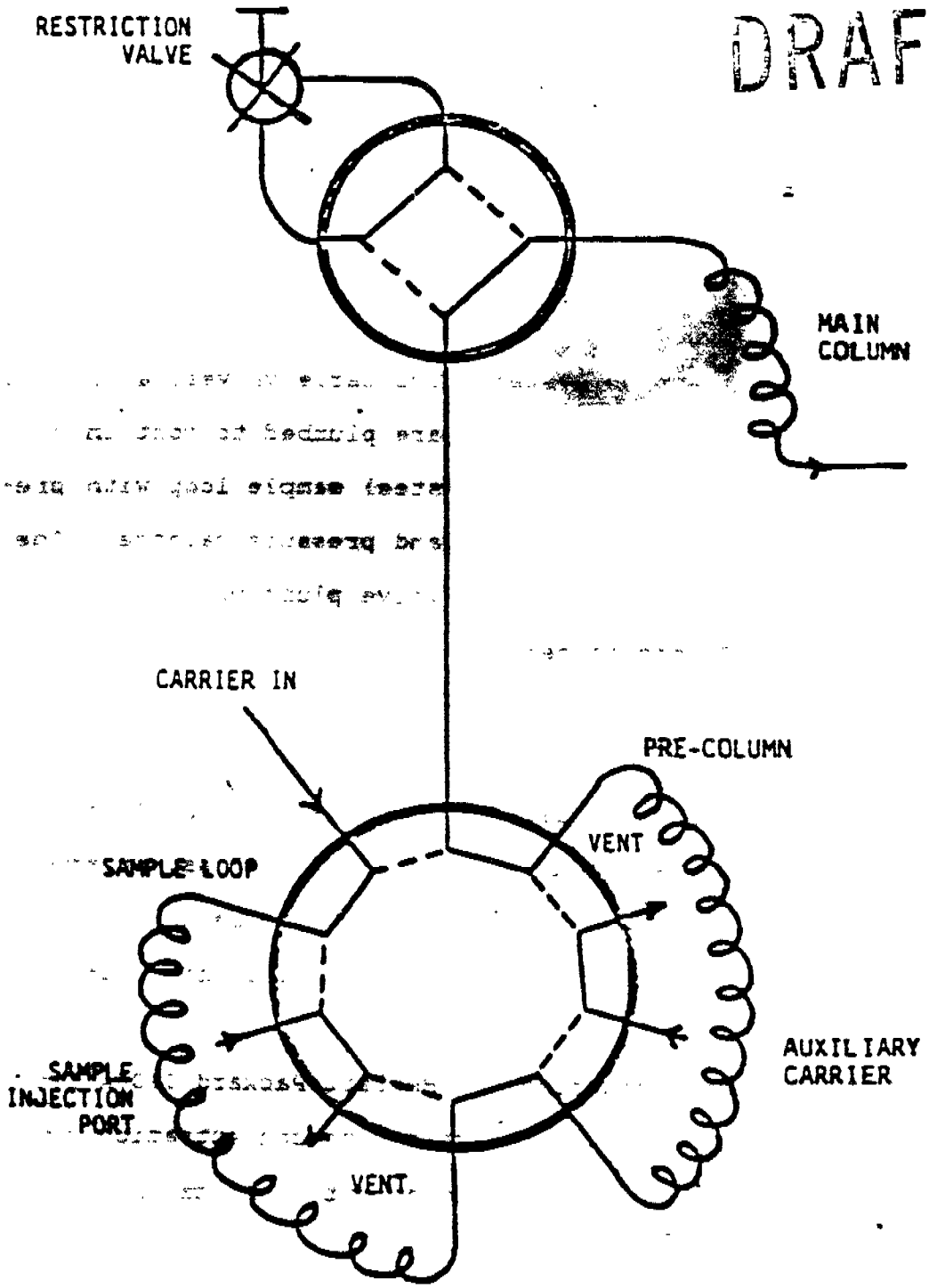

FIGURE D:
Valve Plumbing

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Standard: Approximately 1 ppm vinyl chloride is prepared by Scot Environmental Technology and certified to ±2% analysis.

Range: 2 ppb to 1% vinyl chloride

Accuracy: ± 1 ppb in the range 2 - [redacted] range 50 ppb to 1%.

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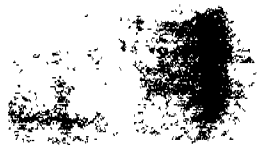

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APPENDIX II

DESCRIPTION OF GLEIT'S METHOD

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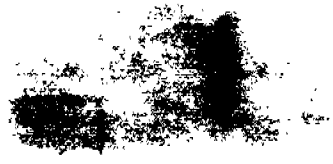

APPENDIX I

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APPENDIX II

DESCRIPTION OF GLEIT'S METHOD

Gleit's method accounts for the concentrations below the [illegible] setting them equal to the "below-LOD mean" μ_{BLOD}, the [illegible] of the normal distribution below the [illegible] and the equations reported in Gleit's paper show that his method is more accurate than other commonly used approximations.

The below-LOD mean of a normal distribution of a variable with a limit of detection L is given, in terms of L and the mean μ and the standard deviation σ of the distribution, by equation (1):

$$\mu_{BLOD} = \mu - \sigma * [\, f((L-\mu)/\sigma) / F((L-\mu)/\sigma) \,] \qquad (1)$$

In equation (1), f and F are, respectively, the probability density function and cumulative distribution function of the standard normal distribution. The "Estimated Concentrations for Samples Below the LOD" reported in Table II-2 are the below-LOD means of the assumed lognormal distributions of the concentrations. These below-LOD means are computed from equation (2) in terms of parameters of the associated normal distribution: the LOD L, the mean concentration from Table II-2, and the estimated standard deviation (which is not tabulated).

$$\exp(\mu + 0.5 * \sigma^2) * F((L - \mu - \sigma^2)/\sigma) / F(L - \mu/\sigma) \qquad (2)$$

We now describe how Gleit's method estimates the mean and variance of the assumed normal distribution. The mean and variance cannot be estimated by merely substituting into standard formulas, if below-LOD concentrations are to be set to th below-LOD mean. On the one hand, the mean and variance must be known in order to calculate the below-LOD mean from (1); on the oth r hand,

the below-LOD mean must be known if it is to be used in the calculation of the mean and variance. Statistical theory, by asserting that a "best -fitting " mean and variance for the distribution exist, provides a way out of this dilemma. Gleit uses a simple iterative procedure to compute these best-fitting parameters. Since his procedure can be simply described in words, a written description is given, supplemented where necessary by equations written in a notation more convenient than Gleit's.

Starting with initial guesses $\mu(0)$ and $\sigma^2(0)$ for the mean and variance, the procedure repeatedly generates new estimates of the mean and variance by the two-step computation described below until successive estimates of the mean and variance converge sufficiently (The K-th pair of estimates are denoted by $\mu(K)$ and $\sigma^2(K)$.). The two steps are:

(a) The K+1-st below-LOD mean $\mu_{BLOD}(K+1)$ is computed by substituting $\mu(K)$ and $\sigma(K)$ (the square root of $\sigma^2(K)$) into equation (1).

(b) The K+1-st estimate of the mean, $\mu(K+1)$, is computed in the usual way with $\mu_{BLOD}(K+1)$ substituted for the sample values below the LOD. The K+1-st estimate of the variance, $\sigma^2(K+1)$, is also computed in the usual way, with an analogous substitution for sample values below the LOD: the squared deviations from the mean of concentrations below the LOD are set equal to the average squared deviation from the mean of the below-LOD portion of the distribution.

Let the N sample items be X(1),....,X(N), and let p be the number of sample items below the LOD. $\mu(K+1)$ is computed by:

$$\mu(K+1) = (1/N)\,\Sigma\, Y(J), \text{ where } Y(J) = X(J) \text{ if } X(J) \geq L$$
$$\text{and } Y(J) = \mu_{BLOD}(K+1) \text{ otherwise.}$$

$\sigma^2(K+1)$ is computed by:

$$\sigma^2(K+1) = (1/N)\,\Sigma\, D^2(J), \quad \text{where } D^2(J) = (X(J) - \mu(K+1))^2$$
$$\text{if } X(J) \geq L, \text{ and } D^2(J) = \sigma^2_{BLOD}(K+1) \text{ otherwise.}$$

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The quantity $\sigma^2_{BLOD}(K+1)$, the average squared deviation of the below-LOD portion of the distribution, is computed from the following equation:

$$\sigma^2_{BLOD}(K+1) = \sigma^2(K)*[1 - Z(K)* (f(Z(K)) / F(Z(K)))],$$

where $Z(K) = ((L-\mu(K)) / \sigma(K))$.

Gleit's method nearly always converges in a few st[illegible] only a few distinct values above the detection limit, in which [illegible] converge very slowly. Gleit's method and closely related methods appear to be the best available estimates of the mean when the sample includes values below the LOD, as is demonstrated by the simulations reported in Gleit's paper.

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APPENDIX III

ESTIMATE OF TOTAL EXPOSURE TO VINYL CHLORIDE FROM INDOOR AIR

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INDOOR AIR EXPOSURE/OTHER ROUTES OF EXPOSURE ASSESSMENT FOR VINYL CHLORIDE

I. BACKGROUND

Health and Safety Code Section 39660.5 directs the Board, in its toxic air contaminants identification process, to assess exposures to toxic air contaminants in indoor as well as outdoor environments. Indoor exposure assessment has become increasingly important as an integral part of air exposure assessment because (ARB 1987, 1989):

1. people spend a predominant proportion of their time indoors; and

2. personal and indoor air monitoring data indicate that some pollutant concentrations are regularly higher indoors than outdoors.

Indoor air exposure data, combined with outdoor air exposure data, can provide a realistic estimate of personal exposure through the air environment. A more detailed discussion of indoor air exposure is contained in Appendix A.

Indoor air data can be obtained either by personal air sampling or by fixed-site air sampling. In personal sampling, the sampling equipment is carried by an individual and air samples are taken wherever the individual may be. In contrast, fixed-site air samplings refer to air samples taken at a fixed location. Personal air sampling data generally provide a more realistic estimate of individual exposure. Since most people spend 80-90% of their time in indoor environments, personal air sampling data are strongly weighted by indoor air exposure data.

While the main objective of this report is to define exposure through the air, this report also presents personal exposure data through other media. The inclusion of these data will provide an useful perspective of the overall exposures to toxic air contaminants through environmental media. The need for total exposure assessment and some of the issues and concepts involved in total exposure estimates are discussed in Appendix B.

II. INDOOR AIR EXPOSURE TO VINYL CHLORIDE

A. PERSONAL AIR SAMPLING

Personal air sampling data for most organic compounds come from the Total Exposure Assessment Methodology (TEAM) studies conducted by the Environmental Protection Agency (EPA) during 1980-85 (Wallace, 1987; USEPA 1987a,b; Wallace & Clayton, 1987; Wallace et al., 1986; Pellizzari et al., 1986). Although vinyl chloride was included in the initial pilot study (Phase I) of the TEAM project, vinyl chloride was deleted from the subsequent main studies (Phase II and III). The deletion of vinyl chloride was due to two

factors (Pellizzari, 1987). First, Tenax, the most cost-effective sampling medium which could collect a number of compounds of concern, was not suitable for vinyl chloride collection. In addition, the alternative sampling method used to collect vinyl chloride in the pilot study did not provide the required reliability for detecting low vinyl chloride concentrations.

Consequently, the pilot study provides the only available personal air sampling data for vinyl chloride. Based on this limited information, indoor air exposure to vinyl chloride is apparently low. In monitoring nine subjects in New Jersey and three from North Caroline for several days on three separate visits over a 6-month period, all of the 136 air samples taken were below the limit of detection (Wallace et al. 1984). The range of the limit of detection was from 0.63 to 2.84 ug/m^3.

B. FIXED-SITE AIR SAMPLING

As part of a recent follow-up TEAM study in California, fixed-site monitoring stations were installed to monitor indoor and outdoor air concentrations of a number of organic compounds (Pellizzari, et al., 1989). Specially designed stainless steel canisters were used for collecting vinyl chloride air samples from homes in the Los Angeles area for two seasons. Ten homes were sampled in the Winter season and eight of the original home were sampled in the Summer season. Canister air samples were collected indoors and outdoors at each home during two, 12-hour periods. Samples obtained in the Winter season did not provide reliable data due to technical problems. All outdoor or indoor samples, a total of 32 samples, obtained in the Summer season indicated that vinyl chloride air concentrations were below th limit of detection. The samples were analyzed by two analytical methods with limits of detection at about 0.55 and 148 ug/m^3, respectively.

A similar TEAM study was conducted in Baltimore. Indoor air concentrations of vinyl chloride in about 160 homes were monitored by fixed-site sampling stations. Based on partially analyzed results, vinyl chloride was not detected in indoor air environments. The limit of detection was quoted by the researcher as 20-40 ug/m^3 (Pellizzari, 1987).

C. SPECIAL SITUATION AIR MONITORING

In [redacted] Coast Air Quality Management District (SCAQMD) collected [redacted] samples in the vicinity of the BKK landfill (a Class I site). A total of more than 500 air samples were taken at two outdoor [redacted] of four sites inside downwind residences (SCAQMD, 1982). All the [redacted] (24% of the total sampled) that equaled or exceeded th state vinyl chloride air quality standard of 10 ppb (26 ug/m^3) were taken inside the residences. The highest recorded indoor vinyl chloride concentration was 50 ppb (130 ug/m^3). The limit of detection was 2 ppb (5.2 ug/m^3).

In late 1984, the SCAQMD staff took about ten grab-samples inside the water meter boxes of residences adjacent to the Operating Industrial Inc.

(OII) landfill (SCAQMD, 1985a). Vinyl chloride with other landfill gases, had migrated to and accumulated in water meter boxes at concentrations ranging from 13 to 36000 ppb (31.2-93600 ug/m^3). In 1985, the SCAQMD (1985b) conducted further monitoring by grab-samples inside some of the residences and found indoor vinyl chloride air concentrations at 8 to 100 ppb (20.8-260 ug/m^3). Present indoor concentrations of vinyl chloride in these residences near OII landfill may be lower since recent routine monitoring of water meter boxes have not detected significant levels of landfill gases due to improvements of OII's landfill gas collection system (Coy, 1987).

C. SUMMARY

Except for houses near landfills, the vinyl chloride concentration in indoor air appears to be low. However, this conclusion is based on the evaluation of a very limited database. In addition, the sampling and analytical procedures for vinyl chloride indoor air monitoring are less than satisfactory as evidenced by the wide range for reported limits of detection. The limit of detection, 0.55 ug/m^3, reported in the latest California TEAM study appears to be the most reliable. This limit of detection will be used to estimate the upper limit exposure for house not adjacent to landfills.

For houses near landfills, the measured high indoor vinyl chloride air concentrations may indicate the potential impact of nearby emission sources to indoor environments. A more detailed discussion of landfill emissions as a source of indoor vinyl chloride is presented in section III(C).

III. POTENTIAL SOURCES OF INDOOR VINYL CHLORIDE

A. PLASTIC MATERIALS AND CONSUMER PRODUCTS

Vinyl chloride has not been used in any consumer products since 1974 when vinyl chloride was banned as a propellant in household aerosol products and as an ingredient of drug and cosmetic products (IARC, 1979).

Because of its versatility, plastic products made of polyvinyl chloride (PVC) and other vinyl chloride polymers are ubiquitous in any household. Before being made into different products, PVC polymer is in the form of a resin that is made by chemically linking the vinyl chloride molecules. Individual vinyl chloride molecules are also called vinyl chloride monomer (VCM). [illegible] can remain in the PVC resin for some time depending on the int[illegible] amount of the unreacted VCM. Therefore, an indirect source of vinyl c[illegible] may come from the release of unreacted VCM from these plastic [illegible]. For example, during 1975 to 1976, low VCM concentrations, ranging from below 2 ppb to 1.2 ppm, were measured in automobile interior air space under experimental conditions (U.S.EPA, 1976; 1977).

Emissions of unreacted VCM have been greatly reduced due to improvements in monomer stripping technology (Wheeler, 1981). In the past, residual VCM

concentrations in the PVC resins at the time of shipment ranged as high as 2000 ppm. Currently, PVC resins contain about 10 ppm residual VCM at the time of shipment and may lose VCM at a rate of 20 to 50% per month during storage. In addition, most of the VCM will vaporize and escape during the high temperature processes in which PVC resins are melted and made into final products. Thus, commercial products made of PVC resins do not now contain significant residual vinyl chloride for later emission.

B. VAPORIZATION FROM WATER SOURCES

Water can serve as a medium to carry pollutants from outdoor to indoor environments. Once in contact with air indoors, volatile chemicals such as vinyl chloride can leave the water and enter the air. Human activities such as using water for cooking, heating or showering can promote rapid vaporization of vinyl chloride from water. Industrial solvent contaminated surface or ground water may, therefore, bring outdoor vinyl chloride indoors via the water supply.

In California, surface water is generally free of vinyl chloride (Sharrp, 1987). In assessing ground water quality, the California Department of Health Services (CDHS, 1986) reported that only one out of the 2,947 wells for large public water systems was contaminated with vinyl chloride. The maximum concentration found in that well was 23 ug/l with a median value of 20 ug/l. Vinyl chloride has not been detected in wells used for small public water systems (CDHS, 1987). The limit of detection of vinyl chloride in water is 0.5 ug/l. Based on this information, vinyl chloride in the water supply will have an insignificant impact on the indoor vinyl chloride air concentration.

C. VINYL CHLORIDE FROM LANDFILL GAS

Homes built on or near landfills containing vinyl chloride or related chlorinated hydrocarbons may have high indoor air concentrations of vinyl chloride. Vinyl chloride emission from landfills can be caused by the vaporization of vinyl chloride that was originally disposed there. Class I landfills that are designated for toxic waste are likely to contain vinyl chloride waste. In addition, microbiological conversion of chlorinated hydrocarbons can produce and emit vinyl chloride in situ (Walton, Hallen and Pyne, 1987).

[redacted] (1987) reported their evaluations of over 20 Class II landfills that are designated only for municipal waste. Ninety percent of these landfills contained measurable amounts of vinyl chloride and the concentrations at half of these landfills were above 1000 ppb. These high concentrations were measured by grab-sampling, an instant filling of a two-liter evacuated flask, at ground levels or at landfill gas collection points. For five of the landfills, 24-hour bag sampling was also conducted. Only one of these five landfills produced measurable 24-hour concentrations of vinyl chloride off-site.

There are at least two ways that vinyl chloride from landfills may contribute to indoor vinyl chloride concentrations of nearby residential houses. First, houses that are located downwind from landfills can receive vinyl chloride through direct outdoor air influx into indoor environments. Secondly, landfill gases, carrying vinyl chloride, can migrate underground and enter houses through substructures. The rate of accumulation of vinyl chloride indoors depends heavily on the soil permeability, source strength, air exchange rate and structure of the house. Higher indoor than outdoor vinyl chloride concentration may occur because vinyl chloride is more rapidly destroyed by direct exposure to sunlight. Another contributing factor is the trapping of migrating, subterranean landfill gas by the house.

As discussed in Section II(B), houses located near Class I landfills had higher indoor than outdoor air concentrations of vinyl chloride. The accumulation of high vinyl chloride concentrations in the water meter boxes indicated that landfill gas containing vinyl chloride can migrate underground and enters nearby indoor environments. Controlled release or combustion of landfill gas on site may slow down vinyl chloride subterranean migration.

D. OTHER FACTORS THAT MAY INFLUENCE INDOOR CONCENTRATIONS

A minute amount of vinyl chloride has been identified in the smoke of cigarettes (1.3-16 ng/cigarette) and of little cigars (14-27 ng/cigar) (IARC, 1985; Hoffmann, Patrianakos and Brunnemann, 1976). The vinyl chloride level in the mainstream smoke may be determined by the total inorganic chloride content of the tobacco. The contribution from tobacco smoke appears to have insignificant impact on the indoor-air concentration of vinyl chloride.

E. SUMMARY

In general, there are very few, minor emission sources of vinyl chlorid indoors. However, houses that are situated near landfills may accumulate vinyl chloride in the indoor environment due to subterranean gas migration and direct air infiltration. Some of these houses may have indoor air levels f vinyl chloride higher than the State of California Ambient Air Quality Standard for vinyl chloride.

The results from SCAQMD's five hundred 24-hour bag samples can be used to estimate the upper limit of indoor air exposure to vinyl chloride in houses near landfills (SCAQMD, 1982). The results obtained by grab-sample monitoring, however, are not useful for estimating long-term indoor exposure to vinyl chloride.

IV. OTHER ROUTES OF VINYL CHLORIDE EXPOSURE

A. WATER INGESTION

The major source of drinking water for California is surface water which does not have detectable vinyl chloride concentrations. Ground water used for

public water systems is also relatively free of vinyl chloride (CDHS, 1987, 1986). The detectable limit of vinyl chloride in water is 0.5 ug/l (0.5 ppb). Based on this information, vinyl chloride exposure through drinking water is judged to be insignificant under ordinary situations.

