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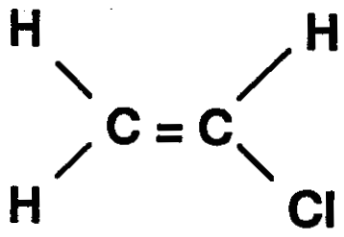

VINYL CHLORIDE

AS A TOXIC AIR CONTAMINANT

OCTOBER 1990

State of California

Air Resources Board

Stationary Source Division

HEALTH EFFECTS OF AIRBORNE VINYL CHLORIDE

CALIFORNIA DEPARTMENT OF HEALTH SERVICES

October 1990

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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 above 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 to 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), exposure to concentrations above approximately 250 ppm would not necessarily be expected to lead to a perceptibly 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 the staff recommends that vinyl chloride be considered as not having a threshold for carcinogenicity.

Several studies of carcinogenicity of vinyl chloride in animals and in occupationally exposed workers have been analyzed for risk assessment purposes. The lowest lifetime equivalent concentration associated with an increased incidence of tumors in laboratory animals is 0.06 ppm or 6 to 60-fold above potential human exposure concentrations. Although measurements of actual exposure levels are not available for vinyl chloride, worker exposure estimates have been used to evaluate the Waxweiler et al. (1976) study. Based on these estimates, the present analysis calculates that the 95% upper confidence limit (UCL) on lifetime unit risk of contracting cancer from vinyl chloride, assuming liver, brain and lung cancer are all related to vinyl chloride exposure, is 4.5×10^{-5} ppb^{-1}. In the case that only liver cancer is assumed to be linked to exposure, the UCL on unit risk is 2.5×10^{-5} ppb^{-1}. These predictions are uncertain due to inadequate exposure data, follow-up time and other methodological problems. Evaluation of animal experiments by the linearized multistage model yields predictions of UCLs on unit risks for humans to be in the range of 3.7×10^{-5} to 20×10^{-5} ppb^{-1}. Evaluation of animal tumorigenicity data indicates that vinyl chloride's carcinogenic potency is dependent on sex, tumor site and age of exposure. Taking all these factors into account, DHS staff conclude that the best estimate to use in order to assure the public health is the top of the range of animal UCLs of unit risk, 20×10^{-5} ppb^{-1}. The overall range of UCLs on unit risk suitable for regulatory purposes is 2.5×10^{-5} to 20×10^{-5} ppb^{-1}.

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. The model predicts that the 95% upper confidence limit on cancers due to lifetime exposure of 131,000 residents to 1 ppb would be in the range of 3 to 36. 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.

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: Sufficient evidence of mutagenic activity exists, both with and without an exogenous metabolic activation system.

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

3. Human evidence: Sufficient evidence of carcinogenicity to humans exists. 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 metabolic activation system, for both DNA damage and mutation.

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

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. Throughout 1987 the South Coast Air Quality Maintenance District monitored near two landfill sites in the Los Angeles area. The highest annual average obtained at any of three stations near the BKK site was 2.6 ppb, and the

highest annual average at any of three stations near the OII site was 2.0 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 exposures 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 the equivalent of 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. The current DHS analysis obtained UCLs on unit risks for humans estimated from animal data in the range from 3.7×10^{-5} ppb^{-1} to $20. \times 10^{-5}$ ppb^{-1}, depending on experimental exposure levels, tumor type observed, and sex, species, and age of animal evaluated. The DHS analysis also obtained a UCL on unit risk of 4.5×10^{-5} for liver, lung, and brain cancer and 2.5×10^{-5} for liver cancer only from an occupational study.

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 the results in other species, the percent absorption of vinyl chloride at the concentrations tested in humans did not depend upon concentration. Data from rodent studies suggest that the absorption of vinyl chloride depends on its rate of metabolism and the extent of metabolic saturation. The metabolic pathways of vinyl chloride exhibit substantial satuation at exposure concentrations above 100 ppm in the monkeys and above 200 ppm in rats.

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, because 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 five 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 finding indicates a 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 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 vinyl chloride, Bolt and co-workers (1976) exposed male Wistar rats to initial concentrations of "less than 100 ppm" ^{14}C labeled 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 saturable and that this metabolism was inhibited by 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 polar 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).

Gehring et al. (1978) have investigated the extent to which the metabolism of vinyl chloride in rats quanitatively follows Michaelis-Menten kinetics. Over the exposure range of 1.4 to 4600 ppm for six hours the data follow approximately the Michaelis-Menten equation with:

Vm = 8558 $\pm$ 1147 (SD) μg/6 hr, maximum velocity;
Km = 860 $\pm$ 159 (SD) μg/liter (336 $\pm$ 62 (SD) ppm), saturation constant;
R = 0.88, correlation coefficient.

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 aldehyde dehydrogenase inhibitor, disulfiram (Buchter et al., 1980).

Gargas et al. (1986, 1988) have used gas uptake data to determine the kinetic constants of vinyl chloride and other organic gases in the F-344 male rat. The results for vinyl chloride are V_{max} = 40 μmol/h, near previous values; K_m = 0.1 mg/l blood, lower than previous values by 10-fold; and blood-air partition coefficient = 1.68, near recent determinations. See also Chen and Blancato (1989).

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 carbon-labeled vinyl chloride on the last day. The fate of the labeled vinyl chloride from these rats was compared with a separate group exposed for a single 6-hour period to 5,000 ppm of labeled 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.

Watanabe 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 the labeled 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

Metabolism of vinyl chloride involves both microsomal and nonmicrosomal enzymes and results in the conversion of vinyl chloride to 2-chloroethylene oxide and subsequent oxidation to 2-chloroacetaldehyde and monochloroacetic acid. This saturable pathway appears to operate at low exposures ($\leq$ 100 ppm), leading 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), suggested a possible 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 or 95% ethanol significantly reduced both the uptake and metabolism of inhaled vinyl chloride (Hefner et al., 1975a). This inhibition now appears more likely due to competition by a P450 isozyme (Brady et al. 1989).

Another proposed pathway, which involves only microsomal enzymes, is that following the formation of chloroethylene oxide, it may 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 chloridemetabolism. Their results demonstrated that the uptake of 50 ppm vinyl chloride in a 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 chloride 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.

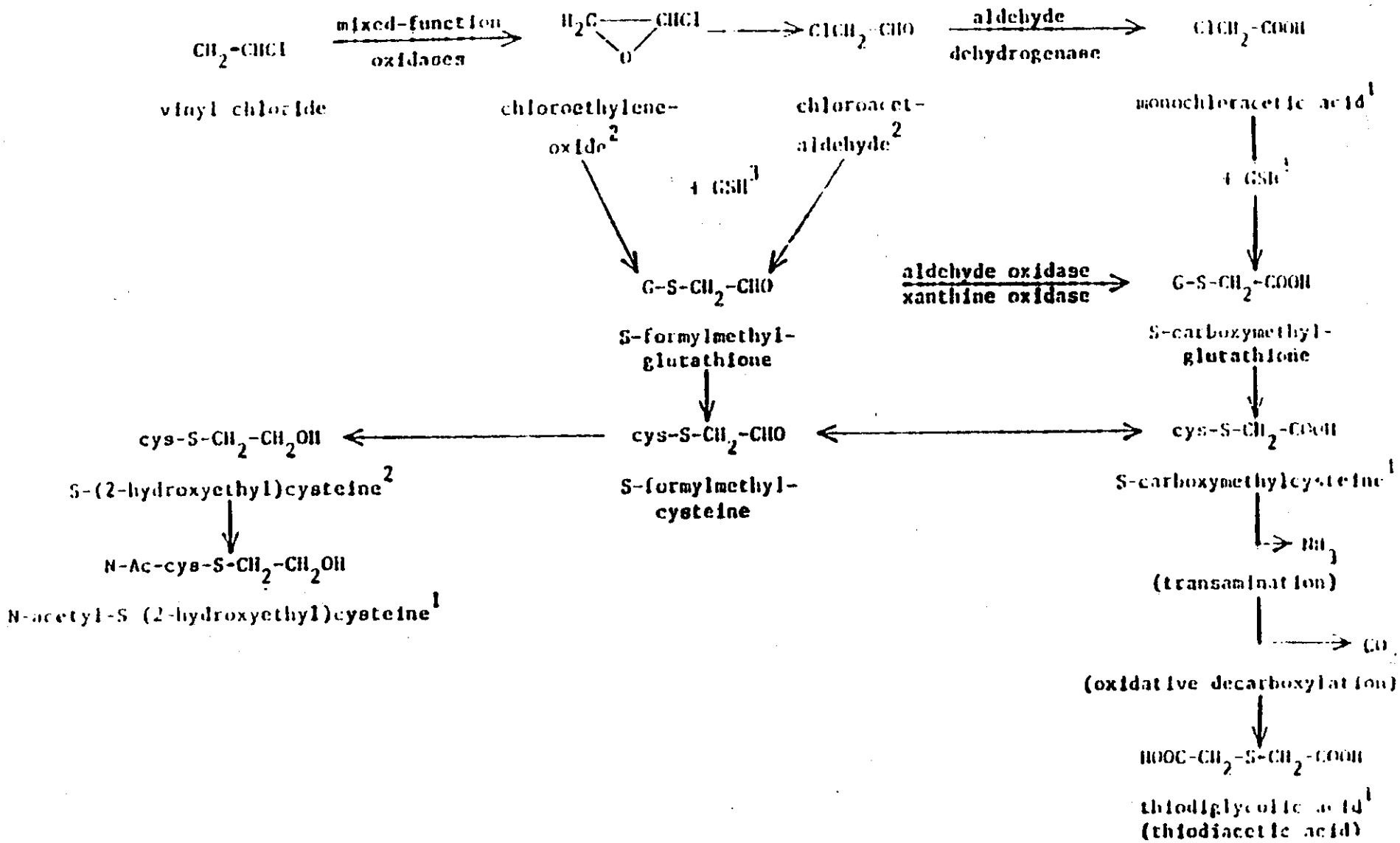
Radiolabeled vinyl chloride has been shown to bind covalently to cellular macromolecules in vivo and in vitro (Watanabe et al., 1978b; Woo et al., 1985; International Agency for Research on Cancer [IARC] 1979). Watanabe et al. (1978b) exposed rats to C-vinyl chloride (range 1-5000 ppm) for six hours, 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 14C-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 nor 2-chloroacetaldehyde appear to be responsible for destruction the heme group of cytochrome P-450 occuring after administration of vinyl chloride. Other mechanisms (or reactive metabolites) may account for the destruction. See also Sections 6.2 and 6.6 for recent discussions of the role of metabolites in the mechanisms of genotoxicity.

Figure 2.1

Metabolism of Vinyl Chloride



Source: IARC (1979)

1 Detected in vivo

2 Detected in vitro

3.0 ACUTE TOXICITY

Several investigators have reviewed the toxic effects of acute exposure to vinyl chloride. (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984b). The sections below present a brief account of the principal findings.

