Development Support Document
Final March 23, 2016

Ethylene Dichloride

CAS Registry Number: 107-06-2

Prepared by
Jessica L. Myers, Ph.D.
Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
ACGIH	American Conference of Industrial Hygienists
ADAF	age-dependent adjustment factor
AEGL	Acute Exposure Guideline Level
ALT	alanine aminotransferase
AMCV	Air Monitoring Comparison Value
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMR	benchmark response
°C	degrees Celsius
CNS	central nervous system
d	day
DSD	development support document
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effect
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effects
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects

Acronyms and Abbreviations	Definitions
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
ET	extrathoracic
GD	gestational day
GLP	good laboratory practice
h	hour(s)
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
HPV	high production volume
HQ	hazard quotient
i.p.	intraperitoneal
IARC	International Agency for Research on Cancer
kg	kilogram
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MW	molecular weight
µg	microgram(s)
$µg/m^3$	micrograms per cubic meter
mg	milligram(s)
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
min	minute(s)
MOA	mode of action
n	number

Acronyms and Abbreviations	Definitions
N/A	Not applicable
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment
PND	postnatal day
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
ReV	reference value
RGDR	regional gas dose ratio
SD	Sprague-Dawley
TAMIS	Texas Air Monitoring Information System
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
URF	unit risk factor
USEPA	United States Environmental Protection Agency

Acronyms and Abbreviations	Definitions
wk	week(s)
yr	year(s)

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values resulting from an acute and chronic evaluation of ethylene dichloride (1,2-dichloroethane; EDC). Please refer to Section 1.6.2 of the TCEQ Toxicity Factor Guidelines (2012) for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on EDC's physical/chemical properties.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	Concentration	Notes
Acute ReV [1 h]	2,200 µg/m^3 (550 ppb) **1-h Short-Term Health**	**Critical Effect(s):** Very slight degeneration and necrosis of the olfactory epithelium in rats
Acute ReV [24 h]	380 µg/m^3 (93 ppb) **24-h Short-Term Health**	**Critical Effect(s):** Very slight degeneration and necrosis of the olfactory epithelium in rats
$^{acute}ESL_{odor}$	---	Pleasant odor; odor-based ESL significantly above health-based values
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	44 µg/m^3 (11 ppb)	**Critical Effect(s):** Suggestive liver and kidney toxicity in rats
$^{chronic}ESL_{nonthreshold(c)}$	2.9 µg/m^3 (0.71 ppb) **Long-Term Health**	**Critical Effect(s):** Increased incidence of combined mammary gland tumors in female rats
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; **$^{chronic}ESL_{threshold(nc)}$**, chronic health-based ESL for threshold dose-response noncancer effects; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

Table 2. Air Permitting Effects Screening Levels (ESLs)

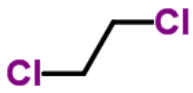
Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	650 µg/m^3 (160 ppb)[a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Very slight degeneration and necrosis of the olfactory epithelium in rats
$^{acute}ESL_{odor}$	---	Pleasant odor; odor-based ESL significantly above health-based values
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	13 µg/m^3 (3.3 ppb)[b]	**Critical Effect:** Suggestive liver and kidney toxicity in rats
$^{chronic}ESL_{nonthreshold(c)}$	2.9 µg/m^3 (0.71 ppb)[c] **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Increased incidence of combined mammary gland tumors in female rats
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] Based on the acute ReV of 2,200 µg/m^3 (550 ppb) multiplied by 0.3 and rounded to two significant digits to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 44 µg/m^3 (11 ppb) multiplied by 0.3 and rounded to two significant digits to account for cumulative and aggregate risk during the air permit review.

[c] Based on the URF of 3.4E-06 (µg/m^3)$^{-1}$ or 1.4E-05 (ppb)$^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_2H_4Cl_2$	ATSDR 2001
Chemical Structure		ChemSpider 2014
Molecular Weight	98.96 g/mol	ATSDR 2001
Physical State at 25°C	Heavy liquid	ATSDR 2001
Color	Colorless	ATSDR 2001
Odor	Pleasant	ATSDR 2001
CAS Registry Number	107-06-2	ATSDR 2001
Synonyms	Ethylene dichloride; 1,2-dichloroethane; EDC; Dutch liquid	ATSDR 2001
Solubility in water	8.69×10^3 mg/L at 20°C	ATSDR 2001
Log K_{ow}	1.48	ATSDR 2001
Vapor Pressure	79.1 mm Hg at 25°C	ATSDR 2001
Relative Vapor Density (air = 1)	1.23 g/cm^3 at 25°C	ATSDR 2001
Melting Point	-35.5°C	ATSDR 2001
Boiling Point	83.5°C	ATSDR 2001
Conversion Factors	1 μg/m^3 = 0.247 ppb 1 ppb = 4.05 μg/m^3 at 25°C	ATSDR 2001

Chapter 2 Major Sources and Uses

EDC is a manufactured chemical that is not found naturally in the environment. EDC is primarily used in the production of vinyl chloride, which is used to manufacture many other products such as plastic and polyvinyl chloride (PVC) products, construction materials, furniture and automobile upholstery, wall coverings, housewares, packaging materials, and automobile parts (ATSDR 2001). In the past, EDC was used as a gasoline additive to scavenge inorganic lead compounds, but the transition to unleaded gasoline removed the need for this addition (OEHHA 2000).

EDC is mostly released into the environment through the air, although it can also be released into soil and water. Although large amounts of EDC from a leak or spill may remain in the soil for more than 40 days, small amounts typically evaporate very quickly and are mostly found in air. Once in the air, EDC is broken down in a slow process by sunlight and has a half-life of approximated 73 days (ATSDR 2001). The Agency for Toxic Substances and Disease Registry (ATSDR) estimates that daily atmospheric concentrations range from 0.01-0.1 ppb for most U.S. rural, suburban, and urban areas, although concentrations may be higher near point sources. In 2014, annual averages for EDC from 50 canister samplers across the state of Texas ranged from not detected to 0.18 ppb (Texas Air Monitoring Information System, TAMIS). The 2008 – 2015 annual averages from four industry-sponsored monitors located in Point Comfort, TX at a site with historical EDC emissions ranged from 0.21 ppb to 1.62 ppb.

Chapter 3 Acute Evaluation

The Development Support Document (DSD) is a summary of the key and supporting studies and procedures used by the Toxicology Division (TD) to derive inhalation toxicity values. This section is based on a review of current literature as well as background readings in ATSDR (2001) and USEPA (2010), which describe in detail the acute toxicity of EDC.

3.1 Health-Based Acute 1-Hour ReV and ^{acute}ESL

3.1.1 Physical/Chemical Properties

EDC is produced as a liquid. It is soluble in water and other organic solvents such as alcohols and ethers, and volatilization occurs easily as well. The primary physical and chemical properties of EDC are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

Several studies have described the effects of acute or occupational exposure to high levels of EDC. Although significant detail about the exposure parameters is typically lacking, such as air concentrations and exact times of exposure, the studies all seem to point to similar biological targets for EDC. Disruptions in the whole body processes such as the central nervous system (CNS), and damage to multiple organs including the liver, kidney and lungs suggests that although these short term studies may be lacking in exposure information, EDC appears to have both a point-of-entry (POE) and systemic mode of action. The following studies were found as individual research papers and/or detailed in ATSDR (2001):

- Nouchi et al. (1984) reported a case study of a 51-year-old man who was exposed to a “thick vapor” of EDC for about 30 minutes (min) while cleaning out a tank. Specific information was not given on the air concentration of EDC, the possibility of other contaminants in the tank, or the precise route of exposure, although the report assumed that it was primarily

through inhalation with some dermal exposure. Coworkers found the man squatting and lethargic in the tank, but he became more alert shortly after being removed. He vomited sporadically overnight and was found drowsy and in respiratory distress approximately 20 hours after the initial exposure. He was admitted to the hospital "delirious and tremulous" and fell into a coma shortly after. He died five days later from cardiac arrhythmia. An autopsy revealed congestion in the lungs, degeneration in the myocardium, liver and renal tubular necrosis, and shrunken nerve cells in the brain.

- Cheng et al. (1999) examined liver function in workers exposed to EDC and vinyl chloride monomer (VCM). EDC is used in the manufacturing of VCM, so occupational exposures often occur concurrently. Cheng et al. surveyed 251 workers from four different VCM plants (mean age 39 years; mean duration of employment 1.1 years) and conducted personal and area sampling. Blood tests for markers of liver function including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) were performed on each of the subjects. Area sampling showed median EDC concentrations generally below 0.5 ppm, with some higher concentrations found in specific area of the plants (1.31 ppm in the oxychlorination area and 2.63 ppm in the EDC loading area). Personal samplers were consistent with area monitors, with EDC unloading operators having a median exposure of 0.77 ppm EDC (range of 0.17 – 333.70 ppm). The subjects were placed into three categories based on their job/exposure: low-EDC-low-VCM, moderate-EDC-low-VCM, and low-EDC-moderate-VCM. When using the low-EDC-low-VCM group as a reference, both the moderate-EDC-low-VCM and low-EDC-moderate-VCM groups had higher odds ratio (OR) for developing an abnormal ALT. The moderate-EDC-low-VCM group also had a higher OR for developing an abnormal AST. GGT was not associated with exposure to EDC or VCM. These results suggest that co-exposure to EDC and VCM may lead to decreased liver function; however the effects of EDC exposure alone were not examined.
- Bowler et al. (2003) reported on the effects of EDC exposure in a group of 221 hazardous waste clean-up workers. This study was done as part of a lawsuit, however the article was peer reviewed and published in a scientific journal. A large spill occurred in the southern US where over 69 million pounds of EDC leaked from an underground pipeline. Approximately 1,600 hazardous waste clean-up workers were hired to clean up the spill, which involved standing in contaminated water and soil without protective equipment. Although dermal exposure was thought to be the primary route of exposure, inhalation of EDC also likely contributed to their exposure. No estimates were given on the exposure concentrations or durations. Approximately 800 of the workers were examined by physicians, with about 400 having mental health and neurological complaints. Of these 400 workers, 221 were referred by the physicians for this study and a complete neuropsychological evaluation. It is important to note that these workers were referred for the study because they had what the physicians considered to be the highest exposures and the most health complaints, so this study has an inherent bias. After several rounds of exclusions, the researchers narrowed the pool down to 137 workers. The researchers concluded that the "available hazardous waste clean-up workers had significantly poorer performance on the neuropsychological tests and

significantly more emotional dysfunction compared to normative test data". The lack of exposure data and the bias inherent in this study make it difficult to use in the development of a ReV.

A lack of well-conducted human studies has led to the use of an animal study to derive the 1-hour (h) acute ReV and ESL.

3.1.2.2 Animal Studies

3.1.2.2.1 Key Animal Study (Hotchkiss et al. 2010)

Hotchkiss et al. (2010) conducted an acute toxicological and neurological evaluation of the effects of EDC inhalation in rats. These studies were in accordance with good laboratory practice (GLP) regulations and followed regulatory guidance set by the USEPA for testing of high production value (HPV) chemicals. Equal numbers of male and female Fischer 344 rats were exposed to target concentrations of 0, 200, 600, and 2,000 ppm EDC for 4 h. Because significant histological changes were observed in the lowest exposure group, an additional set of animals was exposed to concentrations of 0, 50, 100, and 150 ppm for 8 h and 50 ppm for 4 h. Animals were divided into three groups based on their exposure and histological examination:

- Acute inhalation toxicity group 1: equal numbers of male and female Fischer 344 rats with target concentrations of 0, 200, 600, and 2,000 ppm (mean analytical concentrations 0, 196.4, 607.8, and 2029.0) for 4 h (5/sex/group)
- Acute inhalation toxicity group 2: equal numbers of male and female Fischer 344 rats with target concentrations of 0, 50, 100, and 150 ppm (mean analytical concentrations 0, 52.8, 107.5, 155.8 ppm) for 8 h and 50 ppm (mean analytical concentration 52.4) for 4 h (5/sex/group)
- Acute neurotoxicity group: equal numbers of male and female Fischer 344 rats with target concentrations of 0, 200, 600, and 2,000 ppm (mean analytical concentrations 0, 196.4, 607.8, and 2029.0 ppm) for 4 h (10/sex/group)

All rats were exposed in 2 m^3 or 4 m^3 stainless steel and glass whole-body exposure chambers. EDC was vaporized in atmospheric nitrogen using a glass J-tube method, then mixed in the exposure chambers until the test concentrations were achieved. EDC concentrations were measured every 2 h, and the mean concentrations were calculated for each exposure group. Animals were weighed and clinically evaluated throughout the exposure duration, and were sacrificed 24 h after the last exposure. Body weights, gross organ weights and pathology, and detailed histopathology were examined following exposure.

There were no treatment-related clinical abnormalities observed in any of the animals tested at the end of the exposure period. Rats at the highest exposure concentration (2,000 ppm) had an incoordinated gait that the author's attributed to EDC exposure that resolved itself after day 2.

Body weights were decreased in the two highest exposure groups (600 and 2,000 ppm) by an average of 6-11 grams (g) (3-5%), which was more than the weight loss seen in the 200 ppm exposure group and controls (3-4 g, 1.5-2% loss). None of these differences were statistically significant but they were dose-dependent. No changes in body weight were observed at concentrations of 150 ppm or less. There were no gross pathological observations on the organs that were treatment related. Rats exposed to the highest concentration of 2,000 ppm had statistically significant increases in the relative and absolute adrenal gland weights. Male rats also had slightly increased liver weights, but the female rats had slightly decreased liver weights, so it was not determined whether this change was treatment related. No other gross organ changes were observed.