B. FOOD INGESTION

Vinyl chloride is not one of the compounds that have been monitored routinely in U.S. food and food products. However, before 1973, vinyl chloride was found in food and beverages markated in vinyl chloride polymer containers or packaging materials (IARC, 1979). At that time, levels as high as 20 mg/kg (ppm) of vinyl chloride monomer were present in alcoholic beverages packaged in this material. Vinyl chloride was also found in edible oils, butter and margarine at 0.05-14.8 mg/kg.

When cleaner PVC resins became available after 1978, vinyl chloride polymer containers contained only about 10 ppb of residual vinyl chloride monomer. In its recent rule-making proposal, the Food and Drug administration (FDA) (1986) estimated vinyl chloride exposure from food and beverages packaged with vinyl chloride polymer materials. These materials include liquor bottles, wine bottles, oil bottles, vinyl chloride homopolymer film and materials made with vinyl chloride-vinylidene chloride copolymers. Based on a conservative approach, the FDA's estimated lifetime-averaged individual exposure to vinyl chloride would not exceed 25 nanograms per day.

V. ESTIMATES OF TOTAL EXPOSURE FROM INDOOR AIR AND OTHER ROUTES

The estimated daily dose of vinyl chloride from different environmental media are presented in Table 1. From the Table, exposure to vinyl chloride in indoor air, food and water appears to be insignificant. However, exposure to vinyl chloride indoors in homes near landfills may be the major portion of total vinyl chloride exposure.

A. AMBIENT AIR EXPOSURE

The 24-hour average concentration of vinyl chloride outdoors rang s from below the LOD of 2 ppb (5.2 ug/m^3) to the maximum 24-hour average concentration of 15 ppb (39 ug/m^3) as measured near BKK in 1987.

B. [illegible] EXPOSURE

The [illegible] concentration of vinyl chloride indoors in houses not near landfill[illegible] estimated to be below the limit of detection (0.55 ug/m^3 or 1.4 ppb). For homes that are located near landfills, the highest observed daily average measurement, 50 ppb or 130 ug/m^3, is used for a conservative estimate.

C. FOOD INGESTION

The estimate of daily dose reported by FDA (1986) is directly used.

D. DRINKING WATER

The relative contribution of drinking water to daily exposures of vinyl chloride appears to be insignificant. The average concentration of vinyl chloride in drinking water is estimated to be below the limit of detection (0.5 ppb or 0.5 ug/l).

E. ASSUMPTIONS

Some of the assumptions used for making the daily dose estimates from different environmental media are:

1. The average person ingests 2 liters of drinking water per day;
2. The average person inhales an average of 20 cubic meters of air daily;
3. Dermal exposure is negligible; and
4. 100% of the pollutant ingested or inhaled is absorbed.

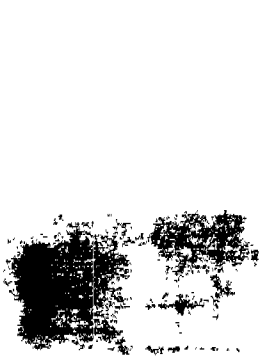

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Table 1: Estimated Doses Of Vinyl Chloride Exposure Through Different Media

Media	Daily Dose	Refs.
AIR		
Outdoor air	< 104 to 780 ug	Table II-1
Indoor Air		
Homes not near landfills	less than 11 ug	Pellizzari et al., 1989
Homes near landfills	up to 2600 ug	SCAQMD, 1982
FOOD		
Including beverages	less than 0.025 ug	FDA, 1986
WATER-DRINKING PURPOSES		
Surface/Ground Water	less than 1 ug	CDHS, 1986; 1987

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APPENDIX A

INDOOR AIR EXPOSURE

Prediction of health risk from pollutants depends upon knowledge of total personal exposure to the pollutants. For direct exposure to air pollutants, the dose of pollutant received through the respiratory system is the basic quantity needed for risk assessment. In general, that dose depends on: a) the pollutant concentration in the environment occupied by an individual (exposure concentration); b) the length of time spent in that environment (exposure duration); c) the rate of breathing in that environment; and d) other physiological factors. Exposure through air can be estimated by using only the first two parameters, exposure concentration and exposure duration.

Historically, outdoor air concentrations of an air pollutant have been used as a surrogate for estimating personal air exposure. However, studies of indoor environments and of personal exposures to pollutants have revealed that indoor concentrations of some pollutants are regularly higher than outdoor concentrations of those pollutants. In addition, human time-activity pattern studies show that people spend most of their time in non-outdoor microenvironments such as in their homes, work places, transportation vehicles and public buildings. On the average, people spend 80-90 percent of their time indoors.

The California Legislature recognizes the importance to risk assessment of considering both indoor air exposure and outdoor air exposure. The current statute requires the Board, when identifying toxic air contaminants, to assess exposures in indoor, as well as outdoor, environments (H&SC Sec. 39660.5). This combined indoor plus outdoor, or total air, exposure assessment permits more accurate public health risk estimates for airborne toxics. Indoor air exposure information can also provide direction for the control of many toxic air contaminants.

An even more realistic estimate of total air exposure would be the sum of the products of the pollutant concentration in each microenvironment and the fraction of time people spend in that microenvironment. However, time-activity and indoor/personal monitoring data are limited and insufficient at this time for quantifying the concentration of most air pollutants in each microenvironment. Based on this limited database, indoor air exposure assessments of most of the toxic air contaminants will be crude estimates.

Risk assessments, based only on outdoor air concentrations, may greatly underestimate health risk to the public. For some pollutants present in high concentrations indoors, ventilation with clean air is the only feasible method of reducing exposure. The Board must, therefore, manage outdoor concentrations of toxic air contaminants, not only to reduce significant outdoor exposures where they occur, but also to preserve a clean air supply for controlling indoor exposure to these substances.

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APPENDIX B

TOTAL EXPOSURE FROM ALL MEDIA

The concentrations of some pollutants have been measured in different environmental media such as air, water, food, pesticides and drugs. Ideally, these measurements can be integrated to estimate the total exposure to those pollutants through all the environmental media. Total exposure data are critical for setting priorities and formulating regulatory actions that can best achieve overall personal risk reduction.

While one of the main objectives of this report is to define exposure through the air medium, personal exposure data through other media are also included. Exposure data are presented according to three basic routes of exposure which are inhalation, ingestion, and skin absorption.

The combination of exposure data from all media will allow the determination of the total human exposure to a toxic air contaminant through the environment. To determine the added risk caused by a particular exposure, both the shape of the dose-response curve and the previously existing exposure level must be known. Although the exposure through a particular medium may be small, its addition to exposures through other media could provide a total dose in excess of a postulated "safe level".

In addition, the pathway of pollutants in the environment is dynamic and complex. Pollutants emitted into the environment in one medium can remain in that medium, transfer to another medium, and/or disperse into a number of media. This results in different routes of exposure. For example, solvents emitted as water pollutants can become airborne and cause exposure through inhalation. Airborne lead particles can be deposit onto food and result in exposure through ingestion. Thus, inclusion of exposure through all media will provide a more accurate exposure estimate for each route of exposure, including inhalation, which is the Board's primary concern.

Documenting exposure to toxic substances through different media can serve as a stimulus for coordinated risk reduction efforts among different regulatory agencies. Other regulatory agencies are more likely to increase their efforts to control the overall exposure through other media if they are made aware of such exposure data.

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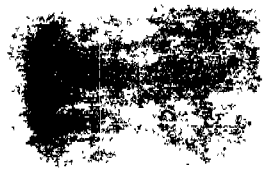
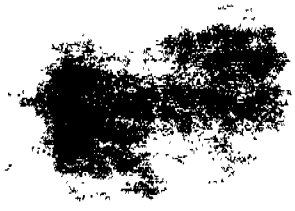
APPENDIX IV

INFORMATION REQUEST LETTER WITH ATTACHMENTS AND RESPONSES





STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

DRAFT

April 4, 1985

Dear Sir or Madam:

Subject: Request for Information Regarding Vinyl Chloride

I am writing to request information on the health effects of vinyl chloride as part of our toxic air contaminant program. This program is based on Health and Safety Code Sections 39650, et seq. which require the ARB to identify compounds as toxic air contaminants and once identified to develop and adopt control measures for such compounds. After consultation with the staff of th Department of Health Services (DHS), we have selected vinyl chloride as a candidate toxic air contaminant to be evaluated in accordance with the provisions of Health and Safety Code Sections 39650, et seq. During our evaluation of vinyl chloride, we will consider all available health information regarding this compound. Additionally, we are soliciting information regarding possible biological production of vinyl chloride.

Before the ARB can formally identify a compound as a toxic air contaminant, several steps must be taken. First, the ARB must request the Department of Health Services to evaluate the health effects of candidate compounds. Second, the ARB staff must prepare a report which includes the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted in response to this request will be considered in the ARB report to the Panel. Although any person may also submit information directly to the Panel for its consideration, I urge you to submit all information at this time for our consideration in the development of the report to the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Last, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the Air Resources Board and will be the basis for any regulatory action by the Board officially to identify a compound as a toxic air contaminant.

Prior to formally requesting the DHS to prepare a health effects evaluation of vinyl chloride, we are providing, pursuant to the provisions of

CMA 010618

Section 39660(e) of the Health and Safety Code, an opportunity to interested parties to submit information on the health effects of vinyl chloride which he or she believes would be important in DHS's evaluation of vinyl chloride as a candidate toxic air contaminant.

In March 1985, we received a reference search on vinyl chloride health effects using the MEDLINE and TOXLINE Information Services. These information services include material available to the public in late 1984. The attached bibliography lists the references from this information search. We are requesting pertinent information on vinyl chloride health effects, including any material that may not be available to the public, that is not included in the attached bibliography.

Pursuant to the provisions of the Public Records Act (Government Code Sections 6280 et seq.), the information you provide will be a public record and subject to public disclosure, except for trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law. The information may also be released to the Environmental Protection Agency, which protects trade secrets and confidential information in accordance with federal law, and to other public agencies which are also required to protect such information.

To expedite the review process, we ask that any information which you believe should be regarded as "trade secret" be clearly marked and separated from other information. You may identify portions of the information you submit as "trade secret" in accordance with Health and Safety Code Section 39660(e). The claim of trade secrecy must be supported upon the request of the Air Resources Board. Other information claimed to be trade secret and information otherwise claimed to be exempt from disclosure may be identified as confidential in accordance with Section 91011, Title 17, California Administrative Code. Section 91011 requires that the claim of confidentiality be accompanied by specific supporting information.

I would appreciate receiving any relevant information you wish to submit by May 19, 1985. Your help in expediting our review will be greatly appreciated. Please send the information to the attention of:

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Vinyl Chloride
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have any further questions regarding health effects information, please contact Mr. John Batchelder at (916) 323-1505. For any other questions, please contact Mr. Don Ames at (916) 322-8285.

April 4, 1985

DRAFT

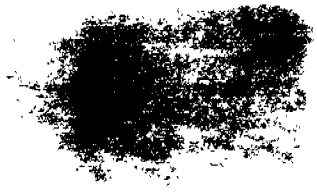
If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate compounds, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

for Peter D. Venturini, Chief
Stationary Source Division

cc: Alex Kelter, DHS
Lori Johnston, DFA
Wayne Morgan, President, CAPCOA
Jan Bush, Executive Secretary, CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Sally Tanner, Chairwoman, Committee on Toxic Materials
Senator Ralph Dills, Chairman, Committee on Governmental Organizatio
Senator Art Torres, Chairman, Committee on Toxics and
Public Safety Management
Emil Mrak, Chairman and Scientific Review Panel
Members
APCOs

Attachment



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DRAFT

CHA 010630

The Law and Policy of Toxic Substances Control

A Case Study of Vinyl Chloride

David

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By The Johns Hopkins
Baltimore and London

dards, however, give virtually no guidance on the relative weight to be accorded health and environmental interests in comparison to economic ones, and to date, the agencies' actions reflect Congress's lack of consensus on the issue of acceptable risk.

A measure of guidance to decision makers in the face of uncertainty and lack of consensus is provided by the observation that regulatory decisions involve moral as well as economic values. We may begin with the observation that the sacrifice of an individual for the benefit of a group is acceptable if the benefit served is the group's survival or the fulfillment of some other basic need. The sacrifice is morally unacceptable, however, if it is for no more important benefit than the provision of the luxuries of our consuming society. That some must die so that all can eat is one thing; that some must die so that all can have see-through food packaging is another.[80] Particularly where non-essential products are concerned, the long term goal of toxic substances control and the long-term effect of each regulation should be to channel economic growth away from industries hazardous to health and towards safer products and forms of employment.

As the case study in Part II shows, the problems of deciding under uncertainty and of balancing incommensurable interests have pervaded the regulation of VC. Reluctance to face these difficult problems accounts in part for the fact that in more than four years the agencies have set standards for only two of the major sources of exposure to VC. While the standards that have been set and the proposals that have been put forward are by no means totally deficient, there have been significant instances in which the agencies have made factually or logically insupportable conclusions, or in which they have ignored evidence and failed to draw conclusions the evidence virtually demands. In all instances, the agencies have held back from imposing standards that would require any significant economic change in the regulated industries. The industries' profits, volume of production of the regulated substances, and future growth prospects have been virtually unaffected. One may question whether the benefits of VC production and use are substantial enough to justify such extreme deference to the

80. Many value judgments are not so easily made as the distinction between food and food packaging. Typically, economists take the position that neutrality is required at all times in this regard, because of the difficulty of making so many of these value judgments. *See, e.g.*, *Evaluation of Life and Limb*, *supra* note 74, at 495-96, 703. But the difficulty of making the hard decisions does not require us to avoid making the clearcut ones. And one need not accept the view that the values of a society must be regarded as inviolate. They change in a manner not fully understood, but certainly not free from the influences of groups, such as the business community, with strong financial interests in promoting the materialistic, consuming behavior of the public. As Professor Tribe puts it: "[W]e cannot simply assume that we must stand mute when confronting the ultimate question of whether we want our children, and their children's children, to live in—and enjoy—a plastic world." Tribe, *Ways Not to Think About Plastic Trees* in WHEN VALUES CONFLICT 61, 70 (L. Tribe, C. Schelling, & J. Voss eds. 1976) (emphasis in original). *See also* Dorfman, *An Afterword: Humane Values and Environmental Decisions* in *id.* at 153-73.

industries' market position. This question is pursued in the sections that follow, each detailing the regulatory situation with regard to one or more of the many sources of human exposure to VC.

II

VINYL CHLORIDE CASE STUDY

A. An Introduction to Vinyl Chloride

In the previous section the problems of deciding under uncertainty and determining socially acceptable risks were discussed as they apply to toxic substances regulation generally. In this case study, these problems are considered as they have affected agency decision making with respect to the regulation of vinyl chloride. The case study begins with essential background material on the applications of VC, on the industries which create, transform, and use it, and on its deadly properties. Subsection 1 surveys the chemical's uses and the industries associated with them. Subsection 2 surveys VC's toxicity and the sources of human exposure to it.

1. *Vinyl Chloride's Uses and the Associated Industries*

The carcinogen vinyl chloride is the basis of the second most widely used plastic in the United States.[81] VC, a gas, is made from petrochemicals and chlorine. When polymerized into polyvinyl chloride, a solid, it is fabricated into a phenomenal array of products. VC was first manufactured commercially in the United States in 1939;[82] by 1976, VC production exceeded 5.5 billion pounds.[83]

The wide variety of uses of PVC is testimony to its adaptability. The major use of PVC is in construction products; other important uses are packaging and consumer products of all kinds. Figure 1 summarizes the applications of PVC in 1974. Woods, metals, glass, other plastics, and other materials can substitute for nearly all of PVC's uses, but PVC is preferred because of better performance or lower cost.[84] However, there are only a few uses for which no direct substitutes exist.[85]

Several direct uses of VC gas itself once existed, but these have been discontinued. In the late 1940s, VC was tested for use as an anaesthetic, but

81. *See Thermoplastics Priced For a Climb Over Years*, CHEM. & ENG. NEWS, Nov. 8, 1976, at 19. Polyethylene is the highest volume plastic. *Id.*

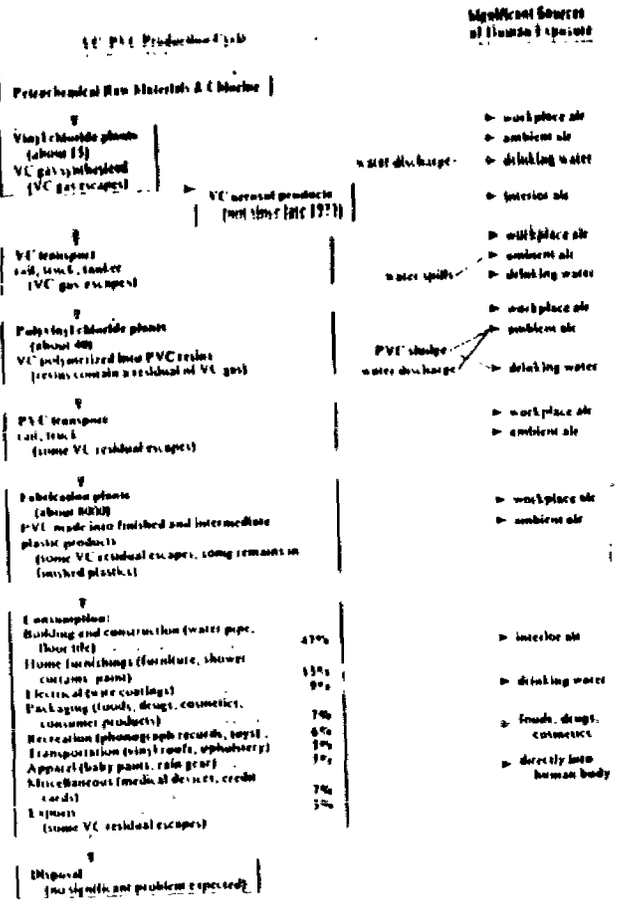
82. *OSHA Permanent Standard for VC*, *supra* note 1, at 35,890.

83. *Key Chemicals: Vinyl Chloride*, CHEM. & ENG'G NEWS, Aug. 23, 1976, at 11.

84. *Second Thoughts On Using PVC*, CHEMICAL WEEK, July 10, 1974, at 19.

85. U.S. Environmental Protection Agency, Standard Support and Environmental Impact Statement: Emission Standard for Vinyl Chloride 2-4 (Oct. 1975) [hereinafter cited as EPA EIS]; U.S. Environmental Protection [illegible] Assessment of the Environmental Pollution Associated with Vinyl [illegible] Vinyl Chloride: Report on the Activities and Findings of the Vinyl Chloride [illegible] app. 1, table 2 (Sept. 1974) [hereinafter cited as EPA Task Force Report].

FIGURE I
THE LIFE CYCLE OF VINYL CHLORIDE - POLYVINYL CHLORIDE



it was rejected because it upset cardiac function.[86] There are also indications that VC was once used as a refrigerant in cooling equipment.[87] Until late 1973, a small percentage of the VC produced was used as an aerosol propellant in some cosmetics, drugs, pesticides, and other consumer products. In 1974, when VC's carcinogenicity became generally known, millions of VC-propelled aerosols were still on the market or in consumer hands. The use of VC in aerosols has since been prohibited.[88]

Figure I illustrates the cycle of VC's creation, transformation, use, and disposal, and the routes of human exposure. There are three industries of central importance. The VC industry produces VC from petrochemicals. The PVC industry polymerizes the gas into the solid plastic, known in its raw form as resin. The fabrication industry converts PVC resins into finished products ready for consumer use or for incorporation into products of other industries. It is in these three industries that the workers are most heavily exposed to VC, and that the known human cancers have occurred.

Outside of these plants, additional people are exposed to VC in two major ways. First, VC emissions escape from factories to the surrounding air.[89] Second, since the polymerization process is imperfect, some VC remains a gas trapped in PVC materials. This residual escapes from the plastic in later production in fabrication plants and beyond, and in subsequent use and disposal.

As one moves through the production cycle of VC and PVC, the number of plants and companies increases, and plants become smaller and more labor intensive. The VC industry is composed of 10 companies operating 15 plants; in 1973, Shell, Dow, and Goodrich together held 56 percent of capacity.[90] In 1975, 23 companies operating 37 plants comprised the PVC industry. Goodrich is the major PVC producer with 15 percent; Firestone, Conoco, Union Carbide, Borden, Diamond Shamrock, and Tenneco each produce between five and nine percent.[91] There are about 8,000 fabrication companies of all sizes.[92] Beyond this point industries cease to be identified primarily by their use of VC.

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86. Oster, Carr, Kramer, & Sauerwald, *Anesthetic Vinyl Narcosis with Vinyl Chloride*, 8 Anesthesiology 339, 361 (1947).

87. 24 Patty, Industrial Hygiene and Toxicology 811 (1963).