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 Animal Studies

A report of exposures causing 50% lethality (LD_{50}) in groups of animals exposed to vinyl chloride by inhalation for two hours indicates a low acute toxicity: 27,419 ppm in mice, 47,640 ppm in rats, 236,215 ppm in guinea pigs, and 263,215 ppm in rabbits. 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).

3.3 Human Data

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 investigators have reviewed the toxic effects resulting from subchronic and chronic exposure to vinyl chloride. (Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984b). The sections below present a brief account of the principal findings.

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. Those 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 may produce adverse health effects even at levels below 50 ppm (Spirtas et al., 1975). However, it should be noted

the exposure estimates based on probable scenarious may not reflect individual exposures due to person-specific work practices.

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	500, 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

5.0 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

5.1 Summary

Experimental and epidemiologic studies have investigated the developmental and reproductive toxicity of vinyl chloride. (Barlow and Sullivan, 1982; Bardin et al., 1982; Hemminki and Vineis, 1985). Vinyl chloride crosses the placenta of experimental 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.

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 chloride on testicular seminiferous tubules in rats. Groups of 75 male Wistar 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 each 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

Several authors have reviewed the genotoxicity of vinyl chloride. (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. This observation is supported by in vitro experiments in E coli examining mutagenesis by the vinyl chloride metabolite 2-chloroacetaldehyde (CAA). CAA generated predominantly cytosine-to-thymine (C-to-T) transitions and less often cytosine-to-adenine (C-to-A) transversions or other mutations at adenine (Jacobsen et al. 1989). Further investigations (Jacobsen and Humayun, 1990) of CAA mutagenesis have provided evidence against a strong role for DNA repair by induction at SOS genes in mutagenesis at cytosine lesions, suggesting that these predominant lesions do not block DNA replication. Several investigators have marshalled evidence that chloroethylene oxide, the first metabolite of vinyl chloride and an immediate precursor for CAA, is responsible for mutagenesis in vivo. See sections 2.3 and 6.5.

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 and others have recently been summarized (IARC, 1987). 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 increased 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 strain TA1538, which is specifically reverted by frameshift mutagens, was unaffected by concentrations of 20% vinyl chloride in air (Bartsch et al., 1975). Vinyl chloride in water or methanol when tested in S. typhimurium strains TA100, TA1530, TA1535 or G46, even with S-9 liver fractions from phenobarbital-induced mice, did elicit a mutagenic response. The apparent 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. This medium probably helped retain vinyl chloride in this system. 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 and others suggest that radical metabolites may also be important determinants of mutagenic activity (Duverger-Van Bogaert et al., 1982; 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, (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 mmol 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 mmol) 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).

Maier and Schawalder (1988) found a dose-dependent increase in gene mutations at the 6-thioguanine locus in fibroblast-like cells isolated from subcutaneous granuloma tissue of male Sprague-Dawley rats dosed with vinyl chloride. This "granuloma pouch assay" is believed to detect genotoxins activated by peroxidative pathways like the xenobiotic co-oxidation pathway mediated by prostaglandin H synthase. Nevertheless, other factors precluded the conclusion that vinyl chloride was being metabolically activated by these pathways (Maier and Schawalder, 1988).

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 two 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 seen 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 C57Bl/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 individual clastogenic effect (including chromatid gaps, breaks, and fragments) was significantly increased in bone marrow cells obtained from male Wistar rats exposed to vinyl chloride at 1500 ppm, six hours per day for five days. However, there was a significant increase in the number of cells with any abnormality following this exposure scenario. Although the percent of cells with gaps was elevated, no statistically significant increase was observed when vinyl chloride exposure was extended to three months (Anderson and Richardson, 1981).

Walles et al. (1988) observed induction of single-strand breaks in liver DNA by the unwinding technique. Female mice received exposures of 100, 250, and 500 ppm vinyl chloride for 27 hours. Single-stand breaks increased in a dose-dependent manner that appeared to saturate by the 500-ppm exposure. Measurements of adduct levels in hemoglobin and inferred levels in DNA also indicated a saturation effect. Calculations indicate a greater mutagenic efficiency of vinyl chloride than other agents that have been similarly tested. The same techniques showed that 80% of the single-strand breaks are repaired in 20 hours.

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 other 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).

Cytogenetic studies of peripheral lymphocytes from 67 workers occupationally exposed for 15 years to vinyl chloride (current occupational level of 5 ppm) were made to determine the location and frequency of chromosomal breaks (Fucic et al., 1990). Chromosomal breakage in newborns presumed to have minimal exposure to clastogens is found to be random (Funes-Gravioto et al., 1974). In the 67 workers exposed to vinyl chloride, some chromosomal locations were found to be more sensitive to breakage (non-random pattern of breaks). The authors conclude that vinyl chloride induces localized chromosomal breaks (Fucic et al., 1990). There is however, some uncertainty concerning this conclusion since this study did not employ an unexposed control group for comparison.

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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 mg/cm^3 (75,781 ppm) (Hatch et al., 1981).

6.5 Relationship to carcinogenesis

Bolt (1986), Bolt et al. (1986). Bolt (1988) and Van Duuren (1988) reviewed DNA adduct formation by vinyl chloride (metabolites) and other halogenated mono- and bi-functional alkylating agents and related this process to carcinogenesis. Products of vinyl chloride reactions with DNA identified in vivo include 1,N^6-ethenoguanine; 3N^4-ethenocytosine (Eberle et al., 1989); 7(2-oxoethyl)guanine (Singer and Grunberger, 1983) and N^2,3-ethenoguanine (Laib et al., 1985). Singer et al. (1987) found N^2,3-ethenoguanine to be a highly efficient mutagen when incorporated into a single strand RNA template read by AMV reverse transcriptase. In contrast, 1,N^6-ethenoadenine, 3,N^4-ethenocytosine and 7-(2-oxoethyl)guanine were not markedly mutagenic (Singer et al., 1987; Barbin et al., 1985; Barbin and Bartsch, 1986; Singer and Spengler, 1986). Bolt (1988) and others have argued that chloroethylene oxide is the ultimate genotoxic metabolite of vinyl chloride based on in vitro metabolism studies, in vivo studies with a metabolic precursor of chloroacetaldehyde (2,2,-dichlorodiethyl ether), mutagencity data and carcinogenicity data. Further comparisons made between the nucleophilic selectivity of vinyl chloride metabolites (chloroacetaldehyde and chloroethylene oxide) and the carcinogenic potency of vinyl chloride support this conclusion (Barbin and Bartsch, 1989; Barbin et al., 1990).

Several investigations into the relationship between DNA alkylation by vinyl chloride and cancer susceptibility have been made. In 11-day old and adult Wistar rats administered vinyl chloride via inhalation, approximately 5-fold more 7-(2-oxoethyl)guanine adducts per mg hepatic DNA were recovered from young than from adult animals (Ciroussel et al., 1990). In 7-day old and

13-week old BD VI rats dosed with 500 ppm vinyl chloride for 2 weeks, approximately 6-fold more $1,N^6$-ethenoadenosine and $3,N^4$-ethenodeoxycytidine adducts per mg of hepatic DNA were recovered from young than from adults animals (Croussel et al., 1990). In addition the investigators found these adducts in the liver, lung and brain of the group exposed starting at 7 days of age, is consistent with tumors produced by vinyl chloride in these organs. The increased level of adduction in young animals correlates with their increased sensitivity to the carcinogenic effects of vinyl chloride (See section 7.1.4.3).

7.0 CARCINOGENICITY

7.1 Animal Studies

7.1.1 Summary

Recent reviews of the evidence for the carcinogenicity of vinyl chloride in laboratory animals include those 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 have 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 the 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: Maltoni and associates assayed 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 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 observed. In fact, a threshold cannot be demonstrated. Vinyl chloride induced hepatocellular alterations at allconcentrations 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 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 male Wistar rats following inhalation exposure to 0, 10, 100 or 3000 ppm (six hours/day, six days/week) for up to 12 months. 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.

Adkins et al. (1986) exposed strain A/J mice to 50, 200, and 500 ppm vinyl chloride to test the oncogenic response of this strain via inhalation. The result was that incidence of pulmonary adenomas was statistically increased at all exposures of vinyl chloride.

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.

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. When adjusted to average lifetime exposure, the lowest concentration associated with tumor production is 0.06 ppm (1 ppm * 4/24 * 5/7 * 12/24 = 0.3 ppm).

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 exposure 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 male 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. The incidence of mammary gland carcinomas in treated females was higher than in controls at all concentrations of vinyl chloride exposure. The differences from control values were statistically significant at concentrations of 1 ppm and above. 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 male and female mice exposed to vinyl chloride, but a dose response was not seen in the male animals. In

addition, a high incidence of mammary gland adenocarcinomas occurred in treated female mice. These results are presented in Table 7.10 (data from Maltoni et al., 1984).

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 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 retrospectively, based on some combination of job classification and length of exposure. Only two studies (Ott et al., 1975; Buffler et al., 1979 reported measurements of vinyl chloride exposure.

All the studies traced workers to determine the number of deaths that had occurred in the defined cohort. Death certificates provided the cause of death. In the studies from Sweden 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 was tested.

7.2.3 Difficulties in Interpreting the Epidemiologic Evidence

There are two major 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.

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, 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 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 (1975) reported on 257 workers in the 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. 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.

Based on similar criteria, Waxweiler et al. (1976) studied a larger cohort 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.

Buffler and co-workers (1979) performed the only other study using quantified human exposure data. 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) reported on 777 vinyl chloride workers in Sweden, where the investigators had access to an excellent cancer registry. The study reported a significantly increased mortality due to LAS and to CNS cancers. There was also 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.

Jones et al. (1988) followed up the study of Fox and Collier (1977) of British vinyl chloride workers. The new study used stricter criteria for the cohort, reducing the size of the cohort to 5498 male workers, and used more detailed occupational information as well as data from the additional ten years. Deaths due to non-secondary liver tumors rose from 4 to 11 (SMR = 567). The new study could find no evidence for any other increase of cancer deaths due to vinyl chloride.

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.

A further study of the vinyl chloride industry in Italy (Belli, et al., 1987) has detected statistically significant excess for all malignant cancer (SMR = 159) and for lung cancer (SMR = 217). That plant had 437 workers in the cohort. A related study Pirastu et al. (1990) has reported seven cases of liver angiosarcoma and seven primary liver cancers that are not angiosarcoma. The combined study of all Italian facilities is of 5000 workers.

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 were 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 Japanese 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 et al. (1984) 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 in Norway. 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, using an excellent cancer registry, reported cancer incidence, as well as mortality, unlike most other studies.

This observation of an increased incidence of malignant melanoma is the first to be reported in humans. 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).

A follow-up study of 434 of the original workers has strengthened the association between vinyl chloride exposure and three categories of cancer, malignant melanoma, lung cancer and colon cancer (Heldaas et al., 1987).