Histopathological effects were observed in the nasal tissue, kidneys, and liver of EDC exposed rats. The incidence of nasal lesions in male and female rats is presented in Table 4 and Table 5, respectively. Very slight to slight degeneration and necrosis of the olfactory epithelium occurred in all of the rats exposed to 600 and 2,000 ppm, and 3 out of 5 males and 4 out of 5 males in the 200 ppm group. Because these nasal effects were seen in all of the experimental groups, a second cohort was exposed to concentrations of 50, 100, and 150 ppm for 8 h. Degeneration and necrosis of the olfactory epithelium was also observed in 4 out of 5 males and 5 out of 5 females in the 150 ppm group, and 1 out of 5 males and 3 out of 5 females in the 100 ppm group. Exposure to 50 ppm gave results similar to those seen in the control animals. An additional group of rats sacrificed 15 d after the last exposure showed no degeneration in the nasal epithelium, but signs of regeneration were observed in some, suggesting that these effects may be reversible. A statistical analysis was not conducted. The no observed effect level (NOEL) for degeneration and necrosis of the olfactory epithelium is 50 ppm.

Table 4. Incidence of olfactory epithelium degeneration and necrosis in male rats.

EDC (ppm)	n per group	Very Slight, Unilateral	Very Slight, Bilateral	Slight	Moderate	Total
0	5[a]/5[b]/5[c]	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
50	5[a]/5[b]	0/0	0/0	0/0	0/0	0/0
100	5[b]	1	0	0	0	1
150	5[b]	2	2	0	0	4
200	5[a]/5[c]	1/0	2/0	0/0	0/0	3/0
600	5[a]/5[c]	0/0	1/0	4/0	0/0	5/0
2,000	5[a]/5[c]	0/0	1/0	4/0	0/0	5/0

[a] 4-h exposure, 24 h sacrifice
[b] 8-h exposure, 24 h sacrifice
[c] 4-h exposure, 15 d sacrifice

Table 5. Incidence of olfactory epithelium degeneration and necrosis in female rats.

EDC (ppm)	n per group	Very Slight, Unilateral	Very Slight, Bilateral	Slight	Moderate	Total
0	5[a]/5[b]/5[c]	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
50	5[a]/5[b]	0/0	0/0	0/0	0/0	0/0
100	5[b]	3	0	0	0	3
150	5[b]	0	4	1	0	5
200	5[a]/5[c]	2/0	1/0	1/0	0/0	4/0
600	5[a]/5[c]	0/0	1/0	4/0	0/0	5/0
2,000	5[a]/5[c]	0/0	2/0	2/0	1/0	5/0

[a] 4-h exposure, 24 h sacrifice
[b] 8-h exposure, 24 h sacrifice
[c] 4-h exposure, 15 d sacrifice

At 2,000 ppm, male rats had very slightly increased basophilia in the renal tubular epithelium and females had degeneration and individual cell necrosis of a segmented portion of the nephron. Kidney effects were not observed in any other exposure group. Male rats exposed to 2,000 ppm had very slight macrophage aggregates and less hepatocyte cytoplasmic vacuolation in the liver compared to controls. Female rats had altered cytoplasmic homogeneity of hepatocytes and slight but statistically significant increased liver weights at 2,000 ppm. No treatment-related histological effects were observed in the livers of animals exposed to less than 2,000 ppm.

Several neurobehavioral tests were also conducted, and nine abnormalities were observed, one at 600 and 2,000 ppm and eight at 2,000 ppm, that could be associated with EDC exposure. These effects included decreased resistance to removal from the home cage, increased palpebral closure, increased lacrimation, decreased exterior thrust response, decreased response to sharp noise and tail pinch, increased urination and defecation, and slight incoordination of gait. Females exposed to 200 ppm had lower activity counts, but it was not statistically significant. The lowest observed adverse effect level (LOAEL) for neurological effects was 600 ppm.

The NOEL from this study was 50 ppm with a lowest observed effect level (LOEL) of 100 ppm for degeneration and necrosis of the olfactory epithelium. Results indicate this NOEL is also protective against kidney, liver, and neurological effects.

3.1.2.2.2 Supporting Animal Studies

Other animal studies evaluating the short-term effects of EDC inhalation are more limited (e.g., number of animals, endpoints examined, high doses used). However, the studies discussed below are informative as supporting studies in the derivation of the 1-h acute ReV and ESL.

- Storer et al. (1984) compared the hepatotoxicity and genotoxicity following EDC exposure of male C57BL/6 x $C3HF_1$ mice by inhalation, oral gavage, and intraperitoneal (i.p.) injection. For the inhalation route, exposures were performed in a 30L stainless steel and glass chamber, and EDC was vaporized in a gas washing bottle by a metered air flow. Concentrations were monitored at 15 min intervals, with target concentrations of 150, 500, 1,000, and 2,000 ppm (time-weighted average concentrations of 158, 499, 1,072, and 1,946 ppm). For the gavage and i.p. routes, animals were treated with 200, 300, 400, 500, and 600 mg/kg EDC. All animals were exposed for 4 h and sacrificed 24 h later. The researchers collected the livers and kidneys of all the animal and analyzed organ weights, and collected blood to measure serum enzyme activities and blood urea nitrogen levels. Storer et al. concluded that EDC is hepatotoxic and nephrotoxic by all three routes of exposure, with threshold exposure levels at 500 ppm for inhalation, 400 mg/kg for i.p., and 500 mg/kg for gavage. In the inhalation study, kidney-to-body weight ratios, serum $_L$-iditol dehydrogenase, and blood urea nitrogen levels were increased at 500 ppm. No differences were observed in the 150 ppm exposure group compared to controls. The authors note that the route of exposure plays an important role in the toxicity and genotoxicity of EDC.
- Zhang et al. (2011) exposed equal numbers of male and female Sprague-Dawley (SD) rats to EDC concentrations of 0, 2,500, 5,000, and 10,000 mg/m^3 (617, 1,235, and 2,470 ppm) for 6 h and to 5000 mg/m^3 for 0, 3, 6 and 12 h (6 rats/exposure group). Details on the exposure methods were not provided. The researchers found that exposure to 5,000 mg/m^3 for a minimum of 2 h caused an increase in water content in the cortex tissue in the rat brains. Abnormal brain histopathology, including loose tissues and enlarged spaces around the cells, was also observed after exposure to 5,000 mg/m^3. No significant differences were observed at the lowest concentration tested; 2,500 mg/m^3 (617 ppm).
- Hepel et al. (1946) exposed mice, rats, guinea pigs, cats, dogs, and rhesus monkeys to target EDC concentrations of 100, 200, 400, and 1,000 ppm for 7 h/d, 5 d/wk, for varying lengths of time. Details on the strains/breeds were not provided, and not all species were exposed to every concentration. All of the animals were exposed in a 4'x4'x6' chamber and EDC was volatilized by passing a steady flow of air through the liquid. EDC concentrations were calculated using the air flow rate and the rate of volatilization, and measurements were taken daily through gas samples from the chamber. The analytical concentrations were 0.42, 0.73, 1.54, 3.9 mg/L (420, 730, 1,540, and 3,900 mg/m^3, respectively). At 1,000 ppm, high mortality rates were seen in the rats, rabbits, and guinea pigs after only a few exposures. The cats and dogs were more resistant, but eventually died at 1,000 ppm EDC. One monkey died after the second exposure, while a second monkey survived for 43 exposures. Autopsy of the animals revealed lung congestion, fatty degeneration in the liver, and fatty changes in the liver. Mortality was also seen in the 200 and 400 ppm groups; however more animals survived a greater number of exposures than in the 1,000 ppm group. Similar causes of death were determined after autopsy. At 100 ppm, all 16 female and 23 male rats survived at least 74 exposures. Breeding of the 16 female rats during the exposure period resulted in pregnancies in all but one of the rats. Survival records of the pups did not appear to be affected. Two guinea pigs died after 20 and 69 exposures, but an unusually high mortality

rate in the controls animals made this data unreliable. All 19 mice exposed repeatedly to 100 ppm also survived, and no gross effects were observed.

- Wang et al. (2013) exposed female albino mice via inhalation to nominal EDC concentrations of 225, 450, and 900 mg/m^3 (56, 111, and 222 ppm respectively) for 3.5 h/d for 10 d. EDC was placed on filter paper on a plate suspended in a 100 L chamber, and eight mice were exposed concurrently. Two hours after the final exposure, open field tests were performed, after which the animals were sacrificed and their brains examined. Several behavioral changes were observed, including a significant and dose-dependent decrease in the number of line crossings at 450 and 900 mg/m^3, a significant increase in vertical activity at 225 mg/m^3 that was not dose-dependent, an increase in time spent in the central zone that was not significant or dose-dependent, and a significant increase in the production of urine. Examination of the brains revealed higher levels of malondialdehyde in animals exposed to 225 mg/m^3 EDC, and higher levels of superoxide dismutase in animals exposed to 0.9 g/m^3 EDC, but neither response showed a dose-dependent trend. The researchers also found significantly higher levels of nitric oxide at 450 mg/m^3 EDC and inducible nitric oxide synthase at 225 mg/m^3 EDC, suggestive of damage from reactive nitrogen species. The lowest observed effect level (LOEL) from this study was 225 mg/m^3 EDC (56 ppm) for enzyme changes in the brain and 450 mg/m^3 (111 ppm) for neurobehavioral changes.
- Igwe et al. (1986) exposed male Sprague-Dawley (SD) rats to 150, 300, and 450 ppm EDC continuously for 30 d (24 h/d, 12 rats/exposure group). Animals were treated in stainless steel and glass exposure chambers, and EDC vapors were generated by pumping liquid EDC through an air feed. Concentrations were monitored continuously and recorded hourly, with mean average chamber concentrations of 153, 304, and 455 ppm. Animals were sacrificed on day 31, and body and liver weights were recorded. Blood samples were taken to analyze for enzymes that are representative of liver function. Increased liver-to-body weight ratios and increased 5-nucleotidase activity were observed following exposure to 450 ppm EDC. At 300 ppm, exposed rats had statistically significant increases in hepatic protein content and glutathione levels and decreased hepatic cytochrome P_{450} content. At 150 ppm, exposed rats also had statistically significant increases in hepatic protein content; however, this trend was not dose-dependent.

3.1.2.3 Reproductive and Developmental Studies

Studies regarding the reproductive and developmental effects of EDC are limited. A single inhalation study on the possible reproductive effects of EDC in humans is available and is detailed in ATSDR (2001).

- Zhao et al. (1989) observed an increase in the rates of premature birth in female workers and the wives of male workers at a Chinese synthetic factory that were exposed to EDC. Concentrations ranged from 0.4 to 384 ppm at two locations, and around 100 workers were included in the study. Workers were exposed either throughout their pregnancy (female workers) or for at least one year prior to their wife giving birth (male workers). No

information was given on the other chemical exposures that may have also occurred, or any other physical/environmental confounders that may have also been present.

Several animal inhalation studies have examined the reproductive and developmental effects of EDC, although the exposure durations span multiple days. ATSDR (2001) concluded that "the overall evidence from inhalation studies in rats and rabbits indicate that EDC is not a developmental toxicant".

- Rao et al. (1980), as described in USEPA (2010), exposed pregnant SD rats and White New Zealand rabbits to 0, 100, or 300 ppm EDC for 7 h/d on gestational days (GD) 6-15 (rats) or 6-18 (rabbits). Details on the exposure method were not given. Animals were sacrificed on GD 21 (rats) or 29 (rabbits), and the uteri and fetuses were examined. Maternal mortality occurred at 100 ppm in rabbits and 300 ppm in rabbits and rats. None of the fetuses from rats exposed to 300 ppm survived, possibly due to maternal toxicity. Exposure to 100 ppm in rats did not affect the mean litter size, the incidence of resorptions, fetal body measurements, or sex ratio. Exposure to 100 and 300 ppm in rabbits did not affect the incidence of pregnancy, number of implantation sites, resorption incidence, litter size, sex ratio, or fetal measurements in surviving rabbits.
- Rao et al. (1980), as described in USEPA (2010), also conducted a one-generation reproductive study and exposed groups of SD rats to 0, 25, 75, and 100 ppm (20/sex/group with controls at 30/sex) for 6 h/d, 5 d/wk for 60 d. Rats were mated after the initial 60 d exposure, and exposure was continued through gestation, discontinued from GD 21 to postnatal day (PND) 4, and then continued until the second breeding cycle. The first sets of pups were sacrificed at PND 21 and the adult animals were allowed to mate again. All animals were sacrificed once the second set of pups reached PND 21. No treatment-related abnormalities in fertility, reproduction, or fetal development were observed. There were no exposure-related changes in fetal growth, organ weight or histology.
- Payan et al. (1995) exposed groups of 26 pregnant SD rats to 0, 150, 200, 250, and 300 ppm (analytical concentrations of 150 ± 5, 195 ± 8, 254 ± 11, and 329 ± 18 ppm, respectively) EDC for 6 h/d on GD 6-20. Concentrations within each chamber were continuously monitored. Two out of 26 females exposed to 300 ppm EDC died during the exposure, although the total number of exposures that resulted in mortality was not reported. Maternal body weight was significantly decreased during GD 6-21 in rats exposed to 300 ppm but not in any other exposure group. The pregnancy rate in the 250 ppm group was significantly decreased compared to controls, but not in the 300 ppm exposure group. No significant differences were observed in the mean numbers of implantation sites, resorptions, live fetuses, fetal sex ratio, or fetal body weights. Several external, visceral, and skeletal malformations were observed but none that reached statistical significance. An oral exposure study was also conducted, and a slight but significant trend toward an increase in the mean percentage of nonsurviving implants per liter following exposure of 2 mmol/kg, suggesting the possibility of embryotoxic effects

following oral gavage of EDC at levels that also result in maternal toxicity. The authors concluded that EDC does not exhibit a selective developmental toxicity in SD rats.