88. The fate of these aerosols is discussed in the text accompanying notes 93-136 *infra*.

89. Most VC escapes directly into the air. Some leaves the plants in effluent water; most of this VC evaporates into the air. Some, however, enters drinking water. See EPA Task Force Report, *supra* note 85, at 9, 10; Appendices at 11; Environmental Protection Agency, Preliminary Assessment of Suspected Carcinogens in Drinking Water (Report to Congress) 2, 28, 30, 31, 39 (1975) (hereinafter cited as EPA Preliminary Report on Drinking Water Carcinogens).

90. Office of Research and Development, U.S. Environmental Protection Agency, Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride 20 (June 1975) (hereinafter cited as EPA Scientific and Technical Report).

91. *Id.* at 21-23.

92. EPA TIS, *supra* note 85, at 1-29.

As the above figures indicate, the VC and PVC industries are substantially concentrated. They are also vertically integrated. In 1972, 34 percent of VC produced was sold to PVC plants owned by VC companies, although this figure had dropped from 61 percent in 1962 as the industries grew.[93]

The fact that the VC and PVC industries contain only a small number of relatively concentrated and integrated firms has made it easy for the industries to speak with one voice in regulatory proceedings regarding the limits of their technological and economic capabilities to control VC exposures. The industrial market structure also makes it difficult to analyze the true costs of control measures and to determine the incidence of those costs on product prices, profits, wages, and other inputs.

Most VC plants are open-air, resembling oil refineries. They are located in populated areas in warm states—principally Louisiana, Texas, Kentucky, and California.[94] PVC plants are enclosed, but still emit VC, and they too are located mostly in populated areas. In addition to the above states, New Jersey, Ohio, and Massachusetts are major PVC-producing states.[95]

Only about one third of total VC production is polymerized at the site at which it is produced. Most VC must be transported between VC and PVC plants, mainly by rail tank car, and also by tank truck and barge. In addition, PVC resin must be transported between the PVC and fabrication plants; this is done primarily by train and truck.[96]

VC and PVC plants are highly mechanized and employ a relatively small number of workers. At any one time, there are only about 1,000 employees in the VC industry, and only about 5,500 in the PVC industry.[97] Taking into account the normal turnover of workers, about 30,000 employees are estimated to have worked in these industries since 1939.[98] Fabrication plants are more labor intensive. The number of fabrication workers is estimated at 350,000.[99] These workers are subject to much lower exposures of VC than the workers in VC and PVC plants, as the exposure of the fabrication workers comes only from escaping VC residual.[100] The size of the group, however, gives rise to fears that even a low incidence of cancers may claim a large number of lives.

93 Energy & Envtl. Sci., Inc., Draft Final Report: Economic Impact Studies of the Effects of Proposed OSHA Standards for Vinyl Chloride at III-5 (Sept. 13, 1974) (hereinafter cited as Draft Economic Impact Study).

94 *Id.* at III-2; EPA EIS, *supra* note 85, at 3-31, 39.

95 EPA Scrubber and Treatment Report, *supra* note 90, at 21-23.

96 EPA Task Force Report, *supra* note 85, at 3.

97 Draft Economic Impact Study, *supra* note 93, at III-3, -8.

98 R. Ashford *et al.*, *supra* note 5, at 36-41, 45 (appendix concerning VC regulation in the workplace). The number of cancers found in these workers, while not large in absolute terms, represents an extremely high incidence in the small population.

99 EPA Task Force Report, *supra* note 85, at 11.

100 OSHA Permanent Standard for VC, *supra* note 1, at 33,062-63.

The VC and PVC workers are represented primarily by three unions: the United Rubber Workers, the United Steelworkers, and the Oil, Chemical and Atomic Workers. On their own and through the Industrial Union Department of the AFL-CIO, these unions were major participants in setting the VC occupational exposure standard. The fabrication workers are represented by a variety of unions, and some are not unionized at all.

The technological and economic capabilities of the VC, PVC, and fabrication industries to lower the release of VC—in plants, to the surrounding air, and through later escaping residual in PVC—have been constantly at issue in the regulatory actions described in subsequent sections. The difficulty of predicting the future technological and economic limits to changes in these industries is discussed elsewhere,[101] but here it is useful to give some indication of their clearly demonstrated past and present capabilities.

Without need for any significant technological breakthroughs, in the four years since VC's carcinogenicity became clear, the VC, PVC, and fabrication industries have significantly reduced their releases of VC. In response to the regulations or the threat of regulations, the VC and PVC industries have been shown to be able to reduce workplace airborne concentrations of VC from about 250 parts per million (ppm) to about one ppm,[102] to reduce VC emissions to the outside by about 95 percent,[103] and to reduce the VC residual content of food packaging by several orders of magnitude.[104] New plants face no difficulties meeting these lowered levels.[105] Furthermore, there is no sign that the limits of current technologies have been reached and the possibility remains that fundamental technological breakthroughs could occur.

These reductions have been achieved without any significant economic strain on the companies or damage to PVC's market position and future growth prospects. Throughout the 1960s and early 1970s, PVC consumption grew at a staggering rate as prices declined and the number of uses increased.[106] In 1973, the business analysts forecast uninterrupted growth; the major problem experienced at that time was the tight supply of petrochemical raw materials.[107]

101 See notes 61-72 *supra*.

102 See text accompanying notes 217, 335-361 *infra*.

103 EPA EIS, *supra* note 85, at 1-4; EPA Scrubber and Treatment Report, *supra* note 90, at III-44.

104 See text accompanying note 335 *infra*.

105 *PVC Rolls Out of Jeopardy*, Inter Industrium, Union at Work, Sept. 15, 1976, at 14, 16.

106 See Draft Economic Impact Study, *supra* note 93, at III-3, exhibit III-1; EPA EIS, *supra* note 85 at 2-1.

107 *Tight Monomer Supply Plagues PVC Producers*, Chem. & Eng'g News, May 28, 1973, at 8.

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In 1974 and 1975, VC and PVC consumption dropped sharply, marking the first break in the trend of phenomenal growth. The slump, however, was not caused by a consumer response to the revelation of VC's carcinogenicity and to the costs of complying with subsequently imposed standards. Rather, the slump had two extrinsic causes: (1) attempts in the early 1970s to pass on to consumers the rising costs of petrochemical feedstocks; and (2) the general economic recession in 1974 and 1975, which was particularly severe in the building construction industry, a major user of plastics.[108] The slump was shared equally by all the major plastics.

With the end of the recession and the revival of the housing industry, plastics generally and PVC in particular returned to the prior trend of profitable growth. Presently, new plants are being built to meet anticipated demand, without any apparent hindrance from current and proposed regulations.[109] Hence, it appears that somewhat greater reductions in VC exposure could be demanded of the industries without rendering either current operations or expansion unprofitable.

As the following survey of VC's toxicity will show, there is no basis for thinking the VC hazard has been eliminated by the measures already taken, or that it will be eliminated by the additional measures conceded by the industries to be both technologically and economically within their reach. Further reductions are justified by the medical evidence. The point at which the industries would be seriously burdened economically is, however, impossible to predict reliably.

2. *Health Risks and Sources of Exposure to Vinyl Chloride*

The toxic effects of VC are now known better than those of nearly any other industrial chemical. VC's carcinogenicity has been well established by human experience, animal experiments, and other laboratory tests. The bitter experience of occupational exposure has confirmed VC's ability to cause cancers and a host of lesser effects in humans. The risks extend beyond the workers; millions of other people are exposed to VC. This subsection surveys the evidence of VC's toxicity and the extent of human exposure to the chemical.

a. *Acute and chronic human toxicity*

Before 1974, when VC had not yet been connected to human cancer, other dangers of the chemical were well known. VC is extremely flammable, and concentrations in air exceeding 40,000 ppm are explosive.[110]

108. Ugochi, *1976 Outlook Brighter in U.S. and European Chemical Industries*, Chem. Week & Eng. Rev., Apr. 1976, at 14; Greek, *Vinyl Chloride May Face Shortages By 1977*, Chem. & Eng. News, Aug. 11, 1975, at 8.

109. *PVC Rolls Out of Jeopardy Into Inhibition*, supra note 105, at 14.

110. Haley, *Vinyl Chloride: How Many Unknown Problems?*, 1 J. Toxicology & Envt'l Health 47, 49 (1975) [hereinafter cited as *VC: How Many Unknown Problems?*].

Several workers have died from inhaling extremely high concentrations.[111] Exposure to concentrations greater than 8,000 ppm VC causes one to become dizzy, drowsy, disoriented, and eventually unconscious.[112] Lower doses inhaled over a period of a work shift make one prone to deep, dreamless sleep.[113]

Before 1974, VC concentrations of 250 to 500 ppm were common for many job categories in the VC and PVC industries.[114] Among workers exposed to these concentrations for periods of months or years a number of effects had been identified. Many workers suffered enlargement and fibrosis of the liver and spleen.[115] Many exhibited Reynaud's syndrome, characterized by circulatory degeneration in the extremities and by a cold feeling or a feeling of pins and needles in the hands and feet.[116] Many developed scleroderma, a skin condition, and acroosteolysis, a rare disease characterized by the shrinking of the last bones in the fingers and toes.[117] Although workers who suffered one of these effects did not always suffer the others, the effects were grouped under the name "vinyl chloride disease."[118]

When VC's capacity to cause cancer in humans became clear in 1974, close medical examination of VC and PVC workers identified numerous acute and chronic effects of VC that previously had gone unnoticed. Impaired arterial circulation and fibrosis of the liver and spleen were found to occur at a microscopic level long before they were clinically observable.[119]

111. Spirtas, McMichael, Gamble, & Van Ert, *The Association of Vinyl Chloride Exposures With Morbidity Symptoms*, 36 Am. Indus. Hygiene Ass'n J. 779 (1975).

112. EPA Scientific and Technical Report, supra note 90, at 85–86; *How Many Unknown Problems?*, supra note 110, at 61.

113. *VC Hearings*, supra note 1, at 40 (testimony of Dr. Marcus Key, Director, National Institute for Occupational Safety and Health).

114. Kramer & Mutchler, *The Correlation of Clinical and Environmental Measurements For Workers Exposed to Vinyl Chloride*, 33 Am. Indus. Hygiene Ass'n J. 19 (1972) [hereinafter cited as *Worker Exposure to VC*]; EPA Scientific and Technical Report, supra note 90, at 45, 91–94.

115. Lilis, Anderson, Nicholson, Daum, Fischbein & Selikoff, *Prevalence of Disease Among Vinyl Chloride and Polyvinyl Chloride Workers*, 246 Annals N.Y. Acad. Sci. 22 (1975) [hereinafter cited as *Prevalence of Disease*]; Lange, Juhe, Stein & Veltman, *Further Results in Polyvinyl Chloride Production Workers*, 246 Annals N.Y. Acad. Sci. 18 (1975) [hereinafter cited as *Further Results*].

116. *Prevalence of Disease*, supra note 115, at 32; *Further Results*, supra note 115, at 18.

117. *Prevalence of Disease*, supra note 115, at 22; *Further Results*, supra note 115, at 18; Sakabe, *Bone Lesions Among Polyvinyl Chloride Production Workers in Japan*, 246 Annals N.Y. Acad. Sci. 78 (1975); *VC: How Many Unknown Problems?*, supra note 110, at 62–63.

118. Veltman, Lange, Juhe, Stein & Bachner, *Clinical Manifestations and Course of Vinyl Chloride Disease*, 246 Annals N.Y. Acad. Sci. 6 (1975).

119. Maricq, Johnson, Whetstone, & LeRoy, *Capillary Abnormalities in Polyvinyl Chloride Production Workers: Examination By In Vivo Microscopy*, 236 J. Am. Med. Ass'n 1368 (1976); Popper & Thomas, *Alterations of Liver and Spleen Among Workers Exposed to Vinyl Chloride*, 246 Annals N.Y. Acad. Sci. 172 (1975); Thomas & Popper, *Pathology of Angiosarcoma of the Liver Among Vinyl Chloride-Polyvinyl Chloride Workers*, 246 Annals

Microscopic examination revealed other changes in liver cells.[120] Some workers displayed a wide variety of abnormal liver function and blood tests.[121] Some suffered impairment of lung function.[122]

The medical researchers had hoped that these observable effects could be used to indicate who is at increased risk of developing cancer and how VC produces its carcinogenic effect. To their disappointment, however, none of these effects correlated well enough with observed cases of liver angiosarcoma or of other cancers to indicate clearly which workers are at increased risk, nor has the knowledge of these effects enabled researchers to explain how VC causes cancer.[123]

b. Human cancers

Throughout the spring of 1974, after the deaths of the four Goodrich workers became known, other companies reported additional angiosarcoma deaths among VC and PVC workers.[124] The toll has risen steadily since then. Thirteen cases of angiosarcoma of the liver had been counted among American workers by July 1974,[125] and a total of 25 cases were known

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N.Y. Acad. Sci. 268 (1975); Creech, Muller, & Berbaum-Heimer, *Morphology of Liver Damage Among Polyvinyl Chloride Production Workers: A Report on 51 Cases*, 246 Annals N.Y. Acad. Sci. 278 (1975).

120 *See* sources cited in note 119, *supra*.

121 Blood platelet count has been shown in some but not all victims of liver angiosarcoma. Liver function tests show a wide variety of abnormalities. *Persistence of Disease*, *supra* note 115; *Further Results*, *supra* note 115; Veltman, Lange, Hibe, Stein, & Bachmer, *supra* note 118; Marsteller, LeRoy, Muller, & Creech, *Abnormal Splenoportographic Liver Patterns as Evidenced by Percutaneous Splenoportography and Guided Liver Biopsy Among Polyvinyl Chloride Production Workers*, 246 Annals N.Y. Acad. Sci. 95 (1975).

122 Gamble, Lee, Michaels, & Wagoner, *Effects of Occupational and Nonoccupational Factors on the Respiratory System of Vinyl Chloride and Other Workers*, 181 Dechema-Monographien 659 (1976).

123 In promulgating the permanent standard for workplaces OSHA noted the failure to find in blood tests, liver function tests, and certain other examinations a reliable indicator of increased cancer risk. *OSHA Permanent Standard For VC*, *supra* note 1, at 35,895. Since the fall of 1974, when OSHA's observation was made, there has been little change in the state of knowledge of VC's carcinogenesis. Some hope of identifying VC-induced changes at an early stage is promised by two recent techniques. The first is ultrasonography, a technique for "taking a picture" of internal organs such as the liver and spleen without surgery through a sort of sonar. This technique can reveal fibrosis and other gross changes in these organs. Taylor, Barrett, Williams Smith, & Buck, *Preliminary Results of Grey scale Ultrasonography in the Detection of Vinyl Chloride Related Liver and Spleen Disease*, 69 Proc. Royal Soc. Med. 292 (1976). Another technique detects microscopic changes in the circulatory system in the fingers. It was reasoned that the Raynaud's syndrome and acroosteolysis would be preceded by subclinical changes which, if they could be found, would be an indication of increased risk. Marsteller, Johnson, Whetstone, LeRoy, *supra* note 119. Neither of these techniques, however, offers any assurance of detecting VC-induced changes before the changes at the cellular level which eventually lead to cancer have already occurred.

124 Occupational Safety and Health Administration, *Vinyl Chloride Proposed Standard*, 39 Fed. Reg. 16,896 (1974) (hereinafter cited as *OSHA Proposed Standard for VC*).

125 *OSHA Permanent Standard for VC*, *supra* note 1, at 35,891.

worldwide one month later.[126] Although the majority of cases involved workers at PVC plants, other workers were also affected.[127] There were 38 cases worldwide by June 1975,[128] at least 51 cases by December 1976,[129] and at least 68 cases by the spring of 1978.[130]

Although in absolute terms these numbers are not large, the rate of liver angiosarcoma in various groups of PVC workers studied ranges from 400 to 3,000 times the expected incidence in the general population.[131] Since the latency period – the time between initial exposure to VC and the clinical appearance of liver cancer—has been averaging about 20 years, more cases can be expected as the result of high exposures in the 1950s, 1960s, and early 1970s.[132]

Many of the employees who have died of liver angiosarcoma worked as cleaners of the polymerization reactor (the chamber in which VC is converted to PVC) or worked in areas with similarly high VC exposures.[133] These workers probably were the most heavily exposed, in terms of both momentary peaks and sustained averages. The precise levels are not known but are estimated to have included peak exposures of several thousand ppm and an average of 250 to 300 ppm.[134] Other liver angiosarcoma victims presumably had lower, less sustained exposures to VC.[135]

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126 *VC Hearings*, *supra* note 1, at 60-62 (statement of Dr. Joseph K. Wagoner).

127 Those affected included a worker at a VC plant, a worker who filled pesticide cans with VC propellant, and an accountant and a worker at PVC cloth fabricating plants. *Id.* These last two are assumed to have had very low exposures.

128 *Id.* at 60; EPA Scientific and Technical Report, *supra* note 90, at 32, 83.

129 Reported Cases of Angiosarcoma of the Liver Among Vinyl Chloride Polymerization Workers (Dec. 6, 1976) (unpublished tabular data enclosed with letter to the author from Rose Kaminski, Statistician (Health), Illness Effects Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health (Dec. 6, 1976)).

130 Personal communication with Rose M. Kaminski, Statistician (Health), Illness Effects Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Apr. 10, 1978.

131 The lower figure is from Heath, Falk, & Creech, *Characteristics of Cases of Angiosarcoma of the Liver Among Vinyl Chloride Workers in the United States*, 246 Annals N.Y. Acad. Sci. 231, 233 (1975). The higher figure is from EPA, EPA, *National Emission Standards for Hazardous Air Pollutants; Proposed Standard for Vinyl Chloride*, 40 Fed. Reg. 59,532 (1975) (hereinafter cited as *EPA Proposed Standard for VC*). These figures are the result of comparing the rates of angiosarcoma of the liver in workers with the rates in the general population, assuming that the general population cases are not caused by VC. Part of, as the remainder of this section suggests, some of the cases in the general population may be caused by nonoccupational VC exposure; then these figures understate the potency of the chemical.

132 *VC Hearings*, *supra* note 1, at 25 (statement of Dr. Irving J. Selikoff); Heath, Falk, & Creech, *supra* note 131, at 233.

133 Nicholson, Hammond, Seidman, & Selikoff, *Mortality Experience of a Cohort of Vinyl Chloride Polyvinyl Chloride Workers*, 246 Annals N.Y. Acad. Sci. 225, 226-27 (1975). *See also* Lave & Seskin, *Mortality Experience of Workers Exposed to Vinyl Chloride Monomer in the Manufacture of Polyvinyl Chloride in Great Britain*, 30 Rutg. L. Review 1 (1977).

134 *Worker Exposure to VC*, *supra* note 114.

135 EPA Scientific and Technical Report, *supra* note 90, at 32-83.

The long-term risks of VC exposure may not be limited to liver angiosarcoma. One study of PVC workers identified a statistically significant excess incidence of cancers of the brain and the respiratory system.[136] A study of the causes of death among fabrication workers identified no liver angiosarcomas, but it did suggest an increased incidence of cancers of the digestive system among both men and women and the breast and the urinary system in women.[137] Evidence of other effects has appeared in populations other than workers. One study has shown a statistically significant excess of birth defects and central nervous system tumors among the children of families in three Ohio communities that have hosted PVC plants for as long as 20 years.[138]

c. Animal bioassays and other tests for carcinogenicity

VC's carcinogenicity has been confirmed by the results of experiments on animals and by other laboratory tests. VC has been shown to cause cancer in animals both when inhaled and when ingested. The first hint that the chemical causes cancer came from the publication in 1971 of the results of Italian experiments sponsored by the European and American VC and PVC producers. In these tests rats inhaling high concentrations of VC (30,000 ppm) developed cancerous tumors of the skin, lung, and bone.[139] Further tests sponsored by the producers were concluded and reported to the Occupational Safety and Health Administration (OSHA) in early 1974. As shall be seen in the case study of OSHA's standard setting, the data arrived at a crucial time. On February 15, at OSHA's fact finding hearing on VC, the Italian researchers reported their then-unpublished findings that VC had induced angiosarcoma of the liver in rats inhaling concentrations as low as 250 ppm.[140] On April 15, OSHA received reports from tests conducted in

136. Tabershaw & Gaffey, *Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers*, 16 J. OCCUPATIONAL MED. 509 (1974). *See also* Monson, Peters, & Johnson, *Proportional Mortality Among Vinyl Chloride Workers*, THE LANCET, Aug. 17, 1974, at 397.

137. Chiazze, Nichols, & Wong, *Mortality Among Employees of PVC Fabricators*, 19 J. OCCUPATIONAL MED. 623, 628 (1977) [hereinafter cited as *Mortality Among Fabrication Employees*]. The authors noted a number of flaws in the design and data for their study that precluded drawing firm conclusions from it. In particular, it would be useful to follow the population of fabrication workers for some years into the future, as a sufficient latency period may not yet have elapsed for some effects to manifest themselves.

