Development Support Document
Final, October 15, 2007
Accessible 2013

1,1-Dichloroethylene

CAS Registry Number: 75-35-4

Prepared by

Shannon Ethridge, M.S.

Toxicology Section

Chief Engineer's Office

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

CHAPTER 1 SUMMARY TABLES 4

CHAPTER 2 MAJOR USES OR SOURCES 6

CHAPTER 3 ACUTE EVALUATION 6

3.1 HEALTH-BASED ACUTE REV AND ESL 6
3.1.1 Physical/Chemical Properties and Key Studies 6
3.1.2 Mode-of-Action (MOA) Analysis 10
3.1.3 Dose Metric 10
3.1.4 Point of Departure (POD) for the Key Study 10
3.1.5 Dosimetric Adjustments 11
3.1.6 Critical Effect and Adjustment of POD_{HEC} 11
3.1.7 Health-Based Acute ReV and $^{acute}ESL$ 11
3.2 WELFARE-BASED ACUTE ESLS 12
3.2.1 Odor Perception 12
3.2.2 Vegetation Effects 12
3.3 SHORT-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 12

CHAPTER 4 CHRONIC EVALUATION 13

4.1 NONCARCINOGENIC POTENTIAL 13
4.1.1 Physical/Chemical Properties and Key Studies 13
4.1.2 MOA Analysis and Dose Metric 17
4.1.3 POD for Key and Supporting Studies 17
4.1.4 Dosimetric Adjustments 17
4.1.5 Adjustment of POD_{HEC} and Critical Effect 18
4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ 19
4.1.7 Comparison of Results 19
4.2 CARCINOGENIC POTENTIAL 20
4.3 WELFARE-BASED CHRONIC ESL 21
4.4 LONG-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 21

CHAPTER 5. REFERENCES 21

5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT 21

LIST OF TABLES

TABLE 1 HEALTH- AND WELFARE-BASED VALUES 4
TABLE 2 CHEMICAL AND PHYSICAL DATA 5
TABLE 3 SUMMARY OF ACUTE ANIMAL INHALATION STUDIES 9
TABLE 4 DERIVATION OF THE ACUTE REV AND $^{ACUTE}ESL$ 12
TABLE 5 SUMMARY OF SUBCHRONIC AND CHRONIC ANIMAL INHALATION STUDIES 16

TABLE 6 COMPARISON OF UFS APPLIED TO THE POD_{HEC} 18
TABLE 7 DERIVATION OF THE CHRONIC REV AND $^{CHRONIC}ESL_{NONLINEAR(NC)}$ 20

Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of 1,1-dichloroethylene. Table 2 provides summary information on 1,1-dichloroethylene's physical/chemical data.

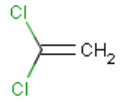
Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentrations**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	210 µg/m^3 (54 ppb) **Short-Term ESL for Air Permit Reviews**	Critical Effect: Centrilobular swelling (hepatic effects) in CD-1 male mice
ReV (HQ = 1)	710 µg/m^3 (180 ppb) *	Critical Effect: Same as above
$^{acute}ESL_{odor}$	---	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)	100 µg/m^3 (26 ppb) **Long-Term ESL for Air Permit Reviews**	Critical Effect: Focal necrosis of liver in rats, dogs, and monkeys
ReV (HQ = 1)	340 µg/m^3 (86 ppb) *	Critical Effect: Same as above
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$	---	Data are inadequate
$^{chronic}ESL_{veg}$	---	No data found

*Values that may be used for evaluation of air monitoring data

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

Table 2 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_2H_2Cl_2$	NIOSH (National Institute of Occupational Safety and Health) chemical safety card
Chemical Structure		Chemfinder 2004
Molecular Weight	96.9 (g/mole)	TRRP (Texas Risk Reduction Program) 2006
Physical State	liquid	TRRP 2006
Color	colorless	NIOSH chemical safety card
Odor	Sweet, chloroform-like	Ruth 1986
CAS Registry Number	75-35-4	TRRP 2006
Synonyms	1,1-Dichloroethene Vinylidene chloride DCE VDC	Chemfinder 2004
Solubility in water	0.25 g/100 ml at 25^{o}C	NIOSH chemical safety card
Log Kow or Pow	Log Kow = 2.12	TRRP 2006
Vapor Pressure	591 mm Hg at 20^{o}C	TRRP 2006
Vapor Density (air = 1)	3.3	NIOSH chemical safety card
Density (water = 1)	1.2	NIOSH chemical safety card
Melting Point	-122^{o}C	NIOSH chemical safety card
Boiling Point	32^{o}C	NIOSH chemical safety card
Conversion Factors	3.97 mg/m^3 = 1 ppm @ 25°C 1 mg/m^3 = 0.25 ppm	American Conference of Governmental Industrial Hygienists

Chapter 2 Major Uses or Sources

1,1-Dichloroethylene (1,1-DCE) is a man-made chemical and is not found naturally in the environment. It is used mainly in the production of polyvinylidene chloride polymers (PVDC). PVDC is used to make certain plastics (such as packaging materials and flexible films like plastic wrap) and flame-retardant coatings for fiber and carpet backing. PVDC is also used for furniture and automobile upholstery, drapery fabric, and outdoor furniture (USEPA 2002).