- Zhao et al. (1989), as described in USEPA (2010) and ATSDR (2001), exposed pregnant Wistar rats to 0, 6.1, or 51.3 ppm EDC for 6 h/d from 2 wk prior to mating until GD 20. The exact duration of exposure is unknown. No effects were observed in the maternal endpoints examined, including body weight gain, impregnation rates, blood cell counts, blood protein content, and urine protein. However, preimplantation loss was significantly increased compared to controls (31.0% versus 10.2%) in the highest exposure group (51.3 ppm). No fetal effects were observed at either dose. The USEPA (2010) and ATSDR (2001) considered these results questionable because of difficulties translating the information from Chinese, including inconsistencies regarding species information and the number of animals used, and because statistical analyses were not conducted.

A recent extended one-generation drinking water study was conducted examining possible reproductive effects of EDC in mice and rats (Charlap 2015). This study was sponsored by the Hazardous Air Pollutants (HAP) Task Force in satisfaction of the Enforceable Consent Agreement (ECA) and submitted to the USEPA. A second study reported on a physiologically based pharmacokinetic (PBPK) model used to extrapolate the oral doses to inhalation exposures (Sweeney and Gargas, 2015).

- Charlap (2015) exposed groups of F_0 and F_1 male and female Crl:CD(SD) rats (27/sex/group) to EDC in drinking water at target concentrations of 0, 50, 150, and 300 mg/kg-d. Actual EDC doses were less than targeted doses in most groups due to what the authors suspected was palatability of the water. F_0 males were exposed throughout mating until euthanasia (day 92 or 93), while F_0 females continued to receive EDC doses throughout mating, gestation, and lactation (lactation day 22). Following mating of F_0 males and females, F_1 offspring were selected on PND 21 in groups of 20/sex/group and continued to receive EDC until euthanasia. An expansive set of parameters were recorded for all the animals, including clinical observations, body weights, food and water consumption, clinical pathology tests, complete necropsies, and reproductive analyses. Lower mean body weights, body weight gains, and food and water consumption were noted in both the F_0 and F_1 groups. These decreases were attributed to the decreased palatability of EDC in the drinking water. No signs of reproductive toxicity were observed in any of the groups tested, resulted in a reproductive NOAEL of 300 mg/kg-d (actual exposure level of 155 mg/kg-d for F_0 males, 182 mg/kg-d for F_0 females, 184 mg/kg-d for F_1 males, and 169 mg/kg-d for F_1 females). Sweeney and Gargas (2015) determined that the lowest NOAEL of 155 mg/kg-d was equivalent to a continuous inhalation exposure of 62 ppm.

All of the available reproductive and developmental data are based on multiple exposures, with the lowest reported effects observed at 51.3 ppm in rats in the Zhao et al. (1989) study, which was deemed by the USEPA (2010) as unreliable. By contrast, no treatment-related abnormalities

in fertility, reproduction, fetal development, or other endpoints (i.e., mean litter size, incidence of resorptions, fetal body measurements, sex ratio) in rats exposed up to 100 ppm (Rao et al. 1980), and no signs of reproductive toxicity were observed following long-term, continuous dose equivalents ≥ 62 ppm (Charlap 2015). Using a point of departure (POD) of 50 ppm from a single 8-h exposure (along with application of appropriate uncertainty factors) is expected to protect against potential reproductive or developmental effects due to acute exposure.

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

Absorption, distribution, and metabolism of EDC following inhalation or ingestion are rapid and complete in rats, with 85% of the metabolites being excreted in urine (OEHHA 2000). Acute inhalation of EDC at relatively high concentrations has been shown to cause CNS, liver, and kidney effects. At low concentrations, EDC has been shown to cause POE effects including degeneration and necrosis of nasal olfactory epithelium. The mechanism by which EDC acts at the POE or systemically is not well understood. Animal studies suggest that EDC may be metabolized to 2-chloroacetaldehyde and other reactive metabolites, which are able to bind and inhibit cellular macromolecules (ATSDR 2001). Exposure to the parent compound is the only available dose metric.

3.1.4 Point of Departure (POD) for Key Animal Study and Critical Effects

Hotchkiss et al. (2010) observed very slight degeneration and necrosis of the olfactory epithelium in 4 out of 10 rats exposed to 100 ppm EDC for 8 h. The NOEL from this study was 50 ppm, which will be conservatively used at the POD in further calculations of the 1-h acute ReV and ^{acute}ESL.

3.1.4.1 Default Exposure Duration Adjustments

The 8-h duration (C_1) in the key study by Hotchkiss et al. (2010) was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity:

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(50 \text{ ppm})^3 \times (8 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 100 \text{ ppm} = POD_{ADJ}$$

3.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

EDC is water soluble and causes POE effects (Category 1 gas) at low concentrations and acts systemically (i.e., as a Category 3 gas) on the CNS, liver, and kidneys at high concentrations. The critical effect of very slight degeneration and necrosis of the olfactory epithelium would suggest using a pharmacokinetic dosimetric animal-to-human adjustment factor (DAF) of 1 as a Category 1 gas acting on the extrathoracic region (ET). For Category 3 gases, when available, animal and human blood:gas partition coefficients are used to dosimetrically adjust for species differences in toxicokinetics (TCEQ 2015a).

$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$

where: $H_{b/g}$ = blood:gas partition coefficient

A = animal

H = human

D'Souza et al. (1987) reported rat blood:gas partition coefficients of 27.6 (SD rats) and 30.4 (Fisher rats), both of which are greater than the reported human blood:gas partition coefficient of 21.1. According to TCEQ guidelines, if the animal/human ratio of the blood:gas partition coefficients is greater than 1, a default value of 1 is used (TCEQ 2015a). Thus, all these considerations support using a dosimetric animal-to-human adjustment of 1 for the POD_{ADJ} (i.e., use a DAF_{ET} of 1). Thus, the POD_{HEC} is equal to the POD_{ADJ} of 100 ppm.

3.1.5 Adjustments to the POD_{HEC}

The POD_{HEC} based on a NOEL from the Hotchkiss et al. (2010) study was used as the POD and UFs were applied to derive the 1-h acute ReV (i.e., assume a threshold MOA). The following uncertainty factors (UFs) were applied to the POD_{HEC} of 100 ppm: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), and 6 for database uncertainty (UF_D), for a total UF of 180.

- An UF_H of 10 was used to account for variation in sensitivity among the members of the human population including possible child/adult differences, those with pre-existing medical conditions, etc.;
- An UF_A of 3 was used to account for potential pharmacodynamic differences between animals and humans (pharmacokinetic adjustment was already performed); and
- An UF_D of 6 was used because although there are several acute studies in multiple species available for EDC, including reproductive and developmental studies, only a single study in a single species evaluated POE (i.e., nasal/respiratory) effects, which appears to be the most sensitive (i.e., critical) effect. Also, EDC shows a very steep dose-response curve depending on the species examined, with mild respiratory effects in rats following a single exposure of 100 ppm (Hotchkiss et al. 2010) and death following multiple exposures to 100 ppm in rabbits and 300 ppm in rabbits and rats (Rao et al. 1980, Payan et al. 1995), which requisites due consideration when selecting the UF_D given the studies available. The quality of the study used as the POD is considered high, and the confidence in the acute database is medium to high.

acute 1-h ReV = $POD_{HEC} / (UF_H \times UF_A \times UF_D)$
= 100 ppm / (10 x 3 x 6)
= 100 ppm / 180
= 0.5555 ppm
= 555.5 ppb or 550 ppb (rounded to two significant digits)

3.1.6 Health-Based 1-h Acute ReV and ^{acute}ESL

In deriving the acute 1-h ReV for EDC, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The resulting 1-h acute ReV is 550 ppb (2,200 µg/m^3) based on the Hotchkiss et al. (2010) study. The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 160 ppb (650 µg/m^3) (Table 6).

Table 6. Derivation of the 1-h Acute ReV and ^{acute}ESL

Parameter	**Values and Descriptions**
Study	Hotchkiss et al. (2010)
Study Population	Male and female Fischer 344 rats, 5/sex/group in two acute inhalation toxicity studies and 10/sex/group in an acute neurotoxicity study
Study Quality	High
Exposure Method	Exposure via inhalation at 0, 50, 100, 150, 200, 600 and 2,000 ppm for 4 or 8 h
Critical Effect	Sight degeneration and necrosis of olfactory epithelium
POD (NOEL)	50 ppm
Exposure Duration	8 h
Extrapolation from 8 h to 1 h (POD_{ADJ})	100 ppm
POD_{HEC} (1 h)	100 ppm
Total UF	180
Intraspecies UF	10
Interspecies UF	3
Incomplete Database UF *Database Quality*	6 Medium to high
acute ReV [1 h] (HQ = 1)	550 ppb (2,200 µg/m^3)
^{acute}ESL [1 h] (HQ = 0.3)	160 ppb (650 µg/m^3)

3.2 Health-Based 24-h ReV

3.2.1 Background on 24-Hour AMCVs

For chemicals detected in the ambient air monitoring network, short-term AMCVs have generally been derived by the TCEQ to evaluate 1-h reported concentrations and long-term AMCVs have been derived to evaluate annual averages. Since a significant amount of ambient air data is collected over a 24-h duration, the derivation of chemical-specific 24-h AMCV values is needed to better evaluate ambient 24-h data. This consideration applies to EDC since it is detected in the TCEQ ambient air monitoring network and toxicity data are available to derive a 24-h ReV. Without a 24-h AMCV for EDC, only a limited evaluation of the reported 24-h levels is possible because 1-h and chronic (i.e., lifetime) AMCVs are generally inappropriate for this purpose. Thus, the development of a 24-h AMCV is necessary for the best possible health effects evaluation of individual 24-h sample results, and would significantly complement the short-term and chronic evaluations of EDC in ambient air data.

3.2.2 Key and Supporting Studies

The key and supporting studies listed in Section 3.1 are the same studies used in the derivation of the 24 h ReV. Hotchkiss et al. (2010) will be used as the key study, as discussed in Section 3.1.2.2 above.

3.2.3 MOA and Dose Metric

Absorption, distribution, and metabolism of EDC following inhalation or ingestion are rapid and complete in rats, with 85% of the metabolites being excreted in urine (OEHHA 2000). Acute inhalation of EDC at relatively high concentrations has been shown to cause CNS, liver, and kidney effects. At low concentrations, EDC has been shown to cause POE effects including degeneration and necrosis of nasal olfactory epithelium. The mechanism by which EDC acts at the POE or systemically is not well understood. Animal studies suggest that EDC may be metabolized to 2-chloroacetaldehyde and other reactive metabolites, which are able to bind and inhibit cellular macromolecules (ATSDR 2001). Exposure to the parent compound is the only available dose metric.

3.2.4 PODs for Key Study, Critical Effects and Dosimetric Adjustments

Hotchkiss et al. (2010) observed very slight degeneration and necrosis of the olfactory epithelium in 4 out of 10 rats exposed to 100 ppm EDC for 8 h. The NOEL from this study was 50 ppm, which will be conservatively used at the POD in further calculations of the acute 24-h ReV.

3.2.4.1 Default Exposure Duration Adjustments

The 8-h duration (C_1) in the key study by Hotchkiss et al. (2010) was adjusted to a POD_{ADJ} of 24-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 1, where both concentration and duration play a role in toxicity:

$C_2 = [(C_1) \times (T_1 / T_2)]$
$= [(50 \text{ ppm}) \times (8 \text{ h}/24 \text{ h})]$
$= 16.6667 \text{ ppm} = POD_{ADJ}$

3.2.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

EDC is water soluble and acts as a POE irritant (Category 1 gas) at low concentrations and acts systemically (i.e., as a Category 3 gas) on the CNS, liver, and kidneys at high concentrations. The critical effect of very slight degeneration and necrosis of the olfactory epithelium would suggest using a pharmacokinetic dosimetric animal-to-human adjustment factor (DAF) of 1 as a Category 1 gas acting on the ET region. For Category 3 gases, when available, animal and human blood:gas partition coefficients are used to dosimetrically adjust for species differences in toxicokinetics (TCEQ 2015a).

$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$
where: $H_{b/g}$ = blood:gas partition coefficient
A = animal
H = human

D'Souza et al. (1987) reported rat blood:gas partition coefficients of 27.6 (SD rats) and 30.4 (Fisher rats), both of which are greater than the reported human blood:gas partition coefficient of 21.1. According to TCEQ guidelines, if the animal/human ratio of the blood:gas partition coefficients is greater than 1, a default value of 1 is used (TCEQ 2015a). Thus, all these considerations support using a dosimetric animal-to-human adjustment of 1 for the POD_{ADJ} (i.e., use a DAF_r of 1). Thus, the POD_{HEC} is equal to the POD_{ADJ} of 16.6667 ppm.

3.2.5 Adjustments to the POD_{HEC}

The POD_{HEC} based on a NOEL from the Hotchkiss et al. (2010) study was used as the POD and UFs were applied to derive the 24-h ReV (i.e., assume a threshold MOA for a noncarcinogenic endpoint). The following uncertainty factors (UFs) were applied to the POD_{HEC} of 16.6667 ppm: 10 for UF_H, 3 for UF_A, and 6 for UF_D, for a total UF of 180.