138. Infante, *Oncogenic and Mutagenic Risk in Communities with Polyvinyl Chloride Production Facilities*, 271 ANNALS N.Y. ACAD. SCI. 49, 50 (1976). *Cf.* Infante, McMichael, Wagoner, Waxweiler, & Falk, *Genetic Risks of Vinyl Chloride*, THE LANCET, Apr. 3, 1976, at 734 (finding increased fetal loss among wives of workers exposed to VC).

139. Viola, Bigotti, & Caputo, *Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride*, 31 CANCER RESEARCH 516 (1971) [hereinafter cited as *Oncogenic Response of Rats to VC*].

140. Occupational Safety and Health Administration, *Emergency Temporary Standard for Exposure to Vinyl Chloride*, 39 Fed. Reg. 12,342 (1974) [hereinafter cited as *OSHA Emergency Temporary Standard for VC*].

Illinois of similar results in mice at the lowest level of exposure then being tested, 50 ppm.[141]

Animal test results stood at this point until early 1975. It was reported then that *ingestion* by rats of as little as approximately 17 milligrams per kilogram of body weight produces liver angiosarcoma and other cancers.[142] Most recently, in September 1976, the results of another round of inhalation experiments demonstrated that VC causes liver angiosarcoma in rats at 25 ppm, and that it causes mammary tumors at one ppm, the lowest concentration yet tested.[143]

The animal experiments also support suspicions that VC causes human cancers other than angiosarcoma of the liver. The experiments have shown increased cancer incidence at many sites other than the liver, including the lungs, spleen, brain, and, as already noted, breast.[144] Experiments demonstrating the induction of cancer in two species other than rats – mice and hamsters – further confirm that VC is carcinogenic.[145] In the animal experiments the subjects were exposed to constant, prolonged doses of VC. The need was noted in mid-1974 for studies of the effects of single and sporadic doses, typical of many humans' exposure.[146] Such a study is now nearing completion, but the results are not yet available.[147]

d. Additional humans at risk

In addition to several hundred thousand workers in VC and PVC production and in PVC fabrication, millions of Americans have been, and continue to be, exposed to VC. First, about 4.6 million people live within

141. *OSHA Proposed Standard for VC*, *supra* note 124, at 16,896. The results of the Italian tests, also showing the induction of liver angiosarcoma at 50 ppm, were published in early 1975. Maltoni & Lefemine, *Carcinogenicity Bioassays of Vinyl Chloride: Current Results*, 246 ANNALS N.Y. ACAD. SCI. 195 (1975).

142. Maltoni, Ciliberti, Gianni, & Chieco, *Gli Effetti Oncogeni Del Cloruro Di Vinile Somministrato Per Via Orale Nel Ratto (Oncogenic Effects of VC Administered Orally to Rats: Preliminary Report)*, GLI OSPEDALI VITA, Dec., 1975 (unpaginated reprint on file in offices of the *Ecology Law Quarterly*).

143. Memorandum from Cesare Maltoni to the Members of the European Cooperative Group for the Experimental Bioassays on Vinyl Chloride Carcinogenicity (undated) [hereinafter cited as Maltoni Memorandum].

144. See sources cited in notes 140-141 *supra*.

145. EPA SCIENTIFIC AND TECHNICAL REPORT, *supra* note 90, at 56. In addition, metabolites of VC have been shown to mutate bacteria and yeasts in the "quick tests" for mutagenicity. *See, e.g.*, Loprieno, Barale, Baroncelli, Bartsch, Bronzetti, Cammellini, Corsi, Frezza, Nieri, Leporini, Rosellini, & Rossi, *Induction of Gene Mutations and Gene Conversions by Vinyl Chloride Metabolites in Yeast*, 37 CANCER RESEARCH 253 (1977), and sources cited therein. Mutagenicity as revealed in these tests correlates well with carcinogenicity. *See* McCann & Ames, *supra* note 57, *From Microbes to Men*, *supra* note 57.

146. *VC Hearings*, *supra* note 5, at 80-81 (statement of Dr. Theodore R. Torkelson).

147. Telephone interview with Dr. Joseph McLaughlin, Director, Division of Toxicology and Medicine, Consumer Product Safety Commission, Feb. 27, 1976.

five miles of a VC or PVC plant.[148] In 1974, about 220 million pounds of VC escaped into the air surrounding such plants.[149] The plant neighbors appear to have been exposed to more than one ppm less than 10 percent of the time.[150] One air sample, however, measured 33 ppm near a plant,[151] suggesting that there may be short term, localized peak exposures.[152] In addition, VC is found in the sludge waste and water effluent of these plants. VC has been found in sludge at levels as high as 3,000 ppm,[153] and in water effluent as high as 20 ppm.[154] Most of this VC escapes into the air surrounding the plants;[155] some, however, makes its way into drinking water.[156] These VC emissions to the ambient air have been implicated as the cause of increased rates of cancer and birth defects in the surrounding communities.[157]

Another large group of persons is exposed to VC released in transportation. Only about one-third of VC production is polymerized at the site where it is produced. The rest must be shipped between VC and PVC factories under pressure as a liquified gas. About 95 percent of this is shipped in rail tank cars, and the rest in tank trucks, tank vessels, and barges.[158] These tanks may leak, puncture, or explode, sometimes in heavily populated areas.[159] Between 1971 and 1974, there were at least 24 accidental releases of VC from rail tank cars alone.[160] As VC diffuses from the site of a spill or an accident, transportation workers, nearby residents, travellers, and other bystanders can receive short-term exposures to VC concentrations ranging from a few parts per billion (ppb) to thousands of ppm. Transportation workers and emergency personnel such as firemen and police officers may

148 EPA, *National Emission Standard for Hazardous Air Pollutants, Standard for Vinyl Chloride*, 41 Fed Reg 46,560 (1976) [hereinafter cited as *EPA Standard for VC*]

149 EPA Scientific and Technical Report, *supra* note 98, at 38

150 *Id*

151 *Id*

152 *See Id*

153 EPA Task Force Report, *supra* note 85, at 7

154 *Id*

155 *Id*., apps., at 31-32

156 See note 89 *supra*

157 See sources cited in note 138 *supra*

158 EPA Task Force Report, *supra* note 85, at 7.

159 *See* note 169 *infra*

160 Most of these accidents occurred in Texas and Louisiana, the states with the highest concentrations of VC and PVC facilities. There were several other accidents involving no *release*. Data on accidents and releases is derived from a computer file of the Department of Transportation which records incidents of hazardous materials leakage or accidents during this period, and from the appendix to H R Rep No 1083, 93d Cong., 2d Sess 30 34 (1974) One accident, in Fort Wayne, Indiana, necessitated the evacuation of 4,500 people. *Id* at 33 When a rail tank car ruptures, as much as 30,000 gallons of VC escapes and returns to its gaseous state The figure for the maximum tank size comes from an interview with Huey Williams, Chemical Engineer, *Department of Transportation, Office of Hazardous Materials Operations*, Oct 28, 1976

be subject to repeated exposures and, if accidents occur in the same places, so may residents and bystanders. These exposures are less sustained than those suffered by VC and PVC workers and plant neighbors, but peak concentrations may reach those experienced by PVC polymerization reactor cleaners, the most heavily exposed occupational group

Third, people are exposed to VC through consumer products, food, and drinking water. Until late 1973 or early 1974, VC was used as an aerosol propellant in drug, cosmetic, pesticide, and other consumer products.[161] The user of a VC-propelled aerosol product such as a hair spray or a pesticide in a small, enclosed space such as a bathroom may have been exposed to short term concentrations approaching 400 ppm, and persons may have had an average exposure from all VC-propelled products in their homes equivalent to an average exposure of about 16 ppm in the factories.[162] VC has been detected in the air of rooms freshly painted with certain latex paints, but no VC emissions have been detected in a limited sampling of other new PVC products or from automobile interiors.[163] VC leaches into food and beverages from the more than 300 million pounds of PVC packaging and other PVC food-contact materials used annually.[164] VC also enters drinking water from raw water supplies and by leaching from increasingly common PVC pipe.[165] One study estimates average American daily human intake of VC through food, water, and air at 34 micrograms.[166]

The hazardousness of non-occupational exposures to VC is even less well understood than the risk to the workers. The danger from inhaling extremely low concentrations of VC, or from single or sporadic exposures to high VC concentrations, is unknown. Similarly, the relative risks of ingesting and inhaling VC are unknown.[167] Thus the urgency of reducing or eliminating these sources of exposure is impossible to assess

161 See text accompanying notes 551-556 *infra*

162 Gay, Lomonaco, Bridbord, & Moran, *Measurement of Vinyl Chloride from Aerosol Sprays*, 246 Annals N Y Acad Sci 286, 294-95 (1975)

163 Environmental Protection Agency, Office of Toxic Substances, Sampling and Analysis of Selected Toxic Substances Task III—Vinyl Chloride, Secondary Sources, table 6, at 21 (Apr 1976)

164 Food and Drug Administration, *Vinyl Chloride Polymers in Contact with Food, Notice of Proposed Rulemaking*, 40 Fed Reg 48,529, 48,530 (1975) [hereinafter cited as *FDA Proposed Rules for Food-Contact PVC*].

165 EPA Scientific and Technical Report, *supra* note 98, at 38-39; EPA Preliminary Report on Drinking Water Contaminants, *supra* note 89, at 40-44, EPA Task Force Report, *supra* note 85, at 7, 19.

166 EPA Scientific and Technical Report, *supra* note 98, at 41

167 *See* Wahey & Collins *A Statistical Assessment of the Quantitative Uptake of Vinyl Chloride Monomer from Aqueous Solution*, 2 J Toxicology & Environ Health 311 (1976), Wahey, *The Pharmacodynamics and Uptake of Vinyl Chloride Monomer Administered by Various Routes to Rats*, 1 J Toxicology & Envt'l Health 301 (1976) In the former article, the authors estimate that for rats, 0.9 micrograms of VC in the daily intake of water is approximately equal to inhaling 6 ppm for eight hours They caution against any direct extrapolation to human equivalences Wahey & Collins, *supra*, at 319-20

Chemicals

Chlor-Alkali Business Unit
PPG Chemicals
One PPG Place
Pittsburgh, Pennsylvania 15272

DRAFT

May 13, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Re: Vinyl Chloride

Dear Sirs:

Relative to your request for health information on vinyl chloride, we have no information which was not covered in the MEDLINE and TOXLINE information services.

We thank you for asking for our input.

Sincerely yours,

Clete M. Smith
Technical Service

CMS/rs

PACIFIC GAS AND ELECTRIC COMPANY

77 BEALE STREET • SAN FRANCISCO, CALIFORNIA 94106 • (415) 781-4211 • TWX 910 372 6587

DRAFT

May 7, 1985

Mr. William V. Locustoff, Chief
Toxic Pollutants Branch
Re: Vinyl Chloride
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

Request for Public Health
Information Regarding Vinyl Chloride

Pacific Gas and Electric Company received your April 4, 1985 request for additional public health information regarding Vinyl Chloride. We have reviewed the bibliography attached to your request and concluded that we are unaware of any additional information which would be of use to you.

Sincerely,

J. F. McKenzie

CMA 010639

Natural Resources Defense Council, Inc.
[illegible] New York Avenue, N.W., Suite [illegible]
Washington, DC [illegible]
202 783-7800

DRAFT

To: William V. Loscutoff

From: David D. Doniger

Date: April 10, 1985

Subject: Vinyl Chloride

The attached is in answer to your recent inquiry.

TCM

152 Wagoner, J. K., Infante, P F. and Apfeldorf, R. B. (1980) Toxicity of vinyl chlorid and polyvinyl chloride as seen through epidemiologic observations.. J Toxicol Enviro Health 6(5-6):1101-7

153. Watanabe, P. G., Young, J. D. and Gehring, P. J (1977) The importance of non-linear (dose-dependent) pharmacokinetics in hazard assessment.. J Environ Patho Toxicol. 1(2).147-59.

154 Waters, M. D., Garrett, N. E., Covone-DeSerres, C. M., Howard, B. E. and Stack, H. (1983) Genetic toxicology of some known or suspected human carcinogens. Chem Mutagens:Prin methods their detection. 8 261-341.

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South Coast
AIR QUALITY MANAGEMENT DISTRICT
9150 FLAIR DRIVE, EL MONTE, CA 91731 (818) 572-6200

DRAFT

April 22, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Bill:

Vinyl Chloride

In response to Mr. Venturini's request for information on the health effects of vinyl chloride, we are submitting several references which could be of use in your toxic air contaminant program. These references were not included in your bibliography dated March 1, 1985. Also, information regarding possible biological production of vinyl chloride may be obtained from Dr. Freeman Allen of Pomona College.

We would like to continue to receive information inquiries for other candidate compounds and to be kept informed of your program's progress.

Very truly yours,

Jo Anne Aplet
Director of Planning

JAA:cas

Enclosure

CMA 010642

DRAFT

Additional References on
Vinyl Chloride Health Effects

Albert, R.E. Letter to R.S. Naveen, EPA, "Comparison of Vinyl Chloride Carcinogenic Risks with Risk From Other Pollutants," Washington, D.C., June 16, 1978.

Edmonds, L. "Birth Defects and Vinyl Chloride," Proc. Conference on Women and the Workplace, Washington; D.C., 1976, also Teratology 17, 137 (1978).

Equitable Environmental Health, Inc. "Epidemiological Study of Vinyl Chloride Workers, Final Report." Prepared for Manufacturing Chemists Association, Washington, D.C., January, 1978.

Graniger, R.G., A.E. Walker, and A.M. Ward. "Vinyl Chloride Monomer-Induced Disease: Chemical, Radiological and Immunological Aspects," Chapter II in Induced Disease; Drug, Irradiation, Occupation, L. Pregar, ed., Grune and Stratton, London, 1980.

Kuzmack, A.M. and R.E. McGaughy. "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride," U.S. EPA, Washington, D.C., December 5, 1975.

National Academy of Science. Principles of Toxicological Interactions Associated with Multiple Chemicals Exposures 1981, 207 p. AD-A093 809/2 PC A10/MF A01.

National Cancer Institute (1978). Vinyl Chloride - An Information Resource, 112 p. HRP-0028012/3 PC A06/MF A01.

National Institute of Occupational Safety and Health (1977). A Cross-Sectional Epidemiologic Survey of Vinyl Chloride Workers. 50 p. NIOSH Pub. No. 77-177, NTIS No. PB-274.

Ziskind, R.A., Smith, D.F., and Spivey, G.H. Health Effects in Children Exposed to Vinyl Chloride. Final Report to U.S. Environmental Protection Agency, SAI-068-81-569, January 1981.

Air Products

ASL
VC

DRAFT

Date 27 August 1984

INTEROFFICE
MEMORANDUM

Subject Surgical Removal of Angiosarcoma

To L. B. Tepper — Corporate Medical Department
(Location, Organization, or Department)

From J. T. Barr — Regulatory Response
(Location, Organization, or Department)

cc: G. Bays
H. L. Watson

The attached article is a report of an apparently successful surgical removal of an angiosarcoma from the liver of a PVC worker. It appeared at Br. J. Surg. 71 322 (1984).

J. T. Barr

JTB:csb

CMA 010644

Air Products and Chemicals, Inc.
Box 538
Allentown, PA 18105
Telephone (215) 481-4911

AIR PRODUCTS

DRAFT

16 April 1985

W. V. Loscutoff
Chief, Toxics Pollutant Branch
CARB
Box 2815
Sacramento, CA 95812

Re: Vinyl Chloride

Dear Mr. Loscutoff:

We are happy to provide some information relative to vinyl chloride in response to the April request of P. D. Venturini. This includes:

1. A paper by me given at the APCA, New Orleans meeting.

2. A paper presented at a CMA seminar in Washington, 9 December 1983.

3. An unpublished review by me on the safety and health aspects of vinyl chloride, which contains several references not in the bibliography with the Venturini letter.

4. A report from Br. J. Surg. 71 322 (1984) of an apparently successful liver resection on an ASL patient.

5. An article from EST 19 277 (1985) on biodegradation of TCE to VC. Note especially reference 10, Parsons, et. al., for corroborating evidence. You may want to get the Dade County report "An Investigation into the Source of Vinyl Chloride Detected at the Preston and Hialiah Water Treatment Plants" by J. C. Balter, 1983, for more details.

6. A summary of a report on a 1984 bioassay by CIVO.

I hope that these are useful to you in your evaluation of this substance.

Very truly yours,

John T. Barr, Manager
Regulatory Response

CMA 010645

JTB:csb

Vinylchloride induced hepatic angiosarcoma

Y.A. Louagie, P. Gianello, P.J. Kestens, F. Bonbled and J.G. Haot

Department of Surgery of the Alimentary Tract, Louvain-en-Woluwe Medical School, and St. Luc Hospital, 1200 Brussels, Belgium

Correspondence to: Dr Y.A. Louagie, 20 Avenue d'Huart (bte 3), 1150 Brussels, Belgium

The relationship between vinylchloride exposure and human angiosarcoma of the liver (ASL) received attention in 1973 when a case of this rare tumour was diagnosed at autopsy[1].

Case report

A 39-year old man was first seen in July 1979 with pain in the right upper quadrant. The liver was palpated at the right costal margin. Oral cholecystography and barium swallow were normal and liver function tests were in normal limits. From 1965 to 1970 he had cleaned reactors used for the polymerization of the vinylchloride monomer in PVC and was thus exposed to high amounts.

He was admitted 3 months later with persisting right upper quadrant pain, loss of appetite and fatigue. The liver edge was by then hard and 4 cm below the costal margin. The ESR was accelerated (80 mm/h) and alkaline phosphatases and GGTP were elevated. Carcino-embryonic antigen (CEA) and α fetoglobulin were normal. Ultrasound showed a large dense tumour of the right hepatic lobe with areas of necrosis. The ^{99m}Tc hepatic scan confirmed the presence of an ill-defined filling defect in the inferior part of the right lobe with two small defects at the level of the hilum.

The liver computerized tomography confirmed the integrity of the left lobe.

A selective angiography of the celiac artery revealed a hypervascularized tumour of the right hepatic lobe (*Figure 1*).

At a right thoracophrenolaparotomy the tumour was found to be confined to the right lobe. An extended right lobectomy was then performed. The postoperative recovery was uneventful and the patient was sent home with a monthly administration of Vincristine (1 mg IV) and Adriamycin (150 mg/m² IV) which was discontinued in June 1981.

Repeated controls up to September 1981 by liver scan and computerized tomography remained normal. The patient is still in good health 38 months after the resection.

Pathology

The resected specimen was 2050 g. On macroscopical examination the main tumour (13-5 × 8 cm) was yellowish and spongy and contained cystic and haemorrhagic zones. A second small haemorrhagic mass was found at the inferior aspect of the right lobe surrounded by numerous purple masses.

Macroscopically, the main tumour showed large areas of necrosis and haemorrhagic pseudocystic spaces (*Figure 2*). These spaces were surrounded by areas of dense vascular proliferation. The sinusoids were lined with variably sized irregular sarcomatous cells with hyperchromatic nuclei. Elsewhere, blood-filled spaces were surrounded by sarcomatous cells. The sarcoma cells encompassed adjacent liver cells and bile ductules and infiltrated the parenchyma. The pathological diagnosis of multicentric angiosarcoma was made. The rest of the liver was normal except for some moderately enlarged portal tracts. Progressive fibrosis separating hepatocytes at the margins of the portal tracts from adjacent hepat

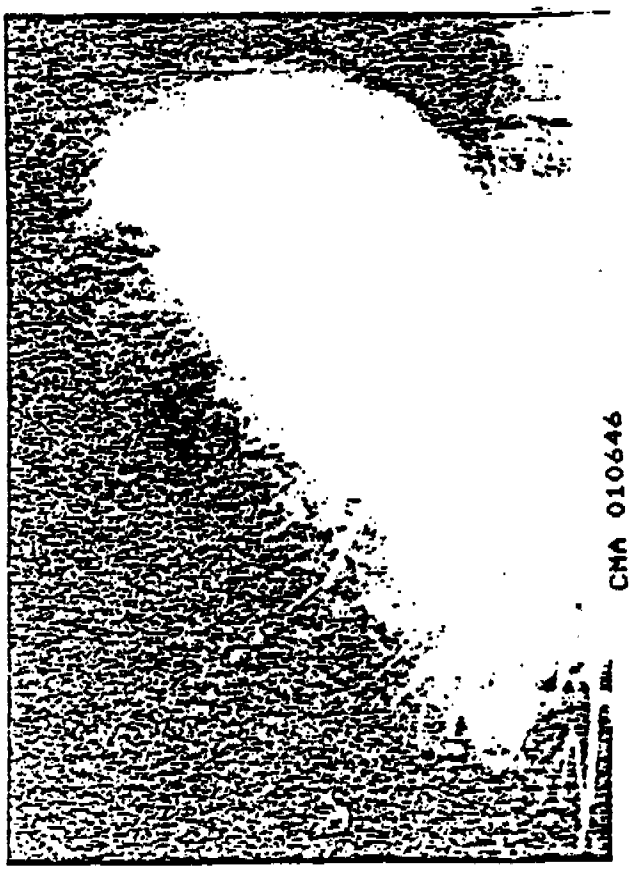

Figure 1 *Selective angiography of the celiac artery. The hypervascularized tumour is supplied by an anterior branch (arrow) of the*

Figure 2 *Photomicrography of the main tumour showing blood filled spaces surrounded by sarcomatous cells. Haematoxylin eos*

cord cells. Anisocaryosis and anisocytosis were frequent. A cross-section biopsy of the left lobe showed normal tissue with slight hepatocytic anisocaryosis. The lymph nodes taken from the liver hilum were hyperplastic. The main features of this tumour were its multicentricity and the presence of mild fibrosis.

