Development Support Document
Final, February 13, 2009
Accessible 2013

Vinyl Chloride

CAS Registry Number: 75-01-4

Prepared by

Shannon Ethridge, M.S.

Toxicology Division

Chief Engineer's Office

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values from an acute and chronic evaluation of vinyl chloride (VC). Table 2 provides summary information on VC's chemical and physical properties.

Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentrations**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	20,000 µg/m^3(7800 ppb) **Short-term ESL for Air Permit Reviews**	**Critical effect:** mild headache and dryness of eyes and nose in humans
acute ReV (HQ = 1.0)	68,000 µg/m^3 (26,000 ppb)[a]	Same as above
$^{acute}ESL_{odor}$ [1 h]	---	Data are inadequate. See section 3.2.1 for information
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentrations**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	18 µg/m^3 (6.9 ppb)	**Critical effect:** increase in incidence of centrilobular hypertrophy in liver of female rats
chronic ReV (HQ = 1.0)	60 µg/m^3 (23 ppb)[a]	Same as Above
$^{chronic}ESL_{linear(c)}$	1.2 µg/m^3 (0.45 ppb)[a, b, c] **Long-term ESL for Air Permit Reviews**	**Cancer Endpoint:** increase in incidence of liver angiosarcoma
$^{chronic}ESL_{veg}$	---	No data found

[a] Values that may be used for evaluation of air monitoring data

[b] Unit risk factor (URF) = 8.4 x 10^{-6} per µg/m^3 (2.2 x 10^{-5} per ppb)

[c] Value is protective of early-life exposure. If children are not expected to be exposed, the higher value of 2.3 µg/m^3 (0.90 ppb) may be used

Abbreviations: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **ReV**, Reference Value; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; **$^{chronic}ESL_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effects; **$^{chronic}ESL_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effects; **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL; and **HQ**, hazard quotient

Table 2 Chemical and Physical Data – Vinyl Chloride – CASRN 75-01-4

Parameter	Value	Reference
Molecular Formula	C_2H_3Cl	Chemfinder 2004
Chemical Structure		Chemfinder 2004
Molecular Weight	62.5 g/mole	Texas Risk Reduction Program (TRRP) 2006
Physical State	Gas	TRRP 2006
Color	Colorless	USEPA 2000
Odor	Mild, sweet	USEPA 2000
CAS Registry Number	75-01-4	TRRP 2006
Synonyms	Chloroethene Chloroethylene Ethylene monochloride Monochloroethene	USEPA 2000
Solubility in water	1100 to 2760 mg/L at 25^{o}C	TRRP 2006, Chemfinder 2004
Log K_{ow} or P_{ow}	Log K_{ow} = 1.62	TRRP 2006
Vapor Pressure	2800 mm Hg at 20^{o}C	TRRP 2006
Vapor Density (air = 1)	2.2	Chemfinder 2004
Density (water = 1)	0.91	Chemfinder 2004
Melting Point	-153.7 ^{o}C	Chemfinder 2004
Boiling Point	-13.9 ^{o}C	Chemfinder 2004
Conversion Factors	1 ppm = 2.60 mg/m^3 1.0 mg/m^3 = 0.39 ppm	USEPA 2000

Chapter 2 Major Uses or Sources

VC is a man-made chemical and is one of the highest production volume chemicals in the world. It is used mainly in the production of polyvinyl chloride polymers (PVC). PVC is used to make automotive parts, packaging products, pipes, construction materials, furniture, and a variety of other products. The United States Environmental Protection Agency (USEPA) National Toxics Inventory estimated that 1650 tons (3.3 million pounds) of VC were released to the atmosphere in the contiguous United States (US) plus Puerto Rico and the Virgin Islands in 1996 (USEPA 2005). The National Toxics Inventory estimated that emissions of VC from Texas totaled 846,000 pounds in 1996. Ambient monitoring data indicate that VC is generally not detected above the method detection limit of 0.17 ppb in Texas. Higher levels may be found in the air near VC production facilities, hazardous waste sites, or municipal landfills (ATSDR 2006).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

VC is a colorless gas at room temperature. It has a mild, sweet odor and is slightly soluble in water. The main chemical and physical properties of VC are summarized in Table 2.

3.1.1.2 Essential Data and Key Studies

Numerous toxicity studies have been conducted in humans and animals after acute exposure to VC. These studies are discussed in detail in ATSDR (2006) and AEGL (2004). Baretta et al. (1969) was selected as the key study over other available human or animal studies because of the demonstration of effects below levels reported in other studies.

3.1.1.2.1 Human Studies

The primary acute effect of VC inhalation exposure in humans is central nervous system (CNS) depression (Holmberg 1984). The most commonly reported symptoms of VC-induced CNS depression include dizziness, headache, drowsiness, and/or loss of consciousness (ATSDR 2006). In one study, four to eight human volunteers were exposed by inhalation in a whole-body chamber to 59, 261, 491, or 493 ppm VC for up to 7.5 hours (h) (3.5 h of exposure, 0.5 h break, then another 3.5 h exposure) (Baretta et al. 1969). Subjective and neurological responses were measured before each subject entered the chamber, 15 minutes after they entered the chamber, and at 1 h intervals thereafter. Two out of seven subjects exposed to 491 ppm for 3.5 h and two out of four exposed to 493 ppm for 7.5 h reported mild headache and dryness of their eyes and nose. A No-Observed-Adverse-Effect Level (NOAEL) of 261 ppm (analytical) was identified for this study.

In a study conducted by Lester et al. (1963), three men and three women were exposed for five minutes, twice a day, separated by a 6 h interval, for three days to 0, 4000, 8000, 12,000, 16,000,

and 20,000 ppm VC. Volunteers were exposed via an oral-nasal mask. No effects were reported at 4000 ppm. Two volunteers reported dizziness and reeling at 12,000 ppm. One subject reported feeling “slightly heady” at 8000 ppm, did not report any effects at 4000 ppm, and reported feeling “slightly dizzy” at 0 ppm so the effects experienced by this subject at 8000 ppm are questionable as to whether they were treatment-related.

As reported in AEGL (2004), Patty et al. (1930) reported that two male volunteers exposed to 25,000 ppm VC for three minutes reported dizziness and disorientation to the space and size of surrounding objects. They also reported a burning sensation on the soles of their feet.

No clear association exists between VC exposure and developmental effects in humans. Studies have indicated an increase in some forms of developmental toxicity in members of communities near VC polymerization facilities although the studies did not demonstrate a statisically significant correlation between developmental toxicity and parental occupation or proximity to the facility (Edmonds et a. 1978, Infante 1976, Rosenman et al. 1989, Theriault et al. 1983). Several studies have examined the effects of inhalation exposure to VC on the incidence of fetal loss and birth defects and no solid associations have been found (Hatch et al. 1981, Infante et al. 1976). For a complete review see ATSDR (2006).

3.1.1.2.2 Animal Studies

The most conservative Lowest-Observed-Adverse-Effect Level (LOAEL) identified from an acute inhalation animal experiment (less than 24 h exposure) was 1500 ppm for liver effects in mice after a 2 h exposure (Taitra and Ungvary (1981) as reported in AEGL (2004)). Hehir et al. (1981) reported no clinical signs of toxicity in mice after a 1 h exposure to 5000 ppm. Acute effects in other animal species are reported to occur at much higher concentrations.

In addition, animal experiments have not demonstrated an association with VC exposure and developmental effects at doses below those that cause maternal toxicity. John et al. (1977) exposed mice to 0, 50, and 500 ppm VC by inhalation for 10 days, 7 h/day, during gestational day (GD) 6-15. Rats and rabbits were exposed to 0, 500, and 2500 ppm VC by inhalation for 10 days, 7 h/day, during GD 6-15 in rats and for 13 days, 7 h/day, during GD 6-18 in rabbits. A NOAEL was identified for mice at 50 ppm and a LOAEL at 500 ppm (delayed ossification and unfused sternebrae); however, maternal toxicity was observed at 500 ppm (including decreased maternal weight gain during pregnancy, decreased food consumption, decreased absolute liver weight, and 17% mortality). A LOAEL of 500 ppm was identified for rabbits for delayed ossification although this effect was not observed at 2500 ppm. Maternal toxicity was observed in rabbits exposed to 500 ppm (reduced food consumption during gestation), although this effect was not observed at 2500 ppm. A LOAEL of 2500 ppm was identified for rats (ureter dilation); however, this dose was associated with increased absolute liver weight and decreased food consumption during gestation in dams. The effects observed in fetuses could be secondary to maternal toxicity, and the results from this study do not demonstrate developmental toxicity.

Ungvary et al. (1978) exposed pregnant rats to 0 or 1500 ppm VC for 24 h/day during the first, second, or third week of pregnancy to determine possible teratogenic or embryotoxic effects. No significant increases in abnormalities were observed in fetuses from VC exposed mothers. There

was an increase (although not statistically significant) in the number of resorbed fetuses in the groups subjected to VC exposure during the first week of pregnancy. Maternal toxicity was reported in this group as increased relative liver weight.

Thornton et al. (2002) conducted a developmental and reproductive toxicity study in Sprague-Dawley rats and did not observe any developmental effects of VC exposure up to 1100 ppm (the highest dose tested).

Because acute human inhalation studies are available and animal experiments have not demonstrated an association with VC exposure and developmental effects at doses below those that cause maternal toxicity, the Toxicology Division (TD) chose Baretta et al. (1969) as the key study.

3.1.2 Mode-of-Action (MOA) Analysis and Dose Metric

VC is thought to depress the CNS by a solvent effect on lipids and protein components of neural membranes that disrupts signal transmission (ATSDR 2007). It is assumed that the parent chemical, rather than a metabolite, is responsible for these effects. The MOA for VC effects on the eyes and nose is most likely due to irritant effects of the parent chemical. In the key study, data on exposure concentration of the parent chemical are available. For eye and nose irritation in humans, the dose metric is exposure concentration of the parent chemical. For induction of headache, since data on other more specific dose metrics (e.g., blood concentration of parent chemical or area under blood concentration curve of parent chemical) are not available for this study, exposure concentration of the parent chemical will be used as the default dose metric. “One mechanism of action of liver toxicity including cancer in mice are thought to be the induction of peroxisome proliferation (and resulting increases in hydrogen peroxide and oxidative damage) by TCA, a metabolite of tetrachloroethylene (Odum et al., 1988 in ATSDR, 1997). However, because humans produce little TCA following tetrachloroethylene exposure, and because the peroxisome proliferation response in humans is minimal, liver hypertrophy and tumor development as it is observed in mice may not occur by the same mechanism in humans.” (ATSDR, 1997)

3.1.3 Point of Departure (POD) for the Key Study

A NOAEL of 261 ppm was identified in the Baretta et al. (1969) study based on mild headache and dryness of eyes and nose in human volunteers and will be used as the human equivalent concentration POD (POD_{HEC}).