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

1,1-DCE is a volatile, colorless liquid that evaporates quickly at room temperature. It has a sweet, chloroform-like odor. The main chemical and physical properties of 1,1-DCE are summarized in Table 3. It is soluble in most organic solvents and is very slightly soluble in water.

3.1.1.2 Essential Data and Key Studies

Limited information is available on the systemic effects of inhaled 1,1-DCE in humans. Information comes primarily from case reports and/or insufficiently detailed mortality studies in humans in which the concentration and duration of exposure to 1,1-DCE were not quantified. Concurrent exposure to other toxic substances could not be ruled out in most of the cases. The information available indicates that 1,1-DCE can cause neurotoxicity after acute exposure in humans (USEPA 1976). Animal data show the target organs for 1,1-DCE after acute inhalation exposure include the central nervous system, liver, kidney, lungs, and occasionally the heart (ATSDR 1994). The liver is the major target organ of toxicity after acute inhalation exposure. Liver effects of 1,1-DCE in mice are among the effects observed at the lowest exposure levels following acute inhalation exposure as discussed in Section 3.1.1.2.2.

3.1.1.2.1 Human Studies

The health effects observed in humans occur at high concentrations and include odor perception (Section 3.2) and neurological effects. Central nervous system depression and symptoms of inebriation, which may progress to unconsciousness, have been observed in humans after acute inhalation exposure to high concentrations (approximately 4000 ppm) of 1,1-DCE (USEPA 1979). Complete recovery generally occurs if exposure is not prolonged. Two cases of persistent cranial nerve disorders were observed following acute inhalation of 1,1-DCE in workers involved in manually cleaning tanks used in the transport of 1,1-DCE copolymers (Fielder et al. 1985). The effects were most likely the result of dichloroacetylene formation from 1,1-DCE due

to heat and the presence of alkali from the soaps used. Since relevant, well-conducted human studies are not available, animal studies were used to develop the acute ReV.

3.1.1.2.2 Animal Studies

See Table 4 for information regarding acute inhalation exposure animal studies with a LOAEL (Lowest Observed Adverse Effect Level) below 160 ppm (ATSDR 1994). Mice appear to be the most sensitive animal species to the acute effects of 1,1-DCE inhalation exposure. Reitz et al. (1980) evaluated the effects of 6-h continuous inhalation exposure to 0, 10, and 50 ppm 1,1-DCE in CD-1 male mice (three to six per group) and Sprague Dawley male rats (three to six per group). This study was designed to examine the effects of 1,1-DCE on DNA synthesis and DNA repair in the kidney and liver. Samples of kidney and liver tissue were removed from treated animals at necropsy and examined histologically to determine the extent of tissue damage. DNA alkylation was determined to be very low in rats and mice although tissue damage was observed and reported in mice. Hepatic effects (centrilobular swelling) were observed in male mice in the 50 ppm exposure group. Renal nephrosis was observed in male mice in the 10 and 50 ppm exposure groups; however, renal nephrosis may be a species and gender specific effect because of enzymatic differences (CYP2E1) in male mice compared to female mice and other species (Speerschneider and Dekant 1995). Histopathological data were not presented for rats. The Reitz et al. (1980) study was selected as the key study.

Short et al. (1977) evaluated the developmental toxicity of 1,1-DCE administered by inhalation to pregnant CD-1 mice and CD rats. Pregnant rats were exposed to 0, 15, 57, 300, or 449 ppm for 22-23 h/day on gestational days (GDs) six through sixteen. Dams were sacrificed on GD twenty. Maternal toxicity in rats was indicated by severe maternal weight loss at $\geq$ 15 ppm and by maternal mortality at $\geq$ 57 ppm. Statistically significant increases in multiple skeletal and soft tissue anomalies were observed in rats but were attributed to severe maternal toxicity. Pregnant mice were exposed to 0, 15, 30, 57, 144, or 300 ppm for 22-23 h/day on GDs six through sixteen. Dams were sacrificed on GD seventeen. Maternal toxicity in mice occurred at $\geq$ 30 ppm, as indicated by statistically significant decreases in maternal weight gain. At $\geq$ 30 ppm there was severe fetal toxicity with complete early resorptions of the litters. Ossification problems with the incus and sternebrae occurred in mice exposed to 15 ppm although a similar effect was observed in a feed restricted group exposed to 0 ppm 1,1-DCE. In Part 2 of the study, pregnant mice were exposed to 0, 41, 54, and 74 ppm for three to nine day intervals that ended on GD fifteen. In Part 3 of the study, mice were exposed to 0, 56, 81, and 112 ppm for two to three day intervals beginning and ending at various times during gestation. Fetal effects in Part 2 and 3 of the experiment were either attributed to maternal toxicity or determined to be unrelated to 1,1-DCE exposure. The authors concluded that 1,1-DCE is a weak teratogen with little primary effect on development. The TS (Toxicology Section) determined that this study was not useful in evaluating the developmental toxicity of 1,1-DCE because fetal effects occurred at concentrations that produced maternal toxicity except for the 15 ppm exposure group in mice. The fetal effect observed in this treatment group were similar to those observed in a feed restricted group exposed to 0 ppm 1,1-DCE.