Discussion

The occurrence of liver angiosarcoma in vinylchloride polymerization workers was reported in 1974[1,2]. Prolonged exposure and long interval from initial exposure is required before liver disease becomes apparent. The average interval is 12 years (range 6–29)[3]. Our patient was exposed for 5 years and became symptomatic 14 years later.

It is a rapidly progressing fatal disease, especially in adults. The clinical features include rapid liver enlargement with haemorrhagic ascites, fast deterioration and cachexia usually with death within 6 months.

The treatment is disappointing and chemotherapy and radiation of palliative value only. If the diagnosis is made early, the disease is localized and there is no associated liver fibrosis or portal hypertension, resective operation might prove to be curative. However, there are few reported cases of successful operative removal of hepatic angiosarcoma and the longest survival has been 16 months[4].

In our case the tumour was confined to the right lobe and there was no sign of the extensive fibrosis. So far the patient is apparently free of disease after 38 months. This is, to our knowledge, the longest published survival.

References

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2. Block JB. Angiosarcoma of the liver following vinyl chloride exposure. *JAMA* 1974; 229: 53–4.
3. Heath CW, Flak H, Creech JL Jr. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann NY Acad Sci* 1975; 246: 231–6.
4. Adam YG, Huvos AG, Hajdu SI. Malignant vascular tumours of the liver. *Ann Surg* 1972; 175: 375–83.

Paper accepted 27 July 1983

face morphology, there was no evidence that the surface nodules were composed of any special, unique element. These particles from these particular collections seem to be quite similar to the micrometer size particles emitted in the ash (2). It is not clear, therefore, why the collected ash shows a bimodal distribution of micrometer size particles centered around 5 μm and submicrometer size particles centered around 0.5 μm. X-ray photoelectron spectroscopy (XPS) and depth profile XPS have been applied to these samples to determine surface composition. Results of these analyses will be presented in the near future.

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TCE Biology JC

Anaerobic Degradation of Trichloroethylene in Soil

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Region VII Laboratory, U.S. Environmental Protection Agency, Kansas City, Kansas 66115

David E. Jackson†

Ecology and Environment, Inc., Kansas City, Kansas 66101

Charles J. Wurrey

Department of Chemistry, University of Missouri, Kansas City, Missouri 64110

■ When trichloroethylene (TCE) isotopically labeled with one ^{13}C atom is used and gas chromatography/mass spectrometry is employed to monitor the production of 1,2-dichloroethylene-$^{13}C_1$ (DCE), it has been demonstrated that reductive dechlorination of TCE takes place in the soil. Microbial involvement in this process is indicated since unsterilized soil samples yielded up to 78 ppb of labeled DCE while sterilized soil samples produced none. Isomer specificity was also found; only 1,2-DCE was produced—no 1,1-DCE was observed.

Introduction

Since trichloroethylene (TCE) is a major industrial solvent (234 000 metric tons produced annually, worldwide (*1*)) used for degreasing and cleaning metal parts and electronic components, it is perhaps not surprising that TCE has found its way into the environment. In fact, TCE appears to be widely distributed in the aquatic environment (*1*).

However, the environmental fate of TCE has not been well documented, and considerable controversy still exists concerning its behavior in environmental matrices. Early literature references have concluded that C_1 and C_2 halogenated hydrocarbons are not metabolized by microorganisms (*2*, *3*). More recent studies, however, are split on the issue of whether TCE is biodegraded (*4*–*7*), with one research group reporting both "no appreciable anaerobic degradation" and 40% degradation of TCE in similar methanogenic cultures (*8*, *9*).

In a very recent publication, Parsons et al. have demonstrated that tetrachloroethylene (herein referred to as perchloroethylene, PCE) is reductively dechlorinated to TCE, dichloroethylene (DCE), and vinyl chloride in Florida muck/surface water microcosms (*10*). Whether TCE, which was present as a 1.6% impurity in the PCE study, was similarly biotransformed was not directly investigated but was implied by the results for PCE (*10*).

Therefore, in order to determine whether TCE itself undergoes biodegradation, we have undertaken a study using TCE with single atom ^{13}C isotopic labeling, soil from a TCE spill site in Des Moines (*11*), and very sensitive gas chromatography/mass spectrometry (GC/MS) analytical techniques. Since DCE-$^{13}C_1$ could only arise via a soil or soil–microbe-induced reductive dechlorination of TCE-$^{13}C_1$, this experimental method should provide concrete evidence in support of such a pathway. The results of our investigation of this problem are reported herein.

Experimental Section

Materials. Since any microbes present had probably adapted to TCE, soil samples were collected at the Des Moines site, at depths of 1–2 ("A" samples), 6–8 ("B" samples), and 15–17 ft ("C" samples), by using an 18 in. long by 2 in. o.d. split barrel sampler (*11*). These soil samples were analyzed by GC/MS for the presence of TCE and DCE. In spite of the TCE sludge application having been discontinued in 1979 (*11*), all soil samples contained 6 ppb of "native" (unlabeled) TCE. No DCE's were found in any soil sample. (An analysis of the Des Moines TCE sludge itself by this laboratory and by an independent testing laboratory showed very high levels of TCE (3000 ppm), but no DCE was detected.)

TCE-$^{13}C_1$ was purchased from Merck Sharp & Dohme Isotopes. Single ^{13}C labeling was used to produce molecular and fragment ion peaks which did not have the same m/z values as the ^{12}C/ECI GC/MS

† Present address: Department of Civil Engineering, University of Illinois, Urbana, IL 61801.

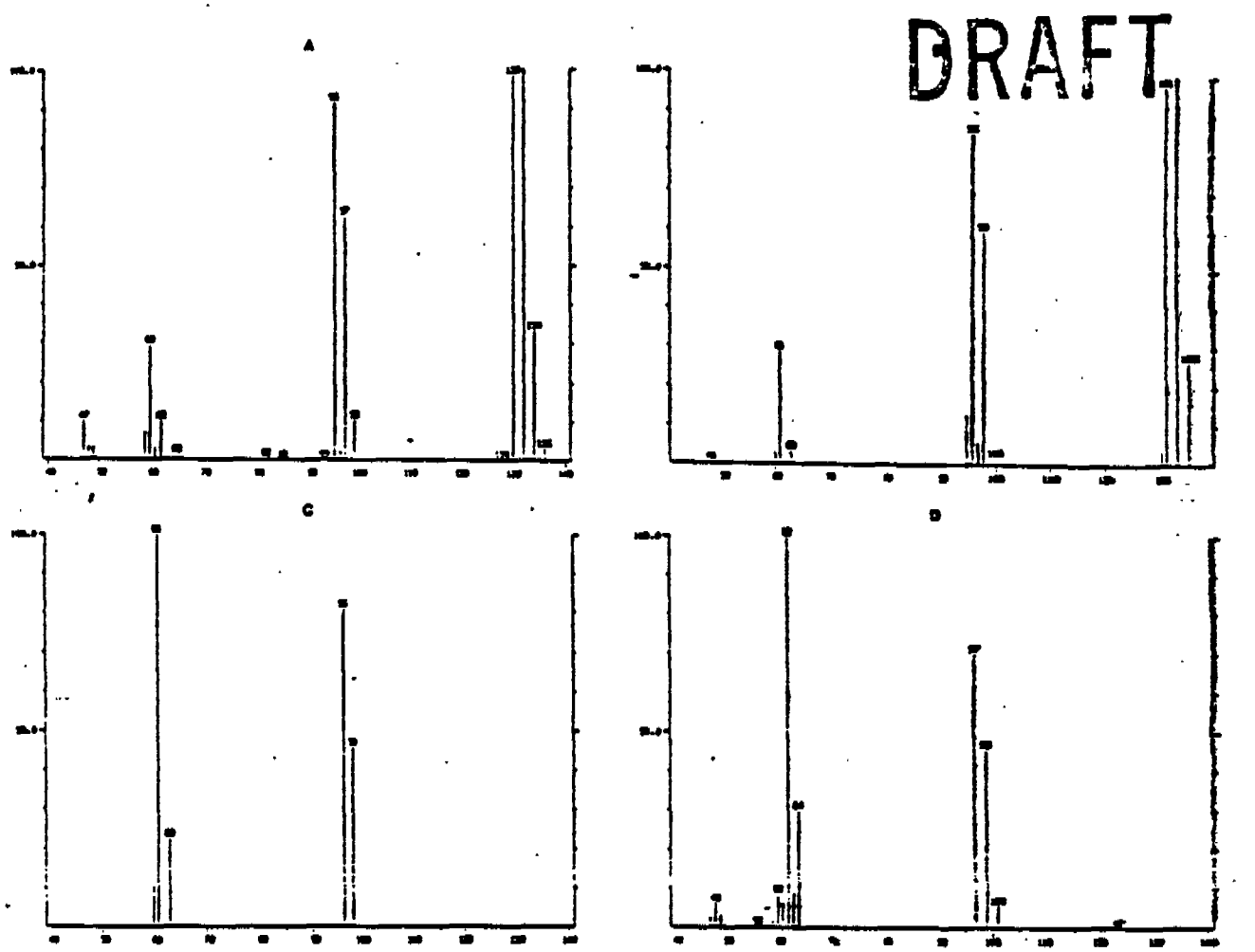

Figure 1. Representative mass spectra of trichloroethylene and 1,2-dichloroethylene: (A) trichloroethylene; (B) trichloroethylene-$^{13}C_1$; (C) 1,2-dichloroethylene; (D) 1,2-dichloroethylene-$^{13}C_1$.

contamination. Volatile organic standards were purchased from Supelco, Inc., and were diluted appropriately with methanol to contain 200 ppb of TCE and DCE. Soybean meal was obtained commercially.

Methods. Five grams of soil from each depth was placed in 5-mL amber vials which had been baked at 150 °C for 3 h to remove any adhering volatile organic compounds. One gram of soybean meal was added to each vial to ensure anaerobic conditions, and the vials were then filled with "organic-free" distilled water (which had been purged with nitrogen). (Organic-free water is distilled, passed through a carbon column, and checked for organics by using GC/MS methods.) The vials were sealed with Teflon septa. Samples to be sterilized were placed in an autoclave for 30 min at 15 psi. Each vial was then injected with 10 μg of TCE-$^{13}C_1$ (2000 ppb, or μg/kg). Duplicates of each sample were prepared. The sealed vials were transferred into CO_2/H_2 Anaerobic-Paks (BBL, Division of Bioquest), which were then placed in an incubator at 23 °C. As much as possible, the samples were kept in the dark to avoid photolytic degradation of the TCE. Subsets of the vials were removed for analyses at 6, 17, and 41 weeks.

Control and method blank samples were prepared as follows: (1) Vials containing only organic-free water, both with and without the TCE-$^{13}C_1$ spike, were prepared to monitor volatilization losses and to check for cross-contamination throughout the procedure. (2) Vials containing only soybean meal (both sterilized and unsterilized) and TCE to DCE by the soybean meal itself or any "foreign" microbes and to monitor adsorption of the TCE onto this organic matter. (3) For the 6-week samples only, vials containing soils A–C, soybean meal, and water without the TCE-$^{13}C_1$ spike were prepared as method blanks.

For the analyses, the contents of each vial were transferred to a 25-mL vial by using organic-free water to eliminate headspace again, sealed with a Teflon septum, mixed, and allowed to settle. Five milliliters of the supernatant liquid was then removed for volatile organics analysis using a Finnigan Model OWA GC/MS and standard purge and trap methodology (*12*, *13*). Detection limits for TCE and DCE by this method are estimated to be 1 ppb.

Results and Discussion

All compounds involved in this study were identified by their characteristic GC elution times and mass spectra. (Figure 1 shows the observed mass spectra of labeled and unlabeled TCE and DCE.) Both qualitative and quantitative identifications were effected from several selected ion mass chromatograms for each substance. For example, the ions at the listed m/z values were used for the analyses of the following compounds: TCE (m/z (95, 97, 130, 132, 134); TCE-$^{13}C_1$ (m/z 96, 98, 131, 133, 135); DCE (m/z 61, 63, 97, 99); DCE-$^{13}C_1$ (m/z 62, 64, 98, 100). No confusion resulted from peaks having the same m/z values for these substances since each compound (exclusive of its isotopomer) eluted at a different time. For quantitation, ...

Table I. Amounts (μg/kg) of 1,2-Dichloroethylene-$^{13}C_1$ Produced by Degradation of Trichloroethylene-$^{13}C_1$ in Unsterilized Soils

time, weeks	soil A[a]	soil B[a]	soil C[a]
6	8	7	11
17	28	31	8
41	78[b]	27	25

[a] See text for soil depth designations. Results are averages for duplicate samples; ranges were ±50%. [b] No duplicate value was obtained.

for the ^{12}C and ^{13}C compounds were identical. This assumption appears to be valid since we observed natural abundance ^{13}C peaks in the unlabeled TCE and DCE mass spectra having 2% of the intensity of the corresponding ^{12}C peaks (theoretical value 2.2%). The pertinent results of this study are discussed as follows:

(1) In the water-only samples, no cross-contamination was observed at any stage of the experiment. Therefore, no exogenous substances appear to have entered the sample vials.

(2) The vials containing the water with the TCE-$^{13}C_1$ spike showed considerable variability in their percent recoveries, indicating substantial and inconsistent volatilization losses of the TCE. We were thus unable to obtain reliable quantitative data measuring the conversion of TCE to DCE by following the rate of loss of TCE. Any experiment that measures only the loss of TCE appears to suffer from these volatilization problems and from adsorption problems (to be discussed next). No degradation products of TCE-$^{13}C_1$ were observed in these water and TCE-$^{13}C_1$ samples, so soil or microorganisms contained in the soil must be present to effect this conversion.

(3) In the samples containing water, soybean meal (whether sterilized or not), and the TCE-$^{13}C_1$ spike, no conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ was observed. Thus, these control samples eliminate the soybean meal as a potential source of TCE degradation. However, adsorption of the TCE on the soybean meal was significant. From 50 to 60% of the TCE spike was adsorbed after 6 weeks. As seen from the sterilized soil samples (where, except in one case of incomplete sterilization, *no* conversion of TCE to DCE occurred), another 10–15% of the TCE was adsorbed on the soil. Thus, adsorption losses pose another major problem in a study like this. Experiments that monitor the loss of, for example, TCE and attribute it solely to degradation are potentially suspect, particularly if care is not taken to account for volatilization and adsorption losses.

(4) The 6-week method blanks (containing water, soil, and soybean meal with no TCE-$^{13}C_1$ spike) showed no generation of any substance (TCE or DCE, labeled or unlabeled) not already present in the soil itself.

(5) Conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ was noted in *all* unsterilized soils. Table I summarizes the amounts of labeled DCE produced. As seen from Table I, a general and gradual increase in the amount of DCE-$^{13}C_1$ produced occurs with time. (Of course, due to adsorption and volatilization losses, the amounts of DCE-$^{13}C_1$ actually produced are no doubt larger than those reported here. Actual amounts of TCE — DCE conversion in "real" soils may be even larger than those reported here, since the soybean meal added to ensure anaerobiosis may well have been a more attractive energy source for the soil microbes than the TCE. Indeed, breakdown products of the soybean meal were also noted in the unsterilized soil samples.)

soil samples showed the presence of 2 ppb of DCE-^{13}C This may, however, be the result of an incomplete ster lization since this was only observed for one of the longe time samples.

Since conversion of TCE-$^{13}C_1$ to DCE-$^{13}C_1$ occurre almost exclusively in unsterilized soils, microbial partic pation seems certain. Some caution should be exercise in drawing this conclusion, however, since Kaufman (*1* has reported that autoclaving changes not only the bi logical properties of the soil but also its physical ar chemical properties. Nevertheless, on the basis of o results for TCE and those of Parsons et al. (*10*) for PC it appears that the degradation of TCE to DCE in the s is indeed of biological origin.

(7) Only 1,2-DCE-$^{13}C_1$ was produced whenever TCE-^{13} was degraded. No 1,1-DCE-$^{13}C_1$ (which elutes more rapid than 1,2-DCE) was found in any sample. Under our e perimental conditions, *cis*- and *trans*-1,2-DCE coelut (and cannot be differentiated on the basis of their ma spectra). Thus, we could not identify which geometric isomer was formed, or if a mixture of the two was pr duced. (In their study of PCE biodegradation, Parso et al. (*10*) were able to separate the cis and trans isome chromatographically. They found that *cis*-1,2-DCE significantly fawored over the trans isomer.)

Summary

By using TCE isotopically labeled with a single ^{13}C ato we have shown that TCE is definitely dechlorinated in t soil to 1,2-DCE. Isomer specificity was also observed; 1,1-DCE was detected. The TCE — DCE degrada appears to be biological in nature, since soil samples whi had been sterilized exhibited no such conversion.

Since it has been shown that microbes that have adap to degrade one member of a homologous series have el simultaneously adapted to degrade other members of t same series (*15*), the possibility exists that DCE can further biotransformed into vinyl chloride in soils. M itoring data at the Des Moines site (*11*) and elsewhere (*1* this work and the work of Parsons et al. (*10*) all strong support this DCE — vinyl chloride contention. Consi ering the well-known carcinogenicity of vinyl chlorid further research along these lines is definitely warrante

Acknowledgments

We gratefully acknowledge John Casile (of Ecology a Environment, Inc.) for obtaining the soil samples and C. Bailey and Angelo Carasea (of the Region VII Envir mental Protection Agency Laboratory) for providi technical assistance.

Registry No. TCE, 79-01-6; DCE, 540-59-0.

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(13) Longbottom, J. E.; Lichtenberg, J. J. "Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater"; U.S. Environmental Protection Agency: 1982; EPA 600/4-82-057, Method 624.
(14) Kaufman, D. D. In "Pesticides in Soil and Water"; Guenzi, W. D, Ed.; SSSA Publishers: Madison, WI, 1974; pp 133–202.
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Gas-Phase Hydrogenolysis of Polychlorobiphenyls

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■ Chloroarenes in an atmosphere of hydrogen are thermally dechlorinated to yield HCl and benzene as major products between 700 and 925 °C, with residence times of ca. 10 s. Polychlorobiphenyls (PCBs) are both dechlorinated and split into chlorinated benzenes, with splitting about twice as fast as dechlorination. Thermal hydrogenolysis, which occurs via radical mechanisms involving *H* atoms, may therefore be considered as a useful method for workup of (toxic) chlorinated wastes.

Following studies on thermolysis (*1–3*) and on several free-radical gas-phase aromatic substitutions—chlorination (*4*), cyanation (*5*), nitration (*6*), and oxidation (*7*)—we are now engaged in thermal conversions of benzene and derivatives with hydrogen. Within this category, "hydrocracking" of chlorinated arenes deserves special attention. In general, reaction 1 is of potential interest as a method

$$\mathrm{Ar(R)Cl + H_2 \xrightarrow{\Delta} Ar(R)H + HCl} \qquad (1)$$

for dechlorination of (highly) chlorinated industrial waste materials etc. Thermolysis of chlorinated benzenes in an excess of H_2 (quartz flow reactor, atmospheric pressure, residence time 5–15 s) proceeds smoothly at 750 °C and shows very high degrees of conversion (HCl formation) at ca. 900 °C (*8*). Sooting is unimportant even at 900 °C provided that the H_2:arene molar intake ratio is above 10. Aliphatic and olefinic chlorides, in general, react much faster than chlorobenzenes (*8*).

Polychlorobiphenyls (PCBs) have found widespread application, especially as transformer oil, its use and disposal entailing considerable environmental problems. We therefore thought it worth while to examine the behavior of PCB in hydrocracking (eq 1). Our observations, including those on appropriate model compounds reported below, confirm our expectation that PCB can be completely converted into HCl and non-chlorinated organic products, mainly benzene. Hydrocracking thus constitutes an environmentally clean alternative to incineration.