3.1.4 Dosimetric Adjustments

3.1.4.1 Default Exposure Duration Adjustments

Since there is not sufficient evidence to show that the critical effects in the key study (mild headache and dryness of eyes and nose) are both concentration and duration dependent, and the exposure duration is greater than 1 h, no duration adjustment was conducted as recommended by the TCEQ ESL guidelines (TCEQ 2006). Therefore, the POD_{HEC} of 261 ppm is conservatively not adjusted.

3.1.5 Critical Effect and Adjustment of POD_{HEC}

The specific critical effects for the key study (Baretta et al. 1969) are mild headache and dry eyes and nose in humans following acute exposure to VC. Since these effects are considered to have a threshold (i.e., a nonlinear MOA), uncertainty factors were applied to the POD_{HEC}.

The following uncertainty factors (UFs) were applied: a UF of 10 for intraspecies variability to account for sensitive members of the population (UF_H) and a UF of 1 because the acute database is considered complete (UF_D) based on numerous studies discussed in ATSDR (2006) and AEGL (2004). The total UF = 10.

acute ReV = POD_{HEC} / (UF_H x UF_D)
acute ReV = 261 ppm / 10
acute ReV = 26 ppm (26,000 ppb) = 68 mg/m^3 (68,000 µg/m^3)

3.1.6 Health-Based Acute ReV and ^{acute}ESL

As shown in Table 3, the acute ReV is 68,000 µg/m^3 (26,000 ppb). The acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 20,000 µg/m^3 (7,800 ppb). All numbers were rounded to two significant figures at the end of all calculations.

3.1.7 Special Considerations

VC carcinogenicity is thought to occur by a mutagenic MOA via DNA adduct formation as described in Section 4.1.2. It is possible, although unlikely, that a single exposure to VC could lead to DNA adduct formation and subsequent tumor formation. While the TD does not routinely examine the possibility of an increased risk of cancer after acute exposure to a chemical, the TD thought that VC deserved special consideration because of its mutagenic MOA and the fact that the acute ReV and ^{acute} ESL are significantly higher than the $^{chronic}ESL_{linear(c)}$.

AEGL (2004) provides a detailed discussion of the possibility of an increased risk of cancer after a single exposure to VC. They estimated an air concentration that corresponds to a 1 x 10^{-5} cancer risk for a single 1-h exposure to VC of 32.1 ppm based on an analysis of liver angiosarcoma incidence in newborn rats exposed to VC for 5 weeks by inhalation (Maltoni et al. 1981). AEGL (2004) emphasized that there are considerable uncertainties in estimating cancer risk from a single exposure. The acute ReV of 26 ppm and ^{acute} ESL of 7.8 ppm are below 32.1 ppm, the estimated air concentration associated with a 1 x 10^{-5} cancer risk for a single 1-h exposure.

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Summary**
Study	Baretta et al. (1969)
Study population	4-8 healthy human volunteers
Study quality	Medium
Exposure Methods	Exposure chamber
Critical Effects	Mild headache and dryness of eyes and nose
POD (original study)	261 ppm (NOAEL)
Exposure Duration	7.5 h
POD_{ADJ}	261 ppm (no duration adjustment)
POD_{HEC}	261 ppm
Total UFs	10
Interspecies UF	Not applicable
Intraspecies UF	10
LOAEL UF	Not applicable
Incomplete Database UF	1
Database Quality	High
Acute ReV [1 h] (HQ = 1)	**68,000 µg/m^3 (26,000 ppb)**
^{Acute} ESL [1 h] (HQ = 0.3)	**20,000 µg/m^3 (7800 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

VC has a sweet, chloroform-like odor with 50% detection odor thresholds reported from 260 ppm to 3000 ppm (Van Gemert 1977, Amoore and Hautula 1983). Since these sources are not accepted odor reference sources listed in the TCEQ ESL guidelines (TCEQ 2006) and other acceptable odor references were not identified, the TD did not develop an $^{acute}ESL_{odor}$ value.

3.2.2 Vegetation Effects

No acute vegetative studies were identified for VC.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

- acute ReV = 68,000 µg/m^3 (26,000 ppb)
- ^{acute}ESL = 20,000 µg/m^3 (7,800 ppb)

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 20,000 µg/m^3 (7800 ppm) (Table 1). The acute ReV of 68,000 µg/m^3 (26,000 ppm) is the acute comparison value for the evaluation of ambient air monitoring data (Table 1). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.4 Comparison of Results

The Agency for Toxic Substances and Disease Registry (ATSDR 2006) has developed an acute inhalation minimal risk level (MRL) for VC of 500 ppb for a continuous 9-day exposure based on a NOAEL of 50 ppm for developmental effects in mice (John et al. 1977 and 1981). The TD did not use these studies in the development of the acute ReV for reasons stated in Section 3.1.1.2. California Environmental Protection Agency (CalEPA) published an acute Reference Exposure Level (REL) for VC of 72 ppm in 1999 based on a NOAEL of 261 ppm for reports of mild headaches and dryness of eyes and nose in human volunteers (Baretta et al. 1969). An Acute Exposure Guideline Level (AEGL)-1 of 250 ppm was developed based on the Baretta et al. (1969) study with a total UF of 3 (AEGL 2004). The TD ReV of 26 ppm is comparable to the values based on human data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

The physical/chemical properties of VC are summarized in Chapter 3.

4.1.1.1 Human Studies

A large number of occupational exposure studies are available in the literature and have identified a wide range of target organs that may be affected by chronic inhalation exposure to VC (see USEPA 2000 and ATSDR 2006 for reviews). The target organs include the liver, lungs, blood, immune system, cardiovascular system, skin, bones, nervous system, and reproductive organs, although the liver appears to be the most sensitive organ to VC toxicity. Characteristic hepatic lesions are produced by VC exposure and include the following characteristics: hypertrophy and hyperplasia of hepatocytes, activation and hyperplasia of sinusoidal lining cells, fibrosis of the portal tracts and the septa and intralobular perisinusoidal regions, sinusoidal dilation, and focal areas of hepatocellular degeneration (Gedigke et al. 1975, Berk et al. 1975, Falk et al. 1974, Ho et al. 1991, Jones and Smith 1982, Lilis et al. 1975, Liss et al. 1985, Marstellar et al. 1975, Popper and Thomas 1975, Suciu et al. 1975, Tamburro et al. 1984, Vihko et al. 1984). According to the TCEQ ESL guidelines (TCEQ 2006), human data are the preferred source on which to base toxicity factors; however, relevant human occupational studies do not provide accurate information on VC exposure levels and use of the data is limited. Therefore, data from an animal study were used to derive the chronic ESL for noncarcinogenic potential.

4.1.1.2 Animal Studies

Refer to Table 4 for animal studies considered in the development of the chronic ESL for noncarcinogenic potential.

4.1.1.2.1 Key Study

Thornton et al. (2002) conducted a two-generation reproductive study in Sprague-Dawley rats. F_0 (parental generation) male and female rats were exposed via inhalation to VC concentrations of 0, 10, 100, or 1100 ppm for 6 h/day for a 10-week premating period and a 3-week mating period. The F_0 generation male rats were exposed to VC until terminal euthanasia. F_0 female rats were exposed from GD 0 through GD 20 and lactation day (LD) 4 through LD 25 (for a total of approximately 19 weeks with a break for delivery of litters). Reproductive tissues, adrenal glands, brain, kidneys, liver, lungs, spleen, thymus, mammary glands, nasal tissues, and pituitary glands from F_0 rats were weighed and examined histologically. At weaning, fifteen male and fifteen female F_1 (first generation of offspring) rats/group were selected for gross and microscopic examinations. Other F_1 rats were selected to form 30 rats/sex/group and were subjected to the same treatment as the F_0 rats during the production of the F_2 generation. F_2 generation rats were subjected to gross and microscopic evaluation at weaning. The results are as follows: Absolute and relative mean liver weights were significantly increased at all exposure levels in F_0 males and in F_1 males exposed to 100 and 1000 ppm VC. Slight centrilobular hypertrophy was observed in the livers of all male and female F_0 and F_1 rats exposed to 1000 ppm VC, most male and female F_0 and F_1 rats exposed to 100 ppm VC, and in 2/30 and 6/30 female F_0 and F_1 rats exposed to 10 ppm VC.

The incidence of 6/30 in female F_1 rats exposed to 10 ppm VC was statistically significantly different from controls ($p < 0.05$ according to Fisher's Exact Test performed by ATSDR 2006). The study identified a LOAEL of 10 ppm for liver effects (centrilobular hypertrophy) in F_1 female rats. This study was selected as the key study for the development of the chronic ReV for noncarcinogenic effects because it was well-designed and it demonstrated toxic effects below the LOAELs reported in other chronic animal inhalation studies. Analytical concentrations were not reported so nominal concentrations (0, 10, 100, and 1100 ppm) were used in the analysis.

4.1.1.2.2 Supporting Studies

Bi et al. (1985) evaluated the testicular toxicity of VC in male Wistar rats. Rats were exposed by inhalation to 0, 10, 100, and 3000 ppm VC for 6 h/day, 6 days/week. Rats from each group (8, 30, 6, and 10 respectively) were sacrificed at 3, 6, 9, and 12 months. Surviving animals were sacrificed at 18 months (6 months after the termination of exposure). Body weight was recorded once per month before and after exposure. Testes, lungs, liver, heart, kidneys, spleen, and brain were examined visually and microscopically for lesions and hemorrhage in all sacrificed animals. See Table 4 for a summary of NOAELs and LOAELs reported for various endpoints. The lowest LOAEL reported in this study is 10 ppm based on increased relative liver, spleen, and heart weight at 6 months. These effects were only observed and reported for the liver and kidney in the 3000 ppm exposure group at 12 months and the kidney in the 100 ppm exposure group at 18 months. Interpretation of the organ weight data for this study is complicated because the authors did not report absolute organ weights, relative weights for groups with no significant

differences, or standard deviations. The authors only discussed the histopathology of the testicular effects in detail. The authors reported the incidence of damage of testicular tubules in the 0, 10, 100, and 3000 ppm exposure groups to be 18.9, 29.7, 36.5, and 56.0% respectively. The incidence of damage to seminiferous tubules was statistically significant in the 100 and 3000 ppm exposure groups ($p < 0.05$ and $p < 0.001$).