Laplanche et al. (1987) compared the cancer cases occurring among 1100 exposed and 1100 nonexposed workers in vinyl chloride polymerization plants in France. One case of liver angiosarcoma of the liver occurred among those exposed. Six cases of lung cancer occurred among those exposed versus two among those not exposed. Neither of those results reached statistical significance in the comparison.

Dahar et al. (1988) recently published an update to the vinyl chloride mortality study of Ott et al. (1975). In contrast to the earlier study, the new study found there was no statistically significant excess for any neoplasm or disease of interest among the exposed cohort of 593 Dow chemical workers in Michigan. In a much larger study Rinsky et al. (1988) evaluated the mortality rate and cause of death for a cohort of 29,139 male chemical workers in West Virginia. Statistically significant increases in liver cancer (SMR = 174) and lympho- and reticulo-sarcoma (SMR = 140) were seen among the workers. For biliary and liver cancer the SMR was 301 for those who worked at least 25 years and whose deaths occurred 30 years or more after first employment.

Smelevich et al. (1988) reported a large increase in deaths from malignancies of the lymphatic and hemopoietic tissues among 43,216 (27059 men and 16,157 women) workers in the oldest vinyl chloride and polyvinyl chloride plants in the USSR. The SMR for females was 2000 for all levels of exposure and 4000 for the highest exposures. The SMR of 385 for stomach cancer in women was also significantly increased. The SMR of 500 for leukemia in men and women combined was significantly increased. None of the increases in cancer categories in males alone reached statistical significance. The study did not detect any cases of liver angiosarcoma in the cohort during the follow up period.

Wu et al. (1989) reported a cohort study and a case-control study of workers at one of the four vinyl chloride plants previously studied by Waxweiler (1976). The cohort of 3635 workers was exposed to high concentration of vinyl chloride monomer prior to 1974, when concentrations dropped dramatically. The overall SMR's for brain cancer, lung cancer, laryngeal cancer and all respiratory cancers ranged from 115 to 223, above normal but not statistically significant. The SMR for liver cancer in that cohort was statistically significant at 333, and the SMR rose to 371 when workers with less then 15 years of follow up were excluded. Among that subcohort the risk of mortality due to cancer of the liver was consistently elevated for all durations of employment beyond five years. Neither lung cancer nor brain cancer exhibited a clear increase with duration of exposure. The highest SMR in that subcohort was 1429 for liver cancer in workers with 10-15 years exposure. A brief calculation using data in their Table 5 shows that the SMR for liver cancer in all workers in that subcohort with more than five years' exposure was 1000.

Hagmar et al. (1990) reported a significant increase in total cancer morbidity among 2031 male workers at a polyvinyl chloride processor plant in Sweden (SMR = 128). Respiratory cancers were also significantly increased

(SMR =213). The six brain tumors observed, versus 2.6 expected, gave an SMR = 229, which was not statistically significant.

Their case-control study found that there was a statistically significant association between cumulative dose of vinyl chloride monomer and liver cancer, but that study did not find a significant association for any other cancer. Upon dividing the liver cancers into angiosarcomas and others, the positive dose response was found to exist only for angiosarcomas. At the highest level of exposure the odds ratio for liver cancer was 8 while for liver angiosarcoma alone the odds ratio was 110.

7.2.5 Cancer Risks Associated with Exposure to Vinyl Chloride

This summary of cancer risks assocated with exposure to vinyl chloride focuses on each of the important sites at which such association's have been reported.

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. The evidence strongly 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 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).

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.

7.2.5.3 Recent Review of Human Studies

Doll (1988) assessed the evidence from the epidemiologic literature that vinyl chloride workers experienced more cancer and other types of disease than did the general population. He found that (a) "men occupationally exposed to vinyl chloride have experienced a specific hazard of angiosarcoma of the liver" and (b) "any other occupational hazards that may have existed must have been small." He also concluded that "No positive evidence of a hazard of any nonmaligant disease or any type of cancer other than angiosarcoma of the liver has been found except possibly for a small hazard of lung cancer when exposure was heavy."

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. Although the United States Environmental Protection Agency (1986), reached the conclusion that a dose-response relationship cannot be constructed based on these kinds of data, the risk analysis below did use historic estimates of exposure in an occupational study having an ample cohort with well documented worker statistics.

7.2.7 Conclusions

Epidemiologic studies of workers exposed to high levels of vinyl chloride indicate that this chemical is a human carcinogen. The evidence strongly suggests that vinyl chloride causes an increased risk for angiosarcoma of the liver. The evidence also suggests that vinyl chloride may be associated with a moderately increased risk for brain cancer, and with development of lung cancer. Although actual exposure data in humans are lacking for most studies, the past exposure levels can be estimated in order to obtain useful predictions of human risk at low concentrations of vinyl chloride.

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:

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

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:

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

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.

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 Hemangiosarcomas	control	0	0.9 (1/112)
	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 Adenocarcinoma	control	0	4.5 (5/112)
	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 Carcinoma	control	0	0.9 (1/112)
	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 (all sites)	control	0	5.8 (4/69)
	6	2.23	68.7 (46/67)
	12	4.46	76.7 (69/90)
	18	--	--
Mammary Gland Carcinoma	control	0	4.3 (3/69)
	6	2.23	43.2 (29/67)
	12	4.46	41.1 (37/90)
	18	--	--

TABLE 7.4 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)

TABLE 7.5

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

Experiment Number	Dose (ppm)	Exposure Duration (weeks)[1]	Species/ Strain	Age at Start of Exposure (weeks)	Number of Animals per Dose Level[2]
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 5	Rat/SD	21 (parents) 1 day (offspring)	6 F (no controls) 21-22 M, F (no controls)
BT4001	0, 2,500	76 69	Rat/SD	13 1 day	54 F (60 F) 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.

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	1 (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.

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] Male	LAS Incidence[1] Female	Corrected LAS Incidence[2] Male	Corrected LAS Incidence[2] 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.

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 (Rat)	0	0/30	0/29
	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 (Rat)	0	2/60	2/100
	100	4/60	4/60
	150	6/60	6/60
	200	5/60	5/60
BT6 (Rat)	30,000	2/30	2/30
BT9 (Rat)	0	9/50	9/43
	50	59/150	59/142
BT15 (Rat)	0	6/60	6/60
	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 (Mice)	0	1/80	1/67[3]
	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).

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	5/27	24/29	24/29	18/25	23/27	20/24	36/491
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).

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.	Waxweiler 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[a]	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.	EEH 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, Reint, 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		360(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]	10,173	496(4.8%)	707(6.9%)	>1	33.4%	EST	89	104	75[3](8)	203[a]	107	112
	USA (1981)												
14.	Nakamura	4,524	29(0.6%)	209(4.6%)	>1	mean 16.3yrs	EST	87	138[a]	236[a](3)	--	86	--
	Japan (1983)												
15.	Heldass et al.	454	0(0%)	50(11%)	>1	>1	EST	84	114	(1)	--	180	--
	Norway (1984)												
								---------- 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	ALL CANCER	LIVER CANCER	BRAIN CANCER	LUNG CANCER	LYMPHOMA
	O - E - SMR	O - E - SMR	O - E - SMR	O - E - SMR	O - E - SMR	O - E - SMR
1. Munson 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. Tabershaw & 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. EEH	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. Masuda 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. Heldaas	----------	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

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[4]	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	413	Significant[a]	---	Yes
Waxweiler et al.	1155	Significant[b]	---	Yes
Fox & Collier	141	Significant[a]	Yes	---
Bertazzi et al.	800	Significant[a]	---	---
Masuda	500	Significant[a]	---	---
Weber et al.	1523	Significant[b]	Yes	Yes
Theriault & Allard	(6.25)[3]	Significant[a]	---	No
Nakamura	236	Significant[a]	Yes	Yes
Wu	300	Significant[b]	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
4 - a: $p < 0.05$, b: $p < 0.01$

TABLE 7-14

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

STUDY	SMR	RESULT[4]	INCREASING DOSE[1]	INCREASING F/U TIME[2]
Byren et al.	612	Significant[a]	---	---
Waxweiler et al.	329	Significant[a]	---	Yes
Fox & Collier	55	-	Yes	---
Bertazzi et al.	125	+	---	---
Weber et al.	535	Significant[a]	No	No
Cooper[3]	203	Significant[a]	---	---
Wu	145	+	No	Yes

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.
4 - a: $p < 0.05$
+ = non-significant positive trend for increased risk ($p > 0.05$)

TABLE 7-15

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

STUDY	SMR	RESULT[5]	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	Significant[a]	---	---
Bertazzi et al.	91	-	---	---
Masuda et al.	125	+	---	---
Cooper[3]	107	+	Yes	No
Heldass et al.	180	+	---	---
Theriault & Allard	(.36)[4]	-	---	---
Nakamura	86	-	---	---
Wu	115	+	No	No

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

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	Significant[a]	+	---
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.
4 - a: $p < 0.05$
+ = non-significant positive trend for increased risk ($p > 0.05$)

8.0 QUANTITATIVE CARCINOGENIC RISK ASSESSMENT

8.1 Introduction

Inhalation studies discussed in Chapter 7 have demonstrated that vinyl chloride is a carcinogen in three species of laboratory rodents: rats, mice and hamsters. Those studies generally found an elevated occurrence of the otherwise rare tumor, liver angiosarcoma, over a wide range of concentrations of atmospheric vinyl chloride. Those studies also found cases of elevated incidence of carcinoma of the liver and both angiosarcoma and carcinoma of the lung. In addition those studies found elevated incidence of tumors of the mammary gland. Feeding studies have supported the inhalation results. Epidemiologic evidence has associated occupational exposure to vinyl chloride with the development of liver angiosarcomas in chronically exposed workers, and possibly with other tumors. IARC (1979), the EPA (1984b) and the State of California (CDHS, 1985) have identified vinyl chloride as a human carcinogen. Vinyl chloride has been identified as a "chemical known to the State to cause cancer" under California's Proposition 65, California Health and Safety Code Section 25249.8.

The analyses below derive risk estimates from an occupational study and from rodent bioassays. The selected occupational study provided the best available for quantitative epidemiological analysis. The multistage model of carcinogenesis adequately characterized the results of the rodent bioassays. All of the analyses applied a simple metabolic (pharmacokinetic) model to convert atmospheric concentrations of vinyl chloride to estimates of exposure in terms of the metabolites assumed to produce tumorogenesis in the affected tissue.

8.2. The Metabolic Model

Two related aspects of vinyl chloride metabolism (reviewed in Chapter 2 of this document) are relevant to understanding the dose-response character of its carcinogenicity. First, the oncogenicity of vinyl chloride appears to be due to one or more reactive metabolites, rather than the parent molecule. Second, the metabolism of vinyl chloride is a saturable, dose-dependent process because rate of formation of the carcinogenic metabolites is limited by the metabolism of the parent compound.