Murray et al. (1979) evaluated the developmental toxicity of 1,1-DCE administered by inhalation to pregnant Sprague-Dawley rats and New Zealand white rabbits. Pregnant rats were exposed to 0, 20, 80, or 160 ppm 1,1-DCE for 7 h/day on GDs six through fifteen. No significant effects on maternal toxicity were observed at 20 ppm. Decreases in maternal food consumption and weight gain were observed in dams exposed to 80 and 160 ppm and an increase in maternal liver weight relative to body weight was observed at 160 ppm. The incidence of major malformations among litters of rats exposed to 1,1-DCE were not significantly different from controls. Minor skeletal alterations were observed in litters of rats exposed to 80 or 160 ppm. In the same study, pregnant rabbits were exposed to 0, 80, or 160 ppm 1,1-DCE for 7 h/day on GDs six through eighteen. The body weight gain of dams exposed to 160 ppm but not 80 ppm was significantly decreased during the period of exposure. The incidence of major malformations among litters of rabbits exposed to 1,1-DCE was not significantly different from controls at 80 or 160 ppm. Minor skeletal alterations were observed in litters of rabbits exposed to 160 ppm. The authors concluded that 1,1-DCE was not teratogenic in rats or rabbits inhaling the compound 7 h/day at concentrations sufficiently high to produce maternal toxicity. The TS determined that this study was not useful in evaluating the developmental toxicity of 1,1-DCE because fetal effects occurred at concentrations that produced maternal toxicity.

Anderson et al. (1977) evaluated the reproductive toxicity of 1,1-DCE administered by inhalation in CD-1 mice. Male mice were exposed by inhalation to 0, 10, and 30 ppm 1,1-DCE for 6h/day for five days then mated with undosed female mice. Doses of 50 and 75 ppm were also tested but produced significant mortality in exposed male mice. No adverse reproductive effects were reported at 30 ppm.

Reitz et al. 1980 based on hepatic effects in mice (ie. centrilobular swelling) was selected as the key study over other available acute studies because it used the most sensitive species and exhibited toxic effects below the LOAELs reported in other studies.

Table 3 Summary of Acute Animal Inhalation Studies

Study	Effect Type	Animal Strain	Exposure Duration	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Reitz et al. 1980	Systemic	CD-1 mouse (male)	6 h per day for 1 day	10	50	Centrilobular swelling
Reitz et al. 1980	Systemic	CD-1 mouse (male)	6 h per day for 1 day	---	10	Renal nephrosis[a]
Short et al. 1977	Developmental	CD rat	23 h per day for 11 days, GD6-16	---	15	Lateral ventricular hydrocephalus[b]
Short et al. 1977	Developmental	CD-1 mouse	23 h per day for 11 days, GD6-16	---	15	Unossified incus, incompletely ossified sternebrae
Short et al. 1977	Developmental	CD-1 mouse	23 h per day for 8 days, GD8-15	---	41	Unossified incus, incompletely ossified supraoccipital[b]
Short et al. 1977	Developmental	CD-1 mouse	23 h per day for 4 days, GD12-15	---	54	Fetal resorptions[b]
Murray et al. 1979	Developmental	Sprague Dawley rat	7 h per day for 10 days, GD6-15	20	80	Wavy ribs and delayed ossification of skull[b]
Murray et al. 1979	Developmental	New Zealand rabbit	7 h per day for 13 days, GD6-18	80	160	Fetal resorptions[b]
Anderson et al. 1977	Reproductive	CD-1 mouse	6 h per day for 5 days	30	---	

[a]Effects may be species and sex specific.

[b]Fetal effects occurred at concentrations that caused maternal toxicity.

3.1.2 Mode-of-Action (MOA) Analysis

1,1-DCE is rapidly absorbed following inhalation. The majority of absorbed 1,1-DCE is rapidly metabolized to nonvolatile compounds and covalently bound derivatives. Experiments in laboratory animals demonstrate that 1,1-DCE is metabolized by CYP2E1 (Cytochrome P450 2E1) to produce three metabolites: dichloroethylene epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde. All of these metabolites react with glutathione (GSH) and/or water. The epoxide, and possibly to a lesser extent the chloroacetaldehyde, are believed to be associated with the tissue reactivity and toxic effects in tissues that ensue after significant depletion of GSH (USEPA 2002).

The major metabolites of 1,1-DCE in human liver and lung microsomal incubations include the GSH epoxide-derived conjugates 2-(glutathionyl)acetyl glutathione and 2-S-glutathionyls acetate (Dowsley et al. 1999). 1,1-DCE is metabolized to epoxide-derived GSH conjugates at 2.5-3-fold higher levels in human liver microsomes than in mouse liver microsomes. These conjugates were also the major products formed in eight human lung microsomes. CYP2E1 catalyzes the formation of the 1,1-DCE epoxide in both human and animal tissues (Dowsley et al. 1996).