Sokal et al. (1980) evaluated the toxicity of VC in Wistar rats. Rats were exposed via inhalation to 0, 50, 500, or 20,000 ppm VC for 5 h/day, 5 days/week for 10 months. Body weight, appearance, and behavior were recorded weekly. Hematology and urinalysis were performed at 1, 3, 6, and 10 months. Histopathological examination of organs was conducted on rats sacrificed after 1.5, 3, 6, and 10 months of exposure. The livers of 36 rats exposed to VC for 3, 6, and 10 months and 18 controls were examined by electron microscopy. Treatment-related pathomorphological changes were observed in the liver and testes. Liver effects were observed at lower concentrations than effects in the testes. A LOAEL of 50 ppm was reported for this study based on a decrease in body weight, increased relative weight of some organs (spleen and heart), slight hematological and biochemical changes, and ultrastructural changes in hepatocytes.

Wisniewska-Knypl et al. (1980) evaluated the toxicity of VC in male Wistar rats. Rats (7-10 per group) were exposed via inhalation to 0, 50, 500, and 20,000 ppm VC for 5 h/day, 5 days/week for up to 10 months. Sacrifices were performed at 1, 3, 6, and 10 months. This experiment was designed to examine the effects of VC on the activity of cytochrome P-450 monooxygenase and the ultrastructure of the liver. A statistically significant decrease in body weight was reported at 20,000 ppm after 10 months. Relative liver weight was significantly increased at 500 and 20,000 ppm after all sacrifices. Electron microscopic examination of the liver tissue from rats exposed to 50 ppm showed hepatocellular changes characterized by proliferation of the smooth endoplasmic reticulum at 3 months (although this effect subsided by 6 months) and accumulation of lipid droplets in the cytoplasm after 10 months. Rats exposed to 500 and 20,000 ppm for 3 months exhibited hypertrophy of the smooth endoplasmic reticulum, distension of canals of rough-surfaced membranes, swelling of mitochondria, and an increased number of lipid droplets in cytoplasm. These changes persisted through the 10 months of the study and were more intensive at 20,000 ppm. A LOAEL of 50 ppm was identified in this study for the 10 month exposure period based on minor liver effects (accumulation of lipid droplets).

Torkelson et al. (1961) evaluated the toxicity of VC in rats, guinea pigs, rabbits, and dogs. Animals were exposed by inhalation to 0, 50, 100, 200, or 500 ppm VC for 1.5 to 7 h/day for 4.5 to 6 months. Growth, mortality, organ weight, and body weight were recorded for all animals. Hematology, histopathology, and urinalysis were also performed. Histopathological changes and increased liver weights were observed after repeated exposure to 500 ppm in rats. Repeated exposure to 200 ppm for 6 months resulted in increased average liver weights of rats and micropathological changes in livers of rabbits. Repeated exposure to 100 ppm 7 h/day for 6 months resulted in increased liver weight in rats. The NOAEL reported for this study is 50 ppm and the LOAEL is 100 ppm for increased relative liver weight in rats.

Table 4 Summary of Chronic Animal Inhalation Studies (13 Weeks Duration and Longer)

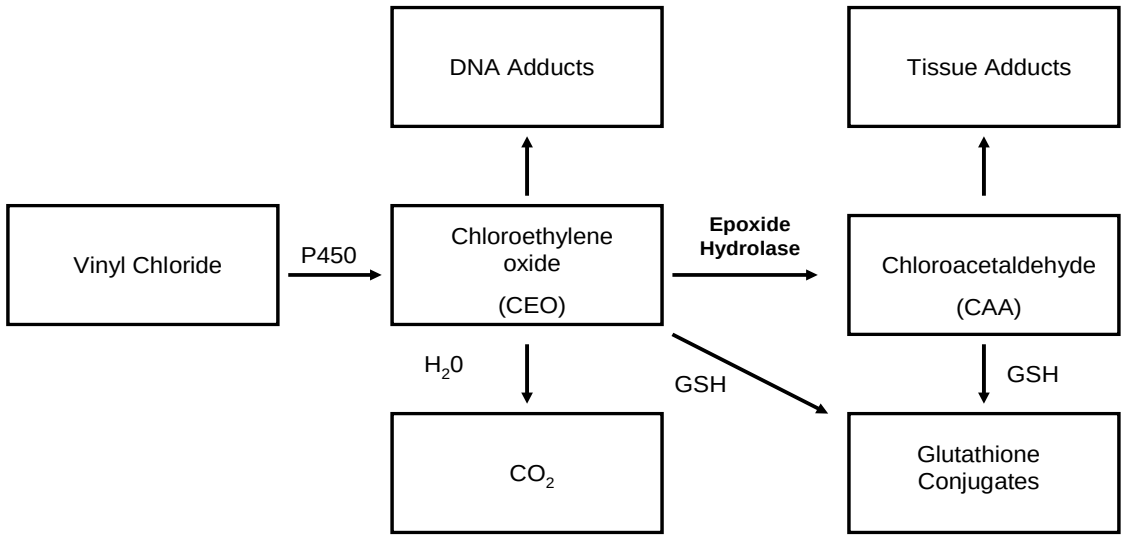
Study	Animal Strain	Exposure Duration	System	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Thornton et al. (2002) [a]	Sprague-Dawley Rats	16 weeks (males) 19 weeks (females) 2 gen, 6 h/day	Hepatic	--	10 [b] (females)	Centrilobular hypertrophy in F1 female rats
Bi et al. (1985)	Wistar Rats	6 months 6 days/week 6 h/day	Cardio	--	10	Increased relative heart rate
			Hepatic	--	10	Increased relative liver weight
			Immunological/ Lymphoreticular	--	10	Increased relative spleen weight
		3, 6 months 6 days/week 6 h/day	Reproductive	10	100	Decreased relative testes weight
		12 months 6 days/week 6 h/day	Hepatic	100	3000	Increased relative liver weight
			Renal	10	3000	Increased relative kidney weight
			Body Weight	10	100	14% decrease in body weight
			Reproductive	10	100	Degenerative seminiferous tubule changes
Sokal et al. (1980)	Wistar Rats	10 months 5 days/week 5 h/day	Hepatic	--	50	Fatty changes in liver
			Renal	50	500	Increased kidney weight
			Body Weight	--	50	10% decrease in body weight
			Immunological/ Lymphoreticular	--	50	Increased spleen weight
			Reproductive	50	500	Spermatogenic necrosis
Torkelson et al. (1961)	Rat (NS)	6 months 5 days/week 0.5-7 h/day	Hepatic	50	100	Increased relative liver weight
Wisniewska-Knypl et al. (1980)	Wistar Rats	10 months 5 days/week 5 h/day	Hepatic	--	50	Fatty changes in liver

[a] Key study used to derive the chronic ReV. ATSDR used this study to derive an intermediate-duration inhalation MRL of 0.03 ppm.

[b] POD for key study

4.1.2 MOA Analysis and Dose Metric

Evidence is strong that the liver toxicity and carcinogenicity of VC are related to the production of reactive metabolic intermediates. Upon absorption and distribution, VC is metabolized by the cytochrome P450 oxidation system in the liver (Ivanetich et al. 1977, Sabadie et al. 1980, Salmon 1976). VC is primarily metabolized to chloroethylene oxide (CEO), which is a highly reactive, short-lived epoxide intermediate. Some CEO spontaneously rearranges to form chloroacetaldehyde (CAA). Metabolites of VC are detoxified by a reaction with glutathione (GSH) catalyzed by glutathione-*S*-transferase. The GSH conjugates may then undergo hydrolysis to be excreted in urine. The metabolites may bind to macromolecules in the body; CEO is thought to bind primarily to deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and CAA is thought to bind primarily with protein. The mechanism for liver toxicity is thought to be related to the production of reactive metabolites that covalently bind to liver proteins. Animal studies indicate that metabolism of VC is a dose-dependent saturable process (ATSDR 2006). Saturation is thought to occur in humans at air concentrations above 250 ppm (Clewell et al. 2001). See Figure 1 for a description of VC metabolism.



Adapted from USEPA (2000)

Figure 1 Metabolism of Vinyl Chloride

The most appropriate pharmacokinetic dose metric for a reactive metabolite is the total amount of the metabolite generated divided by the volume of tissue in which it is produced (Anderson et al. 1987 as reported in USEPA 2000); however, only data on exposure concentration of the parent chemical are available from the key study. Since data on other more specific dose metrics (metabolite concentrations divided by the volume of tissue in which it is produced) are not available for this study, exposure concentration of the parent chemical will be used as the default dose metric.

4.1.3 POD for Key and Supporting Studies

Benchmark dose (BMD) modeling was conducted to determine the air concentration associated with the 95% upper confidence limit (UCL) for extra risk of the benchmark concentration at a 10% response ($BMCL_{10}$) from the Thornton et al. (2002) study using USEPA Benchmark Dose Software version 1.4.1b (Table 5). Modeling was performed on centrilobular hypertrophy data from F_1 female rats (Appendix A). As noted in Table 5 and Appendix A, the multistage model provided the best fit as assessed by a chi-square goodness of fit test and the Akaike Information Criteria (AIC). Therefore, the $BMCL_{10}$ value of 2.72 ppm, derived from the multistage model, was selected as the POD for calculating the chronic ReV. The $BMCL_{10}$ was chosen as the POD as opposed to the $BMCL_{05}$ because the critical effects in the key study were considered mildly adverse based on the TCEQ ESL guidelines (2006).

