PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

VINYL CHLORIDE

September 2000

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Public Health Goal for VINYL CHLORIDE In Drinking Water

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or

MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR VINYL CHLORIDE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a public health goal (PHG) of 0.05 µg/L (or ppb) for vinyl chloride in drinking water. The PHG is based on carcinogenic effects observed in an inhalation study by Drew *et al.* (1983). Vinyl chloride is carcinogenic in mice, rats, and hamsters when given orally and by inhalation. It has been found to cause tumors in a dose-related manner at several sites, including liver, lung, and mammary gland. In humans, vinyl chloride via inhalation has been shown to increase the risk of cancer of the liver. Additionally, there is suggestive evidence for cancer of the brain, lung, and digestive tract in humans. The International Agency for Research on Cancer has listed vinyl chloride as a Group 1A (known human) carcinogen.

In the inhalation study by Drew *et al.* (1983), the authors observed lung carcinoma in female Swiss mice. Cancer potency estimates were made by fitting the linearized multistage model to the experimental data to establish the lower 95 percent confidence bound on the dose associated with a ten percent increased risk of cancer. The resulting inhalation cancer potency factor was 0.27 $(mg/kg\text{-}day)^{-1}$.

Cancer risk was determined using a multipathway approach in which cancer potency was multiplied by sum of drinking water exposure from each of three pathways, ingestion, inhalation, and dermal. The multipathway approach accounts for vinyl chloride exposure via drinking water from ingestion and other sources of exposure such as showering or bathing. The PHG was calculated assuming a *de minimis* theoretical excess individual cancer risk level of one-in-a-million ($1x10^{-6}$) from exposure to vinyl chloride.

In addition to the 0.05 ppb value based on its carcinogenicity, a value of 3 µg/L (3 ppb) was calculated based on noncancer effects of vinyl chloride. The study selected for the derivation of the noncancer PHG was that of Til *et al.* (1991) in which the authors observed liver cell polymorphism and hepatic cysts in male and female rats at the 1.3 mg/kg-day level, but not at the 0.13 mg/kg-day level, the latter being the no-observed-adverse-effect-level (NOAEL). The noncancer PHG incorporates a 10-fold uncertainty factor to account for interspecies variation and an additional 10-fold uncertainty factor to account for human variability. This value also incorporates a water exposure rate of 7.1 liters/day that includes 5.1 liter/equivalents to account for exposure by inhalation and dermal exposure from bathing or showering. As the difference between the cancer-based and noncancer values is approximately 60-fold, the final PHG, based on cancer, contains an adequate margin of safety to protect against potential noncancer adverse effects.

The current U.S. Environmental Protection Agency (U.S. EPA) maximum contaminant level (MCL) for vinyl chloride is 2 ppb. The value is apparently based on the oral data from the animal cancer study of Feron *et al.* (1981). California's current drinking water standard (MCL) for vinyl chloride is 0.5 ppb, which was adopted by the California Department of Health Services (DHS) in 1989. The state and federal MCLs are based on the carcinogenic potential of vinyl chloride. The major difference between the two approaches is that OEHHA used the inhalation data from Drew *et al.* (1984), and included a multipathway approach to account for human exposure to vinyl chloride via inhalation and dermal pathways in addition to ingestion.

INTRODUCTION

The purpose of this document is to develop a PHG for vinyl chloride in drinking water.

In this document, the available data on the toxicity of vinyl chloride are evaluated, with a primary focus on the literature related to both oral and inhalation exposures which are appropriate for the establishment of a PHG for drinking water. The studies that can be used to identify public health-protective levels are reviewed and summarized. We make extensive use of information presented in the DHS' document titled *Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant* (DHS, 1990a). We also reviewed information presented in U.S. EPA's draft Toxicological Review of Vinyl Chloride (U.S. EPA, 1999a), in particular for comparison of prospective health protective concentrations using different cancer potency factors. The results of this evaluation are described below.

CHEMICAL PROFILE

Chemical Identity

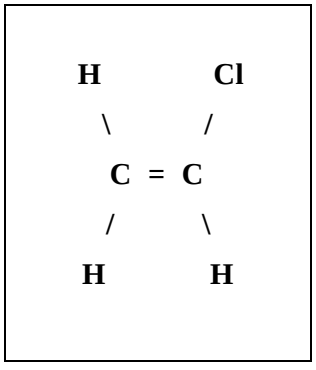
Vinyl chloride is a colorless organic gas. Vinyl chloride can be identified by various chemical names and synonyms. Please see Table 1.

Table 1. Chemical identity of vinyl chloride

Attribute	**Chemical Identity**
Chemical Name	Chloroethene, chloroethylene
Synonyms	Vinyl chloride, chloroethylene, monochloroethylene, VC, VCM
Chemical formula	CH_2CHCl
CASRN	75-01-4

As shown in Figure 1, vinyl chloride is a short-chain halogenated hydrocarbon.

Figure 1. Chemical Structure of Vinyl Chloride



Physical and Chemical Properties

Table 2. Physical and chemical properties

Property	Value or Information	References
Molecular weight	62.5	(HSDB, 1999)
Color	Colorless	(NIOSH, 1994)
Physical state	Gas	(NIOSH, 1994)
Odor	Pleasant, sweet odor	(NIOSH, 1994; HSDB, 1999)
Odor threshold	3,000 ppm	(U.S. EPA, 1999c)
Melting point	-256 °f	(NIOSH, 1994)
Boiling point	7°F	(NIOSH, 1994)
Flash point	N/A (gas)	(NIOSH, 1994)
Flammability limits	UEL=33%, LEL=3.6%	(NIOSH, 1994)
Autoignition temperature	472°C	(ATSDR, 1992)
Solubility		
Water	0.1 % (@77 °F)	(NIOSH, 1994)
Organic solvents	Sol in alcohol, ether, benzene	(HSDB, 1999)
Specific gravity, density	N/A (gas)	
Partition coefficient		
Log K_{ow}	0.6	(HSDB, 1999)
Soil sorption coeff. (K_{oc})	56	(U.S. EPA, 1999b)
Bioconcentration factor	7 (est.)	(U.S. EPA, 1999b)
Vapor pressure	2,600 mm Hg at 25 °C	(U.S. EPA, 1999b)
Conversion factor	1 ppm = 2.6 mg/m^3	

Production and Uses

In 1993, the production of vinyl chloride in the United States was nearly 14 billion pounds (U.S. EPA, 1999b). Vinyl chloride is used in the manufacture of numerous products in construction such as electrical wire and cable insulation, piping, industrial and household equipment, and medical supplies. There is heavy demand from the automobile, rubber, paper and glass ` industries. Proportions consumed among various uses in 1989 were: polyvinyl chloride products, 91 percent; exports, 7 percent, and chlorinated solvents and other products, 2 percent (U.S. EPA, 1999b).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Vinyl chloride has not been detected in the ambient air of California at or above a detection limit of 0.5 ppb, except for measurements taken adjacent to vinyl chloride related industries and landfills (DHS, 1990a). Ambient air exposure to vinyl chloride is expected to occur from the discharge of exhaust gasses from factories that use or manufacture the chemical, or from evaporation from areas at which chemical wastes are stored (U.S. EPA, 1999c). Vinyl chloride

released to the atmosphere is expected to remain in the vapor phase and to degrade rapidly via reactions with hydroxyl radicals with an estimated half-life of 1.5 days (U.S. EPA, 1999b). Under calm conditions, with a vapor density of 2.15, concentrated vinyl chloride vapor may disperse slowly and flow along the ground, accumulating in low spots (ATSDR, 1992).

The California Air Resources Board staff has monitored vinyl chloride emissions adjacent to two southern California landfills. Estimates of peak exposure concentrations for maximally exposed receptors ranged from about 0.6 to 10 ppb (DHS, 1990a).

Soil

Vinyl chloride is a product of anaerobic degradation of chlorinated solvents such as trichloroethylene and occurs at some landfills. Vinyl chloride volatilizes rapidly from soil, with reported half-lives of 0.2 and 0.5 days for evaporation from soil at 1 and 10 cm incorporation, respectively, assuming a vapor pressure of 2,600 Torr at 25 ^{0}C (U.S. EPA, 1999b). U.S. EPA estimated a soil sorption coefficient of 56, meaning that the gaseous monomer is highly mobile in soil and may leach into ground water. U.S. EPA further suggested that vinyl chloride would biodegrade in anaerobic soil conditions (U.S. EPA, 1999b).

Water

Vinyl chloride rapidly evaporates from water (U.S. EPA, 1999b). For example, a half-life of 0.8 hour was calculated for a model river 1 m deep with a water flow rate of 3 m/sec and a wind velocity of 3 m/sec. Photodegradation of vinyl chloride occurs rapidly, especially in waters containing photosensitizers such as humic acid. Vinyl chloride would be expected to biodegrade under anaerobic conditions and would apparently not be expected to biodegrade under aerobic conditions. Vinyl chloride would not be expected to undergo hydrolysis in natural waters (U.S. EPA, 1999b).