Representative examples with Aroclor 1248 (Cl = 48% wt) are outlined in Table I. That conversion of PCB is essentially complete and is illustrated by Figure 1. Dechlorination of chlorobenzene (PhCl) is ≥97%; monochlorobiphenyls are seen in minor amounts only, biphenyl comprising ca. 0.7% on the PhCl feed. This biphenyl stems from PhCl—or better, from benzene made therefrom—rather than from PCB (vide infra). Notable

Table I. Thermolysis of PCB in Chlorobenzene with Hydrogen[a]

	run no.			
	1	2	3	4
T, °C	715	780	805	875
τ, s	8.9	8.3	8.3	7.8
conversion[b] of PCBs, %	(ca. 10)	28	70	>98.9[c]
$PhCl_2$[d,e] %	4.8	8.5	1.5	0.2
$PhCl_3$[e] %	1.2	1.5	0.16	0
Ph_2[e] %	0.010	0.034	0.040	0.60
$ClPh_2$[d,f] %	0.053	0.18	0.13	<0.02
PhH:PhCl molar ratio	0.059	0.19	0.92	35

[a] Spiralized quartz tubular flow reactor (3.5 m, 46 cm³); inflow (mmol/h): H_2, 221 ± 4; PhCl, 10.2; Arochlor 1248 (0.69); duration of runs 40–65 min.; product collected in a trap cooled with liquid N_2. [b] By GLC with PhBr as internal standard; total of surface areas from dichlorobiphenyl on (retention time > 27 min, Figure 1), assuming response to be independent of chlorine content. These numbers parallel those for degrees of dechlorination of PhCl, $PhCl_2$ or $PhCl_3$ under the same conditions. [c] Mole percent on PCB in × 0.5. [d] Mole percent on benzene out. [e] Isomer distribution (ortho:meta:para, %): run 1, 40:25:35; run 2, 37:27:36; run 3, 32:33:35. [f] Isomer distribution (ortho:meta:para, %): run 1, 31:31:38; run 2, 32:35:33; run 3, 34:38:28. [g] Confirmed by GC with electron capture detection.

The di- and trichlorobenzenes clearly stem from splitting of PCB and account for ca. 6% of the Arochlor feed. Chlorobenzene is produced via the same route but is obscured by its use as diluent. Its amount can be estimated from what is known about the composition of the PCB mixture. Specifically, the identified portion of Arochlor 1248, ca. half, is composed of the following ratios of phenyl units: Ph:PhCl:$PhCl_2$:$PhCl_3$ = 0.02:1:1.3:0.16. If changes due to the small degree of dechlorination are neglected, PhCl from PCB would thus be 1:(1.3 + 0.16) × 6 = 4%, so as to give a total degree of splitting of about 10%. PhCl alone yields ca. 6% of HCl under these conditions so this mode of hydrogenolysis is about twice as fast as dechlorination.

As we have reported elsewhere (*8*, *9*), methane is also formed, ranging from 0.2% (run 1) to 1% (run 4) on PhCl feed; small amounts of C_2H_4 and C_2H_6 and traces of C_2H_2 are also produced.

Simultaneous splitting and dechlorination of PCB will cause the yields of $PhCl_2$ and $PhCl_3$ to pass through a maximum with increasing temperature. The same holds

DRAFT

THE DOW CHEMICAL COMPANY

THE DOW CENTER
MIDLAND, MICHIGAN 48640

October 5, 1984

Document Control Officer
Management Support Division
Office of Toxic Substances (WH-557)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

AIRBORNE

Dear Sir/Madam:

Attached for your information please find a copy of a summary of a report on a Lifespan Oral Carcinogenicity Study of Vinyl Chloride in Rats which we recently received and which I discussed with David Williams on Tuesday, October 2, 1984. This study was conducted in Europe by Civo Institutes TNO and was sponsored by Verband Kunstofferzeugende Industrie E.V. (VKI).

It is our understanding from VKI that the EPA will soon be receiving a copy of the final report. We do not have a copy.

Upon review of this summary, we have been unable to determine whether this study presents any substantial risk information under the EPA's Statement of Interpretation and Enforcement Policy. 43 Fed. Reg. 11110 (March 16, 1978). It appears from the minimal data presented in this summary that the study is corroborative of effects already documented in the scientific literature.

Sincerely,

John A. Gray

John A. Gray
Attorney
2030 Willard H. Dow Center
517/636-0933

To: Bob Oubre
From Fred Hoerger

Page 1 of 4

Attachment

Dcc: F. D. Hoerger, 2020 WHDC
H. Schumacher, Horgen

CMA 010652

SUMMARY

3071

1. The oral carcinogenicity of vinyl chloride monomer (VCM) was examined in a lifespan study (149 weeks) with five groups of Wistar rats, each consisting of 100 males and 100 females, except for the top-dose group which comprised 50 males and 50 females. VCM was administered by incorporating polyvinyl chloride (PVC) powder with a high VCM content into the diet. The diet was provided daily for a period of 4 consecutive hours, whereas food was withdrawn during the other 20 hours. The use of this way of oral VCM administration resulted in the following exposure levels: 0 (control), 0.014, 0.12 and 1.3 mg VCM/kg body weight/day. An extra control group of 100 rats/sex was housed in a separate room.
Additional satellite groups of 18 male and 18 female rats, each receiving the same treatment as the main groups were used for determinations of glutathione levels in the liver after 9 and 18 months.
Observations were made of general appearance, mortality, growth, food intake, thrombocyte count, prothrombin time, glutathione levels in the liver, gross pathology and microscopic pathology of the liver and of all grossly visible tumours or presumable tumours in the abdominal cavity, the glands of Zymbal and the mammary glands.

2. General health, behaviour, body weight and food intake were not adversely affected by the test substance.

3. In the second half of the experimental period, mortality in the extra control group was higher than in all other groups. This was most probably due to a high incidence of chronic respiratory disease in the extra control group. In the final stage of the study, the mortality in the top-dose group was slightly higher than in the lower dose groups and the controls.

4. Thrombocyte count, prothrombin time and liver glutathione levels did not show treatment-related differences among the groups.

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5. A clearly higher incidence of grossly visible, tumourous, liver nodules was found in both males and females of the top-dose group than in any of the other groups. Moreover, in females of the top-dose group the incidence of hepatic cysts was considerably higher than in controls.

6. Microscopic examination of the liver revealed increased incidences of liver-cell polymorphism, hepatic cysts, foci of cellular alteration, neoplastic nodules and hepatocellular carcinomas in the top-dose group as compared to the control group. Moreover, a hepatic angiosarcoma was found in one male and two females of the top-dose group, whereas no such tumours were encountered in any of the other groups.
The number of animals bearing foci of cellular alteration in the liver was also statistically significantly increased in females of the mid-dose group as compared to controls. In addition, in females but not in males, the incidence of basophilic foci of cellular alteration in the liver was statistically significantly higher in both the low- and the mid-dose group than in the control group.

7. There was no evidence of VCM-feeding affecting the incidence of abdominal mesotheliomas or the type and incidence of mammary gland tumours. No Zymbal gland tumour was found.

8. It was concluded that under the conditions of the present experiment

- VCM at a level of 1.3 mg/kg body weight/day induces neoplastic and non-neoplastic changes in the liver of rats,
- VCM at a level of 0.13 mg/kg body weight/day may lead to more female rats bearing foci of cellular alteration in the liver,
- VCM at levels of 0.014 or 0.13 mg/kg body weight/day may result in an increased incidence of basophilic foci of cellular alteration in the liver of female rats,
- 0.13 mg VCM/kg body weight/day is a "no-observed-adverse-effect-level" with respect to the induction of tumours in rats.

9. Risk estimation based on the results of the present rat study and taking into account the prudence of the linear model applied and a lesser sensitivity of humans to the carcinogenic action of VCM in comparison with rats, indicates that the cancer risk of a likely maximum oral daily intake of 0.1 µg VCM per person per day can be practically neglected.

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RISK MANAGEMENT OF EXISTING CHEMICALS

Proceedings of a Seminar
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CHAPTER 10

VINYL CHLORIDE AND TSCA

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Air Products and Chemicals, Inc.[1/]

INTRODUCTION

The well-known regulatory history of vinyl chloride and its role as a bellwether of current regulatory philosophy makes it a useful paradigm for examining the relationship of existing laws and the Toxic Substances Control Act (TSCA) for control of chronic hazards.

To this end, we will first review some of the highlights of its regulatory history, and then engage in some speculation as to the response these events might elicit today under TSCA.

INDUSTRIAL AND COMMERCIAL USE OF VINYL CHLORIDE

Vinyl chloride became of industrial importance about fifty years ago, approximately a hundred years after its discovery, when Semons discovered that its polymer could be converted into useful articles by plastization with phthalate esters. Commercial development began first in Europe and then in this country in the late

1/ Air Products and Chemicals, Inc., 1983.

thirties, largely using existing rubber processing equipment, for it was rubber which it initially replaced in the market. For the same reason, the use of polyvinyl chloride (PVC) was sequestered by the government during the war years, and it was not until the early fifties that widespread consumer applications developed. PVC is now a mature product, and its growth rate falls in step with the Gross National Product. Presently, about six billion pounds are used annually in this country, and about four times that in the world.

Some of the broader toxicological attributes of vinyl chloride (VC) were recognized in the thirties. It was known to be an anesthetic, but problems with cardiac arrythmia prevented its use in that application.[2/] As pathological techniques improved, industry scientists recommended in the early sixties that exposure be limited to 50 ppm, because of temporary liver enlargement in animals at that level,[3/] but the American Conference of Governmental and Industrial Hygienists considered this overly conservative and accepted instead the 500 ppm recommendation of Harvard scientists.[4/] This was the value adopted by the Occupational Safety and Health Administration (OSHA) in its formative days.

Also in the early sixties, the European industry recognized among its workers a disease termed acroosteolysis, AOL, which is a degenerative disease of the bone tufts, particularly in the fingers, that is accompanied by Reynaud's phenomenon.[5/] An extensive epi-

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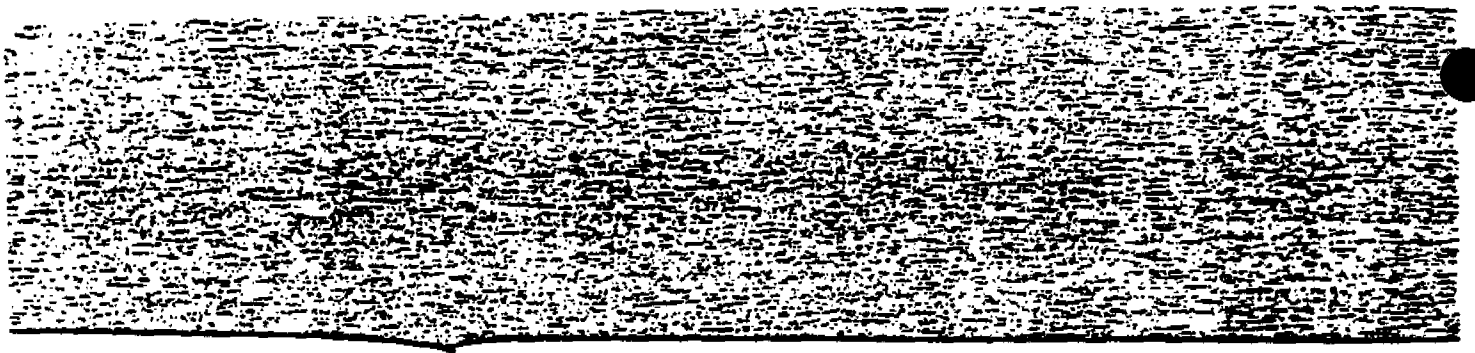
2/ W. F. von Oettigin, "The Halogenated Hydrocarbons, Their Toxicity and Potential Dangers," Public Health Service Publication No. 414 (Washington, D.C.: U.S. Department of Health, Education and Welfare, 1955).

3/ T. R. Torkelson, F. Oyers, and V. K. Rowe, "The Toxicity of VC as Determined by Repeated Exposures of Laboratory Animals," American Industrial Hygiene Association Journal, XXII (1961), p. 354.

4/ American Conference of Governmental and Industrial Hygienists, "Documentation of the Threshold Limit Value, 1963" (Cincinnati, OH, 1963).

5/ S. Suciu, J. Drejman, and M. Valaskai, "Study of Diseases Caused by Vinyl Chloride," Medical Interna. XV (1963), p. 967.



demiological survey here and in Europe found about a hundred possible cases which were associated closely with manual cleaning of reactor walls between polymerization batches, but neither the precise etiological agent nor the disease mechanism was identified.[6/]

An attempt was made to reproduce this disease in rats by the medical department of one of the European producers. An exact duplication of the human disease was not seen, but many of the rats developed tumors at numerous sites. The reporting of this finding by Viola[7/] in 1970 evoked little interest in the regulatory community, possibly because of the very high doses used, several thousand ppm, which were frankly toxic to the animals, and the fact that the tumors were largely metastatic from the Zymbal gland, an organ not present in humans.

Nevertheless, both the European and domestic producers formed consortia to perform bioassays at lower concentrations and also began epidemiological surveys of their employees.

Preliminary results of the European bioassay became available first in early 1973, and showed tumor development at much lower concentrations in organs which do have human counterparts. This result was transmitted to regulatory officials that summer, and industry screening of employee records was intensified.[8/] This resulted in the recognition that winter by an industry medical director of a cluster of three rare liver tumors termed angiosarcoma, ASL, in the employees of one facility.[9/] The reporting of this fact to

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6/ W. A. Cook, et al., "Industrial Hygiene Evaluation of Thermal Degradation Products from PVC Fetus in Meat-wrapping Operations," Arch. Environ. Health, XXII (1971), p. 74. Also, B. D. Diman, et al., "Occupational Acroosteolysis I, An Epidemiological Study," Ibid., p. 61.

7/ P. L. Viola, "Pathology of Vinyl Chloride," Medicina d l Lavoro, LXI (1970), p. 174.

8/ A. W. Barnes, "ICI Ends Its Silence on Vinyl Chloride," Chemical Engineering News, (July 8, 1974), p. 21.

9/ J. L. Creech and M. N. Johnson, "Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted for Studies in Rats," Journal of Occupational Medicine, XVI (1974), p. 150.

government officials led to the current regulatory status of vinyl chloride.

It also led to a virtual explosion of research on the chroni toxicity of VC. The body of scientific literature on the oncogenicity of vinyl chloride is as large as that for any other substance. It is recognized that VC is a classical procarcinogen. Metabolism by the mixed function oxidase in the liver converts it to the ultimate carcinogen, an epoxide. Detoxification of this intermediate by the sulfhydryl group of glutathione or other proteins removes the toxic potential.[10/] Both of those mechanisms are saturable.[11/] An overload of the metabolic step assures that the vinyl chloride will pass through the liver and some will be metabolized in other organs. An overload of the detoxification step allows escape of the toxicant into the sinusoidal passages of the liver where interaction with th chromosomal protein causes ASL to develop. An overload of both mechanisms can lead to tumor development outside of the liver, as is seen in mice and rats at very high doses. Despite the large data base, however, information on the precise mechanism of these various steps still is lacking. We do not even understand why some persons respond with AOL and some with ASL, but none with both diseases.

REGULATORY STANDARDS

OSHA proceeded promptly in early 1974 to set an emergency temporary limit of 50 ppm for worker exposure, and later that year reduced the limit to one ppm, the current figure. Industry was given a grace period during which respirators could be used to meet this requirement, but now that level must be met by engineering practices.[12/]

10/ W. K. Lelbach and H. J. Marsteller, "Advance in Internal Medicine and Pediatrics" Springer-Verlag, XLVII (New York, 1981).

11/ R. Hefner, P. Watanabe, and P. Gehring, "Percutaneous Absorption of Vinyl Chloride Gas in Rhesus Monkey," Toxicology and Applied Pharmacology, XXXIV (1975), p. 529.

12/ OSHA Standard for Vinyl Chloride, 29 CFR 1910.1017.

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onkey," Toxicology and

FR 1910.1017.

The Environmental Protection Agency (EPA) promulgated a combined engineering and works practice standard in 1976 which has resulted in ambient concentrations in the fractional ppb range near producing or using facilities.[13/]

In the meanwhile, the Food and Drug Administration (FDA) and Consumer Product Safety Commission (CPSC) established prohibitions on the use of VC in aerosol or other consumer applications, a practice which had been discontinued in 1973. The Bureau of Alcohol, Tobacco and Firearms of the Treasury Department (BATF) had already banned the use of PVC liquor bottles in 1973 because of concern for taste effects from migration of residual VC into th contents. In 1975 the FDA proposed revocation of the generally regarded as safe (GRAS) status of rigid PVC packaging under the Delaney clause, also because of migration concerns, but that proposal never has been promulgated, and the FDA has stated that it is considering withdrawal of the proposal and recommending to BATF the reauthorization of plastic liquor bottles in light f the current very low residual monomer levels in fabricated PVC articles.

Other regulations have followed as new statutes and rules have come into play. The Department of Transportation (DOT) and the Coast Guard regulate the transportation of VC, of course, and VC is listed as a priority pollutant and hazardous waste under various water and solid waste rules, and has a reportable quantity of one pound under Superfund.

Did the existing laws operate satisfactorily at the tim of discovery of the chronic hazards of VC? It appears that they did. A leading medical authority who was deeply involved in the worker health evaluation in 1974 has termed VC a "success story." Reevaluation of the risk to employees under the [illegible] ppm standard by a conservative nonthreshold extrapolation method[14/] yields a lifetime estimate of less than 10^{-8}, a risk level which is not thought to be of concern. The comparable risk estimate for the general populace is

13/ EPA Standard for Vinyl Chloride, 40 CFR 61.60.

14/ P. J. Gehring, P. G. Watanabe, and C. N. Park, "Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted for Studies in Rats," Toxicology and Applied Pharmacology," XLIX (1979), p. 15.

several orders of magnitude lower. EPA has stated on several occasions that it believes that vinyl chloride is regulated adequately.

RISK ASSESSMENT

Risk assessment has been a popular avocation among those interested in VC, and more than a dozen have been performed.[15/] These can be divided generally into two classes: those which rely solely on animal data; and those which attempt to incorporate the human experience.

Those in the first class yield similar results, and show the normal spread of estimates from the various mathematical models in common use. These range from 1,500 to 10^{-5} ppb for a lifetime risk of 10^{-6}, or eight orders of magnitude. It is necessary to eliminate the high-dose data points, that is, those over 2,500 ppm from the Maltoni data[16/] in order to get reasonable fits to most models, because these doses show broad systemic toxicity. The lower doses, 500 ppm and below, as a group fall into a general pattern on a log-probit plot, but individual two or three dose experiments show tremendous differences in slope when plotted separately. The popular multihit model predicts a lifetime risk of 10^{-6} at fractional ppb levels.

The human factor was accounted for in two ways. The EPA used some preliminary employee epidemiological data to confirm its animal-based extrapolation.[17/] Unfortunately, the human data were

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15/ J. T. Barr, "Risk Assessment for Vinyl Chloride in Perspective," (Paper 82-9.2 presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, LA, 1982), Lines 20-25.

16/ C. Maltoni, et al., "Vinyl Chloride Carcinogenicity Bioassays (BT Project)," (Paper presented at "Le Club de Cancerogenese Chemique," Institute Curie, Paris, November 10, 1979).

17/ A. M. Kusmack and R. E. McGeughy, "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride," (Washington, D.C.: U.S. Environmental Protection Agency, December 5, 1975).

selected from those locations known to have ASL cases, while other facility data were omitted. They also were in error on the past exposures by more than an order of magnitude. This resulted in an estimate of 20 cases per year from the estimated 1974 ambient concentrations for the population within five miles of production and processing facilities.

The EPA seldom bothers to check its estimates against available data, so it sometimes comes up with results such as that made for arsenic a few years ago that would have predicted 18 million cases of skin cancer a year in this country if it had been applied to Agency data on the average arsenic concentrations in drinking water. Similarly, a survey of all known ASL cases in this country for the ten years before 1974 showed no cases associated with residency near such plants,[18/] rather than the 200 predicted cases. It is reasonable to assume that if any cases had developed since that time, the publicity associated with it would have brought them to light. Thus we have 110 million-person years of negative history for nearby residents. This places an upper limit on risk of less than 10^{-7} per ppm-yr.

Two studies applied pharmacokinetics in an attempt to obtain relevant human data. Gehring and coworkers estimated a lifetime risk of 10^{-8} at one ppm from the probit model, based on a biotransformation of rat data. The unconstrained linear model predicted no risk at less than 99 ppm.[19/]

Anderson, Hoel and Kaplan carried this procedure one step further, and applied it to bound metabolic products, rather than to the total amount metabolized. Their results gave a lifetime risk of 10^{-7} at less than one ppm, with the probit model, or at less than tw ppm with the linearized multistep model.[20/]

18/ H. Popper, et al., "Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic," American Journal of Pathology, XCII (1978), p. 349.

19/ P. J. Gehring, P. G. Watanabe, and C. N. Park, Toxicology and Applied Pharmacology, XLIX (1979), p. 15.

20/ M. W. Anderson, D. G. Hoel, and N. L. Kaplan. "A General Scheme for the Incorporation of Pharmacokinetics in Low-dose Risk Estimation for Chemical Carcinogens. ibid., LV (1980), p. 154.

Thus we see that risk is in the eye of the estimator, but it is clear that estimates incorporating human data reflect th human experience for VC far better than do the direct application f animal data.