Table 5 Benchmark Dose Modeling Results

BMDS Model	AIC	Goodness of fit p-value	Chi-Square p-value (Scaled Residual)	BMC	BMCL10
Weibull	34.02	0.9992	0.000[c]	6.72	3.02
Probit	34.02	0.9997	0.000[c]	8.57	5.09
Log-logistic	34.02	0.9997	-0.000[c]	9.14	5.21
Gamma[a]	34.02	0.9995	0.000[c]	7.77	3.14
Multistage[b]	32.02	1.0000	-0.000[c]	6.87	2.72
Quantal Linear	35.27	0.3286	-1.126[d]	3.03	2.04

[a] Restrict power >=1

[b] Restrict betas >=0; Degree of polynomial = 2

[c] Scaled residual at estimated probability of 0.2

[d] Scaled residual at estimated probability of 0.29

4.1.4 Dosimetric Adjustments

4.1.4.1 Exposure Duration Adjustments

The POD ($BMCL_{10}$) from the Thornton et al. (2002) study was adjusted to a continuous exposure concentration:

POD_{ADJ} = POD x D/24 x F/7

POD_{ADJ} = 2.72 ppm × 6/24 × 7/7

POD_{ADJ} = 0.680 ppm

where: POD_{ADJ} = POD from an animal study, adjusted to a continuous exposure duration

POD = POD from an animal study, based on a discontinuous exposure duration

D = exposure duration, hours per day

F = exposure frequency, days per week

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

A dosimetry adjustment from an animal concentration to a human equivalent concentration (POD_{HEC}) was performed for VC, which is a vapor producing remote effects. The measured blood/air partition coefficients in the rat and human are 2.4 and 1.16, respectively (ATSDR 2006). Because the ratio of the animal-to-human partition coefficients (2.4/1.16 = 2.1) is greater than one, a default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A/(H_{b/g})_H$) as recommended by the TCEQ ESL guidelines (2006). The resulting POD_{HEC} from the POD_{ADJ} of 0.680 ppm in the Thornton et al. (2002) study is 0.680 ppm.

4.1.5 Adjustment of POD_{HEC} and Critical Effect

4.1.5.1 Critical Effect

The critical effect identified in the key study (Thornton et al. 2002) was centriolobular hypertrophy in the liver. Since this effect is considered to have a threshold (i.e., a nonlinear MOA), uncertainty factors were applied to the POD_{HEC} to derive the chronic ReV.

4.1.5.2 Uncertainty Factors

A subchronic-to-chronic UF was not applied because the animals were exposed for a total of 19 weeks which is more than 10% of the animals' lifetime. A UF of 3 for interspecies variability (UF_A) was applied because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences. A UF of 10 for intraspecies variability (UF_H) was applied to account for sensitive members of the population. BMD modeling was used to derive the POD_{HEC} based on a mild adverse effect (centrilobular hypertrophy in the liver); therefore, a LOAEL-to-NOAEL UF (UF_L) of 1 was applied. The database is robust for this chemical and the key study was well designed; therefore, a UF_D of 1 was applied. A total UF of 30 was applied to the POD_{HEC}.

chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_D x UF_L)

chronic ReV = 0.680 ppm / 30

chronic ReV = 0.0227 ppm = 22.7 ppb

4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Rounding to two significant figures at the end of all calculations yields a chronic ReV of 23 ppb (60 µg/m^3). At the target HQ of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 6.9 ppb (18 µg/m^3) (Table 6).

4.1.7 Comparison of Results

USEPA (2000) has derived a reference concentration (RfC) of 100 µg/m^3 (40 ppb) for VC. The RfC derivation was based on a route-to-route extrapolation (using PBPK modeling) from a $NOAEL_{HEC}$ of 2.5 mg/m^3 for liver cell polymorphism in rats administered VC in the diet for a lifetime (Til et al. 1983 and 1991) (the Thornton et al. (2002) inhalation study was not available when USEPA (2000) developed the RfC). ATSDR (2006) published an inhalation intermediate-duration MRL of 30 ppb based on a $BMCL_{10}$ value of 5 ppm derived from the centrilobular hypertrophy data from F_1 female rats in Thornton et al. (2002). The TD chose to use Thornton et al. (2002) as the key study because it was a recently published, well-conducted animal inhalation study. The TCEQ chronic ReV of 23 ppb is similar to the USEPA RfC of 40 ppb and the ATSDR MRL of 30 ppb.

Table 6 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Study	Thornton et al. (2002)
Study Population	Female Sprague-Dawley rats
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Centrilobular hypertrophy in the liver
POD	2.72 ppm ($BMCL_{10}$)
Exposure Duration	6 h/day, 7 days/week for 19 weeks
Extrapolation to continuous exposure (POD_{ADJ})	0.680 ppm
POD_{HEC}	0.680 ppm
Total UFs	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	1
Subchronic to chronic UF	Not applicable
Incomplete Database UF	1
Database Quality	High
Chronic ReV (HQ = 1)	**60 µg/m^3 (23 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**18 µg/m^3 (6.9 ppb)**

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight-of-Evidence

VC is a known human carcinogen as evaluated by numerous sources including the USEPA, the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP). Epidemiologic studies provide clear and consistent evidence of a causal association between VC exposure and the development of angiosarcoma and hepatocellular carcinoma (USEPA 2000, ATSDR 2006). As reviewed in ATSDR (2006), other cancers have previously been reported in VC workers, including cancers of the brain and central nervous system, respiratory tract, connective and other soft tissues, and the lymphatic/hematopoietic system. However, recent follow-up studies do not demonstrate a clear association between VC exposure and tumor formation (Boffetta et al. 2003, Lewis 2001, Lewis and Rempala 2003, Lewis et al. 2003, Mundt et al. 2000, Ward et al. 2001). VC has also been shown to cause cancer by the oral and inhalation routes of exposure in multiple animal species including rats, mice, and hamsters with the target organ being the same as in humans (the liver). Experimental evidence in both *in vivo* and *in vitro* systems indicate that VC is mutagenic and can form DNA adducts (by VC and

its metabolites). Animal studies have also provided evidence of increased sensitivity during early-life exposure (ATSDR 2006). Evidence is considered strong for the carcinogenicity of VC.

4.2.2 MOA Analysis

VC carcinogenicity is thought to occur by a genotoxic mechanism as discussed previously in Section 4.1.2. VC is metabolized to a reactive metabolite (CEO) which then binds to DNA forming DNA adducts that, if not repaired, can lead to mutations and tumor formation (USEPA 2000). Because carcinogenicity is thought to occur by a mutagenic MOA, and other more specific biologically-based models are not available, it is appropriate to use a linear (non-threshold) approach to develop the $^{chronic}ESL_{linear(c).}$

4.2.3 Key Studies

4.2.3.1 Human Epidemiologic Studies

Human epidemiology studies demonstrate a clear association between VC exposure and liver cancer (i.e., angiosarcoma and hepatocellular carcinoma) (see USEPA 2000 and ATSDR 2006 for complete reviews). Quantitative exposure information is only available for a few studies and is associated with a high level of uncertainty. Due to uncertainties associated with human exposure information, the TD adopted the risk estimate derived by USEPA (2000) using animal data which was subsequently used to develop the $^{chronic}ESL_{linear(c)}$. Cancer potency estimates derived from human studies are presented in Section 4.2.4.1 for comparison.

4.2.3.2 Animal Studies

VC is carcinogenic by the oral and inhalation routes of exposure in multiple animal species including rats, mice, and hamsters with the target organ being the same as in humans (the liver). Maltoni et al. (1981, 1984) conducted the most comprehensive set of experiments in animals. Maltoni et al. (1981, 1984) evaluated the carcinogenicity of VC in Sprague-Dawley and Wistar rats, Swiss mice, and Golden hamsters. In an initial series of experiments, male and female Sprague-Dawley rats were exposed by inhalation to 15 different doses of VC (0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, 10,000, and 30,000 ppm) for 4 h/day, 5 days/week, for 52 weeks. Other experiments were performed over 5-, 17-, and 25-week periods.

Experiments were also performed on pregnant Sprague-Dawley rats and embryos. The study examined effects between strains of rats (Sprague-Dawley versus Wistar) and different species (rats, mice, and hamsters) as well. Animals were kept alive until spontaneous death. Full autopsy was performed on each animal and all parts of the body were examined.

In Sprague Dawley rats, statistically significant increases were reported in the incidence of liver angiosarcoma, mammary gland carcinomas, Zymbal gland carcinomas, nephroblastoma, neuroblastoma, and forestomach tumors. The incidence of liver angiosarcoma was comparable between rat strains at doses up to 10,000 ppm. The incidence of several other tumor types were comparable between rat strains. In Swiss mice, liver angiosarcoma was reported in greater proportions at lower-dose levels after 30-week exposures than in Sprague-Dawley rats exposed for 52 weeks; however, the incidences were comparable at higher doses. The incidence of liver

angiosarcoma in male hamsters was much less after a 30-week exposure than in male rats or male mice. Mammary gland tumors were reported in only rats and mice; Zymbal gland tumors, neuroblastomas, and nephroblastomas were reported in only rats; lung tumors were found in only mice; and melanomas, acoustical duct epithelial tumors, and leukemias were reported in only hamsters.

Other animal studies have supported the carcinogenicity of VC (e.g., Bi et al. 1985, Drew et al. 1983, Holmberg et al. 1976, Hong et al. 1981, and Lee et al. 1977 and 1978). However, the Maltoni et al. (1981, 1984) study is considered the most comprehensive in terms of dose-response information. The results from the Maltoni et al. (1981, 1984) study were used to develop the $^{chronic}ESL_{lin}ear(c)$.

4.2.4 Dose-Response Assessment

4.2.4.1 Dose Metrics and Potency Estimates Based on Human Epidemiological Studies

4.2.4.1.1 USEPA (2000)

Clewell et al. (1995a) developed a PBPK model for OSHA and USEPA to support a cancer risk assessment of VC. The PBPK model was basically a refined version of a PBPK model developed for 1,1-dichloroethylene (D'Souza and Anderson 1988). The model consisted of four compartments: the liver, fat, highly perfused tissue, and poorly perfused tissue. All metabolism was assumed to occur in the liver by two saturable pathways, one high affinity, low capacity (CYP2E1) and one low affinity, high capacity (CYP2C11/6 and CYP1A1/2). The reactive metabolites (CEO, CAA, or other intermediates) were assumed to then either be metabolized further, producing carbon dioxide; react with GSH; or react with other cellular materials, including DNA. Because VC has been shown to deplete GSH levels, a description of GSH kinetics was also included. Other PBPK models have been developed for VC (i.e., USEPA 1987, US Air Force 1990, and Reitz et al. 1996), although the Clewell et al. (1995a, 1995b, 2001) model is the most comprehensive in terms of VC metabolism and is better validated.