Gehring et al. (1978) developed a metabolic model relating the rate of formation of adducts of macromolecules to the concentration of vinyl chloride in atmospheric exposure of rats. In the experiments used to obtain data for the model, the exposures lasted for 6 hours. The rats were of the Sprague-Dawley strain, Spartan substrain, and weighed 200-250g. The study assayed the liver tissue for adducts of macromolecules. The authors used the data to estimate the parameters of an equation of Michaelis-Menten form, relating the velocity of the reaction to the exposure concentrations:

$$F = aV_mX/(K_m + X), \qquad (8\text{-}1)$$

where F = rate of adduct formation (hr^{-1}),
V_m = maximum velocity of the reaction (1g/hr),
K_m = Michaelis saturation concentration (ppm),

X = atmospheric exposure (ppm),
a = constant ($1g^{-1}$).

This equation multiplied by an appropriate constant (K_m/aV_m) yields another expression for metabolite formation (Y):

$$Y = K_m/aV_m = 1/(K_m^{-1} + X^{-1}). \quad (8\text{-}2)$$

For sufficiently low concentration this measure of dose rate becomes equal to actual exposure, thus avoiding the need for conversions in low dose risk estimates for any sufficiently homogeneous group under analysis.

The present analysis will proceed to relate cancer incidence to the estimated metabolized exposure. Although there is uncertainity about the accuracy of using the adjusted exposure of Equation 8-2 as a measure of carcinogenically active metabolites, this measure appears to be superior to atmospheric exposure (Anderson et al. 1980). The accuracy of this measure is subject to improvement by adjusting parameters when applying the result to different organs and to different sizes and strains of rats and to other species. Gehring et al. (1978) determined the Michaelis saturation constant for Sprague-Dawley rats to be K_m = 336 ppm. In Appendix B the present analysis uses for humans K_m = 150 ppm, a value which was estimated from data on monkeys.

8.3 Analysis of Human Data from Waxweiler et al.

The 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. However, none of the occupational cohort studies presented exposure data for a large enough cohort to derive a dose-response curve; so the present analysis uses historical industrial hygiene data to reconstruct a range of likely exposures, from which risk estimates can be extrapolated.

This risk analysis proceeds by selecting the Waxweiler et al. (1976) study of 1294 workers who experienced high sustained exposures to vinyl chloride and who were followed long enough (10 years) to develop substantial numbers of cancers that appeared to be related to the exposure. The retrospective estimates of Barnes et al. (1976) for the relevant industrial processes furnished concentrations of the exposures of vinyl chloride, having an overall average value of 647 ppm. The analysis converts these annual average exposure estimates to a lifetime daily equivalent tissue exposure of 3.6 ppm on the assumption of a saturable metabolic process (Michaelis-Menten) leading to active carcinogens (See equation 8-2). This is based on extrapolated measurements of binding rates to macromolecules (Gehring et al. 1977). The seven liver cancer deaths reported for that cohort project to a lifetime risk of .039 (.089 upper confidence limit) per worker for liver cancers. That risk divided by the overall lifetime daily equivalent of effective exposure yields unit risk estimates for that malignancy. See Appendix B for the calculations, which also include the case of all observed cancers.

The calculations provided the following upper confidence limits (UCL) on unit risks: 2.5×10^{-5} ppb^{-1} for liver cancers, and 4.5×10^{-5} ppb^{-1} for three

sites of cancer combined, liver, lung and brain. Each of these three sites of cancer had a significantly elevated SMR when calculated for a 15-year follow up time. The unit risks calculated in this manner are about six times greater than would be calculated by using actual exposures instead of the effective exposures that take account of the metabolic saturation in the tissue. A committee of The National Health Council of the Netherlands (1987), using mortality data from three studies including Waxweiller, calculated maximum likelihood estimates of unit risk. That council's committee obtained in present terms 1.2×10^{-6} ppb^{-1} for liver tumors and 2.5×10^{-6} ppb^{-1} for all tumors. Both these results were based on estimated atmospheric exposure. When those results are modified to take account the pharmacokinetics and to provide 95% upper confidence limits, the results are close to the present results.

8.4 Models of Carcinogenesis Fitted to Rodent Data

Mathematical models of carcinogenesis provide a means of extrapolating the results of rodent bioassays to the much lower concentrations that human society is likely to find acceptible. The present analysis employs the multistage model because it is a biologically plausible model and as used here takes into account metabolism.

Three sets of cancer bioassays provide adequate data for quantitative models of carcinogenesis. See Table 8-1 for the basic data. The Maltoni et al. experiments together provide an unusually large set of data on cancer incidence in both males and females rats over a large range of exposures at many concentrations--altogether fifteen groups beyond the four control groups. The Drew et al. experiments provide incidence data on female rodents for an unusual exposure protocol in that the duration varied -- two or three groups beyond controls -- while the concentration remained fixed for each species. The Bi et al. experiments provide incidence data on male rats for three exposures beyond controls.

Individual analyses proceeded in attempts to obtain risk estimates for each homogeneous experimental grouping within species, strain, sex and tumor type. One analysis did eventually group together experiments BT-1 and BT-2 and another grouped together experiments BT-9 and BT-15, all by Maltoni et al. These groupings, which followed from similarities of body weight, colony survival characteristics, and tumor response, tended to strengthen results, for example by reducing confidence intervals. The spectrum of risks obtained from all the acceptable analyses provides some insight into uncertainties expected in extrapolating the rodent results to humans.

8.4.1 Computational Methods

The analyses that follow used the linearized multistage computer program, GLOBAL86, to calculate potential risks associated with vinyl chloride exposure. The form of multistage model in that program may be expressed as:

$$P(d) = 1 - \exp(-q_0 - q_1 d - q_2 d^2 - \ldots - q_k d^k) \quad (8\text{-}3)$$
$$\text{with } q_i \geq 0 \text{ for all } i.$$

where P(d) is the lifetime probability of cancer for a given dose rate d of carcinogen, exp is the exponential function (e raised to the power indicated

in parentheses), 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. (Howe et al. 1986).

The analyses used several adjustments to the experimental exposure data in order to calculate the lifetime daily exposure (LDE) levels. For these inhalation experiments, the metabolized exposure determined by Equation 8-2 was 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 of exposure 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. Table 8-1 displays the resulting ranges and other basic data on experiments used in the analysis.

8.4.2 Model Results

Significant trends for liver angiosarcoma dominated the results of the multistage modeling. All three analyses of female rats and two of the three analyses of male rats met the statistical criterion ($p > .05$) for goodness of fit of the dose-dependent response of liver angiosarcoma (LAS) to vinyl chloride. In addition the following experimental groups met that criterion: lung carcinoma in the Swiss mice of Drew et al., lung angiosarcoma in the Wistar rats of Bi et al., and mammary tumors in both the Sprague Dawley rats of Maltoni et al. and the F-344 rats of Drew et al.

Table 8.2 gives unit risk estimates calculated by using the linearized multistage model for LAS and other tumor types from both male and female rats and for female mice for inhalation experiments done by Maltoni et al. (1984), Bi et al. (1985), and Drew et al. (1983). The entries in Table 8.2 include all those instances in which an adequate fit ($p>.05$ and $q_1^*/q_1<3$) of the data is achieved by the model using all data points for each species, sex, and tumor type at exposures not greater than 500 ppm, when practical. Because there is an abundance of experiments available for the risk assessment of vinyl chloride, this stringent measure of adequate fit ($p > 0.05$ and $q_1^*/q_1 < 3$) was chosen to focus the risk assessment on the best available studies. This exposure limitation tends to reduce the effects of the parent compound (including mortality) at the higher exposure levels. The analyses did include one higher exposure, the 3000 ppm exposure of Bi et al., which was retained in order to obtain an adequate number of exposure groups (four) to establish a clear trend.

In Table 8.2 the column indicating which coefficients were nonzero provides some evidence that two stages were appropriate for the model fitted by the maximum-likelihood procedure in these bioassays. Only for the analysis of BT-9,15 rats with liver angiosarcoma did the occurrence of an excessive ratio (16) of $q_1^*(r)/q_1(r)$ prompt the selection of a single-stage model to

human unit risk resulting from use of this formula. This surface area correction results in an estimated 2.6 fold increased risk for humans, compared to rats exposed to the same ppb concentration.

For the parameters of this equation the current analyses used values from the studies when available; otherwise standard values were used. Humans were assumed to weigh 70 kg and to inhale 20 m^3/day. The inhalation rates (I_R) for mice and rats were estimated using the following formulas (EPA, 1985c):

$$\text{For mice: } I_R = 0.0345\ [\text{wt (kg)}/0.025\ (\text{kg})]^{2/3}\ m^3/\text{day} \quad (8\text{-}5)$$
$$\text{For rats: } I_R = 0.105\ [\text{wt (kg)}/0.113\ (\text{kg})]^{2/3}\ m^3/\text{day}$$

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. They were estimated to be 300 g for rats, 30 g for mice, and 92 g for hamsters. See Table 8-1 for values of body weight and inhalation rate used in the analyses.

8.6 Risk Predictions for the Regulation

The rank ordering of Table 8-3 and the points of Figure 8-1 provide the range of UCL on unit risk for humans, q_1^*, for the present assessment: from 2.5×10^{-5} to 20×10^{-5} ppb^{-1}.

In the opinion of DHS staff, the best estimate for regulation in this assessment coincides with the top of the range, when rounded, 20×10^{-5} ppb^{-1}. This is approximately the value obtained from the more recent Maltoni et al. experiments, with lower exposure concentrations than the previous experiments. That result is at the top of the range of six experiments that provided clear dose response relationships for liver cancer. The bottom of that range at 4.4×10^{-5} ppb^{-1} is not far below. The selected top of the range, 20×10^{-5} ppb^{-1} is also equal to the Drew et al. result for lung carcinoma in mice. That result is one of the lowest for mice. The other, higher results for mice are not explicitly reported in the present risk analysis because of scattering of points in each case not providing a clear exposure-response trend. The results for hamsters, not reported quantitatively for the same reason, were close to those for the rats.

As indicated in Chapter 7, based on laboratory animals, females appear to be more sensitive than males to vinyl chloride exposure. Furthermore, earlier initiation of exposure appears to increase vinyl chloride susceptibility (as discussed below, p. 8-13). Two different approaches permit indirect estimation of the unmeasured overall risk of carcinogenesis in human females, providing an instructive consistency check. The first is to take the result for all cancers in the (male) occupational study, 4.5×10^{-5} ppb^{-1}, and multiply it by ratio of female-to-male cancers in animals. The best ratio available is 3.1 for liver angiosarcoma from experiments in rats (BT-9,15). The resulting multiplication gives 14×10^{-5} ppb^{-1}. This result allows in humans for the probably greater susceptibility of the female to contracting cancer from vinyl chloride exposure, as observed in rodents. The second approach starts with the result of the analysis that uses all Maltoni et al.

obtain a more consistent ratio. In this case very little improvement was achieved by including the second stage. Despite the substantial effect on q_1, the effect of selecting the single-stage over the two-stage model was to increase q_1^* by only 4%.