A physiologically-based pharmacokinetic (PBPK) model is available for 1,1-DCE in the rat for oral and inhalation exposure (D'Souza and Anderson 1988). No validated model is currently available for humans. D'Souza and Anderson (1988) used allometric scaling to estimate comparative amounts of epoxide formed in rats and humans. Cardiac output and pulmonary ventilation were scaled by (body weight)$^{0.7}$, V_{max} was scaled by (body weight)$^{0.74}$, and body fat was estimated at 7% in the 200 g rat and 20% in the 70 kg human. The estimated amount of epoxide formed was fivefold lower in humans than in rats when the inhalation exposure was less than 100 ppm.

3.1.3 Dose Metric

In the acute study selected as the key study, data on exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), exposure concentration of parent chemical will be used as the default dose metric.

3.1.4 Point of Departure (POD) for the Key Study

A NOAEL (No Observed Adverse Effects Level) of 10 ppm based on a 6-h exposure from the Reitz et al. (1980) study was used as the POD.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

As stated in Section 3.2 of the ESL guidelines (TCEQ 2006), a duration adjustment is required to convert a 6-h concentration POD to a 1-h concentration POD_{ADJ}. Haber's Rule as modified by ten Berge (1986) is applied in this situation to determine the 1-h concentration ($C_1^n \times T_1 = C_2^n \times T_2$). Since 1,1-DCE toxicity is both concentration- and duration-dependent, and a concentration greater than 1 h is being adjusted to 1 h, a default value of "n" = 3 was used as recommended in the ESL guidelines to calculate the POD_{ADJ} (TCEQ 2006).

$C_1^n \times T_1 = C_2^n \times T_2$
10^3 ppm x 6 hr = C_2^3 x 1 hr
C_2 = 18 ppm

3.1.5.2 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 1,1-DCE, which is a vapor producing remote effects, based on a default value of 1 for the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A/(H_{b/g})_H$).

$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$
POD_{HEC} = 18 ppm x 1
POD_{HEC} = 18 ppm

3.1.6 Critical Effect and Adjustment of POD_{HEC}

As indicated in Section 3.1.1.2.2, data from animal studies suggest that liver toxicity is the most sensitive endpoint for acute exposure to 1,1-DCE. The specific critical effect for the key study (Reitz et al. 1980) is centrilobular swelling in CD-1 male mice exposed to 1,1-DCE.

The following uncertainty factors (UFs) were applied: a UF_H of 10 for intraspecies variability, a UF_A of 3 for interspecies variability because a dosimetric adjustment was made, and a UF_D of 3 to account for deficiencies in the key study (small sample size and the use of only two chemical exposure groups). The total UF = 100.

$ReV = POD_{HEC} / (UF_H \times UF_A \times UF_D)$
ReV = 18 ppm / 100
ReV = 0.18 ppm = 180 ppb = 710 µg/m^3

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

As shown in Table 5, the acute ReV is 710 µg/m^3 (180 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 210 µg/m^3 (54 ppb).

Table 4 Derivation of the Acute ReV and ^{acute}ESL

Parameter	Summary
Study	Reitz et al. 1980
Study population	3 - 6 CD-1 male mice
Study quality	Medium
Exposure Methods	6 h exposure via inhalation, 0, 10 and 50 ppm
Critical Effects	Centrilobular swelling in liver
POD (original study)	10 ppm (NOAEL)
Exposure Duration	6 h
POD_{ADJ} (extrapolated to 1-h concentration)	18 ppm
POD_{HEC}	18 ppm (default RGDR = 1)
Total UFs	100
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable (NA)
Incomplete Database UF	3
Database Quality	Medium to high
Acute ReV [1 h] (HQ = 1)	**710 µg/m^3 (180 ppb)**
^{Acute} ESL [1 h] (HQ = 0.3)	**210 µg/m^3 (54 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

1,1-Dichloroethylene has a sweet, chloroform-like odor with odor thresholds reported from 190 ppm to 500 ppm (Amoore and Hautula 1983; Ruth 1986). Since the these two sources are not accepted odor reference sources listed in the TCEQ ESL guidelines (TCEQ 2006), the TS did not develop an $^{acute}ESL_{odor}$.

3.2.2 Vegetation Effects

No acute vegetative studies were identified for 1,1-DCE.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

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

- acute ReV = 710 µg/m^3 (180 ppb)
- ^{acute}ESL = 210 µg/m^3 (54 ppb)

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 210 µg/m^3 (54 ppb) (Table 1). The acute ReV of 710 µg/m^3 (180 ppb) is the acute comparison value for the evaluation of ambient air monitoring data (Table 1). The ^{acute}ESL is not used to evaluate ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical and chemical properties of 1,1-DCE are discussed in Chapter 3. Limited information is available on the toxic effects of inhaled 1,1-DCE in humans. Information comes primarily from case reports and/or insufficiently detailed mortality studies in which the concentration and duration of exposure to 1,1-DCE were not quantified. Concurrent exposure to other toxic substances could not be ruled out in most of the cases. The information available indicates that 1,1-DCE is possibly associated with hepatotoxicity and nephrotoxicity after repeated, low-level exposure in humans (USEPA 1976). Animal data show the target organs for 1,1-DCE after chronic inhalation exposure include the central nervous system, liver, kidney, lungs, and occasionally the heart (ATSDR 1994). The liver is the major target organ of toxicity after chronic inhalation exposure.