Three dose metrics were evaluated in the model: the amount of metabolite divided by the volume of the liver (RISK), the total amount of metabolite not detoxified by GSH divided by the volume of the liver (RISKM), or the total amount reacted with GSH divided by the volume of the liver (RISKG). The average amount of metabolite generated in a single day was used and was averaged over a lifetime (the lifetime average daily dose). Three epidemiological studies were identified and evaluated that reported a positive association between VC exposure and liver cancer and also provided quantitative exposure information sufficient to support separate exposure concentration and duration estimates (as opposed to just cumulative exposure estimates): Fox and Collier 1977, Jones et al. 1988, and Simonato et al. 1991. Separate exposure concentration and duration estimates for each subcohort were required to compute a PBPK-based cumulative dose. Jones et al. (1988) was an update of the Fox and Collier (1977) study. Dose-response assessments were developed for these studies despite the fact that exposure was not adequately characterized. The PBPK model was run for the exposure scenario appropriate to

each of the selected subcohorts and was used to generate the appropriate internal dose metric (RISK) for each study. The dose metric was then input into a linear relative risk dose response model to determine the 95% UCLs on risk estimates. The other dose metrics previously mentioned (RISKM and RISKG) were considered but not used in the USEPA (2000) assessment.

Table 7 lists the range of risk estimates for each of the three epidemiological studies. The lower risk estimate in each range was calculated using the background probability of liver cancer death derived in the original study while the higher risk estimate was calculated using an estimate of lifetime liver cancer mortality rate in the US population from Chen and Blancato (1989). The risk estimate determined from human studies by USEPA (2000) is 2.4×10^{-6} per $\mu g/m^3$ based on the higher of the two values calculated for the Jones et al. (1988) study. Ultimately, USEPA (2000) used animal data to derive cancer potency estimates because of the limitations of the human epidemiology studies, although the risk estimates derived from the human studies provide support for those derived from animal studies.

The Simonato et al. (1991) study was updated in Ward et al. (2001) which was not available at the time of the USEPA (2000) assessment. Because the Ward et al. (2001) study did not reduce the uncertainty regarding exposure concentrations and duration of exposure for the original Simonato et al. (1991) study, the TD adopted the USEPA (2000) cancer risk estimate based on animal data discussed in Section 4.2.4.2.

Table 7 Risk Estimates for Angiosarcoma based on Epidemiological Studies (USEPA 2000)

Study	**95% UCL risk per µg/m3 a**
Fox and Collier (1977)	0.46 to 2.8×10^{-6}
Jones et al. (1988) [b]	0.65 to 2.4×10^{-6} [c]
Simonato et al. (1991)	0.27 to 0.53×10^{-6}

[a] Risk estimates based on RISK dose metric

[b] Jones et al. (1988) was an update of Fox and Collier (1977).

[c] Highest value in range reported by USEPA (2000) as the best risk estimate from human studies.

4.2.4.1.2 Clewell et al. (2001)

Clewell et al. (2001) developed a PBPK model for VC which was described in Section 4.2.4.1.2 and applied this PBPK model with slight modifications in some parameters to develop human risk estimates for angiosarcoma based on human epidemiological studies (Table 8) and animal studies (Section 4.2.4.2.2). Risk estimates developed for angiosarcoma based on the RISK dose metric from the Fox and Collier (1977), Jones et al. (1988), and Simonato et al. (1991) studies are presented in Table 8. Risk estimates obtained from all three dose metrics were reportedly very similar but only those based on the RISK dose metric were presented in the study. The lower risk estimate in each range was calculated using the background probability of liver cancer death derived in the study while the higher risk estimate was calculated using an estimate of lifetime liver cancer mortality rate in the US population from Chen and Blancato (1989).

Table 8 Risk Estimates for Angiosarcoma based on Epidemiological Studies (Clewell et al. 2001).

Study	95% UCL risk per µg/m3 a
Fox and Collier (1977)	0.27 to 1.6 x 10^{-6}
Jones et al. (1988) [b]	0.37 to 1.38 x 10^{-6}
Simonato et al. (1991)	0.15 to 0.30 x 10^{-6}

[a] Risk estimates based on RISK dose metric

[b] Jones et al. (1988) was an update of Fox and Collier (1977) .

4.2.4.2 Dose Metrics and Potency Estimates Based on Animal Data

4.2.4.2.1 USEPA (2000)

USEPA (2000) applied the PBPK model for VC developed by Clewell et al. (1995a) to calculate human risk estimates from animal data. Human risk estimates were calculated based on this PBPK model and the 1-hit version of the linearized multistage (LMS) model for extra risk using liver tumor incidence data (liver angiosarcomas, angiomas, hepatomas, and neoplastic nodules) from animal studies (Maltoni et al. 1981 and 1984, Feron et al. 1981). Doses were not converted to human equivalents prior to calculation of risk. Risk modeling using the LMS or the LED_{10} method was conducted based on the animal dose metric (RISK), and the resulting risk was converted to a human risk value based on an equivalence factor. The other dose metrics previously mentioned (RISKM and RISKG) were considered but not used in the assessment. The LED_{10}/linear method draws a straight line from the point of departure from the observed data (in this case, the LED_{10} or the lower 95% limit on a dose that is estimated to cause a 10% response) to the origin.

The equivalence factor for inhalation exposure was calculated by determining the human dose metric for continuous human inhalation exposure to a range of exposure concentrations (1 µg/m^3 (0.38 ppb) to 10,000 mg/m^3 (3846 ppm)). This calculation showed that the model was linear up to nearly 100 mg/m^3 (38.46 ppm), and the calculated equivalence factor was used to convert the risk from the inhalation experiments conducted in animals (in the units of the dose metric) to human risk values.

The inhalation unit risk estimate of 4.4 x 10^{-6} per µg/m^3 based on liver tumor incidence data from female rats (Maltoni et al. 1981 and 1984) was derived by modeling the RISK dose metric with the LMS model (extra risk), and for comparison, a risk estimate of 4.2 x 10^{-6} per µg/m^3 was derived using the LED_{10}/linear method (see Table 10 for data used in assessment). Risk estimates based on data from female rats were recommended over those based on male rats or female or male mice because they are the most conservative. The risk estimate is based on continuous lifetime exposure beginning at adulthood. However, the application of a two-fold uncertainty factor to this value is recommended if exposure begins in early life (see Section 4.2.5).

Table 9 Dose and Tumor Incidence Data from Inhalation of VC by Female Sprague-Dawley Rats (Maltoni et al. 1981 and 1984/Experiments BT1, BT2, and BT15) as Reported in USEPA (2000)

Exposure Concentration (ppm) [a]	Metabolite (mg/L liver) [b]	Human Equivalent Concentration (ppm) [c]	Tumor Incidence [d]
0	0	0	0/141
1	0.59	0.2	0/55
5	2.96	0.98	0/47
10	5.90	1.95	1/46
25	14.61	4.6	5/40
50	31.27	10.1	1/29
100	55.95	19	1/43
150	76.67	26	5/46
200	90.00	31	10/44
250	103.45	35	3/26
500	116.94	40	11/28
2500	134.37	48	10/24
6000	143.72	51	13/25

[a] Animals exposed 4 h/day, 5 days/week, for 52 weeks

[b] Dose metric (lifetime average delivered dose in female rats) calculated from PBPK modeling of the administered animal concentration.

[c] Continuous human exposure concentration over a lifetime required to produce an equivalent mg metabolite/L of liver.

[d] Based on number of animals alive after detection of first liver tumor.

4.2.4.2.2 Clewell et al. (2001)

Clewell et al. (2001) used their PBPK model to calculate each of the three dose metrics for angiosarcoma (RISK, RISKM, and RISKG) from animal studies (Maltoni et al. 1981 and 1984, Maltoni and Cotti 1988, Feron et al. 1981). The 95% UCLs on human risk estimates for lifetime exposure were then calculated on the basis of each of the sets of animal data using the linear multi-stage (LMS) model. Risk estimates obtained from all three dose metrics were reportedly very similar but only those based on the RISK dose metric were presented. The human risk estimates derived from animal studies, based on the RISK dose metric, ranged from 0.42×10^{-6} to 1.99×10^{-6} per $\mu g/m^3$ (Table 9) with a geometric mean of 1.1×10^{-6} per $\mu g/m^3$.

Table 10 Human Risk Estimates for Inhalation Exposure based on Angiosarcoma Incidence in Animal Studies (Clewell et al. 2001).

Study	Route of Exposure	Species and Sex	95% UCL risk per µg/m3 [a]
Maltoni and Cotti (1988)	Inhalation	Male Mice	0.59×10^{-6}
Maltoni and Cotti (1988)	Inhalation	Female Mice	1.26×10^{-6}
Maltoni et al. (1981, 1984)	Inhalation	Male Rats	1.99×10^{-6}
Maltoni et al. (1981, 1984)	Inhalation	Female Rats	0.86×10^{-6}
Feron et al. (1981)	Ingestion	Male Rats	1.17×10^{-6}
Feron et al. (1981)	Ingestion	Female Rats	0.42×10^{-6}

[a] Risk estimates based on RISK dose metric

4.2.4.2.3 Comparison of USEPA (2000) and Clewell et al. (2001)

The USEPA (2000) and Clewell (2001) risk estimates based on female rat data from Maltoni et al. (1981, 1984) differ by a factor of about 5. The more conservative USEPA (2000) estimate may be explained by the fact that they modeled tumor incidence data for several liver tumor types (liver angiosarcomas, angiomas, hepatomas, and neoplastic nodules) and used data from three different inhalation experiments in rats conducted by Maltoni et al. (1984) (BT1, BT2, and BT15), whereas Clewell et al. (2001) only modeled liver angiosarcoma incidence data and used data from two inhalation experiments in rats conducted by Maltoni et al. (1984) (BT1 and BT15).

Hepatomas, angiomas, and neoplastic nodules were not statistically significantly increased in the Maltoni et al. (1981, 1984) studies. However, because hepatocellular tumors were significantly increased in the Feron et al. feeding study evaluated in the cancer assessment, USEPA (2000) concluded that all liver tumors in the Maltoni et al. studies are likely the result of exposure to VC as well, and should be included as a conservative approach. The USEPA (2000) assessment underwent two formal external panel peer reviews in which the issue of inclusion of hepatomas and neoplastic nodules in the cancer risk assessment was raised. Three reviewers believed that including all liver tumors would result in an overestimate of cancer risk, two reviewers believed that it might address the possibility of tumor induction at other sites, and the other reviewers were either uncertain or had no opinion. The USEPA (2000) response to this concern was that there is evidence in both human epidemiological and animal feeding studies that hepatocellular tumors as well as angiosarcomas are induced by VC and that the inclusion of all liver tumors, even from studies in which hepatocellular tumors were not significantly increased, is appropriate. USEPA (2000) also noted that there were relatively few tumor types other than angiosarcomas included in the assessment and that their effect upon cancer potency was minimal.