The highest levels of vinyl chloride in drinking water are expected to occur near sites of polyvinyl chloride production (U.S. EPA, 1985). As of 1990, two industrial facilities used vinyl chloride to produce polyvinyl chloride (PVC). Two other facilities that were producing PVC ceased production, one in 1982 and the other in 1985 (CARB, 1990). Vinyl chloride can also leach directly into drinking water from PVC pipes. The levels of vinyl chloride monomer migration will decrease with the age of the PVC system (ATSDR, 1992). The U.S. EPA estimated in 1985 that the majority of persons using public drinking water supplies would be exposed to intake levels below 0.028 µg/kg-day (U.S. EPA, 1985). The majority of the general population is not expected to be exposed to vinyl chloride through ingestion of drinking water (ATSDR, 1992). Current certification standards regulating the residual level of vinyl chloride monomer in polyvinyl chloride pipe are sufficiently stringent that significant vinyl chloride exposure from leaching into drinking water is not likely (CMA, 2000).

Food

No current information on daily intake of vinyl chloride from food and food packaging sources is available (CARB, 1990).

METABOLISM AND PHARMACOKINETICS

The metabolism of vinyl chloride involves both microsomal (cytochrome P-450) and non-microsomal enzymatic pathways, and results in the conversion of vinyl chloride to the polar metabolite 2-chloroethylene oxide and subsequent oxidation to 2-chloroacetaldehyde and monochloroacetic acid. This saturable pathway appears to operate at low exposures (< 100 ppm) leading to the production of polar metabolites which are predominately excreted in the urine (DHS, 1990a).

Absorption

Vinyl chloride is rapidly and virtually completely absorbed via oral or inhalation exposure (Withey, 1976; Feron *et al.*, 1981; ATSDR, 1992; Zenz, 1994). Absorption of vinyl chloride after oral administration has been measured in rats in dietary studies (Feron *et al.*, 1981) and in gavage studies (Watanabe *et al.*, 1976b). In these reports, nearly 100 percent 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 at dose ranges reported at 12.5-28.2 mg per test animal (Withey, 1976). Green and Hathaway (1975) observed absorption of 98.7 percent of vinyl chloride from the gastrointestinal tract following an oral dose of 450 mg/kg (Green and Hathway, 1975).

Results from inhalation exposure studies in humans, monkeys, and rats using direct and indirect test methods indicate that vinyl chloride is rapidly (but not completely) absorbed and metabolized, rapidly distributed throughout the body, and excreted by the kidneys (DHS, 1990a). Pulmonary absorption of vinyl chloride by rats occurs rapidly and blood levels of vinyl chloride increase with the dose. For example, blood levels in rats exposed via inhalation to 7,000-ppm vinyl chloride reached equilibrium after 30 minutes. Blood concentrations rapidly decline after cessation of exposure (Withey, 1976). Krajewski *et al.* (1980) observed that about 40 percent of vinyl chloride in inhaled air was retained in the lungs from human volunteers. The authors exposed five health male humans, for up to six hours, to vinyl chloride concentrations of 7.5, 15, 30, and 60 $\mu g/m^3$ of vinyl chloride. Exposures were administered via a mask, taking measurements of both inspired and expired air. The amount retained averaged 42 percent, and was not dependent upon vinyl chloride concentration.

Buchter *et al.* (1978) reported that humans exposed to 2.5 ppm vinyl chloride retained 26-28 percent of the administered dose. 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 (Bolt *et al.*, 1981; DHS, 1990a).

Distribution

The distribution of vinyl chloride through body tissues is widespread (Zenz, 1994). Studies in rats and monkeys suggest that the vinyl chloride monomer is highly mobile and diffuses rapidly through body tissues following absorption (DHS, 1990a). 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, shortly following inhalation administration, the liver and the kidneys contained the highest concentrations of ^{14}C activity, followed by the lungs,

spleen, and small intestine (Watanabe *et al.*, 1976a; Bolt *et al.*, 1976). The ^{14}C counts quickly decreased after cessation of exposure.

Watanabe and colleagues (1976a) 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 percent, expired vinyl chloride for 2 percent, expired CO_2 for 12 percent, feces for 4 percent, and carcass and tissues for 14 percent of the recovered radioactivity.

Metabolism

Metabolism of vinyl chloride occurs primarily by microsomal enzymes in the liver. The evidence strongly demonstrates that the toxicity of this compound is attributable to its enzymatic oxidation and conversion to reactive polar metabolites (U.S. EPA, 1985). Metabolism of vinyl chloride in animals is a dose dependent, saturable process (ATSDR, 1992; Withey, 1976; Guengerich and Watanabe, 1979; Green and Hathaway, 1977). For example, inhalation exposure to low concentrations (50-105 ppm) in the rat are metabolized with a relatively short half-life of 86 minutes compared with a longer metabolic half-life of 261 minutes from a saturating dose of 200-1,167 ppm (Hefner *et al.*, 1975; Withey, 1976; DHS, 1990a). About 100 times more vinyl chloride was metabolized at the higher dose (an 1,800-fold difference in dose). Saturability of the enzyme metabolism was also demonstrated by Guengerich and colleagues (1979) by the observation that phenobarbital had no effect on either metabolism or binding to protein or RNA of Sprague-Dawley rats exposed for six hours at 250 ppm vinyl chloride levels, while at 10 ppm covalent binding was enhanced 3-fold (Guengerich and Watanabe, 1979).

The first step in the metabolism of vinyl chloride involves microsomal oxidation leading to oxidation across the double bond (Andrews and Snyder, 1991). Vinyl chloride is changed to chloroethene oxide via this microsomal enzyme pathway, which may spontaneously rearrange to form 2-chloroethylene oxide and, subsequently, monochloroacetic acid. The latter can then undergo conjugation with glutathione. Further metabolism of the resulting glutathione conjugates can produce a number of compounds, including monochloroacetic acid, S-(carboxymethyl)cysteine, thiodiglycolic acid, N-acetyl-S-(2-hydroxymethyl) cysteine, and N-acetyl-vinylcysteine in the urine of rats exposed to vinyl chloride by both the inhalation and oral routes (Green and Hathway, 1975; Green and Hathaway, 1977; Watanabe *et al.*, 1976a; Watanabe *et al.*, 1976a). Thiodiglycolic acid and chloroacetic acid chloride have been detected in the urine of workers exposed to atmospheric vinyl chloride (Muller *et al.*, 1978).

Studies by Bolt and colleagues (1976) indicate that the cytochrome P-450 system is involved in vinyl chloride metabolism. The authors demonstrated that the uptake of 50 ppm of 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-benzothiodazole. Pretreatment with the insecticide 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; DHS, 1990a). These findings suggest that the cytochrome P-450 system may play an important role in vinyl chloride metabolism at low doses.

Studies by Hefner *et al.* (1975) and Bolt *et al.* (1977) suggested that the enzyme systems responsible for vinyl chloride metabolism in rats become saturated at atmospheric concentrations greater than 250 ppm, and higher concentrations produce relatively little additional reactive metabolite.

Excretion

Green and Hathaway (1975) examined the excretion pattern of single doses of 0.25 and 450 mg/kg of radiolabeled ^{14}C-vinyl chloride administered to rats via the i.g., i.p., and i.v. routes. More than 90 percent of the administered dose was excreted within the first 24 hours. The principal elimination route for labeled vinyl chloride after all three routes of administration to rats was pulmonary with both unmetabolized vinyl chloride and also labeled CO_2 being released via the lungs. Polar vinyl chloride metabolites are excreted via the kidneys. Following intragastric administration, pulmonary output of unchanged vinyl chloride is proportional to the logarithm of the reciprocal dose. Excretion patterns after i.v. and i.p. injections are similar to the characteristics of vinyl chloride excretion following oral administration (Green and Hathaway, 1975; DHS, 1990a).

Following inhalation exposure to 10 or 1000 ppm, elimination half-lives were described as 20.4 and 22.4 minutes, respectively (Watanabe *et al.*, 1976a). Pulmonary excretion of unmetabolized vinyl chloride following oral administration is complete within three to four hours. However, pulmonary excretion of labeled CO_2 and also the renal excretion of polar metabolites takes about three days (Green and Hathaway, 1975).

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

The acute toxic effects of vinyl chloride (which are similar for both animals and humans) include central nervous system depression (anesthesia) and cardiac, circulatory, and respiratory irregularities (DHS, 1990a).

A report of exposures causing 50 percent lethality (LD_{50}) in groups of animals exposed to vinyl chloride via 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.*, 1975; DHS, 1990a).

Conolly and colleagues (1978) compared the oral, acute, inhalation toxicity of vinyl chloride to other vinyl halides following Aroclor 1254 pretreatment. The authors exposed male Holtzman rats (six or seven per group) to 10,000, 24,000, or 50,000 ppm vinyl chloride monomer for four hours (with no mortality) and observed significant elevations of serum alanine-α-ketoglutarate transaminase levels as well as increases in liver weights when compared with controls. The effects increased with dose (Conolly *et al.*, 1978).