4.1.1.1 Human Studies

Case reports and mortality studies in humans have reported hepatotoxicity and nephrotoxicity after repeated, low-level exposures to 1,1-DCE (USEPA 1976; Ott et al. 1976). USEPA (1976) reported a 50% or greater loss in liver function in twenty-seven of fourty-six workers (59%) exposed to 1,1-DCE for six years or less at a 1,1-DCE polymerization plant. The results from this study were not well-reported and no follow-up study was conducted. These investigations were conducted in industrial environments and the possibility of exposure to other chemicals could not be ruled out. Since relevant well-conducted human studies are not available, animal studies were used to develop the chronic ReV.

4.1.1.2 Animal Studies

In animal studies, data suggest the most sensitive endpoints for long-term exposure to 1,1-DCE are hepatotoxicity and nephrotoxicity. The long-term effects of 1,1-DCE in animals are discussed in USEPA (2002) and ATSDR (1994). See Table 6 for information regarding subchronic inhalation studies ninety days in duration and chronic inhalation exposure animal studies with a LOAEL ≤ 55 ppm.

4.1.1.2.1 Subchronic Inhalation Studies

Two subchronic inhalation studies with an exposure duration of ninety days were identified in the literature (Prendergast et al. 1967 and Balmer et al. 1976). Balmer et al. (1976) reported mild

cytoplasmic vacuolization in the livers of male and female rats exposed to 25 or 75 ppm 1,1-DCE 6 h/day, 5 days/week, for ninety days. The authors concluded that this effect was reversible. Prendergast et al. (1967) identified adverse hepatic and/or renal effects in rats (fifteen or fourty-five per group), Hartley guinea pigs (fifteen or fourty-five per group), beagle dogs (two or six per group), and squirrel monkeys (three, nine, or twenty-one per group) exposed to inhaled 1,1-DCE. Continuous exposure to 1,1-DCE, 24 h/day over ninety days, produced more severe effects than intermittent exposure, 6 h/day, 5 days/week for six weeks, in the species tested. This study included multiple exposure levels of 0, 5, 15, 25, and 48 ppm. Mortality, hematologic, and body weight data were well tabulated and presented in this study. Histopathologic evaluation was conducted on the heart, lung, liver, spleen, and kidneys.

Following continuous exposure, adverse hepatic effects included focal necrosis in monkeys, dogs, and rats (LOAEL = 48 ppm, NOAEL = 25 ppm); and altered lipid content and increases in serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase (AP) in guinea pigs (LOAEL = 48 ppm, NOAEL = 5 ppm). Additionally, renal alterations were observed in rats as nuclear hypertrophy in the tubular epithelium (LOAEL = 48 ppm, NOAEL = 15 ppm). Monkeys exposed to 1,1-DCE also displayed a greater than 25% decrease in body weight (LOAEL = 48 ppm, NOAEL = 5 ppm).

4.1.1.2.2 Chronic Inhalation Studies

Several chronic inhalation studies were identified in the literature (Maltoni et al. 1985, Quast et al. 1986, Lee et al. 1977). Quast et al. (1986) evaluated the toxicity of 1,1-DCE in male and female Sprague Dawley rats exposed to 1,1-DCE by inhalation for eighteen months. Rats were exposed to 0, 10, and 40 ppm 1,1-DCE for 6 h/day, 5 days/week, for the first five weeks of the study. No treatment-related effects were observed in animals sacrificed at five weeks at the highest level of exposure (40 ppm), so exposure concentrations were changed to 25 and 75 ppm for the remainder of the study. Rats were exposed to 0, 25, and 75 ppm 1,1-DCE for 6 h/day, 5 days/week, for the remainder of the eighteen months (Quast et al. 1986). After the eighteen-month exposure period, surviving animals were held for another 6 months and then sacrificed. No exposure-related changes were noted in mortality, body weight changes, appearance and demeanor, clinical chemistry determinations, hematololgy, urinalysis, or cytogenetic evaluation of bone marrow preparations. Female rats exposed to 25 and 75 ppm were reported to exhibit fatty changes in the liver during the eighteen-month exposure period with the effects reversing at the twenty-four-month sacrifice. The effect was statistically significant ($p<0.05$) only at the highest exposure (75 ppm).

Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Sprague Dawley rats and Swiss mice. Rats were exposed to 0, 10, 25, 50, 100, or 150 ppm for 4 h/day, 4-5 days/week for fifty-two weeks. Following the fifty-two-week exposure period, animals were observed until death. Full necropsy and histopathological examination were performed. No biologically significant changes in mortality or body weight were observed, and there were no biologically significant noncancer effects in any organ in either sex. In the same study, swiss

male and female mice were exposed to 0, 10, or 25 ppm 1,1-DCE for 4 h/day, 4-5 days/week for fifty-two weeks. Groups of animals exposed to ≥ 50 ppm showed extreme toxicity after only a few exposures and this portion of the experiment was terminated. Following the fifty-two-week exposure period, animals were observed until death. Full necropsy and histopathological examinations were performed. No biologically significant noncancer effects were observed in any organ, except for a marginal increase in regressive changes in the kidney and a marginal increase in kidney abscesses and nephritis. The results for male mice were statistically significant ($p<0.05$) for both effects at both exposures. The results for female mice were statistically significant ($p<0.05$) only for regressive changes at 25 ppm. There was no investigation of the effects at the termination of the one-year exposure. The LOAEL reported for this study was 25 ppm based on tubular necrosis.