The most conservative risk estimate from an animal inhalation study derived by Clewell et al. (2001) was from male rats (1.99 x 10^{-6} risk per µg/m^3). This risk estimate is only a factor of about 2 greater than the most conservative risk estimate derived by USEPA (2000) (4.4 x 10^{-6} risk per µg/m^3 based on female rat data using the LMS method, or 4.2 x 10^{-6} risk per µg/m^3 using the LED_{10}/linear method). Clewell et al. (2001) recommended using the geometric mean from all three animal studies evaluated in their cancer assessment of 1.1 x 10^{-6} risk per µg/m^3. The TD chose to use the USEPA (2000) URF of 4.2 x 10^{-6} risk per µg/m^3 based on female rat data using the LED_{10}/linear method because it conservatively incorporated data on all liver tumor types in the assessment versus only angiosarcomas.

4.2.5 Evaluating Susceptibility from Early-Life Exposures

Human studies that specifically address the effects of VC in children were not identified in the literature. However, several animal studies provide evidence for early life sensitivity associated with VC-induced carcinogenicity. Maltoni et al. (1981) reported a greater incidence of hepatomas and liver angiosarcomas in rats exposed from 1 day of age for 5 weeks than in rats exposed to the same concentrations beginning at 3 months of age. Hepatomas were reported in 47.6% and liver angiosarcomas in 40.5% of rats exposed from 1 day of age for 5 weeks to 6000 ppm VC.

Drew et al. (1983) examined the effects of age and exposure duration on cancer induction by VC in mice, rats, and hamsters. Higher death rates were observed when 2-month-old female hamsters, mice, and rats were exposed to VC for 12 months than when 8- or 14-month-old animals were exposed. The incidence of several tumor types including hemangiosarcoma of the liver were greater in animals exposed for 12 months, starting immediately after weaning, compared to animals that were 1 year older at the time of exposure. The incidence of mammary gland carcinoma was higher in 2- or 8-month-old hamsters exposed to 200 ppm VC for 6 months than in 14- or 20-month-old hamsters. Overall, exposures of equal duration were most effective in producing cancer when started early in life.

Mechanistic studies are consistent with tumor studies. Laib et al. (1979) reported that VC induced preneoplastic foci in newborn rats but not adult rats. This effect was determined to be a result of the increased rate of cell proliferation in newborn animals. Laib et al. (1989) reported that inhaled, radiolabeled VC was incorporated into physiological purines of 11-day-old rats eight times more than in adult rats, reflecting the higher degree of DNA replication activity in younger animals. In the same study, approximately five-fold higher levels of a DNA adduct (7-N-(2-oxyethyl)guanine) were found in the livers of young animals compared to adult animals, reflecting a higher alkylation rate in younger animals. Similarly, Fedtke et al. (1990) reported an increased alkylation rate in preweanling rats exposed to VC compared to adults. Ciroussel et al. (1990) reported a six-fold increase in the formation of ethenonucleosides in immature rats compared to adults. Similarly, Morinello et al. (2002) reported a two- to three-fold increase in the concentration of ethenoguanine adducts in weanling rats compared to adults exposed to the same dose for the same time period.

USEPA (2000) incorporated information from these studies into the development of a two-fold adjustment factor for early-life exposure to VC (see USEPA 2000 for a complete explanation of how this factor was derived). Since the USEPA (2000) evaluation was published, a PBPK model was developed by Clewell et al. (2004) to evaluate the potential age- and gender-specific pharmacokinetic differences on the dosimetry of VC. In this model, the rate of metabolite production per volume of liver was estimated to rise rapidly from birth until about age 16, after which it remains relatively constant before rising again later in life. The rate of metabolite production per volume of liver (the dose metric used in the cancer risk assessments for VC by Clewell et al. 2001 and USEPA 2000) varies four-fold from birth to 75 years of age, with peak values estimated in adolescence at age 14 to 16 and again later in life. Other factors that may affect VC toxicity early in life include the presence of fetal CYP450s, different levels of glutathione conjugation in developing animals, and differences in DNA repair capacity and other pharmacodynamic factors (ATSDR 2006). Although the results of this study provide support for the potential for early-life sensitivity to VC carcinogenicity, the authors did not intend for this information to be used quantitatively in risk assessments (Clewell et al. 2004). In the absence of more recent and definitive information to suggest the use of a different age-adjustment factor, the TD recommends the use of a two-fold age-adjustment factor as recommended by USEPA (2000) for early-life exposure. The exposure factor does not need to be applied if exposures only occur during adulthood. By applying the two-fold age-adjustment factor, the URF would be 8.4×10^{-6} per $\mu g/m^3$.

4.2.6 Calculation of Air Concentration at 1 x 10^{-5} Excess Cancer Risk

The 2005 USEPA Cancer Guidelines recommend the use of the LED_{10}/linear method to develop cancer risk estimates for chemicals with a mutagenic MOA; therefore, the TD chose to use the URF of 4.2×10^{-6} per $\mu g/m^3$ (or 8.4×10^{-6} per $\mu g/m^3$ corrected for an increased susceptibility of children) derived by USEPA (2000) using the LED_{10}/linear method based on data from female rats (Maltoni et al. 1981 and 1984). By using the inhalation URF of 4.2×10^{-6} per $\mu g/m^3$, the $^{chronic}ESL_{linear(c)}$ for VC at the TCEQ no significant risk level of 1×10^{-5} is calculated below:

$$^{chronic}ESL_{linear(c)} = [1 \times 10^{-5}] / [4.2 \times 10^{-6}(\mu g/m^3)^{-1}] = 2.4\ \mu g/m^3 \text{ or } 0.9 \text{ ppb}$$

The use of this value would be appropriate in situations in which you would not expect children to be exposed (possibly in an industrial environment with no residential areas nearby).

By applying the two-fold age-adjustment factor, the $^{chronic}ESL_{linear(c)}$ for VC at the TCEQ no significant risk level of 1×10^{-5} is calculated below:

$$^{chronic}ESL_{linear(c)} = [1 \times 10^{-5}] / [8.4 \times 10^{-6}(\mu g/m^3)^{-1}] = 1.2\ \mu g/m^3 \text{ or } 0.45 \text{ ppb}$$

The use of this value would be appropriate in situations in which you would expect children to be exposed.

4.2.7 Comparison of Results

Table 11 is a comparison of URFs derived by the TCEQ and other sources. Although it is preferable to use human data to derive risk estimates, similar to the USEPA (2000), the TD used animal studies to develop risk estimates because of the limitations regarding exposure concentrations and durations in the available human studies. The TCEQ URF is similar to the URFs derived from human epidemiological studies developed by Clewell et al. (2001) and WHO (2000), and is about 10 times less conservative than that derived by CalEPA based on a VC risk assessment conducted by the California Department of Health Services in 1990.

Table 11 Comparison of VC Inhalation URFs and Chronic Toxicity Benchmarks

Parameter	Inhalation URF	Air Concentration at 1 x 10-5 Cancer Risk Level
$^{chronic}ESL_{linear(c)}$ [a]	4.2×10^{-6} $(\mu g/m^3)^{-1}$ 8.4×10^{-6} $(\mu g/m^3)^{-1}$ [b]	2.4 $\mu g/m^3$ (0.9 ppb) 1.2 $\mu g/m^3$ (0.45 ppb)
USEPA (2000) [a]	4.4×10^{-6} $(\mu g/m^3)^{-1}$ 8.8×10^{-6} $(\mu g/m^3)^{-1}$ [b]	2.3 $\mu g/m^3$ (0.88 ppb) 1.1 $\mu g/m^3$ (0.42 ppb)
Clewell et al. (2001) [c]	1.1×10^{-6} $(\mu g/m^3)^{-1}$	9.1 $\mu g/m^3$ (3.5 ppb)
Clewell et al. (2001) [d]	0.15 to 1.6×10^{-6} $(\mu g/m^3)^{-1}$	66.7 $\mu g/m^3$ (25.6 ppb) to 6.3 $\mu g/m^3$ (2.4 ppb)
WHO (2000) [d]	1.0×10^{-6} $(\mu g/m^3)^{-1}$	10.0 $\mu g/m^3$ (2.6 ppb)
CalEPA (1994) [e]	7.8×10^{-5} $(\mu g/m^3)^{-1}$	0.13 $\mu g/m^3$ (0.05 ppb)

[a] URFs were estimated based on a cancer risk assessment of Maltoni et al. (1981, 1984) rat inhalation data

[b] URF incorporates a two-fold age-adjustment factor for early-life exposures

[c] URF estimated based on a cancer risk assessment of Maltoni et al. (1981, 1984), Maltoni and Cotti (1988), and Feron et al. (1981) animal data. URF is the geometric mean of risk estimates from all three animal studies.

[d] URFs were estimated based on human epidemiological data

[e] URF estimated based on a cancer risk assessment of Drew et al. (1983), Maltoni et al. (1984), and Bi et al. (1985) animal data

4.3 Welfare-Based Chronic ESL

No chronic vegetative studies were identified for VC.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

This chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 83 $\mu g/m^3$ (32 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 25 $\mu g/m^3$ (9.6 ppb)
- URF = 8.4×10^{-6} per $\mu g/m^3$ (2.2×10^{-5} per ppb)-using the two-fold factor for early life exposure
- $^{chronic}ESL_{linear(c)}$ = 1.2 $\mu g/m^3$ (0.45 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{linear(c)}$ of 1.2 µg/m^3 (0.45 ppb) as it is lower than the $^{chronic}ESL_{nonlinear(nc)}$ (Table 1). This value is protective of early-life exposure. If children are not expected to be exposed, the higher value of 2.3 µg/m^3 (0.90 ppb) may be used.

For evaluation of air monitoring data, the $^{chronic}ESL_{linear(c)}$ of 1.2 µg/m^3 (0.45 ppb) is lower than the chronic ReV of 83 µg/m^3 (32 ppb), although these two values may both be used for the evaluation of air data (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 5 References

5.1 References Cited in the Development Support Document

Acute Exposure Guideline Leve (AEGL). 2004. Acute Exposure Guideline Levels (AEGLs) for vinyl chloride (CAS Reg. No. 75-01-4). Interim. Available from: http://www.epa.gov/oppt/aegl.