Gehring and coworkers (1978) used vinyl chloride to test the hypothesis that incremental response for chemicals requiring biotransformation to produce toxicity becomes diminishingly smaller with increasing dose. Male Sprague-Dawley rats, in groups of three to six per level, were exposed to 1.4, 9.3, 24.7, 51, 109, 250, 511, 1020, and 4600 ppm. Animals were exposed for six hours via inhalation. The non-volatile radioactivity on tissue and carcass provided a good estimate of the total amount of vinyl chloride metabolized. The authors observed that the ratio of

vinyl chloride metabolized in rats divided by the dose did not increase proportionately with increasing dose, but rather began to decrease with increasing dose concentrations above 9 ppm. The dose-dependent biotransformation of vinyl chloride by rats, characterized by Michaelis-Menten type kinetics, may present estimation problems for extrapolation of animal cancer test data to human carcinogenic risk (Gehring *et al.*, 1978).

Subchronic Toxicity

Feron *et al.*, (1975) investigated the subchronic effects of orally administered vinyl chloride on rats. Vinyl chloride monomer was dissolved in soy-bean oil and administered via gavage to male and female rats at levels or 0, 30, 100, and 300 mg/kg body weight, once daily for 6 days/week over 13 weeks. Several hematological, biochemical and organ weight values differed to a statistically significant degree from those of the controls, but these differences were considered by the authors to have only minor, if any, toxicological significance. A slight increase in liver-to-body weight ratio occurred in males and females at the highest dose level. This increase was not accompanied by liver damage, as was evident from the histological examination, enzyme histochemistry and electron microscopy. The no-effect level in this 90-day study was placed by the authors at 30 mg/kg-day, however, the authors were skeptical of the toxicological significance of the NOAEL. The histological liver changes observed (foci of hyperbasophilic hepatocytes) may not have been a result of the treatment and were not related to enzyme level changes or evident liver damage (Feron *et al.*, 1975).

Genetic Toxicity

Several authors have reviewed the genotoxicity of vinyl chloride (Bartsch and Montesano, 1975; Duverger-Van Bogaert *et al.*, 1982; U.S. EPA, 1999a; 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*, 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, of 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-enhanced mammalian cell transformation *in vitro*. This strong evidence of genotoxicity of vinyl chloride suggests that its reported carcinogenicity proceeds by genotoxic mechanisms (DHS, 1990a).

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 (DHS, 1990a). A summary of the mutagenicity data is given in Table 3.

The formation and persistence of certain etheno DNA adducts, with known miscoding properties, can indicate potential for genotoxicity. Swenberg *et al.* (1992a) observed that in pre-weanling rats exposed to 600 ppm vinyl chloride (four hours per day for five days) three DNA adducts, present in the tissues at relatively low concentrations, were poorly recognized by DNA repair enzymes and had potential to accumulate upon chronic exposure. The adducts, epsilon G, epsilon dC, and epsilon dA, were present in the liver at three- to eight-fold greater concentrations than in the lung and kidney.

Swenberg *et al.* (1999) exposed rats to 0, 10, 100, or 1,100 ppm vinyl chloride for five days or four weeks. Exposure to 10 ppm for five days caused two- to three-fold increases in epsilon G over controls, and the four-week exposure at this level caused a 5-fold increase. The authors observed a 25-fold increase in epsilon G from exposure at 100 ppm at four weeks and a 42-fold increase at 1,100 pm for the same exposure period. The target cells for vinyl chloride carcinogenesis, the non-parenchymal cells, have a much lower expression of etheno DNA adduct repair enzyme.

Swenberg and associates (1992) presented an environmental case study review in which the authors describe the age-related differences in DNA adduct formation due to vinyl chloride exposure in the rat. Following exposure via inhalation to 600 ppm vinyl chloride (four hours per day for five days) rat pups yielded four times the amount of DNA adducts 3-ethenoguanine and 7-(2'oxoethyl) guanine as did adult rats. The authors suggested that the increased relative level of 3-ethenoguanine DNA adduct, which is a highly efficient mutagen causing G→A transitions, leads to a greater susceptibility of newborn rats compared with adult rats to vinyl chloride induced carcinogenesis (Swenberg *et al.*, 1992b).

Table 3. Mutagenicity of vinyl chloride

ASSAY	RESULT	COMMENT	AUTHOR(S)
Ames, *E. coli*	Increased mutation rate, several strains	Mutation rate increased with S-9	(McCann *et al.*, 1975; Bartsch and Montesano, 1975; Bartsch, 1976; Bartsch, 1976)
Yeast, *S. pombo*	Induced forward mutation	with metabolic activation	(Bartsch and Montesano, 1975; Loprieno *et al.*, 1976)
Fungi, *Neurospora*	No effect		(Drodzdowicz and Huang, 1977)
Chinese hamster ovary /HGPRT	Mutagenic	positive only with S-9	(Krahn, 1979)
Drosophila	Increase in recessive lethal mutations	30 ppm, 17 days	(Verbergt and Vogel, 1977)
Sprague-Dawley rats	Dose dependant gene mutations at 6-thioguanine locus		(Maier and Schawlder, 1988)

Table adapted from DHS (1990a)

Developmental and Reproductive Toxicity

John *et al.* (1977) tested for effects of maternally inhaled vinyl chloride on embryonic and fetal development in rodents. Pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to 500 ppm of vinyl chloride for seven hours per day during the period of major gestational organogenesis. Other groups of mice and rabbits were exposed to respective vinyl chloride concentrations of 50 and 2500 ppm. Fetotoxicity occurred in mice at 500 ppm, and the effects included increased fetal resorption, decreased fetal body weight, reduced litter size, and retarded cranial and sternebral ossification. Rat offspring showed body weight decrease at 500 ppm maternal exposure and dilated ureters at maternal exposure to 2500. No sign of maternal or developmental toxicity was observed in rabbits at either concentration (John *et al.*, 1977)

Rice (1981) described vinyl chloride as an unequivocal transplacental carcinogen for the rat. This review of transplacentally administered vinyl chloride in animals described the carcinogenic role of metabolic conversion of vinyl chloride to reactive intermediates, such as chlorooxirane, in both maternal and fetal tissues (Rice, 1981).

Maltoni (1981) exposed pregnant Sprague-Dawley rats to vinyl chloride via inhalation to 6,000 and 10,000 ppm four hour/day for days 12–18 of pregnancy. After 143 weeks, offspring showed increased incidence of nephroblastoma (3/51) and Zymbal gland cancer (5/51) following 6,000 ppm maternal exposure and Zymbal gland cancer (3/32) following 10,000 maternal exposure. Mammary gland tumors were observed in offspring (2/32) from the 10,000 ppm maternal exposure group (Maltoni *et al.*, 1981).

The Chemical Manufacturers Association (CMA) (1998) conducted a study to ascertain maternal toxicity and developmental toxicity on rats. 100 female CD rats were exposed via inhalation to 0, 10, 100, and 1,100 ppm for six hours per day during the day 6-19 gestation interval. Oral equivalent doses were 0, 9.2, 92 and 1,012 mg/kg-day. No maternal toxicity was seen at the 10 ppm level. At 100 ppm, an increase in kidney weight relative to controls at Day 20 of gestation was observed. In the fetuses, no developmental toxicity was observed at either the 100 or 1,000 ppm exposure levels. The fetuses were examined for external, visceral, and skeletal abnormalities.

Immunotoxicity

In 1979, Sharma and Gehring investigated the effects of vinyl chloride exposure on the immune system of mice. Male CD-1 mice were exposed to inhalation concentrations of vinyl chloride at 0, 10, 100, or 1,000 ppm for six hour/day, 5 days/week, up to eight weeks of duration. Spleen weights were increased at the 1,000 ppm dose. Stimulation of spontaneous lymphocyte transformation was observed in mouse splenic cultures. This immune system stimulating effect was observed at 1,000 ppm after two weeks and at all levels of vinyl chloride exposure after four and eight weeks (Sharma and Gehring, 1979).

Exon (1984) reviewed the immunotoxicity of vinyl chloride. The author observed that studies in animals suggest that vinyl chloride or its metabolites may have immunostimulatory properties. For example, lymphocyte transformation studies in mice and rabbits treated with vinyl chloride showed increased stimulation of both T and B cells, in excess of levels normally induced by mitogens. Further, enlargement of thymus without accompanying splenomegaly was observed in rabbits treated with vinyl chloride (Exon, 1984).

Neurotoxicity

Viola (1970) and Viola *et al.* (1971) exposed Wistar rats to vapors of vinyl chloride for 4 hours/day, 5 days/week for 12 months. Following ten months of exposure, the authors observed that the treated animals had decreased responses to external stimuli and disturbed equilibrium. Histopathological examination showed diffuse degeneration of both gray and white matter as well as cerebellar degeneration. Peripheral nerve endings were surrounded with fibrous tissue (Viola, 1970; Viola *et al.*, 1971; ATSDR, 1992).