- An UF_H of 10 was used to account for variation in sensitivity among the members of the human population including possible child/adult differences, those with pre-existing medical conditions, etc.;

- An animal-to-human UF_A of 3 was used to account for potential pharmacodynamic differences between animals and humans (pharmacokinetic adjustment was already performed); and
- A database deficiency UF_D of 6 was used because although there are several acute studies in multiple species available for EDC, including reproductive and developmental studies, only a single study in a single species evaluated POE (i.e., nasal/respiratory) effects, which appears to be the most sensitive (i.e., critical) effect. Also, EDC shows a very steep dose-response curve depending on the species examined, with mild respiratory effects in rats following a single exposure of 100 ppm (Hotchkiss et al. 2010) and death following multiple exposures to 100 ppm in rabbits and 300 ppm in rabbits and rats (Rao et al. 1980, Payan et al. 1995), which requisites due consideration when selecting the UF_D given the studies available. The quality of the study used as the POD is considered high, and the confidence in the acute database is medium to high.

$$\text{acute 24-h ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 16.6667 \text{ ppm} / (10 \times 3 \times 6)$$
$$= 16.6667 \text{ ppm} / 180$$
$$= 0.0926 \text{ ppm}$$
$$= 92.6 \text{ ppb or } 93 \text{ ppb (rounded to two significant digits)}$$

3.2.6 Health-Based 24-h ReV

In deriving the acute 24-h ReV for EDC, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The resulting 24-h acute ReV is 93 ppb (380 µg/m^3) based on the Hotchkiss et al. (2010) study (Table 7).

Table 7. Derivation of the 24-h Acute ReV

Parameter	Values and Descriptions
Study	Hotchkiss et al. (2010)
Study Population	Male and female Fischer 344 rats, 5/sex/group in two acute inhalation toxicity studies and 10/sex/group in an acute neurotoxicity study
Study Quality	High
Exposure Method	Exposure via inhalation at 0, 50, 100, 150, 200, 600 and 2,000 ppm for 4 or 8 h
Critical Effect	Degeneration and necrosis of olfactory epithelium
POD (NOEL)	50 ppm
Exposure Duration	8 h
Extrapolation from 8 h to 24 h (POD_{ADJ})	16.6667 ppm
POD_{HEC} (24 h)	16.6667 ppm
Total UF	180
Intraspecies UF	10
Interspecies UF	3
Incomplete Database UF *Database Quality*	6 Medium to high
acute ReV [24 h] (HQ = 1)	93 ppb (380 µg/m^3)

3.3 Welfare-Based Acute ESLs

3.3.1 Odor Perception

EDC has a pleasant odor and a sweet taste (ATSDR 2001). Published odor detection threshold values are summarized in Table 8 (TCEQ 2015b).

Table 8. Accepted Odor Studies Conducted for EDC

Investigator	Odor Detection Threshold Value
Hellman (1974)	24,000 µg/m^3 (6,000 ppb)
May (1966)	450,000 µg/m^3 (110,000 ppb)

Because these odor values are significantly higher than the determined acute ESLs, and the odor of EDC is described as pleasant and sweet, an $^{acute}ESL_{odor}$ will not be derived (TCEQ 2015b).

3.3.2 Vegetation Effects

After a literature review, there was no data found on any adverse effects of EDC on vegetation.

3.4 Short-Term ESL and Values for Air Monitoring Evaluation

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

- Acute 1-h ReV = 550 ppb (2,200 µg/m^3)
- ^{acute}ESL [1 h] = 160 ppb (650 µg/m^3)
- Acute 24-h ReV = 93 ppb (380 µg/m^3)

For the evaluation of ambient air monitoring data, the acute 1-h ReV for EDC is 550 ppb (2,200 µg/m^3) (Table 6), and the acute 24-h ReV is 93 ppb (380 µg/m^3) (Table 7). The short-term ESL used for air permit reviews is the health-based ^{acute}ESL of 160 ppb (650 µg/m^3) (Table 2).

3.5 Acute Inhalation Observed Adverse Effect Level

Risk assessors, and the general public, often ask to have information on the levels in air where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015a). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. Regarding critical effects due to acute EDC exposure, the animal study by Hotchkiss et al. (2010) found a 8-h rat LOEL of 100 ppm for nasal effects. This animal LOEL was used as the animal acute inhalation observed adverse effect level for extrapolation to humans. No duration adjustment was made (TCEQ 2015a). As discussed in Section 3.1.5.2, for these effects the animal-to-human dosimetric adjustment results in a $LOEL_{HEC}$ equal to the animal exposure concentration (e.g., a DAF of 1 is used). Thus, the 8-h $LOEL_{HEC}$ based on this animal study is estimated to be 100 ppm. This value is applicable to both the 1-h and 24-h ReV.

The $LOEL_{HEC}$ determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study (8 h) or longer. Importantly, effects are not a certainty due to potential

interspecies and intraspecies differences in sensitivity. The acute inhalation observed adverse effect level of 100 ppm (400 µg/m^3) is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the estimated acute inhalation observed adverse effect level of 100 ppm and the acute 1-h ReV of 550 ppb is a factor of 180 and the 24-h ReV of 93 ppb is a factor of over 1,000.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Data on the chronic toxicity of EDC, other than those from carcinogenicity studies, are limited. Unlike acute exposures, long-term studies tend to show negative results at concentrations that do not also induce mortality. The toxicological profiles of EDC from the USEPA (2010), ATSDR (2001), and IARC (1999) were reviewed for this section along with conducting a literature review for any more current studies. Because of the insufficient nature of the human data, an animal study with the appropriate UFs will be used to derive the chronic ReV.

4.1.2 Physical/Chemical Properties

The primary physical and chemical properties of EDC are discussed in Chapter 3 and summarized in Table 3.

4.1.3 Key and Supporting Studies

4.1.3.1 Human Studies

Several occupational studies have looked at workers exposed to EDC, but unfortunately these data are not very informative due to either co-exposures to other hazardous chemicals, such as vinyl chloride, insufficient exposure data, and/or lack of a dose-response relationship. A few of these studies can be found in the USEPA (2010) and ATSDR (2001) toxicological reviews of EDC and are detailed in in Section 3.1.2.1.

Due to the lack of sufficient human data, animal data were used to develop the chronic ReV.

4.1.3.2 Animal Studies

4.1.3.2.1 Key study

Spreafico et al. (1980) and Maltoni et al. (1980), as detailed in USEPA (2010) and OEHHA (2000), exposed male and female SD rats and Swiss mice (90/sex/group) to inhalation of 5, 10, 50, or 150-250 ppm EDC for 7 h/d, 5 d/wk, for up to 18 months. Spreafico et al. (1980) reported on the methods and chronic toxicity of EDC, while Maltoni et al. (1980) reported the neoplastic endpoints. Control groups consisted of 180 rats (chamber control and untreated) and 249 mice (untreated only). Originally the highest exposure concentration was set at 250 ppm, but due to

high toxicity in the animals after several days, the concentration was reduced to 150 ppm. Body weights were recorded every 2 wks, and 8-10 animals from each group were sacrificed at 3, 6, and 18 months. A series of parameters were examined, including hematology, serum chemistry, urinalysis, gross necropsy, and microscopic examination of the major tissues, including liver, lungs, kidneys, and gonads.

No non-neoplastic histology findings were reported, and no information was given as to the toxicity observed at 250 ppm. No exposure-related mortality was reported at 150 ppm. Several changes in hematology, serum chemistry, and urinalysis were statistically significant, but none showed a dose- or temporal-response. A second group of 8-10, 14-month old rats was exposed to 50 ppm for 12 months and they showed significant and dose-dependent increases in in ALT and uric acid in the serum. This effect was not observed in the rats exposed to the same concentration for 18 months, which the authors suggest could be because they were younger when treatment began (3 months old). No differences in any of the parameters examined were observed following 18-month exposure to 5 or 10 ppm. USEPA determined that the LOAEL from this study was 50 ppm for suggestive liver and kidney toxicity (increased ALT and uric acid, respectively) with a NOAEL of 10 ppm.

4.1.3.2.2 Supporting studies

Several studies have looked at chronic exposure of laboratory animals to EDC, although there have not been many significant findings at concentrations that do not also induce mortality. Several of these studies are summarized in USEPA (2010) and OEHHA (2000), and brief descriptions are provided below.

- Nagano et al. (2006) exposed male and female specific pathogen free (SPF) F344/DuCrj rats and Crj:BDF1 mice to EDC via inhalation at concentrations of 0, 10, 40, and 160 ppm (rats) and 0, 10, 30, and 90 ppm (mice) for 2 years (yr) (50/sex/exposure group). Concentrations were determined from an initial 13-wk study where rats and mice showed high mortality rates when exposed to 320 and 160 ppm, respectively, but no overt toxicity at 160 and 80 ppm. EDC was vaporized by bubbling clean air through the liquid in a temperature-regulated glass flask, and exposures were conducted in a 7,600 L chamber for rats and a 3700 L chamber for mice. Chamber concentrations were measured every 15 min, with 2-yr averages of 10, 39.8, and 159.7 ppm for the rats, and 10, 30, and 89.8 ppm for the mice. Body weights and food consumption were monitored once a week for the first 14 wk, then once a month for the remaining two years. A number of non-neoplastic endpoints were examined, including survival, urinary parameters, hematology and blood chemistry, and organ weight and gross pathology. Microscopic evaluations of neoplastic lesions were also conducted and are discussed in Section 4.2.2.2. No differences were observed in the survival rates, growth rates, or food consumption in any of the exposed rats compared to control. Female mice exposed to 30 ppm EDC had significantly lower survival rates than the control animals, but there was no difference in the survival rate of the exposed male mice. Since this decrease in survival was not dose-dependent, the authors concluded that it was not exposure-related. No differences

were observed in the growth rates or food consumption in any of the exposed mice compared to control. No exposure-related differences were observed in any hematological, blood biochemical or urinary parameter in any of the exposed animals. No exposure-related, non-neoplastic lesions were observed in any of the EDC-treated animals. The free-standing NOAEL from this study for non-neoplastic changes is 160 ppm for rats and 90 ppm for mice.

- Cheever et al. (1990) exposed groups of 50 SD [Crl:CD(SD)BR outbred] rats to 50 ppm EDC for 7 h/d, 5 d/wk for 2 yr (except for holidays). Animals were exposed in 2.2 m^3 stainless steel and glass chambers. EDC was volatilized by passing compressed air through liquid EDC. Nominal concentrations were calculated on a daily basis, and analytical concentrations were measured hourly. The average chamber concentration was 50.4 ppm for the target concentration of 50 ppm. Body weights, food and water consumption were measured weekly. Animals that either died during the study or were sacrificed after 2 yr were examined for gross histopathological changes and blood parameters related to the metabolism of EDC. Exposure to 50 ppm had no effect on mortality, body weight, food or water consumption, or the appearance of the animals. Female rats had a slight increase in basophilic focal cellular changes in the pancreas, but this was not observed in the male rats.
- Hofmann et al. (1971, as cited in USEPA 2010) exposed cats (2/sex/group), rabbits (2/sex/group), guinea pigs (5/sex/group), and SD rats (5/sex/group) to 0, 100, or 500 ppm EDC for 6 h/d, 5 d/wk for up to 17 wk. The researchers looked at a number of endpoints including body and organ weights, hematology, urinalysis, serum chemistry, liver function, and microscopic examination of specific organs. However not all of the parameters were evaluated for each species. At 500 ppm, 3/4 rabbits died after 10-17 exposures, 9/10 guinea pigs died after 4-14 exposures, and all the rats died after 1-5 exposures. At 100 ppm, there were no exposure-related differences in clinical signs, clinical chemistry, body weights, liver or kidney weights, or histopathology. The USEPA noted a NOAEL for this study of 100 ppm.
- Spencer et al. (1951) exposed male and female Wistar rats, guinea pigs, albino rabbits, and rhesus monkeys to 0, 100, 200, and 400 ppm EDC for 7 h/d, 5 d/wk for up to 35 weeks. The animals were exposed in a metal chamber, and EDC vapor was generated by passing air through a vaporizer containing liquid EDC. Chamber concentrations were measured continuously, and although the analytical concentrations were not provided, the authors state that "in every case the vapor was uniformly held within 10% of the desired concentration." Animals were examined for several toxicity endpoints including body and organ weights, gross organ histology, hematology, and serum chemistry. At 400 ppm, significant mortality occurred in all of the species tested, with the rats surviving no more than 40 exposures, guinea pigs no more than 24 exposures, and the monkeys no more than 12 exposures. Three rabbits survived 165 exposures with no changes in the toxicity parameters examined. At 200 ppm, all of the exposed rats and guinea pigs survived 151 and 180 exposures, respectively; they were only the species tested at this concentration. The exposed rats showed no signs of toxicity on body and organ weights, gross organ histology, hematology, and serum chemistry. Male and female guinea pigs had smaller body weights throughout the study, but only the male guinea pigs were significantly smaller than their control counterparts at the end

of the study. The authors noted that about half of the guinea pigs showed slight parenchymatous degeneration of the liver, dispersed fat vacuoles, and a slight increase in total lipid, phospholipid, fat, and cholesterol compared to controls. No other effects were observed. At 100 ppm, all of the exposed rats and guinea pigs survived 151 and 121 exposures, respectively. No changes were observed in any of the toxicity parameters tested. The NOAEL for this study is 100 ppm with a LOAEL for liver function changes and decreased body weight at 200 ppm.

4.1.3.3 Reproductive and Developmental Studies

Studies regarding the potential reproductive and developmental effects of EDC in humans are limited. A single inhalation study on the possible reproductive effects of EDC in humans is available and is detailed in ATSDR (2001) and detailed in Section 3.1.2.3.