Lee et al. (1977) conducted a toxicity study of 1,1-DCE in albino CD-1 mice and CD rats. Mice and rats (36 of each sex per group) were exposed to 0 or 55 ppm 1,1-DCE for 6 h/day, 5 days/week, for twelve months. Four animals of each species, sex, and exposure level were terminated for various laboratory tests and gross histopathological examinations at the end of one, two, three, six, and nine months; the surviving animals were terminated at the end of twelve months. Mice exposed to 55 ppm 1,1-DCE exhibited hepatocellular necrosis and tubular necrosis (LOAEL = 55 ppm).

The subchronic study by Prendergast et al. (1967) was selected as the key study because of its superior design (use of multiple doses, use of multiple species including non-human primates, evaluation of multiple endpoints, and continuous exposure regimen). Quast et al. (1986) was used as a supporting study. Lee et al. (1977) was not used as a supporting study because only one dose was tested, and the LOAEL from this dose is based on severe effects in the liver and kidney. Maltoni et al. (1985) was not used as a supporting study because there was no investigation of the effects at the termination of the 1-year exposure period.

Table 5 Summary of Subchronic and Chronic Animal Inhalation Studies

Study	Animal Strain	Exposure Duration	System	NOAEL (ppm)	LOAEL (ppm)	Response at LOAEL
Subchronic						
Prendergast et al. 1967	Rat	90 d/ 24 h/ d	Resp	48		None
			Hepatic	25	48	Focal necrosis
			Renal	15	48	Nuclear hypertrophy of tubular epithelium
	Squirrel monkeys	90 d/ 24 h/ d	Resp	48		
			Hepatic	25	48	Focal necrosis of liver
			Other (body weight)	5	48	>25% decrease in body weight
	Beagle dogs	90 d/ 24 h/ d	Resp	48		None
			Hepatic	25	48	Focal necrosis of liver
	Hartley Guinea pigs	90 d/ 24 h/ d	Resp	48		
			Hepatic	5	48	Increased SGPT and AP enzyme activity; decreased lipid content
Balmer et al. 1976	Rat	90 d 5 d /wk 6 h/ d	Hepatic		25	Cytoplasmic vacuolization
Chronic						
Quast et al. 1986	Rat	18 mo/ 5 d /wk 6 h/ d	Resp	75		None
			Hemato	75		None
			Renal	75		None
			Hepatic	25	75	Decreased liver weight; fatty changes in the midzonal region
Lee et al. 1977	Mouse	1 yr 5 d/ wk 6 h/d	Hemato	55		None
			Hepatic		55	Hepatocellular necrosis
			Renal		55	Tubular necrosis
Maltoni et al. 1985	Mouse	52 wk 5 d/ wk 4 h/ d	Renal	10	25	Tubular nephrosis

4.1.2 MOA Analysis and Dose Metric

The MOA analysis for 1,1-DCE is discussed in Section 3.1.2. For key and supporting studies, data on exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics is not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), exposure concentration of parent chemical will be used as the default dose metric.

4.1.3 POD for Key and Supporting Studies

A NOAEL of 25 ppm was identified from the Prendergast et al. (1967) study based on adverse hepatic effects (focal necrosis) in rats, dogs, and monkeys. The NOAEL of 5 ppm reported for adverse hepatic effects (increased SGPT and AP enzyme activity and decreased lipid content) in guinea pigs was not used as a POD because only two doses (5 and 48 ppm) were evaluated for these endpoints and there is some degree of uncertainty as to what dose would begin causing adverse effects as histopathological data from the 15 and 25 ppm exposure groups did not indicate adverse hepatic effects. The NOAEL of 5 ppm reported for reduced body weight in monkeys was not used as a POD because a dose-response effect could not be determined for this endpoint (9.8% increase at 5 ppm, 10.3% decrease at 15 ppm, 6.1% decrease at 25 ppm, and 28.1% decrease at 48 ppm) and a definite adverse effect attributable to the chemical exposure did not occur until the 48 ppm treatment group.

USEPA conducted benchmark dose modeling based on fatty changes in the liver and decreased liver weight reported in Quast et al. (1986). A detailed discussion is available in Appendix B of USEPA (2002). A $BMCL_{10}$ (Benchmark Concentration Level) of 9.8 ppm was identified.

4.1.4 Dosimetric Adjustments

4.1.4.1 Exposure Duration Adjustments

No duration adjustment was required for the POD from the Prendergast et al. (1967) study because the inhalation exposure was continuous.