Chronic Toxicity

Feron *et al.* (1981) conducted a lifetime oral toxicity study of vinyl chloride in Wistar rats. The authors used five groups of rats, each group consisting of 60-80 males and 60-80 females. Vinyl

chloride was administered by incorporating vinyl chloride-containing PVC powder into the diet or by gastric intubation of 10 percent vinyl chloride in soya bean oil. Actual vinyl chloride doses were 0, 1.7, 5.0, and 14.1 mg/kg-day via PVC powder in the diet and 300 mg/kg-day via gastric intubation. The death rate exceeded that for controls in all vinyl chloride treated groups. Aside from cancer-related effects, which are discussed later, the authors observed shortened blood clotting times, slightly increased α-foetoprotein levels in the blood serum, liver enlargement, and increased hematopoietic activity in the spleen at 14.1 and 300 mg/kg-day.

Til *et al.*, (1991) performed a 149 week oral carcinogenicity study of vinyl chloride on Wistar rats. Four groups of animals were used, each group consisting of 50 male and 50 female rats. The methods were similar to Feron (1981), in that dosing was performed with vinyl chloride-containing PVC powder; however, the dose levels were lower and the detailed histopathological examination was restricted to the liver. The actual vinyl chloride oral exposure levels were 0, 0.014, 0.13, and 1.3 mg/kg-day. In the high dose group, along with cancer related effects described later, the authors observed hepatic cysts ("many") and moderate and severe lever cell polymorphism (Till *et al.*, 1991). Please see Table 4. The chronic non-cancer NOAEL for this study is 0.13 mg/kg-day (Till *et al.*, 1991; U.S. EPA, 1999a).

Table 4. Incidence of histopathologic changes in rats exposed orally to vinyl chloride

Observed effects		**Incidence of change**							
	Treatment group	**Males**				**Females**			
	mg/kg -day	0	0.014	0.13	1.3	0	0.014	0.13	1.3
Liver cell polymorphism									
Moderate		4	4	7	10**	14	13	8	15***
Severe		1	1	1	3	2	3	4	9***
Cysts									
Few		4	4	3	4	11	11	12	7
Many		0	0	0	0	3	4	9	24***

** P<0.01; ***P<0.001

Table adapted from Til *et al*., 1991

Carcinogenicity

Feeding Studies in Animals

Reviews of vinyl chloride carcinogenicity data from exposed laboratory animals available at the time the document "*Health Effects of Airborne Vinyl Chloride*" (DHS, 1990a) was released include those by Kalmaz and Kalmaz (1984), IARC (1979), 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; Drew *et al.*, 1983; Bi *et al.*, 1985).

As described earlier, Feron *et al.* (1981) conducted a lifespan oral toxicity study of vinyl chloride in rats. Groups of 60-80 male and 60-80 female five-week old Wistar rats were fed polyvinyl chloride powder (10 percent of diet) with or without a high vinyl chloride monomer content (0 to 4,000 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. Necrosis, centrilobular degeneration and mitochondrial damage were seen in the hepatic parenchyma of rats administered vinyl chloride. Significantly increased incidence of liver and lung angiosarcomas and hepatocellular carcinomas was observed in both male and female rats. Tumor incidence is listed in Table 5. It is possible that underreporting of tumors at all sites occurred because of the incomplete histopathologic examinations performed and the fact that only the longest-surviving high-dose animals were chosen for complete histopathologic evaluation.

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 percent 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.

The results of this study demonstrated increases in the incidence of hepatic foci or 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 which are potential precursors to tumor formation. No pathologic effects in other organ systems were attributed to vinyl chloride exposure (Til *et al.*, 1983). Histopathology of all organs was not performed on all animals; therefore, tumors not grossly observable or palpable could have been missed.

Inhalation Studies in Animals

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; Bi *et al.*, 1985). All experiments confirm the carcinogenicity of vinyl chloride, although only a few of the studies are adequate for a quantitative evaluation of carcinogenic risk. This summary will concentrate on the studies (Drew *et al.*, 1983; Maltoni *et al.*, 1984; Bi *et al.*, 1985) used by DHS (1990a) for quantitative risk assessment purposes.

Table 5. Tumor incidence in male and female Wistar rats exposed to dietary vinyl chloride (Feron *et al.*, 1981)

	Incidence[1]				
Tumor type/Sex	**Vinyl chloride (mg/kg-day)**	**0**	**1.7**	**5.0**	**14.1**
Liver angiosarcoma					
male		0/55	0/58	6/56[*2]	27/59[***]
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[***]
Lung angiosarcoma					
male		0/55	0/58	4/56[*]	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 tumors[3]					
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 as determined using the Chi-square test. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
[3]Including mammary adenomas, adenocarcinomas, and anaplastic carcinomas.

Bi *et al.* (1985) evaluated the tumorigenic potential of vinyl chloride in male Wistar rats following inhalation exposure to 0, 10, 100 or 3,000 ppm (6 hours/day, 6 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 incidence of liver angiosarcomas in the 100 and 3,000 ppm groups was significantly greater than controls ($p = 0.004$, $p < 0.001$, respectively); the incidence of lung angiosarcomas in the 3,000 ppm group was also significantly greater than controls ($p = 0.001$). This study probably underestimated the carcinogenic potential of vinyl chloride because of the less-than-lifetime exposure (Bi *et al.*, 1985).

Drew *et al.* (1983) examined 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, $B6C3F_1$ mice, Fischer 344 rats, and Golden Syrian hamsters (n = 54 for mice, n = 56 for rats and hamsters) were exposed to vinyl chloride for 6 hours/day, 5 days/week for 6, 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 exposed to 50, 100, and 200 ppm vinyl chloride, 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). $B6C3F_1$ 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. The incidence of

hemangiosarcomas was a function of the duration of exposure and age at start 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 (Drew *et al.*, 1983). Tumor incidence in vinyl chloride-exposed rats is listed in Table 6.

Table 6. Tumor incidence in 100 ppm vinyl chloride-exposed female Fisher 344 rats (Drew *et al.*, 1983)

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Liver hemangiosarcomas	control	0	1/112 (0.9)
	6	4.5	4/76 (5.3)
	12	8.9	11/55 (20.0)***
	18	13.4	13/55 (23.6)***
	24	17.9	19/55 (34.7)***
Mammary adenocarcinomas	control	0	5/112 (4.5)
	6	4.5	6/76 (7.9)
	12	8.9	11/56 (19.6)**
	18	13.4	9/55 (16.4)*
	24	17.9	5/55 (9.1)
Hepatocellular carcinomas	control	0	1/112 (0.9)
	6	4.5	3/75 (4.0)
	12	8.9	4/56 (7.1)*
	18	13.4	8/54 (14.8)***
	24	17.9	9/55 (16.4)***

[a]LDE = Lifetime Daily Exposure.
[b]Value in parentheses is percent incidence.
*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$ (Fisher's exact test)

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with vinyl chloride exposure (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. Tumor incidence in vinyl chloride-exposed hamsters is listed in Table 7.

Table 7. Tumor incidence in 200 ppm vinyl chloride-exposed female Golden Syrian hamsters (Drew *et al.*, 1983)

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Hemangiosarcomas (all sites)	control	0	0/143 (0)
	6	8.9	13/88 (14.8) ***
	12	17.9	4/52 (7.7) **
	18	26.8	2/103 (1.9)
Mammary carcinomas	control	0	0/143 (0)
	6	4.5	28/87 (32.2) ***
	12	8.9	31/52 (59.6) ***
	18	13.4	47/102 (46.1) ***
Skin carcinomas	control	0	0/133 (0)
	6	4.5	2/80 (2.5)
	12	8.9	9/47 (18.8) ***
	18	13.4	3/90 (3.3)

[a] LDE = Lifetime Daily Exposure.
[b] Value in parentheses is percent incidence.
** $p < 0.01$; *** $p < 0.001$ (Fisher's exact test)

Mice, especially the $B6C3F_1$ strain, appeared to be the species most sensitive to the carcinogenic effects of vinyl chloride (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 $B6C3F_1$ mice, exposure to vinyl chloride for six months resulted in 60-70 percent incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in $B6C3F_1$ mice was greatest when the animals were exposed early in life. Lower incidence of this tumor was 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 incidence of all tumors was observed in animals exposed later in life. Tumor incidence in vinyl chloride-exposed mice is listed in Table 8.

Table 8. Tumor incidence in 50 ppm vinyl chloride-exposed female B6C3F$_1$ and CD-1 Swiss mice (Drew *et al.*, 1983)

Strain/Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
B6C3F$_1$			
hemangiosarcomas (all sites)	control	0	4/69 (5.8)
	6	2.23	46/67 (68.7)**
	12	4.46	69/90 (76.7)**
	18	--	--
mammary carcinomas	control	0	3/69 (4.3)
	6	2.23	29/67 (43.2)**
	12	4.46	37/90 (41.1)**
	18	--	--
CD-1 Swiss			
hemangiosarcomas (all sites)	control	0	1/71 (1.4)
	6	2.23	29/67 (43.3)**
	12	4.46	30/47 (63.8)**
	18	6.69	20/45 (44.4)**
mammary carcinomas	control	0	2/71 (2.8)
	6	2.23	33/67 (49.3)**
	12	4.46	22/47 (46.8)**
	18	6.69	22/45 (48.9)**
lung carcinomas	control	0	9/71 (12.7)
	6	2.23	18/65 (27.7)*
	12	4.46	15/47 (31.9)*
	18	6.69	11/45 (24.4)

[a]LDE = Lifetime Daily Exposure.
[b]Value in parentheses is percent incidence.
*$p < 0.05$;
**$p < 0.001$ (Fisher's exact test)

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. 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). Details of the experimental protocol for the BT experiments are provided in Table 9.