Agency for Toxic Substances and Disease Registry (ATSDR). 2006. Toxicological profile for vinyl chloride. Atlanta, GA.

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Medical management guidelines for vinyl choride. Atlanta, GA.

Air Force. 1990. Development and validation of methods for applying pharmacokinetic data in risk assessment. Volume 5. Vinyl chloride. Wright-Patterson AFB, OH: U.S. Air Force, Air Force Systems Command, Human Systems Division, Harry G. Armstrong Aerospace Medical Research Laboratory. ADA2373652.

American Conference of Governmental Industrial Hygienists (ACGIH). 2003. Vinyl chloride. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290.

Andersen, M; Clewell, H; Gargas, M; et al. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Baretta ED, Stewart RD, Mutchler JE. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am Ind Hyg Assoc J 30:537.

Berk PD, Martin JF, Waggoner JG. 1975. Persistence of vinyl chloride induced liver injury after cessation of exposure. Ann NY Acad Sci 31:70-77.

Bi W, Wang Y, Huang M, et al. 1985. Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Safety 10:281-289.

Boffetta P, Matisane L, Mundt KA, et al. 2003. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 29(3):220-229.

California Environmental Protection Agency. 1999. Determination of acute reference exposure levels for airborne toxicants: vinyl chloride.

Ciroussel F, Barbin A, Eberle G, et al. 1990. Investigations on the relationship between DNA ethenobase adduct levels in several organs of vinyl chloride-exposed rats and cancer susceptibility. Biochem Pharmacol 39:1109-1113.

Clewell, HJ; Gentry, PR; Gearhart, JM; et al. 1995a. The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride. Prepared by ICF Kaiser for the Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, and the Directorate of Health and Standards Programs, Occupational Safety and Health Administration, Washington, DC.

Clewell HJ, Gentry JM, Gearhart BC, et al. 1995b. Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: Examples with vinyl chloride and trichloroethylene. Chemosphere 31(1):2561-2578.

Clewell HJ, Gentry PR, Gearhart JM, et al. 2001. Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. Sci Total Environ 274:37-66.

Clewell HJ, Gentry JM, Covington TR, et al. 2004. Evaluation of the potential impact of age-and gender-specific pharmacokinetic differences on tissue dosimetry. Toxicol Sci 79:381-393.

Drew RT, Boorman GA, Haseman JK, et al. 1983. The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol Appl Pharmacol 68:120-130.

D'Souza RW, Andersen ME. 1988. Physiologically based pharmacokinetic model for vinylidene chloride. Toxicol Appl Pharmacol 95:230-240.

Falk H, Creech JL Jr, Heath CW Jr, et al. 1974. Hepatic disease among workers at a vinyl chloride polymerization plant. JAMA 230:59-63.

Fedtke N, Boucheron JA, Walker VE, et al. 1990. Vinyl chloride-induced DNA adducts. II: Formation and persistence of 7-(2-oxoethyl)guanine and N^2,3-ethenoguanine in rat tissue DNA. Carcinogenesis 11(8):1287-1292.

Feron VJ, Hendriksen CFM, Speek AJ, et al. 1981. Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet Toxicol 19:317-333.

Fox AJ, Collier PF. 1977. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34:1-10.

Gedigke P, Muller R, Bechtelsheimer H. 1975. Morphology of liver damage among polyvinyl chloride production workers. A report on 51 cases. Ann N Y Acad Sci 246:278-285.

Ho SF, Phoon WH, Gan SL, et al. 1991. Persistent liver dysfunction among workers at a vinyl chloride monomer polymerization plant. J Soc Occup Med 41(1):10-16.

Holmberg B, Kronevi T, Winell M. 1976. The pathology of vinyl chloride exposed mice. Acta Vet Scand 17:328-342.

Holmberg B. The toxicology of monomers of the polyvinyl plastic series. In: Industrial hazards of plastics and synthetic elastomers. New York (NY): Alan R Liss, Inc.; 1984. p. 99-112.

Hong CB, Winston JM, Thornburg LP, et al. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: Tumor incidence and mortality subsequent to exposure. J Toxicol Environ Health 7:909-924.

Ivanetich, KM; Aronson, I; Katz, ID. 1977. The interaction of vinyl chloride with rat hepatic microsomal cytochrome P-450 in vitro. Biochem Biophys Res Commun 74:1411-1418.

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: Inhalation teratology study in mice, rats, and rabbits. Environ Health Perspect 41:171-177.

Jones DB, Smith PM. 1982. Progression of vinyl chloride induced hepatic fibrosis to angiosarcoma of the liver. Br J Ind Med 39:306-307.

Jones RD, Smith DM, Thomas PG. 1988. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. Scand J Work Environ Health 14:153-160.

Laib, RJ; Stoeckle, G; Bolt, HM; et al. 1979. Vinyl chloride and trichloroethylene. Comparison of alkylating effects of metabolites and induction of preneoplastic enzyme deficiencies in rat liver. J Cancer Res Clin Oncol 94:139-147.

Laib RJ, Bolt HM, Cartier R, et al. 1989. Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol Lett 45:231-239.

Lee CC, Bhandari JC, Winston JM, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ Health Perspect 21:25-32.

Lee CC, Bhandari JC, Winston JM, et al. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J Toxicol Environ Health 4:15-30.

Lester D, Greenberg LA, Adams WR. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am Ind Hyg Assoc J 3:265-275.

Lewis R. 2001. Use of rank-order analysis of ordinal exposure data: Application to vinyl chloride exposure. Appl Occup Environ Hyg 16(2):188-191.

Lewis RJ, Rempala G, Dell LD, et al. 2003. Vinyl chloride and liver and brain cancer at a polymer production plant in Louisville, Kentucky. J Occup Environ Med 45(5)533-537.

Lewis R, Rempala G. 2003. A case-cohort study of angiosarcoma of the liver and brain cancer at a polymer production plant. J Occup Environ Med 45(5):538-545.

Lilis R, Anderson H, Nicholson WJ, et al. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. Ann NY Acad Sci 246:22-41.

Liss GM, Greenberg RA, Tamburro CH. 1985. Use of serum bile acids in the identification of vinyl chloride hepatotoxicity. Am J Med 78:68-76.

Maltoni C, Cotti G. 1988. Carcinogenicity of vinyl chloride in Sprague-Dawley rats after prenatal and postnatal exposure. Ann NY Acad Sci 534:145-159.

Maltoni C, Lefemine G, Ciliberti A, et al. 1981. Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. Environ Health Perspect 41:3-29.

Maltoni C, LeFemine G, Ciliberti A, et al. 1984. Experimental research on vinyl chloride carcinogenesis. Archives of Research on Industrial Carcinogenesis, Vol. II. Princeton, NJ: Princeton Scientific Publishers.

Marsteller HJ, Lelbach WK, Muller R, et al. 1975. Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 246: 95-134.

Morinello EJ, Ham A-JL, Ranasinghe A, et al. 2002a. Molecular dosimetry and repair of N2,3ethenoguanine in rats exposed to vinyl chloride. Cancer Res 62:5189-5195.

Mundt KA, Dell LD, Austin RP, et al. 2000. Historical cohort study of 10,109 men in the North American vinyl chloride industry. 1942-1972. Update of cancer mortality to 31 December 1995. Occup Environ Med 57(11):774-781.

Patty FA, Yant WP, Waite,CP. 1930. Acute response of guinea pigs to vapors of some new commercial organic compounds. 5. Vinyl chloride. Publ Health Reports 45:1963-1971.

Popper H, Thomas LB. 1975. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann NY Acad Sci 246: 172-194.

Reitz RH, Gargas ML, Anderson ME, et al. 1996. Predicting cancer risk from vinyl chloride exposure with a physiologically based pharmacokinetic model. Toxicol Appl Pharmacol 137:253-267.

Sabadie N, Malaveille C, Camus AM, et al. 1980. Comparison of the hydroxylation of benzo(a)pyrene with the metabolism of vinyl chloride, N-nitrosonorpholine, and N-nitroso-N'methylpiperazine to mutagens by human and rat liver microsomal fractions. Cancer Res 409:119-126.

Simonato L, L'Abbe KA, Andersen A, et al. 1991. A collaborative study of cancer incidence and mortality among vinyl chloride workers. Scand J Work Environ Health 17(3):159-169.

Sokal JA, Baranski B, Majka J, et al. 1980. Experimental studies on the chronic toxic effects of vinyl- chloride in rats. J Hyg Epidemiol Microbiol Immunol 24:285-294.

Suciu I, Prodan L, Ilea E, et al. 1975. Clinical manifestations in vinyl chloride poisoning. Ann N Y Acad Sci 246:53-69.

Tamburro CH, Makk L, Popper H. 1984. Early hepatic histologic alterations among chemical (vinyl monomer) workers. Hepatology 4:413-418.

Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.

Torkelson TR, Oyen F, Rowe VK. 1961. The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. Am Ind Hyg Assoc J 22:354-361.

Van Gemert, LJ; Nettenbreijer AH. 1977. Compilation of odour threshold values in air and water. National Institute for Water Supply, Voorburg, Netherlands.

Vihko R, Vihko P, Maentausta O, et al. 1984. Assessment of early hepatotoxicity: Biological monitoring and surveillance of workers exposed to chemicals. In: Aitio A, Riihimaki V, Vainio J, eds. Washington, DC: Hemosphere Publishing Co., 309-313.

Ward E, Boffetta P, Andersen A, et al. 2001. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology 12:710-718.

Wisniewska-Knypl JM, Klimczak J, Kolakowski J. 1980. Monooxygenase activity and ultrastructural changes of liver in the course of chronic exposure of rats to vinyl chloride. Int Arch Occup Environ Health 46:241-249.

World Health Organization. 2000. Air Quality Guidelines – Second Edition. Chapter 5.16 – Vinyl Chloride. WHO Regional Office for Europe, Copenhagen, Denmark.

Occupational Safety and Health Administration (OSHA). 2004. Vinyl chloride. Occupational safety and health standards. Toxic and hazardous substances. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1017.

USEPA. 1987. Incorporation of biological information in cancer risk assessment: Example - vinyl chloride. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment. PB87198982.

USEPA. 2000. Toxicological review of vinyl chloride. Washington, DC: U.S. Environmental Protection Agency. EPA635R00004.