All of the available reproductive and developmental data are based on multiple exposures, with the lowest reported effects observed at 51.3 ppm in the Zhao et al. (1989) study, which was deemed unreliable by the USEPA (2010). By contrast, no treatment-related abnormalities in fertility, reproduction, fetal development, or other endpoints (i.e., mean litter size, incidence of resorptions, fetal body measurements, sex ratio) in rats exposed up to 100 ppm (Rao et al. 1980), and no signs of reproductive toxicity were observed following long-term, continuous dose equivalents ≥ 62 ppm (Charlap 2015). Regardless, this result is similar to the LOAEL (50 ppm) from the key animal study (Spreafico et al. 1980), and using a POD of 10 ppm with appropriate UFs to derive the chronic ReV is expected to protect against potential reproductive or developmental effects that may occur at higher doses (e.g., >100 ppm in Rao et al. 1980).

4.1.4 MOA and Dose Metric

Absorption, distribution, and metabolism of EDC following inhalation or ingestion are rapid and complete in rats, with 85% of the metabolites being excreted in urine (OEHHA 2000). Chronic inhalation studies tend to show little to no effects at doses that do not also result in mortality. Liver and kidney changes suggest that chronic EDC exposure acts systemically, although the mechanism is not well understood. Animal studies suggest that EDC may be metabolized to 2-chloroacetaldehyde and other reactive metabolites, which are able to bind and inhibit cellular macromolecules (ATSDR 2001). However, the specific MOA for chronic EDC toxicity remains unknown. Exposure to the parent compound is the only available dose metric.

4.1.5 PODs for Key Study, Critical Effects and Dosimetric Adjustments

Based on the key study presented above (Spreafico et al. 1980), the TCEQ identifies 10 ppm (40 mg/m^3) as the NOAEL and POD based on rat liver and kidney toxicity.

4.1.5.1 Default Exposure Duration Adjustments

Animals were exposed for 7 h/day, 5 d/wk, for up to 18 months. An adjustment from a discontinuous to a continuous exposure duration was conducted (TCEQ 2015a) as follows:

POD_{ADJ} = POD x (D/24 h) x (F/7 d)

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

POD_{ADJ} = 10 ppm x (7/24) x (5/7) = 2.0833 ppm

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The critical effects of kidney and liver pathology are systemic in nature. Therefore, EDC is acting as a Category 3 gas for chronic exposure. For Category 3 gases, when available, animal and human blood:gas partition coefficients are used to dosimetrically adjust for species differences in toxicokinetics (TCEQ 2015a).

$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$

where: $H_{b/g}$ = blood:gas partition coefficient

A = animal

H = human

D'Souza et al. (1987) reported rat blood:gas partition coefficients of 27.6 (SD rats) and 30.4 (Fisher rats), both of which are greater than the reported human blood:gas partition coefficient of 21.1. According to TCEQ guidelines, if the animal/human ratio of the blood:gas partition coefficients is greater than 1, a default value of 1 is used (TCEQ 2015a). Therefore, the POD_{HEC} is equal to the POD_{ADJ} of 2.0833 ppm.

4.1.6 Adjustments to the POD_{HEC}

For the noncarcinogenic effects of EDC, UFs are applied to a POD to derive the chronic ReV (i.e., assume a threshold MOA for a noncarcinogenic endpoint). The following UFs were considered appropriate for application to the POD_{HEC} of 2.0833 ppm: 10 for UF_H, 3 for UF_A, and 6 for UF_D, for a total UF of 180.

- An UF_H of 10 was used to account for variation in sensitivity among the members of the human population including possible child/adult differences, those with pre-existing medical conditions, etc.;
- An animal-to-human UF_A of 3 was used to account for potential pharmacodynamic differences between animals and humans (pharmacokinetic adjustment was already performed); and
- A database deficiency UF_D of 6 was used because although there are several chronic studies in multiple species available for EDC, including reproductive and developmental studies, very few identified levels of toxicity below that which caused mortality. EDC shows a very steep dose-response curve, with mild liver/kidney effects at 50 ppm and high

toxicity/mortality at 250 ppm (Spreafico et al. 1980) and death at 100 ppm in rabbits and 300 ppm in rabbits and rats (Rao et al. 1980, Payan et al. 1995), which requisites due consideration when selecting the UF_D given the studies available. The quality of the study used as the POD is considered medium, and the confidence in the acute database is medium to high.

chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 2.0833 ppm / (10 x 3 x 6)
= 2.0833 ppm / 180
= 0.011574 ppm
= 11.574 ppb or 11 ppb (rounded to two significant digits)

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

In deriving the chronic ReV, no numbers were rounded between equations until the ReV was calculated. The chronic ReV was rounded to two significant figures, resulting in a value of 11 ppb (44 µg/m^3), and then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 3.3 ppb (13 µg/m^3) (Table 9).

Table 9. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Values and Descriptions
Study	Spreafico et al. 1980
Study Population	Male and female SD rats and Swiss mice
Study Quality	Medium
Exposure Concentrations	Untreated, chamber control, 5, 10, 50, 150-250 ppm
Critical Effects	Increased ALT and uric acid in the serum, indicative of liver and kidney toxicity
POD (NOAEL)	10 ppm
Exposure Duration	7 h/d, 5 d/wk for 12 months
Extrapolation to continuous exposure (POD_{ADJ})	2.0833 ppm
POD_{HEC}	2.0833 ppm
Total UF	180
Intraspecies UF	10
Interspecies UF	3
Incomplete Database UF *Database Quality*	6 Medium to high
Chronic ReV (HQ = 1)	**44 µg/m^3 (11 ppb)**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	**13 µg/m^3 (3.3 ppb)**

4.2 Carcinogenic Potential

There has been some debate on the carcinogenic potential of EDC due to the varying results from experimental tests, inconclusive data from epidemiological studies, and differences stemming from route of exposure. Available data on the carcinogenicity of EDC are detailed below.

4.2.1 Carcinogenic Weight of Evidence (WOE)

EDC has been evaluated for carcinogenic potential by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), USEPA, and the American Conference of Industrial Hygienists (ACGIH) (Table 10). Generally, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered by the TCEQ either to be

"Carcinogenic to Humans" or "Likely to Be Carcinogenic to Humans" and for which available data adequately characterize the dose-response curve.

Table 10. Carcinogenic Weight of Evidence

Group	Classification
IARC 1979, updated 1999	Possibly carcinogenic to humans
NTP 2011	Reasonably anticipated to be a human carcinogen
USEPA 1991	Probable human carcinogen
ACGIH 2001	Not classifiable as a human carcinogen

4.2.2 Relevant Data

4.2.2.1 Epidemiological Studies

Several studies have examined the correlation between excess cancer risk and EDC exposure. However, these studies looked at industrial workers exposed to a number of chemicals including EDC, so causality and significance are difficult to tease apart. Several of these studies are detailed in IARC (1999) and ATSDR (2001) and a few are summarized here.

- Austin and Schnatter (1983) conducted a cohort study of 6588 petrochemical workers in the U.S. that had reported an increased risk of brain cancers. There were 765 deaths and 150 deaths linked to cancer. The authors found an increased incidence in brain cancers, but a nested study with the same group found no significant association between the risk of primary brain tumors and exposure to EDC at the facility.
- Benson and Teta (1993) examined mortality in 278 chlorohydrin production workers who were exposed to EDC among other chemicals between 1940 and 1967. Out of 147 deaths, 40 were attributed to cancer, and increased incidences were observed in pancreatic, lymphatic, and hematopoietic cancers. Since the workers were exposed to multiple chemicals, including EDC, ethylene chlorohydrin, and bis(2-chloroethyl) ether, the researchers were unable to link the cancer incidence with a particular chemical.
- Olsen et al. (1997) examined mortality in 1361 workers at two chlorohydrin production plants similar to Benson and Teta (1993). There were a total of 300 deaths observed and 75 cancer deaths. The incidences of pancreatic, lymphatic, and hematopoietic cancers were less than observed in Benson and Teta (1993), and no other correlations were observed. This study lacked information on exposure concentrations and effects of multiple chemical exposures, so no conclusions were made.

4.2.2.2 Animal studies

4.2.2.2.1 Inhalation Studies

Although several inhalation studies examining chronic exposure of EDC in animals have been conducted, only a single study (Nagano et al. 2006) showed a statistically significant increase in neoplastic lesions. IARC (1999) included a discussion of the same data that were originally published in a study that examined several toxicants. The EDC-specific data were later published in 2006 with a more detailed comparison to historical experimental tumor rates.

- Nagano et al. (2006) exposed male and female specific pathogen free F344/DuCrj rats and Crj:BDF1 mice to EDC via inhalation at concentrations of 0, 10, 40, and 160 ppm (rats) and 0, 10, 30, and 90 ppm (mice) for 6 h/d, 5 d/wk for 104 wks (2 yr) (50/sex/exposure group). These concentrations were determined from an initial 13-wk study where rats and mice showed high mortality rates when exposed to 320 and 160 ppm, respectively. No overt toxicity was observed at 160 ppm in rats and a 9% and 7% decrease in body weight was observed in male and female mice, respectively, at 80 ppm. EDC was vaporized by bubbling clean air through the liquid in a temperature-regulated glass flask, and exposures were conducted in a 7,600 L chamber for rats and a 3,700 L chamber for mice. Chamber concentrations were measured every 15 min, with 2-yr averages of 10, 39.8, and 159.7 ppm for the rats, and 10, 30, and 89.8 ppm for the mice. A number of non-neoplastic endpoints were examined and are discussed in Section 4.1.3.2.2. The incidences of the observed neoplastic lesions are presented in Tables 11 and 12 for rats and mice, respectively. In the rat study, there was a statistically significant increase in the incidence of mammary gland fibroadenomas in males and subcutis fibromas, mammary gland adenomas and mammary gland fibroadenomas in females following exposure to 160 ppm EDC compared to controls. There were also significant increasing trends in most of the identified tumors, although the individual incidence may have not reached significance except for one or two exposure groups at the most. The authors point out that the combined incidence of mammary gland adenomas and fibroadenomas in female rats in the 40 ppm exposure group is higher than the maximum tumor number identified in a historical records comparison, however it did not reach statistical significance at 40 ppm, but did at 160 ppm. Thus, combined mammary gland tumors in the rat study showed both a statistically increased incidence over controls (as well as historical controls) at 160 ppm as well as a dose-response relationship. Female rats were more sensitive than male rats to EDC-induced mammary gland tumors at the two highest doses tested (11/50 versus 1/50 at 40 ppm, and 25/50 versus 7/50 at 160 ppm, respectively).

  In the mouse study, there was a statistically significant increase in the incidence of liver hemangiosarcomas in males at 30 and 90 ppm and in malignant lymphomas in females at 10 and 30 ppm; however, neither showed a significant increasing trend (i.e., dose-response relationship), even at the highest dose tested the incidences were within the range of historical control incidences, and the study authors stated that these tumors were not likely to be causally related to EDC exposure. The observed liver, lung, mammary gland, and uterine

tumors in female mice did show a significant increasing trend, however, the individual incidence data did not reach a statistically significant difference from controls.

Table 11. Tumor incidence in rats exposed via inhalation to EDC

Tumor Type/Incidence	Control	10 ppm	40 ppm	160 ppm
Males (#)	(50)	(50)	(50)	(50)
Subcutis fibroma [a]	6	9	12	15
Mammary gland adenoma	1	2	0	2
Mammary gland fibroadenoma [a]	0	0	1	5*
Combined mammary gland tumors [a]	1	2	1	7*
Peritoneum mesothelioma [a]	1	1	1	5
Females (#)	(50)	(50)	(50)	(50)
Subcutis fibroma [a]	0	0	1	5*
Mammary gland adenoma [a]	3	5	5	11*
Mammary gland fibroadenoma [a]	4	1	6	13*
Mammary gland adenocarcinoma [a]	1	2	0	5
Combined mammary gland tumors [a]	8	8	11	25*

* Significantly different from control at $p \leq 0.05$ by Fisher's exact test
[a] Significantly increasing trend at $p \leq 0.05$ by Peto's test

Table 12. Tumor incidence in mice exposed via inhalation to EDC

Tumor Type/Incidence	Control	10 ppm	30 ppm	90 ppm
Males (#)	(50)	(49)	(50)	(50)
Liver Hemangiosarcoma	0	4	6*	5*
Females (#)	(49)	(50)	(50)	(50)
Bronchiolo-alveolar adenoma [a]	4	1	3	8
Bronchiolo-alveolar carcinoma [a]	1	0	1	3
Combined bronchiolo-alveolar tumors [a]	5	1	4	11
Uterine endometrial stromal polyp [a]	2	0	1	6
Mammary Gland Adenocarcinoma [a]	1	2	1	6
Hepatocellular adenoma [a]	1	1	1	6
Hepatocellular carcinoma	1	0	1	0
Combined hepatocellular tumors [a]	2	1	2	6
Malignant lymphoma	6	17*	22*	12

* Significantly different from control at $p \leq 0.05$ by Fisher's exact test
[a] Significantly increasing trend at $p \leq 0.05$ by Peto's test

Several other inhalation studies showed either negative or mixed results.