The results of Table 8.2 do not include the analyses for angiosarcoma and mammary tumors in mice or the angiosarcoma, skin carcinoma, and mammary tumors in hamsters. The estimates for q_1^* for the angiosarcomas and mammary tumors in mice were in the range of 20×10^{-5} to 50×10^{-5} ppb^{-1}, greatly elevated above those for rats, while the estimates for those tumors in hamsters (6×10^{-5} and 10×10^{-5}) were about the same as the highest results in rats. None of these analyses met the stringent criteria for goodness of fit of the MLE as defined above; so they were not included in the tabulation of risk estimates.

The effect of combining the BT (Maltoni et al. 1984) experiments was to lower the value of the resulting q_1^* by a modest amount. Thus BT-1 and BT-2 individually yielded values of 2.5×10^{-5} and 2.2×10^{-5} respectively, compared to 1.9×10^{-5} when combined. Also BT-9 and BT-15 individually yielded values of 6.9×10^{-5} and 10×10^{-5}, compared to 6.7×10^{-5} when combined.

The use of metabolized exposure rather than ambient exposure had the effect of increasing the values of q_1^* by about 30-50% in the BT-1 and BT-2 experiments. The effect on BT-9 and BT-15 was virtually negligible because of the much lower exposures experienced in those experiments. In contrast, Krewski et al. (1987) found the difference obtained by using exposure only and by using a metabolic model of essentially the same type as the above was negligible at (atmospheric) exposures up to 500 ppm. Their method of analysis, robust regression, was quite different, and their selection of data points was somewhat different.

Uncertainties in estimates of unit risk arise from uncertainties mentioned earlier about the accuracy of the model used to determine metabolized exposure. Departures from the present fit of the Michaelis-Menten model could cause calculations of risk to lose accuracy. Cumulative effects or different metabolism, for example, may cause the true risk to differ from that predicted. Nevertheless, uncertain as it is, the metabolic model appears much more likely to provide a more accurate measure of risk than does ambient exposure.

8.5 Extrapolating Rodent Risks to Humans.

Estimates of human risks from the rodent results require an extrapolation based on a scaling assumption. The DHS (1985) has provided guidelines for scaling such that--in the absence of strong arguments to the contrary--dose rate is scaled according to the two-thirds power of body weight. Thus, the current analysis uses

$$q_1^* \text{ human} = q_1^* \text{ rodent} \quad (I_H / I_R) \times (W_R / W_H)^{2/3} \qquad (8\text{-}4)$$

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, where q_1^* is expressed in units of $(ppm)^{-1}$. Table 8.2 displays the values of UCL on

data for LAS in female rats at exposures not greater than 250 ppm (10 groups), which is $q_1^*(h) = 7.7 \times 10^{-5}$ ppb^{-1} (not shown in the table). This result, when multiplied by the ratio of risk for all observed human cancer to observed liver cancer in humans gives 13×10^{-5} ppb^{-1}. This value also allows in humans for all cancers in the probably more susceptible female. Considering the uncertainties involved, these two results are remarkably similar to each other and to the best estimate just discussed. We have not attempted adjustments for the increased susceptibility due to early age of exposure, however, DHS staff believe that such an adjustment would elevate the risk estimate derived from the human date. That is, lifetime exposure is likely to be of greater risk to humans than adult exposure as occurred in the occupational study.

Using data from Maltoni and Lefemine (1975), the EPA (1984b) calculated a UCL on rodent unit risk of 6.8×10^{-6} ppb^{-1}. This is equivalent to a q_1^* of 1.8×10^{-5} ppb^{-1}. Figure 8-1 shows that this result is below the bottom of the present range, reflecting the use of only the earlier Maltoni et al. data, rather than the more recent results published in 1984, and the choice not to use a metabolic model. Note that the lower value of risk for BT-1,2, which are the earlier studies, is among the lowest of the present assessment. EPA has also calculated risks based on feeding studies. Using the later Maltoni et al (1980, 1981) data, EPA (1985b) calculated a human inhalation potency of 2.95×10^{-1} $(mg/kg\text{-}day)^{-1}$, equivalent to a human q_1^* of 11×10^{-5} ppb^{-1}. Figure 8-1 shows that this value is below the top of the present range. EPA has also calculated risks based on feeding studies. Assuming that dietary absorption has the same efficiency as inhalation absorption (both about 40%), the EPA (1984b) oral potency of 2.3 $(mg/kg\text{-}day)^{-1}$ is equivalent to q_1^* of 1.7×10^{-3} ppb^{-1}. This result is approximately 9-fold greater than the top of the range presented in Table 8-3.

In a more recent risk assessment, Chen and Blancato (1989) have used metabolized dose in a multistage model to estimate cancer risk from the Maltoni et al. (1984) data on liver angiosarcoma, experiments BT-1 and BT-15. Their result of 2.3×10^{-5} ppb^{-1} for the UCL on lifetime unit risk actually appears to be for females and not for males as indicated in their report. In Tables 5, 10, and 13 for the Maltoni inhalation data, the males and females were reversed. This value compares to the risk of 18×10^{-5} ppb^{-1} calculated for the DHS analysis. The lower risk estimate of Chen and Blancato (1989) appears to be due to their higher calculated dose rate. Chen and Blancato (1989) used a daily dose rate, which is not clearly documented in the study, but appears to be 8-fold higher than estimates based upon calculation methods used in the current DHS analysis.

Zapponi et al. (1988) have reported that using different bioassays has little effect on unit risks that result from fitting the multistage model. They used the Michaelis-Menten function to establish metabolized exposure, and found $K_m = 950$ ppm (in current terms) for the BT-1 experiment in comparison to the $K_m = 336$ ppm used in the current analysis. For that experiment the UCL on unit risk was 2.5×10^{-5} when adjusted for rat lifetime exposure, which is similar to the estimate for BT-1,2 in the current analysis of 1.9×10^{-5}.

Brown and Hoel (1986) used a time-variable form of the multistage model to determine how well the model was able to predict incidence in appropriate experiments. Their result indicates that the model performed very well for

the rat (F-344) data, adequately for the B6C3F1 mice data and marginally for the Swiss mice and hamster data. Models with 3 to 7 stages produced the fits, and a strong effect of the first stage was apparent. A separate approach explored statistically for effect of age at first exposure, detecting a significant reduction in susceptibility with increasing age of first exposure.

All these estimates are subject to substantial uncertainties, as have been discussed on the scientific literature (DHS, 1986, and EPA, 1984a). The available information does not suggest that there is a threshold for vinyl chloride's carcinogenic effect, though this remains uncertain. The multistage model is the best choice based on the plausible mechanism of vinyl chloride carcinogenicity. Nevertheless, our incomplete understanding of cancer makes this choice subject to uncertainty. Furthermore, the present approach uses other assumptions that are designed to be somewhat health protective in the absence of precise knowledge. One of the most important of these is the extrapolation from humans to animals on the basis of surface area in accordance with DHS guidelines (1985). This approach may overpredict or underpredict human risk.

In spite of such uncertainties and the potential differences in exposure duration, oncogenic sensitivity of different species, age of exposure, sex, and levels of exposure and in spite of the uncertainties in the human data, the estimated unit risk values for the human epidemiologic data and those calculated from animal inhalation data are remarkably consistent with one another.

Because 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 one study of 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.

Because of these considerations, this assessment concludes that it is necessary that the best estimate coincide with the top of the range of estimates of human unit risk extrapolated from rodents. This approach provides adequately health protective estimates of human unit risks, which represent the 95% upper confidence limits for risk calculations.

TABLE 8.1 SUMMARY DESCRIPTION OF RODENT EXPERIMENTS CONSIDERED IN RISK ANALYSES

Experiment	Strain[a]/Species, Sex	Exposures[b] ppm	(no.)	Effective[c] LDE (ppm)	Weight (kg)	Inhalation rate (m^3/day)
Maltoni et al.						
BT-1,2	sd/rat, female	0-500	(10)	0-10.4	.275	.190
	sd/rat, male[d]	0-500	(10)	0-10.4	.425	.254
BT-9,15	sd/rat, female	0-50	(6)	0-2.6	.400	.244
	sd/rat, male	0-50	(6)	0-2.6	.600	.320
Bi et al.	wi/rat, male	0-3000	(4)	0-48.6	.300	.200
Drew et al.	fi/rat, female	0-100	(5)	0-13.7	.300	.200
	bc/mouse, female[d]	0-50	(3)	0-5.8	.030	.039
	sw/mouse, female	0-50	(4)	0-5.8	.030	.039
	gs/hamster, female[d]	0-200	(4)	0-5.8	.092	.086

[a]sd = Sprague-Dawley, wi = Wistar, fi = Fischer-344, sw = CD1 Swiss, bc = B6C3F1, gs = golden Syrian.

[b]Range of exposures for all groups used in the analysis. Number of groups used is in parentheses.

[c]Range of exposures expressed as effective lifetime daily exposure, using Equation 8-1 and the lifetime adjustments of the text.

[d]Did not achieve an adequate fit of the multistage model for any tumor.

TABLE 8.2 RISKS OF CARCINOGENICITY FROM VINYL CHLORIDE EXPOSURE ESTIMATED FROM RODENT DATA

Experiment	Strain[a]/Species, Sex	Tumor[b]	Coefficients[c] /stages	Ratio[d] $\frac{q_1^*(r)}{q_1(r)}$	Rodent UCL $q_1^*(r)$ 10^{-5} ppb^{-1}	Human UCL[e] $q_1^*(h)$ 10^{-5} ppb^{-1}
Maltoni et al.						
BT-1,2	sd/rat, female	LAS	1,2	2.3	1.9	4.9
(≤500 ppm)	sd/rat, female	mammary	0,1	1.7	1.4	3.7
BT-9,15	sd/rat, female	LAS	1,2	1.9	6.7	18.
	sd/rat, male	LAS	1/1	2.5	2.5	6.5
Bi et al.	wi/rat, male	LAS	1,2	1.9	5.0	13.
	wi/rat, male	lung angiosarcoma	1,2	2.8	1.7	4.5
Drew et al.	fi/rat, female	LAS	0,1,2	2.1	3.2	8.4
	fi/rat, female	hepatocellular carcinoma	0,1,2	2.0	1.7	4.4
	fi/rat, female	mammary	0,1	1.7	1.6	4.2
	sw/mouse, female	lung	0,1	1.8	6.9	20.

[a]See Table 8.1 note a

[b]LAS = liver angiosarcoma

[c]Number to the right of the slash indicates degree that is chosen by the user for polynomial in the multistage model. Remaining numbers indicate subscripts of non-zero coefficients of the polynomial for the maximum likelihood estimate, following Equation 8-6.

[d]Ratio of unit risks: the 95% UCL to the maximum likelihood estimate.

[e]Determined by multiplying by the scaling factor on rodent dose.