The POD ($BMCL_{10}$) from USEPA 2002 based on the Quast et al. (1986) study was adjusted to a continuous exposure concentration:

$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$POD_{ADJ} = 9.8 \text{ ppm} \times 6/24 \times 5/7$$
$$POD_{ADJ} = 1.75 \text{ ppm}$$

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

A dosimetry adjustment from an animal concentration to a POD_{HEC} was performed for 1,1-DCE, a vapor producing systemic effects, based on a default $(H_{b/g})_A/(H_{b/g})_H$ = RGDR = 1 for the POD

for each study. The resulting POD_{HEC} from the NOAEL of 25 ppm in the Prendergast et al. (1967) study is 25 ppm. The resulting POD_{HEC} from the POD_{ADJ} of 1.75 ppm in the Quast et al. (1986) study is 1.75 ppm.

4.1.5 Adjustment of POD_{HEC} and Critical Effect

4.1.5.1 Uncertainty Factors

A summary of UFs applied to each POD_{HEC} can be found in Table 7. A subchronic-to-chronic UF of 10 was applied for Prendergast et al. (1967). A UF of 3 for interspecies variability and a UF of 10 for intraspecies variability were used for both studies. A LOAEL-to-NOAEL UF was not used for the Prendergast et al. (1967) study because the POD_{HEC} was based on a NOAEL. Benchmark dose modeling was used to derive the POD_{HEC} from Quast et al. (1986) based on a mild adverse effect (fatty changes in the liver and decreased liver weight); therefore, a LOAEL-to-NOAEL UF was not applied. The database was considered complete for this chemical; however, an incomplete database UF of 3 was used for Quast et al. (1986) to account for deficiencies in the study (use of only one species, dosing regimen was changed after first five weeks, exposure was not continuous, only three doses were evaluated). The Prendergast et al. (1967) study was well-designed (use of multiple doses and use of multiple species including non-human primates, continuous exposure regimen, and evaluation of multiple toxicological endpoints); therefore, a database UF was not applied in this case.

Table 6 Comparison of UFs Applied to the POD_{HEC}

PODHEC	Subchronic–to-chronic	Intra-species	Inter-species	LOAEL-to-NOAEL	Incomplete Database	Total UF	Reference Value
Prendergast et al. (1967) 101 mg/m^3 (25 ppm)	10	10	3	1	1	300	340 $\mu g/m^3$ (86 ppb)
Quast et al. (1986) 1.8 ppm	1	10	3	1	3	30	18 ppb

4.1.5.2 Critical Effect

As indicated in Section 4.1.1.2, data from human and animal noncarcinogenic studies suggest that hepatotoxicity and renal toxicity are the most sensitive endpoints for exposure to 1,1-DCE. The specific critical effect from the key study (Prendergast et al. 1967) is adverse hepatic effects (focal necrosis) in rats, dogs, and squirrel monkeys. This is supported by Quast et al. (1986) which reported adverse hepatic effects (fatty changes in the liver and decreased liver weight) in rats.

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

As discussed in the previous section, UFs are applied to the key study (Prendergast et al. 1967) POD_{HEC} to derive the chronic ReV (Table 7). Rounding to two significant figures at the end of all calculations yields a chronic ReV of 86 ppb (340 µg/m^3) using the NOAEL of 25 ppm as the POD. At the target HQ of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 26 ppb (100 µg/m^3)(Table 8). For the supporting study (Quast et al. 1986), application of the UFs yields a similar value for the chronic ReV (18 ppb or 71 µg/m^3; Table 7) and $^{chronic}ESL_{nonlinear(nc)}$ (5.4 ppb or 21 µg/m^3).

4.1.7 Comparison of Results

The chronic ReVs calculated based on the POD_{HEC} values from Prendergast et al. (1967) and Quast et al. (1986) are similar (less than an order of magnitude apart). USEPA calculated an RfC of 200 µg/m^3 (50 ppb) based on the Quast et al. (1986) chronic inhalation study in rats. California Environmental Protection Agency (CalEPA) calculated a Chronic Reference Exposure Level (REL) of 70 µg/m^3 (20 ppb) based on the NOAEL of 5 ppm for liver enzyme changes in guinea pigs in the Prendergast et al. (1967) subchronic inhalation study (see Section 4.1.3 for an explanation of why the TS did not use this POD). The chronic ReV of 340 µg/m^3 (86 ppb), based on Prendergast et al. (1967), is similar to the CalEPA chronic REL and the USEPA RfC (within an order of magnitude).

Table 7 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	Summary
Study	90 day bioassay (Prendergast et al. 1967)
Study Population	Rats (15 or 45/group), beagle dogs (2 or 6/group), and squirrel monkeys (3, 9, or 21/group)
Study Quality	high
Exposure Method	90 day continuous exposure via inhalation at 0, 20, 61, 101, and 189 mg/m^3
Critical Effects	Focal necrosis of liver
POD (original study)	25 ppm (101 mg/m^3) (NOAEL)
Exposure Duration	24 h/day 7 days/week for 90 days
Extrapolation to continuous exposure (POD_{ADJ})	25 ppm (101 mg/m^3) (no adjustment necessary)
POD_{HEC}	25 ppm (101 mg/m^3) (vapor with systemic effects, based on default RGDR = 1.0)
Total UFs	300
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	NA
Subchronic to chronic UF	10
Incomplete Database UF	1
Database Quality	high
Chronic ReV (HQ = 1)	**340 µg/m^3 (86 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**100 µg/m^3 (26 ppb)**