- Cheever et al. (1990) exposed groups of 50 SD [Crl:CD(SD)BR outbred] rats to 50 ppm EDC for 7 h/d, 5 d/wk for 2 yr (except for holidays). Animals were exposed in 2.2 m^3 stainless steel and glass chambers. EDC was volatilized by passing compressed air through liquid EDC. Nominal concentrations were calculated on a daily basis, and analytical concentrations were measured hourly. The average chamber concentration was 50.4 ppm for the target concentration of 50 ppm. Body weights, food and water consumption were measured weekly. Animals that either died during the study or were sacrificed after 2 yr were examined for gross histopathological changes and neoplastic lesions. Although some tissue lesions and masses were observed at an increased frequency, no statistically significant increase in any neoplastic lesion was observed following 50 ppm EDC exposure. These results are consistent with the lack of statistically significant findings in rats chronically exposed to 40 ppm in Nagano et al. (2006).
- Spreafico et al. (1980) and Maltoni et al. (1980), as detailed in USEPA (2010) and ATSDR (2001), exposed male and female SD rats and Swiss mice (90/sex/group) to inhalation of 5, 10, 50, or 150-250 ppm EDC for 7 h/d, 5 d/wk, for up to 18 months. Spreafico et al. (1980) reported on the methods and chronic toxicity of EDC, while Maltoni et al. (1980) reported

the neoplastic endpoints. Control groups consisted of 180 rats (chamber control and untreated) and 249 mice (untreated only). Chamber controls were kept in an exposure chamber under the same conditions and for the same amount of time as the exposure groups, while untreated controls were kept in a nearby room. Originally the highest exposure concentration was set at 250 ppm, but due to high toxicity in the animals after several days, the concentration was reduced to 150 ppm. Body weights were recorded every 2 wks, and 8-10 animals from each group were sacrificed at 3, 6, and 18 months. No differences were noted in the tumor incidence compared to controls in mice; however, a detailed report was not provided. Although the USEPA (2010) reported no differences in tumor incidence in rats compared to controls, IARC (1979) reported the incidence of mammary fibromas and fibroadenomas to be statistically significantly increased in the 5 ppm (56/90), 50 ppm (49/90), and 150-250 ppm groups (47/90) compared to chamber controls (26/90), but not in the 10 ppm group (33/90). However, they were not significantly different from the untreated controls (47/90), the two control groups were significantly different from each other, and the increased incidence did not show a dose-response (e.g., there was actually a 10% decrease in incidence between 5 and 150-250 ppm). Notwithstanding the lack of a dose-response, the finding of potential increases in mammary fibromas and fibroadenomas at 150-250 ppm is consistent with the statistically elevated incidences for these endpoints found in female rats exposed to 160 ppm in Nagano et al. (2006).

4.2.2.2.2 Oral Study

The USEPA (1991) used an oral gavage study of chronic EDC exposure to derive its inhalation unit risk factor (URF) through route-to-route extrapolation.

- The National Cancer Institute (NCI 1978) exposed Osborne-Mendel rats and B6C3F1 mice (50/species/sex/group) to EDC by oral gavage alongside untreated and vehicle-treated controls (20/species/sex/group). Animals were treated 5 d/wk for 78 wks with time-weighted average doses of 47 and 95 mg/kg-d for rats, 97 and 195 mg/kg-d for male mice, and 149 and 299 mg/kg-d for female mice. Since the doses varied each week, the authors represented the time-weighted average doses as the sum of the doses divided by the total weeks of exposure. For the rat study, mortality was high in the group exposed to 95 mg/kg-d. An increased incidence of squamous-cell carcinomas was observed in the forestomachs of male rats in the 95 mg/kg-d group (9/50) and the 47 mg/kg-d group (3/50) compared to controls (0/40). The incidence of circulatory system hemangiosarcomas was also increased in the male rats in the 95 mg/kg-d group (7/27) and the 47 mg/kg-d group (9/48) compared to controls (0/40). Female rats showed a significant increase in mammary adenocarcinomas. In the mouse study, female mice showed a statistically significant increase in mortality as the dose increased, while male mice showed no association. Mice showed increased incidences of hepatocellular carcinomas and alveolar/bronchiolar adenomas.

The USEPA (1991) used the increased incidence of circulatory system hemangiosarcomas as a POD for developing an inhalation URF. The human equivalent dose was calculated assuming an

average human weight of 70 kg and an average rat weight of 0.5 kg. The 95% upper bound of risk was calculated using 90 wks of exposure. The calculated USEPA inhalation URF was 2.6E-05 per $\mu g/m^3$ (1.05E-04 per ppb), which corresponds to an air concentration of 0.4 $\mu g/m^3$ at an excess risk level of 1E-05 (1 in 100,000) (i.e., 1E-05 / 2.6E-05 per $\mu g/m^3$ = 0.4 $\mu g/m^3$).

4.2.2.2.1 Comparison Studies

A few studies have examined the possible differences in toxicity following exposure to EDC through various routes. ATSDR (2001) states that inhalation exposure to EDC is predicted to produce less metabolites in the liver and lungs than equivalent oral exposures, which may explain some of the differences observed between routes of exposure.

- Storer et al. (1984) compared the hepatotoxicity and genotoxicity following EDC exposure of male C57BL/6 x $C3HF_1$ mice by inhalation, oral gavage, and intraperitoneal (i.p.) injection. For the inhalation route, exposures were performed in a 30L stainless steel and glass chamber, and EDC was vaporized in a gas washing bottle by a metered air flow. Concentrations were monitored at 15-min intervals, with target concentrations of 150, 500, 1,000, and 1,000 ppm (time-weighted average concentrations of 158, 499, 1,072, and 1,946 ppm). For the gavage and i.p. routes, animals were treated with 200, 300, 400, 500, and 600 mg/kg EDC. All animals were exposed for 4 h and sacrificed 24 h later. The researchers collected tissues and blood samples to measure hepatotoxicity and nephrotoxicity, and assessed DNA damage in the liver by measuring the amount of double-stranded DNA that could be recovered (inversely proportional to DNA damage from double-stranded breaks). No evidence of DNA damage in the liver was observed at 150 or 500 ppm following a 4 h inhalation exposure. At the higher exposures of 1,000 and 2,000 ppm, some DNA damage was observed; however, there was also a high level of exposure-related mortality. DNA damage was detected at lower doses following i.p. and gavage exposure. The authors concluded that EDC is genotoxic at non-necrogenic dose levels following i.p. or gavage exposures, but non-genotoxic at comparable doses following inhalation exposure.
- Hooper et al. (1980) compared the data from the oral exposure study by NCI (1978) where several types of tumors were observed and the inhalation exposure study by Spreafico et al. (1980) and Maltoni et al. (1980) where there was no significant carcinogenic effect. Hooper et al. examined several different variables that could have played a role in the observed differences, including the purity of the chemical, dose levels, routes of exposure, strain differences, and statistical significance. The chemical purity appeared to be similar in the two studies, although the study by NCI (1978) tested several different chemicals at the same time, so other contaminants in the air may have been responsible for the observed effects. When conducting route-to-route calculations, it was determined that the inhalation study used doses that were much lower than the oral study, although the two highest doses (50 and 150 ppm) in rats (calculated to be 16 and 48 mg/kg-d) and mice (calculated to be 56 and 171 mg/kg-d) were comparable to the doses used in the oral gavage study (rats exposed to 24 and 48 mg/kg-d, male mice exposed to 60 and 120 mg/kg-d, and female mice exposed to 92.5 and 185 mg/kg-d). For differences in the route of exposure, the authors state that although the

blood concentration, metabolism, and tissue distribution of EDC are approximately the same for oral and inhalation routes of exposure, the possibility of gut flora producing carcinogenic metabolites cannot be ruled out. Hooper et al. (1980) also noted that there was a high level of early mortality in both studies, which could reduce the number of observed tumors as they tend to form later in life. They concluded that the observed difference in the carcinogenic potential of EDC in these two studies was most likely due to multiple factors, but that further data including a life-table analysis would be required to tease out the specific cause.

4.2.3 Carcinogenic MOA

Absorption, distribution, and metabolism of EDC following inhalation or ingestion are rapid and complete in rats, with 85% of the metabolites being excreted in urine (OEHHA 2000). Metabolism can occur through two different pathways: cytochrome P450 and glutathione *S*-transferase (IARC 1997). Animal studies suggest that EDC may be metabolized to 2-chloroacetaldehyde and other reactive metabolites, which are able to bind and inhibit cellular macromolecules (ATSDR 2001). The direct conjugation with glutathione catalyzed by glutathione S-transferase may ultimately result in the putative alkyating agent (episulfonium ion) primarily responsible for toxicity and carcinogenicity (OEHHA 2000). While the GSH metabolic pathway (not the oxidative pathway) appears responsible for the carcinogenic moiety (D'Souza et al. 1987), the specific MOA for the EDC carcinogenicity demonstrated in laboratory animals (e.g., rats) remains unknown. Therefore, a non-threshold MOA was assumed for developing a $^{chronic}ESL_{nonthreshold(c)}$ (i.e., linear low-dose extrapolation was used).

4.2.4 POD for Key Study and Critical Effect

The Nagano et al. (2006) study will be used as the key study as it is the inhalation study that most clearly showed a statistically significant increase for certain tumor types, some of which also showed a dose-response with a statistically significant increasing trend across exposure groups.

Combined mammary gland tumors in female and male rats showed a statistically significant increase at 160 ppm, with female rats being more sensitive than male rats to EDC-induced mammary tumors. Additionally, a statistically significant dose-response relationship was reported (8/50 in controls, 8/50 at 10 ppm, 11/50 at 40 ppm, 25/50 at 160 ppm). The significantly increased incidence of mammary gland tumors in female rats is consistent with the increased incidence of mammary tumors in female rats observed in the oral study by NCI (1978) and is well above (i.e., 2.5- to 13-fold above) the range of incidence in historical controls (Nagano et al. 2006). This information (e.g., statistically significantly increased incidence above controls, strong dose-response, consistency between exposure routes) supports mammary gland tumors in rats being causally related to EDC exposure and selection of this cancer endpoint for dose-response assessment and derivation of the URF.

On the other hand, while liver hemangiosarcomas in mice also appear to be a relatively sensitive endpoint, the study authors stated that these tumors were not likely to be causally related to EDC exposure as there was "no significant dose response relationship." Examination of study results indicates that there was not a statistically significant increasing trend in incidence across the exposure groups, in contrast to the mammary gland tumors in rats. Additionally, even at the highest exposure level (90 ppm), the incidence of liver hemangiosarcomas was within the range of historical control incidence (Nagano et al. 2006). Lastly, information from PBPK modeling of EDC metabolites in the mouse liver suggests that use of a POD for this endpoint for linear low-dose extrapolation is likely to overestimate risk due to nonlinearity in the metabolism of EDC to its carcinogenic moiety. D'Souza et al. (1987) utilized PBPK modeling to demonstrate the nonlinear relationship between intake of EDC (mg/kg) and the amount of mouse liver GC metabolite. More specifically, while the relationship between EDC intake and the amount of its glutathione-conjugated metabolite in the mouse liver show a 1:1 relationship at low doses (due to first-order metabolism), the amount of the metabolite in the mouse liver becomes proportionally much greater as EDC dose increases due to saturation of the oxidative pathway for EDC metabolism (the authors also state that the metabolic relationship in the human liver is predicted to be so similar to that of the mouse as to be virtually superimposable). This nonlinearity is particularly pronounced as intake decreases from high to low doses (e.g., as with a linear low-dose extrapolation from an animal study-derived POD). Accordingly, the authors conclude that by using a linear extrapolation from high doses and not taking into account the nonlinear metabolism of EDC, the risk of liver cancer can easily be overestimated by an order of magnitude. These results indicate that this would be the case for current assessment as the estimated intake corresponding to the POD for liver hemangiosarcomas in mice (≈50-60 mg/kg-d at a $BMCL_{10}$ of 36.5 µg/m^3) is higher than the doses where significant nonlinearities in metabolism occur while intake at the extrapolated air concentration corresponding to the no significant excess risk level of 1 in 100,000 would fall in the very low-dose region where risk would be significantly overestimated due to linear low-dose extrapolation not accounting for nonlinearities in EDC metabolism (see Figure 8 of D'Souza et al. 1987). Based on results of the D'Souza et al. (1987) study, applying an order of magnitude (or even half an order of magnitude) adjustment to the potential mouse POD ($BMCL_{10}$ of 9.02 ppm) to account for the nonlinear relationship between EDC dose and the amount of GC metabolite in the liver would result in a higher POD than that for mammary tumors in female rats. Thus, for the numerous reasons discussed above, mammary gland tumors in female rats was selected for dose-response assessment and derivation of the URF.

4.2.4.1 Benchmark Concentration (BMC) Modeling

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.6) for the data in Table 11 (combined mammary gland tumors in female rats) which was taken from the Nagano et al. (2006) study. Data were used to predict 95% lower confidence limits on the BMCs using dichotomous models. A default benchmark response (BMR) of 10% was selected for extra risk (BMC_{10}) and $BMCL_{10}$. For the combined

mammary gland tumors in female rat data, all of the available dichotomous and multistage cancer models were run (Appendices 1.1 and 1.2), and the best fit models are listed in Table 13.

Table 13. BMC Results for the Best Fit Models for Combined Mammary Gland Tumors in Female Rats

Model	Reason	p value	AIC	BMC_{10}	$BMCL_{10}$
Logistic	Lowest AIC	0.980	213.98	51.0 ppm	40.1 ppm
LogProbit	Lowest $BMCL_{10}$	0.965	215.94	48.8 ppm	13.6 ppm

Modeling of the data for combined mammary gland tumors resulted in a LogProbit model with a BMC_{10}/$BMCL_{10}$ of 48.8/13.6 ppm and a Logistic model with a BMC_{10}/$BMCL_{10}$ of 51/40.1 ppm. Both models fit the data and the $BMCL_{10}$ values are sufficiently close (less than 3-fold apart) (TCEQ 2015a, USEPA 2012b). Therefore, per USEPA guidelines, the model that resulted in the lowest AIC value (Logistic model) was chosen, which provides a $BMCL_{10}$ of 40.1 ppm. Additionally, it is important to note that this $BMCL_{10}$ appears to be better supported by the dose-response data. For example, the $BMCL_{10}$ of 13.6 ppm from the LogProbit model, which has a higher AIC, is only slightly higher than the exposure concentration of 10 ppm that resulted in a 0% increase over controls, and is about 3-fold lower than the 40 ppm exposure that only increased incidence 6% over controls. By contrast, the $BMCL_{10}$ of 40.1 ppm from the Logistic model is very similar to the 40 ppm exposure associated with a 6% increased incidence over controls. These results suggest that the $BMCL_{10}$ of 40.1 ppm from the Logistic model more accurately describes the dose response, in addition to the Logistic model having a lower AIC and being selected consistent with current guidelines.