There was understandable uncertainty on the part of both the regulators and industry in 1974. This was the first commodity chemical to be regulated under the relatively new statutory situation as the result of new information. Nevertheless, both the regulatory agencies and industry acted promptly to reduce exposures and emissions to an acceptable level.

The current count of occupational ASL cases is about 100 worldwide, with 30 of these in this country.[21/] All these cases had their first exposure in 1964 or earlier, and there appears to b room for optimism that the steps taken in the mid-sixties because f the AOL information will have prevented any significant number of cases developing from exposures commencing after that date. Certainly it is reasonable to expect that there have been no new cases initiated after the early seventies.

Had TSCA been in place in the mid-sixties, would it have made any difference in the course of events? It appears unlikely that it would. Certainly the AOL discovery would have resulted in a series of 8(e) notices to TSCA. The probable outcome of that would have been either a recommendation from the Interagency Testing Committee (ITC) for more tests, or a Section 4 testing requirement. It is possible that, because of its commercial importance, VC could have been placed on the ITC list before the AOL data became available. Additional data could have been called for under Sections 8(a) and (d). The result of all this most likely would have been a negotiated testing rule, under which industry would have initiated a series of studies which would have culminated in a bioassay, and the carcinogenicity of VC would have been discovered in due time. Yet, this is precisely what did happen in the absence of TSCA, except that the preliminaries were omitted, and the bioassay was performed concurrently with the screening tests. Thus it is possible that th

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21/ J. Stafford, personal communication, Liver Angiosarcoma Cases, April 15, 1983.

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final critical data were obtained earlier than would have occurred under present conditions.

Bear in mind that most of today's powerful testing methods were not available twenty years ago. That fact would not have been changed by legislative fiat, and any decision made at that time had to be made in light of the available knowledge.

If the data of Viola suddenly became available today instead, would there be any significant difference in the outcome, or the timing of that outcome? Probably so, but only because of the vastly more powerful scientific tools which we have available to us now. Neither the speed of agency motion nor the rate at which industrial facilities can be built or modified has increased. If anything, the latter has slowed, given the multiplicity of permits and approvals now required. Overall, it is possible that if today we knew nothing more about VC than was known in 1970, we would arrive at a regulated state a few months earlier than was achieved in 1974, but scientific progress, and not legislative or regulatory advancement, should get the credit.

What if VC were to become a new product today? Would it run the same course in which it would be 40 years before there was full recognition of its chronic potential? Certainly not. Again, however, the reason is due more to scientific progress rather than statutory development.

One change might be apparent. If VC were the subject of a Premanufacture Notification (PMN) today, rather than being the model to which all other aliphatic olefins are compared for structure-activity analysis, it would be judged by the others in its family. This comparison would be less dogmatic than the reverse is now. Ethylene and vinylidene chloride are not animal carcinogens; the relevance to humans of the carcinogenicity of high doses of trichloroethylene (TCE) is equivocal and controversial; and vinyl acetate has only a preliminary "non-negative" report. Thus, this class of substances would have lost its leader for structure activity comparison, and a decision as to the need for further testing from that analysis would not be clear-cut, based on analogous compounds.

Neither would a full minimum premanufacture data (MPD) set be of any great assistance. VC responds poorly to the classical in-vitro tests, and only recently has it become possible to obtain reproducible positive results in many of these. If the position were taken

"little lists" for the executioners apparently is too great to be resisted,[26/] as Lester Lave pointed out recently.

We believe that EPA can best obey its statutory mandate by developing a more efficient system for establishing priorities, and by implementing more effectively its Section 9 procedures.

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Risk Assessment for Vinyl Chloride in Perspective

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roduction

combination of circumstances which found the carcinogenic hazard vinyl chloride (VC) being discovered at about the same time as the ence of risk analysis was undergoing rapid development, and the at commercial interest and long history of use of the substance has ulted in a body of literature and pharmacological data greater than can expect to have for most substances. It is therefore instruc- e to review the many risk assessments which have been prepared for against the available biological information to determine if we can luate the extrapolation methods used, and to discuss the current ulations for VC in light of this comparison.

ards of Vinyl Chloride

is necessary to decide first which of the hazards presented by VC uld be the basis for the risk estimation. The substance presents acute hazards of frostbite from exposure to the liquid, of anes- sia at concentrations over 8,000 ppm and suffocation at higher centrations (von Oettinger, 1955). It also forms explosive mixtures air above 3.75 volume percent, and so the efforts to control the sical safety of operations generally preclude exposure to acutely ic concentrations.

se control efforts were reinforced in the mid-1960's where it was overed (Suciu, 1963) that workers who had been exposed to very levels of VC developed "vinyl chloride disease," the primary ifestation of which was acroosteolysis (AOL), a degenerative disease the bone tufts in the hands, and more rarely of the feet and lumbar lon. Although crippling to some degree, this disease is not fatal, is at least partially reversible if exposure is eliminated (Granger, ker and Ward, 1980).

ast ten years later it was found that some of the workers having lar exposure also were developing angiosarcoma of the liver (ASL), pidly fatal disease. Oddly enough, there is only one possible of a worker developing both AOL and ASL (Stafford, 1981) among 80-plus cases of AOL and 90-plus cases of ASL now known worldwide, hough both are diseases of the vascular system. Several large demiology studies were conducted on workers exposed to VC (Baxter Fox, 1976; Chiazze, 1980; Duck, Carter and Coombu, 1975; Equitable ronmental Health, 1978; Fox and Collier, 1977; Frentzel-Beyme, litz, and Theiss, 1978; Theriault and Allard, 1981), and ASL was only fatal disease found consistently to be in excess in these

persons. Animal studies have shown an excess of tumors at other sites, but the lowest exposures at which these occur are considerably higher than that for ASL. For example, Maltoni (1979) reported the following data:

Site	Concentration For Significant Elevation
Forestomach papillomas:	30,000 ppm
Neuroblastomas:	10,000 ppm
Zymbal gland carcinomas:	10,000 ppm
Nephroblastomas:	250 ppm
Liver angiosarcoma male:	200 ppm, 50 mg/kg
female:	50 ppm, 16.7 mg/kg
Mammary adenocarcinoma:	5 ppm

The low concentration for onset of mammary tumors was of concern when a preliminary study of fabrication employees reported an excess of breast tumors (Chiazze, et al., 1979) but a follow-up case-controlled study (Chiazze, 1980) found no association between the cases and VC exposure. The largest study of VC-PVC workers in the United States reported slight excesses of brain and lung tumors (Equitable Environmental Health, 1978), but this was not seen in the other studies referenced above. The excess of brain tumors was small, and not dose- or exposure-related. The overall excess of lung tumors resulted from an excess in one plant only, and reexamination of those cases also showed no association with VC exposure (Waxweiler, 1978).

Vinyl chloride has been found to be active in several *in vitro* mutagenetic tests with bacteria and yeasts (Hopkins, 1979) and it appears to cause chromosome abnormalities in exposed workers, but these changes are reversible when exposure is reduced (Hansteene, 1978) and several studies of neighborhoods around PVC plants have failed to show a supportable association with birth defects (Edmonds, 1975, 1976). It is not a teratogen in rodents (Johns, 1977).

Therefore it appears reasonable to assume that if there is any significant chronic risk other than ASL, it is considerably smaller than that for ASL, and that an adequate risk assessment can be based on only the liver tumors.

view of Risk Assessments

1. Schneiderman, 1975

One of the first attempts to utilize animal data to estimate risks at very low exposures was that of Schneiderman, Mantel and Brown (1975). They used preliminary Maltoni results to compare the estimates obtained from three possible mathematical models. The 99% assurance level of a "safe" dose at a lifetime risk of 10^{-6} was estimated from several extrapolation models as follows:

Log Probit (slope = 1)	73 ppb
Logit (slope = 3.45)	119 ppb
Logit (slope 2.3, one-hit)	2.1 ppb

The authors discussed the recognized difficulties of extending these rat data to humans and of providing animal experiments that could answer satisfactorily the question of human risk at very low doses.

2. Kuzmack and McGaughy, 1975

The EPA was the first group to attempt a human risk assessment for vinyl chloride (Kuzmack and McGaughy, 1975). This pioneering effort attempted to use both animal and human data, and to show comparative results from both the linear and log-probit models. It concluded that there was an individual risk of 71×10^{-6} per ppm of lifetime exposure to VC by the linear extrapolation method, and that the log-probit results were one-tenth to one-hundredth of that.

This effort is subject to several serious criticisms. The exposure data used for human experience was that from a group with less than average exposure, while the ASL rate was chosen from only those plants which did report cases, and ignored the remainder of the population. Thus, their incidence rate of 7.5% compares to an actual figure of about 0.1%.

They used as their primary method a linear extrapolation of rat data, which often has been seen to overestimate the actual rates by at least two orders of magnitude, and they assumed the total cancer rate to be twice that found for ASL.

This same estimate was used by the EPA (1979) to estimate the concentration of VC in drinking water which would produce various levels of risk. These estimates are, of course, subject to the same criticisms.

Nisbet (1978) challenged the estimate of Kuzmack and McGaughy (1975) when it was used by Wilson in testimony before the OSHA hearing on its generic cancer policy. Nisbet stated that his calculations showed the risk to be 10-30 times greater, by the same calculation method. Wilson (1978) suggested several flaws in the Nisbet procedure, including the fact that he chose for his extrapolation one point at 25 ppm from Maltoni experiment BT-15, and that this point is not in good agreement with the whole body of data. Further, he chose to use total cancer incidence in the rats, including those at zymbal glands, which have no counterpart in humans. Both Wilson and Kuzmack and McGaughy had used a factor of two times ASL to account for possible cancer at other sites. Wilson did acknowledge a mathematical error which made his results half the proper number.

Albert (1978) applied this same general procedure to other potentially carcinogenic air pollutants in the United States and calculated the expected annual cancer deaths as follows:

Arsenic	15.6
Benzene	77.8
Cadmium	26.2
Coke ovens	149.5
VC (after regulation)	1.0

3. Gehring, 1979

Gehring, et al., (1979) applied an experimentally derived biotransformation correction (Gehring, et al., 1978) to rat data and estimated the incidence in humans at two different exposures by means of four different extrapolation models. Their estimates at 500 and 200 ppm TWA bracket the observed experience for humans when derived from the probit and the unconstrained linear models. The linear-through-zero and one-hit models consistently overestimated the incidence. Although not considered by the authors, the linear and probit models match rather closely the total U.S. experience of occupational ASL at an assumed 1,000 ppm exposure. The linear model predicts no incidence below 99 ppb in humans. The probit model predicts a human risk of 1.5×10^{-6} at 1 ppm. Thus, a mechanism for adjusting for the difference in metabolism between animals and humans appears to be useful.

A limitation of the Gehring procedure is that it uses partial Maltoni data, and tests the results against the CMA epidemiology study. That study was not the "end of the experiment"; it stopped at the end of 1973, and several deaths have occurred since then. Neither did it cover the entire population, but only the employees of those plants which met certain criteria for data retention and length of operation. The Stafford (1981) data does cover the entire population and extends the history for seven years. The size of the population is not known, but a reasonable estimate, based on normal worker turnover rates and the number of plants not included in the CMA study, is certainly not less than 25,000. This would give a gross incidence of about 0.1%. Of these, the number actually exposed to substantial exposures would be about 25-30 per plant at any one time. Multiplication by 25 plants, and a factor of three for the turnover during this period, would give about 2,000 highly exposed persons, for an effective inci-

dence of just over 1%. Personal experience would indicate that, for the period prior to 1964, when all of the first exposures of the fatal 26 cases had occurred, the average exposures of this highly exposed group certainly was in excess of 1,000 ppm for the working day. Maltoni (1979) found a 1% incidence at about 3-10 ppm in rats. Calculation of the dose equivalent to a 1% incidence in rats gives 0 ppm by the linear method and 7.5 ppm from the log-probit equation for the combined Maltoni inhalation experiments. This crude and subjective estimate would then say that man is about 100 times as resistant as the rat to VC inhalation, a figure generally in agreement with other estimates (NCAB, 1979).

Food Safety Council 1978, 1980

The Food Safety Council has recommended (FSC, 1978) the use of the gamma multi-hit model because of its flexibility in handling dose response data of varying curvilinearity at low doses. It has calculated (FSC, 1980) the maximum likely and lower 97.5% limit doses for substances at various risk levels and with different models. For VC, at 10^{-6} risk, these results are as follows (based on early Maltoni data):

One-hit	2.0×10^{-2} ppm
Armitage-Doll	2.8×10^{-2} ppm
Weibull	2.1×10^{-9} ppm
Multi-hit	3.9×10^{-10} ppm

For this substance, the goodness of fit of the Weibull model (0.56) was superior to that of the multi-hit (0.32). Neither of the other two models gave acceptable fits. This was in part because of the concave shape of the curve, which included all of the high doses in the dose response data.

Dow, 1979

A Dow Health Team performed a relative risk estimation for several compounds (Langer, et al., 1979) which considered probable exposure, the consequence of exposure, the physical state of the substance during processing, and the current exposure standards. This resulted in a value of 480 for VC in a "closed system but with employees in the vicinity." The same procedure assigned hazard rating values to some other substances as follows: benzene, 10; phosgene, 410; hydrogen sulfide, 5; arsine, 9,700; and bis-chloromethyl ether, 69,700. In a batch operation with occasional manual handling, the hazard rating for VC increased to 9,700 by this method.

Mehlr, 1980

Mehlr, et al., (1980) conducted a series of tests for the Consumer Product Safety Commission, a part of which consisted of exposing rats and mice to a series of short, high exposures, rather than the usual extended low dosage. They included one-hour exposures to rats and mice at 50, 500, 5,000, and 50,000 ppm, 10 and 40 hour exposures at 500 ppm, and 49 and 100 one-hour exposures at 50 ppm. After lifetime observation they found no effects on rats, or their offspring, nor on mice exposed to less than 500 ppm. Those exposed to over 500 ppm developed pulmonary adenomas, but they also had suffered from pneumonitis.

They considered the published data on animal exposures and concluded that there was a lifetime dose below which no oncogenic response is seen. This was estimated to be 5,000 ppm-hrs for mice and greater than 50,000 ppm for rats, regardless of whether the dose was administered over a short or long period. This concept of equality of effectiveness for all modes of exposure does not have general acceptance and would not appear to be correct, based on our present understanding of carcinogenesis. Dose-rate effects are, of course, well known. However, the degree to which this can be extended to all types of effects is not known.

These authors also used the Crump-Guess model (Crump, Guess and Deal, 1977) to evaluate their data on mouse pulmonary cancer, and estimated that exposure to 5,000 ppm VC doubles the probability of cancer, while 50,000 ppm increased the risk nine-fold. In view of the fact that pneumonitis was present in all animals exposed above 500 ppm, it is questionable if this was a direct oncogenic response, or the result of an nongenetic event because of severe lung damage. Maltoni (1979) also reports an increase in lung tumors in mice, but not in rats or hamsters. Thus, the significance of this finding to risk in humans is questionable.

7. Anderson, 1980

Anderson, et al., (1980) extended the work of Gehring, et al., (1978 and 1979) to incorporate the amount of metabolic products from VC which actually was bound to the DNA of exposed rats, (Gehring and Blau, 1977) rather than the total amount metabolized. They assigned various values to the parameters in a Michaelis-Menten equation depicting the kinetics of the metabolic process, and compared the results from extrapolation to low doses by log-probit and multi-hit models. They found that the two extrapolation models responded quite differently to these variations at very low doses, and that it was not possible to select one model as the more appropriate from the high-dose data. Use of the values of Gehring for the primary parameters gave estimates of the dose equivalent to lifetime risks of 10^{-6} of less than 1 ppm for the probit model and less than 2 ppm for the multistage model, a correspondence which the authors pointed out was better than the precision of interspecies comparisons.

1. EPA, 1980

The final version of the water quality criteria document for VC (EPA, 1980) used a different approach for risk estimation. The slope of the incidence of all tumors at the lowest doses of Maltoni experiment BT-1 was adjusted for the fraction of exposure, the equivalent feeding level to give the same blood concentration of VC as by inhalation (see Withey and Collins, 1976), and the ratio of the surface area of humans vs. rats, to produce an estimate that a lifetime risk of 10^{-5} would be caused by drinking 2 l/day of water containing 20 g/l. There is some confusion in the mathematics given in the report, and the assumptions on which the adjustments are made are far from having general acceptance, although generally following NAS recommendations. It appears that this procedure overstates the risk by several orders of magnitude.

. NAS, 1980

The National Academy of Science (1977) calculated the upper 95% confidence limit for risk from drinking water containing vinyl chloride from the probabilistic multistage model and early Maltoni rat data. They report (NAS, 1980) a lifetime risk of 10^{-5} as being equivalent to 3.0×10^{-5} mg/kg/day. For a 70 kg person consuming 2 l/day, this would calculate to an acceptable level of 1 g/l. The difference between the EPA and NAS numbers comes from the different curve-fitting methods for the animal data.

. Gaylor and Kodell (1980) applied linear "interpolation" to the same early Maltoni data used by the Food Safety Council (1978) to arrive at a predicted maximum risk of 10^{-6}. The upper 97.5% confidence limit of the animal data was taken as one point on the interpolative line, and zero incidence at zero exposure as the other. This produced a lower 97.5% confidence limit dosage of 7.1×10^{-4} ppm for a lifetime risk of 10^{-6} in rats. Their application of the Armitage-Doll multistage model gave 6.2×10^{-4} ppm as the dosage at 10^{-6} lifetime risk compared to 2×10^{-4} by the Food Safety Council. The difference is due to alternative assumptions on the value of the exponential dose term.

. Crump and Guess (1980) reviewed some of the earlier risk estimates for vinyl chloride in drinking water, and recalculated the risks, using the one-hit and multistage models. They arrived at an upper 95% confidence limit of lifetime risk for drinking water containing 1 g/l of VC of 4×10^{-6}, based on early Maltoni inhalation data. Using the assumption that a 0.2% incidence of ASL in workers had resulted from a lifetime exposure of 70 g/kg, they obtained a maximum likelihood risk of 10^{-6} from 0.34 g/l by both the multistage and linear models, with 95% lower confidence limits of the same risk at 0.24 g/l. These two models reduce to a linear form when used at very low doses and with the assumption of no threshold value.

These authors cite EPA data on the occurrence of VC in public water supplies which by their methods yield a lifetime risk of 3.7×10^{-6}, or 12 deaths per year from this cause in the United States. None of these has been observed, despite the accumulation of 15 years' data on ASL deaths (Popper, 1978).

12. Scott (1981) ascribed the decreased incidence of tumors in rats at the higher doses to a cell killing process, and adopted the Weibull model to account for this. Application of the model to some early Maltoni data produced a curve which fit the data from 50-10,000 ppm. He did not attempt to extrapolate to doses beyond the experimental range.

13. Carlborg, 1981, also applied the Weibull model to 31 bioassay reports on a variety of animal carcinogens. He concluded that the one-hit model was not appropriate and that carcinogens could be divided into categories according to the shape of the curve, e.g., concave or convex. He found that the early Maltoni data on VC fell into the former category. Application of his parameter estimates to those data, assuming no spontaneous incidence of ASL, gives 2.5×10^{-4} ppm for a lifetime risk of 10^{-6} for rats. Later calculations including all of the published Maltoni data did not change the results significantly (personal communication).

He found the Weibull shape parameter to be approximately 0.5, which is assumed to be the number of stages for tumor initiation. This is consistent with the finding by Gehring (1977) of a saturable metabolic path which produces the proximate carcinogen. It also suggests that the number of "stages" is the number of finite-rate steps before the rate-limiting step. There may be other stages following, but they are not rate controlling. Actually, there appears to be at least two saturable mechanisms involved in the pharmacokinetics of VC, the metabolism to the ultimate carcinogen and the detoxification by sulfhydryl groups.

14. One further evaluation of human risk can be made from the experience of persons residing near VC-PVC plants. The EPA estimated (Kuzmack and McGaughy, 1978) that five million persons lived within five miles of these plants, and were exposed to an annual average concentration of 17 ppb. The present distribution of plants was generally well-established by 1959, thus we have 22 years of history, or about 110 million person-years. About five or six of these plants, with 1-2 million neighbors, go back another 20 years, but these data are not firm enough for inclusion.

The fact that no case of ASL has been confirmed as arising from these ambient exposures places the upper bound of risk at less than 2.7×10^{-7} per ppm-yr. It is believed that the exposure data were overestimated by EPA, and thus this result may be too low, but it is in the same general range as that arrived at by Gehring (1979) and Andersen (1980) after making corrections for pharmacokinetics.

Extending this crude calculation, these five million persons are now supposed by EPA to be exposed to 0.2 ppb (probably a high figure), which would predict no more than 0.0003 deaths per year, or one per 3,700 years in that whole population due to VC exposure. But it also must be recognized that with approximately 20 cases per year of ASL in the general population, there can be expected from a purely statistical basis that there should be one case every two years or so among this group of 5 million plant neighbors.