4.2 Carcinogenic Potential

Using the 1999 draft USEPA cancer guidelines, USEPA (2002) concluded that 1,1-DCE has suggestive evidence of carcinogenic potential; however it is not sufficient to assess human carcinogenic potential following inhalation exposure studies in rodents. This is consistent with the USEPA 2002 cancer guidelines. Maltoni et al. (1985) reported that male mice developed kidney tumors at one exposure, although similar results were not observed in female mice or male or female rats. Further studies have suggested that this effect may be species and sex-specific based on enzymatic differences between male and female mice, male and female rats, and human kidney cells. 1,1-DCE causes gene mutations in bacterial systems with metabolic activation, although most genotoxicity studies in mammalian cells indicate a lack of genotoxicity. Human epidemiological data on the carcinogenicity of 1,1-DCE is inconclusive.

The carcinogenic potential of 1,1-DCE is discussed in USEPA (2002) and ATSDR (1994). The TS determines that information to assess human carcinogenicity following inhalation exposure is not sufficient at this time.

4.3 Welfare-Based Chronic ESL

No chronic vegetative studies were identified for 1,1-DCE.

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 = 340 µg/m^3 (86 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 100 µg/m^3 (26 ppb)

The long-term ESL for air permit evaluations is 100 µg/m^3 (26 ppb) (Table 1). The chronic ReV of 340 µg/m^3 (86 ppb) is used for evaluation of air monitoring data (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ is not used to evaluate ambient air monitoring data.

Chapter 5. References

5.1 References Cited in the Development Support Document

Agency for Toxic Substances and Disease Registry (ATSDR). 1994. Toxicological profile for 1,1-dichloroethylene. Atlanta, GA.

Amoore JE and E Hautala. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatiles for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3(6): 272-290.

Anderson D, MCE Hodge, IFH Purchase. 1977. Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice. *Environ Health Perspect* 21:71-78.

California Environmental Protection Agency (CalEPA). 2000. Chronic toxicity summary of 1,-dichloroethylene. Determination of Noncancer Chronic Reference Exposure Levels. Batch 2A.

ChemFinder.com. 2004. 1,1-Dichloroethylene. ChemFinder.com Database and Internet Searching. http://chemfinder.cambridgesoft.com/result.asp, accessed June 6, 2007.

Dowsley TF, JB Ulreich, JL Bolton, et al. 1996. CYP2E1-dependent bioactivation of 1,1-dichloroethylene in murine lung : formation of reactive intermediates and glutathione conjugates. *Toxicol Appl Pharmacol* 139:42-48.

Dowsley TF, K Reid, D Petsikas, et al. 1999. Cytochrome P-450-dependent bioactivation of 1,1-dichloroethylene to a reactive epoxide in human lung and liver microsomes. *J Pharmacol Exp Ther* 289 : 641-648.

Fielder RJ, EA Dale, SD Williams. 1985. Toxicity review 13 : Vinylidene chloride. Her Majesty's Stationary Office, London, England.

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

Maltoni C, P Lefemine, G Cotti, et al., eds. 1985. Experimental research on vinylidcne chloride carcinogenesis: Archives of research on industrial carcinogenesis. Vol. 3. Princeton, NJ: Princeton Scientific Publishers.

Murray FJ, KD Nitschke, LW Rampy, et al. 1979. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. *Toxicol Appl Pharmacol* 49:189-202.

National Institute for Occupational Safety and Health (NIOSH). 2000. International chemical safety card for 1,1-dichloroethylene. ICSC: 0083

Prendergast JA, RA Jones, LJ Jenkins, and J Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. *Toxicol Appl Pharmacol*. 10: 270-289.

Quast JF, MJ McKenna, LW Rampy, et al. 1986. Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. *Fund Appl Toxicol* 6:105-144.

Reitz RH, PG Watanabe, MJ McKenna, et al. 1980. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. *Toxicol Appl Pharmacol* 52357-370.

Ruth J. 1986. Odor thresholds and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 47: A142-A151.

Short RD, JL Minor, JM Winston, et al. 1977. Toxicity studies of selected chemicals: Task II. The development of vinylidene chloride inhaled by rats and mice during gestation. Washington, DC: US Environmental Protection Agency. EPA-560/6-77-022.

ten Berge, WF, A Zwart, LM Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *J Hazard Mater* 13: 301-09.

United States Environmental Protection Agency (USEPA) 1979. Status of toxic chemicals: Vinylidene chloride. Cincinnati, OH: United States Environmental Protection Agency. EPA 600/2-79-2100 (PB80-146442).

United States Environmental Protection Agency (USEPA) 1976. Summary characteristics of selected chemicals of near-term interest. Washington, DC: United States Environmental Protection Agency. EPA 56014-76-004.

United States Environmental Protection Agency (USEPA) 2002. Toxicological review of 1,1-dichloroethylene. Washington, DC: United States Environmental Protection Agency. EPA/635/R02/002.