4.2.4.2 Default Exposure Duration Adjustments

In the Nagano et al. (2006) study, animals were exposed for 6 h/d, 5 d/wk for 104 wk. An adjustment from a discontinuous to a continuous exposure duration was conducted (TCEQ 2015a) as follows:

POD_{ADJ} = POD x (D/24 h) x (F/7 d)

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

POD_{ADJ} = 40.1 ppm x (6/24) x (5/7) = 7.1607 ppm

4.2.4.3 Default Dosimetry Adjustments from Animal-to-Human Exposure

Mammary gland tumors are systemic in nature; therefore, EDC is acting as a Category 3 gas. For Category 3 gases, when available, animal and human blood:gas partition coefficients are used to dosimetrically adjust for species differences in toxicokinetics (TCEQ 2015a).

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$$

where: $H_{b/g}$ = blood:gas partition coefficient

A = animal

H = human

D'Souza et al. (1987) reported rat blood:gas partition coefficients of 27.6 (SD rats) and 30.4 (Fisher rats), both of which are greater than the reported human blood:gas partition coefficient of 21.1. According to TCEQ guidelines, if the animal/human ratio of the blood:gas partition coefficients is greater than 1, a default value of 1 is used (TCEQ 2015a). Therefore, the POD_{HEC} is equal to the POD_{ADJ} of 7.1607 ppm.

4.2.5 Calculation of a Unit Risk Factor

From this data, an inhalation URF can be derived using the following equation (TCEQ 2015a):

$$URF = 0.1 / POD_{HEC}$$

$$URF = 0.1 / 7.1607 \text{ ppm} = 0.0140 (\text{ppm})^{-1} \text{ or } 0.0034 (\text{mg/m}^3)^{-1}$$

$$URF = 1.4E\text{-}05 (\text{ppb})^{-1} \text{ or } 3.4E\text{-}06 (\mu\text{g/m}^3)^{-1} \text{ (rounded to two significant figures)}$$

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

The calculated URF based on increased incidence of combined mammary gland tumors in female rats from the Nagano et al. (2006) study is 1.4E-05 $(\text{ppb})^{-1}$ or 3.4E-06 $(\mu\text{g/m}^3)^{-1}$. The no significant risk level of 1E-05 is calculated as follows (TCEQ 2015a):

$$^{chronic}ESL_{nonthreshold(c)} = 1E\text{-}05 / URF$$

$$= 1E\text{-}05 / 1.4E\text{-}05 (\text{ppb})^{-1}$$

$$= 0.71 \text{ ppb } (2.9 \mu\text{g/m}^3)$$

4.2.7 Comparison of Cancer Potency Factors

Table 14 lists the inhalation URF and toxicity values calculated at a cancer risk level of 1E-05 that are available. Both the USEPA and OEHHA toxicity values are based on route-to-route extrapolation from oral studies, while TCEQ's URF is based on more exposure route relevant inhalation carcinogenicity study data.

Table 14. Available Inhalation URFs and Chronic Toxicity Values

Agency	Inhalation URF	Chronic Toxicity Value
TCEQ $^{chronic}ESL_{nonthreshold(c)}$	3.4E-06 $(\mu g/m^3)^{-1}$	2.9 $\mu g/m^3$
OEHHA (2009)	2.1E-05 $(\mu g/m^3)^{-1}$	0.5 $\mu g/m^3$
USEPA (1991)	2.6E-05 $(\mu g/m^3)^{-1}$	0.4 $\mu g/m^3$

4.2.8 Evaluating Susceptibility from Early-Life Exposures

TCEQ (2015a) states that carcinogens acting through a mutagenic MOA need to be evaluated for the potential increase in cancer due to early-life exposures compared with adult and whole-life exposure. USEPA (2005) provides default age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis. Storer et al. (1984) reported an increase in double-strand DNA breaks in mice following a 4-h exposure to 1000 ppm EDC (although this concentration also induced significant mortality), and single-strand breaks were also observed in rat liver following oral gavage of EDC (IARC 1999). On the other hand, Hotchkiss et al. (2014) reported no exposure-related DNA damage in mammary epithelial cells following inhalation exposure to 200 ppm EDC, although the study did not identify a specific MOA for EDC-induced mammary tumors. Similarly, Hachiya and Motohashi (2000) reported no increase in the mutation frequency in the liver and testis of male Muta™Mice following an oral dose of up to 150 mg/kg EDC. *In vitro*, EDC has been shown to interact with DNA and induce genotoxic effects (ATSDR 2001). EDC was mutagenic in *Salmonella typhimurium* and *Drosophila melanogaster*, as well as mouse and rat liver, lung, and kidney cells (IARC 1999), but it did not induce micronuclei in mouse cells (ATSDR 2001). Although these changes suggest the potential for genotoxic and/or mutagenic effects under certain conditions, once a carcinogen has been determined to have mutagenic potential, there are several important considerations in assessing evidence for a mutagenic MOA for cancer. For example: (1) whether the chemical-induced mutation occurs prior to the initiation of the carcinogenic process (i.e., early in relation to the key events that lead to cancer) in the target tissue (i.e., site and temporal concordance between mutagenicity and carcinogenicity), and if so (2) whether the chemical-induced mutation is the key event that initiates the carcinogenic process in the target tissue. See Section 5.7.5.1.2 of TCEQ (2015a) for additional information, including a hierarchy for types of relevant evidence. Most importantly, for a chemical to act by a mutagenic MOA, either the chemical or its direct metabolite must be the agent inducing the mutations that initiate cancer in the target tissue. As there is no default carcinogenic MOA, the scientific burden of proof is a reasonably robust demonstration through direct evidence that the specific mutation(s) caused by the chemical or its metabolite is in fact the first step in target tissue which initiates a cascade of other key events that are critical to the carcinogenic process in the specific tumors. Mere plausibility (whether or not information on other possible MOAs is available) is not tantamount to an adequately robust demonstration that mutagenicity is in fact the initiating event in target

tissues. Thus, if the weight of evidence supports a chemical's genotoxic and/or mutagenic potential, for evaluation of the MOA emphasis should then be placed on evidence of the chemical's mutagenicity being the critical, initiating carcinogenic event in target cells (at relevant doses if possible). In the event scientifically convincing data on the carcinogenic MOA are lacking, the carcinogenic MOA may ultimately be judged simply to be unknown or not sufficiently elucidated or established (TCEQ 2015a). This is the case for EDC, for which the carcinogenic MOA is certainly unclear. As the MOA for EDC has not been demonstrated to be mutagenic, consistent with TCEQ guidance (TCEQ 2015a), ADAFs will not be applied to the URF at this time. This issue will be reevaluated periodically as new scientific information on EDC's carcinogenic MOA becomes available.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 44 µg/m^3 (11 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 13 µg/m^3 (3.3 ppb)
- $^{chronic}ESL_{nonthreshold(c)}$ = 2.9 µg/m^3 (0.71 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{nonthreshold(c)}$ of 2.9 µg/m^3 (0.71 ppb). For evaluation of long-term ambient air monitoring data, the $^{chronic}ESL_{nonthreshold(c)}$ of 2.9 µg/m^3 (0.71 ppb) is lower than the chronic ReV of 44 µg/m^3 (11 ppb) (Tables 1 and 2). However, the ReV value may be used for the evaluation of air data as well as the $^{chronic}ESL_{nonthreshold(c)}$ and URF. The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) would not be used to evaluate ambient air monitoring data (Table 2).

4.5 Noncarcinogenic Chronic Inhalation Observed Adverse Effect Level

Observed inhalation adverse effect levels are described in more detail in Section 3.4 and in TCEQ (2015a). This section is for noncarcinogenic effects only; variability in the carcinogenic data makes it unsuitable for determination of an observed adverse effect level. The chronic POD of 10 ppm determined from the Spreafico et al. (1980) and Maltoni et al. (1980) study was based on liver and kidney effects observed in rats following 50 ppm EDC inhalation exposure for 7 h/day, 5 d/wk, for up to 18 months. The LOAEL of 50 ppm, where effects occurred in some animals, represents a concentration at which similar effects could possibly occur in some individuals exposed over the same duration or longer. Based on the TCEQ guidelines (2015a), no duration adjustment is conducted; however an animal-to-human dosimetric adjustment is used to calculate the $LOAEL_{HEC}$. Since the RGDR is 1, based on updated guidelines from the USEPA (2015a), the $LOAEL_{HEC}$ is equal to the LOAEL of 50 ppm. Effects are not a certainty as there may be inter- and intraspecies differences in sensitivity. The chronic inhalation observed adverse

effect level of 50 ppm is provided for informational purposes only (TCEQ 2015a). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose.

The margin of exposure between the observed adverse effect level (50 ppm) and the chronic ReV (0.011 ppm) is a factor of approximately 4,500.

Chapter 5 References

5.1 References Cited in the Development Support Document

ACGIH. 2001. American Conference of Industrial Hygienists. Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH.

ATSDR. 2001. Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,2-Dichloroethane. U.S. Department of Health and Human Services.

Bowler, R.M., Gysens, S., and Hartney, C. 2003. Neuropsychological effects of ethylene dichloride exposure. NeuroToxicology. 24:553-562.

Charlap JH. 2015. An extended one-generation drinking water reproductive toxicity study of ethylene dichloride in rats. WIL-417007. WIL Research, Ashland, OH. Audited Draft Report.

Cheever, K.L., Cholakis, J.M., El-Hawari, A.M., Kovatch, R.M., and Weisburger, E.K. 1990. Ethylene dichloride: The influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundamental and Applied Toxicology. 14:243-261.

ChemSpider. 2015. http://www.chemspider.com

Cheng, T., Huang, M., You, N., Du, C., and Chau, T. 1999. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. Journal of Occupational and Environmental Medicine. 41:1128-1133.

D'Souza, R. W., Francis, W. R., Bruce, R. D., and Andersen, M. E. (1987). Physiologically based pharmacokinetic model for ethylene dichloride and its application in risk assessment. In Pharmacokinetics in Risk Assessment: Drinking Water and Health, pp. 286–301. National Academy Press.

Washington, DC. Davis, J.A., Gift, J.S., and Zhao, Q.L. 2011. Introduction to benchmark dose methods and U.S.EPA's benchmark dose software (BMDS) version 2.1.1. Toxicology and Applied Pharmacology. 254(2): 181-191.

Hachiya, N. and Motohashi, Y. 2000. Examination of *lacZ* mutant induction in the liver and testis of Muta™Mouse following injection of halogenated aliphatic hydrocarbons classified as human carcinogens. Industrial Health. 38: 213-220.

Hellman, T.M., and Small, F.H. 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. Journal of the Air Pollution Control Association. 24(10):979-982.

Heppel, L.A., Neal, P.A., Perrin, T.L., Endicott, K.M., and Porterfield, V.T. 1946. The toxicology of 1,2-dichloroethane (ethylene dichloride): V. The effects of daily inhalations. The Journal of Industrial Hygiene and Toxicology. 28(4):113-120.

Hotchkiss, J.A., Andrus, A.K., Johnson, K.A., Krieger, S.M., Woolhiser, M.R., and Maurissen, J.P. 2010. Acute toxicologic and neurotoxic effects of inhaled 1,2-dichloroethane in adult Fischer 344 rats. Food and Chemical Toxicology. 48:470-481.

Hotchkiss, J.A., Marshall, V.A., Luna, L., Sura, R. and Visconti, N. 2014. Investigation of the mode of action for 1,2-dichloroethane-induced mammary tumors in female F344/DuCrl rats. The Dow Chemical Company. Study ID 121180.

Hooper, K., Gold, L.S., and Ames, B.N. 1980. The carcinogenic potency of ethylene dichloride in two animal bioassays: A comparison of inhalation and gavage studies. Banbury Report 5: Ethylene Dichloride. Cold Springs Harbor Laboratory.

IARC. 1999. 1,2-Dichloroethane Exposure Data. IARC Monographs: Overall Evaluations of carcinogenicity to humans. Available from: http://monographs.iarc.fr/ENG/Monographs/vol71.

Igew, O.J., Que Hee, S.S., and Wagner, W.D. 1986. Interaction between 1,2-dichloroethane and tetraethylthiuram disulfide (disulfram) II: Hepatotoxic manifestations with possible mechanism of action. Toxicology and Applied Pharmacology. 86:286-297.

May, J. 1966. Odor thresholds of solvents for assessment of solvent odors in the air. Ataub. 26:385-389. (in German).

Nagano, K., Umeda, Y., Senoh, H., Gotoh, K., Arito, H., Yamamoto, S., and Matsushima, T. 2006. Carcinogenicity and chronic toxicity in rats and mice exposed by inhalation to 1,2-dichloroethane for two years. Journal of Occupational Health. 48(6):424-436.

National Cancer Institute (NCI). 1978. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. NCI Carcinogenesis Technical Report Series No. 55. DHEW Publ. No. (NIH) 78-1361, Washington DC.

Nouchi, T., Miura, H., Kanayama, M., Mizuguchi, O., and Takano, T. 1984. Fatal intoxication by 1,2-dichloroethane – a case report. International Archives of Occupational and Environmental Health. 54:111-113.

OEHHA. 2000. Chronic Toxicity Summary Ethylene Dichloride. Determination of noncancer chronic reference exposure levels for airborne toxicants. California Environmental Protection Agency, Berkeley, CA.