The results of these estimates discussed above are compared in Table 1, after conversion to a uniform 10^{-6} lifetime risk. Estimates 5, (Dow 1979) and 12 (Scott, 1981) were not in a form to permit this comparison. See OSHA, (1980), for references to a few other estimates that were not considered here.

It can be seen that the results fall into two major categories, those which project that the risk of 10^{-6} occurs at exposures of greater than 1 ppm, and those which find that risk in the ppb range. The estimates which yield the higher allowable exposures are based on human data (Nos. 3, 7 and 14) or use a log-probit extrapolation model (No. 2, second estimate), or predict a threshold (No. 6). The remainder generally are based on the linear, non-threshold model, and make no biological correction. The result is a difference of 3 or 4 orders of magnitude. The estimates which yield the higher allowable exposures are in better agreement with human experience than are those of the other group.

Additional Data

All of the extrapolations reported here have used for the original Maltoni data from his experiment BT-1. He has now reported (Maltoni, 1979) three other comparable inhalation experiments on the same strain of rats, and one on another strain, in addition to two ingestion studies. The results of these experiments are shown in Figure 1, on a log-probit scale. It can be seen that they all follow a similar pattern, but that there are large variations in slope between the various data groups. Table III contains the log-probit equations calculated from some of the individual experiments, and various groups of experiments. Excellent fits are obtained for a single experiment, as would be expected from the small number of data points, but adequate fits are obtained for the group as a whole. Inclusion of the historic control data on ASL (0.09% spontaneous incidence) did not affect the fit substantially, except for the very low dose data. Inclusion of the 0,0 (origin) as a data point did give significantly poorer fits. The combined experiments indicate that a lifetime risk of 10^{-6} for rats is obtained from a dose in the 1-2 ppb range.

Similar variation is seen with the other mathematical expressions, such as linear or exponential equations.

Regulatory Status

The current regulatory status of vinyl chloride is summarized in Table II. The first regulatory action on VC was taken in 1973 when the Bureau of Tax, Alcohol and Firearms prohibited the use of rigid PVC as liquor containers. This was based on it being present as an adulterant, and not on any consideration of risk. The Consumer Product Safety Commission (CPSC), the Food and Drug Administration, (FDA), and the EPA all acted to ban the use of VC as an aerosol propellant thus establishing a zero risk position. The FDA proposed (FDA, 1975) to withdraw the prior sanction status of rigid PVC as a food package component because of the concern for residual VC that might migrate. The FDA has taken no further action on this proposal, and now is considering a "constituent" policy which would permit a lifetime exposure at some acceptable risk level. This risk has been proposed recently to be 10^{-6} lifetime for the gluttonous consumer. As was discussed above, the EPA required a best available technology approach which reduces the average exposure to those within 5 miles of a plant to about 0.2 ppb, by EPA estimates. OSHA established a rule in 1974 which set 1 ppm for 8 hours as the maximum permissible exposure, and also set 0.5 ppm as an action level below which most features of the regulation did not apply. These were chosen as feasible levels, and not necessarily "safe" doses (OSHA, 1974; EPA, 1976).

The EPA has established an exposure to the general population only 0.1% of that allowed in the workplace. The CPSC has required zero exposure, and the FDA has considered that approach. Depending on which method of estimation the FDA may choose, its allowable exposure could be either greater or less than those currently set by EPA and OSHA. It has been estimated that the maximum amount of VC ingested by the average European, who uses much more plastic packaging than we, is less than 2_6 g/day, (CEFIC, 1976) which would be in the order of a 10^{-5} or 10^{-6} lifetime risk by even the most conservative models.

There have been various estimates made of the cost-effectiveness of the Federal regulation for vinyl chloride. Graham and Vaupel (1981) estimated that the OSHA rule cost $7.5 million per life saved, and $490 thousand per life-year saved over the option of leaving the exposure limit at 50 ppm. Luken and Miller (1981) state that the imputed value of a life from the OSHA standard is $4 million. Morrell (1982) uses an annual cost of $20 million and an annual benefit of 0.1 life saved to derive a cost/benefit of $200 million per life for the OSHA rule. The EPA has reported (EPA, 1979) that the cost of compliance with its VC standard was $296 million through July 7, 1981, and will be an additional $470 million during the next five years, all in 1977 dollars. If the EPA estimate of up to 20 deaths per year were correct, this would be a cost of $4.7 million per life. However, as discussed here, there is no evidence that any lives have been saved by this rule.

There are many difficulties in obtaining accurate estimates of this type, and serious problems in determining the proper value to be assigned to a life. Nevertheless, the doubtful nature of the claims

r any significant benefit from these rules suggests that at best, ese regulations are excessively costly to society. Therefore, we st attempt to improve both our data base and our methods for inter- eting and applying the data.

scussion

at can be learned from this exercise other than the already cognized fact that various extrapolation models can yield very ifferent results? In this case, at least, there are several points ich are worth considering.

1. Vinyl chloride is no exception to the rule that human data always must be incorporated whenever possible. The epidemic of occupationally induced ASL which was feared in 1974 has not materialized, probably due to the steps that were taken in the early 1960's to reduce exposure because of the discovery of AOL. No instances of ASL from exposure to VC in the general population have been substantiated. The overprediction of occupational cases was due to the underestimation of worker exposure and overreliance on raw animal data without proper pharmacokinetic adjustment. We are not now able to extrapolate reliably between similar species and certainly not from rodents to humans, without much additional data.

2. The regulations for vinyl chloride were not based primarily on scientific data, but on socioeconomic and political decisions. This is no surprise (Crandall and Lave, 1981), but is a fact which should be acknowledged openly, along with the understanding that this position will continue to penalize good science.

3. Mathematical extrapolation models are not adequate in themselves for predictions of risks much beyond the experimental range, no matter how good the fit is to the data in the observed range. The variability of relatively small experimental groups adds to the error range. Thus, bioassays intended for quantitative risk assessment applications should be at as low doses as possible, and as large as possible, and should be interpreted very cautiously.

4. The current state of the art is such that quantitative risk assessments may be useful for determining relative risks from similarly acting carcinogens, but are not suitable for across-the-board application to all mechanisms of carcinogenesis.

   This is not to say that we should abandon efforts at developing more effective risk assessment methods. We must, however, recognize the problems inherent in blind application of mathematical models without proper assessment of the available biochemical data, or an understanding of how applicable the experimental data are to humans.

We have available to us at least as much data regarding vinyl chloride as we have for any other substance, and we still have difficulty in deriving a suitable expression for risk from a purely mathematical or statistical basis. Only when human relevance is considered can we arrive at a prediction that approximates actual experience.

The regulators are faced with a tremendously difficult task when they are presented with a few pieces of animal data which suggest the need for concern and potential regulation. We must develop a suitable program to obtain and use as much relevant data as possible to assure that rational regulations are possible. The vinyl chloride experience can help us understand the kind of data which are needed.

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FIGURE 1
GRAPHICAL REPRESENTATION OF TABLE III
LOG-PROBIT PLOT

82-9.2

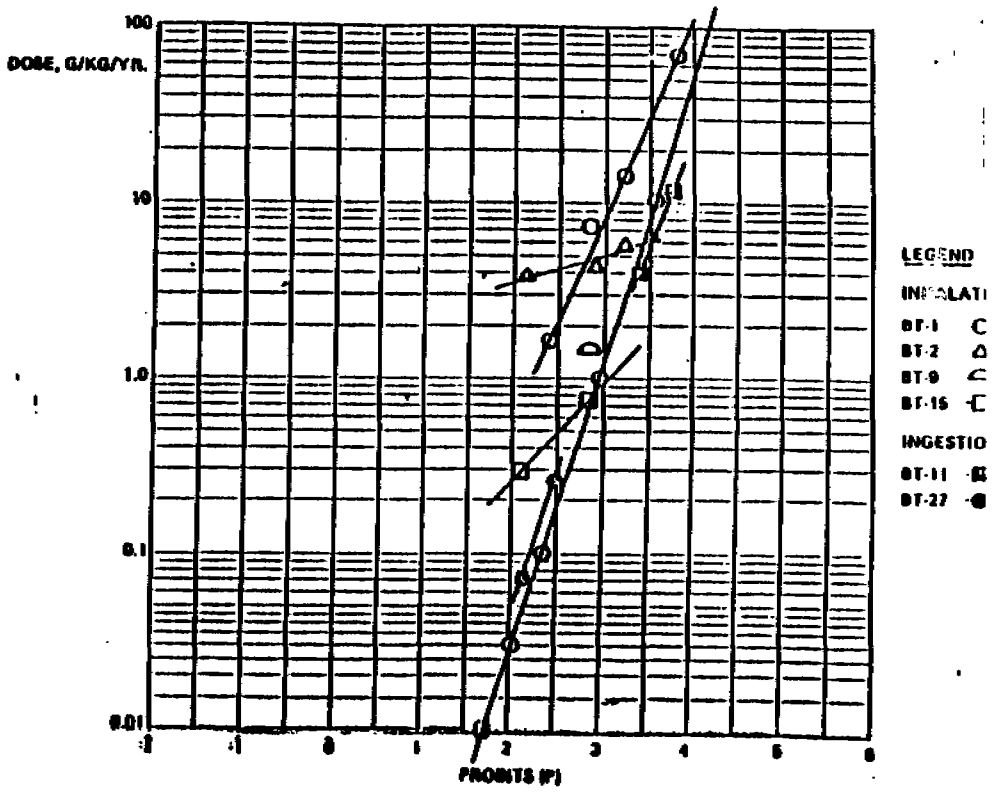

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TABLE I
SUMMARY OF
QUANTITATIVE RISK ASSESSMENTS FOR VC

ESTIMATE NO.	AUTHOR	BASE SPECIES	EXPOSURE FOR 10^{-6} LIFETIME RISK	COMMENTS
1	SCHNEIDERMAN, 1975	RAT	73 ppb	LOG-PROBIT
			110 ppb	LOGIT SLOPE = 3.46
			2 ppb	LOGIT SLOPE 2.3, 1-HIT
2	KUSMACK & McGAUGHY, 1975	RAT, HUMAN	14 ppb	LINEAR THROUGH ZERO
			140-1400 ppb	LOG-PROBIT
3	GEHRING, 1975	RAT, HUMAN	> 1 ppm	BIOTRANSFORMAL DATA AND LINEAR OR LOG-PROBIT
4	FOOD SAFETY COUNCIL, 1980	RAT	2×10^{-6} ppb	WEIBULL
6	HEHR, 1980	RAT, MOUSE	THRESHOLDS SEEN IN BOTH SPECIES	
7	ANDERSON, 1980	RAT, HUMAN	> 1 ppm	DNA BINDING
8	EPA, 1980	RAT	4 μ G/DAY	FOOD OR WATER
9	NAS, 1980	RAT	3×10^{-5} MG/KG/DAY	WATER
10	GAYLOR & KODELL, 1980	RAT	0.7 ppb	UPPER 97.5% CONFIDENCE LIMIT OF LINEAR MODEL
			0.5 ppb	ARMITAGE-DOLL MODEL
11	CRUMP & GUESS, 1980	HUMAN	0.7 μ G/DAY	APPLYING WORKER DATA TO WATER, UPPER 95%
		RAT	0.5 μ G/DAY	CONFIDENCE LIMITS
13	CARLBORG, 1981	RAT	2.5×10^{-5} ppb	WIEBULL
14	THIS PAPER	HUMAN	> 1 ppm	NEGATIVE EPIDEMIOLOGY

TABLE II
REGULATORY STATUS OF VINYL CHLORIDE

AGENCY	CONTROLLED LEVEL	PHILOSOPHY
BATF	BANNED AS LIQUOR BOTTLE	ADULTERANT
CPSC	BANNED IN CONSUMER PRODUCTS	ZERO RISK
FDA	USE IN RIGID FOOD PACKAGING QUESTIONED	CONSIDERING ACCEPTABLE RISK
EPA	APPROXIMATELY 0.2 ppb	BEST AVAILABLE TECHNOLOGY
OSHA	1 ppm 8-HR TWO MAXIMUM 0.5 ppm ACTION LEVEL	LOWEST FEASIBLE LEVEL

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TABLE III
EQUATIONS FOR CURVES FITTED TO VARIOUS SINGLE AND COMBINED MALTONI EXPERIMENTS

EXPERIMENT	LINEAR y=ax + b			LOG PROBIT P=a IN DOSE + b			CONCENTRATION AT 10^{-6} RISK, (LOG-PROBIT), ppm
	a	b	r	a	b	r	
BT-1	0.26	3.36	0.97	0.35	2.76	0.99	0.03
PLUS CONTROLS	0.27	2.47	0.97				
BT-2	3.05	-8.59	1.0	1.60	0.88	1.0	25
PLUS CONTROLS	1.52	-1.13	0.88				
BT-15	6.5	-1.06	1.0	0.69	3.46	1.0	0.34
PLUS CONTROLS	5.26	-0.30	0.95				
ALL INHALATION STUDIES (4)	0.26	3.07	0.91	0.27	2.98	0.82	0.002
PLUS CONTROLS	0.27	2.80	0.91				
ALL INGESTION STUDIES (2)	1.75	0.15	0.95	0.30	3.22	0.88	0.002
PLUS CONTROLS	1.74	0.20	0.95				
ALL STUDIES (6)	0.29	3.60	0.73	0.27	3.05	0.82	0.001
PLUS CONTROLS	0.29	3.41	0.72				
ALL STUDIES; LOW DOSES ONLY				0.51	2.53	0.75	0.42
PLUS CONTROLS	1.03	0.97	0.79	0.17	2.71	0.49	0.0002

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APPENDIX V

HEALTH EFFECTS REQUEST-TO DHS AND LETTER OF RESPONSE

Memorandum

DRAFT

To : Kenneth Kizer, Director
Department of Health Services
714 P Street
Sacramento, CA 95814

Date : June 17, 1985

Subject: Evaluation of Vinyl Chloride

From : James D. Boyd
Executive Officer
Air Resources Board

I am writing to request formally that the Department evaluate the health effects of vinyl chloride as a candidate toxic air contaminant in accordance with Assembly Bill 1807 (Tanner). According to Health and Safety Code Sections 39660-62, your Department has ninety days to submit a written evaluation and recommendations on the health effects of vinyl chloride to the Air Resources Board and may request a thirty day extension.

Attached for your staff's consideration in evaluating vinyl chloride are: Attachment I - a suggested list of topics that we believe should be included in your vinyl chloride evaluation and recommendations; Attachment II - a list of references on vinyl chloride health effects which were presented in an ARB letter of public inquiry; Attachment III - additional references and comments received from the public in response to the inquiry letter; and Attachment IV - ambient vinyl chloride concentration data and emission data which should be used to estimate the range of risk t California residents as required in Health and Safety Code Section 39660(c).

My staff is available for consultation in conducting this health effects evaluation. We look forward to continuing to work closely with you and your staff in carrying out this legislative mandate. If you have any further questions regarding this matter, please contact me at 445-4383.

Attachments

cc: Jananne Sharpless
Alex Kelter, w/attachments
Raymond Neutra, w/attachments
Peter D. Venturini
Assemblywoman Sally Tanner
Claire Berryhill
Emil Mrak, Chairman and Members
of the Scientific Review Panel
Senator Ralph Dills
Senator Art Torres
John Holmes ARB

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ATTACHMENT IV A

SUMMARY OF AMBIENT VINYL CHLORIDE CONCENTRATIONS

Vinyl chloride has been produced in one industrial facility and used by four facilities in California, all of them in the South Coast Air Basin (SCAB). In May 1978, the Air Resources Board (ARB) adopted an ambient air quality standard for vinyl chloride of 10 ppb, 24-hour average. Subsequent ambient monitoring in the SCAB found the 10 ppb standard to be exceeded frequently in the vicinity of these facilities from 1979-1981. However, sinc 1982 the recent monitoring data for VC near these vinyl chloride facilities has shown all values to be below 10 ppb, without a determination of the actual value. These reductions in ambient concentrations are likely due to the closure of the production facility in 1982 and implementation of regulations by the South Coast Air Quality Management District (SCAQMD) designed to reduce vinyl chloride emissions.

Vinyl chloride has been detected in the community near the BKK Class I landfill in West Covina. In 1983, the Department of Health Services (DHS), ARB, and the South Coast Air Quality Management District issued a report detailing ambient concentrations (report attached). As the report indicates, the average vinyl chloride concentrations varied with location. The worst cas residential location, Station A, had mean 24-hour VC concentrations of 7.1-7.3 ppb, with a maximum reading of about 39 ppb. Data for this report were collected over three months (July 19-October 15, 1982), with 24-hour samples taken five days per week.

A newly discovered potential source of vinyl chloride emissions into the air is that of sewage treatment facilities. An EPA contractor recently made some estimates of vinyl chloride emissions, as well as other volatile aromatic compounds, from the "Top 20" sewage treatment plants, nationwide. (Please see Appendix D of Versar Memorandum, Attachment IVC.) In this document, the Hyperion facility, which is located in the SCAB, was calculated to release 171 metric tons/year of vinyl chloride. ARB staff m del d this emission estimate (assumptions on Attachment IVB) and predicted 8 ppb above any background as an annual average vinyl chloride concentration. The 24-hour maximum VC concentration prediction is 23 ppb above background. ARB and SCAQMD plan to confirm these estimates with source and ambient vinyl chloride testing at the Hyperion facility in the summer of 1985.

Summary of the Health Effects of Vinyl Chloride DRAFT

I. HEALTH EFFECTS

The health effects of vinyl chloride have been reviewed by several sources. Two good reviews are by the International Agency for Research on Cancer (IARC, 1979) and the U.S. Department of Health, Education and Welfare (U.S. HEW, 1978).

A. Carcinogenicity

1. Humans - Epidemiological studies have shown that vinyl chloride causes angiosarcoma of the liver in humans. Strong evidence also exists that vinyl chloride may cause cancer of the central nervous system, especially glioblastoma multiforme. Evidence also exists that vinyl chloride induces cancers of the lung and lymphatic system but this evidence is weaker. (IARC, 1979; U.S. HEW, 1978)

2. Animals - Vinyl chloride has been shown to be carcinogenic in several animal species after oral and inhalation administration. Liver angiosarcomas were observed in mice, rats and hamsters exposed to vinyl chloride. Other tumors seen were mammary adenocarcinomas, lung adenomas, Zymbal gland tumors and angiosarcomas at sites other than the liver. Doses in the inhalation experiments ranged from 50 to 10,000 ppm. A significant increase in some tumors (angiosarcomas) was seen at the low dose (50 ppm) level. (IARC, 1979; U.S. HEW, 1978)

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B. Mutagenesis

Vinyl chloride is mutagenic in several test systems. Vinyl chlorid has been found to be mutagenic in several strains of bacteria, insects and mammalian cells. Chromosomal aberrations have been induced in workers exposed to vinyl chloride. (IARC, 1982)

C. Teratogenicity

Evidence that vinyl chloride causes teratogenic effects in humans or animals is equivocal. Vinyl chloride has been implicated in causing increased fetal deaths in the wives of vinyl chloride exposed worker's and birth defects in children of workers. Evidence is inconclusive. (IARC, 1979)

D. Pharmacokinetics

The metabolism of vinyl chloride has been reviewed by several authors (IARC, 1979). Absorbed vinyl chloride is eliminated predominantly via metabolism and exretion of metabolites into the urine. A small amount is excreted via the expired air as unchanged vinyl chloride. As the concentration of vinyl chloride to which an animal is exposed is raised, a larger percentage of the absorbed dose is eliminated as unchanged vinyl chloride in the expired air. The initial product of metabolism is believed to be chloroethylene oxide. Vinyl chloride, in the presence of a microsomal enzyme fraction, binds to RNA *in vitro* and to RNA and DNA *in vivo*. Chloroethylene oxide is believed to be involved in the covalent

binding to RNA and DNA. Since an abundance of animal pharmacokinetic data exists, it may be possible to incorporate it into the dose-response assessment. (IARC, 1979)

E. Acute and Chronic Effects (non-carcinogenic)

Acute exposure to vinyl chloride causes narcosis, cardiac irregularites and liver and kidney toxicity. These effects are seen at relatively high doses. Liver toxicity is evident as centrilobular degeneration, hepatic fibrosis and necrosis. Degeneration of bone, nerves and connective tissue is seen after chronic exposure. Acroosteolysis, a degeneration of the bones in the fingers, occurs in workers. Disturbances in liver, kidney and pulmonary function also occur after chronic exposure.

II. THRESHOLD

The U.S. EPA proposed a National Emission Standard for vinyl chloride in 1975, which was promulgated in 1976. The proposal for the emission standard states that there is no known threshold for vinyl chloride's toxic effects. (Federal Register, 1975)

III. DOSE-RESPONSE ASSESSMENT

The U.S. EPA's Carcinogen Assessment Group has performed a risk assessment of vinyl chloride's carcinogenic effects (U.S. EPA, 1975). The potency slope for vinyl chloride, derived from an animal inhalation study, is $1.75 \times 10^{-2} (mg/kg/day)^{-1}$.