Table 9. Protocol for vinyl chloride inhalation studies by Maltoni *et al.* (1984)

Experiment number	Dose (ppm)	Exposure duration (weeks)[1]	Species/strain	Starting exposure age (weeks)	animals/exposure concentration[2]
BT1	0, 50, 250, 500, 2500, 6000, 10000	52	rat/SD	13	30 M, 30 F
BT2	1, 100, 150, 200	52	rat/SD	13	60 M, 60 F (85 M, 85 F)
BT3	0, 50, 250, 500, 2500, 6000, 10000	17	rat/SD	12	30 M, 30 F
BT4	0, 50, 250, 500, 2500, 6000, 10000	30	mouse/ Swiss	11	30 M, 30 F (80 M, 70 F)
BT5	6000, 10000	1	rat/SD	19 (fetus)	30 F 13-29 M, F (no controls)
BT6	30000	52	rat/SD	17	30 M, 30 F (no controls)
BT7	0, 50, 250, 500, 2500, 6000, 10000	52	rat/ Wistar	11	30 M (40 M)
BT8	0, 50, 250, 500, 2000, 6000, 10000	30	hamster/Syrian Golden	11	30 M (62 M)
BT9	0, 50	52	rat/SD	13	150 M, 150 F (50 M, 50 F)
BT14	6000, 10000	5	rat/SD	21 (parents)	6 F (no controls)
		5		1day (offspring)	21-22 M, F (no controls)
BT15	0, 1, 5, 10, 25	52	rat/SD	13	60 M, 60 F
BT4001	0, 2500	76	rat/SD	13	54 F (60 F)
		69		1 day	68 M, 68 F (158 M, 149F)
BT4006	0, 2500	15	rat/SD	1 day	60 M, 60 F

[1]Exposures were for 4 hours/day, 5 days/week.

[2]Number in parentheses = number of control animals when not equal to number of animals in experimental groups.

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 in all of the species tested. A summary of these tumors is provided in Table 10 (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. A summary of the lowest concentrations at which a statistically significant excess of tumors was observed is given in Table 11. 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).

Table 10. Tumors associated with inhalation exposure to vinyl chloride in rats, mice, and hamsters in the BT experiments (Maltoni *et al.*, 1984)

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	+	(+)	+

\+ Tumor incidence was statistically significant ($p < 0.05$) by the Fisher exact test.
(+) Association was not statistically significant, but was considered biologically significant.

Table 11. Lowest concentration of vinyl chloride at which a significant incidence of tumors ($p < 0.05$) was reported by Maltoni *et al.* (1984) in Sprague-Dawley rats

Tumor type	Vinyl chloride concentration (ppm)
forestomach papilloma	30,000 (male, female)
Zymbal gland carcinoma	10,000 (male, female)
neuroblastoma	10,000 (female)
nephroblastoma	250 (female)
liver angiosarcoma	200 (male); 25 (female)
mammary adenocarcinoma	1 (female)

EXPERIMENT BT1

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 for up to 135 weeks. Survival of both males and females decreased in a dose-related manner, especially at concentrations above 500 ppm. Vinyl chloride was 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 12 (Maltoni *et al.*, 1984). In addition to liver angiosarcomas, vinyl chloride (at concentrations above 2,500 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.

Table 12. Incidence of liver angiosarcomas (LAS) in male and female Sprague-Dawley rats exposed for 52 weeks to vinyl chloride (Maltoni *et al.*, 1984)

Study	Exposure level (ppm)	LAS incidence[1]		Corrected LAS incidence[2]	
		male	female	male	female
BT1	0	0/30	0/30	0/22	0/29
	50	0/30	1/30	0/26	1/29
	250	1/30	2/30	1/28	2/26
	500	0/30	6/30	0/22	6/28
	2,500	6/30	7/30	6/26	7/24
	6,000	3/30	10/30	3/17	10/25
	10,000	3/30	4/30	3/21	4/25
BT2	0*	0/85	0/100	0/61	0/68
	100	0/60	1/60	0/37	1/43
	150	1/60	5/60	1/36	5/46
	200	7/60	5/60	7/42	5/44
BT6	30,000	5/30	13/30	5/22	13/24
BT9	0	0/50	0/50	0/29	0/38
	50	1/150	12/150	2/70	12/110
BT15	0	0/60	0/60	0/25	0/44
	1	0/60	0/60	0/48	0/55
	5	0/60	0/60	0/43	0/47
	10	0/60	1/60	0/42	1/46
	25	1/60	4/60	1/41	4/40
LAS incidence in historical controls		1/1179	2/1202	1/364	2/541

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

Experiment BT 15

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.

Table 13. 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 (mice)		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).

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 percent 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 13.

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 13 (data from Maltoni *et al.*, 1984).

Toxicological Effects in Human Studies

In their review of risk to humans from occupational exposure to vinyl chloride, Purchase and colleagues (1987) stated that until the 1960s, vinyl chloride was regarded as a chemical with low human toxicity and that the main human risk concerns were related to the compound's narcotic effect. The authors mentioned several reports of employees becoming dizzy and losing consciousness from vinyl chloride exposure (Purchase *et al.*, 1987).

Acute Toxicity

Pransky (1995), in his discussion on occupationally related hepatic disease, restated animal observations that describe acute hepatotoxicity arising from the metabolic conversion of vinyl chloride to 2-chloroethylene oxide and subsequent spontaneous rearrangement to chloroacetaldehyde, which binds to protein (Pransky, 1995). Several human deaths following very high exposure (concentrations unreported) to vinyl chloride by inhalation have been reported. Autopsies revealed congestion of the liver, spleen, and kidneys. Suciu *et al.* (1975) reported that workers exposed to vinyl chloride (levels not given) experience euphoria, intoxication, and narcosis. They also reported generalized transient contact dermatitis after dermal exposure (Suciu *et al.*, 1975; DHS, 1990a).

Subchronic Toxicity

Data on subchronic human exposure to vinyl chloride could not be located.

Genetic Toxicity

As mentioned earlier, genetic toxicity has been demonstrated in animals exposed to vinyl chloride. Vinyl chloride is also genotoxic to humans although fewer studies exist and dose levels and duration of exposure are not well known.

In his review of reproductive toxicology of occupational exposures to vinyl chloride, Zenz (1994) related that several types of chromosomal aberrations have been observed following occupational exposure to vinyl chloride. Significant human genotoxic events were elevated chromosomal aberrations and incidence of sister chromatid exchanges.

Awara *et al.* (1998) studied the effects of different lengths of exposure on three groups of plastic industry workers using the single-cell gel electrophoresis technique. Levels of DNA damage were assessed by both the extent of DNA migration and numbers of DNA damaged spots in the peripheral blood lymphocytes from 32 plastics workers grouped according to length of exposure to the vinyl chloride monomer. Workers were apportioned into three groups, (1) 0.5-2 years, (2) 2-5 years, and (3) 5-10 years exposure. The authors observed increasing genetic damage corresponding to increased durations of exposure (Awara *et al.*, 1998).

Developmental and Reproductive Toxicity

As with the animal case, several studies relate human exposure to vinyl chloride with reproductive toxicity.

Savitz *et al.* (1994), in their review article on paternal exposure and spontaneous abortion, describe a link between occupational exposure to vinyl chloride and elevation of risk of spontaneous abortion, with a risk ratio of 1.8 (Savitz *et al.*, 1994).

Zentz (1994) listed several additional male reproductive effects due to occupational exposure to vinyl chloride, including impotence, loss of libido, and depressed levels of testosterone. Female reproductive effects include increased incidence of preeclampsia in pregnant workers exposed to vinyl chloride. The author further stated that several studies reported increases in fetal death, birth defects, and congenital malformations in populations of workers exposed to vinyl chloride and in cities with polyvinyl chloride manufacturing industries (Zenz, 1994).

Immunotoxicity

Exon (1984) reviewed the immunotoxicity of vinyl chloride. Among the toxic effects in humans associated with occupational exposure to vinyl chloride, several immunotoxic effects were noted. The author described circulating immune complexes in vinyl chloride workers, the frequency of which is related to the severity of the clinical signs of the intoxication. Aggregates of immune complexes have been observed from skin, muscle, and pulmonary tissue samples biopsied from vinyl chloride workers. Also observed were hypergammaglobulinemia, cryoglobulinemia, cryogibrinogenemia, and a deficiency of the C3 component of the complement in serum. The above observations, when taken together, suggest an autoimmune or immune complex disease (Exon, 1984). The author concludes that prolonged exposure to vinyl chloride or its metabolic products may result in hyperactive humoral immune responses and appearance of circulating immune complexes (Exon, 1984).

Neurotoxicity

Before the 1960s, vinyl chloride was regarded as a chemical with low human toxicity and earliest human risk concerns regarding exposure to vinyl chloride were related to the compound's acute narcotic effect (Purchase *et al.*, 1987; Binns, 1979).