5.2 Other References Reviewed But Not Cited:

Bolt HM, Kappus H, Buchter A, et al. 1976. Disposition of (1,2-14C) vinyl chloride in the rat. Arch Toxicol 35:153-162.

Cheng T-J, Huang M-L, You N-C, et al. 1999. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. J Occup Environ Med 41(12):1128-1133.

Creech JL, Johnson MN. 1974. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16:150-151.

Danziger H. 1960. Accidental poisoning by vinyl chloride: report of two cases. Can Med Assoc J 82:828-830.

Du C-L, Kuo ML, Chang HL, et al. 1995. Changes in lymphocyte single strand breakage and liver function of workers exposed to vinyl chloride monomer. Toxicol Lett 77:379-385.

Du C-L, Wang J-D. 1998. Increased morbidity odds ratio of primary liver cancer and cirrhosis of the liver among vinyl chloride monomer workers. Occup Environ Med 55:528-532.

Duprat P, Fabry JP, Gradiski D, et al. 1977. Metabolic approach to industrial poisoning: Blood kinetics and distribution of 14C-vinyl chloride monomer (VCM). Acta Pharmacol Toxicol Suppl 41:142-143.

Elliott P, Kleinschmidt I. 1997. Angiosarcoma of the liver in Great Britain in proximity to vinyl chloride sites. Occup Environ Med 54:14-18.

Esmen NA, Hall TA, Phillips ML, Jones EP, Basara H, Marsh GM, Buchanich JM. 2007. Chemical process-based reconstruction of exposures for an epidemiological study. Part II. Estimated exposures to chloroprene and vinyl chloride. Chem Biol Interact Mar 20;166(1-3):264-76. Epub 2006 Aug 22.

Forman D, Bennett B, Stafford J, et al. 1985. Exposure to vinyl chloride and angiosarcoma of the liver: A report of the register of cases. Br J Ind Med 42:750-753.

Infante PF, Wagoner JK, Waxweiler RJ. 1976b. Carcinogenic, mutagenic, and teratogenic risks associated with vinyl chloride. Mutat Res 41:131-142.

Fortwengler P, Lewis RD, Reynolds L, et al. 1999. Empirical evidence that angiosarcoma of the liver caused by vinyl chloride exposure has a relatively high threshold dose in humans. Hepatology 30(4 Pt 2):504A.

Hehir RM, McNamara BP, McLaughlin J, Jr, et al. 1981. Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ Health Perspect 41:63-72.

Hozo I, Andelinovic S, Ljutic D, et al. 1997. Two new classes of liver angiosarcoma: History and perspectives of liver angiosarcoma among plastic industry workers. Toxicol Ind Health 13(5):639-648.

Hsieh HI, Wang JD, Chen PC, et al. 2003. Synergistic effects of hepatitis virus infection and occupational exposures to vinyl chloride monomer and ethylene dichloride on serum aminotransferase activity. Occup Environ Med 60:774-778.

Huang CY, Huang KL, Cheng TJ, Wang JD, Hsieh LL. 1997. The GST T1 and CYP2E1 genotypes are possible factors causing vinyl chloride induced abnormal liver function. Arch Toxicol 71(8):482-488.

Krajewski J, Dobecki M, Gromiec J. 1980. Retention of vinyl chloride in the human lung. Br J Ind Med 37:373-374.

Laplanche A, Clavel-Chapelon F, Contassot JC, et al. 1992. Exposure to vinyl chloride monomer: Results of a cohort study after a 7 year follow-up. Br J Ind Med 49(2):134-137.

Lee FL, Smith PM, Bennett B, et al. 1996. Occupationally related angiosarcoma of the liver in the United Kingdom 1972-1994. Gut 39:312-318

Lelbach WK. 1996. A 25-year follow-up study of heavily exposed vinyl chloride workers in Germany. Am J Ind Med 29:446-458.

Maroni M, Mocci F, Visentin S, et al. 2003. Periportal fibrosis and other liver ultrasonography findings in vinyl chloride workers. Occup Environ Med 60:60-65.

Marsh GM, Youk AO, Buchanich JM, Cunningham M, Esmen NA, Hall TA, Phillips ML. 2007. Mortality patterns among industrial workers exposed to chloroprene and other substances. II. Mortality in relation to exposure. Chem Biol Interact Mar 20;166(1-3):301-16. Epub 2006 Aug 22.

Marsh GM, Youk AO, Buchanich JM, Cunningham M, Esmen NA, Hall TA, Phillips ML. 2007. Mortality patterns among industrial workers exposed to chloroprene and other substances. I. General mortality patterns. Chem Biol Interact Mar 20;166(1-3):285-300. Epub 2006 Aug 22.

Mastrangelo G, Fedeli U, Fadda E, et al. 2004. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: Synergistic effect of occupational exposure with alcohol intake. Environ Health Perspect 112(11):1188-1192.

Mastromatteo E, Fisher M, Christie H, Danzinger H. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am Ind Hyg Assoc J 1960;4:394-398.

Monson RR, Peters JM, Johnson MN. 1975. Proportional mortality among vinyl chloride workers. Environ Health Perspect 11:75-77.

NIOSH. 1977. A cross-sectional epidemiologic survey of vinyl chloride workers. Cincinnati, OH:U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies. PB274193.

Pirastu R, BAccini M, Biggeri A, Comba P. 2003. Cohort study of vinyl chloride exposed workers in Porto Marghera: update of the mortality follow-up. Epidemiol Prev 27: 161-172.

Purchase, IFH, Stafford J, Paddle GM. 1987. Vinyl chloride: an assessment of the risk of occupational exposure. Food Chem Toxicol 25(2):187-202.

Rinsky RA, Ott G, Ward E, et al. 1988. Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am J Ind Med 13:429-438.

Scélo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabiánová E, Cassidy A, Slamova A, Foretova L, Janout V, Fevotte J, Fletcher T, Mannetje A, Brennan P, Boffetta P. 2004. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (europe). Cancer Causes Control Jun;15(5):445-52.

Sugita M, Masuda Y, TDuchiya K. 1986. Early detection and signs of hepatoangiosarcoma among vinyl chloride workers. Am J Ind Med 10:411-417.

Teta MJ, Schnatter AR, Ott MG, et al. 1990. Mortality surveillance in a large chemical company: The Union Carbide Corporation experience, 1974-1983. Am J Ind Med 17:435-447.

Theriault G, Allard P. 1981. Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. J Occup Med 23:671-676.

Ungvary G, Hudak A, Tatrai E, et al. 1978. Effects of vinyl chloride exposure alone and in combination with trypan blue-applied systematically during all thirds of pregnancy on the fetuses of CFY rats. Toxicology 11:45-54

Watanabe PG, McGowan GR, Madrid EO, et al. 1976. Fate of [14C] vinyl chloride following inhalation exposure in rats. Toxicol Appl Pharmacol 37:49-59.

Watanabe PG, Zempel JA, Gehring PJ. 1978. Comparison of the fate of vinyl chloride following single and repeated exposure in rats. Toxicol Appl Pharmacol 44:391-399.

Waxweiler RJ, Stringer W, Wagner JK, et al. 1976. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271:40-48.

Weber H, Reinl W, Greiser E. 1981. German investigations on morbidity and mortality of workers exposed to vinyl chloride. Environ Health Perspect 41:95-99.

Weihrauch M, Lehnert G, Kockerling F, et al. 2000. p53 Mutation pattern in hepatocellular carcinoma in workers exposed to vinyl chloride. Cancer 88(5):1030-1036.

Withey JR. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J Toxicol Environ Health 1:381-394.

Wong R-H, Chen P-C, Du C-l, et al. 2002. An increased standardized mortality ratio for liver cancer among polyvinyl chloride workers in Taiwan. Occup Environ Med 59:405-409.

Wong R-H, Chen P-C, Wang J-D, et al. 2003. Interaction of vinyl chloride monomer exposure and hepatitis B viral infection on liver cancer. J Occup Environ Med 45(4):379-383.

Wu W, Steenland K, Brown D, et al. 1989. Cohort and case-control analyses of workers exposed to vinyl chloride: An update. J Occup Med 31:518-523.

Appendix A. Benchmark Dose Modeling Results for Thornton et al. (2002)

BMD modeling was conducted to determine the $BMCL_{10}$ from the Thornton et al. (2002) study using USEPA Benchmark Dose Software version 1.4.1b. Modeling was performed on centrilobular hypertrophy data from F_1 female rats (see Table 11 of Thornton et al. 2002). A similar effect was seen in F_0 female rats although the incidence observed at 10 ppm was not statistically significant as in the F_1 females. See the table below for model inputs. The highest concentration of 1100 ppm was not included in the modeling because 100% incidence occurred at both the 100 and 1100 ppm concentrations and in order to obtain a better visualization of fit in the lower dose range. Similar results were obtained if the highest concentration was included (data not shown).

Dose (ppm)	Incidence of centrilobular hypertrophy observed	Sample Size
0	0	30
10	6	30
100	30	30
1100	30	30

[a] Concentration of 1100 ppm was not included in the modeling.

All available dichotomous models were run to determine which model best fit the data. The results of the modeling are presented below.

BMDS Model	AIC	Goodness of fit p-value	Chi-squared p-value (Scaled Residual)	BMC	$BMCL_{10}$
Weibull	34.02	0.9992	0.000[c]	6.72	3.02
Probit	34.02	0.9997	0.000[c]	8.57	5.09
Log-logistic	34.02	0.9997	-0.000[c]	9.14	5.21
Gamma[a]	34.02	0.9995	0.000[c]	7.77	3.14
Multistage[b]	**32.02**	**1.0000**	**-0.000[c]**	**6.87**	**2.72**
Quantal Linear	35.27	0.3286	-1.126[d]	3.03	2.04

[a] Restrict power >=1
[b] Restrict betas >=0; Degree of polynomial = 2
[c] Scaled residual at estimated probability of 0.2
[b] Scaled residual at estimated probability of 0.29

The results for the six dichotomous models are presented in this Appendix. The Multistage model provided the best fit as assessed by the AIC value. Therefore, the $BMCL_{10}$ value of 2.72 ppm, derived from the Multistage model, was selected as the POD for calculating the chronic ReV.

In order to obtain the full benchmark dose modeling outputs from the benchmark dose modeling software, please send an email providing the name of the DSD and requesting the benchmark dose modeling results to the following email: tox@tceq.texas.gov.