TABLE 8.3 RANK ORDERING OF ESTIMATES OF HUMAN RISK BY CATEGORY

Rank	Experiment	Strain[a]/Species, Sex	Tumor[b]	Individuals[c]	Unit Risk, UCL q_1^*(h) ppb^{-1}
1	Drew	sw/mouse, female	lung carcinoma	228	20×10^{-5}
2	BT-9,15	sd/rat, female	LAS	380	18×10^{-5}
3	Bi	wi/rat, male	LAS	78	13×10^{-5}
4	Drew	fi/rat,female	LAS	353	8.4×10^{-5}
5	BT-9,15	sd/rat, male	LAS	298	6.5×10^{-5}
6	BT-1,2	sd/rat, female	LAS	313	4.9×10^{-5}
7	Waxweiler	oc/human, male	liver + brain + lung	1294	4.5×10^{-5}
8	Bi	wi/rat,male	lung angiosarcoma	78	4.5×10^{-5}
9	Drew	fi/rat, female	hepatocellular carcinoma	353	4.4×10^{-5}
10	Drew	fi/rat, female	mammary	354	4.2×10^{-5}
11	BT-1,2	sd/rat, female	mammary	394	3.7×10^{-5}
12	Waxweiler	oc/human, male	liver	1294	2.5×10^{-5}

[a]oc = occupational cohort. See Table 8.1 for other abbreviations.

[b]LAS = liver angiosarcoma.

[c]Number of all individuals entered in the analysis, exposed and unexposed.

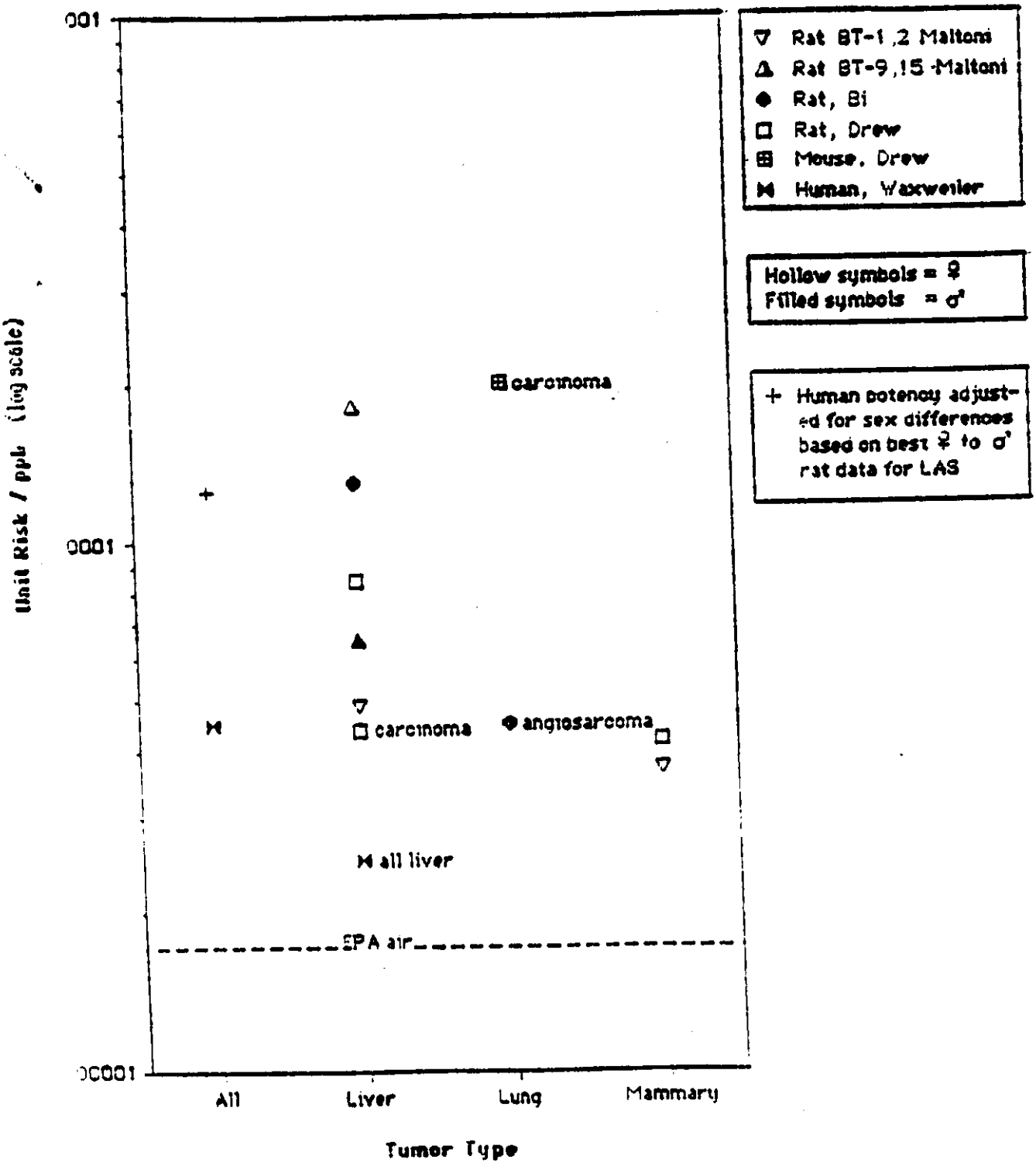

Figure 8-1. Upper Confidence Limits on Unit Risk to Humans from Lifetime Exposure to Vinyl Chloride. Estimates were derived from the indicated studies in Table 8-2. Liver tumors are angiosarcomas unless otherwise indicated.

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. Human exposure for longer than five minutes to concentrations of 8000 ppm or more may lead to narcosis, cardiovascular and respiratory irregularity, convulsions, cyanosis and death. Several human deaths have been attributed to occupational exposure at 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 at exposure levels even 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 rate of metabolism of vinyl chloride appears to depend upon the level of exposure, with higher levels being incompletely metabolized. The saturation of the metabolizing enzymes becomes substantial in monkeys above exposures of 100 ppm, and in the absence of better data this value may be extrapolated to humans.

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 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 inadequate exposure data to base a quantitative carcinogenic risk assessment on epidemiological studies, the present risk assessment includes an analysis of an occupational study of Waxweiler et al. (1976), using a retrospective estimate of exposure (Barnes, 1976; Paddle 1986) that was converted to an effective exposure on the basis of a pharmacodynamic model which takes account of the metabolic conversion.

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 because of their use of more sensitive categories, the young and females, reflect a wider range of population sensitivity.

The staff of the Department of Health Services conclude that:

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

2. Because 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 equivalent 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 this risk assessment 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 unit risks from 4×10^{-5}/ppb to 20×10^{-5}/ppb (Table 8.3). The human unit risk from occupational vinyl chloride exposure for males has been estimated herein to be 4.5×10^{-5} ppb^{-1} for cancer at all sites and to be 2.5×10^{-5} ppb^{-1} for liver cancer alone. Thus, although the human risk estimates are based on a historical reconstruction of occupational exposures, the results overlap the range estimated from animal studies.

5. 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 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. The present assessment predicts that there is only a 5% chance that a lifetime exposure of 131,000 residents to 1 ppb would result in more than 3 to 26 excess cancer cases, and there is a 95% chance that there would be less cases.

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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 olive 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, Maltoni et al., 1984). The insufficient protocol prevents any assessment of the carcinogenicity of vinyl 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 almost 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 to 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 controls. 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 significantly, nor did the increased tumor incidence in offspring exposed to vinyl chloride for 15 weeks appear to differ substantially from the tumor incidence in exposed 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).

Appendix B

Cancer Risk Estimates for

Vinyl Chloride

Based on Human Data

Introduction

Epidemiological data from many studies provide strong evidence that vinyl chloride is a human carcinogen. See Tables B-1 and B-2. As with the evaluation of toxic effects of many other substances, the main problem that occurs in using the epidemiological data for quantitative predictions of effects of vinyl chloride is the lack of suitable exposure data. For vinyl chloride, some indirect exposure estimates are available.

The quantitative risk assessment developed in this appendix uses cancer incidence data from one study, Waxweiler et al (1976). The industry-wide estimates of exposure by Barnes et al (1976) furnish the data for estimating year-by-year exposures of the known worker population in the Waxweiler study. The analysis uses these atmospheric exposures to estimate values of the metabolized exposure at the tissue, based on the satuation (Michaelis-Menton) model of formation of an active carcinogen. The calculations provide risk per unit of metabolized exposure, which closely approximates atmospheric exposure at concentrations below 10 ppm.

Mortality data

Of the many occupational studies that have been reported, the cohort study reported by Waxweiler et al (1976) contains the most thoroughly documented information for risk assessment purposes. That study selected a cohort of polyvinyl chloride (PVC) workers 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.

Among the cohort of 1294 workers, only 7 were lost to follow up. There were 136 deaths during the follow-up period, of which 35 were due to cancer. Eleven of these cancer deaths were due to angiosarcoma of the liver, more than any other study, and three were due to billiary cancer. The standardized mortality ratio (SMR) for billiary and liver cancer was 1155, for brain cancer, 329, and for lung cancer, 156. All of these values represent statistically significant increases. 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, however, 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.

Exposure Data

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., 1975; Jones, 1974; Paddle, 1986). Table B-3 summarizes proposed estimates of exposure for several countries.

Most of the specific exposure data available for the United States derive from measurements at a single plant operated by Dow Chemical Company (Jones, 1974). Although exposures for some job classes were quite high, most

exposures were less than proposed international levels during commensurate time periods because 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., 1975; Paddle, 1986). This standard was well below industry-wide acceptable limits during the 1960's and early 1970's and probably well below 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).

The exposure estimates presented by Barnes (1976) and summarized in Table B-3 of this appendix are likely to describe the average exposures for the Waxweiler et al. cohort, which spanned the years, 1942-1973. Barnes did not substantiate his exposure estimates but simply stated, "the general consensus of opinion throughout the world, today, is that average atmospheric exposure for polymerization workers between 1940 and 1970 might have been of the following order" (Barnes, 1976). The Barnes estimates approach the existing standards during the corresponding time periods. The current analysis used those Barnes estimates, which are expected to be within a factor of five of the actual values experienced by these workers.

Some work histories started before the first time period provided by Barnes (January 1, 1945). The present analysis counted those histories separately and assigned exposures prior to 1945 a concentration of 1000 ppm, which is equal to Barnes' estimates of concentration in the first ten years, on the assumption that exposure during early process days (pre-1945) was the same as that during the 1945-1955 exposure period.

Recorded deaths due to angiosarcoma of the liver occurred between 1964 and 1973. The present analysis examined work histories to identify the person-time in each calendar year for the cohort which had at least five years of employment and who began work (and thus vinyl chloride exposure) prior to 1964. The analysis incorporated these restrictions to correspond to the same restrictions used by Waxweiler and co-workers (1976) in generating their SMR values. Thus, both the exposure and 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.

Relationship of Risk to Exposure

This development of a relationship of risk to exposure considers a cohort of individuals, each subcohort of which is exposed at a constant rate to a particular chemical during each time period of one calendar year. The rates of exposure may differ among subcohorts and time periods. The development here makes no distinction according to age.