Several reports exist of neurological symptoms among employees of dizziness, lightheadedness, and loss of consciousness as well as dulling of vision and hearing, drowsiness, headache, memory loss, euphoria, nervousness, and numbness or tingling in toes from exposure to vinyl chloride (Bahlman *et al.*, 1979; Purchase *et al.*, 1987).

Chronic Toxicity

U.S. EPA (1985) observed that several investigators have reported impaired liver function from workers chronically exposed to vinyl chloride. U.S. EPA further described another well-documented effect from chronic vinyl chloride, which is acro-osteolysis, which includes lesions in the distal phalanges of the hands and feet, and scleroderma-like skin lesions.

In his review of human health effects from occupational exposure to vinyl chloride, Binns (1979) described several toxic effects, which follow:

- Acro-osteolysis. A rare syndrome seen primarily in workers engaged in hand-cleaning of large vessels used to polymerize vinyl chloride. The syndrome has three main components:
    1. Raynaud's phenomenon of the fingers and toes, including feeling of tingling and numbness.
    2. Skin changes resembling scleroderma, usually on backs of hands or forearms.
    3. Bone changes on terminal phalanges, including bony changes and growths and foreshortened spatulate appearance of affected digits.
- Hepatic fibrosis. Liver fibrosis of a non-cirrhotic type, often associated with splenomegaly and portal hypertension, the latter factors being most frequent in workers with longer exposures.
- Liver angiosarcoma. A rare, malignant tumor of the liver.
- Tumors of other sites.
- Pulmonary effects. These effects include breathlessness, focal alveolar wall thickening, granuloma formation and fibrotic changes (Binns, 1979).

Coultas and Samet (1992) reviewed epidemiological associations of occupation and lung cancer. For vinyl chloride, the authors reviewed several studies and concluded that the association between occupational exposure to vinyl chloride and lung cancer is very weak. One study, however, Waxweiler *et al.* (1981) determined that occupational exposure to polyvinyl chloride dust as the most likely cause of lung cancer mortality among 4,806 men employed at a synthetic plastics plant from 1942 through 1973 (Coultas and Samet, 1992).

More recently, a cohort study of male employees at a large chemical production and research facility. The authors found a "suggestive" association between liver and biliary cancer based on presumed exposure to vinyl chloride monomer (Bond *et al.*, 1990).

Carcinogenicity

Human Studies

U.S. EPA (1999b) observed that exposure to vinyl chloride via inhalation has been shown to increase the risk of cancer of the liver. Additionally, there is suggestive evidence for cancer of the brain, lung, and digestive tract in humans.

In 1974, Creech and Johnson described three cases of angiosarcoma of the liver (LAS) among workers at the B.F. Goodrich Tire and Rubber Company 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 15 epidemiologic studies relating vinyl chloride exposure to the incidence of various cancers had been completed. A summary of the data from these earlier studies (published from 1974-1984) is provided in Table 14.

The epidemiologic studies also demonstrate a strong and consistent association between vinyl chloride exposure and primary cancer of the liver. All of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMRs). 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 included in Table 14 indicate that the SMRs of exposed workers were elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time.

Table 14: Summary of epidemiologic data for occupational exposure to vinyl chloride

STUDY	Place	Cohort	Deaths (%)	Exposure in years	SMR				
					All Sites	Liver (LAS)	Brain	Lung	Lymphoma
(Tabershaw and Gaffey W, 1974)[1]	U.S.	8,384	352 (4.7)	> 1 10.2%>20 yrs	110	94[3] (6)	155[4]	112	106
(Duck *et al*., 1975)	U.K.	2,122	152 (7.2)	> 0	96	93[3] (0)	--	103	--
(Nicholson *et al*., 1975)	U.S.	257	24 (9.3)	> 5	231	- (3)	--	--	--
(Ott *et al*., 1975)[2]	U.S.	594	79 (13.3)	> 0	81	- (0)	--	77	--
(Byren *et al*., 1976)	Sweden	771	58 (75)	> 0	--	413[a] (2)	612[a]	168	--
(Waxweiler *et al*., 1976)	U.S.	1,294	136 (10.5)	> 5 (f/u > 10 yrs)	149[a]	1,155[b] (11)	329[a5]	156	159
				> 5 (f/u > 15 yrs)	189[b]	1,606[b] -	498[a]	194[a]	176
(Fox and Collier, 1977)	U.K.	7,717	409 (5.3)	> 0 8% > 20 yrs	90.7	1,408[a] (2)	54.6	89.8	90.9
EEH (1975)[1]	U.S.	10,173	707 (6.9)	> 1 19.3%>20 yrs	104	75[3] (5)	203[a]	107	112
(Buffler *et al*., 1979)	Texas	464	28 (6.0)	> 0	138	- (0)	--	208[a]	--
(Bertazzi *et al*., 1979)	Italy	4,777	62 (1.3)	> 0.5	97	800[a] (3)	125	81	133
(Masuda, 1979)	Japan	304	26 (8.5)	> 1	138	500[a] (0)	--	125	--

Table 14: Summary of epidemiologic data for occupational exposure to vinyl chloride (Continued)

STUDY	Place	Cohort	Deaths (%)	Exposure in years	SMR				
(Weber *et al.*, 1981)	Germany	7,021 production	414 (5.9)	> 0	112	1,523[b] -	162	--	214[a]
		4,007 processing	360 (9)	> 0	85	434[a] -	535[a]	--	34
		4,910 unexposed	417 (8.5)	n/a	83	401[a] -	184	--	77
(Cooper, 1981)[1]	U.S.	10,173	707 (6.9)	> 1	104	75[3] (8)	203[a]	107	112
(Heldaas *et al.*, 1984)	Norway	454	50 (11)	> 1	114	- (1)	--	180	--
					Relative Risk				
(Theriault and Allard, 1981)	Canada	451 exposed	59 (2.6)	> 5	1.48	6.25[a] (10)	--	.36	--
		871 unexposed	233 (26.8)	n/a					
(Jones *et al.*, 1988)	U.K.	5,498	780	> 1	--	560 (360)	--	--	--
(Wu *et al.*, 1989)	U.S.	3,635	843	> 1	--	333	145	115	--
(Pirastu *et al.* 1990)	Italy	n/a	253[6]	> 1	--	--	--	--	--
(Simonanto *et al.* 1991)	Italy, Norway, Sweden, and U.K.	10,981	1,438	> 1	104	286	107	97	--
(Wong *et al.* 1991)	U.S.	10,173	1,536	> 1	--	641	180	--	--
(CMA, 1999)	U.S.	10,109	1,569	> 1	--	359	142	--	--

LAS = angiosarcoma of the liver; f/u = follow-up
[1]The studies of Cooper and EEH are reanalysis of the Tabershaw and Gaffey cohort
[2]SMR subjects also in the Tabershaw and Gaffey cohort
[3]SMR is for the "digestive system cancer", not liver cancer
[4]SMR is for "other and unspecified cancer", 40 percent of which were brain cancer
[5]SMR is for cancer of CNS, not brain
[6]14 primary liver cancers, including 7 angiosarcomas of the liver
[a]$p < 0.05$
[b]$p < 0.01$

The potential association of occupational exposure to vinyl chloride with cancers other than liver was an area of uncertainty, and several epidemiological investigations followed.

Jones *et al.* (1988) performed a mortality study of vinyl chloride monomer workers employed in the United Kingdom from 1940-1974. A total number of 5,498 males were traced and 780 deaths were recorded. The authors found an overall statistically significant excess of mortality from nonsecondary liver cancer (eleven cases observed while 1.94 expected). Seven of the liver cancers were due to liver angiosarcoma, and each of these men was an autoclave worker. These

men had the highest exposure to vinyl chloride monomer, vividly demonstrating the association between vinyl chloride monomer exposure and increased risk of primary liver cancer. Except for one new cancer, no increased risk of cancer to lung, brain, or other sites could be associated to vinyl chloride exposure by the authors.

Wu and coworkers (1989) performed a retrospective cohort mortality study on 4,835 white men who worked at a polyvinyl chloride polymerization plant, of whom 3,635 had exposure to vinyl chloride monomer (the VCM subcohort). Data were collected between 1942 and 1973. The authors observed 18 deaths for liver cancer versus six expected for the whole cohort (SMR = 300 with a 90 percent confidence interval of 196-449). Twelve of the 18 liver cancers within the whole cohort were diagnosed as angiosarcoma. For the VCM subcohort, the authors observed 14 deaths versus four expected (SMR = 350 with a 90 percent confidence interval of 202-521).

Pirastu and colleagues (1990) performed an epidemiological study to examine the causes of 253 deaths among seven vinyl chloride/polyvinyl chloride workers in Italy. The study focused on mortality from liver disease from vinyl chloride exposure to the workers. The authors observed seven cases of angiosarcoma and two cases of hepatocellular carcinoma from among 14 cases of primary liver cancer. The authors concluded that vinyl chloride monomer exposure may have a broad carcinogenic action on the liver, leading to both angiosarcoma and non-angiosarcoma neoplasia.