OEHHA. 2009. Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors. California Environmental Protection Agency, Berkeley, CA.

Payan, J.P., Saillenfait, A.M., Bonnet, P., Fabry, J.P., Langonne, I. and Sabate, J.P. 1995. Assessment of the developmental toxicity and placental transfer of 1,2-dichloroethane in rats . Fundamental and Applied Toxicology. 28: 187-198.

Spencer, H.C., Rowe, V.K., Adams, E.M., McCollister, D.D., and Irish, D.D. 1951. Vapor toxicity of ethylene dichloride determined by experiments on laboratory animals. A.M.A. Archives of Industrial Hygiene and Occupational Medicine. 4:482-493.

Storer, R.D., Jackson, N.M., and Conolly, R.B. 1984. *In vivo* genotoxicity and acute hepatotoxicity for 1,2-dichloroethane in mice: Comparison of oral, intraperitoneal, and inhalation routes of exposure. Cancer Research. 44:4267-4271.

Sweeney, L.M. and Gargas, M.L. 2015. Route-to-route extrapolation of 1,2-dichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: extended one generation toxicity study and reproductive toxicity studies in the rat. Draft Report.

TCEQ. 2015a. TCEQ guidelines to develop toxicity factors. Texas Commission on Environmental Quality. Chief Engineer's Office.

TCEQ. 2015b. Approaches to derive odor-based values. Texas Commission on Environmental Quality. Chief Engineer's Office.

ten Berge, W.F., Zwart, A., and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. Journal of Hazardous Materials. 13:301-309.

USEPA. 1991. Toxicological review of 1,2-Dichloroethane on the Integrated Risk Information System. United States Environmental Protection Agency. Office of Research and Development. Washington, D.C.

USEPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. United States Environmental Protection Agency. Office of Research and Development. Washington, D.C.

USEPA. 2010. Provisional Peer-Reviewed Toxicity Values for 1,2-Dichloroethane. United States Environmental Protection Agency. Office of Research and Development. Washington, D.C.

USEPA 2012a. Advances in inhalation gas dosimetry for derivation of a reference concentration (RfC) and use in risk assessment. United States Environmental Protection Agency. Washington, D.C. EPA/600/R-12/044.

USEPA 2012b. Benchmark Dose Technical Guidance. United States Environmental Protection Agency. Washington, D.C. EPA/100/R-12/001.

Wang, G., Qi, Y., Gao, L., Li, G., Lv, X., and Jing, Y.P. 2013. Effects of subacute exposure to 1,2-dichloroethane on mouse behavior and the related mechanisms. Human and Experimental Toxicology. 32(9):983-991.

Zhang, Q., Niu, Q., Li, L., Yang, L., Guo, X., Huang, J., Wang, L., and Liang, Y. 2011. Establishment of a poisoned animal model of toxic encephalopathy induced by 1,2-dichloroethane. International Journal of Immunopathology and Pharmacology. 24(1):79-83.

Appendix 1 Benchmark Concentration (BMC) Modeling

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.6) for the incidence of combined mammary gland tumors in female rats presented in Table 11 which was taken from the Nagano et al. (2006). Data were used to predict 95% lower confidence limits on the BMCs using dichotomous and multistage cancer models. A default BMR of 10% was selected for extra risk (BMC_{10}) and $BMCL_{10}$. All of the available dichotomous and multistage cancer models were run (Appendices 1.1 and 1.2). All of the models are presented below, with the best fit model based in the lowest $BMCL_{10}$ and the best fit to the curve shown in bold and graphically below its respective table.

Appendix 1.1 Dichotomous models

Tumor Type/Incidence	Control	10 ppm	30 ppm	90 ppm
Females (#)	(50)	(50)	(50)	(50)
Combined mammary gland tumors	8	8	11	25*

Table 15. Dichotomous models for combined mammary gland tumors in female rats

Model[a]	Goodness of fit		BMD_{10Pct}	$BMDL_{10Pct}$	Basis for model selection
	***p*-value**	**AIC**			
Gamma	0.908	215.95	50.3	22.6	Of the models that provided an adequate fit and a valid BMDL estimate, the Logistic model was selected based on the lowest AIC.
Dichotomous-Hill	N/A[b]	217.94	44.8	15.0	
Logistic	**0.980**	**213.98**	**51.0**	**40.1**	
LogLogistic	0.915	215.95	49.7	18.1	
Probit	0.978	213.99	48.5	38.0	
LogProbit	0.965	215.94	48.8	13.6	
Weibull	0.895	215.96	50.6	22.6	
Multistage 4°	error	error	error[c]	error[c]	
Multistage 3°[d] Multistage 2°	0.850	215.98	51.7	22.6	
Quantal-Linear	0.830	214.31	32.9	22.1	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 10, 40, and 160 were 0.03, -0.03, 0.01, 0, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

Selected Model - Logistic Model (Lowest AIC). (Version: 2.14; Date: 2/28/2013)

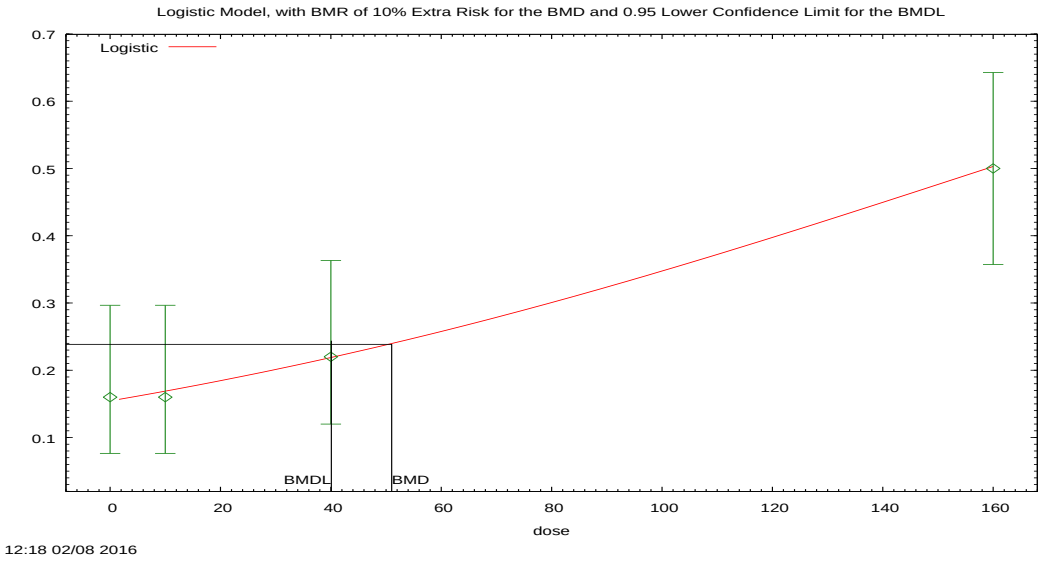


Figure 1. Plot of incidence rate by dose with fitted curve for Logistic model for combined mammary gland tumors in female rats; dose shown in ppm.

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 51.0174

BMDL at the 95% confidence level = 40.0805

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.7045E+00	-1.6562E+00
slope	0.0106538	0.0103423

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-104.97	4			
Fitted model	-104.99	2	0.0403563	2	0.98
Reduced model	-114.61	1	19.2833	3	0

AIC: = 213.98

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1539	7.694	8	50	0.12
10	0.1683	8.413	8	50	-0.16
40	0.2178	10.892	11	50	0.04
160	0.5	25.001	25	50	0

Chi^2 = 0.04 d.f = 2 P-value = 0.9801

Alternate Model – LogProbit Model (Lowest BMDL). (Version: 3.3; Date: 2/28/2013)

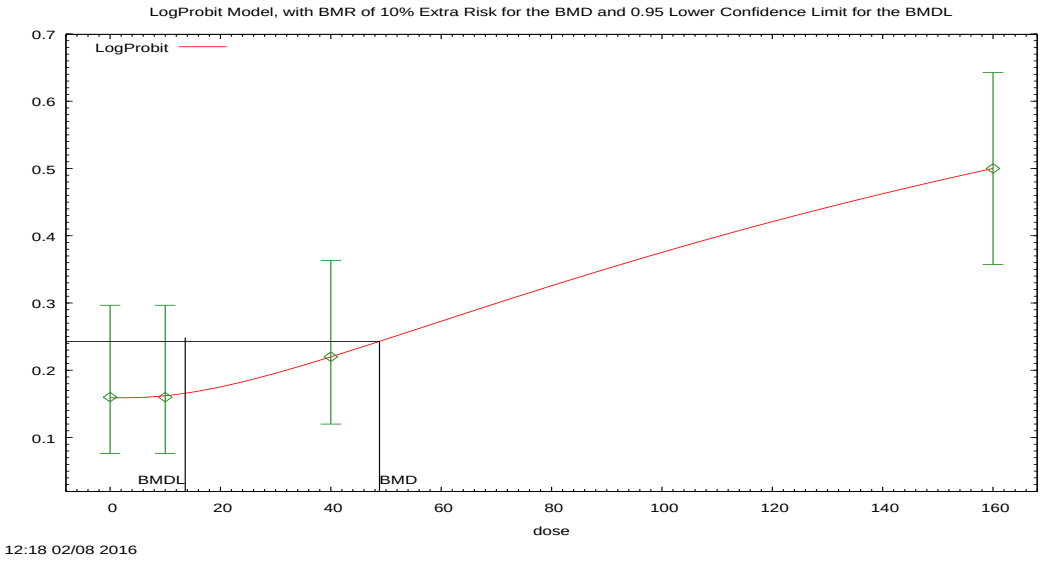


Figure 2. Plot of incidence rate by dose with fitted curve for LogProbit model for combined mammary gland tumors in female rats; dose shown in ppm.

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 48.8161

BMDL at the 95% confidence level = 13.613

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.158556	0.16
intercept	-4.6990E+00	-4.1310E+00
slope	0.878957	0.754792

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-104.97	4			
Fitted model	-104.97	3	0.00188386	1	0.97
Reduced model	-114.61	1	19.2833	3	0

AIC: = 215.941

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1586	7.928	8	50	0.03
10	0.1617	8.085	8	50	-0.03
40	0.2197	10.983	11	50	0.01
160	0.5001	25.005	25	50	0

Chi^2 = 0 d.f = 1 P-value = 0.9654

Appendix 1.2 Multistage cancer models

Tumor Type/Incidence	Control	10 ppm	30 ppm	90 ppm
Females (#)	(50)	(50)	(50)	(50)
Combined mammary gland tumors	8	8	11	25*

Table 16. Multistage cancer models for combined mammary gland tumors in female rats

Model[a]	Goodness of fit		BMD_{10Pct}	$BMDL_{10Pct}$	Basis for model selection
	***p*-value**	**AIC**			
Four	error	error	error[b]	error[b]	
Three	0.850	215.98	51.7	22.6	
Two					
One	**0.830**	**214.31**	**32.9**	**22.1**	

[a] Best model in bold; scaled residuals for selected model for doses 0, 10, 40, and 160 were 0.36, -0.17, -0.41, 0.2, respectively.
[b] BMD or BMDL computation failed for this model.

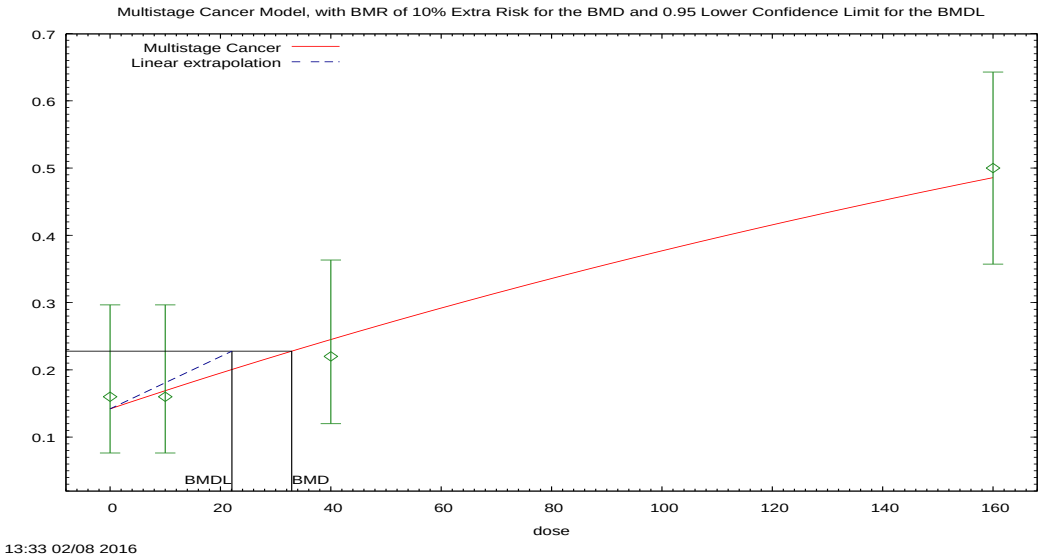


Figure 3. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for combined mammary gland tumors in female rats; dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 32.9083

BMDL at the 95% confidence level = 22.0752

BMDU at the 95% confidence level = 56.8491

Taken together, (22.0752, 56.8491) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00452996

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.141984	0.135551
Beta(1)	0.00320164	0.00336983

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-104.97	4			
Fitted model	-105.16	2	0.372502	2	0.83
Reduced model	-114.61	1	19.2833	3	0

AIC: = 214.312

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.142	7.099	8	50	0.36
10	0.169	8.451	8	50	-0.17
40	0.2451	12.256	11	50	-0.41
160	0.4859	24.296	25	50	0.2

Chi^2 = 0.37 d.f = 2 P-value = 0.8301