The model assumes proportionality between excess risk and the metabolized exposure, a measure of the amount of vinyl chloride ever bound to macromocules in the course of an individual life time (Gehring et al 1977, Anderson et al 1980). Thus, the excess risk due to a lifetime daily equivalent metabolized exposure, Y_{ij}, of subcohort i during time period j is assumed to be given by

$$P_{ij} = QY_{ij}T_j/T, \qquad \text{(B-1)}$$

where P_{ij} = excess probability of cancer in subcohort i due to exposure during time period j.
Q = the lifetime unit risk, a coefficient of proportionality, independent of subcohort and period,
Y_{ij} = metabolized exposure for subcohort i during time period j, defined in Equation B-3 and representing adduct formation,
T_j = time of exposure during time period j,
T = general population lifetime (life expectancy).

This analysis uses a metabolic model of formation of active carcinogen because occupational exposures experienced in the older studies are well above the saturation level for adduct formation for all species in which the kinetics have been determined. The analysis assumes that Michaelis-Menton kinetics govern the rate at which adducts form in target tissue due to a reactive metabolite (Gehring, 1977). That rate is given by

$$F_{ij} = aV_mX_{ij}/(K_m + X_{ij}), \quad \text{(B-2)}$$

where Fij = rate of adduct formation in subcohort i due exposure during time period j
a = proportionality constant
Vm = maximum velocity of the reaction,

K_m = Michaelis saturation constant,
X_{ij} = atmospheric exposure.

Instead of using the target dose rates F_{ij} in the subsequent analysis, it is convenient to use the proportional quantity, the metabolized exposure, defined as,

$$Y_{ij} = K_mF_{ij}/aV_m = K_m\ X_{ij}/(K_m + X_{ij}). \quad \text{(B-3)}$$

See Figure B-1 for monkey data used to estimate K_m = 150 ppm. The analysis uses this value for humans.

The metabolized exposure has the convenient property of becoming essentially equal to (atmospheric) exposure for values of exposure sufficiently below the saturation level K_m (less than 1% error for exposure less than 1% of saturation level). Strictly speaking, Y_{ij} is the difference in metabolized exposure between the study population and the comparison population used in calculating relative risk. However, the exposure of the comparison population is usually negligible when contrasted to that of the exposed study population. The exposed study population also usually experiences the background population exposure. In the case of occupational exposures, estimation of workplace exposures effectively gives an estimate of the difference between the worker cohort exposure and the exposure of the comparison population.

In order to estimate the unit risk Q, the analysis continues by equating the modeling prediction of Equation B-1 to the risk of excess cancers in subcohort i due to the life time daily equivalent to the exposure in time period j.

$$P_{ij} = (A_{ij} - E_{ij})/N_{ij}, \quad \text{(B-4)}$$

where A_{ij} = specific (liver in this case) cancer deaths that occurred in subcohort i due to life time daily equivalent to the exposure in time period j,
E_{ij} = number of specific cancers expected to occur in the lifetime of those N_{ij} workers, based on experience in the general population,
N_{ij} = number of individuals in subcohort i during time period j.

Equating the expressions for P_{ij} in Equations B-1 and B-4, then multiplying by N_{ij} and summing over the indices i and j yields an equation for Q in terms of overall quantities that were observed or reconstructed.

$$Q \, \Sigma_{ij} N_{ij} Y_{ij} T_j / T = \Sigma_{ij} (A_{ij} - E_{ij}). \quad \text{(B-5)}$$

Dividing by the sum on the left-hand side,

$$Q = (A-E)/NY(T_y/T), \quad \text{(B-6)}$$

where Σ_{ij} = summation over i,j
$A = \Sigma_{ij} A_{ij}$, overall observed cancer deaths,
$E = \Sigma_{ij} E_{ij}$, overall expected cancer deaths,
$N = \Sigma_{ij} N_{ij}$, overall person-years exposed,
$Y = \Sigma_{ij} N_{ij} Y_{ij}/N$ overall average exposure intensity, (B-7)
T_y = actual time of exposure during each time period of one year.

Equation B-6 takes a convenient form by using an expression for relative risk, which is the SMR divided by 100.

$$Q = (R-1)(S/D)H/Y(T_y/T)N, \quad \text{(B-8)}$$

where R = A/E = relative risk,
E = STH = SH/D = expected number of deaths in the lifetime of individuals from the general population matched to those in the overall cohort,," to the definatin of E,
S = yearly background rate of this specific cancer in the general population,
H = number of individuals in the cohort,
T = 1/D = 70 years for humans,
D = probability of death in the general population per year.

The actual computations had available estimates of only the overall exposures for each time period. The analysis first proceeds by assuming that each of these estimated exposures represents the population-weighted average for that time period, so that

$$Y_{ij} = Y_j.$$

On this assumption Equation B-7 becomes the single summation,

$$Y = \Sigma_j N_j Y_j / N, \qquad \text{(B-9)}$$

where $N_j = \Sigma_i N_{ij}$, the number of individuals exposed in time period j.

The analysis next determines the effect of a distribution of subjects and exposures. In the absence of data on distributions of the number of subjects, N_{ij}, in each subcohort experiencing atmospheric exposure X_{ij} within each time period j, calculations for a uniform distribution indicate how much the actual value of Y in Equation B-7 may differ from that calculated in Equation B-9, assuming all the N_j values of X_{ij} are at one exposure level, X_j, the time-period mean. The uniform distribution is that in which, for each year (j), the number of persons exposed at each level is uniformly distributed over the exposure range from 0 to $2X_j$. With that distribution an integration produces the expression for metabolized exposure during the year, for use in Equation (B-9).

$$Y_j = (K_m/2X_j)\,[2X_j - K_m \mathrm{Ln}(1+2X_j/K_m)], \qquad \text{(B-10)}$$

where Ln is the natural logarithm of the designated argument.

A numerical exploration for Km = 150 ppm shows that the expression in Equation (B-9) is between 0.89 and 0.92 of that using the case, $X_{ij} = X_j$ in Equation B-3, over the range of exposures 100-1000 ppm. This range covers that of the study Waxweiller et al. (1976). So for each year the analysis of that study will use 0.9 times the average metabolized exposure Y_j for the year based on Barnes estimates for X_j. Therefore, the analysis multiplied 0.9 by the value of overall metabolized exposure obtained in Equation (B-9) using a single average value of metabolized exposure for each year.

Table B-4 provides quantities needed to estimate the average metabolized exposure Y in Equation B-8.

$$\Sigma_j N_j Y_j = 1.72 \times 10^6 \text{ ppm-persons}$$
$$N = \Sigma_j N_j = 1.44 \times 10^4 \text{ persons}$$

Thus the modified Equation B-7 gives the overall average metabolized exposure,

$$Y = 0.9 \times 1.72 \times 10^6 \text{ ppm} / 1.44 \times 10^4 = 108 \text{ ppm}$$

In the Waxweiler study the time during each year spent working furnishes

$$T_y = (8\text{hr}/24\text{hr})(5\text{days}/7\text{days})(46 \text{ weeks}/52\text{weeks}) \text{ yr} = 0.211 \text{ yr}$$

for all years. Equation B-8 requires this quantity.

Risk Calculations for Liver Cancer

The remaining quantity needed to obtain unit risk in Equation B-8 is the background mortality ratio S/D. The present analysis used information on deaths in the general population during the same time period as the study. 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 the background from liver cancer, S/D.

Finally the analysis estimates unit risk for liver cancer per person by using Equation B-8. The numerator contains the added lifetime risk of liver cancer per person, which is the excess relative risk, 10.55, times the background rate of one liver cancer death per 270 deaths to all causes or 0.039. The denominator contains the lifetime equivalent of exposure during one calendar year: the average metabolized exposure, 108 ppm, times 0.211 years of exposure divided by 70 years of life expectancy. The equation then calls for multiplying the resulting quantity by the ratio, person-years of exposure to cohort size or N/H, which is the average number of years of exposure, 11.3 years, in order to obtain the lifetime daily equivalent of average metabolized exposures.

The expected unit risk Q, then, is the lifetime added risk per person divided by the lifetime daily equivalent of average metabolized exposure, 3.6 ppm.

$$Q = (11.55-1)(1/270)\ 1294/108\ ppm\ (0.211/70)\ 14442$$
$$= 0.039/3.6\ ppm = 1.1 \times 10^{-2}\ ppm^{-1}$$

Cancer Risk Scenarios Including Brain and Lung Cancer as Well as Liver Cancer

This analysis adopts the same approach for brain cancer and lung cancer. The next sections discuss evidence for the relationship of these cancers to vinyl chloride exposure. In the absence of evidence to the contrary, the analysis 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, (R-1)S/D for the added brain cancer lifetime risk was one in 100 and, for lung cancer, was one in 33.4. Substituting these ratios in Equation B-8 yields the most likely values, given in Table B-6.

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 to brain cancer in occupational studies, but not to 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 more consistent when considered in conjunction with the liver cancer excess 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.

A more recent large study presents evidence against a relationship between lung cancer and vinyl chloride exposure (Wong et al., 1986). 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 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% confidence limit for the excess risk estimate, the upper limit of excess risk (24.04 - 1 = 23.04) is multiplied by the lifetime risk for the average person of dying from liver cancer (1/270). Therefore, the upper 95% confidence limit for the added risk due to vinyl chloride exposure is 23.04 x 1/270 = 0.085 or 1/11.7.

The same sort of calculation estimates 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 exposures. 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 turn, the one-hit model extrapolation is very close to a multistage extrapolation with linearization as recommended by the U.S. Environmental Protection Agency (EPA) Carcinogen Assessment Group 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.

Equation B-1 provides the formula for downward extrapolation in the current analysis. The values of Q for each case come from use of Equation B-8. The numerator contains the

most likely value or the 95% confidence limits of (R-1)S/D for the cancer sites considered. Table B-6 provides the results for the three cancer sites.

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. These 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 excess relative risk and lifetime average exposure rate is assumed to be linear. If the relationship is better described by a supralinear curve, then a linear assumption will understate the risk. 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. It is assumed that the effect of a given cumulative exposure is the same in men and women.

Conclusions

This risk assessment analysis suggests that a lifetime daily equivalent exposure to 3.6 ppm of vinyl chloride may result in an added Xlifetime 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 a lifetime exposure to one part per billion of vinyl chloride has a 95% upper confidence limit of 4.5×10^{-5} risk of cancer, if all these cancers are related to such exposure. In the most likely case that only liver and brain cancer are related to exposure, a lifetime to one part per billion has a 95% upper confidence limit of 2.6 x 10-5 risk of cancer.