Simonato and collaborators (1991) studied the incidence of cancer in vinyl chloride workers from a large European multicentric cohort study coordinated by the International Agency for Research on Cancer. The authors investigated the dose-response relationship between liver cancer and exposure to vinyl chloride as well as assessing cancer risk for sites other than the liver. They observed that 24 deaths related to liver cancer were nearly 3-fold higher than the expected value of 8.4 yielding an SMR of 286 with a 95 percent confidence interval of 186-425. The liver cancer incidence was clearly related to the time since first exposure, duration of exposure, and quantity of exposure. Lung cancer was not in excess of expected values and brain cancer and lymphoma were apparently unrelated to exposure variables.

Wong *et al.*. (1991) evaluated a cohort of 10,173 men who worked at least one year in one of 37 vinyl chloride/polyvinyl chloride plants in the United States from 1942-1982. The observed mortality, by cause, was compared to expected and analyzed based upon exposure, latency, age at first exposure, year of first exposure, and types of processes worked. In addition to a clear excess in deaths due to liver angiosarcoma, the authors observed significant excess deaths in cancer of the liver and biliary tract (SMR = 641), cancer of the brain and other nervous system (SMR = 180), and emphysema/chronic obstructive pulmonary disease (SMR = 179).

The above cohort of Wong *et al.* (1991) was re-evaluated by CMA (1999) whose authors refined the cohort by (1) removing duplicate inclusions and ineligible inclusions, (2) restoring members of the cohort previously lost in the follow-up process, (3) revising referent population based on regional mortality rates, and (4) increasing the numbers of categories of death that could be evaluated from 61 to 92. The author's observations and conclusions upheld the strong occupational association of vinyl chloride exposure to increased risk of death from cancer of the liver and biliary tract. Additionally, associations were made for cancer of the brain and connective and soft tissue. The authors noted that excess brain cancer was seen in men of older age at employment, and may be due to exposure to a different carcinogenic chemical at an earlier age. They also stated that some of the connective and soft tissue cancers may have been misdiagnosed or misreported angiosarcomas of the liver (a form of soft tissue sarcoma).

Doll (1988) reviewed the epidemiological literature regarding the effects of human occupational exposure to vinyl chloride. The author selected four epidemiological studies that fulfilled his criteria of providing substantial numbers of observations more than 25 years following first exposure and over a sufficiently long period of time that more than ten percent of the workers would have been expected to die. The author concluded that (1) men occupationally exposed to

vinyl chloride have experienced a specific hazard of liver angiosarcoma, and (2) there was no positive evidence of other cancers or nonmalignant hazards.

The potential association between vinyl chloride exposure and increased risk for other cancers is not as clear as that for liver cancer. The evidence associating exposure to vinyl chloride with increased mortality ratios for brain cancer, lung cancer, and lymphoma is more suggestive than conclusive (DHS, 1990a; U.S. EPA, 1999c).

DOSE-RESPONSE ASSESSMENT

Noncancer Effects

Of the studies conducted in experimental animals, the one most relevant for the purpose of calculating a PHG for noncancer effects in drinking water is that of Til *et al.* (1991). In this study, which is described earlier in this report, the authors incorporated vinyl chloride monomer-containing polyvinyl chloride powder into the diets of Wistar rats at actual exposure levels of 0.014, 0.13, and 1.3 mg/kg-day for 149 weeks. The authors found both neoplastic and non-neoplastic changes in the livers of both male and female rats at the 1.3 mg/kg-day dose. The noncancer effects were "many" hepatic cysts in female rats and moderate-to-severe liver cell polymorphism in male rats. Accordingly, the oral non-cancer lowest-observed-adverse-effect-level (LOAEL) for this study was 1.3 mg/kg-day and the NOAEL was 0.13 mg/kg-day vinyl chloride (Till *et al.*, 1991; U.S. EPA, 1999a).

Carcinogenic Effects

Estimation of Cancer Potency

Cancer potency or cancer potency factor (CPF) is a slope derived from a mathematical function used to extrapolate the probability of incidence of cancer from a bioassay in animals using high doses to that expected to be observed a the low doses which are likely to be found in chronic human exposure. The mathematical model, such as the Linearized Multi-Stage (LMS) model, can be used in quantitative carcinogenic risk assessments in which the risk is assumed to be proportional to the exposure to the chemical agent at very low doses. Risk is estimated from q_1*, the upper 95 percent confidence limit on the cancer potency slope calculated by the LMS model.

Estimation of multipathway exposure

Estimates of relative percentages of human exposure (ingestion, inhalation, and dermal) to vinyl chloride were estimated using the CalTOX™ model (DTSC, 1994). The model results indicated that for vinyl chloride exposure, humans are exposed to 5.1 liter-equivalents per day by using water for such purposes as bathing and showering. For this calculation, we assumed drinking water consumption of 2 L/day and that 40 percent of inhaled vinyl chloride is absorbed into the bloodstream (Krajewski, *et al.*, 1980).

Basis for Cancer Potency

Animal, inhalation. Three sets of animal cancer bioassays (Drew *et al.*, 1983; Maltoni *et al.*, 1984; Bi *et al.*, 1985) were considered by DHS (1990a) to provide adequate data for quantitative risk assessment purposes. The Maltoni *et al.* experiments together provide an unusually large set of data on cancer incidence in both male and female rats over a large range of exposures at many concentrations - altogether 15 groups besides 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 for two or three groups in addition to controls, while the concentration remained fixed for each species. The Bi *et al.* experiments provide incidence data on male rats for three doses plus controls. OEHHA selected the results from Drew *et al.* (1983) as the most appropriate study upon which to base the calculation for the PHG calculation.

Table 15 gives unit risk estimates calculated by using the linearized multistage procedure 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 15 include those instances in which an adequate fit 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.

Table 15. Risks of carcinogenicity from vinyl chloride exposure via inhalation estimated from rodent data

Experiment	Strain/species, sex	Tumor	Rodent q_1^* (10^{-5} ppb^{-1})	Human[a] q_1^* (10^{-5} ppb^{-1})
Maltoni *et al.*, (1984) BT-1,2 (≤ 500 ppm)				
	SD/rat, female	LAS	1.9	4.9
	SD/rat, female	mammary	1.4	3.7
BT-9, 15	SD/rat, female	LAS	6.7	18.0
	SD/rat, male	LAS	2.5	6.5
Bi *et al.* (1985)	Wi/rat, male	LAS	5.0	13.0
	Wi/rat, male	lung angiosarcoma	1.7	4.5
Drew *et al.* (1983)	F344/rat, female	LAS	3.2	8.4
	F344/rat, female	hepatocellular carcinoma	1.7	4.4
	F344/rat, female	mammary	1.6	4.2
	Sw/mouse, female	lung	6.9	20.0

[a] Determined by multiplying by the scaling factor on rodent dose.
SD = Sprague-Dawley; Wi = Wistar; F344 = Fischer 344; Sw = Swiss; LAS = liver angiosarcoma.

The results of Table 15 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 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 1×10^{-4}) were about the same as the highest results in rats. None of these analyses met the stringent criteria for goodness of fit of the maximum likelihood estimate (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) inhalation 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} ppb^{-1} respectively, compared to 1.9×10^{-5} ppb^{-1} when combined. Also, BT-9 and BT-15 individually yielded values of 6.9×10^{-5} and 1×10^{-4} ppb^{-1}, compared to 6.7×10^{-5} ppb^{-1} 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 percent 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.

Uncertainties in estimates of inhalation 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.

Inhalation cancer risk estimates for vinyl chloride derived from human and animal data provided the range of 95 percent UCLs on cancer unit risk for humans of 2.5×10^{-5} to 2×10^{-4} ppb^{-1}. 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.

Female Swiss mice were the most sensitive sex and species in the inhalation study by Drew *et al.* (1983). The authors observed lung carcinoma. Cancer potency estimates were made by fitting the linearized multistage model to the experimental data to establish the lower 95 percent confidence bound on the dose associated with a ten percent increased risk of cancer. (Please see Table 15.) The resulting inhalation cancer potency factor was 0.27 $(mg/kg\text{-}day)^{-1}$. Accordingly, the inhalation slope factor, based on lung carcinoma in mice, is 0.27 $(mg/kg\text{-}day)^{-1}$.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncancer toxicants must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets, and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

The calculation of the public health-protective concentration (C, in mg/L) for vinyl chloride follows a general formula for noncancer endpoints:

$$C = \frac{NOAEL \times RSC \times BW}{UF \times L/day} = PHG \text{ in mg/L}$$

where,

NOAEL = no-observed-adverse-effect-level (mg/kg-day),

RSC = relative source contribution of 20 percent (0.20), the default value used in absence of appropriate information on other sources,

BW = body weight for an adult male (70 kg),

UF = uncertainty factor of 100 (10-fold for inter-species variation and 10-fold for human variability), and

L/day = volume of drinking water consumed by an adult (7.1 L/day). The default is 2 L/d, however the higher value accounts for additional inhalation and dermal exposure of 5.1 Leq/day from various uses of drinking water, such as bathing.

Therefore,

$$C = \frac{0.13 \text{ mg/kg-day} \times 0.20 \times 70 \text{ kg}}{100 \times 7.1 \text{ L/day}}$$

= 0.003 mg/L, which is equivalent to 3 µg/L and 3 ppb.

The health protective concentration for vinyl chloride in water, based on noncancer effects, is therefore 3 µg/L (3 ppb).

The principal study selected for the derivation of the noncancer PHG for vinyl chloride was that of Til *et al.* (1991). In this study, described earlier, liver cell polymorphism was observed in male and female rats at the 1.3 mg/kg-day level, as well as hepatic cysts at the same level (the LOAEL). These effects were not observed at the 0.13 mg/kg-day level, which was used as the NOAEL for the above calculation.

Carcinogenic Effects

$$C = \frac{R \times BW}{q_1^* \text{ or CPF} \times L/day} = \text{PHG in mg/L}$$

$$C \text{ (multipathway)} = \frac{R \times BW}{(\text{Potency factor}_{(inhal)}) \times (\Sigma \text{ Leq/d})}$$

where,

BW = body weight for an adult male (70 kg),

R = de minimis level for lifetime excess individual cancer risk (a default of 10^{-6}),

q_1^* or CPF = q_1^* is the upper 95 percent confidence limit on the cancer potency slope calculated by the LMS model. The q_1^* (or cancer potency factor) for the inhalation route is 0.27 $(mg/kg\text{-}day)^{-1}$, and

L/day = volume of drinking water consumed by an adult. The default is 2 L/d. For multipathway determination of PHG, L_{eqs}/day are summed for each appropriate pathway. OEHHA determined via the CalTOX model that the inhalation and dermal fractions are 54 percent and 18 percent. The respective liter equivalents are 2, 1.54 and 1.29 for ingestion, inhalation (corrected for absorption) and dermal pathways.

Therefore,

$$C = \frac{70 \times (1 \times 10^{-6})}{(0.27)(2 + 1.54 + 1.29 \text{ L}_{eq}/\text{day})}$$

= 0.053 (0.05 rounded) µg/L = 0.05 ppb.

The health protective concentration for vinyl chloride based on its carcinogenicity uses the inhalation cancer slope factor of 0.27 $(mg/kg\text{-}day)^{-1}$ from the animal data in Drew *et al.* (1983) which was adopted by the California Department of Health Services (1990a) following a comprehensive review of the literature and approval by the Scientific Review Panel. The value was derived using the linearized multistage procedure. The PHG for vinyl chloride in drinking water using this potency is therefore established as 0.05 ppb.

DHS (1990a) used the pharmacokinetic analysis of Gehring et al. (1978) to estimate the effective target dose of vinyl chloride in rodents. In this study, the formation of DNA adducts in the liver of rats exposed to vinyl chloride was shown to be well approximated by a Michaelis-Menten kinetic expression with k_m = 336 ppb.

RISK CHARACTERIZATION

OEHHA has based the PHG value on cancer endpoints (0.05 ppb) as opposed to the non-cancer endpoints (3.6 ppb) because the former is a) a more health-conservative value and, b) is based on potentially more severe and life-threatening health impacts.

There are some areas of uncertainty regarding the development of the PHG for vinyl chloride. As the basis of a multipathway exposure calculation, we used only the inhalation study of (Drew *et al.*, 1983). The study represents the upper value of a range of cancer potencies which were developed by DHS (1990a) and approved by the California Air Resources Board's statutory Scientific Review Panel (DHS, 1990b). DHS (1990a) used the pharmacokinetic analysis of Gehring *et al.* (1978) to estimate the effective target dose of vinyl chloride in rodents. In this study, the formation of DNA non-volatile metabolites in the liver of rats exposed to vinyl chloride was shown to be well approximated by a Michaelis-Menten kinetic expression with k_m = 336 ppb. Gehring *et al.* (1978) estimated the value 336 ppm from data on the amount of nonvolatile metabolites remaining in tissues following inhalation exposure to vinyl chloride. Following inhalation exposure, the level of adduct formation in liver protein is nearly proportional to the exposure dose over the range 1-100 ppm (Watanabe *et al.*, 1978).

From calculated time-weighted-averages of effective doses in carcinogenicity bioassays, a range of upper-bound estimates of potency was calculated. The highest estimates from the selected data sets were 20×10^{-5} $(ppb)^{-1}$ from the incidence of lung carcinomas in female Swiss mice (Drew *et al.*, 1983) and 18×10^{-5} $(ppb)^{-1}$ from the incidence of angiosarcomas of the liver in male Sprague-Dawley rats (Maltoni *et al.*, 1984). The lowest estimates from the data sets selected from rodent bioassays were 4.2×10^{-5} $(ppb)^{-1}$ from the incidence of mammary carcinomas in female Fischer 344 rats (Drew *et al.*, 1983) and 3.7×10^{-5} $(ppb)^{-1}$ from the incidence of mammary carcinomas in female Sprague-Dawley rats (Maltoni *et al.*, 1984).

There is suggestive evidence that children, especially newborn and unborn children, could be more sensitive to vinyl chloride. Swenberg et al. (1992b) found that newborn rats exposed to 4,000 and 10,000 ppm vinyl chloride produced the 3-ethenoguanine DNA adduct in the liver at a rate about four times that of adult rats. This adduct is a highly efficient mutagen, causing G => A transitions in vivo, and has a long half-life of about 32 days in the liver. Maltoni et al. (1981) observed that exposure of younger (newborn and in utero) rats resulted in the development of greater numbers of tumors throughout life than did exposure of rats starting at 12 weeks of age. Drew et al. (1983) concluded that "Exposures were most effective when started early in life." For this reason we considered it appropriate to select the more potent value from the study of Drew et al. (1983) for the risk assessment.

OEHHA has reviewed a recent draft Toxicological Review of Vinyl Chloride (U.S. EPA, 1999a). The document is labeled as "Draft-do not cite or quote"; however, since we received several comments and suggestions based upon the U.S. EPA document, we will briefly discuss it here. In general, OEHHA found it difficult to assess the quantitative analyses in the U.S. EPA draft

toxicological review due to incomplete documentation. As one example, animal potencies were not given. Because of this, and other problems, OEHHA was unable to replicate the analysis that produced the oral potency value. OEHHA has identified several concerns about the Clewell *et al.* (1985) physiologically based pharmacokinetic (PBPK) model and its use in the risk assessments. These concerns include the methods used to parameterize the model for humans, the treatment of oral uptake, the lack of statistical assessment of fit, and in general, very limited documentation. We do look forward, however, to an updated final version of this toxicological review. We will update our PHG value for vinyl chloride on a periodic basis, and we would very much like to examine and include new and verified PBPK modeling and methods such as might be found in a complete and final version of the U.S. EPA (1999a) document.

It is instructive to note that when the potency values from the U.S. EPA draft toxicological review are used to calculate a range of C values, these values are lower than the PHG value of 0.05 ppb. From the estimated carcinogenic potencies in U.S. EPA (1999a) assessment of vinyl chloride, 8.7×10^{-6} $(\mu g/m^3)^{-1}$ for inhalation and 2.4 $(mg/kg\text{-}day)^{-1}$ for ingestion, the PHG would be calculated to be approximately 0.015 ppb if vinyl chloride taken up by the dermal route is assumed to be as potent as that taken up in the lungs. The PHG would be approximately 0.009 ppb if the potency of vinyl chloride taken up dermally were as potent as that taken up in the gastrointestinal tract.

OTHER REGULATORY STANDARDS

The current U.S. EPA maximum contaminant level for vinyl chloride is 2 µg/L (U.S. EPA, 1999b). In 1989, DHS established a maximum contaminant level of 0.5 µg/L. The International Agency for Research on Cancer has listed vinyl chloride as a group 1a (known human) carcinogen (IARC, 1999). In California, vinyl chloride is listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the state to cause cancer. The following table includes selected national and state regulations and guidelines for comparison to the recommended PHG.

Table 16. Selected Guidelines And Regulations For Vinyl Chloride

Agency	Standard or Criterion	Level	Comment
DHS	MCL (maximum contaminant level)	0.5 µg/L (ppb)	1989
ATSDR	oral MRL (minimum risk level), chronic duration	$2x10^{-3}$ mg/kg-d	based on Til *et al.* 1983
NIOSH	REL (recommended exposure level)	--	recommends lowest feasible concentration for occupational exposure to carcinogens
OSHA	PEL (permissible exposure limit)	1 ppm	occupational, inhalation level
U.S. EPA	MCL (maximum contaminant level)	2 µg/L (ppb)	national drinking water standard
U.S. EPA	MCLG (max. contaminant level goal)	0 mg/L	goal, includes safety margin
U.S. EPA	Longer-term Health Advisory	46 µg/L (ppb)	adult
ACGIH	TLV-TWA (threshold limit value-time weighted average)	5 ppm	occupational inhalation
OEHHA	Proposition 65, no significant risk level	3 µg/d	the P-65 levels are set at a significant risk level of $1x10^{-5}$

Table adapted from ATSDR (1992) and NIOSH (1994)

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