Figure B-1
Rate of Adduct Formation from Exposure of Rhesus Monkeys to Vinyl Chloride
(Data points after Buchter, et al., 1980)

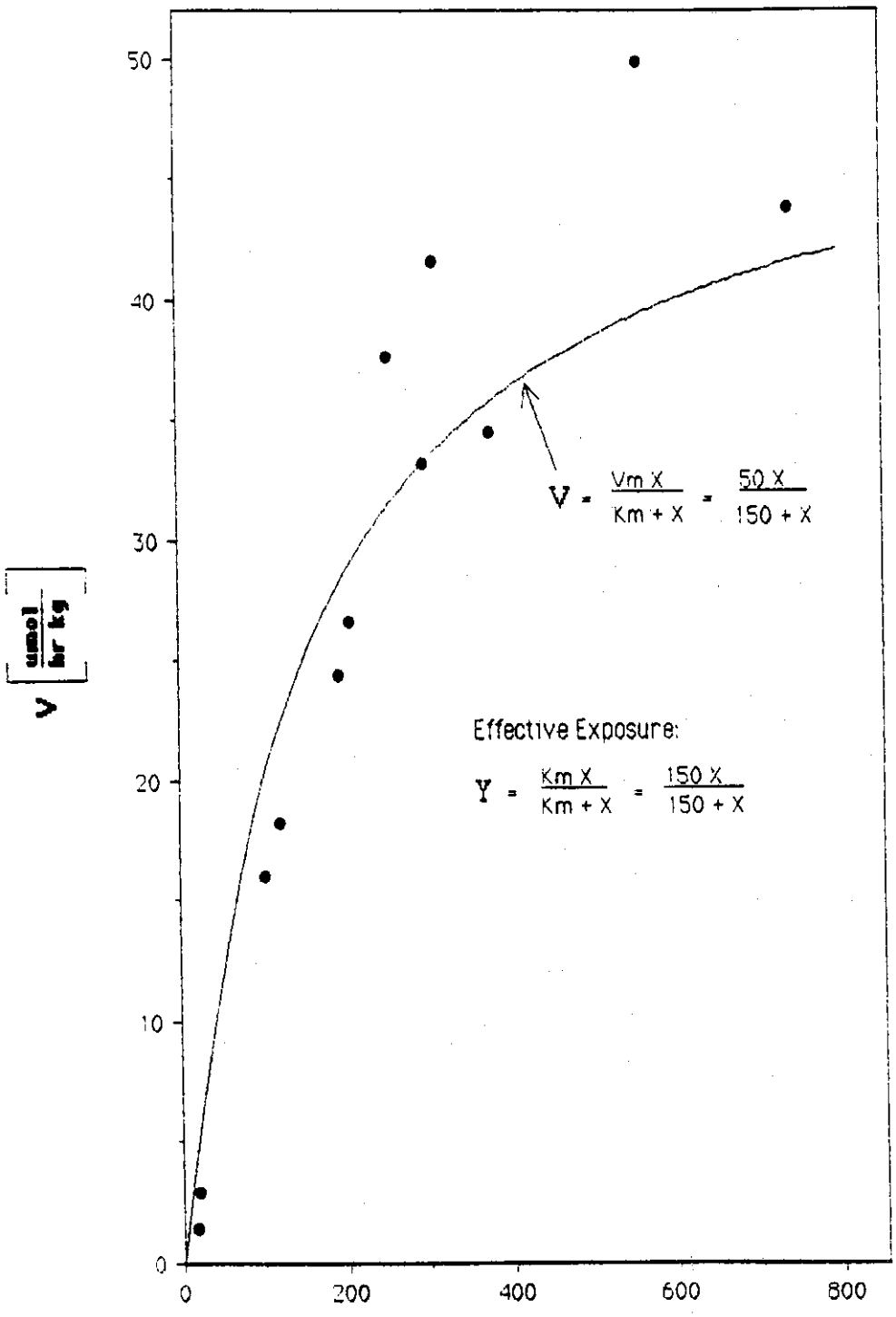

TABLE B-1

COHORT CHARACTERISTICS OF SELECTED VINYL CHLORIDE STUDIES

Author	Cohort Size	Total No. of Deaths	Number of Cancer Deaths	Range of Exposure Duration Minimum	Maximum	Longest Follow-up	Notes on Follow-up	Place of Company Involved
Byren et al., 1976	750	58	11	>0 yr 15% > 10 yrs		1940's - 1974	97%	Sweden
Cooper, 1981++	10173	707	139	> 1 yr	23 yrs	1940's - 1972	95%	37 Plants United St.
Duck et al., 1975	2120	136	35	>0 yr	> 15 yrs	1948 - 1974	99.6%	South Wal
Fox et al., 1977	7561	393	115	>0 yr 23% > 10 yrs, 8% > 20 yrs		1940 - 1974	99.1%	Great Brit
Heldaas et al., 1984	454	50	23	> 1 yr 35% > 5 yrs		1953 - 1979		
Monson et al., 1974++	*	161	41			1946 - 1974	99.2%	Louisvill Kentucky
Nicholson et al., 1975	257	24	9	----------(not given)--------		1947 - 1973		New York
Robershaw et al., 1974++	8384	352	79	> 1 yr	> 30 yrs	1930's - 1972	85%	33 Plants United St.
Akamura, 1983	4524	209	37	> 1 yr	> 15 yrs	1950 - 1975		Japan
Cherlault 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	35	> 5 yrs	27 yrs	1940's - 1973	99.5%	4 Plants I United Sta
Weber et al., 1981	7021	414	94	>0 yr	> 10 yrs	1940's - 1974	90%	West Germa
Wong et al., 1986++	10173	1536	359	>1 yr	30 yrs	1942 - 1982	92%	United Sta

DRAF

*Proportional mortality study

++Overlapping cohorts of Goodrich company workers

TABLE 8-2

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

Author	Liver				Number of Liver Angiosarcomas	Lung				Brain (CNS)			
	O	E	SMR	90% C.I.		O	E	SMR	90% C.I.	O	E	SMR	90% C.I.
	liver and pancreas												
Byren et al., 1976	6	0.97	413	(140.3, 942.9)	2	3	1.78	168	(45.5, 435.1)	2	0.33	612	(104.6, 1904.5)
	digestive					respiratory							
Cooper, 1981*	29	40.8	75	(50.8, 96.9)	8	25	23.9	107	(72.7, 146.1)	12	5.9	203	(117.3, 329.5)
	digestive												
Duck et al., 1975	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, 171.3)
Heldaas et al., 1984	1	7			1	5	2.84	180	(69.2, 370.0)	-	-	-	- -
	biliary and liver												
Monson et al., 1975*	8	0.7	1100	(568.3, 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, 6728.4)
	digestive					respiratory							
Tabershaw et al., 1974*	19	21.67	94	(57.4, 128.6)	6	25	23.93	112	(72.6, 165.9)	-	-	-	- -
Nakamura, 1985	6	2.56	236	(102.7, 466.0)	1	2	2.33	86	(14.8, 269.7)	-	-	-	- -
	digestive					respiratory							
Theriault et al., 1981	14	5.4	259	(156.7, 405.3)	8	2	5.78	34.6	(6.0, 108.7)	0	0.6	0	
	biliary & liver					respiratory							
Waxweiler et al., 1976*	7	0.6	1155	(547.0, 2190.6)	11 ++	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)
	liver and biliary												
Wong et al., 1985*	37	5.77	641.2	(478.2, 843.6)	[15]	115	122	94.2	(80.3, 110)	23	12.76	180	(123.2, 255.4)

*Overlapping cohorts of Goodrich company workers.

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

90% C.I. - 90% confidence interval

TABLE B-3

HISTORIC EXPOSURE LEVELS (ppm): VINYL CHLORIDE

Standards	U.K. Barnes	Location Author Year	USA Ott	USA Ott	USA Barreta et al	USA Kramer & Hutchler	USA Cook et al	USSR Filatova & Gronsberg	Lefevre et al	Romania Suciu et al	Hungary Anghelescu et al	Greece Gitelos	Sweden Byren & Holmberg
	1000	1950				Avg TWA in 1950-155 ppm							
AC = 00 ppm		1951	range TWA 5-385 ppm	most jobs < 80 ppm				(Pub.1957) reactor area avgs 38-310 ppm					
		1952											
		1953											
		1954											
	400-500	1955	peaks = 4000	one job close = 135-825		TWA range for 1950-1965: 10-300 ppm		range: 15 ppm-16,000 ppm (16K-peak)					
		1956											
		1957						precip. & centrifuge:					
		1958						8 - 3050 ppm					
		1959						drying ovens:					
		1960						4 - 15 ppm					
		1961	TWA range = 5-240 ppm										
		1962											
		1963											
CGIH = 0 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	(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 areas 18-20 ppm
		1965											
		1966											
		1967											
		1968			(Pub.1969) TWA range: 5-200 ppm		(Pub.1970) reac.area: 50-100 ppm						
		1969											
		1970											
SHA = 500		1971			peaks > 1000 ppm		peaks: 600-1000 ppm @ scrapers' hands						
SHA = 200		1972											
	150	1973											
SHA = 50		1974											
SHA = 1	5	1975											

MAC = Maximum Allowable Concentration
ACGIH = American Conference of Government 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

TABLE B-4

EFFECTIVE EXPOSURE FOR WAXWEILER ET AL. (1976)

Year	Index	Workers[a]	Exposure (ppm) Estimate[b]	Exposure (ppm) Metabolized[c]	Product person-ppm[d]
		N_j	X_j	Y_j	N_jY_j
1942	1	71	1000	130	9261
1943	2	152	1000	130	19826
1944	3	191	1000	130	24913
1945	4	244	1000	130	31826
1946	5	344	1000	130	44870
1947	6	438	1000	130	57130
1948	7	538	1000	130	70174
1949	8	553	1000	130	72130
1950	9	597	1000	130	77870
1951	10	651	1000	130	84913
1952	11	681	1000	130	88826
1953	12	734	1000	130	95739
1954	13	757	1000	130	98739
1955	14	826	500	115	95308
1956	15	876	480	114	100114
1957	16	879	460	113	99428
1958	17	767	440	112	85800
1959	18	850	420	111	93947
1960	19	837	400	109	91309
1961	20	813	390	108	88075
1962	21	858	380	108	92275
1963	22	889	370	107	94884
1964	23	896	360	106	94871
	Total	14442	Weighted Average	119	

[a]Number of workers exposed.
[b]Estimates of exposure after Barnes, by linear interpolation.
[c]Metabolized exposure by modified Michaelis-Menton Equation B-2. K_m = 150 ppm.
[d]Product of number of workers times metabolized exposure.

TABLE B-5

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 G. Paddle Correspondence (1986).

[2]As a point of interest, this table 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

TABLE B-6

VINYL CHLORIDE UNIT RISK COEFFICIENTS FOR WAXWEILER ET AL (1976)

Cancer Site	Maximum Likelihood Estimate	Lower 95% Limit	Upper 95% Limit
Liver	1.1×10^{-5}	0.38×10^{-5}	2.5×10^{-5}
Liver and Brain	1.4×10^{-5}	0.49×10^{-5}	2.6×10^{-5}
Liver, Lung and Brain	2.2×10^{-5}	0.84×10^{-5}	4.5×10^{-5}